Kinetic analysis of the dimerization and disproportionation of aqueous glyoxal

Alfred Richard Fratzke Jr.

Iowa State University

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KINETIC ANALYSIS OF THE DIMERIZATION AND DISPROPORTIONATION OF AQUEOUS GLYOXAL

Iowa State University

Ph.D. 1985

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Kinetic analysis of the
dimerization and disproportionation
of aqueous glyoxal

by

Alfred Richard Fratzke, Jr.

A Dissertation Submitted to the
Graduate Faculty in Partial Fulfillment of the
Requirements for the Degree of
DOCTOR OF PHILOSOPHY

Major: Chemical Engineering

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For the Graduate College

Iowa State University
Ames, Iowa
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1. INTRODUCTION

1.1. Objectives

The principal objective of this research has been, simply, to contribute significantly to our scientific understanding of carbohydrate reactions in aqueous solution. A secondary objective has been to build an experimental and theoretical framework for use in the study of related but more complex reactions. Although the focus of my research has narrowed considerably during the course of my studies, culminating in the study of glyoxal presented herein, the above objectives have remained unchanged.

The two-carbon dicarbonyl glyoxal, CHOCHO, is in many respects a remarkable compound. In common with other α-dicarboxyls, α-hydroxyaldehydes, and even formaldehyde, glyoxal readily undergoes reversible polymerization in both acidic and basic solution. At a slower rate, glyoxal in alkaline solution undergoes an intramolecular disproportionation characteristic of α-dicarboxyls. However, because of its simple, symmetrical structure, lacking an α-hydroxy moiety or even an enolizable hydrogen, glyoxal polymerizes and disproportionates free of the complications of enolization, such as aldolization, isomerization, and oxidation. More remarkable, perhaps, is the fact that despite its simple two-carbon structure, commercial availability, and known reactivity toward a variety of nucleophilic addition compounds, the chemistry of the self-reactions of glyoxal had heretofore escaped serious examination. It is this author's opinion that detailed knowledge of these reactions should be prerequisite to a systematic study of many of the above addition reactions.

In Secs. 3 and 4 are reported the results of detailed investigations
into the disproportionation and oligomerization, respectively, of glyoxal. In each study the first and overriding goal was to determine as accurately as possible (within constraints of time and support) over a broad range of experimental conditions the equilibrium product distributions and rates of reaction of glyoxal and to express the results in terms of appropriate equilibrium constants and mathematical rate laws. A second objective was to infer possible reaction mechanisms, consistent with the observed rate laws, from which extensions might be made to related reactions.

It is hoped that the kinetic and thermodynamic findings reported herein will prove reliable and so be of benefit to those studying more complex reactions involving glyoxal or related compounds.

1.2. Project History

This work originated from a kinetic study of the oxidation of mono- and oligosaccharides in Somogyi's alkaline copper(II) solution. Although those experiments did produce some intriguing findings, it soon became apparent that such reactions were too complex and undefined to allow much fundamental understanding to be gained from copper reduction rates alone. It was perhaps more surprising to observe in subsequent studies that two- and three-carbon sugar analogues also possessed complex, non-stoichiometric oxidation reactions. In fact, even the oxidation of glycolaldehyde did not appear to consume the expected two moles of copper(II) per mole of glycolaldehyde.

The above studies revealed, however, that the two-carbon dicarbonyl, glyoxal, was an intermediate in the oxidation of glycolaldehyde, a not
unexpected result considering the central role that α-dicarbonyls appear to play in the oxidations of hydroxycarbonyls by single-electron oxidizing agents. It was further observed that the glyoxal formed above appeared to react further to quantitatively yield glycolic acid, as had been reported earlier by O'Meara and Richards. A literature search revealed that the kinetics of the disproportionation of glyoxal to glycolic acid had been reported by Salomaa in 1956, and also pointed up the important position of glyoxal in the study of alkaline carbohydrate reactions.

When a check on the rate of glyoxal disproportionation, using a newly developed spectrophotometric assay, failed to support Salomaa's findings, a careful kinetic study of the reaction was undertaken. Ultimately, the behavior of glyoxal in aqueous solution was found to be far more complex than had been presumed by Salomaa. In fact, the aqueous self-reactions of glyoxal have since been the sole focus of this research. However, the results presented herein should pave the way for complete kinetic analyses of more complex compounds.

To be more specific, the experimental methods developed in the study of glyoxal are directly applicable to methylglyoxal (pyruvaldehyde) and probably to hydroxymethylglyoxal (glycerosone) and to alduloses as well. The above α-dicarbonyls present increasingly complex problems, complicated by first aldolization, then oxidation, and finally isomerizations and ring formations and no doubt a myriad of other side reactions. A kinetic study of the self-reactions of methylglyoxal is, in fact, presently underway. That study also has produced findings substantially at odds with those of the only previously published study, that by Königstein and Fedoronko in
1973, and has convinced this investigator of the need for thorough and exacting kinetic studies of the type presented here for glyoxal.
2. RELATED LITERATURE

Glyoxal, the simplest $\alpha$-dicarbonyl compound, exists in a variety of chemical forms dependent on physical and chemical conditions. An anhydrous (dialdehdo) monomeric form has been reported as a greenish-yellow liquid, which readily polymerizes in the presence of traces of water. Anhydrous glyoxal is believed to possess a planar, trans structure. In dilute aqueous solution, glyoxal is thought to exist primarily as a monomeric hydrate, while at higher concentrations oligomeric hydrates are in evidence. Under certain conditions, soluble hydrated polymers may be formed.

In aqueous solutions of greater than 40% glyoxal, a trimeric dihydrate, determined by Raudnitz to possess the structure shown below, has been found to slowly crystallize from solution. Glyoxal trimeric dihydrate is marketed commercially, and was the source of the glyoxal used in this research. The physical and chemical properties of glyoxal were reviewed in a Union Carbide technical bulletin in 1967.

Glyoxal, as is typical of $\alpha$-dicarbonyls, is highly reactive in aqueous solution. Although a large number of reports dealing with the chemistry of glyoxal have been published, surprisingly little research has dealt with
the simple reactions of glyoxal in aqueous solution.

One of the most important reactions of carbonyl compounds in aqueous solution, but one that is not undergone by glyoxal, is that of enolization. It is largely via the enol or enediol forms that such compounds undergo a bewildering variety of reversible and irreversible reactions, including isomerization, aldolization, and oxidation. Because of its unique structure, glyoxal shows no evidence of significant enolization, and thus pure solutions of glyoxal exist free from the complicating reactions above. Glyoxal, however, does undergo two of the general reaction-types characteristic of carbonyls in aqueous solution -- equilibrium addition and disproportionation.

In both acidic and alkaline solution, glyoxal undergoes a variety of highly reversible carbonyl addition reactions with water and with itself to form hydrated monomers and concentration-dependent oligomeric structures. These reactions are included in a broad class of reactions, termed "equilibrium additions", that have usually been found to be subject to general acid-base catalysis, although hydroxide ion is generally the most efficient catalyst. While carbonyl compounds are believed to be far more reactive in the free carbonyl form, in aqueous solution addition products, such as those cited above, usually predominate. Short chain two-, three-, and to some extent, four-carbon carbonyls are often substantially hydrated in aqueous solution, existing as gem-diols; in more concentrated solutions there is often evidence of dimer, trimer and/or polymer formation. Four-carbon and especially longer-chain polyhydroxycarbonyls (and δ- or γ-mono-hydroxycarbonyls) generally exist as intramolecular hemiacetals, forming to various extents pyranoid and furanoid ring structures.
The interconversions of the above carbonyl forms are included within a single family of organic reactions, that of equilibrium additions to carbonyl bonds. Also included in these reactions are the formation of acetals (including oligo- and polysaccharides), cyanohydrins, amino alcohols, and many others — all reactions characteristic of carbohydrates. The equilibrium addition reactions as a group were reviewed by Ogata and Kawasaki in 1970.

According to Ogata and Kawasaki, equilibrium additions to carbonyls can be written in the general form below:

\[
\begin{align*}
R_1\text{C}==\text{O} + \text{XY} & \rightarrow R_1\text{C}\text{C}==\text{OY} \\
R_2 & \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad 
product is virtually totally dissociated at any alkaline pH ($\text{p}K_a = 3.82$),
the disproportionation of glyoxal proceeds with the net consumption of one
mole of hydroxide ion, as indicated below:

\[
\begin{align*}
\text{H—C—OH} + \text{OH}^- & \rightarrow \text{OC—O}^- \\
\text{H—C—OH} & \rightarrow \text{H—C—OH}
\end{align*}
\]

Glyoxal  Glycolate

However, because glyoxal exists predominantly in other forms in aqueous
solution, the actual mechanism of disproportionation should be expected to
be far more complicated than is suggested by the simple representation
above.

The remainder of this chapter will describe the general aspects of
the three predominant reactions undergone by glyoxal in aqueous solution —
hydrations, oligomerization, and disproportionation. The simplest aqueous
equilibrium addition reactions, hydrations, are considered in Sec. 2.1. In
Sec. 2.2 the related but more complex intra- and extramolecular self-
hemiacetalization reactions are described. Finally, in Sec. 2.3 the
related literature concerning disproportionation reactions is summarized.

**2.1. Carbonyl Hydrations**

Carbonyl compounds, especially aldehydes, react rapidly and reversibly
with solvent water to form gem-diols or hydrates, as shown below:
These hydration reactions are perhaps the simplest type of equilibrium addition reactions. In the case of aldehydes such hydrated forms are sometimes referred to as aldehydrols. Carbonyl hydrations were reviewed by Bell\(^{10}\) in 1966.

The chemical equation above also serves to define the thermodynamic hydration constant \(K_h'\), which is defined in terms of the activities of the species involved. For work in dilute aqueous solution, the activity coefficients of the two neutral glyoxal forms as well as the activity of the solvent water can usually be assumed approximately equal to unity. Under those conditions, \(K_h'\) is closely approximated by the "classical" or "concentration" equilibrium constant, \(K_h = [R_1 R_2 C(OH)_2]/[R_1 R_2 CO]\).

Although all of the disproportionation experiments to be reported in Sec. 3 were conducted in glyoxal solutions of 0.02M concentration or less, the dimerization experiments to be described in Sec. 4 employed solutions of up to unit molarity in total glyoxal. However, the variations in \(K_h\) with glyoxal concentration are presumed to be of relatively small magnitude and so will be neglected in analyses of dimerization kinetic and thermodynamic results.

The extent to which aldehydes exist as hydrates varies widely; hydration constants of 28000, 1.4, and 0.00026 have been reported for trichloroethanal\(^{11}\), acetaldehyde\(^{10}\), and carbon dioxide\(^{12}\), respectively, although \(CO_2\) cannot be considered a typical carbonyl. The extent of hydration is thus
influenced by the substituent groups \( R_1 \) and \( R_2 \). As a rule, ketones are far less hydrated than related aldehydes, for which \( R_1 = H \). Hydration is enhanced by the presence of electron-attracting substituents and decreased by the presence of electron furnishing and/or bulky substituents\(^{10}\).

According to Bell, values of the dehydration constant \( K_{\text{dehyd}} (= \kappa_h^{-1}) \) for aldehydes can be predicted with fair accuracy by using Taft's\(^{13}\) polar (\( \sigma^* \)) and steric (\( E_s \)) substituent constants and the empirical relation:

\[
\log_{10} K_{\text{dehyd}} = 2.70 - 2.6 \Sigma \sigma^* - 1.3 \Sigma E_s
\]  

Unfortunately, the appropriate parameters are not available for the determination of the \( K_h \)'s for glyoxal or for most simple dicarbonyls.

Because it is a dialdehyde, glyoxal is an exceptional \( \alpha \)-dicarbonyl in that it has the potential to exist in substantial proportions in a form that is hydrated at both carbonyl groups. In contrast, all other \( \alpha \)-dicarbonyls can be considered \( \alpha \)-ketocarbonyls and should be expected to be predominantly unhydrated at the \( \alpha \)-carbonyl group. For example, the closely related \( \alpha \)-dicarbonyl, methylglyoxal, is believed to exist predominantly as the monohydrate\(^ {14} \). Because of symmetry, the two carbonyl groups of glyoxal are chemically indistinguishable, and thus two effective equilibrium constants \( K_{h1} \) and \( K_{h2} \) can be used to relate the concentrations of the three neutral forms of glyoxal, as depicted in Fig. 2.1.

There exists a fair amount of experimental support for the assertion that glyoxal is highly dihydrated in aqueous solution, including the lack of a characteristic carbonyl UV absorption peak at ca. 280 nm\(^ {15} \) and evidence from proton-NMR spectroscopic studies indicating the absence of lines
Fig. 2.1. Structural relationships and nomenclature for the interconversion of hydrated and anionic monomeric glyoxals presumed present in alkaline solution.
in the region characteristic of aldehydic protons. Recently, Jessen, Kollerup, Nielsen, Ovesen, and Sorensen investigated the hydrations of glyoxal and of methylglyoxal using conventional semicarbazide scavenger techniques to measure the dehydration rates and stopped-flow and temperature-jump methods to determine the hydration rates. Their findings, which represent experiments conducted at unspecified temperature and pH, are listed in Table 2.1. Although the authors were able to determine hydration constants for both carbonyl moieties of methylglyoxal, they were apparently unable to resolve the two hydration constants for glyoxal. A possibly combined hydration constant \( K_{h1}K_{h2} \) of 670 was reported.

The existence of glyoxal substantially in the dihydrated form is also supported by analogy with related monocarbonyl compounds, many of which have been more closely examined. In recent years, several reports of hydration studies of short-chain \( \alpha \)-hydroxyaldehydes have been published. Included in Table 2.1 are available hydration constants for glycolaldehyde and lactaldehyde and, for comparison, the less closely related carbonyls formaldehyde and acetaldehyde. At 25°C, both \( \alpha \)-hydroxycarbonyls appear to be approximately 95% hydrated. In a recent proton-NMR study of various short-chain reducing sugars, Angyal and Wheen reported the ratios of free carbonyl to hydrated forms to be roughly 1:10 for the four-carbon sugars D-erythrose and D-threose as opposed to roughly 1:20 for glycolaldehyde and D,L-glyceraldehyde. They rationalized the difference as being due to the fact that the gem-diol moiety of the two and three carbon compounds might exist in any of three rotational conformations, while with four-carbon polyhydroxyaldehydes one of the three conformations would be relatively unpopulated due 1,3-parallel interactions with the C3-hydroxyl group.17
Table 2.1. Reported hydration constants $K_h$ and catalytic dehydration rate constants following Eq. 2.7\(^a\) for glyoxal and related compounds in aqueous solution at 25°C.

<table>
<thead>
<tr>
<th>Carbonyl compound</th>
<th>$K_h$</th>
<th>$k_{H3O^+}$, s(^{-1}) M(^{-1})</th>
<th>$k_o^b$, s(^{-1})</th>
<th>$k_{OH^-}$, s(^{-1}) M(^{-1})</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glycolaldehyde</td>
<td>20</td>
<td>8.3</td>
<td>0.0096</td>
<td>6000</td>
<td>18</td>
</tr>
<tr>
<td>Lactaldehyde</td>
<td>23</td>
<td>3.4</td>
<td>0.0063</td>
<td>7500</td>
<td>19</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>2000(^c)</td>
<td>2.7</td>
<td>0.0051</td>
<td>1600</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.4</td>
<td>0.0042</td>
<td>2100</td>
<td>21</td>
</tr>
<tr>
<td>Acetaldehyde</td>
<td>1.5</td>
<td>620</td>
<td>0.0052</td>
<td>530000</td>
<td>22</td>
</tr>
<tr>
<td>Glyoxal(^d)</td>
<td>$K_{h1}K_{h2} = 670$</td>
<td>$k_{dehyd}^e = 0.011$ s(^{-1})</td>
<td></td>
<td></td>
<td>14</td>
</tr>
<tr>
<td>Methylglyoxal(^d)</td>
<td>$K_{h1} = 8300$</td>
<td>$K_{h2} = 0.24$</td>
<td>$k_{dehyd}^e = 0.0042$ s(^{-1})</td>
<td>0.0096 s(^{-1})</td>
<td>14</td>
</tr>
</tbody>
</table>

\(^a\) $k_{dehyd} = k_{H3O^+[H_3O^+]} + k_o + k_{OH^-}[OH^-]$ (ignoring catalysis by buffer salts).

\(^b\) $k_o = k_{H2O[H_2O]}$.

\(^c\) Reference 10.

\(^d\) Determined at unspecified temperature.

\(^e\) Probably composite constant.
Although very little reliable information is available on the effect of temperature on carbonyl hydrations, it does appear that the reactions are generally exothermic as written; enthalpies of hydration $\Delta H_h$ of $-59$, $-24$, and $-11$ kJ/mol have been reported for trichloroethanal$^{11}$, acetaldehyde$^{10}$, and carbon dioxide$^{12}$, respectively. Reported values of $\Delta H_h$ for formaldehyde vary widely$^{10}$, although it appears that the actual value is less (more negative) than $-35$ to $-40$ kJ/mol.

Recently, Lavery, De Oliveira, and Pullman$^{23}$ reported the findings of a quantum mechanical study of the acid-catalyzed hydration of glyoxal and related aldehydes using a STO-3G basis. With each carbonyl, the reaction was presumed to proceed via the formation of an intermediate water-carbonyl complex with concomitant distortion of the planar carbonyl moiety. After finding no support for a stable complex between water and the unprotonated carbonyl moiety, the authors assumed prior protonation of the carbonyl oxygen and computed enthalpy changes ranging from $-24.4$ to $-33.4$ kcal/mol for water complexation of those moieties. In Table 2.2 are listed the computed enthalpy changes associated with protonation, complexation and deprotonation (of the complex), as well as the overall heats of reaction for the three hydrations examined.

Although favorable overall enthalpy changes were calculated in each case, the magnitude of the change for anhydrous glyoxal was especially large at $|-39.5|$ kcal/mol. The positive enthalpy changes associated with the presumed rate-limiting deprotonation steps were computed to be significantly lower for both $\Delta H_{h1}$ (+136.3 kcal/mol) and $\Delta H_{h2}$ (+133.8 kcal/mol) than for hydration of any other carbonyl moiety examined. Considering that the above values were much less than that available from the protonation
Table 2.2. Computed (ab-initio) enthalpy changes associated with successive, postulated steps in the acid-catalyzed hydration of carbonyl compounds

<table>
<thead>
<tr>
<th>Carbonyl compound</th>
<th>Enthalpy Change (kcal/mol)</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta H_{\text{protonation}}$</td>
<td>$\Delta H_{\text{complexation}}$</td>
<td>$\Delta H_{\text{deprotonation}}$</td>
<td>$\Delta H_{\text{reaction}}$</td>
</tr>
<tr>
<td>HCHO</td>
<td>-143.0</td>
<td>-33.4</td>
<td>+142.9</td>
<td>-33.5</td>
</tr>
<tr>
<td>HCOCHO</td>
<td>-141.8</td>
<td>-29.0</td>
<td>+136.3</td>
<td>-34.5</td>
</tr>
<tr>
<td>HC(OH)$_2$CHO</td>
<td>-146.6</td>
<td>-26.7</td>
<td>+133.8</td>
<td>-39.5</td>
</tr>
<tr>
<td>CH$_3$CHO</td>
<td>-156.8</td>
<td>-24.4</td>
<td>+149.7</td>
<td>-31.5</td>
</tr>
<tr>
<td>CH$_3$COCHO (aldehydic)</td>
<td>-143.8</td>
<td>-32.7</td>
<td>+141.3</td>
<td>-35.2</td>
</tr>
<tr>
<td>CH$_3$COCHO (ketonic)</td>
<td>-151.8</td>
<td>-26.6</td>
<td>+150.3</td>
<td>-28.1</td>
</tr>
<tr>
<td>CH$_3$COCH(OH)$_2$</td>
<td>-164.9</td>
<td>-18.4</td>
<td>+145.7</td>
<td>-37.6</td>
</tr>
</tbody>
</table>

$^a$From Lavery, Oliveira, and Pullman (Ref. 23, p. 464).
energy of a water molecule (-142.3 kcal/mol), the authors concluded that
the formation of glyoxal mono- and dihydrates could be expected to occur
quite readily. It should be noted that the computed value of ΔH° for
formaldehyde is considerably smaller (more negative) than the reported
experimental values. Recently, Spangler, Williams and Maggiora also
reported quantum mechanical calculations for gas-phase water-formaldehyde
addition. The enthalpy of hydration was roughly three times larger when
calculated by using the STO-3G basis set, the set employed by Lavery et
al., than when calculated by using 4-31G and 6-31G basis sets.

In the course of the above studies, Lavery et al. determined that the
optimal conformation of the gem-diol moiety was a structure wherein both
hydroxyl protons lie in the O—C—O plane. A weak hydrogen bond between
one of the hydroxyl hydrogens and the neighboring hydroxyl oxygen was
indicated.

Perhaps the most important chemical property of carbonyl hydrates is
their relative acidity. Carbonyl hydrates are considerably stronger acids
than either glycols or monohydric alcohols; pK_a's of 10.04, 13.57, and
13.27 were reported by Bell and Onwood for trichloroethanal, acetalde-
hyde, and formaldehyde, respectively. The acidic dissociation of a general
hydrated carbonyl moiety is represented below,

\[
R_1--C--OH + H_2O \xrightleftharpoons[K_a']{K_a'} H_3O^+ + R_1--C--OH
\]

in which the dissociation constant K_a' is defined in terms of the
respective component activities:

\[ K'_a = K'_w / K'_b = \frac{a_{H^3O^+}a_{A^-}}{a_{HA}a_{H_2O}} = \frac{[H_3O^+][A^-]}{[HA] \gamma_{HA} a_{H_2O}} \]  

(2.2)

HA and A\(^-\) denote the acid and conjugate base forms of the hydrate, respectively. However, in dilute aqueous solution the activity coefficient of the neutral hydrate and the activity of the solvent water can be assumed approximately equal to unity. Under those conditions, the concentration equilibrium "constant", \(K_a\), is given approximately by Eq. 2.3:

\[ K_a = K'_a / \gamma_{A^-} \gamma_{H^3O^+} = \frac{[H_3O^+][A^-]}{[HA]} \]  

(2.3)

Under the alkaline conditions required to effect significant dissociation of carbonyl hydrates, it is often preferable to consider the ionization reactions as base neutralizations,

\[ \begin{align*}
R_1-C-OH + OH^- & \xrightleftharpoons{K'_a/K'_w} K'_a/K'_w H_2O + R_1-C-OH \\
R_2 &
\end{align*} \]

for which the corresponding equilibrium constants are defined as follows:

\[ \frac{K'_a/K'_w}{K'_w} = \frac{[A^-] \gamma_{A^-} a_{H_2O}}{[HA][OH^-] \gamma_{HA} \gamma_{OH^-}} \]  

(2.4)
where

\[ K'_w = \frac{a_{H^+}a_{OH^-}}{a_{H_2O}^2} = \frac{[H_3O^+][OH^-]}{[H_3O^+][OH^-]} \]  

(2.5)

and

\[ K_w = k'_w a_{H_2O}^2 / (\gamma_{H_3O^+} \gamma_{OH^-}) = [H_3O^+][OH^-] \]  

(2.6)

Glyoxal probably exists in two distinct hydrated forms, a monohydrate \( M \) and a dihydrate \( D \). In addition, two singly dissociated forms, herein denoted \( M^- \) and \( D^- \), are at least hypothetically possible. Similarly, three doubly dissociated glyoxal hydrates may be postulated — one monohydrate \( M^{2-} \) and two dihydrates \( D^{2-} \) and \( D^{*-2} \). In Fig. 2.1 are depicted the five anionic glyoxals just cited, together with the three neutral forms.

Fig. 2.1 also serves to define the appropriate thermodynamic equilibrium constants, in terms of hydrations and base neutralizations, interrelating the various forms. Although further dissociated dihydrates are conceivable, it is highly unlikely that they would exist in significant concentrations at physically realizable alkalinities.

Carbonyl hydrations have been the focus of much research, especially in recent years. Although accurate kinetic studies of hydration/dehydration reactions have been hard to come by, probably due to the experimental problems relating to the rapidity of the reactions, interpretation of the results obtained is considerably more straightforward than are analyses of results obtained from more complex multi-step carbonyl additions such as mutarotations or dimerizations. Unfortunately, this point does not appear to be widely recognized.

Carbonyl hydrations are subject to general acid-base catalysis, as are most carbonyl equilibrium addition reactions. The observed rates of
hydration/dehydration have generally been found to fit the following empirical rate law 

\[
    k_{\text{obs}} = k_{\text{H}_3\text{O}^+}^1[H_3\text{O}^+] + k_{\text{H}_2\text{O}}^2[H_2\text{O}] + k_{\text{OH}^-}^3[\text{OH}^-] + \Sigma_i (k_{a_i}^4[A_i] + k_{b_i}^5[B_i])
\] 

(2.7)

where \(A_i\) and \(B_i\) denote the acid and conjugate base forms of a particular buffer salt "i".

The most thoroughly studied carbonyl hydration has probably been that of the simplest carbonyl, formaldehyde, which exists almost exclusively (\(K_h = 2000\)) as the hydrate, methylene glycol, in aqueous solution. Recently, Funderburk, Aldwin, and Jencks\(^{21}\) published a detailed kinetic analysis in aqueous solution of the rate of dehydration of methylene glycol as well as the rates of cleavage of six formaldehyde hemiacetals. Because those authors' findings were for the most part in agreement with previous studies and are believed to be generally applicable to related carbonyl additions, the general aspects of formaldehyde hydration will be briefly summarized.

Funderburk et al. concluded that general acid catalysis of formaldehyde dehydration/hydration proceeds preferentially via a class "e" mechanism, as depicted below:

\[
\begin{align*}
    \text{H}^+ + \text{A}^- + \text{HO}--\text{C}--\text{OH} & \xrightarrow{K_b} \text{HO}--\text{C}--\text{OH} + \text{A}^- \\
    \text{H}^+ \quad \text{(fast)} & \xrightarrow{K_b} \text{HO}--\text{C}--\text{OH} + \text{A}^- \\
    \text{H} & \xrightarrow{k_a} \text{C}==\text{O} + \text{HA}, \text{H}_2\text{O} \\
\end{align*}
\]

Class "e" mechanism for general acid catalysis
wherein $K_b (= K_w/K_a)$ denotes the base association constant for methylene glycol and $k_b$ and $k_a$ represent the general base and general acid catalytic constants for the rate-determining step. The transition complex has been omitted from the above scheme. With the class "e" mechanism, the hydrate (or hemiacetal) is presumed to be in rapid equilibrium with the protonated hydrate. The rate-limiting step is, then, the general base-catalyzed formation of the free carbonyl form, in which the catalyst $A^-$ serves to remove a proton from the conjugate acid of the addition compound (methylene glycol) in the forward direction, while $HA$ serves to protonate the oxygen atom of the carbonyl moiety in the reverse direction. The kinetically observed general acid catalysis then corresponds to specific acid-general base catalysis in the forward direction and "true" general acid catalysis in the reverse direction.

The preferred mechanism for the general base-catalyzed reaction was concluded to be the class "n" mechanism depicted below:

\[
\begin{align*}
H & \\
\text{(fast)} & \\
\text{H} & \\
B + \text{HO—C—OH} & \underset{K_a}{\overset{\text{Ka}}{\text{\xrightarrow[\text{H}]{}}}} \text{HO—C—O}^- + \text{BH}^+ & \underset{k_a'}{\text{\xrightarrow[\text{H}]{} C==O} + \text{B, H}_2\text{O}} & k_b' \\
\text{H} & \\
\text{H} & \\
\end{align*}
\]

Class "n" mechanism for general base catalysis

In this scheme, $K_a$ denotes the previously defined acid dissociation constant for the carbonyl hydrates and $k_a'$ and $k_b'$ represent the general acid and base catalytic constants for the rate-governing step. The carbonyl hydrate is assumed to be in rapid equilibrium with its conjugate base form and the general acid and base functions serve to facilitate the deprotona-
tion/protonation step required in the rate-limiting interconversion of the hydrate anion and the free carbonyl form. With the class "n" mechanism above, the kinetically observed general base catalysis corresponds to specific base-general acid catalysis in the forward direction and to true general base catalysis in the reverse direction.

Although solvent water can in theory serve both as a general acid and as a general base catalyst, Funderburk et al.\textsuperscript{21} found evidence that pH-independent, solvent catalysis is predominantly or virtually entirely due to general base catalysis. Catalysis by hydroxide ion, termed specific base catalysis, was suggested to proceed by a step-wise mechanism in which the rate-limiting step is elimination of hydroxide (or alkoxide) ion from the hydrate (or hemiacetal) anion in the forward direction and attack by hydroxide (alkoxide) ion on the free carbonyl in the reverse direction. An analogous mechanism is believed applicable to specific acid (hydronium ion) catalyzed addition reactions\textsuperscript{26}.

The dehydration rates of several simple monocarbonyls have been determined. Sorensen\textsuperscript{18} observed the rate of dehydration of glycolaldehyde hydrate at 25°C over the pH range of 2.6 to 8.5 by using semicarbazide and sulfite scavengers. Later Nielsen and Sorensen\textsuperscript{19} conducted similar experiments on D,L-lactaldehyde at 25.2°C over the pH range of 2 to 8.3. Both α-hydroxylaldehydes were found to follow general acid-base catalysis; the reported hydronium ion, solvent, and hydroxide ion catalytic rate constants following Eq. 2.7 are listed in Table 2.1, along with corresponding rate constants for the dehydration of formaldehyde and acetaldehyde.

From Table 2.1, it may be noted that the rates of dehydration and hydration of glycolaldehyde and lactaldehyde are quite similar by all three
catalytic pathways. This seems reasonable, considering the close structural similarity between the two \( \alpha \)-hydroxycarbonyls. More surprising, however, is the observation that the rate constants for formaldehyde dehydration are of the same order of magnitude, despite an approximately 100-fold larger value of \( K_h \) for formaldehyde. Thus, the high degree of hydration shown by formaldehyde appears to be due largely to more rapid hydration, rather than to slower dehydration.

In contrast, the relatively low degree of hydration observed for acetaldehyde, in comparison with the two \( \alpha \)-hydroxyaldehydes, appears to be due to more rapid specific acid- and specific base-catalyzed dehydration and to slower solvent-catalyzed hydration. Thus, formaldehyde and the two \( \alpha \)-hydroxycarbonyls show a much larger pH range within which solvent catalysis predominates. Although the conditions at which Jessen et al.\(^{14}\) determined the rates of dehydration of glyoxal and methylglyoxal were not specified, the magnitude of the values reported are suggestive of solvent catalysis.

### 2.2. Related Dimerization and Mutarotation Studies

Although hydration is the predominant equilibrium addition reaction undergone by short-chain \( \alpha \)-hydroxycarbonyls and \( \alpha \)-dicarbonyls in dilute aqueous solution, in more concentrated solutions the reversible formation of bimolecular cyclic hemiacetals and hemiketals generally becomes the dominant reaction. With longer-chain \( \delta \)- or \( \gamma \)-hydroxycarbonyls the formation of intramolecular hemiacetals or hemiketals is usually the preferred reaction. The chemistry of acetals and hemiacetals was reviewed by Schmitz...
and Eichorn in 1967. Generally, the formation of hemiacetals represents nucleophilic attack by an alcohol moiety on the carbonyl carbon. Free hemiacetals are generally too unstable to isolate, because under strenuous conditions acetals are formed.

Etherification of hemiacetal or hemiketal hydroxyl moieties results in the formation of acetals or ketals, although the term "acetal" is often applied to both classes of compounds. While simple acetals are generally not found in nature, cyclic acetals, as represented by oligo- and polysaccharides, are very abundant. In contrast to the formation of hemiacetals, acetalization appears to proceed almost exclusively via formation of cationic intermediates, and is thus subject to specific acid catalysis. Because cation formation is rate-determining, rates of reaction are influenced by the substituent groups attached to the hemiacetal carbon but not by the participating alcohol molecule. In the presence of even minor amounts of water, acetals undergo hydrolysis at rates dependent on the solution acidity.

Short chain α-hydroxycarbonyls and α-dicarbonyls that are unable to form stable intramolecular hemiacetals undergo concentration-dependent self-addition reactions to form complex dimeric and sometimes higher-order hemiacetal or hemiacetal-acetal structures. Those dimeric carbonyls which have been crystallized and subjected to configurational and conformational analysis have generally been found to exist as substituted 1,4-dioxane structures — symmetrical six-membered ring-forms that are quite similar to the favored pyranosyl structures of many monosaccharides. The crystallized dimers of glycolaldehyde, D,L-glyceraldehyde, lactaldehyde (2-hydroxypropionaldehyde), and 1,3-dihydroxyacetone all possess
symmetrical 1,4-dioxane-based structures.

Until rather recently, it was generally assumed that the predominant dimeric structures of α-hydroxyaldehydes in solution were the same stable pyranose-like structures found for the crystallized dimers. In a recent text on sugar chemistry, Shallenberger\textsuperscript{31} states that the pyranose ring form is slightly more stable than its furanose counterpart, as witnessed by the predominance of pyranosyl configurations for monosaccharides, although he notes that both structures correspond well with the favored structures for the polymerization of water. However, in recent years it has become increasingly apparent that a second type of dimeric structure often predominates in aqueous solutions of short-chain carbonyls. The structure is that of a substituted 1,3-dioxolane — unsymmetrical five-membered ring forms that are similar to the furanosyl structures observed for many saccharides. Perhaps this should not be surprising since, as pointed out by Angyal and Wheen\textsuperscript{17}, crystalline 1,4-dioxane-type dimers are formed not because they are the favored structures in solution, but rather because as symmetrical compounds they crystallize more readily than do the 1,3-dioxolane forms.

The dimeric structures of short-chain α-hydroxycarbonyls, notably glycolaldehyde, have been increasingly studied in recent years. Stassinopoulos and Zioudrou\textsuperscript{32} examined the structures of the various forms of glycolaldehyde in methanol, acetone, and DMSO by NMR spectroscopy. Although they found evidence of only the symmetrical 1,4-dioxane-based dimeric form in freshly prepared solutions, the authors reported evidence of both diastereomers of 2-hydroxymethyl-4-hydroxy-1,3-dioxolane (each of which should exist in two enantiomeric forms) in solutions that had been
left standing. No evidence, under either transient or equilibrium conditions, of any open-chain dimers was found. It is interesting to note that the depolymerization of the symmetrical dimer proceeded via the five-membered ring-form.

Collins and George\textsuperscript{33} investigated the structures of glycolaldehyde in deuterated DMSO and in D\textsubscript{2}O. They also found evidence of substantial proportions of 1,3-dioxolane-based dimers. In DMSO-\textsubscript{d}\textsubscript{6} at 35\degree C after 168 h, Collins and George reported approximately 4\% free aldehyde, 36\% 1,4-dioxane-based dimer, and 60\% 1,3-dioxolane-based dimer. A similar spectrum was observed in D\textsubscript{2}O: 4\% free aldehyde, 9\% 1,4-dioxane dimer, 17\% 1,3-dioxolane dimer, and 70\% hydrated monomer. Note the effect of the hydrated monomer on the overall proportion of monomeric forms. In addition, a number of weaker spectral bands (not present with DMSO) were noted, a finding suggestive of the presence in minor amounts of additional dimeric forms.

More recently, Khomenko, Lezina, Stepanyants, Sakharov, Golovina, and Krylov\textsuperscript{34} reported NMR and UV spectoscopic studies of aqueous solutions of glycolaldehyde under both neutral and alkaline conditions. The authors reported the equilibrium ratio of symmetrical (1,4-dioxane-type) dimers, unsymmetrical (1,3-dioxolane-type) dimers, and linear (monomeric) forms to be 56:31:13 for a 3.02M solution in D\textsubscript{2}O at 29\degree C. Khomenko et al. also noted a much slower rate of hydrogen-deuterium exchange in alkaline solution for the 1,4-dioxane-based dimers in comparison with the 1,3-dioxolane forms, which they attributed to a lower rate of opening of the symmetrical six-membered ring structures. Bystricky, Sticzay, Polakova, and Fedoronko\textsuperscript{35} examined D-glyceraldehyde in water, DMSO, 1,1,1,3,3,3-hexafluoro-2-propanol, and DMSO-water mixtures by circular dichroism and by UV spec-
troscopy. Solutions of glyceraldehyde, freshly prepared from 90% syrup, underwent slow monomerization accompanied by rapid equilibration of the resulting free and hydrated monomeric forms. Increasing temperature markedly shifted the equilibrium distribution of monomeric forms in favor of the free aldehyde.

Zioudrou, Stassinopoulou, and Loukas reported that the NMR spectra of solutions of crystalline lactaldehyde and lactaldehyde-d₆ in pyridine or DMSO-d₆ suggested that two predominant conformers of a 1,4-dioxane-type dimer — a "chair" and a "boat" or "twist-boat" form — were present. Although no evidence of any free aldehyde groups was found in freshly prepared lactaldehyde solutions, upon heating to 90°C for 1 h a weak carbonyl band was noted. Similar findings were obtained with DMSO-d₆ solutions, from which the authors calculated that 25% of the lactaldehyde-2-d exists as open dimer in DMSO-d₆ at 90°C.

Recently, Angyal and Wheen examined the compositions of aqueous solutions of glyceraldehyde, D-erythrose and D-threose. As noted by the authors, 22 different cyclic forms of D,L-glyceraldehyde are hypothetically possible, consisting of six diastereomers with 1,4-dioxane-based structures, eight diastereomers with 1,3-dioxolane rings, and eight diastereomers with 1,3-dioxane rings. Based on their experimental results, Angyal and Wheen reported the predominant dimer of D,L-glyceraldehyde in aqueous solution to be a 1,3-dioxolane.

With the four carbon sugar D-erythrose the predominant dimer was also of the substituted 1,3-dioxolane type, although the overall proportion of dimeric forms was considerably reduced by the presence of intramolecular furanosyl ring forms. Not surprisingly, dimeric forms predominated in
syrupy solutions. Angyal and Wheen also reported that the free aldehyde forms of all three compounds examined were present in proportions greater than 1%.

The cyclic hemiacetal structures of the simple α-dicarbonyls appear to have been little studied, although the few available reports suggest a high degree of similarity with dimers formed from the simple α-hydroxycarbonyls just described. However, because of the presence of the two carbonyl moieties in each dicarbonyl monomer, the potential to form multicyclic oligomers is also present. In fact, higher-order oligomeric glyoxals have been reported\textsuperscript{16} and are also suggested by the results to be presented here.

An NMR study of the oligomeric structures of glyoxal in aqueous solution was described by Whipple\textsuperscript{16} in 1970. He noted that an exhaustive list of all possible dimeric structures would consist of two open-chain dimers (a "D,L" and a "meso" form), five diastereomeric 1,4-dioxane-based dimers, and three diastereomeric 1,3-dioxolane-based dimers. To Whipple's list should be added dehydrated forms of each of the three 1,3-dioxolane-based dimers, since each of those dimers possesses a gem-diol "tail" that could, in principle at least, exist in dehydrated or hydrated form. However, Whipple did not detect significant quantities of any free aldehydic moieties, and on that basis neglected consideration of any free carbonyl forms. Nevertheless, the potential to form cyclic dimers with a free aldehyde moiety is an interesting feature of dicarbonyls — one which is not shared by the simple hydroxycarbonyls.

Whipple concluded that the principal glyoxal dimer in aqueous solution is a diastereomer of 2-dihydroxymethyl-4,5-dihydroxy-1,3-dioxolane, specif-
ically, that form possessing the ring hydroxyls in the "trans" configuration. It should be noted that the five-membered ring structure above should exist in two enantiomeric forms, presumably as a racemic mixture. The second most abundant glyoxal dimer also appeared to have a substituted 1,3-dioxolane structure, probably that diastereomer with the gem-diol moiety on the side of the five-membered ring away from the two "cis" hydroxyl groups. Haworth projections of the above dimers are included in Sec. 4.2.1. Whipple also noted that lesser amounts of a third dimeric form were indicated, presumably one of the substituted 1,4-dioxanes. An effective dimerization constant for all dimeric forms of approximately 1.2 was reported, based on monomer and total glyoxal concentrations.

Further support for the structural assignments above was presented by Whipple, based on spectroscopic studies of glyoxal in the presence of borate salts. The spectral lines assigned to the "cis" isomer were "intensified, shifted, or broadened (p. 7186)"\(^\text{16}\), while those assigned to the "trans" form were unchanged, a finding Whipple found consistent with the known chemistry of borate complexes. Specifically, a structural characteristic of compounds producing strong borate complexes is the possession of "cis" hydroxyl moieties with the O-C-C-O atoms approximately coplanar\(^\text{36}\).

Whipple's results were later supported by the observations of Kliegman, Whipple, Ruta, and Barnes\(^\text{37}\), who found that 4 mol of 80% aqueous glyoxal, in the presence of 32.3 mol of methanol and 0.96 mol of p-toluene-sulfonic acid, produced 2-dimethoxymethyl-4,5-dimethyl-1,3-dioxolane,
in 9% yield and the expected monomeric addition product, 1,1,2,2-tetrakis(methoxy)ethane, in 45% yield. In less methanolic solutions, the dimeric product predominated, and a trimeric product with the structure shown below was obtained in 20% yield.

The authors noted that substantial amounts of unidentified residues were also formed.

In Whipple's earlier study, he obtained some evidence that the observed trimeric forms were based on coupled 1,4-dioxane rings. The structure of crystalline trimeric glyoxal, often referred to as glyoxal trimeric dihydrate, was shown by Raudnitz to be that of 2,3,6,7-tetrahydroxy-1,4,5,8-naphthodioxane. In highly concentrated solutions, more complex structures are conceivable. Cantley, Holker, and Hough, for example, reported that the periodate oxidation products of methyl-D-glucopyranoside included a dimeric aldol dimer composed of two stacked 1,4-dioxane-type dimers.

The dimerization kinetics of the short-chain hydroxycarbonyls and dicarbonyls have not been examined in any detail. Although Bertrand and
later McCleland\textsuperscript{40} had previously published some kinetic data on the depolymerization of dihydroxyacetone, the first actual kinetic study of these reactions was reported by Bell and Baughan\textsuperscript{41} in 1937. Because a considerable increase in volume (about 0.036 ml/g monomer) accompanies the depolymerization of dihydroxyacetone in aqueous solution, Bell and Baughan were able to follow the reaction of 1% (wt) solutions by dilatometry. The results of their experiments, which were conducted at 25\textdegree C and in the presence of a variety of buffer species, showed that the depolymerization was first-order in dimer and was subject to general acid-base catalysis, as expressed by Eq. 2.8

\begin{equation}
\frac{k_{\text{obs}}}{k_{\text{o}}} = k_{\text{H}30^+} + k_{\text{OH}^-}[\text{OH}^-] + \sum_i k_{\text{HA}_i}[\text{HA}_i] + k_{\text{A}_i^-}[\text{A}_i^-] \tag{2.8}
\end{equation}

where \text{HA}_i and \text{A}_i^- denote the acid and conjugate base forms of buffer species \text{i}. Bronsted coefficients of 0.38 for acid catalysis and 0.76 for base catalysis were obtained:

\begin{equation}
k_{\text{HA}_i} = 0.20K_{\text{A}_i}^{0.38} \tag{2.9a}
\end{equation}

\begin{equation}
k_{\text{A}_i^-} = 5.0 \times 10^{-5}(1/K_{\text{A}_i})^{0.76} \tag{2.9b}
\end{equation}

While the former value is comparable to the corresponding value determined for the mutarotation of glucose, the value for base catalysis is substantially greater than the corresponding value for glucose.

Shortly thereafter, essentially the same dilatometric techniques were used by Bell and Hirst\textsuperscript{42} to study the depolymerization of glycolaldehyde.
at 25°C in aqueous solution. It is interesting to note that the monomer-
ization of glycolaldehyde proceeded with contraction (about 0.020 ml/g
monomer) in contrast to the expansion observed with dihydroxyacetone, a
difference Bell and Hirst attributed to the much higher extent of hydra-
tion assumed for the monomeric aldehyde compared with the ketone. As had
been observed for dihydroxyacetone, the depolymerization of glycolaldehyde
was first-order in dimer and found to be subject to general acid-base
catalysis, although insufficient data were obtained too allow accurate
determination of the Bronsted coefficients. Additional details of the
results of Bell and coworkers for dihydroxyacetone and glycolaldehyde are
included in Sec. 4.4.1.

More recently, Stassinopoulou and Zioudrou studied by NMR the
depolymerization of glycolaldehyde in methanol, acetone, and DMSO. They
found evidence that the depolymerization of freshly prepared 1,4-dioxane-
based dimer proceeds via an intermediate 1,3-dioxolane-based dimer. The
depolymerization of a 0.72M solution of glycolaldehyde in methanol, which
in that solvent results in the formation of the methylacetal of glycol-
aldehyde, was fit to first-order consecutive kinetics. No evidence of an
intermediate open-chain dimer was found.

A type of equilibrium addition that is, formally at least, very
closely related to the dimerization reactions just described is that of the
mutarotation of reducing saccharides. Longer-chain aldehydes and ketones
which possess δ- or γ-hydroxyl moieties can form intramolecular hemi-
acetals. The resulting addition compounds, five-membered (furanosyl) and
six-membered (pyranosyl) ring-forms, are precisely analogous to the 1,3-
dioxolane and 1,4-dioxane dimers above. With most aldoses and ketoses four
diastereomeric ring-forms, two furanoses and two pyranoses, are hypotheti-
cally possible; however, generally one or two of those structures predomini-
ate in aqueous solution. In contrast to the dimerization reactions, the
formation of pyranoses and furanoses is independent of substrate concen-
tration, and with most aldoses and ketoses the equilibrium distribution lies
decidedly in favor of the ring structures, as little or no free carbonyl or
carbonyl hydrate forms have generally been detected. Furthermore, except
with the four carbon sugars erythrose and threose, pyranose or furanose
formation usually occurs to the exclusion of dimerization.

The interconversions of the various cyclic sugar forms, termed muta-
rotations, represent one of the earliest studied and most well-known
reactions of organic chemistry. The mutarotation of glucose was first
described by Dubrunfaut in 1846. Kinetic studies in the early 1900's by
Hudson, Lowry, and Bronsted led to the development, in essentially
modern form, of the concept of general acid-base catalysis. A considera-
tion of the mechanistic theories of acid-base catalysis is beyond the scope
of this research, although the presently favored models are exactly analo-
gous to those outlined in Sec. 2.1 for carbonyl hydrations. For more
information the reader is referred to the classic article by Bronsted and
to the more recent contributions of Jencks and Funderburk, Aldwin, and
Jencks. Mutarotation reactions were described at length by Pigman and
Isbell, and in less detail by Pigman and Anet.

As with most equilibrium addition reactions, the mutarotations of
reducing sugars are subject to general acid-base catalysis, as previously
expressed in Eq. 2.7 or Eq. 2.8. In contrast to the preceding dimerization
reactions, many mutarotations have been subjected to kinetic analyses.
This should not be surprising, because the study of mutarotations generally possesses several distinct advantages over the study of dimerizations, including first-order dependencies on substrates, the capability in many instances of examining both the forward and reverse reactions, and freedom from interfering side-reactions (at least under acidic and neutral conditions). The similarity between the two reactions is well-illustrated by the observation that, in view of the close structural similarity between the cyclic saccharides and the dimeric short-chain carbonyls, the postulated reversible first step in the depolymerization of a given carbonyl dimer might in a sense be considered to be a "half-mutarotation".

It is interesting to note that Shallenberger\textsuperscript{31} divides the simple (predominantly two-component) mutarotations empirically into three types -- "very fast", "fast", and "slow" transformations, noting that these generally correspond to furanose-furanose, furanose-pyranose, and pyranose-pyranose mutarotations, respectively. However, in view of the general acid-base dependence exhibited by mutarotations, such generalizations should be treated cautiously. The different reaction types appear to possess distinct thermal properties as well. Pigman and Anet\textsuperscript{51} cite evidence that a number of pyranose-pyranose mutarotations, typified by the mutarotation of glucose, possess (apparent) activation energies of approximately 71 kJ/mol, in contrast to values of about 55 kJ/mol for what are believed or suspected to be pyranose-furanose mutarotations.

As with other general acid-base catalyzed reactions, both an acid and a base function are required for mutarotation. The acid serves essentially to partially protonate of the ring oxygen, while the base function concurrently assists in the abstraction of a proton from the anomeric hydroxyl
moiety. Isbell, Frush, Wade, and Hunter \(^5^2\) in 1969 suggested that mutarotations proceed via pseudo—acyclic or keto intermediates, that is, via intermediates that still retain much of their original conformation.

Wertz, Garver, and Anderson \(^5^3\) recently published a kinetic study of the complex mutarotation of D-galactose, an aldose that exists to measurable extents in all four cyclic tautomeric forms. Their experiments were conducted at \(15^\circ\text{C}\) and \(\text{pH } 4.3\), \(25^\circ\text{C}\) and \(\text{pH } 4.3\), and \(25^\circ\text{C}\) and \(\text{pH } 6.2\). They modelled the reaction as proceeding via the free aldehyde form, and claimed to have determined the individual first-order kinetic constants corresponding to ring opening and ring closing for each of the four cyclic tautomers present. However, based on the author's own model it is not at all clear that they actually determined the individual rates of ring-opening and closing. This point is considered in detail in Sec. 7.5. The authors also determined the rate of hydration of free aldehydo—galactose and estimated (based on reported equilibrium constants for related hydrations) the rate of dehydration of the aldehydrol. Upon obtaining a rate constant for hydration \((0.0092 \text{ s}^{-1} \text{ at } 25^\circ\text{C})\) not substantially different from that previously established for acetaldehyde \(^2^2\), they concluded that the low concentration of aldehydrol present is simply a consequence of the low equilibrium concentration of free carbonyl form. An enthalpy increase of about \(30 \text{ kJ/mol}\) in going from either pyranose to either furanose was noted, an increase substantially offset by a corresponding increase in entropy.

In 1967, Isbell and Wade \(^5^4\) published a oft-cited kinetic study of the mutarotations of the D-glucopyranoses, a so-called "normal" pyranose—pyranose mutarotation, and of \(\beta\)-D-fructopyranose, a pyranose—furanose interconversion. The reactions were observed at \(20^\circ\text{C}\) in both water and
D$_2$O, which allowed the authors to determine isotope effects, defined as $k_H/k_D$, for both reactions as a function of pH. Values greater than unity were obtained for all three catalytic regimes with both substrates, although the isotope effect was greatest for the solvent-catalyzed reaction. The absence of an "inverse" isotope effect ($k_H/k_D < 1$) essentially rules out specific acid or specific base-catalyzed mechanisms, at least over the range of conditions employed.

Nielsen and Sorensen$^{55}$ studied the mutarotation of the D-gluco-pyranoses under alkaline conditions using a stopped-flow polarimeter. The authors noted complex rate dependencies with respect to hydroxide ion concentration and concluded that their results were consistent with a concerted proton transfer mechanism for water catalysis, but were suggestive of specific hydroxide ion catalysis, including parallel kinetic pathways via mono- and divalent (for glucose only) glucosyl anions at high pH.

For further information concerning mutarotations, the reader is referred to the thorough kinetic study of free and substituted gluco-pyranose mutarotations by Capon and Walker$^{56}$ and to recent papers by Andersen and Gronlund$^{57}$ and by Nielsen and Sorensen$^{58}$.

2.3. Related Disproportionation Studies

The base-catalyzed disproportionation of glyoxal to glycolate, the subject of Chapter 3, is closely related to the rearrangement of benzil to benzilate, first described by von Liebig$^{59}$ in 1838, and to the bimolecular Cannizzaro reaction of formaldehyde as well. The net result of these
generally irreversible reactions, more properly termed disproportionations, is the formation of \( \alpha \)-hydroxy acids. The most studied reactions of this type for polyhydroxy \( \alpha \)-dicarbonyls have been the formation of saccharinic acids during the non-oxidative degradation of reducing saccharides and for non-enolizing \( \alpha \)-dicarbonyls the rearrangement of the benzils to benzilates. In either case, the driving force for these reactions can be considered to be the formation of the carboxyl moiety, a process which is made more favorable by the ionization of the product in alkaline solution.

While it is generally acknowledged that \( \alpha \)-dicarbonyls play important intermediary roles in both the oxidative and non-oxidative degradation of reducing sugars, with longer-chain saccharides the reactions are generally quite complex and lead, at least eventually, to the formation of a myriad of products. The overall complexity of the reactions probably accounts for the fact that, while such compounds as glucosone (D-arabino-hexosulose) have been the subjects of numerous end-product analyses, their kinetics are largely unstudied.

It is perhaps less easy to explain why the alkaline degradations of the short-chain analogues of these compounds, notably glyoxal, methyl-glyoxal (pyruvaldehyde), and glycerosone (hydroxymethylglyoxal), have also been ignored. It is this author's belief that the three compounds just cited present an opportunity to study dicarbonyl disproportionation and related reactions under conditions of minimum complexity. Under typical conditions, the disproportionation of glyoxal proceeds quantitatively to glycolic acid. Because of the presence of enolizable hydrogens on the methyl group, the disproportionation of methylglyoxal is further complicated by simultaneous occurrence of an incompletely defined aldolization
reaction, a reaction which is competitive with disproportionation at surprisingly low substrate levels. A further complication under some conditions is the formation by an as yet unknown mechanism of "scission" products. While the alkaline reactions of glycerosone have not been reported, it can be speculated that the presence of a readily oxidized α-hydroxy moiety would predict an even more complex kinetic picture with that substance.

The benzilic acid-type rearrangements are just one example of a family of closely related carbonyl rearrangement reactions, termed "1,2-shifts", which includes α-ketol rearrangements among others. The 1,2-shifts and related carbonyl rearrangements were reviewed by Collins and Eastham in 1970. In each 1,2-shift reaction, a substituent group, which can be aryl, alkyl, or simply hydrogen, is transferred with its electrons from the migration "origin" to an adjacent migration "terminus". According to Collins and Eastham, electron release to the migration origin assists in the transfer while at least a slight electron deficiency at the migration terminus is required.

The general aspects of the benzilic acid rearrangement appear to be firmly established. Ingold in 1928 is credited with the first description of the mechanism of benzilic acid rearrangement in its currently accepted form. Kinetic support for Ingold's theory was furnished by Westheimer in 1936 who studied the rearrangements of benzil and benzil o-carboxylic acid. Although both reactions were first order in both substrate and in hydroxide ion, a very slight positive salt effect was noted with benzil, while a strong positive salt effect was observed for the carboxylic derivative. Westheimer concluded that, because the appendant
carboxyl group, which is not involved in the disproportionation, could be assumed fully dissociated in alkaline solution, both observed salt effects were consistent for the involvement of a singly ionized hydrate moiety. Shortly thereafter, Roberts and Urey\textsuperscript{64} conducted $^{18}$O isotope exchange experiments in aqueous methanol. Upon observing rapid exchange of water oxygen, they ruled out rate-limiting formation of the hydrate anion and concluded that the rearrangement of the ionic intermediate was the rate-controlling step.

Although the benzilic acid rearrangement was long thought to be effected only by hydroxide ion (specific base), Doering and Urban\textsuperscript{65} in 1956 reported a "benzilic ester" rearrangement promoted by t-butyl alkoxide ions, an observation which they argued ruled out the requirement of simultaneous "neutralization" of the nascent carboxyl moiety by migration of a proton. Evidence for the irreversibility of the benzilic acid and benzilic ester rearrangements was obtained by Eastham and Selman\textsuperscript{66} in 1961 from experiments on the stability of $^{14}$C-labeled benzilic ester.

The disproportionation kinetics of $\alpha$-keto-aldehydes and of $\alpha$-diketones with enolizable hydrogens have been far less thoroughly studied than those of the highly substituted $\alpha$-diketones just described. This is probably due in large part to the greater reaction complexity expected for those dicarbonyls. For example, the simplest $\alpha$-diketone, diacetyl (2,3-di-oxo-butane), was found by Machell\textsuperscript{67} to rapidly undergo condensation in dilute aqueous alkali, forming large amounts of an eight carbon acid and lesser amounts of acetic and formic acids. Only a "trace" of the anticipated benzilic acid-type rearrangement product was found. Acetic and formic acids were also obtained from the degradation of D-glyceraldehyde (presum-
ably via methylglyoxal) in strongly basic solution (1.68M NaOH). Small proportions of a D-glucosaccharinic acid lactone were also obtained. Königstein and Fedoronko reported the formation of aldolization products during the disproportionation of methylglyoxal under less stringent conditions.

The role of deoxy-α-dicarbonyls as intermediates in the formation of saccharinic acids during the non-oxidative alkaline degradation of reducing saccharides and polysaccharides has been well-established (the most recent paper in each of three series of papers is cited) on the basis of product analyses carried out on a wide variety of reducing saccharides. Benzilic acid-type rearrangements appeared to account for the production of the "meta", "iso", and "ordinary" saccharinic acids formed. Evidence of short-chain degradation products was also obtained. The significance of saccharinic acids in the alkaline degradation of saccharides and polysaccharides was described in reviews by Kenner in 1955 and by Whistler and BeMiller in 1958.

In 1968 Lindberg and Theander described the alkaline degradation products of glucosone. Calcium hydroxide was found to promote stereoselective rearrangement to mannonic acid (and to a lesser extent glucuronic acid) and NaOH was found to favor "hydrolytic cleavage" to formic acid and arabinose or formaldehyde and arabinonic acid; mannonic acid was observed to a lesser extent. Other products were also detected.

More recently, Lindstrom and Samuelson determined the products formed from the treatment of glucosone and maltosone (0-α-D-glucopyranosyl-(1→4)-D-arabino-hexosulose) with alkali and with O2-alkali. The stereoselectivity of the benzilic acid-type rearrangement for mannonic acid
or mannonic acid moieties was confirmed. In addition, the authors reported that the benzilic acid-type rearrangements were favored by conditions of high temperature and alkalinity, whereas alternate pathways were favored in the presence of oxygen. A number of other papers reporting product distributions of reducing saccharides and polyhydroxy-α-dicarbonyls have also been recently published\(^75,76,77\). Although the precise pathways involved in the degradation of long-chain α-dicarbonyls is not known, they do appear to be quite complex.

It should also be noted that side reactions are not totally foreign to the disproportionation of non-enolizable dicarbonyls. The formation of very small amounts of aldehydic and acidic fragmentation products, for example, were detected during the rearrangement of benzil\(^62,78\) in substantially alcoholic solution. In contrast to the complexity of the reactions just cited, O'Meara and Richards\(^1\) examined the alkaline degradation of glyoxal in the presence of both mono- and divalent bases and observed as product only glycolic acid. However, marked acceleration by divalent cations, especially calcium, was noted.

The results of a brief kinetic study of the alkaline disproportionation of glyoxal to glycolic acid were reported by Salomaa\(^2\) in 1956. Based on integral rate studies over the limited range of alkalinity of 1 to 10mM NaOH, Salomaa concluded that the reaction was first order in glyoxal (G) and second order in hydroxide ion, as represented below:

\[
-d[G]/dt = k[G][OH^-]^2
\]

A third-order rate constant of 161 s\(^{-1}\)M\(^{-2}\) at 25°C and an activation energy
of 76.1 kJ/mol were reported along with a strong positive salt effect. Salomaa's findings have since been cited in more recent studies of the disproportionation of α-dicarbonyls and in the alkaline reactions of glyoxal with amino acids.

Further support for Salomaa's third-order rate law, also based on integral rate studies, was later furnished by Arcus and Jackson, who observed the reaction to be substantially accelerated by a polymeric quarternary hydroxide. Very recently, Vuorinen reported that the rate of rearrangement of glyoxal was retarded in ethanol-water mixtures and enhanced in 1,4-dioxane-water mixtures. Vuorinen attributed the former effect to hemiacetal formation and the latter effect to increased ionization of the substrate.

Kinetic studies of the closely related bimolecular disproportionation of formaldehyde (F) to methanol and formic acid, conducted at various levels of accuracy and over limited ranges of pH, had variously indicated that reaction to be first, second, or of intermediate order in hydroxide ion. Martin resolved those discrepancies in 1954 by showing that over a wide range of alkalinity the reaction could be described as the sum of two parallel reactions, each second order in reactive formaldehyde $F^*$, but with one first order and the other second order in $[OH^-]$:

$$-d[F]/dt = 2k_1[F^*]^2[OH^-] + 2k_2[F^*]^2[OH^-]^2$$  \hspace{1cm} (2.11)

The reactions were suggested to proceed via hydride ion transfer from the hydrate (methylene glycol) anion and dianion, respectively, to the free aldehyde. The two ionic hydrates were presumed to be in equilibrium with
the neutral hydrate and the free aldehyde.

More recently, Hine and Koser\textsuperscript{84} examined spectrophotometrically the disproportionation of phenylglyoxal (P) to mandelic acid at 35.1°C and reported a first-order dependence on substrate and a combined first-order and second-order dependence on \( \text{OH}^- \), if account was taken of the acidic dissociation of phenylglyoxal monohydrate \( K_1 \). Hine and Koser's findings are rewritten in Eq. 2.12 in terms of the experimentally varied parameter — the total concentration of phenylglyoxal \( (P_T) \):

\[
\frac{-d[P_T]}{dt} = \frac{k_1K_w^{-1}[\text{OH}^-] + k_2K_w^{-2}[\text{OH}^-]^2}{1 + K_w^{-1}[\text{OH}^-]} \quad \text{(2.12)}
\]

The authors suggested a mechanism based on the assumption of rate-limiting intramolecular hydride ion transfer from the mono- and divalent hydrate anions, respectively. The value of \( K_1 \) was determined independently by titrimetry. The above findings are in marked contrast to the disproportions of dissubstituted glyoxals, just described, as the latter appear to involve only the monovalent hydrate anion and are reported to be well-described by a rate equation second order overall and first order with respect to \( [\text{OH}^-] \).

The disproportionation kinetics of at least one other short-chain dicarbonyl analogue have been reported. Fedoronko and Königstein\textsuperscript{3,80} employed polarography in conjunction with a pH-stat and observed the rate of disappearance of methylglyoxal in the presence of both NaOH and Na\(_2\)CO\(_3\). The presence of enolizable hydrogens renders methylglyoxal susceptible to aldolization at a rate competitive with its disproportionation to lactic
acid. Fedoronko and Konigstein reported that the disproportionation was first order and the aldolization second order with respect to substrate; both reactions were first order with respect to hydroxide ion. From experiments conducted at 25°C, at an ionic strength of 0.3M and in the presence of Na$_2$CO$_3$, the authors reported rate constants of 0.105 s$^{-1}$M$^{-1}$ for the disproportionation and 40.2 s$^{-1}$M$^{-2}$ for the aldolization. At the same temperature, but at an ionic strength of 0.1M and in the presence of NaOH, corresponding values of 0.098 s$^{-1}$M$^{-1}$ and 37.7 s$^{-1}$M$^{-2}$ were reported. Arrhenius activation energies of 84.1 and 61.9 kJ/mol were reported for the aldolization and disproportionation, respectively. Fedoronko and Konigstein suggested a mechanism for disproportionation based on rate-limiting intramolecular hydride ion transfer from dissociated methylglyoxal hydrate.$^{85}$

The disproportionation of methylglyoxal at lower substrate concentrations than those employed by Fedoronko and Konigstein has been investigated as a part of follow-up studies to those presented in this report. Preliminary results from those experiments indicate that, although the kinetic order with respect to hydroxide ion appears to be approximately first-order over a broad pH range, on closer examination a complex kinetic response of the same form as Eq. 2.12 is actually observed.
3. KINETIC ANALYSIS OF THE DISPROPORTIONATION OF AQUEOUS GLYOXAL

3.1. Experimental Methods and Materials

In all experiments, the rate of glyoxal disproportionation was determined from observations of the rate of disappearance of glyoxal in a batch reactor system. In all but one set of experiments, rates were determined under pseudo-first-order conditions, that is in the presence of a large excess of NaOH (minimally 25-fold) or in the presence of bicarbonate/bicarbonate buffer. Except where otherwise noted, the methods to be described apply to pseudo-first-order experiments. A single set of integral rate experiments was also conducted. Modifications to allow those kinetic studies are described in Sec. 3.1.4.

Because glyoxal is stable in neutral to moderately acidic solution, its disproportionation could be readily and virtually instantaneously stopped by the addition of sufficient formic acid/formate buffer to weakly acidify (pH 2-3) the reaction mixture. Once the reactions were so stopped, the residual glyoxal was determined by spectrophotometric analysis by using Girard's Reagent-T, which is highly specific for α-dicarbonyl compounds.

3.1.1. Analysis for glyoxal

The success of the experiments to be described was in no small part due to the use of the highly sensitive and specific spectrophotometric analysis for α-dicarbonyls recently reported by Mitchel and Birnboim. The method is based on the quantitative (under recommended conditions) reaction of α-dicarbonyls with (carboxymethyl)trimethylammonium chloride
hydrazide — Girard's Reagent-T — to produce from glyoxal the compound indicated in the net reaction below:

\[
\text{H-CO-CO-H + 2 (CH}_3\text{)}_3\text{N}^+\text{-CH}_2\text{-CO-NH-NH}_2 \rightarrow \text{(CH}_3\text{)}_3\text{N}^+\text{-CH}_2\text{-CO-HN-N=CH-CH=NH-CO-CH}_2\text{-N}^+\text{-CH}_3\text{)}_3 + 2 \text{H}_2\text{O}
\]

Ostensibly because of the presence in the addition product of conjugated double bonds involving two C=N bonds, an intense UV absorbance results. The glyoxal adduct apparently exists in two distinct forms depending on pH. Mitchel and Birnboim reported a \(\lambda_{\text{max}}\) of 295 nm and corresponding extinction coefficient \(\varepsilon_{\text{max}}\) of \(2.73 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}\) for the acidic form (at pH 2.9) and a \(\lambda_{\text{max}}\) of 325 nm and an \(\varepsilon_{\text{max}}\) of \(1.88 \times 10^4 \text{ M}^{-1}\text{cm}^{-1}\) for the basic form (at pH 9.2). Because of the need to avoid disproportionation of the glyoxal during the reaction with Girard-T reagent, all spectrophotometric readings were obtained with glyoxal adduct in the acidic form. A formic acid/formate buffer of pH < 3 was used. No absorbance increase (over blank absorbance) due to glycolic acid product was detected. The contribution to the blank absorbance due to unreacted glyoxal was also negligible; an \(\varepsilon_{\text{max}}\) of 5.8 \(\text{M}^{-1}\text{cm}^{-1}\) at a \(\lambda_{\text{max}}\) of 267.5 nm has been reported for glyoxal.

In addition to sensitivity and specificity, the Girard-T analysis was found to have the additional advantages of very low blank absorbance (0.005-0.009 as used) and excellent long-term stability. Although the above authors made no claim for stability beyond 30 min, in this laboratory assayed samples that had been protected from evaporation showed no significant loss of absorbance after 1-2 days at room temperature. This stability was of practical importance in the conduct of these kinetic experiments.
The rate of the Girard-T-glyoxal addition reaction was reported by Mitchel and Birnboim\textsuperscript{85} to be strongly pH-dependent and very rapid below pH 3 and above pH 9. In solutions containing 0.02N (presumably 0.04M) Girard-T at 30°C, the addition reaction was reported to be essentially complete after 10 min. In the disproportionation studies to be described, the final Girard-T concentrations were reduced to 0.02 or 0.01M to further lessen the blank absorbance. Minimum incubation times were 30 min and 1 h with the 0.02M and 0.01M Girard-T solutions, respectively. Because of the high sensitivity of the method, glyoxal concentrations were such that less than 1% of the Girard-T reagent was consumed, even with totally unreacted glyoxal solutions.

Finally, it must be noted that an extinction coefficient $\varepsilon_{\text{max}}$ of 3.8 x10$^4$ at 295 nm (pH 2.9) was found for glyoxal in this laboratory. The total glyoxal concentration had been determined within approximately 0.5% by using Salomaa's titrimetric method\textsuperscript{87}, and so the cause of the 40% disagreement between the above value and that reported by Mitchel and Birnboim\textsuperscript{85} is not readily apparent. All spectrophotometric readings were obtained by using a Beckman Model DU spectrophotometer fitted with a Gilford Model 252-l Modernization System and a Model 2443-A Rapid Sampler.

3.1.2 Experimental design — pseudo-first-order studies

The reactor system described below was specifically designed to minimize any possible interference due to the presence of dissolved carbon dioxide or molecular oxygen. It is especially important to exclude the former because at high pH the absorption of each mole of CO$_2$ results in the neutralization of two moles of OH$^-$, as indicated in the net reaction
below:

\[ \text{CO}_2 + 2 \text{OH}^- \rightarrow \text{CO}_3^{2-} + \text{H}_2\text{O} \]

Although molecular oxygen readily oxidizes hydroxyaldehydes in alkaline solution, there was no reason to expect oxygen interference with glyoxal. Nevertheless, \( \text{O}_2 \) was automatically excluded during the removal of \( \text{CO}_2 \).

It should be noted that if the methods used in these experiments are applied to the study of more complex dicarbonyls, particularly hydroxydicarbonyls, the avoidance of oxidation by dissolved \( \text{O}_2 \) should be an important consideration.

All disproportionation rate determinations were carried out under a nitrogen atmosphere in 250 ml, three-neck, round-bottom borosilicate glass flasks arranged as shown in Fig. 3.1. Each reactor was fitted with the following removable accessories, each connected via 14/20 Standard Taper ground glass joints: a 1-mm I.D. capillary sampling tube, a septum port injector, and a gas-addition port, connected via stopcocks and 1/4" I.D. Tygon vacuum tubing to aspirator vacuum and to a source of compressed \( \text{N}_2 \) (stated 99.999% pure). Each ground-glass joint was located well above the maximum liquid level within the reactor.

The nitrogen stream was rendered \( \text{CO}_2 \)-free by passage through a 300-mm drying tube filled with Ascarite II (A. H. Thomas Co.), followed by bubbling through 2 cm of distilled water in a 500-ml gas-washing bottle. The latter apparatus functioned both as a trap and a flow indicator. The reactor gas exhaust line was fitted with a Nalgene vacuum check valve and was exhausted below water level in a sink trap. This prevented the reentry of atmospheric gases and maintained a slight positive \( \text{N}_2 \) pressure within
Fig. 3.1. Batch reactor system used in the kinetic study of glyoxal disproportionation
the reactor.

The use of glass as reactor material is believed to be the greatest experimental shortcoming in the disproportionation studies to be described. Although the experimental results obtained are not believed to be greatly affected by the use of glass, the presence of that material did prevent the full potential of the reactor system from being realized. It is recommended that in any future studies under similar conditions that quartz glassware, which is more alkali-resistant, be used. The above problem will be described in detail later.

The following procedure was used to prepare reactant solutions (minus glyoxal) substantially free from dissolved CO₂ and O₂. In each instance cited, "evacuation" is understood to be accompanied by stirring and followed immediately (1-2 min) by refilling with CO₂-free N₂. Solutions were added with glass transfer pipettes and/or calibrated Pipetman (P20, P1000, and P5000) air-displacement automatic pipettes. Sodium chloride was added either as solid or as a 0.40M stock solution, or was incorporated in the bicarbonate/carbonate buffer stock solution. Because of the low concentrations utilized, volume changes upon mixing were negligible.

Atmospheric gases were first removed from the otherwise empty reactor by repeated evacuation. Then, while under slight N₂ pressure, the injector port was removed and an appropriate volume of diluent water was added. Following repeated evacuation, a volume of NaOH (or 25mM bicarbonate/carbonate) stock solution necessary to effect a 200.0 ml total volume was added, followed by a final brief evacuation. For the most rapid reactions, a very small flow of N₂ was maintained through the tubing above the reactors, although with longer runs the flow of N₂ was stopped and the reactor
was isolated (via stopcocks) between samplings. Loss of water by evacuation during aspirations totalled less than 0.2 ml (0.1% of the initial reactant volume) and was neglected. All evacuations were conducted on reactant solutions at ambient temperature.

The above procedure was probably more effective at preventing the reentry of CO\textsubscript{2} and O\textsubscript{2} than at eliminating existing dissolved gases from the reactant solutions. For that reason, the following procedure was developed for use in the preparation of unbuffered CO\textsubscript{2}-free solutions of very low alkalinity (less than 2mM NaOH). A 2-l filtration flask was connected via a stopcock to the CO\textsubscript{2}-free nitrogen source. The flask was also fitted with a one-hole rubber stopper that had been enlarged to accept the end of a 100-ml glass transfer pipette. After boiling diluent water in the open flask for ~20 min, the stopper and pipette were added and CO\textsubscript{2}-free nitrogen was allowed to pass through the flask and pipette while the water cooled to room temperature. Up to six 100-ml aliquots of CO\textsubscript{2}-free distilled water could then be removed from the flask and added to the reactor with a Spectroline suction pipettor; virtually no contact was made with atmospheric gases, except during draining of the pipette.

Following immersion of the reactor within the water bath circulant and an appropriate period of preheating (or precooling), the reaction was initiated at time zero by the injection of 0.2-1.0 ml of preheated 10mM glyoxal stock solution with a 1-ml capacity Fisher Varipet syringe. The initial hydroxide concentration was corrected for the resulting 0.1-0.5% dilution. During preheating and throughout all but the slowest reactions, the reactor contents were subjected to stirring with a 1-in. magnetic stir bar actuated by a stir plate located below the water bath.
The means by which the reactor contents were sampled was somewhat unusual, and so will be described in detail. Except at very high reaction rates, 12 to 16 samples were collected. Samples were collected at equally spaced time intervals, except when samples were lost due to mishandling.

At appropriate time intervals, a portion of the reacting solution was removed, the reaction quenched, and Girard-T reagent added in a single operation. This was accomplished by the use of a twin-head peristaltic pump (Cole-Parmer Ultramasterflex Model E650-M6 or Console Model 7565) and an Autoanalyzer D2 glass mixing tube, by which means a constant ratio of acidic buffered Girard-T reagent to sample could be combined and dispensed.

The above method had numerous advantages over more conventional methods, not the least of which was a high sampling precision due to constancy of dilution ratio. Although the flow rates of individual pump heads and tubings could vary considerably (up to several per cent) from one set-up to another, at a constant pump rpm any given pump system produced relative flow rates which were remarkably constant (+0.2%). Furthermore, by the use of minimum I.D. tubing of the shortest possible length and an appropriately rapid pump rpm, the reactor could be sampled (and quenched) rapidly enough to accurately determine first-order rate constants with half-times of reaction down to 3 s or less. Because of the poor thermal conductivity of the silicone pump tubing, even with rapid reactions the disproportionation could be assumed to proceed at virtually unchanged rate right up until the point of mixing with the quenching reagent, assuming that a sufficiently rapid pumping rate was used. Additional advantages of the above system included the exclusion of atmospheric O₂ and CO₂ during sampling and the capability of sampling unattended when necessary using a...
programmable ChronTrol Model CT-4 timer and a Gilson Model FC-220K fraction collector.

Disadvantages of the above system were judged minor, but did include the need to begin sampling slightly before sample collection to ensure steady state. The samples obtained were essentially "cup-mixed" averages of reactor contents collected over time intervals. As explained in Sec. 7.1, this could not have influenced the observed first-order rate constants, due to the fact that during any given run samples of constant duration were collected. However, because of the number of samples collected, even had the above conditions not been met, sampling time errors would have been negligible. The first-order rate determinations did not require accurate knowledge of substrate (glyoxal) concentration; thus, it was not necessary in those studies to accurately determine the dilution ratio. However, this was a problem in later integral rate studies. Finally, despite the relatively large reactor size (200 ml), the high sensitivity of the Girard-T analysis allowed the use of less than 10 μmol of glyoxal per run in pseudo-first-order studies. However, up to 4 mmol per run was required in the integral rate studies.

Reactor temperatures were maintained constant at accurately known values in the following manner. The reactors were fitted with magnetic stir bars and were submerged in Haake Model FS, FS2, or FK constant-temperature circulators controlled to within ±0.01°C. Bath temperatures were monitored by using a Digitek Model 5810 thermistor thermometer reproducible to ±0.01°C, which had been calibrated to within ±0.02°C with a W. H. Kessler mercury-in-glass total immersion thermometer (Model No. 15-041B) certified traceable to the National Bureau of Standards.
Appropriate corrections for emergent stem were applied when required.

The reactors possessed time constants for thermal equilibration of \(-1.5\) min (with stirring). Therefore, the reactors with contents were preheated or precooled for minimally 20-25 min prior to initiation of the reaction. At reaction temperatures other than 25°C, the glyoxal stock solution to be injected was preheated or precooled within the injection syringe for 3 to 5 min prior to injection. Occasionally, the temperature of the reactor contents was checked following a run relative to circulant temperature by using the Digitek thermometer with a glass-encased thermistor probe.

The disproportionation of glyoxal has been reported to be exothermic \(^{88}\), with \(\Delta H_{\text{disp}} = -21\) kJ/mol. However, because of the dilute glyoxal solutions employed, observable heat of reaction effects were found only in the case of the very rapid integral rate studies at the highest initial glyoxal concentrations. A temperature rise due to disproportionation of 0.2°C was observed in the reaction of 20mM glyoxal in a stoichiometric (20mM) concentration of NaOH.

### 3.1.3. Treatment of kinetic data

After having established a linear rate dependence on total glyoxal concentration from preliminary runs, the data collected from each kinetic run conducted under pseudo-first-order conditions (at essentially constant alkalinity) were fit to first-order kinetics by the following procedure. Accurate plots of \(-\log_{e}(\text{Abs}_{\text{Net}})\) vs. time were constructed, where \(\text{Abs}_{\text{Net}}\) was the observed absorbance at time "t" minus the blank absorbance (due to Girard-T and formic acid/formate buffer). Except with very rapid reactions
(t_{1/2} < 5 \text{ s}), in virtually every instance linear plots were very closely approximated, with a mean correlation coefficient of 0.99996 and a standard deviation of 2 \times 10^{-5}. Even with the most rapid (and least accurately observable) reactions conducted, with half-times of reaction ranging from 1 to 5 s, a minimum correlation coefficient of 0.9995 to > 80\% conversion was obtained. Although linearity was apparent to conversions as high as 98\%, scatter increased markedly at very high conversion. Therefore, except with the most rapid reactions, values of -\log_e(Abs_{Net}) vs. t to approximately 65\% conversion were used to determine the observed pseudo-first-order rate constant k_{obs} by linear regression. Nevertheless, except with very slow reactions, data were collected and plotted to 80-90\% conversion.

Reproducibility between runs conducted with identical reagent stocks under the same conditions was adequate, although perhaps not as good as would be predicted based on a simple consideration of the known uncertainties involved. Two sets of triplicate runs conducted at widely different run conditions produced standard errors of 1.9\% (k_{obs} = 0.015 \text{ s}^{-1}, 80^\circ \text{C}, 0.25\text{mM NaOH}) and 0.7\% (k_{obs} = 0.0073 \text{ s}^{-1}, 10^\circ \text{C}, 10\text{mM NaOH}). Errors in derived kinetic parameters caused by uncertainties in [OH^-] were accentuated by the reaction orders of greater than unity with respect to hydroxide ion. Estimated uncertainties in the concentrations of 0.2M and 1.0M NaOH stock solutions were 0.2\%. Errors due to dilution of the above stock solution in the reactors were estimated at 0.3\% or less depending on the dilution factor. The absolute uncertainty in k_{obs} due to inaccurately known and/or varying temperature would, of course, depend on the effective activation energy at the particular run conditions, but the error should not have exceeded 1.4–2.5\%, assuming that the absolute temperature was
known to within 0.02°C.

Confidence intervals associated with particular $k_{obs}$ values determined by linear regression were not computed. To be accurate estimates of experimental uncertainty, values obtained from models in common use must be based on dependent values with constant expected per cent error and must have no significant error in the corresponding independent variables (times of reaction). In general, neither of these two restrictions were met in these experiments, although the latter certainly applied with slower reactions. Furthermore, and especially for highly precise data, the values of the slopes ($k_{obs}$) are influenced by small changes in endpoint values (in this case blank absorbance), a variability which is not reflected in the calculated confidence intervals. The latter are also based on an assumed "perfect" linear relation between dependent and independent variables. However, due to the slight (and quantifiable) decrease in alkalinity which accompanied many runs, calculated confidence intervals would, it must be assumed, also reflect that effect.

Although most of the above problems were perhaps not insurmountable, the relatively large effects of errors in temperature and especially alkalinity make it doubtful that the data obtained warrant more sophisticated treatment. Random experimental errors are perhaps best estimated from the scatter in the resulting plots of $k_{obs}$ vs. $f([\text{OH}^-])$. The standard deviations associated with the modelled rate coefficients in Table 3.2 (see Sec. 3.2.1) must also be interpreted with caution, as those values are also based on the assumption of random errors. Because of the predominant influence of rate coefficient $a_2$ on the observed rate coefficients, even at the lowest NaOH-mediated alkalinitities studied, the "best fit" values
assigned to coefficient $a_1$ are particularly susceptible to systematic
errors, especially errors in the calculated hydroxide ion concentrations.
Furthermore, values of $[\text{OH}^-]$ are least accurately determined at those
same weakly alkaline conditions. Therefore, it must be assumed that the
uncertainties listed in Table 3.2, especially those corresponding to
coefficient $a_1$, probably underestimate the actual errors.

The high sensitivity of the assay allowed the use of very low concen-
trations of glyoxal, typically 50µM. Only at very low NaOH concentrations
or at buffer ratios greatly different from unity was the reactor $[\text{OH}^-]$
significantly effected ($[\text{OH}^-] > 1\%$) by the glycolic acid produced. In
those instances, the base consumed during the portion of the reaction used
to determine $k_{\text{obs}}$ (by linear regression) was calculated from the initial
concentration of glyoxal and the final conversion. The arithmetic average
of the initial and final hydroxide ion concentrations was then used in
subsequent calculations.

No significant curvature over that predicted by the formation of
glycolic acid product was observed in any run with glyoxal. However,
subsequent experiments with the more slowly reacting methylglyoxal indi-
cated that for very slow reactions at very low alkalinity (0.25mM or less)
a significant decrease in rate in excess of that accounted for by dispro-
portionation was observed. For instance, at $25^\circ C$ incubation of 0.25mM NaOH
for 16 h (unstirred) prior to addition of methylglyoxal, 9% and 14% reduc-
tions in initial rates were obtained when compared with controls incubated
for 30 min. Whether these losses in reactivity were caused by reaction of
the alkali with the glass reactor or the entry of $\text{CO}_2$ from some source is
unknown, although the latter is considered unlikely. The same test
conducted with glyoxal at very high temperature showed a rapid loss of reactivity of almost 20% per hour. This effect was presumed caused by loss of alkalinity due to reaction with the glass reactor walls.

If the above explanation is assumed correct, the observed effects can be rationalized in the following manner. Assuming that the rate of loss of alkalinity was proportional to the reactor surface area (a constant) and to hydroxide ion concentration, the per cent loss in solution alkalinity would be independent of hydroxide ion concentration and thus would be a factor only at very low alkalinity where disproportionation is slow. If a moderately low effective activation energy is assumed for the above process, interference during the kinetic reaction would be observed only at low alkalinity at low temperature, at which conditions a somewhat lower kinetic constant would be expected. However, interference at very high temperature would also be observed, but for entirely different reasons. Although no loss of alkalinity would be observed during the rapid disproportionation, a constant percentage loss of alkalinity (independent of [OH\(^-\)]) would occur during the preheating of the alkaline solution.

The above discussion is of course pure speculation. The experimental procedures used for runs at 80°C were modified to minimize the above interference, whatever its cause. In those experiments, the diluent water only was preheated and the required NaOH was added only long enough prior to glyoxal injection to allow sufficient thermal equilibration — 40 s to 4 min, depending on alkalinity. However, the above problems should be dealt with more thoroughly before further experiments are performed under the above conditions, especially if more slowly reacting systems are to be investigated.
3.1.4. **Experimental design — integral rate studies**

The experimental apparatus described in Sec. 3.1.2 was modified to circumvent the additional problems associated with integral rate studies at higher glyoxal concentrations. In most instances, the high initial alkalinity and the high reaction order (approaching third order) necessitated very rapid sampling in the early stages of the reaction. This was accomplished by the use of a Gilson Model FC-220K fraction collector set to sample continuously, which enabled the collection of samples of 0.68 s duration.

The roughly 100-fold greater glyoxal concentrations being sampled required that the quenched samples be diluted before being read spectrophotometrically. Therefore, the samples were quenched with 0.1N formic acid and then diluted into the standard formic acid/formate-buffered Girard-T reagent. Because of the presence at high glyoxal concentrations of major proportions of glyoxal oligomers and their unknown effect on the disproportionation kinetics, the reactions were initiated by the injection of 0.2-4.0 ml of 1M NaOH into 200 ml of moderately dilute glyoxal (maximally 20mM), rather than the reverse procedure used in prior pseudo-first-order studies. A final problem was the requirement that the absolute values of glyoxal concentration be known. This was met by the use of the procedure described in the following paragraphs.

The accurate determination of glyoxal conversion and the elimination of transient effects on sample dilution ratio due to pump start-up were achieved by the use of a dummy reactor system, employing the two identical glass reactors described previously. After the addition of identical glyoxal-NaOH solution into each reactor, a volume of water equal to that of
the NaOH solution to be added to the primary reactor (A) was added to the
dummy reactor (B). A Rheodyne Model 7040 switching valve, fitted with
minimal lengths of 0.02-in. (0.51-mm) I.D. stainless steel tubing, was
inserted between both sample outlets and the sampling pump. This system
enabled sampling to be switched from reactor B (for \( t < 0 \)) to reactor A
at the time of NaOH injection (\( t = 0 \)).

Between 15-60 s prior to the start of each run, the sampling pump was
started, and several fractions from reactor B were collected by manual
advance of the fraction collector. The resulting net absorbance, \( \text{Abs}(t=0) \),
from those unreacted samples was, at steady state, assumed to be equivalent
to that value which would be obtained from reactor A at \( t = 0 \). Hence, for
any run, the conversion \( C(t) \) within reactor A at sample time \( t \) could be
determined from the net sample absorbance \( \text{Abs}(t) \) by using Eq. 3.1:

\[
C(t) = \frac{\text{Abs}(t=0) - \text{Abs}(t)}{\text{Abs}(t=0)} \quad (3.1)
\]

At no point was it necessary to calculate the individual sample concentra-
tions; such calculations would have been inaccurate because of variable
effects of pump tubing and pump rpm on dilution ratio.

After positioning the fraction collector at a convenient starting
point, at time zero the NaOH stock solution was injected into reactor A.
Simultaneously, the Rheodyne valve was switched, allowing flow from reactor
A, and the fraction collector was started, by using a foot-operated
Cole-Parmer Model 8683-30 digital timer. Later samples were taken by hand
in the conventional manner. All other aspects of the experimental
procedure were essentially unchanged from those used in
pseudo-first-order experiments.

3.1.5. Materials

Glyoxal was obtained as the trimeric dihydrate from Sigma and was stated to be of 98% purity. Stock solutions of 10mM concentration (as monomer) were held at 40°C with stirring for approximately 20 h before use. A very small amount of insoluble material remained, but disappeared after many days of storage at 4°C. The clear soluble portion of a freshly prepared stock solution was subjected to HPLC at room temperature on 60 cm columns packed with Aminex Q15-S strong cation exchange resins in either H⁺ or Ca²⁺ forms. A differential refractometer was used as the detector, and no impurities were found. Assuming a partial molal refractive index similar to that of glyoxal, a separable impurity should have been detected, provided it was present to 1% the extent of glyoxal. The small proportion of dimer (1% by weight) present in a 0.01M stock solution was largely converted to monomer during elution at room temperature (see Sec. 4.1.1).

Girard's Reagent-T ((carboxymethyl)trimethylammonium chloride hydrazide) was obtained from Aldrich and Sigma and required no further purification for spectrophotometric use at 295 nm. The blank absorbance of 20mM solutions in 0.1M formic acid/formate buffer was 0.009. Aldrich Gold Label NaCl (stated > 99.999% pure) was used in the maintenance of constant ionic strength. Pretitrated low-carbonate stock solutions of NaOH were obtained from Fisher and were checked by titration against standard sodium biphthalate with phenolphthalein as indicator.

In the preparation of bicarbonate/carbonate buffers, Aldrich Gold Label sodium carbonate (stated 99.95-100.05%) was used. It was dried for
2 h at 260-270°C before use. Reagent grade sodium bicarbonate was obtained from Fisher.

Water used in the preparation of all stock and reactant solutions was minimally of the purity to be described. Recondensed steam was collected and passed through two Barnstead hose-nipple cartridges in series — a combination (D8922) cartridge, containing an organic removal section, followed by a high capacity (D8901) deionizing cartridge. The effluent water was stored in a sealed, pressurized glass container. Resistivity of the water as used was ~0.25 megohm-cm.

3.2. Results — Disproportionation Kinetics

3.2.1. Determination of overall rate expression

With the exception of the last series of experiments to be described, all kinetic determinations were conducted at essentially constant alkalinity, maintained by excess NaOH or bicarbonate/carbonate buffer. The observed physical property $\text{Abs}_{\text{Net}}$ was assumed proportional to the total concentration of all glyoxal forms $[G_T]$. As represented in Eq. 3.2,

$$-\frac{d[G_T]}{dt} = k_{\text{obs}}[G_T] \quad (3.2)$$

in the initial glyoxal concentration range of 15μM to 400μM, a pseudo-first-order dependence on $[G_T]$ occurred over the observed reaction course, typically 0 to 80-90% conversion. The pseudo-first-order rate coefficients $k_{\text{obs}}$ were determined by linear regression from plots of $\log_e(\text{Abs}_{\text{Net}})$ vs. time.
The effect of hydroxide ion concentration on $k_{\text{obs}}$ was observed at 5, 25, 50, and 80°C at a constant ionic strength of 75mM. The results are listed in Tables 3.1a-d. The $k_{\text{obs}}$ values obtained, which at the two lower temperatures span 0.25 to 75mM NaOH, are plotted as $\log_{10} k_{\text{obs}}$ vs. $\log_{10} [\text{OH}^-]$ in Fig. 3.2. A complex relationship between $k_{\text{obs}}$ and [OH\(^-\)] is apparent. At each temperature, a transition from a slope of near unity, indicating a first-order [OH\(^-\)] dependence, to near two, indicating a second-order dependence, occurred. However, at the two lower temperatures, where the rate could be observed at higher alkalinity, a return toward a first-order dependence was evident.

At 5 and 25°C, a relationship between $k_{\text{obs}}$ and [OH\(^-\)] of the form described for phenylglyoxal in Sec. 2.3 is apparent. Therefore, at those temperatures $k_{\text{obs}}$ was fit to Eq. 3.3:

$$k_{\text{obs}} = \frac{(a_1[\text{OH}^-] + a_2[\text{OH}^-]^2)}{(1 + a_3[\text{OH}^-])} \tag{3.3}$$

A non-linear iterative least squares regression routine was used. The results, listed in Table 3.2 and plotted as the broken lines in Fig. 3.2, indicate that an excellent fit was obtained. Thus, at 0 and 25°C the empirical equation to follow describes the overall rate of disproportionation of aqueous glyoxal over the observed concentration ranges:

$$-\frac{d[G_T]}{dt} = \frac{a_1[\text{OH}^-] + a_2[\text{OH}^-]^2}{1 + a_3[\text{OH}^-]} [G_T] \tag{3.4}$$

Due to the rapidity of the reaction at 50°C, $k_{\text{obs}}$ could not be deter-
Table 3.1a. Observed pseudo-first-order rate constant $k_{\text{obs}}$ as a function of mean NaOH concentration at 5.00°C and $\mu = 0.075$M

<table>
<thead>
<tr>
<th>$[\text{OH}^-]$, mM</th>
<th>$[\text{G}]_0$, $\mu$M</th>
<th>$k_{\text{obs}} \times 10^3$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.245</td>
<td>15</td>
<td>0.00642</td>
</tr>
<tr>
<td>0.493</td>
<td>15</td>
<td>0.0219</td>
</tr>
<tr>
<td>0.985</td>
<td>25</td>
<td>0.0787</td>
</tr>
<tr>
<td>1.97</td>
<td>30</td>
<td>0.293</td>
</tr>
<tr>
<td>3.97</td>
<td>40</td>
<td>1.07</td>
</tr>
<tr>
<td>5.45</td>
<td>50</td>
<td>2.22</td>
</tr>
<tr>
<td>7.94</td>
<td>50</td>
<td>3.68</td>
</tr>
<tr>
<td>9.93</td>
<td>50</td>
<td>5.30</td>
</tr>
<tr>
<td>11.9</td>
<td>50</td>
<td>7.19</td>
</tr>
<tr>
<td>15.9</td>
<td>50</td>
<td>11.2</td>
</tr>
<tr>
<td>19.9</td>
<td>50</td>
<td>15.8</td>
</tr>
<tr>
<td>24.9</td>
<td>50</td>
<td>21.5</td>
</tr>
<tr>
<td>34.8</td>
<td>50</td>
<td>34.9</td>
</tr>
<tr>
<td>49.7</td>
<td>50</td>
<td>56.8</td>
</tr>
<tr>
<td>74.6</td>
<td>50</td>
<td>91.3</td>
</tr>
</tbody>
</table>
Table 3.1b. Observed pseudo-first-order rate constant $k_{obs}$ as a function of mean NaOH concentration at 25.00°C and $\mu = 0.075\text{M}$

<table>
<thead>
<tr>
<th>$[\text{OH}^-]$, mM</th>
<th>$[\text{G}]_0$, $\mu\text{M}$</th>
<th>$k_{obs} \times 10^3$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.244</td>
<td>15</td>
<td>0.0583</td>
</tr>
<tr>
<td>0.490</td>
<td>15</td>
<td>0.163</td>
</tr>
<tr>
<td>0.490</td>
<td>15</td>
<td>0.163</td>
</tr>
<tr>
<td>0.987</td>
<td>15</td>
<td>0.514</td>
</tr>
<tr>
<td>1.97</td>
<td>50</td>
<td>1.70</td>
</tr>
<tr>
<td>3.96</td>
<td>50</td>
<td>5.82</td>
</tr>
<tr>
<td>5.95</td>
<td>50</td>
<td>12.2</td>
</tr>
<tr>
<td>7.76</td>
<td>200</td>
<td>19.3</td>
</tr>
<tr>
<td>9.94</td>
<td>100</td>
<td>29.1</td>
</tr>
<tr>
<td>11.9</td>
<td>160</td>
<td>40.1</td>
</tr>
<tr>
<td>14.9</td>
<td>200</td>
<td>54.9</td>
</tr>
<tr>
<td>19.8</td>
<td>200</td>
<td>88.1</td>
</tr>
<tr>
<td>24.8</td>
<td>200</td>
<td>124</td>
</tr>
<tr>
<td>34.7</td>
<td>200</td>
<td>204</td>
</tr>
<tr>
<td>49.7</td>
<td>200</td>
<td>328</td>
</tr>
<tr>
<td>74.8</td>
<td>400</td>
<td>561</td>
</tr>
</tbody>
</table>
Table 3.1c. Observed pseudo-first-order rate constant $k_{obs}$ as a function of mean NaOH concentration at 50.00°C and $\mu = 0.075\text{M}$

<table>
<thead>
<tr>
<th>[OH$^{-}$], mM</th>
<th>$[G]_o$, µM</th>
<th>$k_{obs} \times 10^3$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.240</td>
<td>15</td>
<td>0.872</td>
</tr>
<tr>
<td>0.483</td>
<td>30</td>
<td>2.01</td>
</tr>
<tr>
<td>0.973</td>
<td>25</td>
<td>5.24</td>
</tr>
<tr>
<td>1.95</td>
<td>30</td>
<td>14.3</td>
</tr>
<tr>
<td>3.93</td>
<td>50</td>
<td>43.7</td>
</tr>
<tr>
<td>7.84</td>
<td>50</td>
<td>145</td>
</tr>
</tbody>
</table>

Table 3.1d. Observed pseudo-first-order rate constants $k_{obs}$ as a function of mean NaOH concentration at 80.1°C and $\mu = 0.075\text{M}$

<table>
<thead>
<tr>
<th>[OH$^{-}$], mM</th>
<th>$[G]_o$, µM</th>
<th>$k_{obs} \times 10^3$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.233</td>
<td>15</td>
<td>15.2</td>
</tr>
<tr>
<td>0.473</td>
<td>25</td>
<td>33.6</td>
</tr>
<tr>
<td>0.950</td>
<td>40</td>
<td>77.5</td>
</tr>
<tr>
<td>1.91</td>
<td>50</td>
<td>192</td>
</tr>
<tr>
<td>3.86</td>
<td>50</td>
<td>454</td>
</tr>
</tbody>
</table>
Fig. 3.2. The effect of OH\(^-\) concentration on \(k_{obs}\) at 5, 25, 50, and 80.1\(^\circ\)C. Shown also are the effects of temperature on the isokinetic points and the points of maximum [OH\(^-\)] dependence. Broken lines (-----) indicate fit of data to Eq. 3.3. (o) Bicarbonate/carbonate buffer; (e) NaOH buffer.
Table 3.2. Observed kinetic parameters for the disproportionation of glyoxal at $\mu = 0.075M$ following Eq. 3.3

<table>
<thead>
<tr>
<th>Temperature, °C</th>
<th>$a_1$, s^{-1}M^{-1}</th>
<th>$a_2$, s^{-1}M^{-2}</th>
<th>$a_3$, M^{-1}</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.00</td>
<td>0.0065 ± 0.0004</td>
<td>80.1 ± 0.6</td>
<td>51.2 ± 0.8</td>
</tr>
<tr>
<td>25.00</td>
<td>0.144 ± 0.003</td>
<td>400 ± 4</td>
<td>40.6 ± 0.8</td>
</tr>
<tr>
<td>50.00</td>
<td>3.06 ± 0.05</td>
<td>2470 ± 40</td>
<td>31.6^{b}</td>
</tr>
<tr>
<td>80.1</td>
<td>62.4^{c}</td>
<td>----</td>
<td>----</td>
</tr>
</tbody>
</table>

^{a}Standard error.

^{b}Value of $a_3$ at 50°C determined by Arrhenius extrapolation of values at 5°C and 25°C.

^{c}Value of $a_1$ determined by using values of $a_2$ and $a_3$ extrapolated to 80.1°C.
mined at high alkalinity at that temperature. Therefore, the general rate expression was assumed valid at 50°C and the values of coefficients $a_1$ and $a_2$ were determined after the value of coefficient $a_3$ had been fixed at 31.6M⁻¹ by extrapolation from the values at 5 and 25°C by using the Arrhenius relationship. Little error should have been introduced by this procedure because of the very low magnitude indicated for the activation energy for coefficient $a_3$ (-8 kJ/mol), the small standard deviations obtained for coefficient $a_3$ at the two lower temperatures, and the predicted small influence of coefficient $a_3$ on $k_{obs}$ at the hydroxide ion concentrations employed at the higher temperatures.

### 3.2.2. Effect of temperature on rate coefficients $a_1$ and $a_2$

In contrast to coefficient $a_3$, rate coefficients $a_1$ and $a_2$ showed considerable thermal sensitivity. Therefore, it was desirable to verify whether or not they follow simple Arrhenius dependencies. Minimally, three reliable widely spaced values are required. Although a larger number of values would have been preferred, this was experimentally impractical and would not have increased the temperature range over which the thermal properties were determined.

The three values for coefficient $a_2$ in Table 3.2 were sufficient to determine the thermal properties of that parameter. Those properties are listed in Table 3.3 in terms of Activated Complex Theory and (for convenience) in terms of Arrhenius' law as well. As indicated in Fig. 3.3, the three values for $a_2$ from 5 to 50°C, when plotted as $\log_e(a_2/T)$ vs. $1/T$, closely approximated a straight line, especially considering the range of temperature covered and the apparent reliability of the values plotted.
Table 3.3. Thermal parameters of rate coefficients $a_1$, $a_2$, and $a_3$ at $\mu = 0.075M$ assuming Activated Complex Theory or Arrhenius dependence

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Activated Complex Theory$^a$</th>
<th>Arrhenius Relationship$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta S'$, J mol$^{-1}$K$^{-1}$</td>
<td>$\Delta H'$, kJ mol$^{-1}$</td>
</tr>
<tr>
<td>$a_1$, s$^{-1}$M$^{-1}$</td>
<td>$53.7 \pm 2.7^d$</td>
<td>$93.8 \pm 0.9^d$</td>
</tr>
<tr>
<td>$a_2$, s$^{-1}$M$^{-2}$</td>
<td>$-12.2 \pm 2.6$</td>
<td>$54.4 \pm 0.8$</td>
</tr>
<tr>
<td>$a_3$, M$^{-1}$</td>
<td>$-249$</td>
<td>$-10.5$</td>
</tr>
<tr>
<td>$a_2(\mu \to 0)$, s$^{-1}$M$^{-1}$</td>
<td>$-18.9 \pm 2.3$</td>
<td>$53.7 \pm 0.7$</td>
</tr>
</tbody>
</table>

\[ a_k = \kappa RT(\mu)^{-1}\exp(\Delta S'/R)\exp(-\Delta H'/RT). \]

\[ b_k = k_o \exp(-E_a/RT). \]

$^a$Units of rate coefficient.

$^b$Standard error.

$^c$Units of rate coefficient.

$^d$Standard error.

$^e$\[ a_2(\mu \to 0) = a_2(\mu)\exp_{10}\{-2\Delta v^{1/2}(1 + \mu^{1/2})^{-1}\}. \]
Fig. 3.3. Effect of temperature on rate coefficients $a_1$ and $a_2$ at $\mu = 0.075 M$ as determined by Activated Complex Theory.

$$\Delta H^\ddagger_{a_2} = 54.4 \pm 0.8 \text{ kJ mol}^{-1}$$

$$\Delta H^\ddagger_{a_1} = 93.8 \pm 0.9 \text{ kJ mol}^{-1}$$
Values of 54.5 kJ/mol (13.0 kcal/mol) for the apparent activation enthalpy $\Delta H^\ddagger_{a2}$ and -12.3 J/molK (-2.94 cal/molK) for the apparent activation entropy $\Delta S^\ddagger_{a2}$ were obtained.

The value determined for coefficient $a_1$ at 5°C was not sufficiently reliable to allow its use in determining the thermal properties of that parameter. However, because the apparent activation energy of coefficient $a_1$ was much greater than that indicated for $a_2$, a fourth value for coefficient $a_1$ could be obtained from runs with 0.25 mM NaOH at 80°C. At those conditions, the predicted third-order contribution to $k_{obs}$ (due to coefficient $a_2$), obtained by extrapolation from 50°C, was only 6%, and the predicted "inhibition" due to coefficient $a_3$ was only 0.5%. Therefore, the mean of the triplicate values obtained for $k_{obs}$ at 80°C, along with the extrapolated values for coefficients $a_2$ and $a_3$, were used to determine coefficient $a_1$ at that temperature. Of course, it must be assumed that Eq. 3.3 applies at 80°C.

When plotted as $\log_e(a_1/T)$ vs 1/T, the three believed-reliable values for coefficient $a_1$ also fell close to a straight line, as indicated in Fig. 3.3. For the second-order (overall) coefficient $a_1$, an apparent $\Delta H^\ddagger_{a1}$ of 93.4 kJ/mol (22.3 kcal/mol) and an apparent $\Delta S^\ddagger_{a1}$ of +52.4 J/molK (+12.5 cal/molK) are obtained. It is also evident in Fig. 3.3, that the experimentally obtained value (calculated by non-linear regression) for coefficient $a_1$ at 5°C — $0.0065 \pm 4 \times 10^{-4}$ (std. dev.) s$^{-1}$M$^{-1}$ — appears to be significantly lower than the value predicted by extrapolation of the more accurate values from 25°C (0.0092 s$^{-1}$M$^{-1}$).

Although no explanation for the above inconsistency is proposed, there are several possible causes, the most obvious being that of experimental
inaccuracy. The value for coefficient $a_1$ obtained at $5^\circ C$ was determined under conditions at which the reaction is only about 25% (at 0.25mM NaOH) second order or less. Furthermore, the low alkalinities favoring coefficient $a_1$ also reduced experimental accuracy. Thus, even small systematic errors in those experiments could give rise to large errors in the "best-fit" value for coefficient $a_1$. As described in detail previously, possible errors could have arisen from residual dissolved CO$_2$ or slow loss of alkalinity due to the slow rate of reaction and the low concentration of hydroxide ion. However, the latter should have resulted in non-linear pseudo-first-order plots, a phenomenon which was not observed. The possibility that the values obtained at higher temperatures are also substantially in error must also be recognized.

If, for the sake of argument, the downward curvature in the log$_e(a_1/T)$ vs. $1/T$ plot of coefficient $a_1$ is accepted as fact, several possible causes can be considered. The expectation of an Arrhenius-type thermal response presupposes the rate coefficient of interest to be the product (or quotient) of individual rate constants and equilibrium constants. This is certainly not always the case.

While a dependence of the form $a_1 = k_1 + k_2$ is not consistent with the direction of curvature of Fig. 3.3, a dependence of the form $a_1 = k_1(1 + k_2)^{-1}$ or $k_1(1 + K)^{-1}$ would be consistent providing that $\Delta H_K > 0$. In fact, according to the mechanism to be developed in Sec. 3.3, both rate coefficients $a_1$ and $a_2$ above would be expected to contain factors of the form $(1 + K)^{-1}$, although it appears likely that in this instance $K \gg 1$ and that $\Delta H_K < 0$. Another possible explanation might be a change in the heat capacity of activation and/or changes in the $\Delta H$ of embedded
equilibrium constants with temperature, but the experimental results were far too crude to support this.

The above discussion is pure speculation. Extension of the experiments to lower alkalinites with improvements in experimental methods are required to resolve the above inconsistency.

3.2.3. **Effect of ionic strength on rate coefficients $a_1$ and $a_2$**

Although the study of kinetic salt effects does not provide support for particular reaction mechanisms, it does provide an additional check on the observed rate law and extends its predictive range. The Bronsted relation and Activated Complex Theory both predict strong positive or negative salt effects in aqueous solution for activated complexes arising from ionic species of like and unlike charge, respectively. Only small salt effects are predicted for complexes arising from an ion and a neutral molecule. Furthermore, in the range of ionic strength over which the two-parameter Debye-Hückel relation, below,

$$-\log_{10} \gamma_i = A_0 (\mu^{1/2} (1 + a^* B_\mu^{1/2})^{-1})$$

(3.5)

may be used to estimate the individual ion activity coefficients $\gamma_i$, approximately linear plots of $-\log_{10}(k)$ vs. $2A_\mu^{1/2}(1 + \mu^{1/2})^{-1}$ are predicted. Slopes of +1 and -1 are predicted for complexes arising from like-charged and unlike-charged reactants, respectively. A slope of zero is predicted for complexes formed from neutral species or from an ion and a neutral molecule(s). Note that the product of the ion size parameter $a^*$ and solvent parameter $B$ is in this instance generally taken to be
The effects of increasing ionic strength (as added NaCl) were observed on both coefficients $a_1$ and $a_2$. That on coefficient $a_1$ was studied at 80°C in 0.25mM NaOH over a range of ionic strength from 0.25 to 200mM, at which conditions contributions due to coefficient $a_2$ were 8% or less of $k_{obs}$ and the inhibitory term containing $a_3$ was negligible. Unfortunately, the extreme conditions reduced experimental precision somewhat and necessitated replicate runs. A very slight negative salt effect was observed with increasing ionic strength (Table 3.4). The decrease, when plotted as $\log_{10}(k_{obs})$ vs. $2\alpha_\mu^{1/2}(1 + \mu^{1/2})^{-1}$, is non-linear and much less than would be expected for ionic interactions. Such an effect is typical of reactions involving ions and neutral molecules and is thus consistent with the observed rate law. Plots of $k_{obs}$ vs. $\mu$ are generally non-linear also, and such salt effects are often fit empirically to the following equation:

$$\log_{10} k_\mu = \log_{10} k_{\mu \to 0} + b\mu$$

Because the effect of $\mu$ on $a_1$ was so slight, much less than that observed for coefficient $a_2$, it was necessary to correct $k_{obs}$ for the small but variable influence of $a_2$. This was done by using Eq. 3.7 below,

$$a_1 = k_{obs}/[OH^-] - a_2(T,\mu)[OH^-]$$

$$a_2 \text{[OH]}^2/k_{obs}$$

together with predicted values for coefficient $a_2$ at 80°C as a function of $\mu$ (to be described). The relative contribution of $a_2$ to $k_{obs}$, given by $a_2[OH^-]^2/k_{obs}$, can be seen in Table 3.4 to vary from approximately 3 to 8%.
Table 3.4. Experimentally determined values for $k_{obs}$ and calculated values of $a_1$ as a function of ionic strength $\mu$ at 80.0°C in 0.25mM NaOH ([G]$_o$ = 15μM)

<table>
<thead>
<tr>
<th>$\mu$, M</th>
<th>$k_{obs} \times 10^3$, s$^{-1}$</th>
<th>$a_1$, s$^{-1}$M$^{-1}$</th>
<th>$a_2[OH^-]^2/k_{obs}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00025</td>
<td>16.50</td>
<td>67.9</td>
<td>0.030</td>
</tr>
<tr>
<td>0.00025</td>
<td>17.29</td>
<td>71.3</td>
<td>0.029</td>
</tr>
<tr>
<td>0.025</td>
<td>15.79</td>
<td>64.2</td>
<td>0.043</td>
</tr>
<tr>
<td>0.025</td>
<td>16.37</td>
<td>66.6</td>
<td>0.042</td>
</tr>
<tr>
<td>0.075</td>
<td>14.44</td>
<td>57.8</td>
<td>0.058</td>
</tr>
<tr>
<td>0.075</td>
<td>14.71</td>
<td>58.9</td>
<td>0.057</td>
</tr>
<tr>
<td>0.075</td>
<td>15.87</td>
<td>63.8</td>
<td>0.053</td>
</tr>
<tr>
<td>0.20</td>
<td>13.07</td>
<td>50.9</td>
<td>0.083</td>
</tr>
<tr>
<td>0.20</td>
<td>13.96</td>
<td>54.7</td>
<td>0.077</td>
</tr>
</tbody>
</table>

*Nominal.*
The values of coefficient $a_1$ obtained in the above manner were fit to Eq. 3.6 by linear regression; the resulting fit is shown in Fig. 3.4. A value of $-0.58 \pm 0.09 \text{M}^{-1}$ was obtained for parameter "b". Thus, the effect of ionic strength on rate coefficient $a_1$ is expressed empirically by Eq. 3.8:

$$a_1(u) = a_1(u \to 0) \exp_{10}(-0.58u) \quad (3.8)$$

The above results are largely independent of the accuracy to which the salt effects on coefficient $a_2$ have been determined, as fitting $k_{\text{obs}}$ directly to Eq. 3.6 still yields a value of $-0.47$ for parameter b above.

The effects of ionic strength on coefficient $a_2$ were observed at $10^\circ\text{C}$ in $10.0\text{mM NaOH}$. Although at those conditions experimental precision was excellent (std. dev. $\pm 0.6\%$) and contributions due to coefficient $a_1$ are negligible (1-2%), an approximate 25% inhibition due to coefficient $a_3$ is predicted by Eq. 3.3. For glyoxal the effects of ionic strength on coefficient $a_3$ are not experimentally accessible, but the overall rate expression predicts little effect. From the results listed in Table 3.5, a strong positive salt effect on $a_2$ is apparent. As shown in Fig. 3.5, a plot of $-\log_{10}(k_{\text{obs}})$ vs. $2Au^{1/2}(1 + \mu^{1/2})^{-1}$ indicates an approximately linear relationship with a near-theoretical slope of $+0.93$ (over the ionic strength range of 0.01 to 0.2M), which is also consistent with the observed rate law. The effect of ionic strength on coefficient $a_2$ is therefore approximately described by Eq. 3.9:

$$a_2(u) = a_2(u \to 0) \exp_{10}(2Au^{1/2}(1 + \mu^{1/2})^{-1}) \quad (3.9)$$
Fig. 3.4. Effect of ionic strength $\mu$ on $a_1$ (s$^{-1}$M$^{-1}$) at 80.0$^\circ$C in 0.25mM NaOH

$b = -0.58 \pm 0.09$M$^{-1}$
Table 3.5. Experimentally determined values for $k_{obs}$ as a function of ionic strength $\mu$ at 10.0°C in 10.0mM NaOH ($[G]_0 = 120\mu M$)

<table>
<thead>
<tr>
<th>$\mu$, M</th>
<th>$k_{obs} \times 10^3$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.0100</td>
<td>6.15</td>
</tr>
<tr>
<td>0.0200</td>
<td>6.63</td>
</tr>
<tr>
<td>0.040</td>
<td>7.29</td>
</tr>
<tr>
<td>0.040</td>
<td>7.33</td>
</tr>
<tr>
<td>0.040</td>
<td>7.38</td>
</tr>
<tr>
<td>0.075</td>
<td>8.05</td>
</tr>
<tr>
<td>0.120</td>
<td>8.86</td>
</tr>
<tr>
<td>0.200</td>
<td>9.85</td>
</tr>
<tr>
<td>0.41</td>
<td>11.67</td>
</tr>
<tr>
<td>0.81</td>
<td>13.73</td>
</tr>
</tbody>
</table>
Fig. 3.5. Effect of ionic strength $\mu$ on $k_{\text{obs}}$ (s$^{-1}$) at 5.0°C in 10.0mM NaOH ($A = 0.995$)

Slope = 0.93 (±0.02)
($\mu = 0.01$M to 0.2M)
In aqueous solution, the Debye–Huckel solvent parameter $A$ is a weak function of temperature, which implies a slight thermal effect on the individual ion activity coefficients at constant ionic strength. For thermal studies spanning a broad temperature range, the above effect can lead to slight errors in the determination of $\Delta H^\ddagger$ and $\Delta S^\ddagger$. Therefore, extrapolated values of coefficient $a_2$ as $\mu$ approaches zero, $a_2(\mu \to 0)$, were calculated and the thermal properties were reevaluated. These quantities, which more closely approximate the thermodynamic values for $\Delta H_a^\ddagger$ and $\Delta S_a^\ddagger$, are included in Table 3.3. The effect of temperature on the Debye–Huckel parameter $B$ is much less than that on parameter $A$. Of course, the thermal values calculated for rate coefficient $a_1$ are not described by the Debye–Huckel theory, and so are not corrected for the above effect.

The effects of ionic strength on $k_{obs}$ have been explained above in terms of primary kinetic salt effects. However, kinetic salt effects are a consequence of the observed rate law only and can as readily be explained in terms of secondary salt effects. In fact, for the disproportionation of glyoxal the latter origin appears more likely, as will be discussed in Sec. 3.3.3.

### 3.2.4. Rate determinations in bicarbonate/carbonate buffer

In order to extend the preceding studies to lower alkalinity, a series of experiments was conducted in 25mM (except as noted) bicarbonate/carbonate buffer. Although accurate kinetic studies are not often encountered in the above buffers because of the difficulties of calculating $[OH^-]$, satisfactory results can often be obtained at low to moderate ionic strength if account is taken of the hydrolysis of water by carbonate ion.
and the effects of ionic strength on the apparent dissociation constants for water \(K_w\) and bicarbonate ion \(K_{\text{HCO}_3}\). For experimental purposes, two conveniently varied parameters are the ratio \(R_c\) of the hypothetical initial concentrations of carbonate to bicarbonate salts and \(C_T\), the total concentration of bicarbonate and carbonate ions. When allowances are made for hydrolysis and ionic strength, an equation of the form of Eq. 3.10a to follow is obtained, relating \([\text{OH}^-]\) to \(R_c\), \(C_T\), and the apparent base dissociation constant \(K_b\). The latter is defined in Eq. 3.10b in terms of the thermodynamic dissociation constants \(K_w'\) and \(K_{\text{HCO}_3}'\) and the individual activity coefficients \(\gamma_i\):

\[
[\text{OH}^-] = \frac{[K_b + C_T/(1+R_c)]^2 + 4K_bC_T[R_c/(1 + R_c)]^{1/2}}{2} - \frac{[K_b + C_T/(1 + R_c)]}{2} \quad (3.10a)
\]

where

\[
K_b = K_w'K_{\text{HCO}_3}^{-1}\gamma_{\text{HCO}_3}\gamma_{\text{OH}}\gamma_{\text{HCO}_3}^{-1}/(\gamma_{\text{HCO}_3}\gamma_{\text{OH}}) = [\text{OH}^-][\text{HCO}_3^-]/[\text{CO}_3^-] \quad (3.10b)
\]

The activity of solvent water has again been assumed approximately equal to unity.

Values for \(K_w'\) and \(K_{\text{HCO}_3}'\) have been tabulated as functions of temperature for water \(^{90}\) from 0 to 100°C and for the bicarbonate/carbonate system \(^{91}\) from 0 to 50°C. The required activity coefficients can be estimated up to an ionic strength of ~0.1M with adequate accuracy (1-2%) by any of several equations \(^{92}\). Because the values of activity coefficients are generally estimated as functions of ionic strength \(\mu\), an iterative solution for \([\text{OH}^-]\) is indicated. However, in practice the effects of hydrolysis on ionic
strength are usually negligible, and so the ionic strength can be calculated directly from the hypothetical initial bicarbonate \([\text{HNaCO}_3]_i\) and carbonate \([\text{Na}_2\text{CO}_3]_i\) concentrations by using Eq. 3.11:

\[
= 3[\text{Na}_2\text{CO}_3]_i + [\text{NaHCO}_3]_i - 3[\text{OH}^-]/2 + [\text{NaCl}] \quad (3.11)
\]

Values for \(k_{obs}\) from runs at 25°C with \(C_T = 25\text{mM}\), in which \(R_C\) was varied from 1/8 to 8, are listed in Table 3.6, and are plotted as \(\log_{10}(k_{obs})\) vs. \(\log_{10}[\text{OH}^-]\) in Fig. 3.2 along with values extrapolated from Eq. 3.3. Excellent agreement with the values obtained by using NaOH-buffered solutions is apparent at the highest buffer ratio \((R_C = 8)\), at which conditions no extrapolation of the results obtained with NaOH buffer is required. However, at the lower \(R_C\) values an apparent enhancement of \(k_{obs}\) is seen. Assuming that the extrapolation of Eq. 3.3 is valid, catalysis by \(\text{HCO}_3^-\) or \(\text{CO}_3^{2-}\) (since \([\text{OH}^-]\) increases more rapidly than \([\text{CO}_3^{2-}]\)) or both is suggested. Catalysis by solvent water is consistent neither with the data in Fig. 3.3 nor with the observed stability of glyoxal in acidic and neutral solutions. Since \(k_{obs}\) was determined following the decrease of glyoxal, another possible explanation is that carbonate and/or bicarbonate catalyzes a competing reaction.

The effects of temperatures from 25 to 55°C on \(k_{obs}\) at \(R_C = 0.25\) are listed in Table 3.7. Values of the second-order coefficient \(a_1\) were again calculated by using Eq. 3.7:

\[
a_1 = k_{obs}/[\text{OH}^-] - a_2(T,\mu)[\text{OH}^-] \quad (3.7)
\]
Table 3.6. $k_{\text{obs}}$ as a function of mean carbonate/bicarbonate ratio, $R_{C}$, at $25^\circ \text{C}$, $C_T = 0.025\text{M}$, $\mu = 0.075\text{M}$, and $[G]_o = 50\, \mu\text{M}$

<table>
<thead>
<tr>
<th>$R_{C}$</th>
<th>$[\text{OH}^-]^a$, $\mu\text{M}$</th>
<th>$k_{\text{obs}} \times 10^6$, s$^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1245</td>
<td>17.1</td>
<td>3.53</td>
</tr>
<tr>
<td>0.2494</td>
<td>34.2</td>
<td>7.07</td>
</tr>
<tr>
<td>0.4986</td>
<td>68.1</td>
<td>14.45</td>
</tr>
<tr>
<td>0.9977</td>
<td>135</td>
<td>31.6</td>
</tr>
<tr>
<td>1.995</td>
<td>263</td>
<td>73.2</td>
</tr>
<tr>
<td>3.980</td>
<td>489</td>
<td>172</td>
</tr>
<tr>
<td>7.945</td>
<td>818</td>
<td>375</td>
</tr>
</tbody>
</table>

$^a$Calculated using Eqs. 3.10a and 3.10b with $\frac{\gamma_{\text{CO}_3}}{\gamma_{\text{HCO}_3} \gamma_{\text{OH}}}$ = 0.64.
Table 3.7. Rate coefficient $a_1$ as a function of temperature at $R_C(\text{nominal}) = 0.25, \mu = 0.075 \text{M}$

<table>
<thead>
<tr>
<th>$T$, $^\circ C$</th>
<th>$k_{\text{obs}} \times 10^6$, s$^{-1}$</th>
<th>$K_b \times 10^6$, M</th>
<th>$[\text{OH}^-]$, \mu M</th>
<th>$a_1$, s$^{-1}$</th>
<th>$a_1[\text{OH}^-]$</th>
<th>$k_{\text{obs}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.00</td>
<td>7.08</td>
<td>138.2</td>
<td>34.3</td>
<td>0.1932</td>
<td>0.936</td>
<td></td>
</tr>
<tr>
<td>29.98</td>
<td>16.93</td>
<td>183.2</td>
<td>45.3</td>
<td>0.348</td>
<td>0.932</td>
<td></td>
</tr>
<tr>
<td>34.96</td>
<td>39.5</td>
<td>237</td>
<td>58.5</td>
<td>0.630</td>
<td>0.931</td>
<td></td>
</tr>
<tr>
<td>39.80</td>
<td>88.9</td>
<td>304</td>
<td>74.9</td>
<td>1.104</td>
<td>0.930</td>
<td></td>
</tr>
<tr>
<td>45.00</td>
<td>208.5</td>
<td>398</td>
<td>97.9</td>
<td>1.979</td>
<td>0.929</td>
<td></td>
</tr>
<tr>
<td>50.00</td>
<td>459</td>
<td>509</td>
<td>125</td>
<td>3.40</td>
<td>0.928</td>
<td></td>
</tr>
<tr>
<td>55.02</td>
<td>1000</td>
<td>642</td>
<td>158</td>
<td>5.89</td>
<td>0.928</td>
<td></td>
</tr>
</tbody>
</table>

$$a_K = K_b \times a_2 \times \gamma_{\text{CO}_3^-} \times \gamma_{\text{HCO}_3^-} \times \gamma_{\text{OH}^-}.$$
by which the small (~7%) third-order effect due to coefficient $a_2$ could be subtracted out. Values of $a_2$ were obtained by extrapolation of the results displayed in Table 3.3. When $\log_{10}(a_1/T)$ is plotted vs. $1/T$, as in Fig. 3.6, the resulting values closely approximate a straight line. Analysis of the values obtained at temperatures from 25 to 50°C ($K'_{HCO_3}$ at 55°C was obtained by extrapolation) yielded the following thermal parameters for $a_1$: $\Delta H^\ddagger_{al} = 89.5 \pm 0.4$ kJ/mol ($E_a = 92.1$ kJ/mol) and $\Delta S^\ddagger_{al} = +41.7 \pm 1.0$ J/molK ($k_o = 2.6 \times 10^{15}$ M$^{-1}$s$^{-1}$). It may be noted that the value obtained for $\Delta H^\ddagger_{al}$ is close to that obtained from the NaOH-buffered experiments, possibly reflecting the large influence of the [OH$^-$]-catalyzed reaction. However, the former is slightly lower. Were a secondary reaction involved, this would indicate a lower activation enthalpy for the competing process. Of course, the above discrepancy is consistent also with loss of alkalinity due to etching of the glass reactor at low alkalinity and low temperature, since the bicarbonate/carbonate systems were more strongly buffered than were the NaOH-buffered systems at low alkalinity.

3.2.5. **Disproportionation at intermediate glyoxal concentrations**

The preceding kinetic studies were conducted at initial glyoxal concentrations less than 0.1mM, at which conditions the hydroxide ion concentration could be maintained virtually constant throughout any given run. However, in order to test the validity of the observed rate law at higher substrate concentrations (to 20mM), a series of rate determinations were conducted in which the concentrations of both glyoxal and hydroxide ion were allowed to vary simultaneously. These so-called "integral rate studies" were similar in basic design to those employed by Salomaa$^2$. 
Fig. 3.6. Effect of temperature on rate coefficient $a_1$ according to Activated Complex Theory, as determined in bicarbonate/carbonate buffer ($R_C = 0.25$) at $u = 0.075M$
However, in this case the intent was neither to determine the applicable rate law nor to fit kinetic parameters to an assumed rate law. Rather, the purpose was simply to test the predictive capacity of the empirical rate expression, Eq. 3.4, at moderate total glyoxal concentrations.

It was considered advisable to check the rate equation at the highest glyoxal concentrations practical, since, by analogy with related reactions, a variety of side reactions second-order in \([G]_T\) might become significant at high substrate concentrations. Specifically, an extramolecular disproportionation (Cannizzaro reaction) in which two molecules of glyoxal react to form one molecule each of glyoxylic acid and glycolaldehyde might be envisioned. Alternatively, various other pathways for the intramolecular reaction, catalyzed by substrate, might be considered.

The integral rate studies were far more difficult to conduct than the aforementioned pseudo-first-order studies. Complications arose from the rapidity of the reaction at the initial concentrations of hydroxide ion that were required, the need to determine the absolute values of the reaction time "t" and the conversion of glyoxal \(C(t)\), and the slight effects of the heat of reaction on the reactor temperature. These experimental problems and their resolution were discussed in Sec. 3.1.4.

Despite the above limitations, a set of acceptable integral rate determinations was obtained in which the total glyoxal concentration was observed following rapid injection (at \(t = 0\)) of a small volume of 1M NaOH into a solution of glyoxal. The resulting time courses are plotted as \(\log_{10} C(t)\) vs. \(\log_{10} t\) in Figs. 3.7a-f, together with the time courses predicted by Eq. 3.4, by using the rate parameters obtained at low glyoxal concentration. The means by which the predicted curves were developed is
Fig. 3.7a. Observed disproportionation response vs. predicted response obtained from Eq. 3.13a (---) and numerical integration of Eq. 3.17 (—-). Initial conditions: [OH⁻]₀ = 2mM, [Gₜ]₀ = 2mM
Fig. 3.7b. Observed disproportionation response vs. predicted response obtained from Eq. 3.13a (-----) and numerical integration of Eq. 3.17 (---). Initial conditions: [OH⁻]₀ = 5 mM, [G₆]₀ = 5 mM
Fig. 3.7c. Observed disproportionation response vs. predicted response obtained from Eq. 3.13a (---) and numerical integration of Eq. 3.17 (----). Initial conditions: $[\text{OH}^-]_i = 10\text{mM}, [G_T]_0 = 10\text{mM}$
Fig. 3.7d. Observed disproportionation response vs. predicted response obtained from Eq. 3.13a (-----) and numerical integration of Eq. 3.17 (-----). Initial conditions: $[\text{OH}^-]_i = 20\text{mM}, [G_T]_0 = 20\text{mM}$
Fig. 3.7e. Observed disproportionation response vs. predicted response obtained from Eq. 3.13a (---) and numerical integration of Eq. 3.17 (---). Initial conditions: [OH⁻]₀ = 20mM, [G₆₇]₀ = 10mM.
Fig. 3.7f. Observed disproportionation response vs. predicted response obtained from Eq. 3.13a (—) and numerical integration of Eq. 3.17 (—). Initial conditions: \([\text{OH}^-]_0 = 20\text{mM}, [G_T]_0 = 5\text{mM}\)
summarized below. Six runs were conducted, each at 25°C and μ = 75mM. The initial concentrations of both glyoxal and hydroxide ion were varied from 2 to 20mM.

The two experimentally varied parameters were the total concentration of glyoxal at time t = 0, \([G^\cdot]_0\), and the hypothetical initial concentration of hydroxide ion \([OH^-]_0\). Within any given run, the range of conversion over which accurate results could be obtained was limited to roughly 80%. Therefore, four runs were conducted with stoichiometric initial concentrations \(([OH^-]_0 - [G^\cdot]_0 = \Delta_0 = 0)\), in which \([G^\cdot]_0\) was varied from 2 to 20mM, followed by two additional runs in which the alkalinity was maintained constant at 20mM while the initial substrate concentration was varied from 10 to 5mM. Tabulated below are the experimental conditions at which the predictive capacity of Eq. 3.4 was tested, along with the corresponding figures in which the results are displayed.

<table>
<thead>
<tr>
<th>([OH^-]_0), mM</th>
<th>([G^\cdot]_0), mM</th>
<th>(\Delta_0), mM</th>
<th>Figure No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>2</td>
<td>0</td>
<td>3.7a</td>
</tr>
<tr>
<td>5</td>
<td>5</td>
<td>0</td>
<td>3.7b</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>0</td>
<td>3.7c</td>
</tr>
<tr>
<td>20</td>
<td>20</td>
<td>0</td>
<td>3.7d</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>10</td>
<td>3.7e</td>
</tr>
<tr>
<td>20</td>
<td>5</td>
<td>15</td>
<td>3.7f</td>
</tr>
</tbody>
</table>

Because both \([OH^-]\) and \([G^\cdot]\) were allowed to vary simultaneously in any given run, and because \([OH^-]\) could not be accurately or rapidly monitored
at high pH, it was necessary to relate those concentrations stoichiomet-
rically. Because glycolic acid \( \text{pK}_a = 3.8 \) can be considered totally
dissociated at any alkaline pH, it can be assumed that during any given run
\([\text{OH}^-] \) will be reduced by the formation of the glycolic acid product.
Thus, at any given time "t", the residual hydroxide ion concentration is
given by Eqs. 3.12a,b,

\[
[\text{OH}^-] = [\text{OH}^-]_t - ([G_T]_o - [G_T])
\]
\[
= \Delta_o + [G_T]
\]

wherein the second term on the right side of Eq. 3.12a represents the
reduction in alkalinity brought about by titration with product. The
quantity \([\text{OH}^-]_t - [G_T]_o\), denoted \(\Delta_o\) in Eq. 3.12b, represents the "excess"
(over stoichiometric) alkalinity. The neglect of dimeric forms in Eqs.
3.12 above is based on independent experiments (to be described in
Sec. 4), which have indicated that the presence of neutral dimer may be
ignored in solutions of up to 10mM total glyoxal.

If Eqs 3.12 are used to relate \([\text{OH}^-] \) and \([G_T] \), the kinetic rate
expression, Eq. 3.4, may be integrated analytically to yield expressions
for \([G_T] \) as implicit functions of t. If \(X\) and \(X_o\) are allowed to represent
\([G_T] \) and \([G_T]_o\), respectively, Eqs. 3.13a,b are obtained:

\[
\Delta_o = 0:
\]
\[
(1/X - 1/X_o) + (a_2/a_1 - a_3) \ln \frac{X(a_1 + a_2X_o)}{X_o(a_1 + a_2X)} = \frac{X(a_1 + a_2X_o)}{a_1}
\]

(3.13a)
The above equations represent analytical solutions to Eq. 3.4 for the cases of stoichiometric ($\Delta_o = 0$) and non-stoichiometric ($\Delta_o \neq 0$) initial concentrations, respectively.

Eqs. 3.13a,b represent solutions to the rate equation when any possible substrate acidity is neglected; the "inhibitory" coefficient $a_3$ is assumed not to be associated with any acidity of glyoxal. In that respect, the above solutions are analogous to the integrated rate expressions for the simple second- or third-order rate expressions tested by Salomaa. In Figs. 3.7a-f, plotted as dashed lines, are the predicted reaction time courses corresponding to Eqs. 3.13a or b, as appropriate.

Except at very high conversion with relatively low initial concentrations of glyoxal, Eqs. 3.13a,b overpredict the rate of disproportionation. Furthermore, the discrepancy persists even at high conversion with highly alkaline solutions. The lack of agreement between predicted and observed kinetics under integral rate conditions suggests that glyoxal is significantly dissociated at least at the more alkaline run conditions. If it is assumed that during any given run the alkalinity is suppressed by both formation of product and ionization of substrate, and if it is further assumed that the quantity $a_3[OH^-]$ (where $a_3$ was determined at low substrate
concentrations) represents the ratio of ionized to unionized substrate \([G^-]/[G]\), the previous stoichiometric equation relating the concentrations of substrate and hydroxide ion can be retained in modified form:

\[
[\text{OH}^-] = [\text{OH}^-]_i - [G_T]_o + [G_T]/(1 + a_3[\text{OH}^-]) = \Delta_o + [G_T]/(1 + a_3[\text{OH}^-])
\] (3.14)

Note that with the above assumptions \(a_3\) reflects the "effective" acidity \(K_{eff}\) of glyoxal, that is \(a_3 = K_{eff}K_w^{-1} = [G^-]/[G][\text{OH}^-]\).

As indicated by the expressions to follow, the above implicit expression for \([\text{OH}^-]\) can be put in quadratic form and solved for \([\text{OH}^-]\) as an explicit function of \([G_T]\), \(\Delta_o\), and the empirical rate coefficient \(a_3\).

\[a_3[\text{OH}^-]^2 + (1 - \Delta_o a_3)[\text{OH}^-] - ([G_T] + \Delta_o) = 0\] (3.15a)

\([\text{OH}^-] = \left[\frac{(1 - \Delta_o a_3)^2 + 4a_3([G_T] + \Delta_o)}{(1 - \Delta_o a_3)^2 + 4a_3([G_T] + \Delta_o)}\right]^{1/2} - (1 - \Delta_o a_3)/2a_3\] (3.15b)

Equation 3.15b above can be put in a more convenient form by the multiplication of both numerator and denominator by \((1 - \Delta_o a_3)\) plus the quantity under the square root sign. The following explicit expression for \([\text{OH}^-]\) results:

\[\text{[OH}^-] = \frac{2([G_T] + \Delta_o)/(1 - a_3\Delta_o)}{1 + [1 + 4a_3([G_T] + \Delta_o)/(1 - a_3\Delta_o)]^{1/2}}\] (3.16)

wherein \(\Delta_o\) is defined as in Eqs. 3.13a,b. When Eq. 3.16 is applied to the empirical rate expression, Eq. 3.4, the following differential equation is
obtained for the disappearance of total glyoxal in terms of the excess alkalinity $\Delta_0$, the three empirical rate coefficients $a_1$, $a_2$, and $a_3$, and the single experimentally measurable variable $[G_T]$: 

$$\frac{d[G_T]}{dt} = \frac{2([G_T] + \Delta_0)/(1 - \Delta_0 a_3)}{1 + [1 + 4a_3([G_T] + \Delta_0)/(1 + \Delta_0 a_3)^2]^{1/2}} [G_T] + a_3$$

Given appropriate values for coefficients $a_1$, $a_2$, and $a_3$ (as functions of $\mu$ and $T$), Eq. 3.17 can be integrated numerically to yield times of reaction $t$ corresponding to given concentrations. Again, the results are implicit for $[G_T]$ and the predicted kinetics are best indicated graphically. Predicted reaction time courses corresponding to each of the observed kinetic runs are depicted by the solid lines in Figs. 3.7a–f.

The agreement between the predicted kinetic responses, with coefficient $a_3$ reflecting the acidity of glyoxal, and the observed responses is considered satisfactory, except perhaps at the highest alkalinity of 20mM $[OH^-]$. However, at those extreme conditions the rate of reaction was too high to permit much speculation on the remaining discrepancy between the predicted and observed kinetics. The predicted response appears to slightly overestimate the disproportionation rate. If the results are considered reliable and the rate coefficients accurate, the discrepancy might then suggest that not all of the possible dissociated forms of glyoxal are reflected in the empirical rate equation.

Certainly, the comparative kinetics in Figs. 3.7a–f support the
predominant role of ionized glyoxal in the observed rate coefficient $a_3$.

3.3. Interpretation of Kinetic Results

The empirical rate expression obtained for the disproportionation of glyoxal also describes the disproportionation kinetics observed for methyl-glyoxal and reported for phenylglyoxal. In addition, Eq. 3.4 can be generalized to take into account the molecularity "m" in substrate "S" resulting in the following kinetic rate law:

$$-\frac{d[S]}{dt} = \frac{m(a_1[OH^-] + a_2[OH^-]^2)}{(1 + a_3[OH^-])^m} \quad [S]^m \quad (3.18)$$

Eq. 3.18 describes the reported kinetics of the bimolecular (m = 2) disproportionation (Cannizzaro reaction) of formaldehyde as well as those of the three dicarbonyls above.

The correlation between coefficient $a_3$ and substrate acidity is often considered obvious, and where titrimetric determinations of carbonyl dissociation constants have been made the observed disproportionation rates have been corrected for ionized substrate, based on the mechanism to be described. The reported "observed" rates in that case correspond to the numerator terms of Eq. 3.18. For formaldehyde, the equivalent of coefficient $a_3$ was also determined kinetically to be in adequate agreement with the same parameter determined titrimetrically.

However, the general expression above is perhaps to be preferred. Not only does it relate directly the observed or calculable quantities, but it
also serves to remind one of the assumptions that have to be made in any mechanistic interpretation. As was shown in Sec. 3.2, the relation between coefficient $a_3$ and substrate acidity need not be as simple as has been assumed. In fact, it should be borne in mind that carbonyl compounds may often ionize in several ways.

In the subsections to follow, the observed kinetics of the carbonyls above will first be compared empirically — that is, devoid of any mechanistic interpretation. In Sec 3.3.2, the source of the disagreement between these findings and those previously reported by Salomaa$^2$ and by Arcus and Jackson$^{82}$ will be explained. Then, in Sec. 3.3.3, a kinetic model for the disproportionation of glyoxal in terms of rate-determining intramolecular hydride ion transfer will be developed. In Sec. 3.3.4, speculations about the hypothesized kinetic parameters for glyoxal in relation to analogous quantities for related carbonyls will be presented. In Sec. 3.3.5, the proposed kinetic model will be extended to high concentrations of substrate and alkalinity — conditions experimentally inaccessible in this work. Finally, in Sec. 3.3.6 the role of glyoxal as an intermediate in the oxidation of glycolaldehyde will be briefly summarized. It is hoped that the relations presented might be of help in the planning and analysis of experiments should it be desired to investigate the reaction under those conditions.

3.3.1. **Empirical comparison with related carbonyl compounds**

For comparative purposes, values of the rate coefficients $a_1$, $a_2$, and $a_3$ assignable to glyoxal and the related carbonyls above are listed in Table 3.8. The corresponding modelled hydroxide ion dependencies, based on
Table 3.8. Modelled kinetic parameters following Eq. 3.18 for the disproportionation of glyoxal and related compounds (S) in aqueous NaOH at 1M substrate

<table>
<thead>
<tr>
<th>Substrate (S)</th>
<th>Molecularity in S</th>
<th>Rate Coefficients</th>
<th>Isokinetic Point, mM</th>
<th>Maximum Order in [OH⁻]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$a_1$, s⁻¹ M⁻¹</td>
<td>$a_2$, s⁻² M⁻²</td>
<td>$a_3$, M⁻¹</td>
</tr>
<tr>
<td>Glyoxal (25°C)</td>
<td>1</td>
<td>0.144 + 0.003</td>
<td>400 ± 4</td>
<td>40.6 ± 0.8</td>
</tr>
<tr>
<td>Methylglyoxal (25°C)</td>
<td>1</td>
<td>0.059 ± 0.001</td>
<td>40 ± 3</td>
<td>424 ± 32</td>
</tr>
<tr>
<td>Phenylglyoxal (35°C)</td>
<td>1</td>
<td>0.073 ± ?</td>
<td>22.6 ± ?</td>
<td>247 ± 17d</td>
</tr>
<tr>
<td>Formaldehyde (40°C)</td>
<td>2</td>
<td>0.000335 ± ?</td>
<td>0.0090 ± ?</td>
<td>3.33 ± 17d</td>
</tr>
</tbody>
</table>

\[ \text{[OH}^\text{−}]_{\text{isokinetic}} = \frac{a_1}{a_2}, \]

\[ n_{\text{max}} = 2\{1 + [a_1 a_3/a_2]^{1/2}\}^{-1} \quad (\text{except formaldehyde}). \]

\(^{c}\text{Unpublished results.}\)

\(^{d}\text{Determined by titrimetry.}\)

\(^{e}\text{Determined using Eq. 3.19b.}\)
Eq. 3.18, are plotted in Fig. 3.8. It must be emphasized that these curves, each of which represents the first-order disproportionation rate at unit substrate concentration, are in some regions gross extrapolations from alkalinites at which kinetics were observed, and are intended only to illustrate the basic similarities and differences in the kinetics of the three types of carbonyl compounds. As may be seen in Table 3.8, the kinetic response of methylglyoxal at 25°C is quite similar to that reported for phenylglyoxal at 35°C and, therefore, the former has been excluded from Fig. 3.8 for clarity. Finally, it should be pointed out that the coefficients listed in Table 3.8 were obtained at slightly different temperatures. It is unlikely, however, that the basic features of Fig. 3.8 would be altered if data were available to plot all three functions at a common temperature.

There are several interesting features apparent in Fig. 3.8. The first concerns the similar rates predicted for the three dicarbonyl compounds at very low alkalinity (pH < 10). Although this is perhaps not unexpected for the two substituted glyoxals, in view of the presumed similar electronic effects of the methyl and phenyl groups on the two-carbon carbonyl moiety, it is not so immediately obvious why glyoxal should also behave similarly, considering its unique structure. According to Eq. 3.18, the disproportionation rate at low alkalinity is determined solely by coefficient $a_1$. The above phenomenon will be discussed in terms of the hydride ion transfer model in Sec. 3.3.4.

Listed also in Table 3.8 are the predicted maximum orders $n_{\text{max}}$ with respect to $[\text{OH}^-]$ for the four carbonyls considered. These values were obtained from Eqs. 3.19a and 3.19b:
Fig. 3.8. Rates of disproportionation of glyoxal (25°C), phenylglyoxal (35°C), and formaldehyde (40°C) as a function of $[\text{OH}^-]$ at 1.0M substrate. Isokinetic points (•) are indicated.
for \( m = 1 \) and \( m = 2 \), respectively. The value \( a^* \) in the above equations denotes the dimensionless ratio of rate coefficients \( a_2/a_1a_3 \). The derivation of Eqs. 3.19a,b is outlined in Sec. 7.2.

Also listed in Table 3.8 are values for the isokinetic point \([\text{OH}^-]_{\text{iso}}\), herein defined as that alkalinity at which the reaction proceeds equally via pathways first- and second-order in hydroxide ion — \( m + 1 \) and \( m + 2 \) overall. In contrast to \( n_{\text{max}} \), the isokinetic point is independent of coefficient \( a_3^* \), and is given by \([\text{OH}^-]_{\text{iso}} = a_1/a_2^* \). In terms of Eq. 3.18, both pathways are equally effected by dissociation of the neutral substrate.

Perhaps the most striking feature of Fig. 3.8 is the high maximal kinetic order in hydroxide ion exhibited by glyoxal. It is evident from Eqs. 3.19a that \( n_{\text{max}} \) increases with decreasing \( a_1a_3^*a_2^* \), and thus the high maximal hydroxide order of glyoxal is due to the low isokinetic point coupled with a relatively low effective acidity \( K_{\text{eff}} \), which is assumed equal to \( a_3^*K_w^* \). In terms of the mechanism to be presented, doubly dissociated glyoxal monohydrate influences the reaction rate before sizable proportions of even singly dissociated forms are present.

A third important feature of Fig. 3.8 is the near perfect first-order response predicted for phenylglyoxal (and methylglyoxal) at \( 35^\circ C \) at any alkalinity. In terms of the empirical model \((m = 1)\), a pure first-order
response is observed if the isokinetic point is exactly equal to the half-titration point for the dicarbonyl; that is, when $a_1/a_2 = a_3^{-1}$. Because coefficients $a_1$, $a_2$, and $a_3$ can in general be expected to have different thermal sensitivities, for cases where $a_1a_3/a_2$ is approximately equal to unity there is likely to be a particular temperature at which the above criterion is met exactly. For methylglyoxal, a purely first-order hydroxide dependence is predicted at approximately 40°C. It should also be noted that for $[\text{OH}^-]_{iso} > a_3^{-1} (a_1a_3/a_2 > 1)$ a minimum kinetic order in $[\text{OH}^-]$ is predicted with a value less than unity. This, in fact, has been observed for the disproportionation of methylglyoxal at 48°C.

An important, yet easily overlooked, consequence of the above relationship is the fact that two totally different mechanistic regimes might be indistinguishable by kinetic determinations of order with respect to $[\text{OH}^-]$. If this is in fact the case, the thermal properties and kinetic salt effects at one extreme of alkalinity might very well be substantially different from those evident at the other extreme. This points up the importance of 1) extending kinetic studies over as broad a temperature range as possible, and 2) checking kinetic salt effects near the extremes of observable alkalinitities. The above arguments are of course general, applying to any kinetic system in which similar preequilibria might be considered possible.

Failure to observe the above precautions may lead to promulgation of meaningless or at least misleading kinetic results. The problem is exacerbated if results of low accuracy are relied upon, in which case deviations from linear Arrhenius-type plots, taken from data collected at a single alkalinity, or peculiarities in kinetic salt effects might easily be
overlooked. This was precisely the case with Fedoronko's study of methyl-glyoxal, in which the shift to a third-order mechanism at higher alkalinities was not detected and in which an erroneous "composite" activation energy and kinetic salt effect were reported.

Because rate coefficients $a_1$, $a_2$, and $a_3$ are distinct functions of temperature and ionic strength, both $[\text{OH}^-]_{\text{iso}}$ and $n_{\text{max}}$ should be expected to vary with temperature and ionic strength. With glyoxal, the differences in apparent activation energies $E_a$ are quite marked, as may be seen in Table 3.3. Furthermore, the strong positive salt effect of coefficient $a_2$ predicts a roughly two-fold decrease in $[\text{OH}^-]_{\text{iso}}$ as ionic strength is increased from $\nu \to 0$ to 0.1M. However, the predicted effects of temperature are considerably greater. The effects of temperature at $\nu = 75\text{mM}$ on both $[\text{OH}^-]_{\text{iso}}$ and on the hydroxide ion concentration at which $n = n_{\text{max}}$ designated $[\text{OH}^-]_{n_{\text{max}}}$ and equal to $(a_1/a_2a_3)^{1/2}$ -- are indicated in Fig. 3.3. Values of $[\text{OH}^-]_{\text{iso}}(\text{M})$ and $n_{\text{max}}$ can be calculated as functions of $T(\text{K})$ and $\nu(\text{M})$ using Eqs. 3.20 and 3.21 below, wherein $A(T)$ represents the Debye-Huckel solvent parameter $A$ (a function of temperature) and $R = 0.008314$ kJ/molK:

$$[\text{OH}^-]_{\text{iso}} = 7240\exp(-40.25/RT)\exp_0[-2A(T)\nu^{1/2}/(1 + \nu^{1/2}) - 0.47\nu] \quad (3.20)$$

$$n_{\text{max}} = 2[1 + 108\exp(-16.12/RT)\exp_0[-A(T)\nu^{1/2}/(1 + \nu^{1/2}) - 0.24\nu]}^{-1} \quad (3.21)$$

Due to the high apparent $E_a$ of coefficient $a_1$, the third-order character of glyoxal disproportionation decreases markedly with temperature. At an
ionic strength of 75mM, the predicted \([\text{OH}^-]_{iso}\) can be seen to increase from 0.11mM at 5°C to 4.2mM at 80°C. At the same ionic strength, \(n_{\text{max}}\) decreases from 1.86 at 1.49mM \([\text{OH}^-]\) at 5°C to 1.51 at 13.1mM \([\text{OH}^-]\) at 80°C.

The disproportionation kinetics of formaldehyde differ notably from those of the dicarbonyls in at least two respects. First, the reaction rate (at unit molarity) at low alkalinity obtained by extrapolation is more than 200-fold slower than that for phenylglyoxal and more than 1000-fold slower than that for glyoxal. Second, although showing second-order character at \(n_{\text{max}}\), the hydroxide ion dependence is considerably more influenced by ionization of substrate as a result of the squared denominator in Eq. 3.18. Thus, even in the absence of significant proportions of dianionic forms the reaction rate should tend toward a zero-order dependence on \([\text{OH}^-]\) at high alkalinity. In fact, were methylene glycol not so weakly acidic, a tendency toward a second-order inhibition by hydroxide ion would be predicted at very high alkalinity.

### 3.3.2. Correlation with previous kinetic studies

The kinetic findings reported in Sec. 3.2 are in obvious contradiction with those presented by Salomaa\(^2\) in 1956. On examination, several major flaws are apparent in Salomaa's work. From an experimental viewpoint, the molecularity with respect to hydroxide ion was determined by the relative constancy of calculated second- and third-order integral rate constants. This is at best a marginal method. Furthermore, the reaction was followed over a very narrow range of alkalinity (5 to 14mM). From a theoretical point of view, Salomaa ignored the probable effects of substrate dissociation in the calculation of the above rate constants.
Although Salomaa did note a strong positive salt (NaCl) effect characteristic of reactions between ions of like charge, the magnitude of the effect was much less than that predicted by the application of Debye-Huckel theory, a finding Salomaa dismissed as due to the inapplicability of that theory to such like-charged systems. It appears more likely, however, that the anomalous salt effect was caused by the intermediate (and varying) hydroxide molecularity at the experimental conditions employed. In fact, the Debye-Huckel theory should satisfactorily describe the third-order glyoxal system, provided that multivalent ions of opposite charge (as for example Ca$^{2+}$ or Mg$^{2+}$) are not present. The latter cases have been discussed by Davies$^{94}$, in terms of "ion-pairing" effects, and by Perlmutter-Hayman$^{95}$, and are the physical situations to which the Debye-Huckel theory was not intended to apply. Nonetheless, in the case of glyoxal in NaOH/NaCl solutions, the agreement between the salt effect shown in Fig. 3.5 and that predicted by the Debye-Huckel theory is quite consistent.

Similarly, the values of the thermal properties reported by Salomaa$^{82}$ ($E_a = 76$ kJ/mol, $\Delta S^\neq = +21.2$ cal/molK) are approximately midway between the corresponding values reported in Table 3.3 for the second- and third-order reactions. Because of these problems, Salomaa's lengthy discussion of probable mechanisms can not be justified, at least on the basis of his reported results.

Salomaa's kinetic findings were echoed by Arcus and Jackson$^{82}$ in 1964, in a report on the accelerating effect of polymeric quarternary hydroxide on the disproportionation of glyoxal. Again, the reaction was reported to follow third-order kinetics. Although borrowing, essentially intact, Salomaa's kinetic method and initial conditions, $[\text{OH}^-] = 2.9$ mM, and suf-
fering from an even greater paucity of data, Arcus and Jackson nevertheless noted a "somewhat greater" third-order rate constant (260 vs. 160 s\(^{-1}\) M\(^{-2}\)) in NaOH solution than had been reported by Salomaa. Unfortunately, the cause of the reported discrepancy was not further investigated.

Very recently, a second opportunity to test Salomaa's findings was missed. Vuorinen\(^7\) verified a pseudo-first-order dependence on glyoxal at the single experimental conditions of 5mM NaOH and 25°C, but thereafter elected to assume as correct Salomaa's second-order hydroxide ion dependence.

3.3.3. Kinetic model of the disproportionation of glyoxal

The kinetic results described in Sec. 3.2 are totally independent of any mechanistic interpretation; their validity rests solely on the accuracy of the kinetic data obtained and the fit of that data to the empirical model chosen. However, to gain insight into the chemical processes involved and to allow more meaningful comparisons with or extensions to related compounds and reactions, it is useful to model the preceding results in terms of hypothesized elementary reactions. In view of the close fit of the kinetic results to the empirical model, Eq. 3.18, any such potential mechanism must be consistent with that model without relying on unreasonable assumptions about individual reaction steps. Admittedly, such assumptions cannot be made totally without risk.

The mechanism to be developed for glyoxal is analogous to those currently in favor for a variety of closely related compounds. No doubt many other mechanisms capable of describing the observed kinetics can be envisioned. However, the mechanism derived herein has proven adequate at
explaining virtually all observed phenomena and is, furthermore, in qualitative agreement with known aspects of the chemistry of aldehydes in aqueous solution.

The starting point for the development to follow is the hypothesis that the rate of glyoxal disproportionation is governed by the rate of intramolecular hydride ion transfer (or shift) from the carbon atom of a hydrated carbonyl moiety (migration origin) to the carbonyl carbon of an unhydrated carbonyl moiety (migration terminus), as represented below for a singly dissociated dicarbonyl:

\[
\begin{array}{c}
\text{OH} \\
\text{H:} \quad \text{C—O}^-
\end{array}
\xrightarrow{\text{migration origin}}
\begin{array}{c}
\text{OH} \\
\text{C==O}
\end{array}
\]

\[
\begin{array}{c}
\text{H:} \quad \text{C—O}^-
\end{array}
\xrightarrow{\text{migration terminus}}
\begin{array}{c}
\text{C==O} \\
\text{R}
\end{array}
\]

Discounting the significance of any trace concentrations of positively charged or zwitter-ionic species above pH 10, such a transfer is possible intramolecularly only from glyoxal monohydrate, monohydrate anion, or monohydrate dianion. With these assumptions, the actual disproportionation becomes simply the sum of several true first-order molecular decompositions, as represented in Eq. 3.22:

\[
-d[G_{\text{r}}]/dt = k_o [M] + k_1 [M^-] + k_2 [M^{2-}] \quad (3.22)
\]

Unfortunately, this rate expression is expressed in terms of concentrations that are neither observable (at least in these experiments) nor
independently variable. It thus becomes necessary to describe the above rate expression in terms of a minimum number of independent variables (concentrations). The inevitable complexity of the resulting rate expression is therefore an artifact of the resulting manipulations. The choice of hydroxide ion concentration as an independent variable is, however, justified on the grounds that it allows comparison with other similar systems at standardized conditions.

Before Eq. 3.22 can be put in the desired form, additional assumptions must be made about the chemical system. These include the assumptions that all appropriate proton-exchange reactions and all hydration/dehydration reactions are rapid relative to the above rate-determining step. The former is almost certainly true and the latter, while more demanding, is also judged reasonable on the basis of observed rates at neutral pH and the generally observed base-dependence of equilibrium addition reactions. Finally, all rate and equilibrium constants will, in the interest of simplicity, be presented on a molecular basis rather than on a functional group basis. That is, the symmetry of glyoxal is ignored. For example, Eq. 3.22 represents twice the rate that would be observed for a particular "labeled" carbon.

By making the assumptions that were described above, it becomes possible to rewrite the hypothesized rate expression in terms of equilibrium constants that reflect the interconversion of glyoxal species known or presumed to exist in alkaline solution. In the interest of brevity, the pertinent equilibrium relations are defined in Tables 3.9a,b in terms of the concentrations of the species depicted in Fig. 2.1. The activity coefficients \( \gamma_i \) represent the products (quotients) of all individual
Table 3.9a. Defining relationships following Fig. 2.1 for equilibrium constants of glyoxal addition reactions assumed rapid relative to hydride ion transfer

<table>
<thead>
<tr>
<th>Reaction</th>
<th>Thermodynamic ( a ) Constant</th>
<th>Concentration ( a, b ) Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydrations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K'_{h1} )</td>
<td>( \frac{[M]}{[G]^a_{H2O}} )</td>
<td>( K_{h1} = \frac{K'_{h1}}{[G]} )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \frac{[G]^a_{H2O}}{\Gamma_{h1}} )</td>
</tr>
<tr>
<td>( K'_{h2} )</td>
<td>( \frac{[M]^a_{H2O}}{[M]} )</td>
<td>( K_{h2} = \frac{K'_{h2}}{[M]} )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \frac{[D]}{[G]^a_{H2O}} )</td>
</tr>
<tr>
<td>Dimerization</td>
<td>( K'<em>{Di} = \frac{[G</em>{2i}]}{[M]^2} )</td>
<td>( K_{Di} = \frac{K'<em>{Di}}{\Gamma</em>{Di}} )</td>
</tr>
<tr>
<td></td>
<td></td>
<td>( \frac{[G_{2i}]}{[M]} )</td>
</tr>
</tbody>
</table>

\( a \) \( \Gamma_i \) denote composite of individual activity coefficients.

\( b \) Assumed approximately constant in dilute solution ([G\( _i \) < 1M) at constant low ionic strength (\( \mu < 0.1M \)).

\( c \) For the i-th dimeric form.
Table 3.9b. Defining relationships following Fig. 2.1 for equilibrium constants of acid-base reactions assumed rapid relative to hydride ion transfer

<table>
<thead>
<tr>
<th>Hydrate Form</th>
<th>Thermodynamic Constant</th>
<th>Concentration Constant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monomeric monohydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K_{m1} )</td>
<td></td>
<td>( K_{ml} )</td>
</tr>
<tr>
<td>( K_{m2} )</td>
<td></td>
<td>( K_{m2} )</td>
</tr>
<tr>
<td>Monomeric dihydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K_{d1} )</td>
<td></td>
<td>( K_{d1} )</td>
</tr>
<tr>
<td>( K_{d2} )</td>
<td></td>
<td>( K_{d2} )</td>
</tr>
<tr>
<td>Dimeric dihydrate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>( K_{Didj} )</td>
<td></td>
<td>( K_{Didj} )</td>
</tr>
</tbody>
</table>

\( a \) \( \Gamma_i \) denote composite of individual activity coefficients.

\( b \) \( K'_{w} = [H_3O^+] [OH^-]^{a-2}_w / \Gamma_w = [H_3O^+] [OH^-] \).

\( c \) Assumed approximately constant at constant low (\( \mu < 0.1M \)) ionic strength.

\( d \) For \( j \)-th dissociated form of dimer \( i \).
coefficients involved. The equilibrium constants are self-defining. Table 3.9a defines equilibrium constants for equilibrium addition reactions and Table 3.9b defines acid-base dissociation constants.

If the physical restrictions of dilute solutions of constant low ($\mu < 0.1M$) ionic strength are imposed, the activity coefficients and the activity of water may be combined within concentration equilibrium constants, as indicated in the simplified expressions in Tables 3.9a,b. Because the above restrictions were met in all the experiments conducted (except those involving kinetic salt effects), the simplified equilibrium relations will be employed except where otherwise noted.

Included in these two tables are equilibrium constants involving "i" neutral dimeric forms $C_2^i$, at least two of which are believed present in significant proportions at glyoxal concentrations above 10mM (as noted in Sec. 2.2). Furthermore, because each dimer contains two hemiacetal and in some cases two gem-diol hydroxyl moieties, it can be assumed by analogy with related carbonyls that each dimer might exist in "j" dissociated forms interrelated by acid dissociation constants $K_{D_{idj}}$. Although the kinetic development to follow applies only to dilute glyoxal solutions (less than 10mM) in the absence of significant concentrations of dimeric forms, an extension hypothesized valid to ~1M is presented in Sec. 3.3.5.

Unfortunately, of the ten equilibrium constants identified in Tables 3.9a,b, only $K_w$ and the combination $K_D(1 + K_{h2})^{-2}$ (see Sec. 4.2.2) are accurately known over a range of temperature. However, a rough estimate purportedly for $K_{h1}K_{h2}$ has been published, and estimates to within several orders of magnitude can be made for some of the other constants — estimates of sufficient accuracy to judge their relative importance.
The concentrations of the two ionic glyoxal forms can be eliminated from Eq. 3.22 by using the appropriate equilibrium expressions from Table 3.9b. The resulting expressions, Eqs. 3.23 and 3.24,

\[
[M^-] = K_{m1}K_w^{-1}[OH^-][M] \quad (3.23)
\]
\[
[M^{2-}] = K_{m1}K_{m2}K_w^{-2}[OH^-]^2[M] \quad (3.24)
\]

when substituted into Eq. 3.22 yield the following rate expression in terms of \([OH^-]\) and \([M]\):

\[
-d[G^l]/dt = (k_o + k_{1m}K_w^{-1}[OH^-] + k_{2m}K_{m2}K_w^{-2}[OH^-]^2)[M] \quad (3.25)
\]

However, Eq. 3.25 above cannot be used directly because it is the total concentration of all glyoxal forms \([G_T]\) that is experimentally observed, and not the concentration of neutral monohydrate.

The total glyoxal concentration can readily be obtained by carbon balance. On the basis of the assumptions made to this point, the following expression for \([G_T]\) should be valid at total concentrations less than \(\sim 1\)M:

\[
[G_T] = [G] + [M] + [M^-] + [M^{2-}] + [D] + [D^-] + [D^{2-}] + [D^{*2-}] + 2[G_2] + 2[G_2^-] \quad (3.26)
\]

The last two terms of Eq. 3.26 represent the total concentrations in monomer equivalents of all neutral and anionic dimers. Additional assumptions are warranted, however. At glyoxal concentrations less than 10mM the proportions of dimeric forms should be negligible, barring any unusually
acidic character (pKₐ's ranging from 12.1 to 12.7 were reported for the hemiacetal hydroxyl moieties of a variety of pentoses and hexoses⁹⁶). Furthermore, at the moderate hydroxide concentrations used in these experiments ([OH⁻] < 0.1M), it is also doubtful that doubly dissociated forms would be quantitatively significant. Finally, the high degree of hydration reported for glyoxal makes it very unlikely that unhydrated glyoxal would be present in significant proportions. The above assumptions result in the following simplified expression for [Gₜ]:

\[
[Gₜ] = [M] + [D] + [M⁻] + [D⁻]
\] (3.27)

Once the various terms are written as functions of the concentration of neutral monohydrate, [M] can then be expressed in terms of [Gₜ] as in Eq. 3.29:

\[
[M] = [Gₜ] \{1 + K_{h2} + (K_{m1} + K_{h2}K_{d1}K_w)K_w^{-1}[OH^-]\}^{-1}
\] (3.29)

Substitution of Eq. 3.29 into Eq. 3.25 with kₒ = 0 gives the desired rate expression in terms of [Gₜ] and [OH⁻]. Division by 1 + K_{h2} then produces an expression which, despite its unwieldy appearance, is identical in form to Eqs. 3.4 and 3.18 (with m = 1):
If the final assumption that $K_h^2 \gg 1$ is made, Eq. 3.30 reduces to

\[
\frac{-d[G_T]/dt}{[G_T]} = \frac{k_1K_m^1[OH^-] + k_2K_m^1K_m^2[OH^-]^2}{(1 + K_h^2)K_w} [G_T] \quad (3.30)
\]

Although this last assumption is less easily supported than those preceding it, it is consistent with Whipple's failure to observe evidence of free carbonyl groups in a $C_{14}$-NMR study of aqueous glyoxal and with the high degree of hydration (> 95%) observed for related monocarbonyl compounds. Thus, it seems safe to assume glyoxal to be substantially dihydrated at near ambient conditions, and so errors resulting from the use of Eq. 3.31 should be minimal.

If the kinetic mechanism above is to agree with the experimentally observed results, it is clear that the rate of disproportionation by neutral glyoxal monohydrate must be negligible, at least under the observed conditions; that is, $k_0 \ll k_1K_m^1K_w^{-1}[OH^-]$. The correspondence between the rate and equilibrium constants of Eqs. 3.30 and 3.31 and the empirical rate constants reported in Sec. 3.2 is indicated in Table 3.10. The resulting kinetic model is depicted in Fig. 3.9.

At this point, it should be noted that Eqs. 3.30 and 3.31 express
Table 3.10. Correspondence between hypothesized molecular parameters and empirical rate coefficients $a_1$, $a_2$, and $a_3$ for glyoxal and related carbonyls in terms of rate-limiting hydride ion transfer.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Rate Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$a_1$</td>
</tr>
<tr>
<td><strong>Dicarbonyls:</strong></td>
<td>$k_1 k_{m1} k_{w}^{-1} (1 + K_{h2})^{-1}$</td>
</tr>
<tr>
<td>Glyoxal</td>
<td>$k_1 k_{m1} k_{w}^{-1} k_{h2}^{-1}$</td>
</tr>
<tr>
<td>($K_{h2} \gg 1$)</td>
<td>($K_{h2} \gg 1$)</td>
</tr>
<tr>
<td>Methylglyoxal</td>
<td>$k_1 k_{m1} k_{w}^{-1} (1 + K_{h2})^{-1}$</td>
</tr>
<tr>
<td>($K_{h2} K_{d1} \ll K_{m1}$; $K_{h2} = 1, 2$)</td>
<td>($K_{h2} K_{d1} \ll K_{m1}$; $K_{h2} = 1, 2$)</td>
</tr>
<tr>
<td><strong>Monocarbonyls:</strong></td>
<td>$k_1 k_{m1} k_{h}^{-1}$</td>
</tr>
<tr>
<td></td>
<td>$k_1 k_{m1} k_{h}^{-1}$</td>
</tr>
</tbody>
</table>
Fig. 3.9. Hypothesized hydride ion-transfer rate-determining mechanism for the alkaline disproportionation of dilute aqueous glyoxal
coefficient $a_3$ as functions of $K_{ml}$, $K_{dl}$, and $K_{h2}$. The functionalities representing $a_3$ can be shown to be equal to $K_{eff}/K_w$ and are the same values that would be obtained by independent titration, if the assumption is made that no additional ionized forms are present in significant proportions. Note that the effective acidity of glyoxal need not bear any resemblance to either $K_{ml}$ or $K_{dl}$.

The equilibrium constants in Tables 3.9a,b each contain embedded activity coefficients, which to this point have been assumed approximately constant at constant ionic strength. It is evident from the defining relations in Table 3.9b that only $K_{m2}$ would be expected to be sensitive to ionic strength. This is more clearly indicated when the expression for $K_{m2}$ is written in terms of the individual activity coefficients and the thermodynamic equilibrium constant $K'_{m2} = K_{m2}(\mu \to 0)$, as in the following equations:

$$K_{m2} = \frac{K'_{m2}}{\Gamma_{m2}}$$

where

$$\Gamma_{m2} = \frac{\gamma_{M2}}{(\gamma_{M} - \gamma_{OH-})}$$

If the Debye-Hückel theory is assumed to apply (for $\mu < 0.1 M$), the effect of ionic strength on the individual activity coefficients is given approximately by Eq. 3.33,

$$-\log_{10} \gamma_t = Az_t^2 \mu^{1/2} (1 + a^* B \mu^{1/2})$$

where $A$ and $B$ are temperature-dependent parameters, $a^*$ is an ion-size
parameter and $z_i$ denotes the charge associated with ion "i". While extremely high accuracy cannot be expected (since $a^*$ is undefined in mixed electrolytes), if an "average" $a^*$ is used the following general variation with $u$ is to be expected for $K_{m2}$:

$$K_{m2}(u) = K_{m2}(u \rightarrow 0) \exp_{10}[2A(T)u^{1/2}(1 + B(T)a^*_{1/2})]$$

(3.34)

A strong positive salt effect on $k_{obs}$ would then be predicted under conditions at which the reaction proceeds primarily via the monohydrate dianion, that is, where $k_{m2}K_{w}^{-1}[OH^-] >> k_1$. This effect is a secondary salt effect because it arises not from the influence of ionic strength on a rate-determining bimolecular step, but rather from that on the equilibrium constant of a species with which the reacting species is assumed to be in rapid equilibrium. Of course, the same net effect, albeit a primary salt effect, would be predicted were the rate-determining step assumed to be the bimolecular reaction between a hydroxide ion and a monohydrate anion.

The activity coefficients associated with rate coefficients $a_1$ and $a_2$ should effect only the weak (and generally negative) salt effects caused by interactions between neutral species and between neutral species and singly charged ions. It appears therefore that the salt effects predicted by either Eqs. 3.30 or 3.31 are consistent with the observed kinetic salt effect, as, of course, would be those of any mechanism of the same form as the empirical model.
3.3.4. **Implications of the kinetic model**

With each of the four carbonyl compounds considered in Sec. 3.3.2 the hypothesis of rate-determining hydride ion transfer gives rise to kinetic expressions of the form of Eq. 3.18. In Table 3.10 are listed the empirical rate coefficients \(a_1\), \(a_2\), and \(a_3\) in terms of kinetic constants for rate-determining hydride ion transfer and appropriate equilibrium constants. It can be seen therein that the disproportionation of dicarbonyls is complicated by the presence of both monohydrated and dihydrated forms, while the Cannizzaro reaction of formaldehyde is complicated by the second-order nature of the actual disproportionation. A brief development of the model for the reaction of formaldehyde is presented in Sec. 7.3.

It should be noted that in the expressions for the monosubstituted glyoxals, methyl- and phenylglyoxal, it is implicitly assumed that no significant reaction via methyl- or phenyl-group transfer takes place. Such transfers are believed to occur during benzilic acid-type disproportionations of di-substituted glyoxals, but should be of little consequence with monosubstituted glyoxals, in part because transfer must in that case be effected from substrate singly-hydrated at the 2-carbon. It should be safe to assume that significant proportions of such hydrate forms are not present, based on general hydration chemistry and the ketonic nature of the 2-carbon carbonyl moiety. With the above assumptions, then, \(K_{h_2}\) for monosubstituted glyoxals refers to hydration at the 2-carbon of the 1-carbon hydrated form, as below:
\[
\begin{align*}
\text{H} & \quad \text{OH} & \quad \text{OH} \\
\text{C}=\text{O} & \quad \text{K}_{\text{hl}} & \quad \text{H-}\text{C-OH} & \quad \text{K}_{\text{h2}} & \quad \text{H-}\text{C-OH} \\
\text{C}=\text{O} & \quad \text{H}_2\text{O} & \quad \text{C}=\text{O} & \quad \text{H}_2\text{O} & \quad \text{HO-C-OH} \\
\text{R} & \quad \text{R} & \quad \text{R} & \quad \text{R} \\
\end{align*}
\]

where

\[ R = \text{CH}_3, \text{C}_6\text{H}_5 \]

It should be mentioned that although the same products would be formed via R-group transfers, a totally different set of kinetic and thermodynamic constants would be required to describe the alternative kinetic pathways.

One additional complication is encountered with methylglyoxal. The presence of enolizable hydrogens on the methyl group render the compound highly susceptible to bimolecular aldolization reactions. Although the reaction proceeds quite readily, in that aldolization appears significantly competitive with disproportionation at concentrations above \(1\text{M}\), the dissociation constant for enolization \(K_e\) is assumed to be too low to influence coefficient \(a_3\), which is obtained at low substrate concentrations.

With the above qualifications in mind, some speculation about the relative values of the presumed intrinsic rate constants can be presented. None of the four carbonyl compounds considered have provided any kinetic evidence of significant proportions of doubly-ionized forms, at least not at the alkalinitites investigated. For that reason, the intrinsic rate constant \(k_2\) can not be distinguished kinetically from \(K_{m2}\) and little can be said about the relative value of \(k_2\) as a function of chemical structure.

The situation is somewhat different for the rate constant \(k_1\). In the case of formaldehyde, a value for \(K_1/K_w\) can be assigned directly from
coefficient $a_3$ and can furthermore be checked against values determined by titrimetry. In addition, the value of $K_h$ has been well-established at $2 \times 10^3$. This allows a reasonably accurate estimate of $k_1$ for formaldehyde to be determined directly.

With methylglyoxal, the empirical coefficient $a_3$ is assumed to represent $K_{ml}^{-1}(1 + K_{h2})^{-1}$, which again reflects the "effective" acidity of the dicarbonyl. This value was determined titrimetrically by Hine and Koser to be $247 \pm 17 M^{-1}$. Although $K_{h2}$ has recently been determined to be 0.24, only the effective acidity above is required to calculate the intrinsic rate constant $k_1$.

With glyoxal, the possible presence of significant proportions of dissociated dihydrate necessitates the use of the general expression in Table 3.10 for coefficient $a_3$. Since three unknowns are related by only a single equation, additional non-kinetic information is required. With assumed values for $K_{ml}$ and $K_{d1}$, minimum values for $K_{h2}$ and for $k_1$ can be assigned to glyoxal based on the kinetic results obtained.

By analogy with the carboxylic acid couples glycolic/lactic acid and acetic/propanoic acid, the effect of methyl (or phenyl) substitution on the acidity of glyoxal monohydrate can be assumed to be very small. On this basis, the value of $K_{ml}/K_w$ for glyoxal monohydrate can be estimated to be equal to or slightly greater than the corresponding value for methyl-glyoxal. The latter value can be obtained from coefficient $a_3$ in Table 3.8 and the reported value for $K_{h2}$ for methylglyoxal.

At this point, a minimum for $K_{h2}$ for glyoxal could be obtained by assuming the dihydrate to be non-acidic, i.e. $K_{d1} = 0$. That minimum value of $-12$ is unnecessarily restrictive, however, since the dihydrate should be
at least as acidic as 2 times $K_1/K_w$ for formaldehyde, a value of $5M^{-1}$. Thus, $K_{d1}/K_w$ should be greater than $10M^{-1}$. Actually, while glyoxal dihydrate should be less acidic than the monohydrate, the two carbon dihydrate would be expected to dissociate more readily than formaldehyde. A maximum value of 40 for $K_{d1} > K_{m1}K_w^{-1}$ is established by coefficient $a_3$. In any case, a conservative minimum value for $K_{h2}$ can be set at roughly 17. With a minimum value established for $K_{h2}$, a minimum value for $k_1$ of $4.9 \times 10^{-3} s^{-1}$ can be calculated using the assumed minimum value for $K_{m1}$, the tabulated value for coefficient $a_1$, and the minimum value for $K_{h2}$.

An upper limit on $K_{h2}$ is not so readily available. However, based on the presumption that the gem-diol moiety is less electron-withdrawing than the carbonyl group (as indicated by the relative effects on acidities), a substantially lower value for $K_{h2}$ than for $K_{h1}$ is to be expected. On that basis, a value for the former of $10^{-2}$ to $10^{-3}$ is not unreasonable.

The values obtained for $k_1$ for glyoxal, methylglyoxal, and formaldehyde are listed in Table 3.11 along with corresponding values of $K_{m1}/K_w$ (or $K_1/K_w$) and $K_{h2}$ (or $K_h$). It is apparent from Table 3.11 that hydride ion shift occurs much more readily from the monohydrate monoanion of glyoxal than from methylglyoxal. This is reasonable in terms of what is known about benzilic acid-type rearrangements in general. According to Collins and Eastham, migration is facilitated by electron-withdrawing groups and inhibited by electron-furnishing groups at the migration terminus. In the case of glyoxal and methylglyoxal, the migration origins are, of course, chemically very similar.

A comparison of the intrinsic rate constant for glyoxal with the analogous bimolecular value for formaldehyde at 1M indicates that the gross
Table 3.11. Kinetic and thermodynamic disproportionation constants at 25°C assuming rate-limiting hydride ion transfer

<table>
<thead>
<tr>
<th>Substrate</th>
<th>$k_1 \times 10^3$</th>
<th>$K_{ml} K_w^{-1}$</th>
<th>$K_{h2}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyoxal</td>
<td>4.93 s$^{-1}$</td>
<td>526 M$^{-1}$</td>
<td>$&gt;17^a$</td>
</tr>
<tr>
<td>Methylglyoxal</td>
<td>0.14 s$^{-1}$</td>
<td>526 M$^{-1}$</td>
<td>0.24</td>
</tr>
<tr>
<td>Phenylglyoxal</td>
<td>0.295 s$^{-1}$</td>
<td>247 M$^{-1}$</td>
<td>$&lt;&lt;1$</td>
</tr>
</tbody>
</table>

Formaldehyde        | -----             | 5.3 M$^{-1}$$^b$  | 2000$^c$ |

$^a$ Assuming: $K_{ml}$(glyoxal) = $K_{l}$(methylglyoxal) and $K_{dl} K_w^{-1}$(glyoxal) > 10.

$^b$ $K_l K_w^{-1}$.

$^c$ $K_h^{-1}$. 
difference in disproportionation rate is partially attributable to the much lower acidity of methylene glycol and the assumed higher degree of hydration of formaldehyde. Considering the bimolecular nature of the reaction, the disproportionation actually proceeds quite readily.

Too little is known about the hydration of glyoxal to permit interpretation of the thermal parameters for coefficients $a_1$ and $a_3$ in terms of the kinetic model. If the enthalpy of hydration for glyoxal monohydrate is assumed equal to that for formaldehyde at $-25$ kJ/mol, the value of $-10$ kJ/mol determined for $\Delta H^+$ for $a_3$ together with the enthalpy of ionization for water of $+25$ kJ/mol would yield a value of $+21$ kJ/mol for $\Delta H_{m1}$ or $+46$ kJ/mol for $\Delta H_{d1}$ in the limiting cases where the acidity of glyoxal is presumed due predominantly to monohydrate or dihydrate, respectively. However, neither of these limiting cases appears especially likely.

The obvious conclusion from all of the above speculation is that accurate thermodynamic data for the hydration of simple dicarbonyls as a function of temperature are sorely needed. Reliable estimates of these properties must be available before meaningful conclusions can be drawn about the mechanisms of reactions involving these compounds. It is ironic that reasonably consistent values of $K_n$ for formaldehyde have been obtained many times over.

3.3.5. Extension of the kinetic model to higher substrate concentrations and alkalinities

Based on the disproportionation mechanism proposed for glyoxal in dilute solution and the known dimerization of glyoxal in more concentrated solutions, a general kinetic model predicting the reactivity of glyoxal in
solutions of up to 1M total glyoxal and/or at high alkalinity can be
developed. Although of course largely speculative, the resulting general
equation might nonetheless be of use in the design and analysis of future
kinetic experiments at those more extreme conditions.

The kinetic model developed to this point can not reasonably be
expected to remain valid much above the observed limits of 0.02M total
glyoxal and 0.075M NaOH. Beyond those conditions at least three possible
complications in the kinetic scheme must be considered. These pertain to
the increasing presence of dimeric forms, the possibility of extramolecular
(Cannizzaro) disproportionation, and the possible presence of significant
proportions of dianionic monomers and/or dimers. Above 1M total glyoxal,
the presence of trimeric species and higher-order oligomers would also have
to be considered. Many additional complications are of course conceivable,
but consideration of the basic factors above is probably near the limit of
what is presently experimentally accessible.

If Whipple’s findings\(^\text{16}\) are accepted, the two predominant forms of
glyoxal dimer in aqueous solution are the cis and trans-isomers depicted
in Sec. 4.2.2., although the other cis-form could not be ruled out. These
cyclic structures, containing 5-membered acetal-dihemiacetal linkages,
would not be expected to undergo intramolecular disproportionation, how­
ever, possible involvement in extramolecular reactions and/or the presence
of reactive monohydrate forms are, of course, possible. However, these
will not be considered here. With these simplifications the primary effect
of the neutral dimer on the disproportionation kinetics would be to reduce
the concentration of reactive monomeric forms. If it is further assumed
that any anionic dimers are also unreactive and (for the moment) that the
proportion of any possible dianionic forms is negligible, one is lead to the following expression for total dimer \([G_2]\) in terms of the dimerization constants \(K_{Di}\) and the corresponding acid dissociation constants \(K_{Dij}\) defined previously. Note that each dimer might ionize in several ways:

\[
[G_2] = [M]^2 \sum_i K_{Di} (1 + \sum_j K_{Dij} K_w^{-1} [OH^-])
\]  

Substitution of the above expression into the general mass balance on glyoxal yields an expression for glyoxal monohydrate of the following form:

\[
[M] = -f_2(\text{OH}^-)/2 + [f_2(\text{OH}^-) + 4f_3(\text{OH}^-)[G_T]]^{1/2}/2
\]  

where

\[
\begin{align*}
f_2(\text{OH}^-) &= 1 + K_{h2} + (K_{m1} + K_{h2} K_{d1} K_w^{-1})[\text{OH}^-] \\
f_3(\text{OH}^-) &= \sum_i K_{Di} (1 + \sum_j K_{Dij} K_w^{-1} [\text{OH}^-])
\end{align*}
\]

Of course the form of Eq. 3.37 is independent of whatever dimeric structures are assumed. The above expression for \([M]\), when substituted into the original rate expression with \(k_o = 0\), Eq. 3.38 below,

\[
-d[G_T]/dt = (k_1 K_{m1} K_w^{-1} [\text{OH}^-] + k_2 K_{m1} K_{m2} K_w^{-2} [\text{OH}^-]^2) [M]
\]

\[
= f_1(\text{OH}^-) [M]
\]

yields the desired rate equation in terms of only \([G_T]\) and \([\text{OH}^-]\). The resulting rate expression is represented by the first term on the right side of the rate equation in Table 3.12. Note that \(f_1(\text{OH}^-)\) represents the hydroxide dependence of the intrinsic rate equation, \(f_2(\text{OH}^-)\) represents the
Table 3.12. Hypothesized general rate equation predicting the rate of intra- and extramolecular disproportionation of glyoxal in aqueous solution to unit molarity

\[
-d[G_r]/dt = \frac{2f_1(OH^-)f_2^{-1}(OH^-)[G_r]}{1 + [1 + 4f_3(OH^-)f_2^{-2}(OH^-)[G_r]]^{1/2}} + \frac{4f_1c(OH^-)f_2^{-2}(OH^-)[G_r]^2}{(1 + [1 + 4f_3(OH^-)f_2^{-2}(OH^-)[G_r]]^{1/2})^2}
\]

where

\[
f_1(OH^-) = k_1K_m1K_w^{-1}[OH^-] + k_2K_m1K_m2K_w^{-2}[OH^-]^2
\]

\[
f_{1c}(OH^-) = (k_{1c}K_m1 + k_{2c}K_{d1})K_w^{-1}[OH^-] + (k_{3c}K_m1K_m2 + k_{4c}K_{d1}K_{d2} + k_{5c}K_{d1}K_{d2}K_w^{-2}[OH^-]^2
\]

\[
f_2(OH^-) = 1 + K_{h2} + (K_{m1} + K_{h2}K_{d1})K_w^{-1}[OH^-] + (K_{m1}K_m2 + K_{h2}K_{d1}K_{d2} + K_{h2}K_{d1}K_{d2}K_w^{-2}[OH^-]^2
\]

\[
f_3(OH^-) = 2\{E_{i1}[K_{d1}(1 + \sum_jK_{d1d1}^{-1}[OH^-]) + \ldots \text{ dianionic dimeric forms} \ldots] \}
reduction in rate due to ionization of monomeric glyoxal, and the remaining
function of \( f_2(\text{OH}^-) \), \( f_3(\text{OH}^-) \) and \([G_T]\) represents the reduction in rate due
to the presence of dimeric forms.

A second conceivable complication of disproportionation kinetics in
concentrated solution might be that of an extramolecular disproportiona­
tion, analogous to the Cannizzaro reaction of formaldehyde. The latter
reaction is generally observed only with aryl-monocarbonyls such as
benzaldehyde and only under rather severe conditions. Dicarbonyls undergo
the benzilic acid-type rearrangement while carbonyls with enolizable
alpha-hydrogens undergo second-order aldolizations. Glyoxal, of course,
possesses no enolizable hydrogens and therefore should be free from
enolization-mediated side reactions. However, a Cannizzaro disproportiona­
tion could not be competitive with the intramolecular reaction except at
very high substrate concentrations, and glyoxal monomer concentrations are
limited to roughly 1M because of oligomerization!

Nevertheless, there is no apparent reason why at least a very small
amount of extramolecular disproportionation might not accompany the intra­
molecular reaction in relatively concentrated solutions. The comparison
between the minimum intrinsic rate constant for glyoxal and the correspond­
ing value for formaldehyde at unit molarity indicates that the rate of
hydride ion transfer for the latter is at least roughly comparable at low
alkalinity to that for glyoxal. The anticipated products of glyoxal
Cannizzaro reaction are glycolaldehyde and glyoxylic acid. The former
product possesses enolizable hydrogens and in fact undergoes aldolization
quite readily. However, based on the reported rate of enolization at 25°C,
alcoholization might not be a problem in initial rate studies. Thus,
Cannizzaro disproportionation products might be detectable if suitable specific methods for either of the above compounds are found.

In considering the possibility of Cannizzaro disproportionation, at least one additional set of complications must be considered. Ignoring dimeric forms, the migration terminus would still be glyoxal monohydrate (or free glyoxal). However, the migration origin might conceivably be any of the five anionic monomeric forms — each possessing an intrinsic, bimolecular rate constant \(k_{1c}, k_{2c}, \ldots, k_{5c}\) — although the apparent higher acidity of the monohydrate suggests that those forms might be more reactive.

The general kinetic mechanism can readily be extended to include extramolecular disproportionation. The resulting rate expression for the Cannizzaro reaction is represented by the second term on the right side of Eq. 3.39 in Table 3.12. The development of that expression ignores the possible involvement of dimeric forms and assumes that hydride ion transfer occurs only to unionized monohydrate. The development is otherwise completely analogous to that presented in Sec. 7.3 for formaldehyde.

One final point should be considered in the hypothesized extension represented by Eq. 3.39. Although alkalinites greater than 0.075M were outside the range of the present experimental set-up, the relatively high acidity assumed for glyoxal monohydrate suggests the possible presence of significant proportions of dianionic forms at high alkalinity. Furthermore, it should be noted that the two predominant dimeric forms can ionize at the free carbonyl end or at either of the two hemiacetal hydroxyls — or both.
3.3.6. **Glyoxal as an Intermediate in the Oxidation of Glycolaldehyde**

Glyoxal is believed to be the principal intermediate in the alkaline oxidation of the simple two carbon-hydroxycarbonyl glycolaldehyde. A preliminary HPLC analysis of glycolaldehyde solutions oxidized with complexed \( \text{Cu}^{2+} \) under weakly alkaline conditions at moderately high temperatures indicated a transient accumulation of glyoxal during the oxidation reaction. Although the expected disproportionation product, glycolic acid, was the predominant product observed, it was not the only product detected, even with the relatively insensitive RI detection system employed. The cause of this apparent divergence in the reaction course is presently unexplainable. However, the fact that a transient build-up of glyoxal was observed indicates that at least under some conditions the rates of the oxidation and the corresponding dicarbonyl disproportionation must be comparable. Therefore, it is perhaps worthwhile to briefly correlate the glyoxal disproportionation kinetics just described with recently published kinetic findings on the oxidation of glycolaldehyde with methylene blue.

The oxidation kinetics of glycolaldehyde (hydroxyacetaldehyde) under both acidic and basic conditions were recently reported by Fedoronko, Temkovic, Konigstein, Kovacik, and Tvaroska. Their findings are in agreement with those reported for other hydroxyaldehydes in aqueous solution and can be briefly summarized as follows. At a 1mM initial glycolaldehyde concentration in the presence of millimolar concentrations of methylene blue, the oxidation was zero order in oxidant (methylene blue). At constant alkalinity, maintained by 20 to 60mM NaOH, a pseudo-first-order dependence on substrate was observed, and from the variation of the observed rate constants with alkalinity a first-order dependence on
hydroxide ion concentration was found. Furthermore, the authors found the reaction to be subject to general acid-base catalysis and concluded that the abstraction of a proton from the α-carbon to form the enolate ion was the rate-limiting step in the base-catalyzed reaction. The above kinetic findings are represented by Eq. 3.40, in which $k_e$ designates the enolization-limited kinetic constant for the hydroxide ion catalyzed oxidation:

$$-d[\text{Glycolaldehyde}]/dt = k_e [\text{OH}^-][\text{Glycolaldehyde}] \quad (3.40)$$

A value of 0.089 M$^{-1}$s$^{-1}$ at 25°C was reported for the second-order rate constant, together with an Arrhenius activation energy of 82.9 kJ/mol, obtained over the temperature range of 20 to 40°C.

Kinetically, both the initial oxidation of glycolaldehyde to form glyoxal and the subsequent disproportionation of the latter to form glycolic acid can be considered irreversible. If, for the sake of argument, the oxidation of glycolaldehyde is assumed to proceed quantitatively to glycolic acid, the findings of Fedoronko et al. and those presented here may be combined to predict the accumulation of glyoxal during the oxidation of glycolaldehyde. Specifically, at any constant alkalinity one could consider the overall reaction to consist of two first-order irreversible reactions in series, as represented below,

$$G_A \xrightarrow{k_0} G_B \xrightarrow{k_d} G_C \quad (3.41)$$
wherein $G_A$, $G_B$, and $G_C$ denote the glycolaldehyde reactant, glyoxal intermediate, and glycolic acid product, respectively. The pseudo-first-order rate constants for oxidation and for disproportionation have been denoted as $k_o$ and $k_d$, respectively.

If Fedoronko's results, which covered only a narrow range of experimental conditions, are assumed to be valid over the range of conditions employed in the glyoxal disproportionation studies, the maximum transient accumulation of glyoxal can be predicted as follows. For two reactions in series, the instantaneous concentration of intermediate is conveniently expressed in relative terms as the ratio of the concentrations of intermediate present to substrate originally added, in this case $[G_B]/[G_A]$.

For two irreversible, first-order systems the maximum in the preceding ratio, denoted $[G_{max}]$, is given in terms of the above pseudo-first-order rate constants, $k_o$ and $k_d$, by:

$$[G_{max}] = \frac{k_d}{k_o - k_d}$$

Of course, $k_o$ and $k_d$ can be expressed as functions of alkalinity by Eqs. 3.43 and 3.44, respectively,

$$k_d = (a_1[OH^-] + a_2[OH^-]^2)/(1 + a_3[OH^-]) \quad (3.43)$$
$$k_o = a_e[OH^-] \quad (3.44)$$

where $[OH^-]$ denotes the hydroxide ion concentration and $a_e$ represents the second-order enolization-limited rate coefficient previously designated $k_e$. 
Upon substitution of Eqs. 3.43 and 3.44 into Eq. 3.42, the following equation is obtained for $[G_{\text{max}}]$ as a function of alkalinity:

$$
[G_{\text{max}}] = \frac{a_1 + a_2[OH^-]}{a_e - a_1 + (a_e a_3 - a_2)[OH^-]}
$$

(3.45)

Of course, each of the rate coefficients above is a function of temperature and to a lesser extent of ionic strength.

Values for $a_1$, $a_2$, and $a_3$ can be obtained from 5 to 80°C using the empirical findings presented in Sec. 3.2, while values for $a_e$ can be obtained from the previously cited kinetic parameters reported by Fedoronko et al.\textsuperscript{97} If the unknown, but presumably slight, effects of ionic strength on rate coefficient $a_e$ are ignored (ionic strength was apparently not regulated in Fedoronko's experiments), the maximal relative accumulation of glyoxal can be calculated at any given temperature and alkalinity using Eq. 3.45. The plots depicted in Fig. 3.10 were generated in that manner, using the disproportionation results at $U = 75$ mM.

Because of the complex hydroxide dependence of the disproportionation reaction, the extent to which glyoxal accumulates during the oxidation of glycolaldehyde should be expected to vary greatly with alkalinity. As shown in Fig. 3.10, at low alkalinity the rates of oxidation and disproportionation are sufficiently close that a substantial proportion, roughly 25% at pH 10 and 25°C, of the initial substrate should exist as glyoxal at some point during the oxidation. Furthermore, because the activation energies for enolization and for second-order disproportionation are similar (83 vs.
Fig. 3.10. Predicted maximum relative concentration of glyoxal following Eq. 3.45 during enolization-rate-limited oxidation of glycolaldehyde as a function of hydroxide ion concentration and temperature.
92 kJ/mol), $[G_{\text{max}}]$ at low alkalinity should be relatively insensitive to temperature, decreasing only slightly with increasing temperature. As the alkalinity is increased, however, the maximal accumulation of glyoxal is expected to fall off considerably, as the disproportionation becomes increasingly third-order. Finally, at relatively high pH a bottoming out of $[G_{\text{max}}]$ is predicted, as the disproportionation becomes effectively second-order once again. The predicted $[G_{\text{max}}]$ at 25°C levels out at less than 1%. However, the lower activation energy for $a_2/a_3$ than for coefficient $a_2$ (65 vs. 83 kJ/mol) should result in a greater thermal sensitivity of $[G_{\text{max}}]$ at high alkalinity. Thus, at 80°C $[G_{\text{max}}]$ is predicted to be some five times greater than at 5°C.

Of course, the above predictions are riddled with assumptions. It is assumed, for example, that the kinetic order reported by Fedoronko applies outside the narrow observed range of experimental conditions. For example, at some lower concentration of oxidizing agent, the reaction would no longer be expected to remain zero-order with respect to that substance. At still lower levels of oxidizing agent, a preequilibrium (or steady-state) between enolized and non-enolized glycolaldehyde forms would be anticipated and a hydroxide dependence not unlike that observed for disproportionation, involving dienolate ions, might be envisioned. Such behavior was, in fact, observed in the enolization-mediated "peeling" reaction of cellooligosaccharides reported by Lai and Sarkanen 98,99.

Even if the predictions depicted in Fig. 3.11 are found to be essentially correct, caution should be exercised in discussing the importance of dicarbonyls in hydroxycarbonyl oxidation schemes. A case in point is the reported oxidation of lactaldehyde to lactic acid via methylglyoxal, a set
of reactions also studied by Fedoronko and Konigstein. Although the relative rate of disproportionation was much greater than the rate of oxidation (both reactions are effectively first-order throughout the observed range of alkalinity), the sensitivity of methylglyoxal to aldolization is sufficiently great that even at the $10^{-6}$-$10^{-5}$ M maximal concentrations predicted for typical oxidation conditions significant aldol condensation might be observed.
4. THERMODYNAMIC AND KINETIC ANALYSIS OF THE DIMERIZATION OF AQUEOUS GLYOXAL

The motivation for the following study of glyoxal dimerization arose from a desire to quantitate any possible dimer influence on the disproportionation kinetics described in Sec. 3. During the course of those experiments, the purity of the glyoxal stock solutions was occasionally checked by high pressure liquid chromatographic (HPLC) separation on strong cation exchange resins. Earlier studies of short-chain sugar analogues had shown α-dicarbonyls to be separable from many related hydroxycarbonyls and organic acids by those resins.

Elution profiles obtained with 10 to 40mM glyoxal stock solutions indicated an early eluting "impurity". the magnitude of which, relative to the principal glyoxal peak, appeared to vary with the glyoxal concentration of the solution injected. Further experimentation suggested that this early eluting peak was actually a dimeric form(s) of glyoxal and led also to the hope that, with an appropriate choice of chromatographic conditions, a quantitative separation of the two forms could be obtained. The HPLC method developed thereafter, as well as the thermodynamic and kinetic information eventually obtained for the glyoxal monomer–dimer system, are reported in the subsections to follow.

4.1. Experimental Methods and Materials

Thermodynamic studies of highly reversible systems are complicated by the fact that sufficient kinetic information must first be available to determine when equilibrium has been effectively reached. For the most
part, the thermodynamic findings to be reported were obtained after preliminary kinetic experiments had been undertaken. This allowed the prediction of adequate equilibration times. Furthermore, in most experiments, duplicate or triplicate injections at relatively widely spaced intervals of time were made to check for constancy of results.

4.1.1. Chromatographic separation of dimeric and monomeric glyoxal

The success of the dimerization studies to be described hinged upon quantitative separation of glyoxal monomer from its dimeric form(s). Of course, the interconversion of such forms, as typical equilibrium addition reactions, can be expected to occur relatively rapidly in aqueous solution, even in the absence of added acid or base. Thus, a successful separation must employ conditions at which the respective forms are effectively "frozen" in their original proportions. The chromatographic method by which the above separation was accomplished is probably somewhat unusual. Therefore, a brief description of the method is warranted.

Accepting for the moment the dimeric identity of the above mentioned early eluting peak (experimental evidence for this conclusion will be presented in Sec. 4.2.2), the reasons underlying the rather extreme chromatographic conditions chosen for use in these studies are as follows. Although initial chromatographs obtained with elution at room temperature indicated an ample difference in retention time between the apparent monomer and dimer peaks, the separation appeared incomplete, as evidenced by considerable "smearing" between peaks. Furthermore, although liquid phase chromatographic separations are generally carried out at the highest column temperatures compatible with packing and substrate stability and at
the lowest practicable flow rate (conditions which enhance intraparticle equilibration and hence peak sharpness), it was observed with glyoxal that the apparent resolution actually decreased with increasing elution temperature. Furthermore, this decreased resolution was accompanied by a decrease in the size of the earlier-eluting dimer peak, relative to the principal monomer peak. Elution profiles for a 1M glyoxal solution equilibrated at 25°C as a function of varied elution temperatures are shown in Fig. 4.1. A corresponding negative effect on resolution with decreasing eluent flow rate was also noted and is shown in Fig. 4.2 for elution at 20°C.

The cause of this unusual chromatographic behavior was eventually traced to resin-catalyzed monomerization of the sample dimer as it passed down the column. The driving force for this reaction is the considerable dilution that accompanies chromatographic separations. Further support for the above hypothesis can be found in the kinetic results for dimer hydrolysis to be presented in Sec. 4.3. Those experiments showed that the hydrolysis of dimer was catalyzed by hydronium ion at low pH. Although dilute sulfuric acid is generally used as eluent with the Aminex ion-exchange resins in hydrogen form, the apparent resin-catalyzed hydrolysis rates are far too great to be accounted for by the dilute (0.001N) H₂SO₄ present. It is thus necessary to attribute the apparent hydrolysis to interaction of dimeric glyoxal with the resin.

The Aminex ion-exchange resins employed are known to be composed of a hydrophobic polystyrene-divinylbenzene copolymer matrix with attached hydrophilic sulfonic acid groups at the resin surface. The particular counter-ion bound — H⁺, Ca²⁺, Ag⁺, etc. — profoundly effects the chromatographic properties of the resins. In the case of the 8% cross-linked
Fig. 4.1. Effect of elution temperature on the monomer (G₁)/dimer (G₂) separation of 1.0M glyoxal (equilibrated at 25°C) on Aminex HPX-87H. Chromatographic conditions: eluent 0.001N H₂SO₄, flow rate 0.6 ml/min, injection volume 5 μl, R.I. detector attenuation 32x.
Fig. 4.2. Effect of flow rate on the monomer (G₁)/dimer (G₂) separation of 1.0M glyoxal (equilibrated at 25.0°C) on Aminex HPX-87H. Chromatographic conditions: eluent 0.001N H₂SO₄, elution temperature 20.0°C, injection volume 5 μl, R.I. attenuation 32x
Aminex resins, which were used in these separations, the "effective" counter ion concentration ([H⁺]) within the resin particles has been estimated at about 6 to 8M. Such high intraparticle acidity might readily account for the observed hydrolysis even at low elution temperatures.

In order to minimize the conversion of dimer to monomer during elution, the Aminex column was operated at the lowest practicable temperature. Unfortunately, the elution temperature could not be decreased much below 0°C. Although peak broadening caused by decreased temperatures was relatively unimportant in the separation of monomer and dimer (as can be seen from Fig. 4.1), resolution of the more closely spaced, higher-order oligomers decreased substantially below 5°C. Furthermore, the column temperature became more difficult to regulate and the column pressure drop more objectionable as the temperature was decreased. In most studies, separations were carried out at 0.0°C, although for purposes of calibration two sets of elutions were conducted at -3.5°C. In some early experiments, elution at 5.0°C was employed. The eluent for all chromatographic separations was 0.001N H₂SO₄.

Qualitatively, the expected effects of resin-catalyzed hydrolysis can be summarized as follows. The fractional increase in expected elution time for a given molecule of injected dimer should be proportional to 1 - x, where x is the relative distance down the column at which hydrolysis occurs. Molecules hydrolyzed at the top of the column should elute as monomer while those not hydrolyzed should elute as dimer. Thus, under conditions where significant resin-catalyzed hydrolysis occurs, a substantial reduction in dimer peak height is predicted, along with continuous elution of newly formed monomer in the valley between the two original
Note that while the monomer peak would, in principle, also be reduced by dimerization, the substantial dilution of sample that occurs during elution dictates that the reverse reaction would be far more important. This argument is further strengthened if the injection of prediluted samples (as in the kinetic studies of Sec. 4.3) is considered. Thus, for chromatographic purposes the hydrolysis of dimeric glyoxal can be considered irreversible. If the hydrolysis is further assumed to be first order with respect to substrate, an assumption that is verified experimentally in Sec. 4.3, it follows that the fractional loss of dimer due to hydrolysis would be a function only of the elution temperature and the residence time (or flow rate) within the column. Conversely, the percentage loss of dimer should be independent of the sample dilution and, hence, independent of sample concentration or volume. The preceding arguments are generally supported by the elution profiles in Fig. 4.1, in which the valley between dimer and monomer peaks is seen to be relatively flat at 0°C, where the amount of dimer within the column is only slightly reduced during elution, but is sloped quite steeply at 15°C and especially 30°C, where much of the dimer is hydrolyzed. Finally, it may also be noted from Fig. 4.1 that while the maximum dimer peak height is greatly effected by temperatures between 0 and 30°C, the maximum monomer peak height is effected only at elution temperatures that exceed 30°C.

The above explanation for the sensitivity of the chromatographic method to elution temperature is supported also by extrapolation of the results to be presented in Sec. 4.3. Those results include an apparent activation energy of 74.7 kJ/mol for hydronium ion-catalyzed dimer hydroly-
sis. If the same value is applied to the resin-catalyzed reaction as well, extension of the kinetic results at 5.0°C to 7M H₃O⁺ predicts a half-life of 4 min for glyoxal dimer in the vicinity of the resin surface. This value is in reasonable agreement with the corresponding elution profile shown in Fig. 4.1, if allowance is made for the extent to which dimer penetrates the resin particles, the column void volume, and the obvious uncertainties associated with the effective acidity of the resin.

The apparent activation energy is also in reasonable agreement with the elution profiles in Fig. 4.1. The following amounts of dimer hydrolysis, relative to elution at 25°C, are predicted for the three elution temperatures used:

<table>
<thead>
<tr>
<th>T, °C</th>
<th>Relative Dimer Hydrolysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>25.0</td>
<td>1</td>
</tr>
<tr>
<td>5.0</td>
<td>0.114</td>
</tr>
<tr>
<td>0.0</td>
<td>0.063</td>
</tr>
<tr>
<td>-3.5</td>
<td>0.041</td>
</tr>
</tbody>
</table>

The values listed above appear roughly consistent with the elution profiles in Fig. 4.1.

For the reasons cited above, the lowest temperature at which the Aminex HPX-87H column could be operated was approximately -3.5°C. Unfortunately, even under those conditions loss of dimer during elution was not completely eliminated, although it did appear to be reduced to a few per cent.
Although some preliminary studies were conducted by using 60 cm (3/8" I.D.) columns packed with Aminex Q-15S resin of 22 μm nominal particle diameter in hydrogen form, all of the research to be reported herein was carried out by using a commercially packed 30 cm (7.8 mm I.D.) column (Bio-Rad Serial No. 22194) packed with Aminex HPX-87 in hydrogen form. The nominal particle diameter of this resin was stated to be 9 μm. A 4-cm Bio-Rad Micro-Guard ion exclusion guard column fitted with a deashing cartridge containing 10 μm resin was also used. The guard column employed the same HPX-87H resin.

Because of the above resin-catalyzed hydrolysis and its effect on the indicated dimer/monomer ratio, accurate column temperature control during sample elution was critical in the chromatographic studies conducted. For that reason, both the guard column, within which very slight separation probably occurred, and the primary HPX-87H column were completely enclosed within an Alltech HPLC column water jacket along with a mercury-in-glass thermometer. Elution temperature was maintained by circulation of a propylene glycol/water solution via insulated Tygon tubing with a Haake Model FK refrigerated constant temperature circulator. Although the constancy to which the column temperature could be maintained varied somewhat with ambient conditions, notably humidity, it was generally maintained within ±0.2°C or less of the desired elution temperature -- one of three, -3.5, 0.0, or 5.0°C, at which the separation had been calibrated.

Column elution was effected with a Waters liquid chromatograph equipped with a Model 6000A pump and a Model U6K injector. Because of the very low elution temperatures in combination with a moderately high flow rate (0.6 ml/min), a sizable column pressure drop of roughly 1500 to 2000
psi developed. Despite the high pressure drop and unusual elution conditions, the Aminex HPX-87H column proved quite durable; over 1500 samples were eluted over a six-month period with no significant deterioration in column performance.

Except when samples were collected for analysis with Girard-T reagent, sample elution was monitored with a Waters Model R401 differential refractometer linked to a Houston Instruments OmniScribe recorder. Attenuator settings of 4x and 8x were optimal for most quantitative work.

The chromatographic system employed in the dimerization studies to be reported, as well as the chromatographic conditions chosen as standard for most thermodynamic and all kinetic experiments, are listed in Table 4.1a. Corresponding performance parameters, describing the chromatographic separation of glyoxal monomer and dimer at the standard elution conditions of 0.0°C and 0.6 ml/min flow rate, are listed in Table 4.1b. Because of the effect of dimer hydrolysis on the apparent widths of the monomer and dimer peaks, the tabulated parameters based upon those characteristics are apparent values only. Although noticeable changes in peak resolution with changes in sample size or volume were not observed, those parameters were nevertheless standardized as much as possible to minimize the effects of any non-linearities in the detector response and generally increase experimental precision. A slight increase in monomer elution time at constant flow rate accompanied increased elution temperature, the capacity factor K' increasing from 0.58 at 0.0°C to 0.66 at 30°C, however, the elution time appeared to level out above 30°C. A much smaller increase in dimer elution time with increasing temperature was also noted.

Although the chromatographic system employed in this research was
Table 4.1a. Chromatographic separation of monomeric and dimeric glyoxal by ion-moderated partition HPLC on Aminex HPX-87H

<table>
<thead>
<tr>
<th>Chromatographic system:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ion exchange resin</td>
<td>Bio-Rad Aminex HPX-87 (8% cross-linked)</td>
</tr>
<tr>
<td>Counter-ion</td>
<td>Hydrogen</td>
</tr>
<tr>
<td>Nominal particle size</td>
<td>9 μm</td>
</tr>
<tr>
<td>Column size</td>
<td>300 x 7.8 mm</td>
</tr>
<tr>
<td>Guard column</td>
<td>Bio-Rad Micro-Guard (40 x 4.6 mm)</td>
</tr>
<tr>
<td>Guard column packing</td>
<td>HPX-87H (10 μm)</td>
</tr>
<tr>
<td>Peak detection</td>
<td>Differential refractometer</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Standard chromatographic conditions:</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Column temperature</td>
<td>0.0 ± 0.2°C</td>
</tr>
<tr>
<td>Flow rate</td>
<td>0.6 ml/min</td>
</tr>
<tr>
<td>Eluent</td>
<td>0.001N H₂SO₄</td>
</tr>
<tr>
<td>Injection volume^a</td>
<td>1-100 μl</td>
</tr>
<tr>
<td>Detector attenuation^a,b (dimer/monomer)</td>
<td>8x/8x or 8x/16x</td>
</tr>
</tbody>
</table>

^a All kinetic runs utilized 35 μl injections and 8x/8x attenuation.  
^b For quantitative work.
Table 4.1b. Monomer-dimer separation parameters obtained from the elution of 5 μl of 1.0M glyoxal at standard chromatographic conditions (see Table 4.1a)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Monomer</th>
<th>Dimer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resolution, $R_s^{a,b}$</td>
<td>---</td>
<td>2.02</td>
</tr>
<tr>
<td>Number of theoretical plates $^{b,c}$</td>
<td>5400</td>
<td>4100</td>
</tr>
<tr>
<td>Height equivalent to theoretical plate, HETP $^{b,c}$, mm</td>
<td>0.056</td>
<td>0.073</td>
</tr>
<tr>
<td>Capacity factor, $K_i^{e,f}$</td>
<td>0.58</td>
<td>0.40</td>
</tr>
<tr>
<td>Elution volume, $V_i$, ml</td>
<td>5.82</td>
<td>5.17</td>
</tr>
<tr>
<td>Peak width, $W_i$, ml</td>
<td>0.32</td>
<td>0.34</td>
</tr>
</tbody>
</table>

\[ a_R = \frac{2(V_{\text{monomer}} - V_{\text{dimer}})}{(W_{\text{monomer}} + W_{\text{dimer}})} \]

Peak widths affected by resin-catalyzed dimer hydrolysis.

\[ N_i = 16(V_i/W_i)^2 \]

\[ \text{HETP} = \frac{N}{300} \text{ mm.} \]

\[ K_i' = \frac{V_{\text{ex}} - V_i}{V_{\text{ex}}} \]

Exclusion volume, $V_{\text{ex}} = 3.68$ ml (NaCl, H$_2$SO$_4$).
satisfactory, further improvements could be made. The use of new micro-
particulate resins should allow the use of higher flow rates and/or shorter
columns, either of which would decrease the residence time while achieving
the same resolution. However, at the low temperatures required the column
pressure drop would probably be extremely high. Potentially greater
improvements might be obtained by the use of other resins, by modification
of the HPX-87 resin, or perhaps simply by the use of a different
counter-ion.

An additional improvement might be the use of a fixed-loop injector
rather than the Waters-type (variable-volume) injector used in this work.
Although sample injections of constant volume were not required to accu-
rately determine the dimer to monomer peak height ratios, the injection of
highly reproducible sample volumes would have allowed the total (combined)
peak heights to be correlated with the reaction progress within any given
run, and so might have allowed the determination of the relative detector
sensitivity to the various glyoxal forms and/or furnished some insight
into the minor deviations from the simple thermodynamic and kinetic models
developed in this work.

A very crude correlation, as a plot of dimer peak height vs. total
(dimer plus monomer) peak height, was attempted based on the kinetic data
collected at constant total glyoxal concentration and constant injection
volume. The monomer peak height appeared to increase by an amount approxi-
mately 1.8 times the corresponding decrease in the dimer peak height,
although the results showed far too much scatter to warrant much credence.
Considering that the peak height to width ratio for monomer was approxi-
mately two-fold higher than the corresponding value for dimer, the relative
peak height sensitivity above is consistent with roughly equal refractive index responses for monomer and dimer on a weight or "per carbon" basis.

4.1.2. Experimental design

The experimental methods used in the study of glyoxal dimerization were less involved than those described previously for the disproportionation studies. In all quantitative studies, the experimentally observed quantity was the apparent concentration ratio of chromatographically separated dimeric to monomeric glyoxal.

Thermodynamic experiments consisted simply of the chromatographic analysis of equilibrated solutions of glyoxal. In those studies, accurate knowledge of the absolute concentration of glyoxal was essential. Stock solutions of unit molarity (nominal) were prepared from glyoxal trimeric dihydrate, and the actual concentrations in monomeric equivalents were determined by Salomaa's titrimetric procedure.\(^87\)

With the exception of one set of experiments to be described in Sec. 4.2.4, the pH was not controlled in any of the thermodynamic studies. The glyoxal solutions did appear to be very weakly buffered to pH 4.6 at 25°C, probably by glycolic acid or other acidic impurity. Although it might have been more convenient under some conditions to adjust the pH to permit either more or less rapid equilibration, this was not attempted. In some instances, very long incubation periods of up to four days were required.

No attempt was made to exclude atmospheric gases during any of the dimerization studies to be reported. This was justified on the basis of the lower pH range observed, the lower kinetic order with respect to acidity or alkalinity observed within that range, and the somewhat lower
accuracy of the results obtained compared with those obtained from the prior disproportionation studies.

The effect of total glyoxal concentration on the equilibrium distribution of glyoxal monomer and dimer was examined by the following procedure. Known dilutions of the 1M glyoxal stock solution were prepared by dispensing the stock solution into 5 to 50 ml volumetric flasks. Following dilution, the flasks were covered with Parafilm and submerged within a Haake FS2 constant temperature circulator maintained at 25.00 ± 0.05°C. After a time interval believed sufficient to allow equilibration, sample aliquots of 2.5 to 90 µl were analyzed chromatographically. Because of the extremely small effect of temperature on the equilibrium ratio of dimer to monomer and the slow rate of dimer hydrolysis at 25°C and pH 4.6, no significant change in the dimer to monomer ratio should have arisen from any slight cooling of the injected sample during sample loading.

Thermal studies of the equilibrium distribution were more difficult to conduct for several reasons. The major problems concerned the slow rate of equilibration at low temperature, the extremely rapid rate at high temperature and the possibility of increasing glyoxal concentration due to evaporation at very high temperature. The above problems were largely circumvented, at least at low to moderate temperatures, by the use of the following sampling procedure.

When sampling at high temperature, the equilibrium distribution of glyoxal was effectively "frozen" during sample loading by the rapid pipetting of a solution aliquot into a volume of dilute H₂SO₄ (pH 3) that had been cooled to 5°C. Of course, it is still assumed that a constant small percentage of the injected dimer is hydrolyzed during elution at either 0.0
or 5.0°C, although a portion of that hydrolysis is corrected for (to -3.5°C) by the use of the empirical equations to be developed in Sec. 4.2.1. Because extremely small changes in equilibrium distribution accompanied changes in temperature, the above method may not have been entirely effective at very high temperature. Although the equilibrated solutions were sampled very rapidly (~2 s), it is a shortcoming of the thermal studies to be described that the glyoxal solutions tested were not adjusted to pH 2.8 to further minimize any reequilibration from cooling that might have occurred during pipetting into the 5°C solution.

Two sets of thermal studies were conducted. The earlier study employed 200 µl aliquots of 0.99M (25°C) glyoxal solutions pipetted into 4.0 ml of 0.0012N H₂SO₄. The equilibrated glyoxal solutions were incubated in test tubes and elutions were carried out at 5.0°C. A later study, which was designed to reduce both trimer interference and evaporation effects, employed 200 µl aliquots of 0.60M glyoxal pipetted into 1.2 ml of 0.0012N H₂SO₄. In the later experiments the glyoxal solutions were incubated in 5 or 10 ml volumetric flasks and elutions were carried out at 0.0°C.

All kinetic experiments were conducted batchwise in individual 18 x 150 mm test tubes. A 3.80 ml volume of buffer solution was first added using a calibrated 5 ml capacity (P5000) Pipetman air-displacement automatic pipette. After preheating the buffer for at least 20 min in a Haake constant temperature circulator, 200 µl of preheated and pre-equilibrated 1M glyoxal stock solution was added at zero time using a calibrated 200 µl capacity (P200) Pipetman pipette. Volume changes upon mixing were neglected. At varying time intervals, aliquots of the reaction mixture were removed for analysis.
Slowly reacting mixtures (at intermediate pH and/or low to ambient temperature) were injected directly into the HPLC. More rapidly reacting mixtures were "quenched" before injection by the addition of 50 μl of \( \text{H}_2\text{SO}_4 \) of sufficient normality to acidify the reaction mixture to pH 2-3. Regardless of whether or not quenching was required, sample injections were made as rapidly as possible — usually within 20 to 45 s. The approximately 1% dilution resulting from quenching should have had no significant effect upon the chromatographic separation.

For experiments in which quenching was required, separate reaction tubes were required for each time of reaction to be observed. Actually, because up to 35 min (phthalate buffer produced a broad, late-eluting peak centered at roughly 29 min) was required between chromatographic injections, separate reaction tubes were sometimes necessary even when quenching was not required. In the preparation of reaction mixtures, the actual dilutions were highly precise and virtually no increase in scatter was observed with quench-sampled experiments. To further clarify this point, although the reverse (dimerization) reaction could not be totally ignored, the 19:1 dilution employed resulted in reaction mixtures that were sufficiently dilute that the reverse reaction should have been relatively unimportant.

4.1.3. **Determination of buffer pH**

Three different buffer systems were used in the determination of dimer hydrolysis rates. At low pH, HCl solutions were employed, while in the pH ranges (at 25°C) of 2.6 to 6.3 and 6.0 to 7.7 phthalic acid (1,2 benzene dicarboxylic acid) and orthophosphoric acid systems, respectively, were
used. In contrast to the disproportionation rate studies, no change in the solution acidity during the course of the reaction was expected. This extended somewhat the useful range of the above buffers.

The hydronium ion concentrations of the phthalate and phosphate buffers were not determined electrometrically, but rather were calculated for each solution at each temperature from the known buffer compositions, published values of the thermodynamic acid dissociation constants as functions of temperature, and appropriate approximations of the individual activity coefficients. With careful buffer preparation, the above method was believed to be at least as accurate as the electrometric method available. Furthermore, the need to measure pH values at temperatures higher or lower than ambient was obviated.

The ionic strength \( \mu \) of the buffer solutions was maintained at a constant value of 0.060M with added KCl in HCl and phthalate buffers or with added NaCl in phosphate buffer (except as noted below). At that ionic strength, the simple two-parameter Debye-Hückel approximation for the activity coefficients was considered adequate. A constant concentration of total phthalate or total phosphate of 0.020M was also maintained.

Because of a calculational error in the initial buffer preparation, the ionic strength of the buffers employed in the kinetic runs at 25°C in phthalate buffer were slightly less than the desired value of 0.060M. The low magnitudes of the errors involved, which varied from less than 1% at \( R_{Ph} = 16 \) to 14% at \( R_{Ph} = -0.25 \) (see below for definition), argued against repeating the rate determinations involved. It is important to note that the actual values of \( \mu \) were used in the calculation of buffer pH for the runs in question. The actual ionic strength values are tabulated along
with the observed rate constants at 25°C in phthalate buffer in Sec. 4.3.2.

The phthalate buffer solutions were prepared by the addition of either HCl or KOH to solutions of hydrogen potassium phthalate. The corresponding hydronium ion concentrations were then calculated as functions of the total equivalents of phthalate present, $a_{ph}$ (added as HKPh), and the phthalate buffer ratio $R_{ph}$. The latter is defined below,

$$R_{ph} = b/(a_{ph} - |b|)$$ \hspace{1cm} (4.1)

as a function of the total phthalate and the equivalents of strong base (or acid) "b" added. The preceding buffer parameters are described in detail in Sec. 7.4. The methods by which the pH was calculated are briefly described as follows.

Accurate values of the first and second thermodynamic ($u\to0$) dissociation constants $K_{ph1}$ and $K_{ph2}$ for phthalic acid as empirical functions of temperature (K) from 0 to 60°C were reported by Hamer, Pinching, and Acree\textsuperscript{104} and Hamer and Acree\textsuperscript{105}, respectively, and are reproduced as Eqs. 4.2a,b:

$$\log_{10}K_{ph1} = -561.57T^{-1} + 1.2843 - 0.0078833T$$ \hspace{1cm} (4.2a)

$$\log_{10}K_{ph2} = -2175.83T^{-1} + 9.55095 - 0.025694T$$ \hspace{1cm} (4.2b)

However, calculations of $[H_3O^+]$ for phthalate systems are complicated by both the close spacing of the dissociation constants and the need to consider the hydrolysis of water, at least at low pH. A cubic expression
for \([\text{H}_3\text{O}^+]\) results. A short derivation of and solution to the resulting expression for \([\text{H}_3\text{O}^+]\) is given in Sec. 7.4.

The phosphate buffer solutions were prepared by the addition of NaOH to solutions of monobasic potassium orthophosphate KH\(_2\)PO\(_4\). Calculated values of \([\text{H}_3\text{O}^+]\) for phosphate buffers are not significantly influenced by either hydrolysis of water or by neighboring dissociations in the vicinity of pH 7. The empirical expression,

\[
\log_{10} K_{p2} = -2073.0T^{-1} + 5.9884 - 0.020912T
\]  

reported by Bates and Acree\(^{106}\) was used to calculate the second thermodynamic acid dissociation constant \(K_{p2}\) for phosphoric acid as a function of absolute temperature (K). The values for \(K_{p2}\) together with Debye-Huckel estimates of the individual activity coefficients \(\gamma_i\) were sufficient to calculate the hydronium ion concentration as a function of the phosphate buffer ratio \(R_p\) using Eq. 4.4:

\[
[\text{H}_3\text{O}^+] = K_{a2} \frac{\gamma_{\text{H}_2\text{P}}(a_p - b)}{(\gamma_H \gamma_{\text{HF}} b)}
\]

\[
= K_{a2} R_p^{-1} \frac{\gamma_{\text{H}_2\text{P}}}{(\gamma_H \gamma_{\text{HF}})}
\]

where

\[
R_p = b/(a_p - b)
\]

The buffer ratio \(R_p\) is defined in Eq. 4.5, in which \(a_p\) and \(b\) denote the hypothetical concentrations of added KH\(_2\)PO\(_4\) and NaOH, respectively.

The 1.0M glyoxal stock solution used in the dimer hydrolysis kinetics was not pure, but rather contained roughly 1% impurity, probably glycolic.
acid. Because of the low buffering capacity at some pH values, this impurity was sufficient to alter the pH of the diluted buffers. This was corrected for in the following manner. Electrometric pH readings were taken of buffer solutions to which one volume of water to nineteen volumes of buffer had been added, and of solutions to which one part in twenty of 1.0M glyoxal had been added. The measured differences in pH were used, when detectable, to correct the originally calculated pH values. The same small corrections that were determined at 25°C were assumed applicable at 45°C and at 5°C as well. The pH corrections were consistent for a presumed acidic impurity with a $pK_a$ of 3 to 4.

Nineteen parts of the buffer solutions were diluted with one part of 1.0M glyoxal at the start of each kinetic determination. The effects of this dilution (effected via decreases in both total buffer concentration and ionic strength) on the buffer pH were negligible. With the exception of the buffer solution at $R_p = 16$, the corrected pH values are believed accurate to within ±0.02 pH unit.

4.1.4. Materials

Glyoxal stock solutions of unit molarity or less and Girard-T reagent stocks were prepared in the manner described in Sec. 3.1.5. Concentrated glyoxal solutions were prepared by dilution of an Aldrich 40 wt% glyoxal solution. Aldrich Gold Label KCl (stated 99.999%) was used in the maintenance of constant ionic strength in HCl and phthalate buffer solutions. The use of the potassium rather than sodium salt permitted more accurate correlation of electrometric pH readings with published values for the KHphthalate/KCl system. In the preparation of phthalate buffers, Fisher
pretitrated 1N HCl or KOH was added to Fisher Certified ACS KHphthalate. Phosphate buffers were prepared by the addition of Fisher pretitrated 1N NaOH to Aldrich Gold Label (stated 99.999%) anhydrous monobasic potassium orthophosphate. All other chemicals were reagent grade.

Water used in the preparation of all stock and reactant solutions and chromatographic eluents was subjected to initial purification and storage in the manner described in Sec. 3.1.5. However, in the dimerization studies to follow all water was further purified before use by passage through a Barnstead NANOpure II cartridge purification system. Indicated resistivity of the effluent as used ranged from 17.3 to 18.0 megohm-cm.

4.2. Results — Dimerization Thermodynamics

4.2.1. Quantitation of chromatographic results

The qualitative HPLC results obtained to this point suggested that the two principal peaks obtained from the elution of moderately concentrated (0.01 to 1M) glyoxal were dimer and monomer, respectively. However, the refractive index (RI) response could not be used directly to obtain quantitative information about the dimerization reaction, because 1) the partial molal refractive indices of dimer and monomer could not be assumed to be identically equal, 2) the two peaks possessed different height to width ratios (important if maximum peak heights are used), and 3) at the standard elution conditions separation was not complete. Thus, an independent method of calibrating the RI response was required. This was accomplished by spectrophotometric analysis of the eluted peaks using the Girard-T method described in Sec. 3.1. It was assumed that the Girard-T reagent
reacts initially with pre-existing glyoxal monomer and eventually also with that monomer produced by dimer hydrolysis. Thus, the Girard-T reagent was expected to provide a quantitative estimate of the total glyoxal content as monomer equivalents. The above assumption was, in fact, supported by the observed biphasic rate of absorbance development by eluted peaks at 295 nm (pH 3, 25°C), in which an initial rapid increase in absorbance was followed by a much slower approach to the final value. More importantly, equiliibrated solutions of known total glyoxal concentration, based on trimeric dihydrate, gave totally consistent absorbances upon dilution into standard Girard-T solution.

The installation of a Rheodyne 7040 minimum dead volume switching valve between the column outlet and the RI detector allowed effluent peaks to be diverted for collection without prior passage through the RI detector. The appropriate times at which to start and stop collecting separated glyoxal peaks were first determined from recorder traces following the RI response. The Rheodyne valve was then switched and identical glyoxal samples were injected and the eluted peaks were collected in volumetric flasks. After addition of Girard-T reagent, dilution to volume, and storage for an interval of time sufficient to allow complete conversion of dimer to monomer and reaction of the latter with the Girard-T reagent, the net absorbances of the collected samples were measured at 295 nm. When allowance was made for the presumed stoichiometric production of two moles of monomer from each mole of dimer and for the respective flask volumes, accurate estimates of the molar ratio R of eluted dimer to monomer could be obtained.

A series of glyoxal samples of accurately known total glyoxal concen-
tration $[C_T]$ were prepared by dilution of a stock solution prepared from glyoxal trimeric dihydrate and analyzed by Salomaa's titrimetric method\textsuperscript{87}. These samples were equilibrated at 25.0°C and were then chromatographed at -3.5°C. The relative amounts of dimer and monomer eluted were determined by Girard-T analysis of the respective peaks. The molar ratios of dimer to monomer obtained under those conditions were assumed to represent the actual equilibrium ratio $R_{eq}$ of dimer to monomer existing in the injected samples. The very small amount of dimer hydrolysis occurring at those elution conditions was neglected. However, it must be recognized that the thermodynamic findings obtained probably slightly underestimate the true values, perhaps by up to 5%.

An elution temperature of 0.0°C was judged more suitable for repetitive analyses and was chosen as the standard elution temperature for all subsequent chromatographic work. Furthermore, maximum peak height ratios obtained from recorder traces of RI response were found to be highly reproducible and far more convenient than the Girard-T analysis above. Therefore, samples of the same standard glyoxal solutions used in the determination of the dimer to monomer ratios above, were eluted at 0.0°C and the corresponding maximum peak height ratios $R_H$ were then determined from RI recorder traces. These results were then correlated with the Girard-T-analyzed findings described above. In Table 4.2, the dimer to monomer ratios $R$ obtained at -3.5°C by Girard-T analysis as well as the dimer/monomer peak height ratios $R_H$ obtained at 0.0°C are listed as a function of $[C_T]$.

The maximum peak height ratios presented in Table 4.2 represent the average of values obtained at two different sets of detector sensitivities.
Table 4.2. Apparent equilibrium mole ratios of dimeric to monomeric glyoxal, $R_{eq}$, as determined by Girard-T analysis and by mean maximum peak height ratio $R_H$

<table>
<thead>
<tr>
<th>$[G]_T$, M (±0.5%)</th>
<th>$R_{G-T} (=R_{eq})^a$</th>
<th>$R_H^b$</th>
<th>$R_{eq}^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.02</td>
<td>0.0141</td>
<td>0.0211</td>
<td>0.0131</td>
</tr>
<tr>
<td>0.04</td>
<td>0.0231</td>
<td>0.0318</td>
<td>0.0218</td>
</tr>
<tr>
<td>0.06</td>
<td>0.0328</td>
<td>0.0454</td>
<td>0.0329</td>
</tr>
<tr>
<td>0.08</td>
<td>0.0433</td>
<td>0.0560</td>
<td>0.0415</td>
</tr>
<tr>
<td>0.10</td>
<td>0.0518</td>
<td>0.0668</td>
<td>0.0502</td>
</tr>
<tr>
<td>0.12</td>
<td>0.0620</td>
<td>0.0785</td>
<td>0.0598</td>
</tr>
<tr>
<td>0.20</td>
<td>0.0961</td>
<td>0.120</td>
<td>0.0938</td>
</tr>
<tr>
<td>0.30</td>
<td>0.135</td>
<td>0.166</td>
<td>0.131</td>
</tr>
<tr>
<td>0.40</td>
<td>0.169</td>
<td>0.210</td>
<td>0.167</td>
</tr>
<tr>
<td>0.60</td>
<td>0.222</td>
<td>0.286</td>
<td>0.228</td>
</tr>
<tr>
<td>0.80</td>
<td>0.290</td>
<td>0.355</td>
<td>0.284</td>
</tr>
<tr>
<td>1.00</td>
<td>0.341</td>
<td>0.417</td>
<td>0.335</td>
</tr>
</tbody>
</table>

$^a$Elution at -3.05°C.

$^b$Elution at 0.0°C.

$^cR_{eq} = 0.813(R_H - 0.005)$. 
From the agreement between separations carried out with dimer/monomer attenuations of 8x/8x and separations of twice the volume of identical samples eluted with 8x/16x attenuations, the relative detector sensitivities at 8x and 16x were found to be 0.512 to 1. This value was used to correlate data obtained at one attenuation setting with that obtained at the other. Also calculated was a detector response factor $a_R$, which allowed calculation of $R$, the actual molar ratio of dimer to monomer, from maximum peak height ratios $R_H$. As may be seen from Table 4.2, the detector response is essentially independent of $[G_T]$ except at the lowest and least accurate concentrations. Based on the above results and the graphical results to be presented in Sec. 4.2.3, the following empirical equation was developed to allow accurate calculations of $R$ at moderate total glyoxal concentrations — that is, for $[G_T] < 1M$:

$$R = a_R(R_H - 0.005)$$  \hspace{1cm} (4.6)

The average response factor $a_R$ of 0.813 for elutions at 0.0°C was determined from the individual $a_R$ over the $[G_T]$ range of 0.6-0.08M. A corresponding average response factor $a_R$ of 0.86 was used in the analysis of earlier elutions carried out at 5.0°C. The higher value of $a_R$ for elution at 5°C reflects the increased resin-catalyzed hydrolysis at that temperature.

4.2.2. Determination of $K_{D_{app}}$

To this point, a dimer–monomer relationship between the two principal glyoxal HPLC peaks has been assumed. However, this hypothesis can be
easily tested using the same results presented in Table 4.2. The mathematical framework within which this was done is outlined below. The nomenclature used is consistent with that presented in Sec. 3 with additional dimerization-related quantities defined as necessary.

The hypothetical "total" glyoxal concentration \([G_T]\) must reflect the presence of oligomeric glyoxal. That is, if \([G_1]\) and \([G_n]\) are allowed to represent the total concentrations of monomeric and \(n^{th}\)-order forms, respectively, the total concentration of glyoxal in monomeric equivalents \([G_T]\) may be represented as follows:

\[
[G_T] = \sum_{i=1}^{n} [G_i] = [G_1] + \sum_{i=2}^{n} [G_i] \tag{4.7}
\]

The quantity \([G_T]\) is an important experimental parameter because it is directly variable. Solutions of known \([G_T]\) are readily prepared from crystalline glyoxal trimeric dihydrate. Note that, as before, the total monomer concentration \([G_1]\) denotes the sum of the concentrations of free glyoxal, monohydrate, and dihydrate forms,

\[
[G_1] = [G] + [M] + [D] \tag{4.8}
\]

while the \(n^{th}\)-order oligomers are sums of an unspecified number of isomeric forms. Finally, the HPLC results indicate that, for \([G_T] < \text{1M}\), trimeric forms and, even more so, higher-order oligomers are unimportant, barring extremely rapid resin-catalyzed hydrolysis. Thus, Eq. 4.9 suffices:
If, as reported by Whipple\textsuperscript{16}, only cyclic dimers are quantitatively significant, the pertinent equilibria in aqueous solutions of total glyoxal concentrations less than 1M are those represented below,

\[ [G_T] = [G_1] + 2[G_2] \quad (4.9) \]

\[
\begin{align*}
\text{H}_2\text{O} + M & \xrightleftharpoons{K'_{D1}} \text{D} \\
2 M & \xrightarrow{K'_{D2}} G_{2i}
\end{align*}
\quad (4.10a, b)
\]

where \( G_{2i} \) denotes the \( i \)th cyclic dimer and \( K'_{D2} \) and \( K'_{D1} \) are defined in terms of the respective component activities. Thus, from a stoichiometric viewpoint dimerization is most simply represented as the combination of two molecules of glyoxal monohydrate, as indicated below,

for the two predominant dimeric forms reported by Whipple. Subject to the approximations noted in Sec. 2, "classical" or "concentration" equilibrium
expressions corresponding to the reactions above can be defined, as in Eqs. 4.11a–c:

\[
\begin{align*}
K_{h2} &= [D]/[M] \quad (4.11a) \\
K^*_h &= [D]/([M][H_2O]) \quad (4.11b) \\
K_D &= \Sigma_i K_{Di} = \Sigma_i [G_{2i}]/[M]^2 = [G_2]/[M]^2 \quad (4.11c)
\end{align*}
\]

Note that in Eq. 4.11b an alternative equilibrium constant, which includes the concentration of water, has been defined and, that in Eq. 4.11c a composite equilibrium constant has been defined as \( K_D = \Sigma_i K_{Di} \).

Whipple has presented evidence that a single dimeric form, designated \( G_{2(1)} \) above, predominates in aqueous solution, with a closely related form \( G_{2(2)} \) about 20% as abundant. The HPLC method used in this research would not be expected to resolve structurally similar dimeric forms, even if such isomers are not interconverted during chromatographic elution. Thus, \( K_D \) will be considered to represent approximately the composite dimerization constant of the two predominant dimeric forms. However, considering the close structural similarity between \( G_{2(1)} \) and \( G_{2(2)} \) above and the predominance of the former, \( K_D \) probably closely approximates \( K_{D1} \) as well. It should be noted, however, that multiple dimeric forms might, depending on relative proportions and reactivities, be implied from dimer hydrolysis kinetics.

Because the monohydrate concentration \([M]\), which appears in Eqs. 4.11a–c, was not directly measurable, it is necessary to define an "apparent" dimerization constant \( K_{Dapp} \) in terms of \([G_1]\) and \([G_2]\) as follows. Under conditions at which ionic forms may be neglected, \([G_1]\) can
be expressed in terms of $K_{h2}^*$, [H$_2$O], and [M] by Eq. 4.12, as developed in Sec. 3:

$$[G_1] = [M] + [D] = [M](1 + K_{h2}^*[H_2O])$$  \hspace{1cm} (4.12)

Upon solving for [M] and substituting into Eq. 4.11c, an expression for $K_D$ in terms of $[G_1]$ and $[G_2]$ is obtained:

$$K_D = (1 + K_{h2}^*[H_2O])^2[G_2]/[G_1]^2$$  \hspace{1cm} (4.13)

from which an apparent equilibrium constant can be defined:

$$K_{Dapp} = [G_2]/[G_1]^2$$  \hspace{1cm} (4.14a)

$$= (1 + K_{h2}^*[H_2O])^{-2}K_D$$  \hspace{1cm} (4.14b)

$$= (1 + K_{h2})^{-2}K_D$$  \hspace{1cm} (4.14c)

Finally, it should be noted that with the assumption that $K_{h2} >> 1$ the following simplified expression for $K_{Dapp}$ is obtained:

$$K_{Dapp} = K_{h2}^{-2}K_D$$  \hspace{1cm} (4.15)

Although the HPLC system used could not furnish accurate values for either $[G_1]$ or $[G_2]$, fairly accurate and highly reproducible values of the ratio of total dimer to total monomer, $R = [G_2]/[G_1]$, could be obtained from maximum peak heights, as previously described. As indicated by the equations to follow, knowledge of the equilibrium ratio $R_{eq}$ of dimer to
monomer as a function of $[G_T]$ is sufficient to determine $K_{Dapp}$. Multiplication of Eq. 4.9 for $[G_T]$ by Eq. 4.14a for $K_{Dapp}$ yields:

$$[G_T]K_{Dapp} = [G_2]/[G_1] + 2([G_2]/[G_1])^2$$

(4.16)

$$[G_T]K_{Dapp} = R_{eq} + 2R_{eq}^2$$

$$K_{Dapp} = R_{eq}(1 + 2R_{eq})[G_T]^{-1}$$

(4.17)

Eq. 4.17 expresses $K_{Dapp}$ in terms of the observed ratio of dimer to monomer and the experimentally varied total glyoxal concentration, and is thus central to most of the remainder of this work. In fact, Eq. 4.17 can be used to verify the heretofore assumed monomer–dimer peak relationship as well as provide an accurate estimate of $K_{Dapp}$. In Fig. 4.3, values of $R_{eq}(1 + 2R_{eq})$ calculated from the $R_{eq}$ values determined from elution at $-3.5^\circ C$ by Girard-T analysis are plotted vs. $[G_T]$. Despite some scatter with values obtained from the most concentrated solutions, the resulting points fall quite close to a straight line with an intercept of essentially zero, as would be predicted by the following rearrangement of Eq. 4.17:

$$R_{eq}(1 + 2R_{eq}) = K_{Dapp}[G_T]$$

(4.18)

The resulting slope corresponds to $K_{Dapp}$ for glyoxal at $25^\circ C$ and is given as $0.562 \pm 0.002 M^{-1}$ using the values from 0.04 to 0.4M $[G_T]$. A correlation coefficient of 0.99997 and an $y$-intercept of 0.002 is obtained.

Although the HPLC method at $-3.5^\circ C$ is believed to provide the most accurate estimate of $R_{eq}$, the peak collection and Girard-T analysis was quite tedious and somewhat imprecise. In Fig. 4.3 are plotted also corre-
Fig. 4.3. Determination of $K_{Dapp}$ at 25°C with Eq. 4.18 using $R_{eq}$ from Girard-T analysis (■) and maximum peak heights by R.I. (●)

$K_{Dapp} = 0.56 \text{ M}^{-1}$
spending values of \( R_{ eq}(1 + 2R_{eq}) \) determined from chromatographic elutions at 0.0\(^\circ\)C using maximum peak heights and Eq. 4.6. A linear relationship is again apparent, and in addition considerably less scatter is indicated. Over the \([G^+]\) range of 0.04 to 1.0M a slope of \(0.558 \pm 0.002\text{M}^{-1}\) and a correlation coefficient of 0.99997 is obtained. The small positive intercept, which was also obtained by the use of peak height data, was virtually eliminated (y-intercept = 0.001) by the introduction into Eq. 4.6 of the empirical term \(a_R(0.005)\). The cause of this slight deviation at low \([G^+]\) is not known, but might result from either breakdown of any of the many assumptions made above or from an unknown chromatographic effect.

The value reported above for \(K_{Dapp}\) is in reasonable agreement with the approximate value of 1.2M\(^{-1}\) reported by Whipple\(^{16}\) on the basis of NMR studies. Although the value of 0.56M\(^{-1}\) reported here is probably slightly low, perhaps by up to 15\% (because of resin-catalyzed dimer hydrolysis), a value of \(K_{Dapp}\) much greater than 0.6M\(^{-1}\) would be difficult to reconcile with the results obtained.

The small proportion of trimer present at 1M \([G^+]\), perhaps 2-3\%, should result in slight downward deviations in the curves in Fig. 4.3 at the highest glyoxal concentrations. However, no such discrepancies are detectable. The proportions of trimer would fall off very rapidly with decreasing \([G^+]\), and \(R_{eq}\) values obtained at \([G^+] < 0.4\text{M}-0.6\text{M}\) should be essentially unaffected. Of course, it has been assumed here that the HPLC separation employed afforded reasonable estimates of the actual proportions of higher-order oligomers present. Further support for this assumption can be found in Sec. 4.3.5.
4.2.3. **Effect of temperature on $K_{\text{Dapp}}$**

Having established both the probable monomer-dimer correspondence of the two predominant peaks separable by HPLC and an accurate method for estimating the ratio of dimer to monomer in a given solution of glyoxal, two series of experiments were conducted in which the effects of temperature on the apparent dimerization constant were determined. In those experiments, 0.60M or 0.99M solutions of glyoxal were incubated at varied temperatures for intervals of time sufficient to allow close approach to equilibrium. The required intervals were estimated from preliminary kinetic experiments and were supported by constancy of replicate readings. Values of $K_{\text{Dapp}}$ were then calculated from measured peak height ratios determined from recorder traces.

If the total concentration of glyoxal $[G_T]$, corrected for changes in solvent density, and the equilibrium ratio of dimer to monomer $R_{eq}$ are known, Eq. 4.17 allows the calculation of the apparent dimerization constant. Values of $K_{\text{Dapp}}$ obtained in this way are listed in Table 4.3a,b and are fit to the van't Hoff equation as $\log_e(K_{\text{Dapp}})$ vs. $1/T$ in Figs. 4.4a,b.

Because the experiments employed fairly concentrated glyoxal solutions, where up to several per cent trimer may have been present, the $K_{\text{Dapp}}$ values reported in Tables 4.3a,b are not believed to be as accurate as that reported previously for 25.0°C. The slightly lower values obtained from the experiments at 0.99M $[G_T]$ relative to those from experiments at 0.60M $[G_T]$ are in that respect consistent. It is important to note that the relative proportion of trimer present did not appear to change appreciably with temperature.
Table 4.3a. Effect of temperature on $K_{\text{Dapp}}$ with 0.99M total glyoxal

<table>
<thead>
<tr>
<th>Temperature, °C</th>
<th>$R_{\text{eq}}$</th>
<th>$K_{\text{Dapp}}^a$</th>
<th>$K_{\text{Dapp}}^b$</th>
<th>$K_{\text{Dapp}}^c \times 10^{-3}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.0</td>
<td>0.310</td>
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<td>0.368</td>
<td>0.661</td>
<td>1.937</td>
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</tr>
</tbody>
</table>

1. $R_{\text{eq}} = 0.86(R_h - 0.005)$ — eluted at 5°C.

2. $K_{\text{Dapp}} = R_{\text{eq}} (1 + 2R_{\text{eq}})p_{\text{H}_2\text{O}}(25^\circ\text{C})/([G_T]_{25^\circ\text{C}})_{\text{H}_2\text{O}}(T)$.

3. $K_{\text{Dapp}}^c = R_{\text{eq}} (1 + 2R_{\text{eq}})[\text{H}_2\text{O}]^2_{25^\circ\text{C}}/([G_T]_{25^\circ\text{C}})_{\text{H}_2\text{O}}(25^\circ\text{C})$. 
Table 4.3b. Effect of temperature on $K_{Dapp}$ with 0.60M total glyoxal

<table>
<thead>
<tr>
<th>Temperature, °C</th>
<th>$R_{eq}^a$</th>
<th>$K_{Dapp}^b$</th>
<th>$K_{Dapp}^c$ x10^{-3}</th>
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<tbody>
<tr>
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<td>0.510</td>
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<td>0.214</td>
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<td>1.565</td>
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<td>15.0</td>
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<td>1.661</td>
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<td>0.229</td>
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<td>1.649</td>
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<td>0.223</td>
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<td>1.653</td>
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<td>0.571</td>
<td>1.756</td>
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<td>0.243</td>
<td>0.607</td>
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<td>0.641</td>
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<td>0.251</td>
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<td>1.900</td>
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<td>65.0</td>
<td>0.256</td>
<td>0.652</td>
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<td>0.261</td>
<td>0.680</td>
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<tr>
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<td>0.260</td>
<td>0.676</td>
<td>1.956</td>
</tr>
</tbody>
</table>

$^a_{R_{eq}} = 0.813(R_H - 0.005)$.

$^b_{K_{Dapp}} = R_{eq}(1 + 2R_{eq})^2\rho_{H2O}(25°C)/(G_T)^2\rho_{H2O}(T)$.

$^c_{K_{Dapp}}^* = R_{eq}(1 + 2R_{eq})[^3H]_{25°C}\rho_{H2O}(T)/(G_T)^2\rho_{H2O}(25°C)$.
Fig. 4.4a. Effect of temperature on $K_{Dapp}$ as obtained using the van't Hoff relationship and $R_{eq}(T)$ determined at 0.99M $[G_T]$ (at 25°C).
Fig. 4.4b. Effect of temperature on $K_{Dapp}$ as obtained using the van't Hoff relationship and $R_{eq}(T)$ determined at 0.60M $[G_T]$ (at 25°C)
Over the temperature range of 5 to 65°C, linear relationships between 
\( \log_e(K_{Dapp}) \) and 1/T appear to be closely approximated with both experi­
ments. Over the above temperature range, values for \( \Delta H_{Dapp} \) of +3.18 ± 0.07 
and +3.22 ± 0.06 kJ/mol were obtained from the experiments employing 0.60M 
and 0.99M \([G^*]\), respectively. Close agreement was obtained in spite of 
significant differences in the experimental procedures used. Thus, a mean 
value of +3.20 ± 0.05 kJ/mol (0.76 ± 0.01 kcal/mol) for \( \Delta H_{Dapp} \) appears 
appropriate. At 25.0°C, a value of +10.7 J/molK (2.57 cal/molK) for \( \Delta S_{Dapp} \) 
is obtained. As explained in Sec. 4.1.2, the slight downward deviation at 
very high temperature in both Figs. 4.4a and 4.4b is inconclusive because 
of the presumed rapid rate of dimerization at very high temperature and the 
possibility of slight monomerization during "freezing" of the samples.

Although the apparent dimerization constant shows only a very weak 
thermal dependence, it does not necessarily follow that the true 
dimerization is temperature insensitive, as may be observed from Eq. 4.14c:

\[
K_{Dapp} = (1 + K_{h2})^{-2}K_D
\]  

(4.14c)

If it is assumed that \( K_{h2} \gg 1 \), then \( K_{Dapp} \) is given simply by \( K_D^{-2} \). As 
cited previously, Lavery et al.\(^{23}\) have reported \( \Delta H_h \) values for glyoxal 
monohydrate and formaldehyde of -165 and -140 kJ/mol, respectively, based 
on quantum chemical studies. Reported experimental values of the latter 
hydration constant have been, typically, -25 kJ/mol, and thus, it appears 
that the theoretically based values may be somewhat low. Nevertheless, if 
the trend in \( \Delta H_h \) values is accepted, it follows that \( \Delta H_{h2} \) for glyoxal is 
maximally about -30 kJ/mol, which in turn implies a maximum value for
\[ \Delta H_D \text{ of approximately } -57 \text{ kJ/mol. Thus, it appears that the dimerization of glyoxal monohydrate is moderately exothermic.} \]

A corresponding solvent-independent equilibrium constant \( K_{Dapp}^* \) can also be calculated, if it is once more assumed that \( K_{h2} \gg 1 \) over the temperature span of interest:

\[
K_{Dapp} = K_{h2}^2 K_D \quad (\text{for } K_{h2} \gg 1)
\]
\[
= K_{h2}^2 K_D [H_2O]^{-2}
\]
\[
= K_{Dapp}^* [H_2O]^{-2}
\]

From the equations above, \( K_{Dapp}^* \) can be obtained from \( K_{Dapp} \) or the original dimer to monomer ratios \( R_{eq} \) using:

\[
K_{Dapp}^* = K_{Dapp} [H_2O]^2
\]
\[
= R_{eq} (1 + 2R_{eq})[H_2O]^2[G_T]^{-1}
\]

In contrast to \( K_{Dapp} \), \( K_{Dapp}^* \) is independent of the small but significant decrease in solvent concentration accompanying increases in temperature. Thus, Eq. 4.20 compensates for changes in water concentration with increasing temperature, as well as for changes in \( [G_T] \). Inherent in the use of Eq. 4.20 is the assumption that the relative change in \( \gamma_{H2O} \) with increasing temperature is less than the corresponding change in the density of water. Values obtained for \( K_{Dapp}^* \) are also listed in Tables 4.3a,b.

The corresponding van't Hoff plots for \( K_{Dapp}^* \), indicated in Fig. 4.5 for the experiments at 0.60M \( [G_T] \), show definite curvature at high temperature, although a slope essentially identical to that obtained for \( K_{Dapp} \) is
Fig. 4.5. Effect of temperature on the solvent-independent apparent dimerization constant $K_{Dapp}$ using $R_q(T)$ obtained at 0.60M $[G_T]$ (at 25°C)
apparent at the lower temperatures where the density of water is nearly invariant. The absolute deviations in $K_{Dapp}^*$ corresponding to the above curvature are extremely small and occur at the highest temperatures, at which conditions experimental uncertainty was relatively great. Thus, the possibility of an experimental artifact cannot be ruled out. Furthermore, it should be remembered that Eq. 4.20 are strictly valid only at infinite dilution.

If, for the moment, the above curvature is taken at face value, one possible explanation might involve the assumption that $K_{h2}$ is much greater than unity. If the hydration of glyoxal monohydrate is indeed highly exothermic, the value of $K_{h2}$ would be expected to decrease substantially with increased temperature. If, at some point, the assumption that $K_{h2} \gg 1$ begins to break down a decrease in the value of $\Delta H_{Dapp}$ due to the highly negative value of $\Delta H_D$ might be observed. Once again, the only conclusion from the above speculation is that accurate studies of the hydration of glyoxal are sorely needed.

It should be emphasized, however, that the effects of temperature on the apparent dimerization constant are very slight. Thus, the above value of $\Delta H_{Dapp}$ together with the known value of $K_{Dapp}$ at $25.0^\circ C$ presented earlier should provide reliable predictions of glyoxal dimer-monomer distributions as a function of temperature. Over the temperature range of 0 to $65^\circ C$, $K_{Dapp}(T)$ can be calculated using Eq. 4.21:

$$K_{Dapp}(T) = 2.036e^{(-3200/8.314T)}$$  (4.21)

where $T$ is in K.
4.2.4. Effects of ionic strength and pH on $K_{Dapp}$

It should be anticipated that the ionic strength $\mu$ would have only a very small effect on $K_{Dapp}$. This is due to the involvement of only uncharged species in the presumed equilibrium expression. Of course, individual forward and reverse steps might very well involve charged intermediates. The effect of ionic strength as added NaCl from 10 to 500mM on the equilibrium dimer to monomer ratio $R_{eq}$ of 0.60M $[G_T]$ at 25.0°C was observed. Eq. 4.17 was used to calculate $K_{Dapp}$ from $R_{eq}$, and the results are recorded in Table 4.4. Mean values of $K_{Dapp}$ and $\log_{10}K_{Dapp}$ are plotted vs. $\log_{10}([\text{NaCl}])$ in Fig. 4.6a. A very slight decrease in $K_{Dapp}$ with increasing ionic strength can be noted.

The values of $K_{Dapp}$ in Table 4.4 were fit to the empirical equation to follow; the resulting fit is indicated in Fig. 4.6b.

$$\log_{10}K_{Dapp}(\mu) = \log_{10}K_{Dapp}(\mu \rightarrow 0) + b\mu$$ (4.22)

A reasonably close approximation to a straight line dependence may be noted, with a value of $-0.065 \pm 0.002\text{M}^{-1}$ obtained for parameter "b". The effects of $\mu(\text{M})$ on the classical apparent dimerization constant can thus be expressed as:

$$K_{Dapp}(\mu) = K_{Dapp}(\mu \rightarrow 0)\exp_{10}(-0.065\mu)$$ (4.23)

Note that, according to Eq. 4.23, below an ionic strength of 0.1M $K_{Dapp}$ varies by less than 1.5% with changes in $\mu$.

As with the effects of temperature, it is necessary to correct $K_{Dapp}$
Table 4.4. Effect of ionic strength (as NaCl) on $K_{Dapp}$ and $K_{Dapp}^*$ at 25°C ($[G_T] = 0.60M$)

<table>
<thead>
<tr>
<th>[NaCl] M</th>
<th>$R_{eq}^a$</th>
<th>$K_{Dapp}^b$ M$^{-1}$</th>
<th>$K_{Dapp}^* \times 10^{-3}^c$ M</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.010</td>
<td>0.2304</td>
<td>0.561</td>
<td>1.717</td>
</tr>
<tr>
<td></td>
<td>0.2307</td>
<td>0.564</td>
<td>1.727</td>
</tr>
<tr>
<td></td>
<td>0.2300</td>
<td>0.560</td>
<td>1.714</td>
</tr>
<tr>
<td>0.025</td>
<td>0.2308</td>
<td>0.564</td>
<td>1.727</td>
</tr>
<tr>
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<td>0.2271</td>
<td>0.555</td>
<td>1.700</td>
</tr>
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<td>1.691</td>
</tr>
<tr>
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<td>0.2276</td>
<td>0.556</td>
<td>1.702</td>
</tr>
<tr>
<td>0.10</td>
<td>0.2256</td>
<td>0.552</td>
<td>1.684</td>
</tr>
<tr>
<td></td>
<td>0.2258</td>
<td>0.552</td>
<td>1.685</td>
</tr>
<tr>
<td>0.25</td>
<td>0.2189</td>
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<td>1.627</td>
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<td>0.2205</td>
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<td>1.638</td>
</tr>
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<td>0.2112</td>
<td>0.517</td>
<td>1.557</td>
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<td>1.584</td>
</tr>
<tr>
<td>1.0</td>
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<td>0.484</td>
<td>1.455</td>
</tr>
<tr>
<td></td>
<td>0.1969</td>
<td>0.483</td>
<td>1.452</td>
</tr>
</tbody>
</table>

$^a R_{eq} = 0.813(R_H - 0.005)$.  
$^b K_{Dapp} = R_{eq}(1 + 2R_{eq})/[G_T]$.  
$^c K_{Dapp}^* = R_{eq}(1 + 2R_{eq})[H_2O]^2/[G_T]$. 
Fig. 4.6a. Effect of ionic strength $\mu$ as added NaCl on the mean dimerization constant $K_{\text{Dapp}}$ at 25°C.
Fig. 4.6b. Effect of ionic strength \( \mu \) on \( K_{\text{Dapp}} \) at 25°C ([G_T] = 0.60M) as fit empirically to Eq. 4.22
for changes in the concentration of water as the salt concentration is varied. Solvent-independent equilibrium constants $K_{Dapp}^*$ were calculated using Eq. 4.20, the use of which implies the assumption that $K_{h2}^{*} \gg 1$ at 25°C. As an approximation, the concentration of water was assumed to be unaffected by the presence of the 0.60M glyoxal, and thus, tabulated values\(^{107}\) for the concentration of water in NaCl/H₂O systems were used. The resulting values for $K_{Dapp}^*$ are listed also in Table 4.4. Very little difference is apparent.

The above salt effects must be interpreted with caution, as the injection of samples of high salt content may have adverse effects on the operation of Aminex ion exchange HPLC columns, presumably due to replacement of the $H^+$ counter-ions with $Na^+$. Any resulting changes in bed structure could conceivably alter the column performance. However, the results reported in Table 4.4 represent average values from two separate sets of injections, each set increasing from 0.01 to 0.50M. No detectable trend was apparent in the differences between corresponding values in the two sets of data.

The effect of pH on $K_{Dapp}$ was observed over the limited pH range of 4 to 6. Again, because neither acidic nor basic species are present in the assumed equilibrium expression, no significant effect was anticipated. Listed in Table 4.5 are the calculated $R_{eq}$ values obtained for 0.050M [Gₜ] equilibrated in 0.020M total phthalate buffers at $u = 0.060M$, the same total glyoxal concentration and ionic strength used in later kinetic studies.

Despite the marginal accuracy attainable with 0.050M [Gₜ] (due to the small magnitude of the dimer peak), it is apparent from Table 4.5 that,
Table 4.5. Effect of pH on $R_{eq}$ at 25.0°C ($\mu = 0.060$M, 0.02M total phthalate, $[G_T] = 0.05$M)

<table>
<thead>
<tr>
<th>$R_{Ph}$(nominal)</th>
<th>pH$^a$</th>
<th>$R_{eq}^b$</th>
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</thead>
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<tr>
<td>0.125</td>
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<td>0.0254</td>
</tr>
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</tr>
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<td>4.79</td>
<td>0.0255</td>
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<tr>
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</tr>
<tr>
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</tr>
<tr>
<td>8</td>
<td>6.06</td>
<td>0.0261</td>
</tr>
</tbody>
</table>

$^a$ Determined electrometrically.

$^b$ $R_{eq} = 0.813(R_H - 0.005)$. 
over the observed pH range, acidity has no significant effect on $R_{eq}$. Of course, constancy of $R_{eq}$ at constant $[G]_T$ implies constancy of $K_{D_{app}}$. Assuming no systematic effects due to pH or changes in the concentration of phthalate species, the reproducibility of the $R_{eq}$ values obtained (std. dev. = 1.7%) provides an estimate of the precision attainable in the kinetic studies to follow. This estimate applies to the worst case situation corresponding to injection of samples at very high conversion.

4.2.5. Higher-order oligomers

Chromatographic elution profiles of concentrated (1 to 10M) solutions of glyoxal suggested the presence of substantial proportions of higher-order oligomers. Unfortunately, the chromatographic methods developed for use in the preceding study of dimer-monomer equilibrium did not provide quantitative separation of higher-order species. However, some qualitative observations will be presented.

A commercial preparation of glyoxal, stated to be 40 wt% glyoxal, was subjected to chromatographic analysis. This preparation contained a small amount of insoluble material, presumably trimeric dihydrate. A portion of the clear soluble fraction was accurately diluted and then subjected to analysis for total glyoxal as monomer equivalents by the Girard-T spectrophotometric procedure. Additional dilutions of the above "standard" concentrate, ranging from 0.47 to 9.4M, were prepared. Following incubation for ~32 h at 25°C (pH ~2.6), the glyoxal solutions were eluted at 5.0°C and the resulting profiles monitored by RI. Elution at 5°C resulted in greater resolution of the higher-order oligomers than elution at 0°C. Injection volumes were adjusted so that approximately full-scale
dimer peaks were obtained at a refractometer attenuation of 16x. The early-eluting oligomer peaks were monitored at an attenuation of 8x. Comparisons of the relative peak heights of the partially resolved oligomer peaks to the dimer peak as functions of $[G_T]$ were then made.

As shown in Fig. 4.7, four additional early-eluting peaks were partially resolved. Tentative assignments of oligomeric order were made based on both order of elution (due to size exclusion higher molecular weight solutes with similar chemical properties tend to elute more quickly than smaller solutes) and on the relative changes in peak height with changes in $[G_T]$ as listed in Table 4.6. Two trimeric peaks, denoted $G_{3a}$ (early eluting) and $G_{3b}$ (late eluting), one tetrameric peak $G_4$, and one pentameric $G_5$ peak are suggested. The numerical values presented in Table 4.6 are crude estimates only, since 1) none of the four peaks was quantitatively separated, 2) the rate of oligomer hydrolysis during elution is unknown, and 3) the relative molar refractive indices of the presumed oligomers are unknown.

From the same series of chromatographic elutions, quantitative estimates of the molar ratio of dimer to monomer $R_{eq}$ were obtained, although at the lower glyoxal concentrations additional injections of reduced volume were required to obtain monomer peaks readable at 16x. In Fig. 4.8 are plotted both the observed values of $R_{eq}$ and (as the dashed line) predicted values extrapolated from Eq. 4.24 to follow with $K_{D_{app}} = 0.56M^{-1}$, assuming the absence of any higher-order oligomers.

$$R_{eq} = \frac{1}{4} \left(1 + 8K_{D_{app}}[G_T]\right)^{1/2} - 1$$ (4.24)
Fig. 4.7. Elution profile of 7.5M glyoxal (equilibrated at 25.0°C) on Aminex HPX-87H at 0°C. Chromatographic conditions: eluent 0.001N H₂SO₄, flow rate 0.6 ml/min, R.I. detector attentuations 8x and 32x
Table 4.6. Indicated abundance relative to dimer of presumed higher-order oligomers at 25.0°C as a function of total glyoxal concentration

<table>
<thead>
<tr>
<th>[Gₜ], M</th>
<th>G₃a (early)</th>
<th>G₃b (late)</th>
<th>G₄</th>
<th>G₅</th>
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<tr>
<td>0.469</td>
<td>2.5</td>
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<td>----</td>
</tr>
<tr>
<td>0.937</td>
<td>4.1</td>
<td>4.1</td>
<td>----</td>
<td>----</td>
</tr>
<tr>
<td>1.87</td>
<td>6.5</td>
<td>6.2</td>
<td>2.9</td>
<td>0.9</td>
</tr>
<tr>
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<td>7.7</td>
<td>2.6</td>
</tr>
<tr>
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<td>13</td>
<td>13.9</td>
<td>6.2</td>
</tr>
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<td>21</td>
<td>19</td>
<td>27.2</td>
<td>17.6</td>
</tr>
</tbody>
</table>

*Elution at 5.0°C, 0.6 ml/min, 0.001N H₂SO₄ eluent.*
Fig. 4.8. Observed and calculated equilibrium ratios, $R_{eq}$, of dimeric to monomeric glyoxal at 25.0°C as a function of $[G_T]$. 

Mathematical equation: 

$$R_{eq} = \frac{K_{app} [G_T]}{(1 + 8 K_{Dapp} [G_T])^{1/2} - 1}$$
Close agreement in Fig. 4.8 between observed and calculated \( R_{eq} \) values is apparent for \( [G_T] < \sim 3M \). The slightly lower than predicted response over the intermediate \( [G_T] \) range of 0.5 to 2M is consistent with the indicated accumulation of trimeric forms. At still higher \( [G_T] \), however, the observed ratio of dimer to monomer appears to increase linearly with \( [G_T] \), resulting in values substantially greater than those predicted from the results at low concentration, in spite of the increasing presence of the higher-order oligomers ignored in the prediction of \( R_{eq} \).

The reason for these anomalous results is unknown. However, at high glyoxal concentrations relatively large variations in the activity of solvent water should be anticipated. Other possible explanations include significant tailing of the later-eluting trimer peak, as well as resin-catalyzed hydrolysis to dimer of higher-order oligomers, although hydrolysis of trimer would presumably yield initially equimolar amounts of monomer and dimer. Another possible explanation might be the accumulation at high \( [G_T] \) of an additional higher-order form eluting under the dimer peak.

4.3. Results — Dimerization Kinetics

This section and Sec. 4.4 to follow describe the experimental findings and interpretations concerning the rates of conversion of glyoxal dimeric to monomeric forms. Before proceeding, however, one minor point should be noted about the nomenclature assigned that reaction. Because monomeric glyoxal is assumed to exist predominantly in the doubly hydrated form, the term "dimer hydrolysis" is probably more descriptive of the overall reaction observed in this study than are the more general terms, "solvolyis", "
"depolymerization", or "monomerization". For that reason, "dimer hydrolysis" has been employed in the remainder of this report. Nevertheless, the probable presence of small proportions of monohydrated monomer should be kept in mind.

4.3.1. Mathematical analysis of kinetic results

All kinetic experiments following the rate of dimer-monomer interconversion were conducted at constant alkalinity in dilute HCl or in phthalate or phosphate buffers. Under those conditions, the simplest empirical model against which the kinetic data could be tested is that resulting from the assumption of pseudo-first-order dimer hydrolysis and pseudo-second-order dimerization. As represented in Eq. 4.25, the hydrolysis reaction is herein defined as the "forward" reaction, while the dimerization is defined as the "reverse" reaction:

\[ G_2 \frac{k_f(\text{obs})}{k_r(\text{obs})} \rightarrow 2 \ G_1 \]

(4.25)

Note that in the kinetic studies to be described, it has been assumed that the HPLC method employed monitored the total concentration of mono- and dihydrated monomeric glyoxal \([G_1]\).

The simple dimerization scheme above is conveniently studied by dilution techniques, in which the rate of hydrolysis of an initially pure dimer solution is monitored under conditions at which the reverse (dimerization) reaction remains negligible throughout the observable reaction course. Under those conditions, \(k_f(\text{obs})\) can be obtained directly. Unfor-
ultimately, with the experimental methods available, it was neither possible to start with pure dimer nor possible to accurately observe the reaction at high dilution. Thus, the reverse reaction could not be neglected over the entire reaction course. Although the above design limitations complicated the analysis of the kinetic data, they did not significantly reduce the accuracy of the kinetic results obtained.

The net rate of dimer hydrolysis is given by Eq. 4.26 to follow, in which \( k_f^{\text{obs}} \) and \( k_r^{\text{obs}} \) are represented simply by \( k_f \) and \( k_r \) for brevity:

\[
-d[G_2]/dt = k_f[G_2] - k_r[G_1]^2
\]  

(4.26)

However, for the reasons presented in Sec. 4.2, the experimental quantity that could be most directly and accurately monitored was the concentration ratio of dimer to monomer \( R \). Assuming that appropriate thermodynamic information is available, Eq. 4.26 can be rewritten in terms of the single observed variable \( R \) as follows.

The net rate of change in the observed dimer to monomer ratio \( dR/dt \), is a function of \( [G_1] \) and \( [G_2] \) and their time derivatives, as obtained via Eqs. 4.27a–c:

\[
\frac{dR}{dt} = \frac{d([G_2]/[G_1])}{dt}
\]

(4.27a)

\[
= [G_2]d([G_1]^{-1})/dt + [G_1]^{-1}d[G_2]/dt
\]

(4.27b)

\[
= -[G_2][G_1]^{-2}d[G_1]/dt + [G_1]^{-1}d[G_2]/dt
\]

(4.27c)

However, \( d[G_1]/dt \) and \( d[G_2]/dt \) are related stoichiometrically as follows:
\[ \frac{d[G_1]}{dt} = -2\frac{d[G_2]}{dt} \] (4.28)

Substitution of Eq. 4.28 into Eq. 4.27c yields the following equation relating \( \frac{dR}{dt} \) to \( \frac{d[G_2]}{dt} \):

\[ \frac{dR}{dt} = (2[G_2][G_1]^{-2} + [G_1]^{-1})\frac{d[G_2]}{dt} \] (4.29)

If the original rate expression, Eq. 4.26, is substituted into Eq. 4.29, a differential equation in terms of \( R \), \([G_1]\), and \([G_2]\) results, as shown by Eqs. 4.30a-c:

\[ -\frac{dR}{dt} = (2[G_2][G_1]^{-2} + [G_1]^{-1})(k_f[G_2] - k_r[G_1]^2) \] (4.30a)

\[ = 2k_f([G_2]/[G_1])^2 + k_f[G_2]/[G_1] - k_r(2[G_2] + [G_1]) \] (4.30b)

\[ = k_f(2R^2 + R) - k_r(2[G_2] + [G_1]) \] (4.30c)

The quantity \((2[G_2] + [G_1])\) in Eqs. 4.30b,c represents the total glyoxal concentration in monomer equivalents \([G_T]\), a quantity that is constant throughout any given experiment (in the absence of significant disproportionation). If \([G_T]\) is written in terms of the equilibrium concentrations, Eq. 4.31 is obtained:

\[ -\frac{dR}{dt} = k_f(R + 2R^2) - k_r([G_1]_{eq} + 2[G_2]_{eq}) \] (4.31)

The reverse rate constant and equilibrium concentrations can be eliminated from Eq. 4.31 if it is noted that \( \frac{dR}{dt} = 0 \) at equilibrium. The following relationship is obtained:
Substitution of Eq. 4.32 into Eq. 4.31 above yields the following rate equations in terms of only the observed ratio $R$, the forward rate constant $k_f$, and $R_{eq}$:

$$-\frac{dR}{dt} = k_f (R + 2R^2) - k_f (R_{eq} + 2R_{eq}^2)$$

$$= k_f [(R + 2R^2) - (R_{eq} + 2R_{eq}^2)]$$

Use of the above rate expression requires knowledge of the equilibrium ratio of dimer to monomer $R_{eq}$. While it might be convenient to determine $R_{eq}$ experimentally in the study of relatively rapid reactions, in general $R_{eq}$ is more readily obtained from known thermodynamic information. In the latter instance, an alternative rate expression, written in terms of $K_{Dapp}$ and the known total concentration of glyoxal $[G_T]$, is required.

The thermodynamic results presented in Sec. 4.2 may be readily incorporated if use is made of the following equation developed in Sec. 4.2:

$$R_{eq} (1 + 2R_{eq}) = K_{Dapp} [G_T]$$

It should be recalled that $K_{Dapp}$ represents the apparent equilibrium constant for dimerization and is given by:

$$K_{Dapp} = \frac{[G_2]}{[G_1]^2}$$

Substitution of Eq. 4.18 into Eq. 4.33 results in the desired rate
expression:

\[-\frac{dR}{dt} = k_f[(R + 2R^2) - K_{Dapp}[G_T]]\] (4.34)

In either form, the above rate expressions for \(dR/dt\) can be integrated from time \(t = 0\) and the initial dimer to monomer ratio \(R = R_0\) to yield the following integrated rate expression,

\[t = (k_f(\text{obs})_{\text{eq}})^{-1}\log_e\left(\frac{4R_0 + 1 - R_{\text{eq}}^*}{4R_0 + 1 + R_{\text{eq}}^*}\right) - \log_e\left(\frac{4R + 1 - R_{\text{eq}}^*}{4R + 1 + R_{\text{eq}}^*}\right)\] (4.35)

wherein the expression for \(R_{\text{eq}}^*\) depends on the particular form of the rate expression considered:

\[R_{\text{eq}}^* = [1 + 8R_{\text{eq}}(1 + 2R_{\text{eq}})]^{1/2}\] (4.36a)

\[= 4R_{\text{eq}} + 1\]

\[= [1 + 8K_{Dapp}[G_T]]^{1/2}\] (4.36b)

If \(R_{\text{eq}}\) is obtained experimentally, the expression for \(R_{\text{eq}}^*\) simplifies (as indicated by Eq. 4.36a) as does the integrated rate expression:

\[t = [k_f(4R_{\text{eq}} + 1)]^{-1}\log_e\left(\frac{2R_0 - 2R_{\text{eq}}}{2R_0 + 2R_{\text{eq}} + 1}\right) - \log_e\left(\frac{2R - 2R_{\text{eq}}}{2R + 2R_{\text{eq}} + 1}\right)\] (4.37)

Eq. 4.35 can be solved for \(R\) as an explicit function of time \(t\), yielding Eq. 4.38, wherein the argument of the first logarithmic term in Eq. 4.35,
a constant in any given kinetic run, is denoted $F(R_o, R^*_e)$:

$$
R(t) = \frac{R^*_e - 1 + (R^*_o - 1)F(R_o, R^*_e)\exp\{-k_f(\text{obs})R^*_e t\}}{4(1 - F(R_o, R^*_e)\exp\{-k_f(\text{obs})R^*_e t\})}
$$

A more analytically useful equation of "first-order" form is obtained by slight rearrangement of Eq. 4.35:

$$
\frac{4R^*_o + 1 - R^*_e}{4R + 1 + R^*_e} \frac{4R + 1 - R^*_e}{4R + 1 + R^*_e} = k_f(\text{obs})R^*_e t - \log_e \frac{4R^*_o + 1 - R^*_e}{4R^*_o + 1 + R^*_e}
$$

Note that a linear plot with slope $k_f(\text{obs})R^*_e$ is predicted if the quantity on the left side of Eq. 4.39, hereafter denoted $-\log_e \{F(R, R^*_e)\}$, is graphed vs. time of reaction. This is true regardless of the initial concentration ratio $R_o$ or the final observed conversion. Note that, while it is not necessary to know $R_o$ in order to determine $k_f(\text{obs})$, it is necessary to know accurately either $R^*_e$ or $K_{Dapp}$ and $[G]_T$.

4.3.2 Reaction order with respect to monomeric and dimeric glyoxal

The data obtained from kinetic runs conducted at constant alkalinity were fit to the simple kinetic model described above using Eq. 4.39. Over a broad range of temperature and pH, and in three different buffers, the calculated values of $-\log_e \{F(R, R^*_e)\}$ when plotted vs. reaction time closely approximated straight lines, although slight curvature was often apparent in regions of the log plots corresponding to the earliest stages of reaction. Therefore, values of $-\log_e \{F(R, R^*_e)\} < 1.2$, corresponding
to 23% conversion (see below for definition), were excluded in the calculation of best fit parameters. Conversely, values of $-\log_e{F(R,R_{eq}^*)}$ greater > 3.2, corresponding to 92% conversion, were excluded due to the increase in scatter at high conversion, although in general no systematic deviation from linear was apparent at high conversion. For each kinetic run, values within the above conversion range were fit to a straight line by linear regression. The values obtained for $k_{f(\text{obs})}$ for experiments conducted in HCl, phthalate, and phosphate buffer are listed in Tables 4.7, 4.8a-c, and 4.9, respectively.

For the nine series of experiments conducted, which employed three different buffers at three different temperatures, remarkably constant mean correlation coefficients were obtained, except for the most rapid set of reactions carried out in phosphate buffer at 45°C. A mean correlation coefficient of 0.9996 with a standard deviation of ±0.0002 was obtained. The kinetic results were, therefore, judged to be in sufficient agreement with the simple dimerization model to make consideration of more complex models unwarranted.

A slight concave-upward curvature, suggesting an apparent "lag" in the kinetic response, was noted in most runs conducted at pH < 5-5.5. At higher pH, curvature was not generally noted, although a very rapid initial decrease in $R$ was suggested by comparison of the y-intercepts of the $\log_e{F(R,R_{eq})}$ plots with corresponding experimentally derived values of $R_0$ obtained under less reactive conditions. The apparent inconsistencies in the above log plots were approximately quantitated in the following manner.

Measurement of the initial dimer to monomer ratio $R_0$ was not required in order to calculate $k_{f(\text{obs})}$. Moreover, that value would not be particu-
Table 4.7. Effect of pH (pOH) on $k_f(\text{obs})$ in dilute $\text{HCl}$ at 5, 25, and 45°C and $\mu = 0.060\text{M}$

<table>
<thead>
<tr>
<th>Temperature, °C</th>
<th>Conc. $^a$ HCl, mM</th>
<th>pH $^b$</th>
<th>pOH $^c$</th>
<th>$k_f(\text{obs}) \times 10^6$, s$^{-1}$</th>
<th>%$C_R(t=0)$ $^d$</th>
</tr>
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<tbody>
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$^a$ $\rho_{\text{H}_2\text{O}}(5^\circ\text{C}) = 1.003$ g/cm$^3$
$\rho_{\text{H}_2\text{O}}(25^\circ\text{C}) = 1.000$ g/cm$^3$
$\rho_{\text{H}_2\text{O}}(45^\circ\text{C}) = 0.993$ g/cm$^3$.

$^b$ Calculated assuming:
$\gamma_{\text{H}^+}(5^\circ\text{C}) = 0.812$
$\gamma_{\text{H}^+}(25^\circ\text{C}) = 0.807$
$\gamma_{\text{H}^+}(45^\circ\text{C}) = 0.801$.

$^c$ $pK_a(5^\circ\text{C}) = 14.734$
$pK_a(25^\circ\text{C}) = 13.996$
$pK_a(45^\circ\text{C}) = 13.396$.

$^d$ Extrapolation to zero time (see text).
Table 4.8a. Effect of pH (pOH) on $k_{f(\text{obs})}$ in 0.020M total phthalate buffer at 5.00°C and $c = 0.060M$

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<th>$R_{\text{pH}}$</th>
<th>$pH^{a,b}$</th>
<th>$pOH^{c}$</th>
<th>$k_{f(\text{obs})} \times 10^6^{d}$</th>
<th>$%C_R(t=0)^{e}$</th>
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$^aK_{Ph1} = 1.221 \times 10^{-3}$, $K_{Ph2} = 3.817 \times 10^{-6}$.

$^b$Corrected for acidic impurity.

$^c$pK$_w$(5°C) = 14.734.

$^d$Determined by linear regression of results obtained from 31.5(+6.5)% to 86.5(+3.5)% conversion.

$^e$Extrapolation to zero time (see text).
Table 4.8b. Effect of pH (pOH) on $k_f(\text{obs})$ in 0.020M total phthalate buffer at 25.00°C

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<th>$\mu$, mM</th>
<th>$\text{pH}^{a,b}$</th>
<th>$\text{pOH}^{c}$</th>
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<th>$%C_R(t=0)^e$</th>
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$^{a}K_{\text{Ph1}} = 1.162 \times 10^{-3}$, $K_{\text{Ph2}} = 3.913 \times 10^{-6}$.

$^{b}$Corrected for acidic impurity.

$^{c}pK_w(25^\circ C) = 13.999$.

$^{d}$Determined by linear regression of results obtained from 28.3(±6.6)% to 87.5(±2.7)% conversion.

$^{e}$Extrapolation to zero time (see text).
Table 4.8c. Effect of pH (pOH) on $k_{f(obs)}$ in 0.020M total phthalate buffer at 45.00°C and $\mu = 0.060M$

<table>
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<tr>
<th>$R_{Ph}$</th>
<th>pH$^{a,b}$</th>
<th>pOH$^{c}$</th>
<th>$k_{f(obs)} \times 10^3$ $^{d}$</th>
<th>$%R(t=0)^{e}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4</td>
<td>2.65</td>
<td>10.74</td>
<td>0.272</td>
<td>-10</td>
</tr>
<tr>
<td>-2</td>
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<td>-1</td>
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<td>10.38</td>
<td>0.309</td>
<td>-5</td>
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<td>10.14</td>
<td>0.414</td>
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<td>-1/4</td>
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<td>9.89</td>
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<td>0.820</td>
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<td>5.26</td>
<td>-7</td>
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<td>16</td>
<td>6.32</td>
<td>7.07</td>
<td>37.2</td>
<td>+11</td>
</tr>
</tbody>
</table>

$^{a}K_{Ph1} = 1.064 \times 10^{-3}$, $K_{Ph2} = 3.446 \times 10^{-6}$.

$^{b}$Corrected for acidic impurity.

$^{c}pK_w(45^\circ C) = 13.396$.

$^{d}$Determined by linear regression of results obtained from 34.1 (±3.9)% to 90.1(±3.1)% conversion.

$^{e}$Extrapolation to zero time (see text).
Table 4.9. Effect of pH (pOH) on $k_f(\text{obs})$ in phosphate buffer at 5, 25, and 45°C and $\mu = 0.060\text{M}$

<table>
<thead>
<tr>
<th>Temperature, °C</th>
<th>$R_p$</th>
<th>pH$^{a,b}$</th>
<th>pOH$^c$</th>
<th>$k_f(\text{obs})^d$</th>
<th>$%R(t=0)^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.00</td>
<td>1/8</td>
<td>6.05</td>
<td>8.68</td>
<td>0.309</td>
<td>+2</td>
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<tr>
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<td>1/4</td>
<td>6.36</td>
<td>8.37</td>
<td>0.403</td>
<td>+10</td>
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<tr>
<td></td>
<td>1/2</td>
<td>6.66</td>
<td>8.07</td>
<td>0.526</td>
<td>+7</td>
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<tr>
<td></td>
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<td>7.76</td>
<td>0.668</td>
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<td>7.27</td>
<td>7.47</td>
<td>0.936</td>
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<tr>
<td></td>
<td>4</td>
<td>7.56</td>
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<td>1.34</td>
<td>+11</td>
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<tr>
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<td>8</td>
<td>7.84</td>
<td>6.90</td>
<td>1.96</td>
<td>+12</td>
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<tr>
<td>25.00</td>
<td>1/8</td>
<td>5.96</td>
<td>8.03</td>
<td>2.47</td>
<td>-4</td>
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<td></td>
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<td>6.89</td>
<td>7.11</td>
<td>8.22</td>
<td>+6</td>
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<tr>
<td></td>
<td>2</td>
<td>7.18</td>
<td>6.82</td>
<td>13.5</td>
<td>+7</td>
</tr>
<tr>
<td></td>
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<td>+6</td>
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<tr>
<td></td>
<td>8</td>
<td>7.75</td>
<td>6.25</td>
<td>39.0</td>
<td>+8</td>
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<tr>
<td>45.00</td>
<td>1/8</td>
<td>5.93</td>
<td>7.46</td>
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<td>6.24</td>
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<tr>
<td></td>
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<td>6.85</td>
<td>60.9</td>
<td>+9</td>
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<td>1</td>
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<td>6.54</td>
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<td>2</td>
<td>7.15</td>
<td>6.25</td>
<td>193</td>
<td>+22</td>
</tr>
</tbody>
</table>

$^a$Corrected for acidic impurity.

$^b$pK$^p_2(5^\circ\text{C}) = 7.281$

$^c$pK$^p_2(25^\circ\text{C}) = 7.199$

$^d$pK$^p_2(45^\circ\text{C}) = 7.181$.

$^c$pK$^w(5^\circ\text{C}) = 14.734$

$^d$pK$^w(25^\circ\text{C}) = 13.996$

$^e$(50^\circ\text{C}) = 13.396$.

$^d$Determined by linear regression of results obtained from 32.1(±9.9)%
to 87.3(±5.0)% conversion.

$^e$Extrapolation to zero time (see text).
larly meaningful due to the presumed presence of trimeric forms in the unreacted solution. However, because the total glyoxal concentration \([G_T]\) was accurately known, a hypothetical, thermodynamically based estimate of \(R_o\) was obtainable from the initial (before dilution) total glyoxal concentration \([G_T]\) and \(K_{Dapp}\) as functions of temperature using Eq. 4.24. This predicted value, denoted \(R_o(P)\), represents the initial dimer to monomer ratio that would be observed in the absence of higher-order oligomers. A second, kinetically based value of \(R_o\), denoted \(R_o(E)\), was obtained by extrapolation of the kinetic results to zero time. The difference between the thermodynamically predicted and extrapolated values, provides one estimate of the deviation of the kinetic results from the assumed model.

The deviations above are more meaningfully expressed as fractions of the total predicted changes in the measured variable. These fractional deviations are herein defined as \(C_R = (R_o - R)/(R_o - R_{eq})\) and are analogous to chemical conversions. The use of the \(C_R\) rather than conversion based on either monomer or dimer concentrations is justified on the basis of the relatively small variation in \([G_1]\) occurring over the course of the reaction. The deviation, \(C_R(t=0)\), between the kinetically extrapolated and thermodynamically predicted initial conditions as a fraction of the total predicted reaction is obtained from Eqs. 4.40a,b:

\[
C_R(t=0) = \frac{(R_o(P) - R_o(E))/(R_o(P) - R_{eq})}{R_o(P) + \frac{(1 - R^*_e)(1 + \exp^L)/(1 - \exp^L)}/4} = \frac{R_o(P) - R_{eq}}{R_o(P) - R_{eq}}
\]

where
\[ L = \log_e \{F(R, R^{*}) \}_{t=0} \]

Negative values of \( C_R(t=0) \) quantitate the initial kinetic lag observed at low pH, while positive values quantify the apparent rapid initial reaction observed at higher pH. Values of \( C_R(t=0) \) for each kinetic run are included Tables 4.7-9.

Negative values of \( C_R(t=0) \) indicating a lag equivalent to 10% of the total conversion were obtained from runs at pH < ~5. Conversely, positive values of \( C_R(t=0) \) indicating an initial rapid reaction equivalent to roughly 10% conversion were obtained at more alkaline pH. At each temperature, a fairly abrupt transition from negative to positive values of \( C_R(t=0) \) occurs, centered at pH values corresponding roughly to the inflection points in the corresponding plots of \( \log_{10} k_{obs} \) vs. \( \log_{10} pH \) (see Sec. 4.3.4). Thus, a possible correlation between the initial deviations from pseudo-first-order kinetics and the hydroxide ion dependence of the reaction is indicated.

The proportion of trimeric forms was too low to allow determination of the rates of hydrolysis of those species. Qualitatively, however, it was noted that the small trimer peak detectable in the 1M stock solution disappeared more rapidly than did the dimer peak. While this appeared to be true even at low pH, the rate of trimer hydrolysis at high pH appeared to be extremely rapid. Under those conditions, no trimeric peak was detected even at very low dimer conversions.

The apparent high rate of trimer hydrolysis at near ambient conditions brings into question the reliability of the HPLC estimates of the proportions of higher-order forms present. In that regard, it should be noted
that the rate of trimer hydrolysis appeared to be slowest at low pH, that is, under conditions at which the hydrolysis is likely to be predominantly hydronium ion catalyzed. Secondly, the effect of elution temperature on the relative magnitude of the trimer peak appeared to be greater than that on the dimer peak, suggesting a higher activation energy for the acid-catalyzed hydrolysis of trimer. Thus, under actual elution conditions the rate of trimer hydrolysis might well be sufficiently slow to allow chromatographic separation, as was suggested from the elution profiles of concentrated glyoxal solutions.

It is tempting to correlate the deviations in the kinetic results from the assumed model with the observed rapid disappearance of trimer. Indeed, a moderately more rapid hydrolysis of the roughly 2–3% trimer assumed to be initially present would presumably result in the production of equimolar amounts of both monomer and dimer and so might partially offset the normal decrease in R during the early stages of the reaction. However, at this point other equally plausible explanations can no doubt be proposed.

The discussion above points up an important limitation of these kinetic studies. In the derivation of the simple kinetic model employed, it has been implicitly assumed that all of the dimeric forms presumed initially present react at identical rates. Note that with this assumption it is necessary to assume neither identical refractive index responses nor identical chromatographic elution times. While it might be reasonable to expect similar reactivities for the two structurally similar five-membered ring forms believed predominant, the six-membered ring structure possibly present in minor proportions might react considerably faster or slower.

Finally, one experimental shortcoming in the above kinetic study must
be pointed out. The concentration range over which the ratio of dimer to monomer could be accurately determined was quite limited. Initial total glyoxal concentrations greater than 1M could not be employed because of the above complications of higher-order oligomers. On the other hand, the limited sensitivity of the differential refractometer used to determine the dimer to monomer ratio prevented accurate experiments at higher dilution.

4.3.3. **Effect of buffer salts on $k_f^{\text{obs}}$**

Although the exact sequence of elementary reactions constituting the dimerization of glyoxal are not known, the overall reaction may nonetheless be formally viewed as a typical equilibrium addition reaction. Such reactions have usually been found to be subject to general acid-base catalysis, although the catalytic efficiency of buffer species, in comparison to hydronium ion or especially hydroxide ion, is generally quite low.

The primary objective in the rate studies to be described was the determination of hydronium ion- and hydroxide ion-catalyzed dimer hydrolysis rates. However, the range of hydronium ion and hydroxide ion concentrations over which the reaction could be observed was such that the use of buffer solutions was required. Although the total concentration of buffer salts was kept as low as possible at 0.020M, it was nevertheless necessary to determine the degree to which the various buffer species influenced the observed hydrolysis rates.

The effect of phthalate buffer on $k_f^{\text{obs}}$ was obtained from rate determinations at 25°C on glyoxal solutions containing equimolar mono- and dibasic phthalate ($R_{\text{Ph}} = 1$) at varying total phthalate concentrations. The ionic strength was maintained constant at 0.060M with added KCl, which
helped to minimize the accompanying changes in pH. The same ionic strength was maintained in experiments in which the pH was varied. However, because of the varying effects on buffer pH of phthalic acid formation and hydrolysis of water (see Sec. 7.4) and the decrease in buffer capacity as the total buffer concentration was reduced, the reaction pH varied slightly with changes in total buffer concentration. The net changes in buffer pH, after addition of glyoxal, were measured electrometrically and the observed values of \( k_f(\text{obs}) \) were then corrected to an arbitrary nominal pH, based on the observed reaction order in hydroxide ion at that pH. The changes in pH which accompanied the variations in total buffer concentration were so small that an average order in hydroxide ion could be assumed.

As indicated in Table 4.10, the changes in \( k_f(\text{obs}) \) attributable to the presence of phthalate ions, over the total phthalate concentration range of 0.005 to 0.02M, were extremely small — too small to accurately quantitate. Therefore, in the determination of pH effects on \( k_f(\text{obs}) \), which were carried out at 0.020M total phthalate, catalysis by mono- and dibasic phthalate ions was ignored. Furthermore, in view of the low sensitivity observed toward hydronium ion catalysis, significant general acid catalysis by phthalic acid was considered unlikely at the concentrations used. However, the above assumption should have been verified experimentally.

The effects of phosphate buffer on \( k_f(\text{obs}) \) at 25°C were also obtained from rate determinations employing equimolar buffer solutions maintained at a constant ionic strength of 0.060M. Again, the actual changes in solution pH with changes in total buffer concentration were determined electrometrically. As indicated also in Table 4.10, a small but significant increase
Table 4.10. Effect of phthalate and phosphate buffers on $k_f(\text{obs})$ at $u = 0.060M$, $R = 1.00$, and $25^\circ C$.

### a. Phthalate buffer

<table>
<thead>
<tr>
<th>$a_{\text{Ph}}, M$</th>
<th>pH</th>
<th>$k_f(\text{obs}) \times 10^3, \text{s}^{-1}$</th>
<th>$k_f(\text{pH 5.05}) \times 10^3, \text{s}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>5.05</td>
<td>0.885</td>
<td>0.885</td>
</tr>
<tr>
<td>0.010</td>
<td>5.06</td>
<td>0.927</td>
<td>0.913</td>
</tr>
<tr>
<td>0.020</td>
<td>5.09</td>
<td>0.973</td>
<td>0.914</td>
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</tbody>
</table>

### b. Phosphate buffer

<table>
<thead>
<tr>
<th>$a_{\text{P}}, M$</th>
<th>pH</th>
<th>$k_f(\text{obs}) \times 10^3, \text{s}^{-1}$</th>
<th>$k_f(\text{pH 6.80}) \times 10^3, \text{s}^{-1}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.005</td>
<td>6.80</td>
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<td>6.48</td>
</tr>
<tr>
<td>0.010</td>
<td>6.84</td>
<td>7.38</td>
<td>6.92</td>
</tr>
<tr>
<td>0.020</td>
<td>6.88</td>
<td>8.09</td>
<td>7.11</td>
</tr>
</tbody>
</table>

$a_{k_f(\text{pH 5.05})} = k_f(\text{obs}) \exp_{10} \{n(5.05 - \text{pH})\}; n = 0.70.$

$b_{k_f(\text{pH 6.80})} = k_f(\text{obs}) \exp_{10} \{n(6.80 - \text{pH})\}; n = 0.68.$
was observed with increasing total phosphate concentration.

According to the Bronsted theory of general acid-base catalysis the acid and base catalytic constants, $k_a$ and $k_b$, for a particular catalyst are interrelated by Eqs. 4.41a,b,

\[
\begin{align*}
{k_a} &= g_1 k_a^x q^x p^{1-x} \\
{k_b} &= g_2 k_b^{1-x} q^x p^{1-x}
\end{align*}
\]

(4.41a)

(4.41b)

where $g_1$ and $g_2$ represent proportionality constants and $p$ and $q$ denote constants reflecting statistical factors. $K_a$ and $K_b(=K_w/K_a)$ represent the acid and base dissociation constants for the particular catalyst, while the parameter "x" represents a constant, ranging in value from 0 to 1, the magnitude of which is independent of the particular catalyst employed.

A crude correction for catalysis can be attempted if the following assumptions are made regarding dimer hydrolysis. In view of the much greater sensitivity of dimer hydrolysis to hydroxide ion catalysis, it might first be assumed that the observed phosphate catalysis is primarily a base-catalyzed effect. Furthermore, noting that at 25°C the second acid dissociation constant for phosphoric acid $K_{p2}$ is nearly 10^5-fold less than the first dissociation constant $K_{p1}$ and that $K_b = K_w/K_a$ it might also be assumed that, unless the value of $1-x$ is extremely small, the catalytic effect of phosphate buffer in the range of pH 6 to 8 is mediated primarily by the dibasic anion. Actually, as noted in Sec. 2, Bronsted coefficients for base catalysis ranging from about 0.3 to 0.7 have been reported for similar reactions. Based upon the above assumptions a very crude estimate of 0.077 s^{-1}M^{-1} was obtained for the catalytic constant
for dimer hydrolysis by dibasic phosphate ion.

4.3.4. **Effect of pH (pOH) on $K_f(\text{obs})$**

Values of $k_f(\text{obs})$ obtained by linear regression are listed as functions of pH and pOH in Tables 4.7-4.9 and are plotted as $\log_{10}k_f(\text{obs})$ vs. pH and pOH in Figs. 4.9 and 4.10, respectively. The shapes of the curves in Figs. 4.9 and 4.10 are suggestive of both hydronium ion- and hydroxide ion-catalysis. Furthermore, the broad minima centered at roughly pH 2.7 suggest that solvent catalysis may be important in that region. While the particular curves representing the kinetic response at 25°C are virtually identical in shape, the response curves for 5 and for 45°C are shaped differently when plotted vs. pH than when plotted vs. pOH. This is explained by the sizable increase in $K_w$ with increasing temperature, which causes an increase in $a_{\text{OH}^-}$ at constant $a_{\text{H}^+}$ as the temperature is increased. Conversely, an increase in $a_{\text{H}^+}$ at constant $a_{\text{OH}^-}$ with increasing temperature is noted. Thus, thermal effects on dimer hydrolysis in the alkali-catalyzed region are more clearly represented by plots of $k_f(\text{obs})$ vs. pOH, while the converse is true for hydronium ion-catalysis.

The kinetic response depicted in Figs. 4.9 and 4.10 is typical of general acid-base catalyzed reactions. Ignoring for the moment any influence of buffer catalysis, kinetic rate laws of the following form have generally been advanced for such reactions.

$$k_{\text{obs}} = k_0[H_3O^+] + k_1[H_2O] + k_2[OH^-] \quad (4.42)$$

However, the sigmoidal dependence of $\log_{10}k_f(\text{obs})$ on pOH suggested by
Fig. 4.9. Effect of pH on $k_f(\text{obs})$ at 5, 25, and 45°C at $\mu = 0.060$M. Solid lines denote fit of data points to Eq. 4.43 by non-linear regression. Symbols: (•) HCl; (♦) phthalate buffer; (▲) phosphate buffer.
Fig. 4.10. Effect of pOH on $k_f(\text{obs})$ at 5, 25, and 45°C at $\mu = 0.060$M. Solid lines denote fit of data points to Eq. 4.43 by non-linear regression. Symbols: (■) HCl; (●) phthalate buffer; (▲) phosphate buffer.
Fig. 4.10 cannot be accounted for by the simple model represented by Eq. 4.42. Furthermore, in view of the relatively small rate enhancement effected by increasing total phthalate (as equimolar concentrations of $\text{HPh}^-$ and $\text{Ph}^{2-}$) and by total phosphate (as equimolar $\text{H}_2\text{P}^-$ and $\text{H}\text{P}^{2-}$), the unusual base sensitivity cannot be dismissed as due to buffer catalysis.

Figs. 4.9 and 4.10 suggest a kinetic rate law for glyoxal dimer hydrolysis of the following form:

$$k_f^{\text{obs}} = b_1[H_2\text{O}^+] + b_2 + b_3[\text{OH}^-]/(1 + b_4[\text{OH}^-]) + b_5[\text{H}_2\text{O}]$$  \hspace{1cm} (4.43)$$

Therefore, the observed rate constants in Tables 4.7-9 were fit to Eq. 4.43 by non-linear regression. The predicted kinetic response, calculated using Eq. 4.43 together with the best fit values for $b_1$-$b_5$, are indicated by the solid curves in Figs. 4.9 and 4.10. Rate coefficient $b_2$ undoubtedly represents the catalytic effects of solvent water ($b_2 = b'_2[H_2\text{O}]$). However, the solvent composition was not varied in these experiments.

The values of $k_f^{\text{obs}}$ in Tables 4.7-4.9 are listed as functions of estimated catalyst activities. The corresponding hydronium or hydroxide ion concentrations to which the values in Tables 4.7-9 apply would, of course, be somewhat greater. Under conditions at which the Debye-Huckel theory may be assumed valid (an assumption already invoked in the calculation of buffer pH values) the numerical values assigned to the individual rate parameters depend upon the ionic strength.

The best fit rate parameters in terms of hydronium and hydroxide ion concentrations and corresponding to the experimental ionic strength of 0.060M are listed in Table 4.11 for each temperature, together with
Table 4.11. Observed kinetic parameters following Eq. 4.41\(^a\) for the hydrolysis of glyoxal dimer at \(\mu = 0.060\text{M}\)

<table>
<thead>
<tr>
<th>Rate Parameter</th>
<th>(T, ^\circ\text{C})</th>
<th>Numerical Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>(b_1, \text{s}^{-1}\text{M}^{-1})</td>
<td>5.0</td>
<td>(3.32 (\pm 0.08)^b \times 10^{-4})</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
<td>(2.91 (\pm 0.10) \times 10^{-3})</td>
</tr>
<tr>
<td></td>
<td>45.0</td>
<td>(1.93 (\pm 0.09) \times 10^{-2})</td>
</tr>
<tr>
<td>(b_2, \text{s}^{-1}\text{M}^{-1})</td>
<td>5.0</td>
<td>(6.25 (\pm 0.10) \times 10^{-8})</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
<td>(4.79 (\pm 0.15) \times 10^{-7})</td>
</tr>
<tr>
<td></td>
<td>45.0</td>
<td>(2.90 (\pm 0.15) \times 10^{-6})</td>
</tr>
<tr>
<td>(b_3, \text{s}^{-1}\text{M}^{-1})</td>
<td>5.0</td>
<td>(2.65 (\pm 0.04) \times 10^{5})</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
<td>(7.85 (\pm 0.23) \times 10^{5})</td>
</tr>
<tr>
<td></td>
<td>45.0</td>
<td>(2.08 (\pm 0.09) \times 10^{6})</td>
</tr>
<tr>
<td>(b_4, \text{s}^{-1}\text{M}^{-1})</td>
<td>5.0</td>
<td>(6.00 (\pm 0.22) \times 10^{8})</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
<td>(3.53 (\pm 0.20) \times 10^{8})</td>
</tr>
<tr>
<td></td>
<td>45.0</td>
<td>(2.23 (\pm 0.23) \times 10^{8})</td>
</tr>
<tr>
<td>(b_5, \text{s}^{-1}\text{M}^{-1})</td>
<td>5.0</td>
<td>(1.08 (\pm 0.03) \times 10^{4})</td>
</tr>
<tr>
<td></td>
<td>25.0</td>
<td>(5.69 (\pm 0.15) \times 10^{4})</td>
</tr>
<tr>
<td></td>
<td>45.0</td>
<td>(2.78 (\pm 0.09) \times 10^{5})</td>
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</tbody>
</table>

\(^{a}k_{f(\text{obs})} = b_1[H_3O^+] + b_2 + b_3[OH^-]/(1 + b_4[OH^-]) + b_5[OH^-].\)

\(^{b}\)Standard error.
corresponding standard errors. Despite the presence of five adjustable parameters in the empirical rate model, the agreement between modelled and observed values of $k_{f}(obs)$ is considered quite good at each temperature, although somewhat greater uncertainty is associated with the rate parameters obtained at 45°C and for all three values obtained for rate parameter $b_5$. Assuming the rate equation to be valid, the poorer fit evident at 45°C might be explained by the higher rate of reaction at that temperature, while the greater uncertainty of parameter $b_5$ might reflect the high rates observed at more alkaline conditions, the influence of phosphate buffer catalysis, and/or possible influence of additional, high alkalinity rate parameters.

As may be noted from Figs. 4.9 and 4.10, the disagreement between predicted and observed rate constants, while relatively small (RMSD = 0.026—0.052), does not appear random. The modelled rate expression underpredicts in two pH regions, possibly suggesting slight buffer catalysis.

Although catalysis by equimolar mono- and dibasic phthalate buffer was too small to quantitate, the slight observed phosphate buffer catalysis could be approximately corrected for in the following manner. If the entire catalytic effect of phosphate buffer is assigned to the conjugate base form (a reasonable assumption based on the principles of general acid-base catalysis and the much higher $pK_a$ value associated with the dianionic form), a very crude estimate of the catalytic constant at 25°C for hydrolysis by $\text{HPO}_4^{2-}$ can be obtained based on the results presented in Table 4.10 and the calculated concentrations of $\text{HPO}_4^{2-}$ in the buffer solutions employed. A catalytic constant $b_{\text{HPO}_4}$ of 0.077 s$^{-1}$M$^{-1}$ was so
found and used to correct the observed rate constants in Table 4.11 for phosphate buffer catalysis. The resulting corrections, as percentages of $k_f^{(obs)}$, ranged from $-9.0\%$ at $R_p = 1/2$ to $-3.2\%$ at $R_p = 8$. Finally, the corrected values of $k_f^{(obs)}$ were fit to Eq. 4.43 by non-linear regression. The corrected values for $b_1$ through $b_5$ with per cent standard errors, together with corresponding uncorrected values, are listed in Table 4.12. The corrected and uncorrected values do not differ substantially, although a slightly better fit is evident with the former.

The experimental results were also fit to the extended six-parameter model:

$$k_f^{(obs)} = b_1[H_2O^+] + b_2[H_2O] + \frac{b_3[OH^-]}{1 + b_4[OH^-]} + \frac{b_5[OH^-]}{1 + b_6[OH^-]}$$

(4.44)

Although slight improvement in the fit of uncorrected rate parameters $b_1 - b_4$ and substantial improvement in the fit of parameter $b_5$ was obtained, no improvement was noted in the fit of the rate parameters corrected for phosphate buffer catalysis. Additional kinetic data at higher pH are required.

4.3.5. Effect of temperature on $k_f^{(obs)}$

The effects of temperature on rate coefficients $b_1 - b_3$ and $b_5$, as determined by Activated Complex Theory, are indicated by Eyring plots of $\log_e(b_i/T)$ vs. $1/T$ in Figs. 4.11a,b. The corresponding thermal parameters, obtained by linear regression, are listed in Table 4.13. For convenience,
Table 4.12. Correction of the empirical kinetic parameters $b_1 - b_5$ at 25.0°C and $\theta = 0.060 \text{M}$ for presumed catalysis by $\text{HPO}_4^{2-}$.

<table>
<thead>
<tr>
<th>Rate Parameter</th>
<th>Numerical Value assuming:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$b_{\text{HPO}_4} = 0^a$</td>
</tr>
<tr>
<td>$b_1 \times 10^3, s^{-1}\text{M}^{-1}$</td>
<td>$2.91 \pm 3.6%^b$</td>
</tr>
<tr>
<td>$b_2 \times 10^7, s^{-1}\text{M}^{-1}$</td>
<td>$4.79 \pm 3.1%$</td>
</tr>
<tr>
<td>$b_3 \times 10^{-5}, s^{-1}\text{M}^{-1}$</td>
<td>$7.85 \pm 2.9%$</td>
</tr>
<tr>
<td>$b_4 \times 10^{-8}, \text{M}^{-1}$</td>
<td>$3.53 \pm 5.7%$</td>
</tr>
<tr>
<td>$b_5 \times 10^{-4}, s^{-1}\text{M}^{-1}$</td>
<td>$5.69 \pm 2.7%$</td>
</tr>
</tbody>
</table>

$^a$Uncorrected.

$^b$% Standard error.
Fig. 4.11a. Effect of temperature on rate coefficients $b_1$ and $b_2$ at $u = 0.060M$ as determined by Activated Complex Theory.

$\Delta H_{b_2} = 68.1 \pm 0.2 \text{ kJ mol}^{-1}$

$\Delta H_{b_1} = 72.3 \pm 0.1 \text{ kJ mol}^{-1}$
Fig. 4.11b. Effect of temperature on rate coefficients $b_3$ and $b_5$ at $y = 0.060M$ as determined by Activated Complex Theory
Table 4.13. Thermal parameters of rate coefficients $b_1$-$b_5$ at $\mu = 0.060 M$ assuming Activated Complex Theory or Arrhenius dependence

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Activated Complex Theory$^a$</th>
<th>Arrhenius Relationship$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\Delta S^\ddagger$, J mol$^{-1}$ k$^{-1}$</td>
<td>$\Delta H^\ddagger$, kJ mol$^{-1}$</td>
</tr>
<tr>
<td>$b_1$, s$^{-1}$ M$^{-1}$</td>
<td>$-51.09 \pm 0.23^d$</td>
<td>$72.26 \pm 0.07^d$</td>
</tr>
<tr>
<td>$b_2$, s$^{-1}$ M$^{-1}$</td>
<td>$-104.77 \pm 0.39$</td>
<td>$67.91 \pm 0.11$</td>
</tr>
<tr>
<td>$b_3$, s$^{-1}$ M$^{-1}$</td>
<td>$-13.18 \pm 0.76$</td>
<td>$35.44 \pm 0.23$</td>
</tr>
<tr>
<td>$b_4$, M$^{-1}$</td>
<td>$-$</td>
<td>$-$</td>
</tr>
<tr>
<td>$b_5$, s$^{-1}$ M$^{-1}$</td>
<td>$+38.2 \pm 4.9$</td>
<td>$57.2 \pm 1.5$</td>
</tr>
</tbody>
</table>

$^a_k = \frac{RT}{Nh} \exp(\Delta S^\ddagger/R)\exp(-\Delta H^\ddagger/RT)$.

$^b_k = k_o \exp(-E_a/RT)$.

$^c$Units of rate coefficient.

$^d$Standard error.
corresponding values determined from the Arrhenius relation are also included. The effect of temperature on coefficient \( b_4 \) is properly determined in terms of Arrhenius law and is, thus, indicated by a plot of \( \log_e(b_4) \) vs \( 1/T \) in Fig. 4.12. The corresponding thermal parameters of coefficient \( b_4 \) are included in Table 4.13.

Because approximate corrections for phosphate catalysis were available obtained only at 25°C, rate parameters obtained from uncorrected values of \( k_f(\text{obs}) \) were used in the determination thermal parameters. However, from the results in Table 4.12 it appears that only coefficients \( b_4 \) and \( b_5 \) would be significantly affected. Of course, the degree to which the thermal parameters are effected by phosphate interference would also depend on the relative activation enthalpy for phosphate catalysis.

With the exception of coefficient \( b_5 \), the modelled rate coefficients each produce surprisingly linear Eyring plots over the observed temperature range of 5 to 45°C. Even the Eyring plot derived for coefficient \( b_5 \), which shows slight upward curvature, can be considered reasonably linear considering the greater uncertainties associated with the values of that parameter. The fact that the individual kinetic parameters assigned on the basis of Eq. 4.43 appear to possess simple thermal dependencies is further support for the empirical rate equation (or equivalent form) presented.

Although the empirical rate parameters \( b_1 - b_5 \) undoubtedly represent products or quotients of individual rate and equilibrium constants, some basic comments can be made. Although hydronium ion and, especially, solvent water are rather inefficient catalysts, the thermal sensitivities of those catalysts are relatively high. On the other hand, the two rate coefficients associated with hydroxide ion catalysis, while effective at
Fig. 4.12. Effect of temperature on rate coefficient $b_4$ at $u = 0.060M$ as determined by Arrhenius Law

$E_a = -18.8 \pm 0.1 \text{ kJ mol}^{-1}$
extremely low alkalinities, show substantially lower activation enthalpies, especially $b_3$. The negative activation energy assigned to coefficient $b_4$ indicates that at least that parameter must consist of an equilibrium constant(s) and/or two or more individual rate constants.

### 4.4. Interpretation of Kinetic Results

#### 4.4.1. Empirical comparison with related carbonyls

The dimerization kinetics of simple dicarbonyls have not previously been reported. However, as described in Sec. 2.2, the same general reaction is also undergone by short-chain $\alpha$-hydroxycarbonyls, and the rates of depolymerization (as followed by dilatometric methods) of dimeric glycolaldehyde and dihydroxyacetone, were reported by Bell and coworkers. More recently, the depolymerization kinetics of lactaldehyde dimer under acidic conditions was studied by Nielsen and Sorensen. The dimerization of glyoxal is also closely related to the mutarotation of aldose and ketose saccharides and, less closely, to the simple hydration and dehydration of free carbonyl moieties. A number of other equilibrium addition reactions (see Sec. 2.1) are also related. However, most of those reactions are of less immediate concern in that they involve other functional groups and/or are effectively irreversible under the dilute aqueous conditions employed in this research.

Ever since Bronsted defined the concept of general acid-base catalysis (in part on the basis of results obtained from experiments on the rates of mutarotations), kinetic results for equilibrium addition reactions have generally been reported as fits to the following empirical model,
where \( A_i \) and \( B_i \) denote the acid and conjugate base forms of buffer species "i". All too often, however, kinetic data were not obtained over a sufficiently wide pH range to allow verification of the simple dependencies above. Even so, deviations from the simple kinetic model above have been reported. Recently, Nielsen and Sorensen\(^{55} \) investigated the mutarotation of glucose and related sugars at high alkalinity (in 0.4 to 180mM NaOH) and found a rate dependence on hydroxide ion of form identical to that reported here for glyoxal at much lower alkalinity. However, as will be pointed out in Sec. 4.4.2, the respective origins of these complex hydroxide ion dependencies are almost certainly quite different.

In Table 4.14, the kinetic parameters \( b_1 \) and \( b_2 \) describing the depolymerization of glyoxal at 25°C are compared with corresponding rate constants reported for related compounds for the equilibrium reactions cited above. Predicted pseudo-first-order rate constants (s\(^{-1}\)) based on the values in Table 4.14 are plotted vs pH in Fig. 4.13. It must be emphasized that the values plotted in Fig. 4.13 are intended only to show the general kinetic character predicted by the reported rate constants. Although all tabulated values apply to reaction at 25°C, the presumably minor effects of ionic strength have, when specified been ignored; the references cited should be consulted for the precise conditions.

In comparing the results obtained for glyoxal with those reported for glycolaldehyde, dihydroxyacetone, and lactaldehyde it may be noted that the overall kinetic responses are similar. The rate constants for solvent catalysis are all rather close and of relatively minor importance. The
Table 4.14. Catalytic constants for the hydrolysis of aqueous glyoxal dimer at 25°C compared with corresponding parameters for related equilibrium addition reactions

<table>
<thead>
<tr>
<th></th>
<th>$k_{H_3O^+} \times 10^3$</th>
<th>$k_o \times 10^3$</th>
<th>$k_{OH^-} \times 10^{-3}$</th>
<th>$K$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Depolymerization</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glyoxal ($\mu \rightarrow 0$)</td>
<td>3.6</td>
<td>0.0265</td>
<td>967(b)</td>
<td></td>
<td>77(b)</td>
</tr>
<tr>
<td>Glycolaldehyde</td>
<td>79.3</td>
<td>0.122</td>
<td>52.5</td>
<td></td>
<td>------</td>
</tr>
<tr>
<td>Dihydroxyacetone</td>
<td>28.7</td>
<td>0.0425</td>
<td>672</td>
<td></td>
<td>------</td>
</tr>
<tr>
<td>Lactaldehyde</td>
<td>9.0</td>
<td>0.027</td>
<td>---</td>
<td></td>
<td>------</td>
</tr>
<tr>
<td><strong>Mutarotation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose ($k_a + k_B$)</td>
<td>4.3</td>
<td>0.16</td>
<td>0.10</td>
<td></td>
<td>$K_{a/B} = 1.6$</td>
</tr>
<tr>
<td>Fructose ($k_Bp + k_Bf$)</td>
<td>45.5</td>
<td>1.63</td>
<td>19.7</td>
<td></td>
<td>$K_{Bp/Bf} = 3.6$</td>
</tr>
<tr>
<td><strong>Dehydration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>2840</td>
<td>4.2</td>
<td>2.1</td>
<td></td>
<td>$K_h = 2000$</td>
</tr>
<tr>
<td>Glycolaldehyde</td>
<td>8300</td>
<td>9.6</td>
<td>6</td>
<td></td>
<td>=20</td>
</tr>
</tbody>
</table>

\[ a_k = k_{H_2O}[H_2O]. \]
\[ b_k = K_D(1 + k_{H_2O})^{-2}. \]
\[ c\text{Values for } k_{H_3O^+} \text{ and } K_o \text{ from Hudson}^{44}; \text{ value for } k_{OH^-} \text{ from Bronsted and Guggenheim}^{46}. \]
\[ d\text{Values for glucose (above) multiplied by ratios reported by Isbell and Wade}^{54} \text{ for } 20^\circ C. \]
Fig. 4.13. Rates of dimer hydrolysis (glyoxal, glycolaldehyde, and dihydroxyacetone) and mutarotation (glucose and fructose) as a function of pH at 25°C.
value obtained for $k_0$ for glyoxal dimer is the lowest of any reaction listed. With glyoxal and dihydroxyacetone, there is essentially no pH region in which the reaction proceeds almost exclusively via solvent catalysis.

The catalytic effect of hydronium ion is substantially less for glyoxal than for the other two dimers. The success of the chromatographic analysis employed in this work can in part be attributed to the relative stability of glyoxal dimer to acid hydrolysis. Based on the values listed in Table 4.14 and assuming that the apparent activation energies are not substantially greater for the $\alpha$-hydroxycarbonyl reactions, it is questionable whether the methods used for glyoxal could be applied directly to the simple $\alpha$-hydroxycarbonyls.

The sensitivity of glyoxal to specific base catalysis is quite interesting. In the range of alkalinity of pH 3-5, a region dominated by rate coefficient $b_3$, the overall rates observed for glyoxal are rather close to those observed for dihydroxyacetone, while at higher pH, a region increasingly dominated by rate coefficient $b_5$, the kinetic response resembles that which would be extrapolated for glycolaldehyde by assuming simple base catalysis. Unfortunately, the depolymerization kinetics of glycolaldehyde and dihydroxyaldehyde dimers were observed only to pH 5.1 and 4.8, respectively. Thus, it is not known whether the complex hydroxide dependence of glyoxal represents novel kinetic behavior or whether similar dependencies would be observed also for the $\alpha$-hydroxycarbonyls above pH 5.

The three dimerization reactions characterized in Table 4.14 are quite closely related to the mutarotations of glucose and other reducing saccharides. The latter reactions were among the earliest and most persistently
studied reactions in the chemical literature. The two reaction-types have in common the formation of hemiacetal linkages with concomitant formation of five- and six-membered ring-forms. Because free hemiacetals are generally unstable in aqueous solution, both reactions above provide the opportunity to investigate the reactive properties of hemiacetals. The investigation of mutarotations are somewhat simplified, however, by the first-order nature of both the forward and reverse reactions. Thus, rate constants for mutarotations are generally reported as the sum of the forward and reverse rate constants $k_f + k_r$, from which the individual rate constants can be related by the equilibrium constant $K$.

The apparent simplicity of mutarotations might, in fact, be misleading. Because such reactions are generally considered to proceed via free carbonyl intermediates, the mutarotation of each saccharide actually represents at least two distinct equilibrium addition reactions for which a considerably more complex kinetic picture emerges. In fact, for some saccharides, it is conceivable that a hydroxide dependence similar to that reported here for glyoxal could be observed. This potential for complex acid-base kinetics does not seem to be generally recognized, and for that reason models for simple, two-component mutarotations are discussed in Sec. 7.5 in terms of the steady-state models developed in this section for glyoxal. The above cautions notwithstanding, in Table 4.14 the catalytic constants for glyoxal dimer hydrolysis are compared with corresponding values ($k_f + k_r$) for a typical pyranose-pyranose interconversion ($\alpha$-D-glucopyranose/$\beta$-D-glucopyranose) and for a typical pyranose-furanose interconversion ($\beta$-D-fructopyranose/$\beta$-D-fructofuranose).

In view of the close structural similarities noted above, it is not
surprising that the rates of hydrolysis of the dimeric carbonyls are in most regions not grossly different from those reported for mutarotations. While the sensitivities to hydronium ion catalysis are quite similar, the sensitivities to hydroxide ion appear to be somewhat lower. The mutarotation of fructose shows considerably greater sensitivity to solvent catalysis, while the mutarotation of glucose shows an extreme insensitivity to specific base catalysis.

A second reaction with which the dimerization kinetics can be compared is that of hydration/dehydration of carbonyl moieties. The most closely related compounds for which reliable hydration kinetics have been reported are those for formaldehyde and for glycolaldehyde. In contrast to the two mutarotations cited, the kinetics reported for the two hydrations differ substantially from those for dimer hydrolysis. Specifically, the sensitivities to water and especially hydronium ion catalysis are much greater, 10 to 100-fold and 100 to 1000-fold, respectively. On the other hand, catalysis by hydroxide ions is much weaker, roughly 100-fold less.

This last point is quite important, since any overall mechanism of dimer hydrolysis must presumably incorporate several hydration/dehydration steps. While it appears that any such steps would probably be in rapid equilibrium with slower hemiacetal scission steps at low pH, this might not be true in near neutral solution. From Fig. 4.13, it is apparent that if the free carbonyl ends of glyoxal dimer and/or any transient open-chain dimers are not unlike the closely related structure for glycolaldehyde, the rates of any dehydration steps might actually be slower than the ring-opening (hemiacetal scission) steps above a pH of roughly 7. Furthermore, if the hydration constants for the above carbonyl moieties are not much
greater than that reported for glycolaldehyde ($K_h = 20$) or than the minimum value assumed here for glyoxal monohydrate ($K_{h2} > 17$), the rates of hydration steps might eventually become comparable as well.

4.4.2. **Kinetic models for the dimerization of glyoxal**

The hydroxide ion dependence observed for glyoxal dimer hydrolysis represents a departure from the kinetic behavior previously reported for similar reactions with a variety of related carbonyl compounds. Although it would be desirable to account for this behavior in terms of a particular molecular model, the information obtained from these kinetic studies is quite limited in scope and is far from sufficient to determine the precise mechanism of glyoxal dimerization. Furthermore, accurate information about the rates of hydration or even the equilibrium constants for hydration is lacking. Therefore, the focus of this section will be a brief description of two simple steady-state kinetic schemes that are at least superficially consistent with the observed response. Of course, any number of equivalent schemes might be envisioned; thus, the emphasis here will be on the implications of fitting the empirical results to the resulting mathematical models. Two such possible mechanisms are described; the first model might apply equally well to any of the dimeric forms reported for glyoxal, while the second takes into account the five-membered ring-structures determined by Whipple$^{16}$ for the two predominant glyoxal dimers.

The starting point for the two kinetic developments to follow is a consideration of what forms of glyoxal might be anticipated as intermediates during the interconversion of monomer and dimer. Depicted in Fig. 4.14 are the neutral glyoxals which could conceivably exist (at least in
Fig. 4.14. Neutral dimeric glyoxals hypothesized intermediate in the depolymerization of the predominant glyoxal dimer $G_2(2)$ at extreme dilution. The presence of diastereomeric and enantiomeric dimeric forms is ignored.
very small proportions) in aqueous solution, including three distinct forms of open-chain dimer, differing only in degree of hydration and designated \( G_o, G^*_o, \) and \( G^{**}_o \). Each of these open-chain dimers might be expected to undergo scission to produce various monomeric forms or to undergo interconversion via hydration or dehydration. Although open-chain dimers might well figure in the kinetics of dimerization, it should be noted that Whipple found no evidence of significant proportions of any open-chain forms at equilibrium.

Although only the dimer presumed predominant, a five-membered ring-form with the hydroxyl moieties in the trans configuration, is indicated in Fig. 4.14, analogous schemes involving the same three open-chain dimers can be written for the interconversion of the two remaining five-membered ring-forms. In fact, the interconversions of these forms via ring opening would represent a type of "mutarotation". Assuming rapid conformational change, the same three open-chain dimeric forms could also arise from any six-membered, 1,4-dioxane ring structures, although in that case only the monohydrated open-chain dimer \( G^*_o \) could be formed initially. It is interesting that 1,3-dioxolane structures also appear to be the preferred structures of dimeric short-chain \( \alpha \)-hydroxycarbonyls in aqueous solution, and that Stassinopoulou and Zioudrou\(^ {32} \) reported the monomerization of freshly prepared 1,4-dioxane-type dimeric glycolaldehyde to follow first-order consecutive kinetics and to proceed via a five-membered cyclic intermediate in various non-aqueous solvents.

One further simplifying assumption is implicit in Fig. 4.14. The two acetal-hemiacetal linkages in either of the two enantiomers of the predominant cyclic dimer, designated \( G_c \) in Fig. 4.14, are not identical, as they
vary in the proximity of the hydroxyl moieties to the gem-diol "tail". It must then be assumed that ring opening would occur at slightly different rates at each linkage, although presumably the differences would not be great. With regard to this simplification as well as to the probable existence (in significant proportions) of two distinct five-membered ring-forms, it should be noted that rate expressions of identical form would be obtained for each species or linkage with either of the two kinetic models to be considered. However, unless 1) the corresponding kinetic constants in each pathway are quite similar in value, 2) the involvement of one dimeric form and/or linkage predominates, or 3) preequilibrium of the various ring forms precedes the rate-determining steps of monomerization, the involvement of multiple substrate forms would be expected to result in deviation from pseudo-first-order kinetics. Failure of any of the conditions above as well as the aforementioned presence of trimer might account for the slight deviations from first-order kinetics observed experimentally.

A consequence of the five-membered ring-structures assigned to glyoxal dimers is the possibility of the existence, at least in small proportions, of a dehydrated form possessing a free carbonyl moiety (the corresponding structures for α-hydroxycarbonyls would possess primary hydroxy1 moieties). By analogy with glyoxal monomer and by Whipple's failure to observe any unhydrated forms in aqueous solution, it must be assumed that the dehydration constant, designated K_{hc} in Fig. 4.14, is rather small. The assumed existence of the above unhydrated form G^* implies the possibility of ring opening by an alternate route producing as an intermediate the doubly dehydrated open-chain dimer G^{**}. 
Except for the absence of an unhydrated cyclic dimer, a completely analogous scheme can be written for any 1,4-dioxane ring-form, at least one of which may be present in small proportions. Assuming fast conformational interconversion, the same open-chain structures would again apply. However, the initial ring opening of any 1,4-dioxane form could produce initially only the monohydrated glyoxal dimer $G_0^*$. Each of the interconversions in Fig. 4.14 represents an equilibrium addition reaction, and as such might be expected to be subject to general as well as specific acid-base catalysis. While the molecular mechanisms of these reaction types are of interest, elucidation of the actual mechanism(s) of glyoxal dimer hydrolysis must await more sophisticated studies, in which the effects of varied solvent and the catalytic effects of buffer species are observed. Nevertheless, several general kinetic models, compatible with the restricted experimental conditions, can be put forward. The basis for these models will be the assumption that each individual step "i" in the overall reaction can be described by a pseudo-first-order rate constant $k_i$ of the following form:

$$k_i = k_{10} [H_3O^+] + k_{11} + k_{12} [OH^-]$$

(4.46)

However, because only the hydroxide ion dependence represents novel kinetic behavior, only the kinetic response in the solvent- and hydroxide ion-catalyzed regime will be considered; the catalytic effects of hydronium ion will be ignored in kinetic models describing the reaction within that pH region. It should also be noted that the concentration of solvent water has been taken within the first-order rate constants $k_{11}$. 
Each specific base-catalyzed step in the models to be presented could be further resolved in the manner shown below,

\[
\begin{align*}
G_i & \xrightarrow{k_1[OH^-]} G^-_i \\
& \xleftarrow{k_{-1}} \quad \quad G^-_i & \xrightarrow{k_2[OH^-]} G_{ii}
\end{align*}
\]

for the conversion of species "i" to "ii". However, with the assumption of either preequilibrium between \(G_i\) and \(G^-_i\) or of a steady-state concentration of \(G^-_i\) (almost certainly valid), the above scheme becomes kinetically indistinguishable from the simpler model involving only neutral species.

The two kinetic models to be described treat the monomerization reaction as irreversible, as would be the case at extreme dilution. Although this condition could not be achieved in these kinetic experiments, the mathematical treatment outlined in Sec. 4.3.1 together with the thermodynamic results presented in Sec. 4.2 allowed the calculation of the forward first-order rate constants for dimer hydrolysis. The resulting values for \(k_f\) can be considered to describe a reaction irreversible at the rate-limiting step.

The empirically derived expression for the pseudo-first-order rate constant, repeated below,

\[
k_f = b_1[H_3O^+] + b_2 + \frac{b_3[OH^-]}{1 + b_4[OH^-]} + b_5[OH^-] \tag{4.47}
\]

can be expressed in the following mathematically equivalent form:
where rate coefficients $c_1$-$c_4$ are related to the previously reported rate coefficients $b_2$-$b_3$ as follows:

\[
\begin{align*}
  c_1 &= b_2 \\
  c_2 &= (b_2^2 b_4 + b_3 + b_5) \\
  c_3 &= b_4 b_5 \\
  c_4 &= b_4
\end{align*}
\]

Although the modified equation is more suited to the analysis of particular kinetic mechanisms, it is not kinetically equivalent to the original empirical form. The two models can readily be distinguished experimentally (at least in principle) by their respective kinetic salt effects; Eq. 4.47 predicts no strong salt effects at any alkalinity, while Eq. 4.48 predicts a strong positive salt effect at sufficiently high pH. Unfortunately, salt effects were not examined in this research. However, the models judged more reasonable on chemical grounds involve only singly charged intermediates or activated complexes, and so on that basis the original empirical model is believed to be more appropriate. Further restrictions on Eq. 4.48 will be described later.

Eq. 4.48 would also be consistent for the involvement of singly and doubly charged dimeric intermediates, as is believed to be the case for the dicarbonyl disproportionations discussed in Sec. 3. In that instance, rate coefficient $c_4$ would reflect the effective acidity of $G_\text{c}$ and $G_\text{c}^\ast$. 
However, the magnitude of that rate coefficient, corresponding to a $pK_a$ of approximately 6, appears to be far too low to represent the acidity of a carbonyl compound. Furthermore, such a low value for $pK_a$ would be inconsistent with the observed behavior of concentrated glyoxal at pH > 7. It is thus necessary to explain the denominator term in Eq. 4.48 in some other way.

Perhaps the simplest kinetic scheme consistent with the hydroxide ion dependence of the empirical rate law, one that should be generally applicable to both five- and six-membered ring forms, consists of a simple two-step reaction involving ring opening followed by scission to form two moles of monomer, as indicated below:

$$
\begin{align*}
G_c & \xrightarrow{k_1 + k_2[OH^-]} C^* \xrightarrow{k_{s1} + k_{s2}[OH^-]} 2G_1 \\
& \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \]
The steady-state rate expression corresponding to the kinetic model above is obtained as follows:

\[-d[G^*]/dt = k_f[G_c]\]  
\(= (k_{s1} + k_{s2}[\text{OH}^-])[G^*]\)  

With the assumption of steady state, \([G^*_o]\) is given by:

\([G^*_o] = \frac{k_1 + k_2[\text{OH}^-]}{k_{-1} + k_{-2}[\text{OH}^-] + k_{s1} + k_{s2}[\text{OH}^-]}[G_c]\)  

Substitution of Eq. 4.51 for \([G^*_o]\) into the general rate expression above yields, after some rearrangement, a rate expression which is consistent with the empirical rate law:

\[
k_f = \frac{k_{1}k_{s1}}{k_{-1} + k_{s1}} + \frac{(k_{1}k_{s2} + k_{2}k_{s1})}{k_{-1} + k_{s1}}[\text{OH}^-] + \frac{k_{2}k_{s2}}{k_{-1} + k_{s1}}[\text{OH}^-]^2 \]

The steady-state assumption is essential to the form of Eq. 4.52, as the more restrictive assumption of preequilibrium between \(G_c\) and \(G^*_o\), stated as \(k_{-1} \gg k_{s1}\) and \(k_{-2} \gg k_{s2}\), reduces Eq. 4.52 to the simple kinetic form,
where $K_o$ represents the equilibrium constant for ring opening. At the same time, however, preequilibrium at either of the extreme conditions of low or high pH is not inconsistent with the empirical rate expression.

Neither of the solvent-catalyzed pathways can be considered inconsequential over the observed pH range, as the assumption that either $k_1 \ll k_2[OH^-]$ or $k_{s1} \ll k_{s2}[OH^-]$ results in the loss of the zero-order term. In like manner, neglect of either hydroxide ion catalyzed pathway results in the loss of the term second-order in hydroxide ion.

Even without the assumption of preequilibrium, the general rate expression may still reduce to that of simple solvent-base catalysis. Specifically, for $k_2(k^{-2} + k_{s2})^{-1} = k_1(k^{-1} + k_{s1})^{-1}$, the following simplified rate expression is obtained:

\[-d[G_c]/dt = k_1(k^{-1} + k_{s1})^{-1}(k_{s1} + k_{s2}[OH^-])G_c \] (4.54)

Note that in this instance the steady-state concentration of $G_o^*$ is independent of alkalinity. Alternative expressions for the above criterion can be obtained if it is noted that $K_o = k_1/k_{-1} = k_2/k_{-2}$. The following conditional relationships are obtained:

\[k_{s1}/k_{s2} = k_1/k_2 \] (4.55a)
\[k_{s1}/k_{-1} = k_{s2}/k_{-2} \] (4.55b)
In terms of Eq. 4.55a, complex kinetics will not be observed if the
transition from predominantly solvent catalysis to predominantly hydroxide
ion catalysis occurs at the same pH for both ring opening and chain
scission. Eq. 4.55b expresses the same condition in terms of the relative
importance of chain scission to ring closure.

Although it might appear from Eq. 4.52 that a greater than first-order
or less than zero-order dependence on hydroxide ion might be observed for
some values of the modelled rate constants, a closer inspection indicates
that a maximum kinetic order of less than unity and a minimum kinetic order
of greater than zero is allowed for the steady-state model under considera-
tion. The restriction on the maximum order is most readily shown starting
from the special case where $c_1 = k_1 k_{s1}/(k_{-1} + k_{s1}) = 0$. As described in
Sec. 7.2, the maximum kinetic order $n_{\text{max}}$ in hydroxide ion is given by the
following function of the empirical rate coefficients $c_2-c_4$ ($c_1 = 0$),

$$n_{\text{max}} = 2[1 + a^{*-1/2}]^{-1}$$

(3.19a)

where (in terms of Eq. 4.48) $a^*$ denotes the dimensionless ratio of rate
coefficients $c_3/c_2 c_4$.

Although a value for $n_{\text{max}}$ greater than unity is predicted for $a^* > 1$,
substitution for $c_2-c_4$ in terms of the elementary rate constants in
Eq. 4.52 shows (after some rearrangement) that there exists no combination
of positive rate constants such that the above condition is met. In like
manner, substitution for $c_2-c_4$ in terms of the alternative empirical rate
coefficients $b_3-b_5$, as indicated below,
shows that the original empirical model represented by Eq. 4.47 produces a
\( n_{\text{max}} > 1 \) for \( b_3 > 0 \) and a \( n_{\text{max}} < 1 \) for \( b_3 < 0 \). Thus, the steady-state
kinetic model under consideration, in one way, more closely corresponds to
Eq. 4.47, since with that empirical model a maximum kinetic order of unity
is allowed for positive values of the rate coefficients.

For the general model, where \( c_1 \neq 0 \), the kinetic order with respect
to hydroxide ion is given by Eq. 4.57,

\[
\frac{n(X)}{(c_1 + c_2 X + c_3 X^2)(1 + c_4 X)}
\]

where \( X \) denotes \([OH^-] \). Division of Eq. 4.57 by Eq. 3.19a indicates that
\( n(X) < n_{c_1=0}(X) \) for physically meaningful, positive values of rate coeffi-
cient \( c_1 \). Thus, the restriction on \( n_{\text{max}} \) applies to the general model as
well. The aforementioned limit on the minimum kinetic order \( n_{\text{min}} \) also
follows from Eq. 4.57. Because all four rate parameters \( c_1 - c_4 \) denote
positive quantities, negative kinetic orders can be obtained only for
\( c_1 c_4 > c_2 \). However, substitution of the individual rate constant expres-
sions for \( c_1 - c_4 \) indicates that \( c_2 > c_1 c_4 \) for positive values of the
individual rate constants.

Activation parameters in terms of Activated Complex Theory correspond-
ing to the modelled form of the empirical rate law are tabulated below:
Rate Parameter | $\Delta S$, J mol$^{-1}$K$^{-1}$ | $\Delta H$, kJ mol$^{-1}$
---|---|---
$c_1 (= b_2)$ | $-104.8 \pm 0.4^a$ | $67.9 \pm 0.1^a$
$c_2 (= b_2 b_4 + b_3 + b_5)$ | $-6.8 \pm 2.6$ | $37.1 \pm 0.8$
$c_3 (= b_4 b_5)$ | $140.8 \pm 5.2$ | $38.9 \pm 1.6$

$^a$Standard error.

Rate coefficient $c_4$ is more properly treated according to Arrhenius law; values of $5.7 \pm 0.4 \times 10^7$ M$^{-1}$ for $k_0$ and $70.4 \pm 0.2$ kJ/mol for $E_a$ are obtained. Although rate coefficient $c_2 (= b_2 b_4 + b_3 + b_5)$ produces a near-linear Eyring plot, coefficient $c_3 (= b_4 b_5)$ shows slight curvature due to the influence of coefficient $b_5$.

In correlating the observed thermal properties of the empirical rate coefficients to those of the modelled rate constants, it may not be immediately obvious why any of the empirical parameters should in general conform to Arrhenius behavior, as each collection of individual rate constants contains sums of constants in either the numerator or denominator or both. At the same time, the high linearity found for coefficient $c_1$ makes it difficult to dismiss the non-linearity in coefficient $c_3$ as due to the presence in the denominator of the sum $k_{-1} + k_{sl}$. It should also be noted that coefficient $b_5$ is believed to be less reliable for the experimental reasons cited in Sec. 4.3. However, with values determined at only three temperatures and hence only one degree of freedom in fitting the experimental results, caution must be used in interpreting the thermal
parameters listed (95% confidence intervals associated with the thermal parameters are 12.7 times the standard errors listed).

Actually, the empirical results and the simple kinetic model are not necessarily at odds with each other. If it is assumed that the heat capacity of activation is essentially constant over the observed temperature range, the high linearity for coefficient $c_1$ implies that either $k_{-1} \gg k_{s1}$ or $\Delta H_{-1} \approx \Delta H_{s1}$, that is, assuming that both activation enthalpies are not extremely small. Similar arguments can be made for the numerators of coefficients $c_2$ and $c_3$, although it should be remembered that both $k_{-1}$ and $k_{-2}$ cannot be assumed negligible with respect to $k_{s1}$ and $k_{s2}$, respectively, without loss of the required form for $k_f$. More importantly, it can be shown that combinations of the modelled individual rate constants that result in substantial deviations from simple solvent-base catalytic response also produce expressions for coefficients $c_1$ to $c_4$ possessing numerators and denominators that are dominated by a single term.

If the empirical results are analyzed in terms of the chain scission (or equivalent) model, one can obtain additional information concerning the values assignable to the assumed individual rate constants. However, because the model under consideration is highly speculative, the kinetic implications will not be considered in detail here. For additional information, the reader is referred to Sec. 7.5, wherein an equivalent kinetic model for simple two-component mutarotation reactions is described. In any case, the basic kinetic information obtainable is outlined below.

As with other consecutive kinetic systems, dual solutions are obtained. From the four empirical rate coefficients $c_1$ to $c_4$, one can in principle calculate two sets of values for both the ratio at very low alka-
Unity $R_1$ of the rate constant for chain scission $k_{31}$ to the rate constant for ring closure $k_{-1}$, and for the corresponding ratio at very high alkalinity $R_2$. Furthermore, one can also calculate two sets of values for the rate constants for ring opening at low pH ($k_1$) and at high pH ($k_2$), although once again the correct sets of values cannot be determined without additional, non-kinetic information. Values for the individual rate constants for chain scission cannot be determined without knowledge of $K_0$.

For the hydrolysis of glyoxal dimer at 25°C, values of $R_1 = 0.011$ and $R_2 = 14$ or $R_1 = 96$ and $R_2 = 0.072$ are obtained. Note that the alternative solutions represent reciprocal values. In terms of the chain scission model the substantial deviation from simple acid-base catalytic response is reflected in the roughly 1300-fold difference in $R$ values.

An important question to be considered with any kinetic model is "why have complex hydroxide ion dependencies of the type observed here for glyoxal not been observed with the mutarotation of reducing sugars or with the dimerization of the short-chain $\alpha$-hydroxycarbonyls glycolaldehyde and dihydroxyacetone?" While the simple chain-scission model is not directly applicable to mutarotation reactions, the model does provide a possible explanation for different behavior (assuming such a difference actually exists) for the two types of dimerization reactions.

One structural difference between the dimers of glyoxal and the dimers obtained from $\alpha$-hydroxycarbonyls is the presence at a position "alpha" to the newly-formed free carbonyl moiety of an ionizable hydroxyl group. With glycolaldehyde or dihydroxyacetone the remaining hydroxyl group would be three carbons removed from the newly formed carbonyl group. Admittedly,
this distinction might be irrelevant were hydration/dehydration of \( G^*_O \) much more rapid than chain scission — a likely possibility at low pH in view of the rapidity of hydrations under those conditions.

The presence of a free carbonyl group adjacent to a hemiacetal hydroxyl group should render the latter significantly more acidic and so might make scission of \( G^*_O \) by hydroxide ion catalysis more rapid. This would be reflected in a larger value for \( k_{s2} \) than might otherwise be expected. In contrast to the second model to be considered, the same general arguments would apply as well to open-chain dimer formed from any six-membered ring forms of glyoxal as well.

Perhaps a more obvious chemical characteristic unique to the five-membered ring structures proposed for glyoxal is the aforementioned presence of an appendant carbonyl moiety. This structural feature is central to the second kinetic model to be described. However, while it is tempting to try to attribute the peculiar behavior of glyoxal to this or some other specific chemical characteristic, it must be kept in mind that 1) deviations from simple solvent-base catalysis may well have gone undetected in prior kinetic studies of \( \alpha \)-hydroxycarbonyl monomerization (see Sec. 4.4.1) and that 2) the observation of purely first-order catalysis by hydroxide ion cannot completely rule out the involvement of more complicated kinetic mechanisms.

The cautionary note above notwithstanding, the kinetic scheme to be described incorporates the presumed existence in small proportions of unhydrated glyoxal dimer \( G^*_C \). As indicated below,
the rate-limiting step in this kinetic model is assumed to be the opening of the acetal-dihemiacetal ring. However, in this instance ring-opening is also assumed to occur at competitive rates from the small proportion of unhydrated dimer presumed present.

The forward rate of monomerization is given by:

\[
-k_{d1} + k_{d2}[\text{OH}^-] + (k_1^* + k_2^*[\text{OH}^-])[G^*_c]
\]

in which the rate constants are assigned following the scheme above. Once again, the effects of hydronium ion have been assumed additive and therefore are neglected. With the assumption of steady-state, the following equation is obtained for \([G^*_c]\):

\[
[G^*_c] = \frac{k_{d1} + k_{d2}[\text{OH}^-]}{k_{-d1} + k_{-d2}[\text{OH}^-] + k_1^* + k_2^*[\text{OH}^-]} [G_c]
\]  

Substitution of this expression into Eq. 4.58 yields after some rearrangement a rate expression for solvent and hydroxide ion catalysis which is once again of the required form:
\[-\frac{d[G_c]}{dt} = \frac{c_1 + c_2[OH^-] + c_3[OH^-]^2}{1 + c_4[OH^-]} \] (4.60)

where

\[
c_1 = k_1 + k_{d1}k_1^*/(k_{-d1} + k_1^*) \] (4.61a)
\[
c_2 = k_2 + (k_1k_{-d2} + k_1k_2^* + k_{d1}k_2^* + k_{d2}k_1^*)/(k_{-d1} + k_1^*) \] (4.61b)
\[
c_3 = (k_2k_{-d2} + k_2k_2^* + k_{d2}k_2^*)/(k_{-d1} + k_1^*) \] (4.61c)
\[
c_4 = (k_{-d2} + k_2^*)/(k_{-d1} + k_1^*) \] (4.61d)

Again it may be shown that the assumption of steady-state is essential to the form of Eq. 4.60, as the assumption of preequilibrium (at all alkalinites) between \(G_0\) and \(G_c^*\) results in the simplified expression:

\[k_f = k_1 + k_{d1}k_1^* + (k_2 + k_{d2}k_2^*)[OH^-] \] (4.62)

However, as with the simpler model, even under steady-state conditions a complex hydroxide ion dependence would not be observed for certain combinations of values of the individual rate constants. For

\[k_{d2}(k_{-d2} + k_2^*)^{-1} = k_{d1}(k_{-d1} + k_1^*)^{-1} \]

the general expression for \(k_f\) reduces to the simpler form:

\[k_f = k_{d1}(k_{-d1} + k_1^*)^{-1}(k_1^* + k_2^*[OH^-]) \] (4.63)
\[= k_{d2}(k_{-d2} + k_2^*)^{-1}(k_1^* + k_2^*[OH^-]) \]

The complex hydroxide ion dependence arises simply from a shift in the steady state concentration of \(G_c^*\). The observed pseudo-first-order rate constant changes from a zero-order dependence on [OH\(^-\)] at very low
alkalinity:

\[ k_f = k_1 + k_{d1}k_1^* (k_{-d1} + k_1^*)^{-1} \]  

(4.64)

to a first-order dependence at very high alkalinity:

\[ k_f = [k_2 + k_{d2}k_2^* (k_{-d2} + k_2^*)] [OH^-] \]  

(4.65)

Because the equilibrium proportion of \( G_c^* \) can be assumed to be quite small with the steady-state proportion still smaller yet, monomerization via \( G_c^* \) could not be expected to contribute significantly to the overall reaction unless the rate of ring opening by \( G_c^* \) were substantially greater than by \( G_c \). Such a rate disparity for hydroxide ion catalysis might be justified chemically on the following grounds.

The initial step in ring opening by specific base catalysis would be the removal of a proton from one of the two hydroxyl moieties. Ring opening with carbonyl formation could then occur with transfer of the negative charge to the corresponding 2-carbon oxygen. The presence of a free carbonyl group at a position "alpha" to the 2-carbon of \( G_c^* \) should tend to make the 2-carbon hydroxyl group much more acidic and might in that way enhance ring opening. Because the above arguments would not apply to catalysis by solvent water, the contribution of \( k_1^* \) might be expected to be negligible.

At least one extension to conditions beyond those observed experimentally is suggested by extension of the kinetic schemes presented. In general, either of the two steady-state kinetic models allow for analogous
kinetic behavior in the acid-catalyzed regime. Thus, if it is assumed that hydroxide ion catalysis is negligible under moderately to highly acidic conditions, one could conceivably see a complex dependence of $k_f$ on $[H_3O^+]$ at low pH. It might thus be of interest to extend the dimer hydrolysis studies to more acidic conditions. By extrapolation of the results obtained at 0.06M HCl, it appears that the rates should be sufficiently slow that the same experimental procedures could be employed, at least at 5 and 25°C. However, quenching the reaction by the addition of NaOH (to pH 3) would produce samples of extremely high salt content. In repetitive analyses, this high salt content might cause chromatographic problems. The activity coefficients of $[H_3O^+]$ could be estimated using tabulated values for mean activity coefficients for HCl. However, the effects of the high ionic strength on the kinetic parameters would be uncertain.

With either of the two models described (or equivalent models), the effects of all three catalytic species could be considered together. In that case, a complex expression for the pseudo-first-order rate constant is predicted to be of the following form:

$$k_f = \frac{a[H_3O^+]^2 + b[H_3O^+] + c[H_2O] + d[H_3O^+][OH^-] + e[OH^-] + f[OH^-]^2}{1 + g[H_3O^+] + h[OH^-]}$$

Even if kinetic data were available suggesting complex catalysis at high acidity, extremely accurate data would be required in order to reliably differentiate between the solvent catalysis "c" and cross product "d" coefficients.
5. CONCLUSIONS

5.1 Summary of Results

5.1.1. Analytical findings

A sealed batch reactor system, described in Sec. 3.1, was developed for use in kinetic studies following the rate of disappearance of aqueous glyoxal. The system is constructed from relatively inexpensive laboratory equipment, yet it allows convenient, repetitive reactor sampling free from atmospheric contamination, as is required in work with readily oxidizable substrates or in alkaline solution. The system as used employs a twin-head concentric drive peristaltic pump to achieve rapidly quenched samples of constant dilution ratio. Accurate pseudo-first-order rate constants for reactions with half-times ranging from several seconds to upwards of several weeks can be obtained. Because it is readily adapted to allow automatic and/or unattended sampling, the system is especially convenient in the study of moderately fast and extremely slow reactions.

The primary disadvantage of the reactor system as used is the large reactor volume, which necessitates the use of relatively large amounts of substrate unless a highly sensitive analysis is available. When following reactions in even mildly alkaline solution and/or at high temperature, alkali resistant glassware should be employed.

The success of the above system in the study of glyoxal was due in large part to the use in slightly modified form of Mitchel and Birnboim's sensitive and specific spectrophotometric analysis for α-dicarboxyls. The same analysis has since been used in the study of methylglyoxal disproportionation, and should also be applicable to longer
chain α-dicarbonyls including aldulosones and ketulosones. However, the overall reactions may be quite complex with the longer dicarbonyls.

A high pressure liquid chromatographic separation, described in Sec. 4.1, was developed for use in dimerization studies. The method, which was found to achieve near-quantitative separation (~95%) of dimeric from monomeric aqueous glyoxal, entails low temperature (to -3.5°C) elution of aqueous glyoxal at pH 3 on an Aminex ion-exchange resin in hydrogen form with peak detection by differential refractometry. The procedure might be applicable to similar compounds as well. Similar separations have been obtained with methylglyoxal, but detailed analysis of the column performance was not attempted.

The chromatographic separation was found to be useful in two studies of aqueous glyoxal — thermodynamic studies of 0.01 to 1M solutions and kinetic studies following the rate of monomerization of solutions 0.05M (after dilution) in total glyoxal. With proper calibration, the ratio of dimer to monomer peak heights was found to provide fairly accurate and highly reproducible estimates of monomer-dimer distribution in equilibrated systems and reaction progress in reacting mixtures. Hand measurements of recorder trace peak heights were found to be more accurate and reliable than electronically obtained peak heights or peak integration.

Because of the relative stability of glyoxal under the conditions of elution (pH 3, 0°C), the chromatographic method developed might also prove useful in the preparation of moderately pure aqueous glyoxal dimer for use in other studies. With standardization the method might also serve as the basis for a rapid and direct quantitative analysis of concentrated to moderately concentrated equilibrated glyoxal solutions.
5.1.2. **Empirical findings**

The rate of disproportionation of aqueous glyoxal in mildly to moderately alkaline solution was found to be first order in substrate and to exhibit a complex dependence on hydroxide ion of the form indicated in Table 5.1. Rate coefficients $a_1$ and $a_2$ were found to follow closely Arrhenius dependencies on temperature; activation energies of 96 and 56 kJ/mol, respectively, were obtained over temperature ranges of 25 to $80^\circ C$ and 5 to $50^\circ C$. Only a weak thermal dependence for rate coefficient $a_3$ was observed; an activation energy of $-8$ kJ/mol was obtained over the temperature range of 5 to $25^\circ C$ (an Arrhenius dependence was assumed for coefficient $a_3$). Rate determinations at low alkalinity in carbonate buffer produced an activation energy of 89.5 kJ/mol for coefficient $a_1$ over the temperature range of 25 to $50^\circ C$. Salt effects consistent with the proposed empirical rate law were observed — coefficient $a_1$ shows only a weak negative salt effect, while coefficient $a_2$ shows a strong positive salt effect consistent for the involvement of a doubly charged intermediate. Indirect kinetic evidence obtained from integral rate studies at higher (2-20mM) glyoxal concentrations suggests that the "inhibitory" coefficient $a_3$ reflects the effective acidity of monomeric glyoxal.

For convenience, the most significant empirical disproportionation findings are condensed in Table 5.1. The equations listed there can be used to predict the rate of disproportionation of dilute (less than 10mM) aqueous glyoxal. The empirical rate expression listed, which is valid only in the absence of divalent cations, is believed valid over the temperature range of 5 to $80^\circ C$, pH 9 to 13, and within the range of applicability of the two parameter Debye-Huckel model ($\mu < 0.1-0.2M$). However, considerable
Table 5.1. Summary of empirical findings on the rate of disproportionation of dilute aqueous glyoxal to glycolic acid in dilute NaOH subject to limitations specified in text

\[
-d[G_T]/dt = \frac{a_1(T)a_1^*(\mu)[OH^-] + a_2(T)a_2^*(\mu)[OH^-]^2}{1 + a_3(T)[OH^-]}\]

where

\[
a_1(T) = 1.274 \times 10^{16} \exp\left(-96.5/RT\right) \text{ s}^{-1} \text{M}^{-1}; \quad a_1^*(\mu) = \exp_{10}(0.47\mu)
\]

\[
a_2(T) = 1.760 \times 10^{12} \exp\left(-56.2/RT\right) \text{ s}^{-1} \text{M}^{-2}; \quad a_2^*(\mu) = \exp_{10}\left(2A(T)\mu^{1/2}(1 + \mu^{1/2})^{-1}\right)
\]

\[
a_3(T) = 1.607 \exp\left(+8.00/RT\right) \text{ M}^{-1}
\]

and

\[
R = 8.314 \times 10^{-3} \text{ kJ mol}^{-1}\text{K}^{-1}
\]

\[
A(T) = \text{Debye-Hückel solvent parameter (function of temperature)}
\]

\[
\mu = \text{ionic strength, M}
\]

\[
T = \text{temperature, K}
\]

\[
t = \text{time, s}
\]

\[
[G_T], [OH^-], \text{ M}
\]
caution must be used at conditions within the above limits that depart greatly from those at which observations have been made -- typically at conditions resulting in very high or very low rates. Extrapolations to higher or lower pH, to higher temperatures, or to more concentrated solutions of glyoxal can not be justified for any but the most speculative purposes, as changes in the empirical model are considered either possible or probable under those conditions. Rate enhancement by divalent cations is to be expected.

The equilibrium distribution of monomeric and dimeric aqueous glyoxal was observed over the temperature range of 5 to 85°C by chromatographic separation. The two chromatographic peaks obtained are believed to represent, respectively, the total of all monomeric (G₁) and dimeric (G₂) forms present. An "apparent" classical equilibrium constant K_Dapp of 0.56 M⁻¹ was found to describe the molar equilibrium ratio of dimeric to monomeric glyoxal at 25°C. Over the temperature range 5 to 65°C K_Dapp was found to follow a simple van't Hoff dependence on temperature. The apparent dimerization reaction is very weakly endothermic with an enthalpy of reaction of +3.2 kJ/mol. A very weak negative effect of ionic strength on K_Dapp was noted. The above findings are condensed in Table 5.2.

The rate of monomerization of aqueous glyoxal dimer was observed over the pH range of 1.3 to 7.7 (25°C) and the temperature range of 5 to 45°C. The reaction was found to be first order in substrate, although slight deviations from purely first-order response were noted in the earliest stage of reaction. General acid-base catalysis was observed, with relatively weak catalysis by both hydronium ion and solvent and extremely strong catalysis by hydroxide ion. A complex rate dependence on hydroxide
ion was observed of the form indicated in Table 5.2.

Over the temperature range of 5 to 45°C, rate coefficients $b_1$-$b_4$ displayed thermal sensitivities in close agreement with Arrhenius law, although rates were obtained at only three temperatures. Slight curvature in the corresponding Arrhenius plot for coefficient $b_5$ was noted. Although no significant catalysis by equimolar mono- and dibasic phthalate to 0.20M total phthalate was observed, slight catalysis by equimolar mono- and dibasic phosphate was noted over the same concentration range. The effects of ionic strength were not investigated.

The most significant thermodynamic and kinetic dimerization findings are condensed in Table 5.2. The equations listed therein can be used to predict the ratio of dimeric to monomeric glyoxal as a function of temperature and ionic strength and the rate of monomerization of glyoxal dimer as functions of temperature and pH. Of course, the general precautions elaborated for Table 5.1 apply to Table 5.2 as well. In addition, it must be borne in mind that the quantities listed represent to some extent composite values for an as of yet incompletely defined system.

5.1.3 **Theoretical findings**

While it is believed that the disproportionation and dimerization results reported herein are for the most part reliable, they are not sufficient to provide detailed information about the actual mechanisms of reaction. Specifically, accurate thermodynamic descriptions are required for the hydration of glyoxal monohydrate and for the first acid dissociation constant for either glyoxal monohydrate or dihydrate before the disproportionation of glyoxal can be discussed in terms of elementary
Table 5.2. Summary of empirical findings on the dimerization of aqueous glyoxal

a.) Thermodynamic results a

\[
\frac{[G_2]}{[G_1]^2} = K_{\text{Dapp}}; \quad K_{\text{Dapp}} = 2.04 \exp(-0.065\mu)\exp(-3.20/RT)
\]

b.) Kinetic results b at \( \mu = 0.060M \)

\[
-d[G_T]/dt = \left( b_1(T)[H_3O^+] + b_2(T) + \frac{b_3(T)[OH^-]}{1 + b_4(T)[OH^-]} + b_5(T)[OH^-] \right)[G_T]
\]

where

\[
b_1(T) = (3.62 \times 10^{10})\exp(-74.7/RT) \quad \text{s}^{-1} \quad \text{M}^{-1}
\]

\[
b_2(T) = (1.10 \times 10^6)\exp(-70.5/RT) \quad \text{s}^{-1}
\]

\[
b_3(T) = (3.45 \times 10^{12})\exp(-37.9/RT) \quad \text{s}^{-1} \quad \text{M}^{-1}
\]

\[
b_4(T) = (2.32 \times 10^5)\exp(+18.2/RT) \quad \text{M}^{-1}
\]

\[
b_5(T) = (1.7 \times 10^{15})\exp(-59.6/RT) \quad \text{s}^{-1} \quad \text{M}^{-1}
\]

and

\[
R = 8.314 \times 10^{-3} \quad \text{kJ mol}^{-1} \quad \text{K}^{-1}; \quad \text{T is temperature in K}
\]

\(^a\) Valid for total glyoxal concentration \([G_T] < 1\text{M}\) and \(\mu < 1\text{M}\).

\(^b\) Valid for \([G_T] < 1\text{M}\) and \(\mu = 0.060\text{M}\).
reaction steps. Similar information is needed for glyoxal dimer(s). Nevertheless, a few general observations are noteworthy.

The disproportionation results obtained are consistent with the currently accepted hydride ion transfer rate-determining mechanism. Based upon this hypothesis, the complex hydroxide ion dependence arises from the effect of alkalinity on the quasi-equilibrium concentration of reactive anionic glyoxals; thus, the observed strong salt effect is a secondary one. Furthermore, the observed form of the empirical rate law rules out significant hydride ion transfer from neutral glyoxal monohydrate over the observed range of experimental conditions (at pH > 10 and at temperatures less than 80°C) and also rules out significant extramolecular (Cannizzaro) hydride ion transfer below 0.02M total glyoxal.

The complex hydroxide ion dependence observed for glyoxal dimer hydrolysis is consistent with competitive solvent- and hydroxide ion-catalyzed pathways to a "steady-state" intermediate form, such as an open-chain dimeric form or an unhydrated dimer. Kinetically equivalent mechanisms involving preequilibrium between the predominant dimer and singly- and doubly-charged intermediate forms is considered unlikely on chemical grounds. That the observed rates of monomerization at near neutral pH are comparable to dehydration rates for several related carbonyls at the same conditions is consistent with kinetic involvement of one or more hydration steps.
5.2. Directions for Future Research

It is hoped that the experimental work just described will in some way increase our understanding of α-dicarbonyl reactions in aqueous solution as well as be of benefit in the planning of related future studies. Perhaps the most rewarding (and at the same time frustrating) aspects of these studies was the seemingly endless stream of unanswered questions raised by the results obtained. In fact, it seemed as though for each bit of information obtained, several other tantalizing questions danced just out of experimental view. Some of these questions would require only time and minimal alterations to existing experimental methods and so could be immediately addressed. Others would require substantial modifications and the application of considerable experimental ingenuity before one could reasonably hope to obtain reliable answers.

In the remainder of this report, some possible extensions of these studies will be described. In Sec. 5.2.1, additional experiments designed to more completely describe the kinetics of glyoxal disproportionation will be briefly summarized. In like manner, Sec. 5.2.2 will serve to present direct extensions of the dimerization and oligomerization studies of glyoxal.

5.2.1. Further disproportionation studies with glyoxal

In order to test the extended kinetic model, applicable to high substrate concentration and low alkalinity (see Sec. 3.3.5), the hydroxide ion functionality of the rate expression at high glyoxal concentration must be determined. The integral rate methods described in Sec. 3 would prob-
ably prove too cumbersome for use with such a complex model, even if the possibility of extramolecular side reactions is discounted. A more promising method would be the use of initial rate studies, following the rate of formation of glycolic acid product. Because of the very high initial glyoxal concentrations, the reaction could be accurately followed to roughly 2-10% conversion over an initial glyoxal range of 0.1-1M using the HPLC methods employed in the dimerization studies. At those high glyoxal concentrations, the system could be effectively buffered by glyoxal itself; the pH could be selected by adjusting the ratio of the hypothetical concentration of NaOH added to the concentration of glyoxal initially present.

In the likely absence of significant Cannizzaro disproportionation and significant proportions of doubly dissociated forms, a simplified form the rate expression listed in Table 3.12 would be predicted. This expression,

\[ -\frac{d[G_T]}{dt} = \frac{2f_1(\text{OH}^-)f_2^{-1}(\text{OH}^-)[G_T]}{1 + \left\{1 + 4f_3(\text{OH}^-)[G_T]/f_2(\text{OH}^-)^2\right\}^{1/2}} \]  

(5.1)

where

\[ f_1(\text{OH}^-) = a_1[\text{OH}^-] + a_2[\text{OH}^-]^2 \]
\[ f_2(\text{OH}^-) = 1 + a_3[\text{OH}^-] \]
\[ f_3(\text{OH}^-) = a_4(1 + a_5[\text{OH}^-]) \]

contains two new parameters \( a_4 \) and \( a_5 \). Although \( a_4 \) can be correlated with the known apparent dimerization constant \( K_{\text{Dapp}} \), \( a_5 \) would include a dependence on the as yet unknown dissociation constants for the dimeric forms. Nevertheless, in principle the rate expression could be fit by varying the
initial glyoxal concentration at a constant initial ratio of \([\text{NaOH}] / [G]\) and then repeating the procedure above for different alkalinities. In addition to extending the range of the kinetic model, the above procedure might also allow the effective acidity \(K_{\text{Dd}}\) of the dimeric forms to be estimated.

The above methods would require not only accurate initial rate extrapolations but also accurately known initial concentrations and would require significant corrections for the hydrolysis of water, as described for carbonate/bicarbonate buffers at high alkalinity. Although reaction time would be short, because only initial rates would be determined, the fairly low alkalinitities employed and the presumed inhibitory effects of the dimeric forms might allow the rates to be measured by conventional methods.

The possibility of simultaneous bimolecular (Cannizzaro) disproportionation at high glyoxal concentrations could be tested at low alkalinity by observing the possible accumulation of glyoxylic acid and/or glycolaldehyde -- the presumed initial products of the bimolecular reaction. Assuming that the above products are detectable, estimates of the Cannizzaro rate constants could be obtained from the ratios of the above product(s) to glycolic acid produced, if the Cannizzaro products were sufficiently stable. Unfortunately, the HPLC methods described in Sec. 4.1 can not be used directly, because glyoxylic acid elutes with glyoxal dimer and glycolaldehyde is not sufficiently separated from glycolic acid. The possible effects of glycolaldehyde aldolization were discussed in Sec. 3.3.6.

A test for the possible presence of an alternative disproportionation pathway zero-order in hydroxide ion could be conducted in the following
manner. The much greater activation energy determined for rate coefficient $a_1$ (96 kJ/mol) than for coefficient $a_2$ (56 kJ/mol) suggests a still greater thermal sensitivity for a pathway not involving prior dissociation of the monohydrate, that is, involving the temporary formation of a zwitterionic intermediate. Such disproportionation would then be expected only at very high temperature and very low alkalinity. Studies under those conditions could be conducted with the standard pseudo-first-order methods if a suitable non-interfering buffer were found.

In addition to testing for possible catalysis by buffer species or side-reactions involving them, it would be necessary to vary the alkalinity at least 100-fold to determine the influence of $[H_3O^+]$ and $[OH^-]$. A rough approximation of the expected effect of hydroxide ion could be obtained by extrapolation of the empirical rate law determined at lower temperature and higher alkalinity. Of course, it would also be necessary to establish whether glycolic acid were still the sole product formed at the new reaction conditions.

The possibility of significant proportions of dianionic glyoxal monomers at high alkalinity might be investigated using pseudo-first-order rate determinations at low substrate concentration. Because of the extremely high rate of reaction even at low temperature, it would be necessary to employ some sort of flow reactor system. Actually, the Girard-T analysis should be suitable for use in a quenched-flow reactor system, since the rate of neutralization by formic or other acid can be assumed to be very rapid.

The above experiments should be conducted at relatively low initial glyoxal concentrations to 1) minimize any temperature increase due to heat
of reaction and 2) avoid complications caused by the presence of dimers. Considering the gross differences in activities between various salts at high ionic strength, it might be advisable to allow the ionic strength to vary and employ tabulated values for the combined activity coefficient of NaOH rather than to maintain constant ionic strength with added NaCl.

In an ill-conceived attempt to push the batch reactor system described in Sec. 3. beyond its physical limitations, a set of very interesting observations were made. When high concentrations of glyoxal were allowed to disproportionate in highly alkaline (0.2 to 1M) NaOH solution, the expected immeasurably rapid reaction was followed at high conversion by a much slower but still very rapid first-order reduction in observed spectrophotometric absorbance. Although conceivably due to the presence in the glyoxal of a more slowly reacting α-dicarbonyl impurity or simply a strongly UV-absorbing intermediate or impurity, the extent of the reaction as a function of initial glyoxal concentration was suggestive of a slow hydrolysis of residual dimer (or some such similar reaction) followed by rapid disproportionation of the monomer. It should be noted, however, that such a slow dimer hydrolysis is not predicted by extrapolation of the dimer hydrolysis studies at neutral pH.

An even more surprising aspect of this phenomenon was the roughly inverse dependence of the observed first-order rate constant on the hydroxide ion concentration. Such a functionality is consistent with slow hydrolysis of an acetal linkage, as such reactions are believed to be subject to specific-acid catalysis only. In any case it is an interesting phenomenon.

Study of the above kinetic effect might not require the use of the
quenched-flow system above, since the secondary rates involved could be measured with a batch reactor of the existing type, especially at low temperature. Since $K_{\text{Dapp}}$ is now known, one experimental method would consist of starting the reaction with high substrate concentrations, observing the secondary reaction to completion, and extrapolating the reaction to zero time. The resulting deviation from the initial substrate concentration (substantial dilutions would be involved) could be correlated with $K_{\text{Dapp}}$ and tested for consistency with the above hypothesis. After neutralization in the absence of Girard-T reagent the source of the residual absorbance might be determined by HPLC.

Although O'Meara and Richards reported sizable catalytic effects by various divalent cations on glyoxal disproportionation, the experiments were not closely controlled. The above effects should be readily measurable using the pseudo-first-order batch reactor system described in Sec. 3.1.2. It would, however, be necessary to determine the catalytic effects under both predominantly second-order and predominantly first-order conditions. A convenient set of experimental conditions would be those employed in the conventional salt effect studies, 0.25mM NaOH at 80°C and 10mM NaOH at 5°C for the second- and third-order reactions, respectively. Unfortunately, even at the former conditions the reaction would not be sufficiently second-order to prevent a 3- or 4-fold acceleration of the third-order reaction from affecting the observed reaction rate.

In the analysis of the results obtained, it would have to be assumed that divalent cations have a minimal effect on the effective acidity of glyoxal. The ionic strength would be maintained at a constant value. Although the effects of a number of cations could be determined, the
effects of Ca\textsuperscript{2+} are most commonly reported. The solubilities of alkaline earth hydroxides are in general quite limited and the effects reported are substantial considering the low concentrations involved.

An attempt was made to determine the rate of disproportionation of moderately concentrated solutions of glyoxal in highly buffered solutions of bicarbonate/carbonate. The experiments, which were conducted at 50\degree C with 0.2M glyoxal in equimolar (R\textsubscript{C} = 1) buffer of 1M total buffer concentration, were quickly abandoned due to the high ionic strength and the difficulties associated with assigning a value to the hydroxide concentration. Before this, however, it was noted that the disappearance of glyoxal was accompanied by the development in the reactor of an interfering UV absorbance. The effect was particularly pronounced when starting with glyoxal freshly prepared from glyoxal trimeric dihydrate. The overall character of the pseudo-first-order kinetics was not noticeably effected (the reactor samples were diluted 100-fold), suggesting that the interfering reaction was quantitatively minor.

Although the effects above may have been due to the presence of a reactive impurity in either the buffer or the glyoxal, the possibility also exists of alkali-catalyzed side reactions involving oligomeric glyoxal. It would, therefore, be interesting to study the above effect under more defined conditions. Because the rate of reaction in carbonate buffers is rather low at 50\degree C, it should be possible to accomplish this in a pH-stat employing dilute bicarbonate/carbonate buffer to damp out fluctuations in alkalinity.

Because the rate-limiting step in the disproportionation of glyoxal is believed to involve the intramolecular transfer of a hydride ion, it would
be interesting to observe the effects on the reaction kinetics of replacement of both carbon-bound hydrogens with deuterium. Recently, Bertz reported a convenient method of preparing glyoxal-d$_2$ from a saturated solution of glyoxal bis(sodium bisulfite) in D$_2$O. A strong kinetic isotope effect is predicted from the hypothesized mechanism, and it would thus be interesting to compare the relative rates of disproportionation of glyoxal and glyoxal-d$_2$ as a function of alkalinity and temperature.

No loss of deuterium from the glyoxal before or during the reaction is expected, and therefore the same procedures employed in the kinetic analysis of glyoxal disproportionation could be essentially unchanged for glyoxal-d$_2$. Retention of hydrogen (or deuterium) could be inferred from reactions carried out with tritium-labeled glyoxal. Following disproportionation at varied conditions, neutralized samples could be subjected to separation by HPLC and the glycolic acid product analyzed for retention of radioactivity.

5.2.2. Further dimerization studies with glyoxal

Because the steady-state kinetic models considered allow for the possibility of complex hydronium ion dependence as well as hydroxide ion dependence, it would be interesting to extend the dimerization studies to lower pH. The moderate rates observed at the lowest pH conditions employed in this work indicate that the rates involved would probably not be too rapid for accurate determination using the techniques described in Sec. 4.1. Because of the high ionic strength, it might be better to estimate the hydronium ion activities based on published mean activity coefficients for HCl solutions rather than to maintain a constant ionic strength. However,
the effects of ionic strength on the observed pseudo-first-order rate constant could no longer be assumed approximately constant. At higher temperatures, the reaction rates in strongly acidic solution could be determined using a quenched flow system.

At moderate pH, the effects of ionic strength on the monomerization reaction could, if accurately determined, distinguish between the two mathematically equivalent forms of the empirical rate law described in Sec. 4.4.2 and, thus, would establish whether divalent anionic forms were involved in the reaction. Such effects should ideally be determined for both alkaline-catalyzed kinetic regimes — that is, at about pH 4.8 and above pH 7. Equimolar mono- and dibasic phthalate buffer and mono- and dibasic phosphate buffers could be used to control the pH at total concentrations as low as 0.005M (\(\mu_{\text{buffer}} = 0.010\text{M}\)), although the effect of ionic strength on the buffer pH would be sizable. The effects of changing pH on \(k_{\text{obs}}\) could be corrected for in the manner noted in Table 4.10.

Determination of the effects of various buffer species on the monomerization rate would theoretically allow differentiation between specific and general acid-base catalysis and determination of the Bronsted coefficients. However, because of the complex base dependence observed for the reaction, it is not likely that a linear Bronsted plot would be obtained. Nevertheless such studies would be useful and could in principal be obtained using the same experimental procedures described in Sec. 4.1. Because of the extremely strong effect of hydroxide ion on \(k_{\text{obs}}\), it would be necessary to maintain the ionic strength constant at a relatively high value, probably at least 0.2M, in order to obtain reasonably accurate estimates of the particular catalytic constants. Because individual ion effects become
increasingly important under those conditions, the accuracy to which the pH could be determined would suffer.

Extension of the monomerization studies to higher pH would be interesting for several reasons. Not only was some deviation from the empirical hydroxide dependence suggested at the highest alkalinities employed, but also an increased deviation from pseudo-first-order substrate dependence was observed. A simple quenched-flow kinetic system, in which the reaction is effectively stopped by acidification to pH 3, would probably allow determination of the desired rate constants, although selection of an appropriate buffer for use in the vicinity of pH 8 to 9 might be a problem. Borate buffer complexes with glyoxal, while amine-based buffers tend to undergo addition reactions with glyoxal. Carbonate buffer might be a good choice at higher pH.
6. REFERENCES


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88. de Forcrand, Compt. Rend., 98 (1884) 295.
93. Partially completed follow-up kinetic study of methylglyoxal disproportionation.


7. APPENDIX

With the exception of Sec. 7.5, the short appendices to follow consist of derivations of mathematical relationships or models cited in Secs. 3 and 4. No claim of originality is made for any of these developments; each has no doubt been presented numerous times before in reference to other physical systems. Still, it has been the author's experience that the material presented in those appendices is not in general common knowledge. Secs. 7.1-4 to follow apply specifically to the chemical systems at hand and are included solely for the convenience of the reader. In Sec. 7.5, the proper application of general acid-base catalysis to simple two-component saccharide mutarotations is described.

7.1. Sampling Error in a "Cup-mixed" Sampled First-Order System

A common method of observing the course of a reaction occurring within a homogeneous batch reactor consists of the removal at varying times of discrete samples of reactor fluid. If accompanied by rapid quenching of the reaction, the samples can then be analyzed for appropriate chemical concentrations or related physical properties at some later time. In the disproportionation studies described in Sec. 3, sampling and simultaneous quenching was effected by pumping fluid from the reactor at a constant flow rate. In that case, the sampled volume was withdrawn over a finite interval of time during which the reaction had progressed slightly. Because quenching could be assumed to occur virtually instantaneously as each fluid element mixed with quenching fluid, the exact time at which the obtained
"cup-mixed" samples exactly matched those which would have been obtained by instantaneous sampling is not known. Although it was convenient to use the arithmetic mean time \( t_m \) (or the sample start time \( t_s \)) over which the sample was collected in subsequent calculations, the question of how much error is thereby introduced into the independent variable must be considered.

While it is perhaps obvious that any such sampling time errors would generally be of relatively small magnitude, it may be less obvious that even in highly accurate kinetic studies the error introduced is likely to be insignificant. In fact, for any first-order system which is monitored with samples of equal duration at constant volumetric flow rate, no additional error over that associated with starting and stopping the sampling process itself is generated at all. This is true even in the case of very rapid reactions in which it is necessary to pump continuously in order to obtain even a few samples of sufficient volume and/or representative composition. This can be easily shown as follows.

If \( \tau_1 = k\tau_1 \) and \( \tau_2 = k\tau_2 \), are defined as the dimensionless times at which sampling is started and stopped, respectively, and \( \Gamma(\tau) = \frac{[S]_\tau}{[S]_{\tau=0}} \) is defined as the dimensionless substrate concentration within the reactor at any given time \( \tau \), for a first-order (or pseudo-first-order) reaction sampled at constant flow rate the resulting cup-mixed sample concentration can be calculated from the known first-order relation \( \Gamma(\tau) = e^{-\tau} \):

\[
\Gamma^* = \frac{\int e^{-\tau} d\tau}{\int d\tau} = \frac{(e^{-\tau_2} - e^{-\tau_1})}{(\tau_2 - \tau_1)}
\]

Furthermore, the sample mean time \( \tau^* \), defined as the dimensionless time at
which the concentration within the reactor exactly equals the value obtained from the sample, is given simply by $\tau^* = -\log_e(\tau^*)$. Therefore, $\tau^*$ can be expressed in terms of $\tau_1$ and $\tau_2$:

$$\tau^* = -\log_e\left[\frac{(e^{-\tau_1} - e^{-\tau_2})}{(\tau_2 - \tau_1)}\right]$$  

(7.2)

The difference between the "true" sample mean time $\tau^*$ and the arithmetic mean time $\tau_m$ for any given sample "i",

$$\tau^*_i - \tau_m = -\log_e\left[\frac{(e^{-\tau_{1i}} - e^{-\tau_{2i}})}{(\tau_{2i} - \tau_{1i})}\right] - \frac{(\tau_{1i} + \tau_{2i})}{2}$$  

(7.3a)

$$= -\log_e\left[\frac{e^{-\tau_{1i}}(1 - e^{-\tau_{1i}})}{\tau_{1i}}\right] - \frac{(2\tau_{1i} + \tau_{2i})}{2}$$  

(7.3b)

$$= -\log_e\left[(1 - e^{-\tau_{1i}})/\tau_{1i}\right] - \frac{\tau_{1i}}{2}$$  

(7.3c)

is shown to be a function only of the sample duration $\tau_{Di} = \tau_{2i} - \tau_{1i}$. Thus, if the sample duration is held constant within any given run, generally the most convenient procedure, the sampling time error is constant for each sample and is given by the expression below.

$$\tau^* - \tau_m = -\log_e\left[(1 - e^{-\tau_D})/\tau_D\right] - \frac{\tau_D}{2}$$  

(7.4)

Therefore, the resulting slope and first-order kinetic constant is totally unaffected. It should be noted, however, that the resulting intercept would differ slightly from the actual value. The latter is of little consequence, except perhaps in the dubious situation in which it might be desired and experimentally justified to use the initial conditions in the determination of the rate constant. In that case, $\tau^* - \tau_m$ could be found
by iteration using as an initial estimate for $k$ that value found by setting $\tau^* = \tau_m$.

In a practical sense, the restriction above is rendered academic when the magnitude of any probable error is considered. Accurate kinetic rate determinations on established first-order systems are typically carried out to an overall conversion of 60-70\% during which time eight to twelve equally spaced samples are collected. Tabulated below,

<table>
<thead>
<tr>
<th>$\tau_D$</th>
<th>$\frac{k_{\text{obs}} - k}{k}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1</td>
<td>- 0.00042</td>
</tr>
<tr>
<td>0.2</td>
<td>- 0.00167</td>
</tr>
<tr>
<td>0.5</td>
<td>- 0.01050</td>
</tr>
<tr>
<td>1</td>
<td>- 0.04311</td>
</tr>
<tr>
<td>2</td>
<td>- 0.19253</td>
</tr>
</tbody>
</table>

as a function of sample duration $\tau_D$, are the relative errors in the observed first-order rate constant $k_{\text{obs}}$ that would be obtained from experiments in which only the known initial conditions and a single sample, centered at $\tau_m = 1$, are used in the determination of $k_{\text{obs}}$. From the magnitudes of the errors in these most extreme of cases (the last value represents the use of the average concentration over the entire reaction course to $\tau = 2$), it is apparent that significant errors due to cup-mixed sampling are highly unlikely even in the most exacting work.
7.2. Reaction Order with Respect to Hydroxide Ion Concentration

An important property of a given kinetic rate law is the maximum or minimum kinetic order with respect to a particular concentration "X". For simple rate laws, the rate dependence on X is of the form \( f(X) = X^n \), where \( f(X) \) represents either the overall kinetic rate or a pseudo-\( n \)-th-order rate coefficient and the exponent "n" has any constant value. For elementary rate laws, the value of \( n \) is further restricted to the positive integer values \( n = 1, 2, \) or (rarely) 3. For the simple "power law" rate expressions above, linear plots of \( \log f(X) \) vs. \( \log X \) are predicted with the reaction order \( n \) obtained simply as the slope of the resulting linear fit.

Complex multiterm rate expressions do not produce linear log-log plots. However, at any concentration \( X_0 \) the tangent to the resulting non-linear plots of \( \log f(X) \) vs. \( \log X \) can be considered to reflect the "instantaneous" reaction order. That is, the tangent at \( X_0 \) represents the exponent of a power law rate expression passing through \( f(X_0) \) with the log-log slope at \( X_0 \). The instantaneous order \( n(X) \) is then given mathematically by Eq. 7.5:

\[
 n(X) = \frac{d(\log f(X))}{d(\log X)} \tag{7.5}
\]

For complex rate expressions the determination of \( n(X) \) graphically would often be inaccurate, although to do so would not require knowledge of the actual functionality of \( f(X) \). However, if the form of \( f(X) \) is known, \( n(X) \) can be determined analytically in the following manner.

Applying the chain rule to Eq. 7.5 results in the following expression
for \( n(X) \):

\[
\begin{align*}
n(X) &= \left[ \frac{d(\log_z f(X))}{dX} \right] \frac{dX}{d(\log_z X)} \\
&= \frac{d(\log_z f(X))}{dX} \frac{dX}{\log_z e} \\
&= \frac{dX}{\log_z e}
\end{align*}
\]

(7.6)

If use is made of the equations,

\[
\frac{d(\log_z f(X))}{dX} = \log_z (e)^{-1} \frac{d(f(X))}{dX}
\]

(7.7)

and

\[
\frac{dX}{d(\log_z X)} = \left[ \frac{d(\log_z X)}{dX} \right]^{-1} = \frac{X}{\log_z (e)}
\]

(7.8)

the following expression is obtained for \( n(X) \) in terms of \( X \), \( f(X) \), and \( f'(X) \), where \( f'(X) \) denotes the first derivative of \( f(X) \) with respect to \( X \). Note that \( n(X) \) is independent of the logarithmic base "z" employed:

\[
n(X) = X f(X)^{-1} f'(X)
\]

(7.9)

While \( f(X) \) and \( f'(X) \) may increase or decrease monotonically over the domain of interest, \( n(X) \) may show an extremum at some value \( X_{\text{ext}} \). The reaction order at that point \( n(X_{\text{ext}}) \) represents the minimum or maximum reaction order with respect to \( X \); the corresponding value \( X_{\text{ext}} \) represents the concentration of species \( X \) at which the reaction is minimally or maximally sensitive to changes in \( X \). In order to determine \( X_{\text{ext}} \), it is necessary to analyze the first and second derivatives of \( n(X) \) with respect to \( X \) and to observe where any extrema occur. This may be accomplished by first setting \( \frac{d(n(X))}{dX} \), hereafter denoted \( n'(X) \), equal to zero and then
Two kinetic rate expressions were of interest in Chap. 3 and were generalized as Eq. 3.18, in which \( m = 1,2 \). The rate expression for the intramolecular disproportionation of glyoxal and related dicarbonyls represents the former case for which \( m = 1 \). The corresponding expression for \( k_{obs} \) is represented by Eqs. 7.10a-c:

\[
\begin{align*}
    k_{obs} &= \frac{a_1[OH^-] + a_2[OH^-]^2}{1 + a_3[OH^-]} \\
    f_1(X) &= \frac{a_1X + a_2X^2}{1 + a_3X} \quad \text{(7.10b)} \\
    &= a_1a_3^{-1}X(1 + a^*X)/(1 + X) \quad \text{(7.10c)}
\end{align*}
\]

In Eq. 7.10b,c, \( f_1(X) \) denotes \( k_{obs} \) for \( m = 1 \) and "X" represents the dimensionless hydroxide ion concentration \( a_3[OH^-] \). In Eq. 7.10c, the expression for \( k_{obs} \) has been rendered more tractable by the substitution of the dimensionless parameter \( a^* \) for \( a_2/a_1a_3 \).

The first derivative of \( f_1(X) \) with respect to \( X \) is given in Eq. 7.11:

\[
f_1'(X) = a_1a_3^{-1}(1 + 2a^*X + a^*X^2)/(1 + X)^2 \quad \text{(7.11)}
\]

The desired expression for \( n_1(X) \) is now readily obtained by substitution of the expressions for \( f(X) \) and \( f'(X) \) into Eq. 7.9. The resulting expression for \( n_1(X) \), a function of only \( a^* \) and \( X \),

\[
n_1(X) = \frac{1 + 2a^*X + a^*X^2}{[(1 + a^*X)(1 + X)]} \quad \text{(7.12)}
\]

represents the order with respect to hydroxide ion of the pseudo-first-order rate constant for the disproportionation of glyoxal or related
dicarbonyl at any given (dimensionless) hydroxide ion concentration.

Maxima or minima in the above function are obtained by determining the corresponding expression for \( n_1'(X) \):

\[
n_1'(X) = \frac{[(a^* - 1) - a^*(a^* - 1)X^2]/[(1 + a^*X)^2(1 + X)^2]}{(7.13)}
\]

Values of \( n_1(X) \) for which extrema occur can now be found by setting Eq. 7.13 equal to zero and solving for \( X_{\text{ext}} \). Because \( X \) and \( a^* \) are in this instance restricted to positive values (\( a_1^*, a_2^* \) and \( a_3 \) all represent positive quantities), both factors in the denominator of Eq. 7.13 can be eliminated. Furthermore, the trivial case, in which \( (a^* - 1) = 0 \) (effectively representing purely first-order response), is not of interest, and so one may divide both sides of the resulting expression for \( n_1(X) = 0 \) by \( (a^* - 1) \) to obtain Eq. 7.14:

\[
1 - a^*X_{\text{ext}}^2 = 0 \quad (7.14)
\]

Of the two roots obtained for the above quadratic equation, only the positive root, given below

\[
X_{\text{ext}} = a^{*-1/2} \quad (7.15a)
\]

\[
[\text{OH}^-] = a^{*-1/2}a_3 = (a_1/a_2a_3)^{1/2} \quad (7.15b)
\]

in terms of \( X \) and \( [\text{OH}^-] \), is physically meaningful.

The nature of the above extrema can be determined from the sign of the second derivative of \( n_1(X) \) with respect to \( X \), \( n_1''(X) \), represented by
Eqs. 7.16a,b:

\[ n''_l(X) = \frac{2(a^* - 1)[a^*2X^3 - 3a^*X - (a^* + 1)]}{(1 + a^*X)^3 (1 + X)^3} \]  \hspace{1cm} (7.16a)

\[ n''_l(X_{ext}) = \frac{2(1 - a^*)[2a^{*1/2} + (a^* + 1)]}{(1 + a^{*1/2})^3 (1 + a^{*-1/2})^3} \]  \hspace{1cm} (7.16b)

Because coefficient \( a^* \) represents positive quantities for the model under consideration, Eq. 7.16b indicates \( n''_l(X_{ext}) \) to be negative, representing a maximum in \( n''_l(X) \), for \( a^* > 1 \). Conversely, a positive value of \( n''_l(X_{ext}) \), representing a minimum in \( n'_l(X) \), is indicated for \( a^* < 1 \).

Finally, the extreme value for the kinetic order (a maximum for glyoxal) can be determined by substitution of Eq. 7.15 into Eq. 7.12. The expression obtained for \( n''_l(X_{ext}) \) as well as the expression for \( f''_l(X_{ext}) \), representing \( k_{obs} \) at \( X_{ext} \), are given as Eqs. 7.17 and 7.18:

\[ n''_l(X_{ext}) = 2(1 + 1/a^* - 1) = 2[1 + (a_1a_3/a_2)^{1/2}]^{-1} \]  \hspace{1cm} (7.17)

\[ f''_l(X_{ext}) = a_1/a_3 \]  \hspace{1cm} (7.18)

Note that \( k_{obs} \) at the extreme kinetic order is independent of the value of rate coefficient \( a_2 \).

The pseudo-second-order rate coefficient obtained from Eq. 3.18 with \( m = 2 \), designated \( f_2(X) \), can be analyzed in the manner just described for \( f'_l(X) \). Expressions obtained for \( k_{obs} \) and for \( f_2(X) \) and \( f'_2(X) \) are listed as Eqs. 7.19a-c and 7.20, respectively:
Substitution of the above expressions into Eq. 7.9 leads to the following equations for \( n_2(X) \) and its first derivative with respect to \( X \), \( n'_2(X) \):

\[ n_2(X) = (1 + 2a^* X - X)/[(1 + a^* X)(1 + X)] \quad (7.21) \]

\[ n'_2(X) = \frac{[(a^* - 2) - 2a^* X + a^*(1 - 2a^*)X^2]}{ (1 + a^* X)^2 (1 + X)^2} \quad (7.22) \]

Setting Eq. 7.22 equal to zero and eliminating the non-zero denominator factors again produces a quadratic equation which can be solved for \( X_{ext} \). The physically meaningful root is given in Eq. 7.23:

\[ X_{ext} = \frac{1 + (2/a^*)^{1/2}(1 - a^*)}{1 - 2a^*} \quad (7.23) \]

The expression for \( X_{ext} \) above predicts finite positive roots for \( a^* > 2 \) and for \( a^* < 1/2 \). Thus, log-log plots of \( k_{obs} \) vs. \([\text{OH}^-]\) for bimolecular disproportionation should show no inflection for \( 2 > a^* > 1/2 \), and the reaction order should therein increase monotonically.

The maximum or minimum reaction order, given by substitution of the extreme value of \( n_2(X) \) into the expression for \( f_2(X) \), is given by Eq. 7.24,
\[ n_2(X_{\text{ext}}) = \frac{(1 - 2a^*)^2}{(a^* - 1)[1 + (2a^*)^{1/2}][1 + (2a^*)^{-1/2}](2a^*)^{1/2}} \]  

(7.24)

in which again \( a^* = a_2/a_1a_3 \). From this equation, it can be observed that for values of \( a^* > 2 \) the maximum order \( n_2(X_{\text{ext}}) \) increases from +1 at \( a^* = 2 \) to +2 as \( a^* \) approaches infinity, while for values of \( a^* < 1/2 \) the minimum order decreases from zero at \( a^* = 1/2 \) to minus one as \( a^* \to 0 \).

### 7.3. Kinetic Model of the Disproportionation of Formaldehyde

The disproportionation of two moles of formaldehyde to one mole each of methanol and formic acid (Cannizzaro reaction),

\[ 2 \text{HCHO} \rightarrow \text{H}_3\text{COH} + \text{HCOOH} \]

is so closely related to the disproportionation of glyoxal that a comparison of the corresponding kinetic models currently in favor for each reaction should be of some interest. In both cases, the rate-determining step is assumed to be that of a hydride ion transfer from an activated anionic aldehydrol to an unhydrated carbonyl moiety. However, in the case of formaldehyde this hydride transfer must proceed bimolecularly, rather than via an intramolecular shift. Slight differences are then to be expected in the predicted rate expressions. The following development for formaldehyde parallels exactly that set out in Sec. 3.3.3 for glyoxal.

If \( F \) and \( M \) are allowed to denote the aldehyde and aldehydrol forms of formaldehyde, respectively, and if \( k_1 \) and \( k_2 \) denote the corresponding
bimolecular rate constants for hydride ion transfer from singly- and
doubly-dissociated methylene glycol, respectively, Eq. 7.25,

\[
d[\text{Me}]/dt = d[\text{FA}]/dt = k_1[F][M^-] + k_2[F][M^{2-}]
\]  

(7.25)

expresses the instantaneous total rate of formation of methanol Me and
formic acid FA. The respective activity coefficients will be considered to
be approximately constant (at constant ionic strength) as will be the
activity of solvent water at the concentrations of interest (formaldehyde
undergoes polymerization in highly concentrated solution). The above
constants can be combined within appropriate kinetic and thermodynamic
constants, as was done in Sec. 3.

In order to be useful, the above rate must be expressed in terms of
experimentally variable or observable concentrations, typically [OH\(^{-}\)] and
the total concentration of all formaldehyde forms \([F_\text{T}]\). If, as in the case
of glyoxal, rapid equilibrium between formaldehyde and methylene glycol is
assumed, the concentration of the free aldehyde form can be eliminated via
the hydration constant \(K_h = [M]/[F]\). Again, note that the activity of
solvent water has been incorporated within the equilibrium constant. For
formaldehyde, the value of \(K_h\) has been well established experimentally\(^{10}\)
at \(2(\pm0.2) \times 10^3\) at \(25^\circ\text{C}\). With the above assumption, the rate expression
below is obtained:

\[
d[\text{FA}]/dt = k_1 K_h^{-1}[M][M^-] + k_2 K_h^{-1}[M][M^{2-}]
\]  

(7.26)

If the ionic hydrates are assumed to be in quasi-equilibrium with
methylene glycol (an excellent assumption), and hence with unhydrated formaldehyde as well, the concentrations of the former can be expressed as functions of the neutral hydrate by the use of the appropriate acid dissociation constants. If those constants are defined analogously to those in Sec. 3 for glyoxal, Eqs. 7.27a,b result:

\[
\begin{align*}
K_1/\mathcal{K}_w &= [M^-]/[M][OH^-] \\
K_2/\mathcal{K}_w &= [M^{2-}]/[M^-][OH^-] 
\end{align*}
\]

Upon solving for \([M^-]\) and \([M^{2-}]\) and substituting into Eq. 7.26 above, the following equation relating the rate of disproportionation to the concentrations of hydroxide ion and methylene glycol is obtained:

\[
d[FA]/dt = k_1K_1K_w^{-1}K_h^{-1}[M]^2[OH^-] + k_2K_1K_2K_w^{-2}K_h^{-1}[M][OH^-]^2 
\]

A value of \(5.4 \times 10^{-14}\) M for the first acid dissociation constant \(K_1\) of methylene glycol (at \(40^\circ\)C) was reported by Bell and Onwood\(^{25}\). However, the conjugate base of methylene glycol is likely to be far too weakly acidic to allow determination of \(K_2\) by conventional means.

Because of the rapid interconversions above, analyses for formaldehyde may typically be assumed to yield the total concentration of all formaldehyde forms \([F_T]\). This concentration is readily found by mole balance as in Eq. 7.29:

\[
[F_T] = [F] + [M] + [M^-] + [M^{2-}] 
\]
However, the concentrations of both unhydrated and twice dissociated forms should be quantitatively negligible under virtually any experimentally attainable conditions; that is, $K_h \gg 1$ and $k_2 K_w^{-1}[OH^-] \ll 1$. In that case, $[M^+]$ can be expressed in terms of $K_1$ and $[M]$ to produce the following expression for $[M]$ in terms of $[F_T]$ and $[OH^-]$: 

$$[M] = [F_T](1 + K_1 K_w^{-1}[OH^-])^{-1} \quad (7.30)$$

Upon substituting this expression into 7.28 and noting that $2d[F_A]/dt = -d[F_T]/dt$, the desired rate expression in terms of total formaldehyde and hydroxide ion concentrations is obtained:

$$-d[F_T]/dt = \frac{2\{k_1 K_w^{-1} K_h^{-1}[OH^-] + k_2 K_1 K_w^{-2} K_h^{-1}[OH^-]^2\}}{(1 + K_1 K_w^{-1}[OH^-])^2} [F_T]^2 \quad (7.31)$$

A kinetic model essentially equivalent to that developed above was fit to kinetic data, obtained from integral rate studies at 40°C and $\mu = 0.4M$ by Martin in 1954. By varying the value of the hydrolysis constant, $K_b = K_w/K_1$, from the previously reported approximate value of 0.13M, Martin obtained a best fit for linear plots of $-[F_T]d[F_T]/dt$ vs $[OH^-]$ with $K_b = 0.3M$. For the Cannizzaro reaction of formaldehyde, Martin obtained the kinetic values listed (in equivalent form) in Table 3.8 and defined in Table 3.10. If it is assumed that $K_h(25^\circ C) = 2(\pm 0.2) \times 10^3$ and $\Delta H_h = -2.4 \text{ kJ/mol}$ (see Bell), values for $k_1$ of $-1.0 \text{ s}^{-1}\text{M}^{-1}$ and for $k_2 K_w/K_2$ of $-27 \text{ s}^{-1}\text{M}^{-2}$ can be calculated for formaldehyde at 40°C.
7.4. Preparation of Phthalate Buffers
of Constant Ionic Strength

Thorough thermodynamic studies of the first and the second acid
dissociations of phthalic acid in aqueous solution were published by Hamer,
Pinching, and Acree\(^\text{104}\) and Hamer and Acree\(^\text{105}\), respectively, in 1945. They
reported the thermodynamic dissociation constants \(K_{\text{Ph1}}\) and \(K_{\text{Ph2}}\) as empirical
functions of temperature from 0 to 60°C. In addition, they compiled
extensive tables of pH values as functions of solution composition and
temperature\(^\ast\). Unfortunately, due to the complexity of the phthalate
system, the reported pH values span only a very limited pH range.

In the work presented in Sec. 3, phthalate-buffered solutions of known
acidity were required over as wide a range of pH as possible. At the same
time, however, the accuracy afforded by the above workers' tabulated values
was not considered essential. Therefore, at the moderately low ionic
strength employed (0.06M), calculated pH values of acceptable accuracy were
obtained by the use of the above thermodynamic dissociation constants
together with the simple two-parameter Debye-Hückel model to approximate
the individual activity coefficients.

The equations to be briefly derived below have been found useful by
this author in the calculation of hydronium ion concentration \([\text{H}_3\text{O}^+]\) as a
function of temperature and ionic strength, subject to the limitations

\(^\ast\)The reader is advised of errors in the three plots of pH versus
molality of KCl reported in reference 105, p. 412 above. The captions of
Figures 9 and 11 were apparently interchanged, and the caption to
Figure 10 apparently should read "...from the top correspond to
0.001, 0.002, 0.004, 0.005, 0.008, 0.01, ..." Ignorance of these errors would
lead to interpolation of incorrect pH values.
above. Values calculated for buffer compositions at which direct comparison could be made with the above cited experimentally determined values showed acceptable agreement, generally within 0.01 pH unit.

Calculations of pH (or \([H_3O^+]\)) in phthalate buffer are complicated by the fact that 1) \(K_{Ph1}\) and \(K_{Ph2}\) are not sufficiently separated to allow neglect of either constant under many conditions and 2) hydrolysis of water can not be neglected except at relatively high pH. Thus, a cubic solution for pH is often required.

The two dissociations of phthalic acid are represented as:

\[
H_2Ph + H_2O \underset{K_{Ph1}}{\rightleftharpoons} H_3O^+ + PH^- \quad (7.32a)
\]

\[
PH^- + H_2O \underset{K_{Ph2}}{\rightleftharpoons} H_3O^+ + Ph^2- \quad (7.32b)
\]

where

\[
K_{Ph1} = \frac{a_{HPh}^a}{a_{H2Ph}^a}
\]

\[
K_{Ph2} = \frac{a_{Ph}^a}{a_{HPh}^a}
\]

Note that the activity of solvent water has been assumed approximately equal to unity. Then, at any given conditions the equilibrium constants in terms of concentrations, \(K_{Cl}\) and \(K_{C2}\), are given as functions of the individual activity coefficients \(\gamma_i\) by Eqs. 7.33a,b:

\[
K_{Cl} = \frac{K_{Ph1} \gamma_{H2Ph} (\gamma_{H3O} \gamma_{HPh})}{(\gamma_{H3O} \gamma_{HPh})} \quad (7.33a)
\]

\[
K_{C2} = \frac{K_{Ph2} \gamma_{HPh} (\gamma_{H3O} \gamma_{Ph})}{(\gamma_{H3O} \gamma_{Ph})} \quad (7.33b)
\]

The accuracy with which \(K_{Cl}\) and \(K_{C2}\) can be determined depends on the
accuracy with which the respective activity coefficients can be estimated. It should be noted, however, that the activity coefficient of uncharged $H_2Ph$ may be assumed approximately equal to unity.

In the preparation of phthalate buffers, it is convenient to start with a known amount of acid potassium phthalate (KHPh), a primary chemical standard, and then to add sufficient acid (HCl) or base (KOH or NaOH) to obtain the desired buffer composition. If $a_{Ph}$ and "b" denote the hypothetical concentrations of total phthalate (added as KHPh) and added strong base, respectively, the following balances on phthalate and total ionic charge are obtained:

$$a_{Ph} = [H_2Ph] + [HPh^-] + [Ph^{2-}]$$

$$b = [Ph^{2-}] - [H_2Ph] - [H_3O+]$$

Simply stated, Eq. 7.35 above expresses the fact that at any acidic pH a negligible concentration of hydroxide ion will exist in solution, and so the amount of base (or acid) originally added must be reflected in the amounts of $H_2Ph$, $H_3O^+$, and $Ph^{2-}$ formed. Eqs. 7.34 and 7.35 actually apply equally well to systems obtained by the addition of strong acid, in which case b takes on negative values of magnitude equal to the hypothetical concentration of strong acid added.

At this point, the two equations above, together with the two expressions for $K_{C_1}$ and $K_{C_2}$, constitute a system of four equations and four unknowns — the four molecular concentrations. These may be combined in terms of the single variable $[H_3O^+]$, hereafter abbreviated $[H^+]$:
The above cubic equation expresses the hydronium ion concentration as an implicit function of the thermodynamic parameters (represented by $K_{Cl}$ and $K_{C2}$) and the experimentally varied parameters $a_{ph}$ and $b$.

It should be noted that Hamer, Pinching, and Acree\textsuperscript{104} and Hamer and Acree\textsuperscript{105} developed a completely analogous expression for $[H^+]$ in terms of total phthalate "a" and the concentration of base "b" added (as NaOH) to phthalic acid $H_2Ph$. Although the expression was not used in the experimental work reported, the reader is cautioned that in each reference the squared term coefficient should read "$b+(K_{1f}f_{H2Ph})/(f_{H^+HPh})$" and not "$a+(K_{1f}f_{H2Ph})/(f_{H^+HPh})$".

Solution of Eq. 7.36 yields Eq. 7.37 to follow, from which estimates of $[H^+]$ can be obtained for any given buffer preparation, given appropriate values for $K_{Ph1}$ and $K_{Ph2}$ as functions of temperature and suitable estimates of the activity coefficients:

$$[H^+] = 2(-C_1/3)^{1/2} \cos\{[\cos^{-1}(3C_2/(2C_1(-C_1/3)^{1/2})]/3\} - P/3 \quad (7.37)$$

where

$$C_1 = (3Q - P^2)/3$$

$$C_2 = (2P^3 - 9PQ + 27R)/27$$

and

$$P = a_{ph} + b + K_{Cl}$$

$$Q = (b + K_{C2})K_{Cl}$$
The activity coefficients are, of course, functions of the solution composition. However, if the Debye-Huckel theory is assumed sufficiently accurate, the individual activity coefficients are simply related to the ionic strength. In general, an iterative solution for \([H^+]\) is required, in which the ionic strength is calculated using Eq. 7.38,

\[
\mu = \frac{3a_{\text{ph}} + 2b + |b| + 2s + 3[H^+] - (b + [H^+])(K_{C_2}/[H^+] - [H^+] / K_{C_1})^{-1}}{2}
\]  (7.38)

wherein "s" denotes the concentration of added salt (as KCl or NaCl). Again, note that Eq. 7.38 is valid for the addition of acid \((b < 0)\) as well as for the addition of base \((b > 0)\).

Fortunately, in the preparation of buffers for use in kinetic studies the ionic strength is often maintained constant at some predetermined value. In this instance, an iterative solution is not required and the concentration of salt required to effect the desired ionic strength \(\mu_{\text{des}}\) is given directly by Eq. 7.39, using the calculated value for \([H^+]\):

\[
s = \frac{\mu_{\text{des}} - 3a_{\text{ph}} + 2b + |b| + 3[H^+] - (b + [H^+])(K_{C_2}/[H^+] - [H^+] / K_{C_1})^{-1}}{2}
\]  (7.39)

One further point should be made concerning the use of Eq. 7.37. In the conduct of kinetic experiments in which the effects of pH are to be
observed, it is often useful to vary \([H^+]\) or \([OH^-]\) by some constant factor. At moderate pH and for buffer systems in which the dissociation constants are not too closely spaced, this can be approximately achieved by varying the ratio "R" of the concentrations of conjugate base to weak acid initially added by the same factor. For the above phthalate system this hypothetical "buffer ratio", \(R_{ph}\), is defined in terms of the previously defined hypothetical concentrations of HKPh added \(a_{ph}\) and strong acid or base added \(b\) as expressed in Eq. 7.40 below:

\[
R_{ph} = \frac{b}{a_{ph} - |b|}
\]  

(7.40)

For any desired buffer ratio \(R_{ph}\), the concentration of added base or acid required is given by the magnitude of "b", which is obtained from "a_{ph}" and \(R_{ph}\) by Eq. 7.41:

\[
b = \frac{a_{ph}R_{ph}}{(1 + |R_{ph}|)}
\]  

(7.41)

Note that in the phthalate system above the value of \(R_{ph}\) varies from minus to plus infinity with \(R_{ph} = 0\) corresponding to a solution of pure HKPh.

7.5. Implications of the Steady-state Dimerization Model for Saccharide Mutarotations

An almost countless number of papers of have been published over the years that deal directly or indirectly with the kinetics of saccharide mutarotations, also referred to as ring-chain tautomerizations. Although with any given mutarotation a total of four tautomeric forms (two furanoses
and two pyranoses) are presumably present, with the majority of commonly studied mutarotations only two forms are present in significant proportions. Mutarotations are typically monitored by polarimetry or other changes in physical properties, or more recently, by chromatographic analysis of the individual tautomers. For simple mutarotations the observed first-order kinetic parameters represent the sums of the "forward" and "reverse" pseudo-first-order rate constants, as defined in Eq. 7.42,

\[
S_a \xrightleftharpoons[k_r]{k_f} S_b
\]

for the interconversion of tautomeric saccharides \(S_a\) and \(S_b\). If the tautomeric equilibrium constants are known, the individual forward and reverse rate constants \(k_f\) and \(k_r\) can be obtained directly. Although experimentally more difficult, complex three- or even four-component systems can be similarly resolved, as was recently done by Wertz, Garver, and Anderson for the D-galactose system.

Unfortunately, the physical significance that can be attached to \(k_f\) and \(k_r\) appears to be widely misinterpreted. It is generally accepted that mutarotations proceed via some form of free aldehydo or keto intermediate \(S^*\), either the open form or perhaps some sort of pseudo-cyclic structure. Such a scheme is indicated below:

\[
S_a \xrightleftharpoons[k_{-1}]{k_1} S^* \xrightleftharpoons[k_2]{k_{-2}} S_b
\]
With this scheme, the simplest kinetic model consistent with the observed pseudo-first-order kinetics is that which assumes a "steady-state" concentration for the intermediate aldo- or keto-form, an assumption deemed reasonable in view of the extremely low concentrations of free carbonyl forms believed present.

A problem that is inherent with the kinetic models heretofore proposed or assumed for saccharide mutarotations can be simply stated as follows. While specific catalytic mechanisms have invariably been derived in terms of ring-opening reactions (intramolecular hemiacetalizations), the kinetic expressions obtained from these modelled "half-mutarotations" have been applied directly to the overall rate constants $k_f$ and $k_r$. Were it not for the phenomenon of general acid-base catalysis, the point just made might appear to be of little practical importance. After all, were solvent catalysis the only significant kinetic pathway, the forward and reverse rate constants would be related quite simply by the expressions to follow:

$$\begin{align*}
k_f &= \frac{k_1 k_2}{(k_{-1} + k_2)} \\
k_r &= \frac{k_{-1} k_{-2}}{(k_2 + k_{-1})}
\end{align*}$$

(7.44a)  
(7.44b)

Each rate constant would simply represent an algebraic combination of individual rate constants, and except for the fact that any reported activation parameters would represent composite values, little harm would be done -- the modelled kinetic response could still accurately represent the observed response for any combination of individual rate constants.

Numerous authors have, in fact, noted the limitations inherent in
Eqs. 7.44a,b. If Eq. 7.44a is rewritten as below,

\[
k_f = \frac{k_1}{(1 + k_{-1}/k_2)}
\]  

(7.45)

it is readily seen that while ring opening may be rate "limiting" it is generally not rate "determining", as \(k_1\) represents the maximum possible forward rate. Capon\(^{56}\) goes so far as to note that one possible cause of failure to obtain good correlations between \(k_f\) and tautomeric ring structure is that the "partitioning" ratio \(k_{-1}/k_2\) is not independent of structural variations.

However, the likelihood that \(k_{-1}/k_2\) also varies with pH for a given saccharide appears to have been overlooked. It is precisely this possibility that is ignored when the forward and reverse rate constants are resolved into hydronium ion, solvent, hydroxide ion, and other dependencies as shown in Eqs. 7.46 and 7.47:

\[
k_f = k_{H3O^+}[H_3O^+] + k_{H2O}[H_2O] + k_{OH^-}[OH^-] + \ldots
\]

(7.46)

\[
k_r = \frac{k_f}{K_{a/b}}
\]

(7.47)

The problem is that on a molecular level Eq. 7.46 is meaningful only when applied to individual carbonyl addition reactions, for example, in the consideration of hydration/dehydration or simple hemiacetalization reactions. In the same sense, Eq. 7.46 cannot generally be applied to the mutarotation of saccharides, because the assumption that mutarotation proceeds via a free carbonyl form and, hence, via two distinct carbonyl addition reactions in series requires that each of the individual rate
constants — $k_1$, $k_1$, $k_2$, and $k_2$ — be resolved into specific catalytic dependencies, rather than simply $k_f$ and $k_r$.

Correct treatment of kinetic results in terms of the steady-state model is illustrated below,

$$
S_a \xrightarrow{k_1 + k_1[OH^-]} S^* \xrightarrow{k_2 + k_2[OH^-]} S_b
$$

in which $k_1^o$ and $k_1$ denote catalytic rate constants for solvent and hydroxide ion catalysis, respectively. For simplicity, hydronium ion catalysis or catalysis by general acids and bases is ignored, although the same treatment is directly applicable to those catalytic species as well.

With the assumption of steady-state, the forward and reverse reactions can in principle be separated by assuming first the formation of $S_b$ and then the formation of $S_a$ to be irreversible. The resulting values of $k_f$ and $k_r$ represent the rate constants that would be obtained in the presence of "scavengers" for the final and initial forms, respectively. For the forward reaction the following expressions are obtained for $[S^*]$ and for $k_f$:

$$
[S^*] = \frac{k_1^o + k_1[OH^-]}{k_1^o + k_2^o + (k_{-1} + k_2)[OH^-]} [S_a]
$$

$$
k_f = \frac{a + b[OH^-] + c[OH^-]^2}{1 + d[OH^-]}
$$

where

$$
S_a \xrightarrow{k_1 + k_1[OH^-]} S^* \xrightarrow{k_2 + k_2[OH^-]} S_b
$$

$$
[k_1^o + k_1[OH^-]]
$$

$$
[k_2^o + k_2[OH^-]]
$$
\[ a = \frac{k^0_1k^0_2}{(k^0_{-1} + k^0_2)} \]
\[ b = \frac{(k^0_1k^0_2 + k^0_1k^0_2)}{(k^0_{-1} + k^0_2)} \]
\[ c = \frac{k^0_1k^0_2}{(k^0_{-1} + k^0_2)} \]
\[ d = \frac{(k^0_{-1} + k^0_2)}{(k^0_{-1} + k^0_2)} \]

An expression of identical form is obtained for \( k_f \).

The important point to note from Eq. 7.50 is that simple Hudson-type catalysis is not in general predicted from the steady-state model. Rather, a complex hydroxide ion (or hydronium ion, etc.) dependence should be expected. Complex kinetics are predicted simply because the observed reaction represents two distinct general acid-base reactions (intramolecular hemiacetalizations) in series.

The types of kinetic behavior predicted are more easily illustrated if Eq. 7.50 is put in dimensionless form:

\[
K_f = \frac{1 + BX + CX^2}{1 + X} \tag{7.51}
\]

where

\[ K_f = \frac{k_f}{a} \]
\[ X = \frac{d[OH^-]}{d} \]
\[ B = \frac{b}{ad} \]
\[ C = \frac{c}{ad^2} \]

Furthermore, because the steady-state model places restrictions on allowable values of \( B \) and \( C \), it is convenient to express those parameters in terms of individual solvent and hydroxide ion "partitioning" coefficients,
as in Eqs. 4.52a,b

\[
B = 1 + \frac{R^o + R/R^o}{R + 1}
\]  
\[\text{(7.52a)}\]

\[
C = \frac{R(1 + R^o)^2}{R^o(1 + R)^2}
\]  
\[\text{(7.52b)}\]

where

\[
R^o = \frac{k^o}{k^o_2}
\]

\[
R = \frac{k^{-1}}{k^o_2}
\]

In contrast to B and C, the partitioning ratios R^o and R are physically meaningful quantities, representing the relative rates of ring-closure to S_a and S_b at very low and very high alkalinity, respectively. The values of R^o and R are conceptually free to vary between zero and infinity.

Unique values of R^o and R cannot be extracted from a given set of B and C values, since (as is characteristic of consecutive models) all allowable, non-degenerate sets of B and C yield two sets of corresponding partitioning coefficients. These can be determined using Eqs. 7.53a,b:

\[
R^o = -q + (q^2 - 4p^2)^{1/2}
\]  
\[\frac{2p}{\text{(7.53a)}}\]

\[
R = \frac{R_1 + 1 - B}{B - 1 - R_1}
\]  
\[\text{(7.53b)}\]
where
\[ p = C - B - 1 \]
\[ q = B^2 - 2C - 2B + 2 \]

The two sets of solutions to equations 7.53a,b are interesting in that they represent reciprocal values. Thus, the predicted response for enhanced hydroxide ion-catalyzed ring closure to \( S_b \) (relative to \( S_a \)) is identical to that predicted for the reverse situation. Of course, one case or the other might be preferred on chemical grounds.

It should also be noted that while the form of Eqs. 7.50 and 7.51 suggests the possible existence of pH regions in which a greater than first or less than zero kinetic order with respect to hydroxide ion might be observed, it can be shown that for physically meaningful, positive values of the composite rate constants a-d, the maximum and minimum allowable kinetic orders with respect to \([\text{OH}^-]\) are less than unity and greater than zero, respectively.

In view of the above discussion it is somewhat paradoxical that the concepts of general acid-base catalysis were first defined by Bronsted, Lowry, and others largely on the basis of kinetic studies on the mutarotation of glucose. Presumably, because those early workers did not see complex kinetics, they saw no need to incorporate a steady-state intermediate form. That is, the reaction was assumed to proceed directly from \( S_a \) to \( S_b \).

In any case, the following question must be considered. If a free carbonyl form is indeed an intermediate, why do the reported mutarotation kinetics for glucose and other saccharides fail to show a complex pH
dependence? Although it might be legitimately argued that the accuracy to which kinetic data are obtained are more often than not insufficient to establish minor deviations from simple acid-base catalysis, it is important to note that even with highly accurate results a complex kinetic response might not be observed. Specifically, for steady-state kinetic systems possessing individual rate constants satisfying the following relationship,

\[ \frac{k_1}{(k_{-1} + k_2)} = \frac{k_0}{(k_{-1} + k_0)} \quad (7.54) \]

Eq. 7.50 collapses to simple acid-base catalysis, as follows:

\[ k_f = k_1^o \frac{(k_2^o + k_2[OH^-])}{(k_{-1}^o + k_2^o)} \quad (7.55) \]

In physical terms, Eq. 7.55 implies that the concentration of free carbonyl form is invariant with pH.

The condition above can be expressed in alternative forms by the incorporation of the equilibrium constant \( K_a \) for ring-opening of \( S_a \). Upon rearrangement, the following equivalent conditional relationships are obtained:

\[ k_{-1}^o/k_{-1} = k_2^o/k_2 \quad (7.56) \]
\[ k_{-1}^o/k_2^o = k_{-1}/k_2 \quad (7.57) \]
\[ R^o = R \]

Eq. 7.56 simply states that the mid-points in the transition from solvent to hydroxide ion catalysis must occur at the same pH for both ring-closing
steps, while Eq. 7.57 shows that the partitioning of $S^*$ is independent of catalytic pathway. Of course, the same conditions would also be met by the ring-opening steps. On the surface, at least, Eqs. 7.56 and 7.57 would seem most likely to hold for the interconversion of structurally similar tautomers, as for example the mutarotation of the glucopyranoses.

In any event, the point is that even though simple acid-base catalysis may be observed, $k_f$ and $k_r$ cannot be related to the rates of ring-opening, $k_1^0 + k_1[\text{OH}^-]$ and $k_2^0 + k_2[\text{OH}^-]$, without additional information. Furthermore, because $k_f$ and $k_r$ represent composite rate constants, special significance cannot be attached to the activation parameters obtained, nor in fact should $k_f$ and $k_r$ be expected a priori to follow the simple Arrhenius thermal dependence usually associated with individual rate constants. Bronsted coefficients or "slopes" determined from mutarotation data cannot by themselves be expected to provide detailed mechanistic information for either reaction. This point appears to have been ignored even in rather detailed mutarotation studies. Collaborative information, as from free carbonyl scavengers, is required.

Nevertheless, the question of why complex kinetics have not been reported remains. If for the moment the phenomenon is assumed to exist, several reasons for its failure to be observed may be noted. From an experimental point of view, all too often a simple acid-base dependence is assumed and the kinetic results are fit on that basis. Furthermore, even when verification of the kinetic dependence on pH is attempted, the pH span over which the reaction can be accurately monitored is often rather limited; because of the number of parameters modelled, accurate rate measurements over a minimum of four pH units in the alkali-catalyzed
(and/or acid-catalyzed) regime are probably required to test the applicability of Eq. 7.50. From a chemical point of view, it should be noted that the vast majority of mutarotation studies have involved pyranose-pyranose reactions, probably due in part to the greater abundance of crystalline pyranosyl saccharides, the preponderance of pyranose ring-forms in aqueous solution, and the generally slower nature of the pyranose-pyranose transformations in comparison with those involving a furanose form. By virtue of the greater dissimilarity between furanose-pyranose forms, complex kinetics might seem more likely with such systems.

To pursue the last point a bit further, a recent paper by Andersen, Gronlund, and Jorgensen might provide some evidence of complex acid-base kinetics. Andersen et al. reexamined the mutarotation of fructofuranose to fructopyranose at 25°C in the absence of added buffer and observed an unusual dependence on pH over the pH range of 4 to 7. The authors concluded that their results were best described by a half-order hydroxide ion dependence within that region, although slight systematic deviations were noted. However, no specific theoretical explanation for such a half-order dependence could be proposed. While the fit of their data to the half-order rate law is reasonably good and may, in fact, be preferred on the basis of simplicity, it does appear that Eq. 7.50 would fit the solvent and alkaline region of their plotted results equally well. In the latter instance, the apparent order with respect to [OH⁻], although actually reflecting a combination of hydroxide dependencies, would be represented with satisfactory precision by a term half-order in [OH⁻].

However, the most convincing evidence for complex acid-base kinetics are probably those presented in Chapter 4 for the closely related depolym-
erization of aqueous dimeric glyoxal. Those studies, which were conducted at 5, 25, and 45°C and an ionic strength of 0.060M, revealed the full biphasic dependence on hydroxide ion over a wide range of [OH$^-\text{]$. More importantly, very close fits to an empirical equation of the form of Eq. 7.50 were observed at all three temperatures. Although the depolymerization of dimeric α-hydroxycarbonyls and α-dicarbonyls are formally more complicated than mutarotations, the initial ring-opening steps in both reactions are presumably quite similar and for glyoxal a number of steady-state kinetic schemes that are mathematically identical with Eq. 7.50 can be envisioned. It is also interesting to note that the predominant dimeric structure for aqueous glyoxal was reported by Whipple$^{16}$ to be that of a furanosyl-like substituted 1,3-dioxolane.

However, the central point in the above discussion remains that complex acid-base kinetics are predicted by the mutarotation kinetic model in common use. This point is independent of the actual existence of the free carbonyl forms, the existence of parallel carbonyl addition pathways, or the actual observation of complex kinetics.