Determination of organic acids and carbonyl compounds

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DETERMINATION OF ORGANIC ACIDS
AND CARBONYL COMPOUNDS

by

Stanley Satoshi Yamamura

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

Major Subject: Analytical Chemistry

Approved:

Signature was redacted for privacy.

In Charge of Major Work

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Head of Major Department

Signature was redacted for privacy.
Dean of Graduate College

Iowa State College
1957
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PART I

DETERMINATION OF ORGANIC ACIDS
I. INTRODUCTION

Acid-base titration in nonaqueous solvents provides the analytical chemist with a valuable tool for the determination of inorganic and organic compounds having acidic or basic properties. Acid-base titrations in aqueous systems are limited in scope due to the weakly acidic or basic character of some organic compounds and due to the slight solubility of most organic compounds in water. In addition, the possibilities of differentiating titrations in aqueous systems are reduced due to the leveling effect of water. The use of nonaqueous solvents has increased the scope considerably. Many classes of organic compounds such as aromatic and aliphatic amines, carboxylic acids, phenols, enols, imides, sulfonamides, alcohols and even salts can be determined accurately and rapidly. In addition, many other classes of organic compounds can be determined by indirect acid-base methods. Nonaqueous acid-base titration has the basic requirements of good analytical methods. These are: accuracy, speed, convenience and simplicity.

Except for the recent investigations by Cundiff and Mankunas (1), Harlow, Noble and Wyld (2) and Bruss and Wyld (3), relatively little attention has been paid to the problem of determining individual acids in mixtures using differences in acidity of the acidic constituents as the basis for analysis. The purpose of this work is to study the titration of acids.
in nonaqueous solvents. To begin with, previous work on the titration of acids in nonaqueous solvents will be considered. Second, the conditions for titration will be considered. Finally, the titration of various classes of acidic organic and inorganic compounds will be studied in a systematic manner, and from this study the possibilities of determining individual acids in mixtures will be considered.
II. PREVIOUS WORK ON THE TITRATION OF ACIDS IN NONAQUEOUS SOLVENTS

In recent years, nonaqueous acid-base titrimetry has received considerable attention. The theory and scope of the method has been comprehensively reviewed by Fritz (4), Deal and Wyld (5) and Riddick (6, 7, 8). The booklet by Fritz is especially informative and is recommended for most routine analyses. Guenther and others (9, 10, 11) have reviewed the analytical methods for the determination of acidic substances in essential oils and related products. Pifer, Wollish and Schmall (12, 13, 14), Marsh and Hilty (15) and Ekeblad and Erne (16) have investigated the application of nonaqueous titrimetry to pharmaceutical products. Methods for the determination of organic acids encountered in clinical chemistry have been reviewed (17).

Deal and Wyld (5) used alcoholic potassium hydroxide for the titration of weak acids in ethylenediamine and dimethylformamide but used tetrabutylammonium hydroxide in water-isopropanol solution for the titration of very weak acids. Moss, et al., (18) were able to determine phenols and other weak acids in ethylenediamine using sodium aminoethoxide in a mixture of ethanolamine and ethylenediamine as the titrant. They were able to follow the titrations potentiometrically using hydrogen or antimony indicating electrodes and an amplifier to increase the sensitivity of the system. Katz and
Glenn (19) used essentially the same system but added a recording device to improve the accuracy of determining the equivalence point. Fritz and others used alkali metal alcoholates for the determination of phenols (20, 21), enols and imides (22), salts (23), sulfur drugs and sulfonamides (24) and carboxylic acids (21). Lithium aluminum hydride in tetrahydrofuran has been used by Lintner, Schleif and Higuchi (25) and Steenmark and Weiss (26) for the determination of alcohols and phenols. Higuchi, Concha and Kuramoto (27) used lithium aluminum amide in tetrahydrofuran for the titration of the same compounds. The amide is prepared by reacting lithium aluminum hydride with a secondary amine.

Critchfield and Johnson (28) determined sulfuric-nitric and sulfuric-hydrochloric acid mixtures by titrating with standard morpholine in acetonitrile. Higuchi and Rehm (29) used alkali metal acetates for titrating similar mixtures conductimetrically in acetic acid. Owens and Maute (30) used acrylonitrile as the solvent in the determination of dilute solutions of acids and bases. Warner and Raptis (31) were able to determine formic acid in the presence of acetic acid by selectively distilling the former with chloroform. Various nitro-substituted compounds have been titrated nonaqueously (32, 33, 34, 35).

Other methods of determining organic acids have been proposed. Wawzonek (36) has investigated the determination
of acids and related substances by organic polarography. Meites and Meites (37) used coulometry at controlled potential to assay trichloroacetic acid. The possibilities of following the titration of weak acids photometrically have been reviewed (38). The use of infrared for the determination of fatty acids and the use of a chlorine-36-isotope dilution method for the analysis of carboxylic acid, acid chlorides and acid anhydrides have been reported (39, 40).

More recently, tetrabutylammonium hydroxide in benzene-methanol solution (1) and in absolute isopropanol has been employed in the titration of a wide variety of acidic organic compounds. Cundiff and Markunas (1) investigated many solvents but performed their titrations primarily in pyridine. Harlow, et al., (2) likewise studied many solvents but concentrated their efforts to titrations in ethylenediamine. Bruss and Wyld (3) investigated methyl isobutyl ketone as a solvent for the titration of both acids and bases.

Many electrode systems have been proposed. The applications of potentiometric titrations to acid-base processes both in aqueous and nonaqueous solutions have been reviewed by Furman (41) and Reilley (42). Deal and Wyld (5) followed their titrations potentiometrically using a conventional glass calomel electrode system. Moss, Elliott and Hall (18) investigated the antimony-antimony, hydrogen-antimony and hydrogen-calomel systems. They inserted the indicating electrode in the stem of the buret. The antimony-glass and
antimony-calomel systems have been proposed by Fritz and others (4, 19, 21). Warner and Haskell (43) reported that best results were obtained with the antimony-calomel system when the antimony surface was renewed at frequent intervals. The platinum-calomel and platinum-platinum systems have also been used (44, 45). Cundiff and Markunas obtained better results when they substituted the aqueous potassium chloride solution of the saturated calomel with a saturated solution of the same salt in methanol.

Thymol blue, azoviolet, o-nitroaniline and other nitroanilines have been employed successfully as indicators. Higuchi, et al., (46) have investigated the behavior of acid-base indicators in acetic acid. A report by Ballczo (47) contains a helpful guide for the selection of indicators in the titration of specific compounds.
III. CONDITIONS FOR TITRATION

A. Solvent

1. **General requirements of solvents**

   The general requirements of solvents in nonaqueous titrations have been reviewed by Fritz (48). Both basic and neutral solvents can be used for the determination of individual acids or the sum of two or more acids. On the other hand, relatively neutral solvents are necessary for differentiating titrations of acid mixtures. The requirements of a good solvent for differentiating titrations of amines have been enumerated by Fritz (49). By analogy, the requirements of a good solvent for the differentiating titrations of acids can be listed:

   1. The solvent should be sufficiently non-acidic to permit titration of very weak acids.
   2. The solvent should be non-basic. Basic solvents will exert a leveling effect.
   3. The solvent should dissolve a wide variety of acids and their respective salts.
   4. The solvent should have a sufficiently high dielectric constant to permit potentiometric titrations.
   5. The solvent should not react with the substance being titrated.
6. The solvent should be inexpensive and applicable as received commercially without further purification.

2. **Selection of solvents**

Pyridine and dimethylformamide are slightly basic solvents that have been employed in differentiating titrations. Relatively neutral solvents include acetone, acetonitrile, alcohols, benzene-alcohol solutions, tetrahydrofuran, ethyleneglycoldimethyl ether and chloroform. Preliminary investigation of numerous solvents indicated that acetone, acetonitrile and dimethylformamide were suitable solvents. Most alcohols with the possible exception of isopropanol were too acidic to permit titration of very weak acids. Pyridine frequently gave unsteady potential readings due to its low dielectric constant. Titrations in tetrahydrofuran which had been freshly distilled over lithium aluminum hydride indicated a potential range exceeding 1500 millivolts; however, tetrahydrofuran readily forms peroxides and requires frequent purification.

Acetone was selected as the solvent in the earlier work in view of its small acid blank. Acetonitrile and dimethylformamide showed a number of excellent solvent properties but gave acid blanks which were excessively high for differentiating titrations. Subsequent investigations showed that these solvents could easily be purified by a single passage through
an ion exchange column and an alumina column. The description of the method will be deferred to a later section.

In this work, titrations were performed primarily in acetone and acetonitrile. These solvents have a long potential range which increases the possibilities of differentiating titrations. In addition, steady potential readings are obtained using conventional electrode systems. Curves for the titration of o-nitrophenol in acetone, acetonitrile and dimethylformamide are compared in Fig. 1. Although dimethylformamide has a relatively short potential range it is especially desirable for the titration of those compounds which are not readily soluble in acetone or acetonitrile. Dimethylformamide is also used in indicator titrations because the end point is best observed in this solvent.

3. **Purification of solvents**

Whenever the solvent blank is excessive, it is necessary to purify the solvent prior to its use. Attempts to purify acetonitrile and dimethylformamide by distillation methods were not satisfactory. Subsequent investigations showed that these solvents could easily be purified by means of the apparatus illustrated in Fig. 2. Approximately two and a half liters of the solvent to be purified is placed in a reservoir above the system and is fed by means of gravity through the two columns at the rate of approximately four drops per second. The first column contains a uniform mixture of cation
Fig. 1 Titration of o-Nitrophenol in Different Solvents with Triethyl-n-butylammonium Hydroxide.
Fig. 2 Solvent Purification Apparatus
and anion exchange resins in the hydrogen and hydroxyl forms respectively. The charged resin is washed with acetone and air-dried in order to minimize the introduction of water. The second column contains anhydrous aluminum oxide (alumina). The majority of the acidic and basic impurities are removed by the first column. Smaller quantities of these impurities and water introduced from the first column are removed by the second column. The solvent is protected from carbon dioxide and moisture by equipping the collecting vessel with a drying tube charged with Ascarite and a suitable dessicant. More than 95 per cent of the acid impurities are removed by a single passage of the solvent through the system.

B. Titrant

1. Choice of titrant

Potassium methoxide in benzene-methanol solution was employed in the earlier titrations. Precipitation difficulties and the need for a more widely applicable titrant led to the adoption of tetraalkylammonium hydroxide. This titrant has two main advantages over the alkali metal alcoholates. First, the tetraalkylammonium salt of the acids are soluble in most cases, and second, excellent potentiometric curves with larger, sharper inflections at the equivalence point are obtained in a variety of solvents using a conventional glass-calomel electrode system. With alkali metal alcoholates, precipitation of the salt is frequently encountered and the breaks at
the equivalence point are reduced in magnitude and in sharpness. The curves obtained in the titration of o-nitrophenol in acetone with different titrants and different electrode systems are illustrated in Fig. 3. Titration of o-nitrophenol with potassium methoxide using the conventional glass-calomel electrode system gives a curve with a sharp but relatively small break at the equivalence point. Tetraalkylammonium hydroxide gives a longer break with both the conventional glass-calomel and the modified glass-calomel systems. The glass-methanol-modified calomel system provides a slight advantage over the glass-aqueous calomel system.

2. Preparation of titrant

Tetraalkylammonium hydroxide in benzene-methanol solution was selected as the titrant. This is prepared according to the method proposed by Cundiff and Markunas (1). A methanolic solution of the appropriate quaternary ammonium iodide salt is agitated with silver oxide. The mixture is then filtered under nitrogen and diluted with anhydrous benzene. An alternative method of preparation is to pass an isopropanol solution of the salt through an anion exchange column in the hydroxyl form (2).

Triethyl-n-butylammonium hydroxide was used in this work. The corresponding iodide is initially prepared by gently refluxing equimolar mixtures of triethylamine and n-butyliodide. The salt is filtered, recrystallized from
Fig. 3 Titration of o-Nitrophenol in Acetone with Potassium Methoxide (curve 2) and Triethyl-n-butylammonium Hydroxide (curves 1 and 3).
ethanol-ethylacetate solution and air-dried. A solution of 30 grams of the iodide in 90 ml. of methanol is agitated for about two hours with approximately 27 grams of silver oxide. The mixture is filtered under nitrogen washing with 300 ml. of anhydrous benzene added in several portions. Finally the filtrate is diluted to a liter with benzene and stored under an atmosphere of nitrogen. Filtration in the absence of light is recommended in order to minimize photodecomposition of the silver iodide precipitate.

C. Reagents and Apparatus

1. **Reagents and chemicals**

   Triethyl-n-butylammonium hydroxide, 0.1 N, in 10 to 1 benzene-methanol solution prepared as described above. Standardize against benzoic acid using dimethylformamide as solvent and thymol blue indicator. Thymol blue indicator solution. Dissolve 0.3 grams of thymol blue in 100 ml. of methanol.

   Dimethylformamide, technical grade, purified as described above.

   Acetone, reagent grade.

   Acetonitrile, technical grade, purified as described above.

   Methanol, reagent grade.

   Nitrogen, pre-purified.
Benzoic acid, reagent grade.
Cation exchange resin, Dowex 50 X8, 20-50 mesh. Convert to hydrogen form using 3 N hydrochloric acid. Wash well with distilled water and remove water by washing with acetone and air-drying.
Anion exchange resin, Dowex 3, 20-50 mesh. Convert to hydroxyl form with 3 N sodium hydroxide. Wash well with distilled water and remove water by washing with acetone and air-drying.
Alumina, anhydrous.
Acid samples, analyzed as received; mostly 98 to 100 per cent pure.

2. Apparatus
Precision-Shell Dual AC Titrometer.
Beckman general purpose glass electrode 1190-80.
Beckman fiber-type calomel No. 1170 or Beckman sleeve-type calomel No. 1170-71. Both electrodes were modified by replacing the aqueous potassium chloride solution by a saturated solution of the same salt in methanol.
Buret, 10 ml. (Normax).
Magnetic stirrer.
D. Procedure

In the analysis of acids, 0.4 to 0.8 milliequivalent samples of the acid or acid mixture are titrated with 0.1 N triethyl-n-butylammonium hydroxide using 40 ml. of acetone, acetonitrile or dimethylformamide as the solvent. The titrations are followed potentiometrically and the equivalence points are determined by plotting potential against volume of titrant. The solvent blank is subtracted from the total volume. When two or more inflections are observed, the difference between successive equivalence points is used to calculate the volume of titrant equivalent to the acid represented. The solvent blank is subtracted from the last interval.

The usual method of performing potentiometric titrations is to add constant increments of titrant prior to the equivalence point and smaller increments near the equivalence point. This procedure is satisfactory but relatively time-consuming. It is more convenient and faster to add increments of such size that a relatively constant change of approximately 30 millivolts is obtained. By this method, the size of the increments near the equivalence point is automatically decreased.
IV. TITRATION OF ACIDS IN NONAQUEOUS SOLVENTS

In this study five classes of acidic organic compounds were considered: phenols, carboxylic acids, enols, imides and sulfonamides. In each class, individual compounds were titrated potentiometrically. The compounds selected for titration contained a variety of electron-withdrawing functional groups. The number of these groups and the position of the groups relative to that of the acidic group were also varied. The compounds investigated were analyzed as received and were assumed to be 98 to 100 per cent pure. In addition, several strong mineral acids were investigated.

A. Phenols

1. Individual titrations

In the study of phenols, approximately twenty individual phenols were titrated potentiometrically. The data in Table 1 show that the titrations are stoichiometric since the recoveries are within the 98 to 100 per cent range. Representative curves of phenols are plotted in Figs. 4 and 5.

An examination of the curves shows that electron-withdrawing groups increase the acidity in the order: \(-\text{NO}_2\) > \(-\text{CHO}\) > \(-\text{COR}\) > \(-\text{Cl}, \text{Br}\) > \(-\text{C}_6\text{H}_5\). A group in the ortho or para position affects the acidity more than a group in the meta position. Hydrogen bonding apparently reduces the acidity when the proper group is in the ortho position; consequently,
Table 1. Results of the titration of phenols in acetone

<table>
<thead>
<tr>
<th>Compound</th>
<th>Milliequivalents taken</th>
<th>Milliequivalents found</th>
<th>Per cent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>0.265</td>
<td>0.259</td>
<td>97.8</td>
</tr>
<tr>
<td>o-Bromophenol</td>
<td>0.514</td>
<td>0.514</td>
<td>100.0</td>
</tr>
<tr>
<td>p-Bromophenol</td>
<td>0.531</td>
<td>0.521</td>
<td>98.2</td>
</tr>
<tr>
<td>m-Bromophenol</td>
<td>0.391</td>
<td>0.372</td>
<td>95.2</td>
</tr>
<tr>
<td>2,4-Dibromophenol</td>
<td>0.418</td>
<td>0.410</td>
<td>98.0</td>
</tr>
<tr>
<td>2,6-Dibromophenol</td>
<td>0.473</td>
<td>0.466</td>
<td>98.4</td>
</tr>
<tr>
<td>o-Hydroxybenzaldehyde (Salicylaldehyde)</td>
<td>0.377</td>
<td>0.375</td>
<td>99.4</td>
</tr>
<tr>
<td>p-Hydroxybenzaldehyde</td>
<td>0.425</td>
<td>0.422</td>
<td>99.3</td>
</tr>
<tr>
<td>m-Hydroxybenzaldehyde</td>
<td>0.406</td>
<td>0.401</td>
<td>98.7</td>
</tr>
<tr>
<td>o-Nitrophenol</td>
<td>0.540</td>
<td>0.534</td>
<td>98.9</td>
</tr>
<tr>
<td>p-Nitrophenol</td>
<td>0.521</td>
<td>0.518</td>
<td>99.6</td>
</tr>
<tr>
<td>m-Nitrophenol</td>
<td>0.511</td>
<td>0.503</td>
<td>98.5</td>
</tr>
<tr>
<td>2,4-Dinitrophenol</td>
<td>0.522</td>
<td>0.516</td>
<td>98.5</td>
</tr>
<tr>
<td>o-Hydroxyacetophenone</td>
<td>0.519</td>
<td>0.512</td>
<td>98.7</td>
</tr>
<tr>
<td>p-Hydroxyacetophenone</td>
<td>0.350</td>
<td>0.345</td>
<td>98.7</td>
</tr>
<tr>
<td>Ethyl Vanillin</td>
<td>0.405</td>
<td>0.401</td>
<td>98.9</td>
</tr>
<tr>
<td>Methyl Salicylate</td>
<td>0.413</td>
<td>0.406</td>
<td>98.4</td>
</tr>
<tr>
<td>o-Phenylphenol</td>
<td>0.503</td>
<td>0.497</td>
<td>98.9</td>
</tr>
<tr>
<td>B-Naphthol</td>
<td>0.528</td>
<td>0.527</td>
<td>99.8</td>
</tr>
<tr>
<td>a-Nitroso-B-Naphthol</td>
<td>0.487</td>
<td>0.481</td>
<td>98.7</td>
</tr>
</tbody>
</table>
Fig. 4  Titration of Phenols in Acetone
Fig. 5 Titration of Phenols in Acetonitrile

1. 2,4-DINITROPHENOL
2. SALICYLIC ACID
3. 2,6-DIBROMOPHENOL
4. O-NITROPHENOL
5. α-NAPHTHOL
6. P-BROMOPHENOL
7. METHYL SALICYLATE
p-nitrophenol, p-hydroxyacetophenone and p-hydroxybenzaldehyde are each more acidic than the corresponding ortho compounds. Increasing the number of functional groups invariably increases the acidity of the phenols. For example, 2,4-dinitrophenol and 2,6-dibromophenol are each more acidic than the corresponding monosubstituted compounds.

2. Differentiating titrations

The steep slope of many of the curves reduces the possibilities of differentiating titrations, but several are still feasible. 2,4-Dinitrophenol is sufficiently more acidic to differentiate it quantitatively from any of the other phenols investigated. o-Nitrophenol, p-nitrophenol, 2,6-dibromophenol and salicylaldehyde are moderately acidic and can be differentiated from weaker phenols such as phenol, alkyl-substituted phenols, phenyl-substituted phenols and methylsalicylate. The titration curves of some phenol mixtures are given in Figs. 6, 7 and 8. The quantitative differentiation of a ternary mixture of 2,4-dinitrophenol, o-nitrophenol and methylsalicylate is possible.

The quantitative results of these and other differentiating titrations are summarized on page 48.

3. Criteria for the feasibility of a differentiating titration

The potentiometric titration curves of individual acids can be used to predict the feasibility of a differentiating
Fig. 6 Titration of Phenol Mixtures in Acetone
Fig. 7 Titration of Phenol Mixtures in Acetone
Fig. 8 Titration of Phenol Mixtures in Acetone
titration of two or more acids. By moving the curve of the weaker acid horizontally so that it begins at the equivalence point of the stronger acid, an estimation of the curve for the titration of a mixture of the two is obtained. The curve actually obtained is usually as good as that predicted by this method and in some instances better than the predicted curve. A useful generalization is that a differentiating titration is feasible if the potential at the beginning of the inflection of the stronger acid and the potential at the start of the curve of the weaker acid differ by approximately 100 millivolts.

B. Carboxylic Acids

1. **Monobasic acids**

   Titration curves of several monobasic carboxylic acids are given in Fig. 9. Simple carboxylic acids have about the same acid strength. The presence of halogens on the alpha carbon atom does increase the acid strength significantly as does one or more nitro groups in the benzene ring of an aryl carboxylic acid. The steep slope of the titration curves of most of the carboxylic acids reduces the possibilities of differentiating titrations. Dichloroacetic acid can be differentiated from acetic acid (Fig. 10) but not from chloroacetic acid.
Fig. 9 Titration of Carboxylic Acids in Acetone
Fig. 10 Titration of a Mixture of Dichloroacetic Acid and Acetic Acid in Acetone
2. **Dibasic acids**

Dicarboxylic acids having the structures \( \text{HO}_2\text{C-}(\text{CH}_2)_n\text{CO}_2\text{H} \) (where \( n = 0, 1, 2 \) and 4) and \( \text{HO}_2\text{CH=CH-CO}_2\text{H} \) were titrated. The titration curves are plotted in Figs. 11, 12 and 13. Oxalic acid showed two excellent breaks. Succinic acid likewise gave two breaks, but the second inflection was less pronounced than the corresponding break observed for oxalic acid. Adipic acid on the other hand gave a weak inflection at the first equivalence point and a larger break at the second equivalence point. The titration curve of fumaric acid shows a single break corresponding to the titration of two equivalents of hydrogen, while maleic acid, the cis isomer of fumaric acid, has only one titratable hydrogen. It is possible, therefore, to quantitatively differentiate a mixture of the two (Fig. 14). The interval up to the first inflection corresponds to the maleic acid. The interval between the first and second inflections corresponds to the titration of two hydrogens of fumaric acid.

The titration of succinic acid is especially noteworthy. The acid dissociation constants of succinic acid in water are \( 10^{-4.2} \) and \( 10^{-5.6} \) (50). On this basis a single break is to be expected. Apparently, hydrogen bonding and/or steric hindrance reduces the acidity of the second hydrogen, and two inflections are observed (Fig. 13).
Fig. 11 Titration of Dicarboxylic Acids in Acetonitrile
Fig. 12 Titration of Dicarboxylic Acids in Acetonitrile
Fig. 13 Titration of Succinic Acid in Acetone
Fig. 14 Titration of a Mixture of Fumaric Acid and Maleic Acid in Acetonitrile
Most dicarboxylic acids are not readily soluble in acetone or acetonitrile. In these instances the acetone or acetonitrile is added to the sample which had been initially dissolved in one or two drops of dimethylformamide.

C. Enols

The titration curves of enolic compounds of the type Y-CH$_2$-Y' are given in Fig. 15. Y and Y' represent various electron-withdrawing functional groups such as: -COR, -COOR, -CONH$_2$, CONHC$_6$H$_5$ and -CN. With the exception of 5,5-dimethyl-1,3-cyclohexanedione, the curves of these compounds are very flat and consequently ideally suited for differentiating titrations. On the other hand, with the exception of cyanoacetamide and 5,5-dimethyl-1,3-cyclohexanedione, most of the enols have similar acid strengths. Therefore, differentiation of mixtures of enols is difficult. 5,5-Dimethyl-1,3-cyclohexanedione can be differentiated from compounds weaker than ethylcyanoacetate, and acetoacetanilide can be differentiated from cyanoacetamide. Results of the titration of enols are given in Table 2. Ethylmalonate apparently reacts with the solvent and cannot be titrated.

D. Imides

Imides, thioimides and acidic thioureas are included in this group. These compounds have the basic structure Y-NH$_2$-Y'.
Fig. 15 Titration of Enols in Acetone
Table 2. Results of the titration of enols

<table>
<thead>
<tr>
<th>Compound</th>
<th>Milliequivalents taken</th>
<th>Per cent found</th>
<th>Per cent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dibenzoylmethane</td>
<td>0.489</td>
<td>0.479</td>
<td>98.0</td>
</tr>
<tr>
<td>5,5-Dimethyl-1,3-cyclohexanedione</td>
<td>0.543</td>
<td>0.538</td>
<td>99.0</td>
</tr>
<tr>
<td>2,4-Pentanenedione (Acetylacetone)</td>
<td>0.353</td>
<td>0.353</td>
<td>98.2</td>
</tr>
<tr>
<td>Acetoacetanilide</td>
<td>0.542</td>
<td>0.534</td>
<td>98.5</td>
</tr>
<tr>
<td>Malononitrile</td>
<td>0.300</td>
<td>0.297</td>
<td>99.0</td>
</tr>
<tr>
<td>Cyanoacetanide</td>
<td>0.404</td>
<td>0.398</td>
<td>98.4</td>
</tr>
<tr>
<td>Ethylcyanoacetate</td>
<td>0.376</td>
<td>0.363</td>
<td>96.6</td>
</tr>
</tbody>
</table>

where Y and Y' again refer to electron-withdrawing groups such as: -COR, -CS, -CONH₂, CONHC₆H₅ and -C₆H₅. Titration curves of several imides are plotted in Figs. 16 and 17. Results of quantitative titrations are given in Table 3. Like the enols most of the imides have very flat titration curves and are ideally suited for differentiating titrations.

In general, thioimides and dithioimides can be differentiated from ordinary imides. Thus, 1-acetyl-2-thiohydantoin and 2,4-thiazolidinedione can be differentiated from weaker imides such as phthalimide, succinimide and hydantoin. Titration curves of some imide mixtures are plotted in Fig. 18. N,N'-Diphenylthiourea and phenylthiourea show a significant difference in acidity. A mixture of the two can be quantitatively differentiated.
Fig. 16 Titration of Imides in Acetone
Fig. 17 Titration of Imides in Acetonitrile
Fig. 18 Titration of Imide Mixtures in Acetone
Table 3. Results of the titration of imides and sulfonamides

<table>
<thead>
<tr>
<th>Compound</th>
<th>Milliequivalents taken</th>
<th>Milliequivalents found</th>
<th>Per cent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hydantoin</td>
<td>0.475</td>
<td>0.474</td>
<td>99.7</td>
</tr>
<tr>
<td>Phthalimide</td>
<td>0.418</td>
<td>0.419</td>
<td>100.3</td>
</tr>
<tr>
<td>Dithiobiuret</td>
<td>0.451</td>
<td>0.452</td>
<td>100.2</td>
</tr>
<tr>
<td>Succinimide</td>
<td>0.523</td>
<td>0.520</td>
<td>99.4</td>
</tr>
<tr>
<td>1-Acetyl-2-thioydantoin</td>
<td>0.502</td>
<td>0.503</td>
<td>100.2</td>
</tr>
<tr>
<td>Sym-diphenylthiourea</td>
<td>0.576</td>
<td>0.575</td>
<td>99.9</td>
</tr>
<tr>
<td>Sulfanilamide</td>
<td>0.532</td>
<td>0.530</td>
<td>99.6</td>
</tr>
<tr>
<td>Sulfathioazole</td>
<td>0.445</td>
<td>0.439</td>
<td>98.6</td>
</tr>
<tr>
<td>Sulfapyridine</td>
<td>0.571</td>
<td>0.567</td>
<td>99.4</td>
</tr>
</tbody>
</table>

E. Sulfonamides

The titration curves of sulfathioazole, sulfapyridine and sulfanilamide are shown in Fig. 19. The differentiation of sulfonamides is especially interesting (Fig. 20). These compounds have the basic structure: \( \text{H}_2\text{N-C}_6\text{H}_4-\text{SO}_2\text{NH-R} \). The ionization constants for these and other sulfonamides have been determined by Bell and Roblin (51). They list the pKa's of the sulfonamides given above as 7.12, 8.43 and 10.43 respectively. Sulfathioazole and sulfapyridine were more acidic than sulfanilamide as expected, but sulfathiazole proved to
Fig. 19  Titration of Sulfonamides in Acetone
Fig. 20 Titration of Sulfonamide Mixtures in Acetone
be considerably stronger than sulfapyridine. Consequently, sulfathiazole-sulfapyridine and sulfathiazole-sulfanilamide mixtures can be differentiated. Quantitative data for the titration of sulfonamides are given in Table 3.

F. Mineral Acids

Several strong mineral acids and ethanesulfonic acid were titrated. The titration curves for perchloric acid and sulfuric acid are plotted in Fig. 21. When perchloric acid is titrated in acetonitrile, the potential varies from +600 millivolts at the beginning of the titration to -850 millivolts at the end. On this basis a curve such as the one indicated by the broken line in Fig. 21 is to be expected. The curve actually obtained has an initial break of about 800 millivolts and a second, smaller break. In the titration of sulfuric acid, two breaks are obtained, but the interval between the first and second equivalence points is invariably larger than the interval up to the first equivalence point. The titration curve of ethanesulfonic acid resembles that of perchloric acid. The reason for these peculiar behaviors is that very strong acids apparently react with the solvent and/or impurities in the solvent in which they are dissolved or the methanol introduced with the titrant.

A titration procedure which will give a single inflection at the equivalence point in the titration of strong monobasic acids is desirable. A method which will give a titration
Fig. 21 Titration of Mineral Acids in Acetonitrile
curve with two equal intervals in the titration of strong dibasic acids is equally desirable. With such a method it would be possible to analyze mixtures involving strong acids. For example, a mixture of sulfuric acid and a sulfonic acid could be determined quantitatively. The first interval would correspond to the titration of the sulfonic acid and one hydrogen of the sulfuric acid. The second interval would correspond to the titration of the second hydrogen of sulfuric acid. Mixtures of nitric acid and nitro-substituted phenols could also be analyzed (Fig. 22).

G. Acid Mixtures

A rapid method for the determination of each component in a mixture of compounds having varied acidic functional groups without a preliminary separation is highly desirable. Although this task has been simplified considerably by the introduction of gas-liquid partition chromatography, a chemical method is nevertheless essential. Acid mixtures can be analyzed by titration with a suitable basic titrant provided that there is a sufficient difference in the acid strength of the various compounds. As indicated earlier, the examination of the curves of individual phenols, carboxylic acids, enols, etc. will suggest many possible combinations which can be differentiated. Furthermore, a comparison of the acidity constants of the acidic constituents will suggest other combinations. Comprehensive tables listing the pKa values of
Fig. 22 Titration of a Mixture of Nitric Acid, 2,4-Dinitrophenol and o-Nitrophenol
many types of acidic compounds are available (52, 53). Typical curves for the titration of several combinations are shown in Figs. 23 and 24. Quantitative data for the analysis of these and other mixtures are summarized in Table 4.

The differentiation of salicylic acid and methylsalicylate illustrated in Fig. 23 is especially noteworthy. Structurally, salicylic acid has two acidic hydrogens. Only one is titratable, however, since the acidity of the phenolic hydrogen is reduced through hydrogen bonding. On the other hand, the phenolic hydrogen of methylsalicylate is sufficiently acidic to be titrated.

Table 4. Results of differentiating titrations in acetone

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Milliequivalents</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>takena</td>
<td>found</td>
</tr>
<tr>
<td>2,6-Dibromophenol and p-bromophenol</td>
<td>0.292</td>
<td>0.293</td>
</tr>
<tr>
<td></td>
<td>0.256</td>
<td>0.257</td>
</tr>
<tr>
<td>2,4-Dinitrophenol and o-nitrophenol</td>
<td>0.342</td>
<td>0.346</td>
</tr>
<tr>
<td></td>
<td>0.223</td>
<td>0.227</td>
</tr>
<tr>
<td>p-Nitrophenol and phenol</td>
<td>0.148</td>
<td>0.145</td>
</tr>
<tr>
<td></td>
<td>0.402</td>
<td>0.399</td>
</tr>
<tr>
<td>p-Hydroxybenzaldehyde and phenol</td>
<td>0.226</td>
<td>0.227</td>
</tr>
<tr>
<td></td>
<td>0.415</td>
<td>0.420</td>
</tr>
<tr>
<td>Ethylvanillin and methylsalicylate</td>
<td>0.227</td>
<td>0.231</td>
</tr>
<tr>
<td></td>
<td>0.287</td>
<td>0.287</td>
</tr>
</tbody>
</table>

*aThe purity of the compounds, as found by the individual titration of each compound, is taken into account in the "milliequivalents taken" column of this table.*
Table 4. (Continued)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Milliequivalents taken</th>
<th>Milliequivalents found</th>
<th>Per cent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>2,4-Dinitrophenol and 2,6-dibromophenol</td>
<td>0.307</td>
<td>0.312</td>
<td>101.6</td>
</tr>
<tr>
<td></td>
<td>0.356</td>
<td>0.364</td>
<td>102.2</td>
</tr>
<tr>
<td>2,4-Dinitrophenol and β-nitrophenol</td>
<td>0.222</td>
<td>0.219</td>
<td>98.6</td>
</tr>
<tr>
<td></td>
<td>0.444</td>
<td>0.443</td>
<td>99.8</td>
</tr>
<tr>
<td>2,4-Dinitrophenol and o-nitrophenol and</td>
<td>0.228</td>
<td>0.230</td>
<td>100.9</td>
</tr>
<tr>
<td>methylsalicylate</td>
<td>0.303</td>
<td>0.310</td>
<td>102.3</td>
</tr>
<tr>
<td></td>
<td>0.151</td>
<td>0.153</td>
<td>101.3</td>
</tr>
<tr>
<td>2,6-Dibromophenol and o-bromophenol</td>
<td>0.277</td>
<td>0.280</td>
<td>101.1</td>
</tr>
<tr>
<td></td>
<td>0.315</td>
<td>0.319</td>
<td>101.3</td>
</tr>
<tr>
<td>5,5-Dimethyl-1,3-cyclohexanedione and dibenzoylemethane</td>
<td>0.236</td>
<td>0.238</td>
<td>100.8</td>
</tr>
<tr>
<td></td>
<td>0.266</td>
<td>0.266</td>
<td>100.0</td>
</tr>
<tr>
<td>1-Acetyl-2-thiohydantoin and succinimide</td>
<td>0.356</td>
<td>0.355</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td>0.246</td>
<td>0.253</td>
<td>102.8</td>
</tr>
<tr>
<td>1-Acetyl-2-thiohydantoin and hydantoin</td>
<td>0.363</td>
<td>0.359</td>
<td>98.9</td>
</tr>
<tr>
<td></td>
<td>0.346</td>
<td>0.348</td>
<td>100.5</td>
</tr>
<tr>
<td>Sulfathiazole and hydantoin</td>
<td>0.229</td>
<td>0.230</td>
<td>100.4</td>
</tr>
<tr>
<td></td>
<td>0.203</td>
<td>0.208</td>
<td>102.4</td>
</tr>
<tr>
<td>Sulfathiazole and sulfapyridine</td>
<td>0.247</td>
<td>0.250</td>
<td>101.2</td>
</tr>
<tr>
<td></td>
<td>0.186</td>
<td>0.182</td>
<td>97.8</td>
</tr>
<tr>
<td>Salicylic acid and methylsalicylate</td>
<td>0.316</td>
<td>0.314</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td>0.301</td>
<td>0.306</td>
<td>101.7</td>
</tr>
<tr>
<td>Sulfathiazole and sulfanilamide</td>
<td>0.182</td>
<td>0.184</td>
<td>101.1</td>
</tr>
<tr>
<td></td>
<td>0.171</td>
<td>0.173</td>
<td>101.2</td>
</tr>
<tr>
<td>2,4-Dinitrophenol and sulfapyridine</td>
<td>0.335</td>
<td>0.339</td>
<td>101.2</td>
</tr>
<tr>
<td></td>
<td>0.304</td>
<td>0.307</td>
<td>101.0</td>
</tr>
<tr>
<td>2,4-Dinitrophenol and acetoacetoanilide</td>
<td>0.336</td>
<td>0.336</td>
<td>100.0</td>
</tr>
<tr>
<td></td>
<td>0.260</td>
<td>0.264</td>
<td>101.5</td>
</tr>
<tr>
<td>2,4-Dinitrophenol and 2,4-pentanedione</td>
<td>0.319</td>
<td>0.323</td>
<td>101.3</td>
</tr>
<tr>
<td></td>
<td>0.201</td>
<td>0.204</td>
<td>101.5</td>
</tr>
<tr>
<td>2,6-Dibromophenol and dibenzoylmethane</td>
<td>0.263</td>
<td>0.267</td>
<td>101.5</td>
</tr>
<tr>
<td></td>
<td>0.313</td>
<td>0.317</td>
<td>101.3</td>
</tr>
</tbody>
</table>
### Table 4. (Continued)

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Milliequivalents</th>
<th>Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>taken</td>
<td>found</td>
</tr>
<tr>
<td>N,N'-Diphenylthiourea and phenylthiourea</td>
<td>0.242</td>
<td>0.244</td>
</tr>
<tr>
<td></td>
<td>0.306</td>
<td>0.309</td>
</tr>
</tbody>
</table>
Fig. 23  Titration of Acid Mixtures in Acetone
Fig. 24 Titration of Acid Mixtures in Acetone

POTENTIAL IN MILLIVOLTS

VOLUME OF TITRANT

-2,4-DINITROPHENOL
SULFATHIAZOLE
HYDANTOIN
ACETOACE-TANILIDE
V. SUMMARY

A brief survey of existing methods for the determination of acidic organic and inorganic compounds has been presented. Individual acids or acid mixtures can be titrated in nonaqueous solvents with tetraalkylammonium hydroxide. The titrations can be followed potentiometrically using a conventional glass-calomel electrode system or a glass-methanol-modified calomel system. Either basic or neutral solvents are applicable in the determination of total acids. However, relatively neutral solvents such as acetone, acetonitrile and dimethylformamide are necessary in differentiating titrations. Such solvents can easily be purified by a single passage through an ion-exchange column and an alumina column.

In this investigation five classes of acidic organic compounds were considered (Fig. 25). In addition, several mineral acids were studied. In each class, individual compounds were titrated potentiometrically. The effect of various substituents on the acidity of the compounds was investigated by selecting samples containing a variety of electron-withdrawing functional groups. The number of these groups and the position of the groups relative to that of the acidic group were also varied.

By studying the individual titration curves, it is possible to make several generalizations. The acidity of mono-substituted phenols decreases in the order listed in Fig. 25.
CLASSES OF COMPOUNDS ANALYZED

A. \( \text{OH} \quad \text{WHERE} \quad Y = -\text{NO}_2, -\text{COR}, -X, -\text{COOR}, C_6\text{H}_5 \)

GENERALIZATIONS:
1. ACIDITY OF SUBSTITUTED PHENOLS DECREASES IN THE ORDER LISTED
2. ACIDITY INCREASES WITH INCREASING NUMBER OF CONSTITUENTS
3. EFFECT OF POSITION: ORTHO > PARA > META
   EXCEPT WHERE H-BONDING IS SIGNIFICANT

B. \( \text{COOH} \quad \text{WHERE} \quad Y = -\text{NO}_2, -X, C_6\text{H}_5 \)

\( R-\text{CH-COOH} \quad \text{Y} \)

C. \( \text{Y-}CH_2\cdot\text{Y} \quad \text{WHERE} \quad Y \text{ AND } Y' = -\text{COR}, -\text{COOR}, -\text{CONH}_2, -\text{CONH}C_6\text{H}_5, -\text{CN} \)

D. \( \text{Y-NH-Y'} \quad \text{WHERE} \quad Y \text{ AND } Y' = -\text{CS}, -\text{COR}, C_6\text{H}_5 \)
   GENERALIZATION: \(-\text{CS-NH-CO} \gg -\text{CO-NH-CO} \)

E. \( \text{SO}_2\text{-NH-Y} \quad \text{WHERE} \quad Y = \text{ELECTRON WITHDRAWING AROMATIC GROUP} \)

Fig. 25 Summary of Acidic Properties of Phenols, Carboxylic Acids, Imides, Enols and Sulfonamides
Ortho and para-substituted phenols are stronger than the corresponding meta-substituted phenols. Increasing the number of functional groups invariably increases the acidity. The substitution of halogen or phenyl groups on the alpha carbon atom of aliphatic carboxylic acids increases the acidity significantly. Nitro-substituted benzoic acids are similarly more acidic than benzoic acid. Enols and imides have very flat titration curves and are well-suited for differentiating titrations. Thioimides are considerably stronger than ordinary imides. Consequently, a mixture of the two can be analyzed. The three sulfonamides titrated showed a pronounced variation in acid strength. Mixtures of sulfathiazole and sulfanilamide and of sulfathiazole and sulfapyridine can be quantitatively differentiated. Mixtures of acids including one or more mineral acids could not be differentiated quantitatively due apparently to the reaction of the mineral acid with the solvent.

The feasibility of differentiating titrations of acid mixtures can be predicted from the potentiometric titration curves of the individual acids. An estimate of the shape of the titration curve of a mixture of two acids is obtained by moving the curve of the weaker acid horizontally so that it begins at the equivalence point of the stronger acid. In general, a differentiating titration is feasible if the potential at the beginning of the inflection of the stronger acid and the potential at the beginning of the titration of
the weaker acid differ by more than 100 millivolts. The feas-
sibility of quantitatively differentiating acid mixtures can
also be predicted from a comparison of the acid constants of
the individual acids. However, since acid constants are fre-
quently determined in water or water-alcohol mixtures, some
qualification is necessary.
VI. SUGGESTIONS FOR FUTURE WORK

Prior to the adoption of triethyl-n-butylammonium hydroxide as the titrant, potassium methoxide in benzene-methanol solution was employed in the titration of dibenzoylmethane and 2,4-pentanedione in acetone. A comparison of the potentiometric curves showed dibenzoylmethane to be the stronger acid. This is to be expected because of the electron-withdrawing effect of the two phenyl groups in dibenzoylmethane. However, when the same compounds were titrated in acetone with triethyl-n-butylammonium hydroxide, 2,4-pentanedione proved to be the stronger acid. Further investigation of this anomalous behavior may be both interesting and fruitful.

The peculiar behavior in the titration of strong acids was described. A good method for the determination of these acids quantitatively in nonaqueous solvents is still needed.

Finally, an electrode system which will give identical, reproducible potentials over extended periods is desirable. Such a system would be considerably valuable for qualitative as well as quantitative determination of acids and bases.
PART II

DETERMINATION OF CARBONYL COMPOUNDS
I. INTRODUCTION

In recent years, the precise quantitative determination of organic compounds via their functional groups has received much consideration. Excellent reviews of chemical analytical methods for organic substances have been prepared by Siggia (54) and more recently by Smith and co-workers (55, 56). The titration of acids in nonaqueous solvents was considered in Part I. The analysis of aldehydes and ketones via a modified oximation procedure will now be considered.

Numerous methods have been proposed for the determination of aldehydes and ketones. Some of the difficulties of these procedures are: lack of versatility, poor detection of the end point or equivalence point, poor accuracy and precision, and poor reagent stability.

The purpose of this investigation was to develop a simple and versatile method for the accurate analysis of carbonyl compounds. Such a method is described below.

The oximation is performed in an anhydrous alcohol medium using half-neutralized hydroxylamine hydrochloride as the reagent. This is prepared by mixing appropriate quantities of hydroxylamine hydrochloride and 2-dimethylaminoethanol. The excess hydroxylamine is titrated potentiometrically with standard hydrochloric acid. A reagent blank is determined simultaneously, and by using the difference between the re-
agent blank and the sample titration, a quantitative measure of the aldehyde or ketone is obtained. The dimethylaminoethanol and hydroxylamine hydrochloride solutions are stored separately and are stable over extended storage. By working at room temperatures, serious decomposition of free hydroxylamine is avoided. The potentiometric break at the equivalence point is exceedingly sharp, and excellent results with good precision are obtained.

The subsequent sections will include a review of hydroxylamine procedures, a discussion of the conditions for analysis and finally a description of the experimental work.
II. REVIEW OF HYDROXYLAMINE PROCEDURES

A. Miscellaneous Methods

The importance of the determination of aldehydes and ketones is indicated by the considerable time and effort that have been spent in developing suitable methods for their analysis. Comprehensive reviews by Farr (57), Guenther and co-workers (9, 10, 11) and Smith and co-workers (55, 56) illustrate the magnitude of the problem and the diversity of the methods which have been developed. The analysis of aldehydes, ketones and related products by oximation has received considerable attention. In addition, the oxidation of aldehydes with Tollen's reagent (58, 59, 60, 61) and with bivalent mercury (62) and the addition of sodium bisulfite to aldehydes (63, 64, 65) have been made the basis of numerous analytical procedures. Higuchi and co-workers (25, 27) and Nystrom and Brown (66) investigated the use of lithium aluminum hydride and lithium aluminum amides. The condensation reactions of carbonyl compounds with phenylhydrazine or substituted phenylhydrazines (67, 68, 69, 70) and with hydrazine or substituted hydrazines (71, 72) have also been examined. Siggia and Segal (73) used lauryl amine for the selective determination of aldehydes. The application of peroxytrifluoroacetic acid (74) and methone, 5,5-dimethyl-1,3-cyclohexanediione, have been reported (75). Wawzonek (36, 76)
and Prévost and Souchay (77) have prepared comprehensive re-
views of polarographic methods for carbonyl compounds. The
detection and determination of aldehydes and ketones by means
of infrared spectroscopy (78, 79) and mass spectrometry (80)
have also been reported.

B. Hydroxylamine Methods

Of all the methods proposed, the oximation method is
used most widely because of its versatility, speed, accuracy
and reagent stability.

The reactions involved are

\[
RR'C=O + NH_2OH\cdot HCl = RR'C=NOH + H_2O + HCl \tag{1}
\]

\[
NH_2OH\cdot HCl + B: = B\cdot HCl + NH_2OH \tag{2}
\]

\[
RR'C=O + NH_2OH = RR'C=NOH + H_2O \tag{3}
\]

\(R' = \text{alkyl or aryl radical or hydrogen}\)

The procedures employing hydroxylamine hydrochloride are of
four general types. The carbonyl compound may be allowed to
react with hydroxylamine hydrochloride. The hydrochloric
acid liberated as shown in Equation 1 is then titrated with
standard alkali. In an alternative method, free hydroxyl-
amine is liberated by the addition of a suitable base (Equa-
tion 2). After reaction with aldehyde or ketone, the excess
reagent is titrated with standard acid. The water produced
may be determined by a Karl Fischer titration. Finally, the
changes in pH caused by the liberation of hydrochloric acid during the oximation may be followed. An excellent summary of hydroxylamine procedures has been prepared by Mitchell (81).

1. Alkalimetric hydroxylamine procedures

In 1895, Brochet and Cambier (82) used hydroxylamine hydrochloride for the determination of formaldehyde. Some years later, Marasco used it to determine acetone (83). Bennett and Salamon (84) and Bennett and Cocking (85) applied the reagent for the analysis of a greater number of aldehydes and ketones. These methods, however, were not quantitative due to the excessively acidic conditions involved. The hydrochloric acid liberated during the reaction shifted the equilibrium to the left (Equation 1) and low results were obtained. In 1935, Bryant and Smith (86) forced the reaction to completion with pyridine and titrated the liberated hydrochloric acid (actually pyridine hydrochloride) with methanolic sodium hydroxide to a bromphenol blue end point. Due to the presence of a large excess of hydroxylamine hydrochloride, the end point was not very sharp. The potentiometric titration curve was somewhat better but not totally satisfactory. However, by controlling the conditions carefully and matching the color of the blank and the sample, good results were obtained. The application of the Bryant and Smith method to 140 compounds has been reported by Montes and Grandolini (87).
Novikova and Petrova (88) proposed two procedures for the analysis of carbonyl compounds. They recommended hydroxylamine hydrochloride for fast reacting ketones. The reagent was added to the sample and immediately thereafter the liberated hydrochloric acid was titrated with sodium hydroxide to a bromphenol blue end point. On the other hand, half-neutralized hydroxylamine hydrochloride was recommended for less reactive ketones such as hindered aliphatic ketones and aromatic ketones. The hydroxylamine was liberated by the addition of alcoholic potassium hydroxide and the excess reagent was subsequently titrated with sulfuric acid to a thymol blue end point. High results were obtained for several unsaturated ketones (89). These high results were attributed to addition of the reagent to the double bond. Smith and Mitchell (90) used a modified hydroxylamine procedure for the determination of carbonyl compounds in the presence of organic acids.

2. Acidimetric hydroxylamine procedures

The principal difficulties of the alkalimetric hydroxylamine procedures have been mentioned. In 1899, Walther (91) modified the procedure of Brochet and Cambier (82). Aldehydes in oil of lemon were treated with an excess of alcoholic hydroxylamine hydrochloride. A measured amount of sodium bicarbonate was added to neutralize the hydrochloric acid and the excess hydroxylamine was titrated acidimetrically. The
carbon dioxide apparently carried out some hydroxylamine and high results were obtained. Bennett (92) modified Walther's procedure by substituting alcoholic potassium or sodium hydroxide for the sodium bicarbonate. Some years later Bennett and Donovan (93) used the half-neutralized reagent for the estimation of a greater number of aldehydes and ketones in essential oils. Leone and Tafuri (94) collected acetaldehyde in a hydroxylamine hydrochloride solution which had been neutralized to the phenolphthalein end point with sodium hydroxide. The excess hydroxylamine was titrated with sulfuric acid to a methyl orange end point. In 1932, Stillman and Reed (95) used the method of Bennett and Donovan for the analysis of numerous carbonyl compounds. They proposed refluxing and back titration of the excess reagent with hydrochloric acid using bromphenol blue indicator. A similar method has been developed by Schultes (96). Trozzolo and Lieber (97) suggested a hydroxylamine number, defined as the milligrams of potassium hydroxide equivalent to the amount of hydroxylamine required to oximate the carbonyl function in one gram of sample, for the characterization of ketones. They applied the procedure of Stillman and Reed to the determination of an impressive list of ketones. More recently, Metcalfe and Schmitz (98) used a 1 to 1 mixture of hydroxylamine and hydroxylamine hydrochloride for the analysis of high molecular weight ketones. The reagent was prepared by mixing appropriate
ate quantities of octadecylamine and the hydroxylamine salt. After 30 minutes of reaction at 70°C., the excess reagent was titrated with alcoholic hydrochloric acid to a bromphenol blue end point. Good results were reported for numerous ketones. The analysis of aromatic aldehydes in the presence of aromatic ketones has been reported (99, 100). Fowler, et al., determined vanillin in the presence of acetovanillone (100). Higuchi and Barnstein (101) recently investigated the use of hydroxylammonium acetate as a reagent for aldehydes and ketones. The oximation was performed in glacial acetic acid and the excess reagent was titrated potentiometrically with perchloric acid. An excellent break at the equivalence point was observed for samples of aromatic aldehydes or ketones. However, the potentiometric curves for the lower aliphatic carbonyl compounds were considerably poorer due to the appreciable basicity of the corresponding oximes. The preparation of the reagent and the actual analysis is relatively time consuming.

3. Miscellaneous hydroxylamine procedures

The change in pH accompanying the addition of carbonyl compounds to hydroxylamine hydrochloride solutions has been made the basis for several methods of analysis. Byrne (102) used a differential pH method for the determination of acetone. Roe and Mitchell (103) applied a similar procedure to the analysis of a greater number of compounds. Berridge and
Watts (104) analyzed several methyl ketones after a preliminary separation of the components by means of gas-liquid partition chromatography. The effluent gases were allowed to react with a continuous stream of dilute alcoholic hydroxylamine hydrochloride solution. By recording the pH of samples taken at given intervals and plotting this pH against time, a curve with several peaks was obtained. Quantitative results were obtained by comparison with a standard working curve.

Mitchell and Bryant (105) used a Karl-Fischer titration to determine the water formed in the oximation of carbonyl compounds.

4. Summary

The alkalimetric hydroxylamine procedures such as the method of Bryant and Smith (86) have been used extensively. The principal disadvantage of these methods is the difficulty of detecting the end point. The acidimetric methods of Stillman and Reed (95), Trozzolo and Lieber (97), etc. have sharper end points and give results that are quite good. However, except for the method of Metcalfe and Schmitz (98), the instability of the half-neutralized hydroxylamine hydrochloride reagent is a definite disadvantage of current acidimetric methods. The introduction of water and the use of reflux temperatures have resulted in further complications. The method of Higuchi and Barnstein (101) is quite novel, but
poorly defined potentiometric breaks for the lower aliphatic carbonyl samples tend to reduce the precision and accuracy considerably.

These difficulties have been minimized in the method to be described. In addition, the interferences of several types of organic compounds have been studied.
III. ANALYTICAL CONSIDERATIONS

A. General Considerations

The development of an analytical method based upon a functional group reaction requires a careful consideration of several factors. The most important of these are equilibrium limitations and kinetic considerations. Equilibrium considerations indicate whether a given reaction will be quantitative. Kinetic considerations will indicate whether a given reaction is rapid enough for analytical purposes. The solvent composition, temperature, reaction time and catalysis frequently affect the final position of equilibrium and the rate at which equilibrium is obtained, consequently, these factors must also be investigated. Finally, interfering side reactions and the ultimate method of analysis must be considered.

B. Choice of Organic Base

The organic base used to neutralize the hydroxylamine hydrochloride should meet the following requirements.

1. The base should be sufficiently basic ($pK_b$ of 4 or 5) to force the equilibrium to the right in the reaction:

$$\text{NH}_2\text{OH} \cdot \text{HCl} + B = B \cdot \text{HCl} + \text{NH}_2\text{OH}$$

Tertiary amines do not form Schiff bases and have the required basicity.
2. The hydrochloride of the base should be soluble in isopropanol. Precipitation of the salt may lead to coprecipitation or occlusion of the sample.

3. The base should be stable over extended storage. Triethanolamine was used initially to liberate the hydroxylamine. It proved to be sufficiently stable and basic, however, copious precipitation of triethanolamine hydrochloride resulted. Further investigation showed that 2-dimethylaminoethanol and 2-diethylaminoethanol fulfilled the above requirements. A solution of 2-dimethylaminoethanol in absolute isopropanol was finally adopted.

C. Optimum Hydroxylamine-Hydroxylamine Hydrochloride Ratio

Since the oximation of carbonyl compounds is an acid catalyzed process (106), a faster reaction rate is obtained by using an excess of hydroxylamine hydrochloride. A 1 to 1 mixture prepared by the mixing of suitable quantities of 2-dimethylaminoethanol and hydroxylamine hydrochloride has proven to be satisfactory.

D. Choice of Titrant

Since perchloric acid has been used extensively for the determination of organic and inorganic basic compounds, a solution of the acid in absolute isopropanol was employed as the titrant. Periodic standardizations against sodium hy-
droxide revealed no noticeable change in its molarity. However, the results of the analysis of several aromatic aldehydes were frustratingly low and inconsistent. A careful examination of the potentials during the titration of one of the samples revealed a peculiar drifting in the vicinity of the potentiometric break. (A curve for the blank titration is plotted in Fig. 26.) Although the addition of the titrant was discontinued at a potential of +250 millivolts, a fairly rapid change followed, and after 15 minutes, a potential of +365 millivolts was observed. At first this drifting was attributed to the decomposition of acetals or ketals and the subsequent liberation of hydrochloric acid resulting from the reaction of the aldehyde or ketone with hydroxylamine hydrochloride. Later investigation showed that this was not the case since a similar drifting was noted in the blank titration. A more probable explanation is given below.

Perchloric acid is a non-oxidizing acid in cold, dilute solutions. However, the concentrated acid (72 per cent) apparently behaves as an oxidizing agent when it is added to absolute isopropanol. The product of the oxidation, acetone, is introduced along with the titrant. Reaction of the acetone with hydroxylamine or free hydroxylamine follows and the potential drifts to more acid regions. Since a greater volume of titrant is added in the blank titration, the blank is reduced more than the sample titration and low results are ob-
Fig. 26 Potentiometric Curve for Blank Titration
tained. Also, the drifting is not readily noticeable below +250 millivolts because of the flat shape of the titration curve. On the other hand, at potentials greater than +250 millivolts, fairly rapid changes are noted since small variations in the hydrochloric acid concentration result in large variations of the potentials. As a final test, isopropanol from an identical container was used to prepare solutions of perchloric acid and hydrochloric acid. Each of these solutions were used to titrate a mixture of hydroxylamine and hydroxylamine hydrochloride. Considerable drifting was observed for the perchloric acid titration whereas little or no drifting was noted for the hydrochloric acid titration. In view of this, hydrochloric acid in isopropanol was selected as the titrant.

E. Order of Reagent Addition

Since acetal or ketal formation is an acid catalyzed process (106), it can be minimized by the addition of the base to the sample prior to the addition of hydroxylamine hydrochloride. This problem was recognized earlier by Metcalfe and Schmitz (98) who suggested a similar sequence for the addition of the reagents. In addition to acid catalysis, the ease of formation of acetals or ketals is dependent upon the nature of the alcohol. Primary alcohols form acetals and ketals most readily, secondary alcohols less readily and tertiary alcohols least readily of all (106). Johnston (107)
proposed tert-butyl alcohol as the solvent to minimize these interferences. Isopropanol has proven to be quite satisfactory.

F. Reaction Time and Reaction Temperature

The choice of reaction conditions is dependent upon the reactivity of the carbonyl compounds with hydroxylamine. Increased reaction rates are observed at elevated temperatures, however, high temperatures should be avoided due to the enhanced rate of decomposition of the reagent at such temperatures. On the other hand, free hydroxylamine is quite stable at room temperatures. The change in the reagent blank with time is illustrated in Table 5. A suitable approach is to use room temperatures and varied reaction times. An alternative method is to use a more concentrated reagent. Specific reaction times for various groups of compounds are given in the experimental procedures.

Table 5. Variation of the reagent blank with time at 26°C

<table>
<thead>
<tr>
<th>Time in minutes</th>
<th>Ml. 0.2 M hydrochloric acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>24.75</td>
</tr>
<tr>
<td>15</td>
<td>24.75</td>
</tr>
<tr>
<td>30</td>
<td>24.74</td>
</tr>
<tr>
<td>60</td>
<td>24.67</td>
</tr>
<tr>
<td>120</td>
<td>24.50</td>
</tr>
</tbody>
</table>
IV. REAGENTS AND APPARATUS

A. Reagents

Hydroxylamine hydrochloride, 0.4 M. Dissolve 27.8 grams of the salt in 300 ml. of absolute methanol and dilute to a liter with absolute isopropanol.

2-Dimethylaminoethanol, 0.25 M. Dissolve approximately 22.5 grams of freshly-distilled 2-dimethylaminoethanol (Eastman white label grade) in absolute isopropanol to make a liter of solution. 2-Diethylaminoethanol is equally satisfactory.

Hydrochloric acid, 0.2 M. Prepare in absolute isopropanol and standardize against sodium hydroxide.

Sodium hydroxide, 0.1 M. Prepare a carbonate free solution and standardize against potassium acid phthalate.

Carbonyl samples. The compounds analyzed were primarily Eastman white label chemicals with an estimated purity of 98 to 100 per cent. Some of these were purified by distillation or crystallization prior to the analysis.

B. Apparatus

Beckman general purpose glass electrode, No. 1190-80.
Beckman fiber-type calomel, No. 1170.
Precision-Shell Dual AC Titrometer or other direct-reading titrimeters.
Buret, 25 ml. (Exax) and pipets, 25 ml. and 20 ml.
Magnetic stirrers.
V. EXPERIMENTAL WORK

A. Procedures

1. Procedure for the determination of aldehydes

Weigh 1.5 to 2.5 millimoles of the sample into a 150 ml. beaker. Add 20 ml. of 0.25 M 2-dimethylaminoethanol followed by 25 ml. of 0.4 M hydroxylamine hydrochloride. Cover the beaker with a sheet of aluminum foil and stir for 20 minutes. Titrate the excess hydroxylamine potentiometrically with 0.2 M alcoholic hydrochloric acid. Determine the reagent blank by titrating a similar reagent mixture after 20 minutes of standing. Use the difference between the reagent blank, $V_b$, and the sample titration, $V_s$, to calculate the per cent purity.

$$\text{Per cent purity} = \frac{(V_b - V_s)(\text{Molarity of HCl})(\text{Mol.wt.)100}}{\text{(Weight of sample) 1000}}$$

2. Procedure for the determination of aliphatic and cyclic ketones

Follow the above procedure for aldehydes but use 30 minutes reaction time. Straight-chained aliphatic, cyclic and other unhindered ketones can be analyzed by this procedure.
B. Analysis of Carbonyl Compounds

1. Aldehydes

The quantitative results for the analysis of several aliphatic and aromatic aldehydes are given in Table 6. Representative titration curves of several aldehydes and ketones are plotted in Fig. 27. One striking feature of the titration curves is the sharpness of the break at the equivalence point. Another advantageous feature is the reproducibility of the potentials. For example, it is possible to determine the potentials at the equivalence point for various carbonyl compounds. Subsequent titrations to the predetermined potentials will yield surprisingly good results.

The results for the most part show a recovery greater than 99 per cent. The analysis of salicylaldehyde is especially noteworthy. Bryant and Smith (86) obtained a recovery of 98.0 ± 0.6 per cent after two days of reaction but only 96.4 per cent after 30 minutes. A recovery of 98.8 per cent after 60 minutes was obtained by the procedure described above.

On few occasions, the addition of the hydroxylamine hydrochloride reagent to the mixture of the sample and 2-dimethylaminoethanol resulted in the formation of a precipitate which disappeared when the sample was titrated with hydrochloric acid. No harmful effects were observed for the analysis of aldehydes and the more reactive ketones. However,
<table>
<thead>
<tr>
<th>Compound</th>
<th>Millimoles taken</th>
<th>Millimoles found</th>
<th>Per cent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vanillin</td>
<td>2.121</td>
<td>2.108</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td>2.086</td>
<td>2.070</td>
<td>99.2</td>
</tr>
<tr>
<td></td>
<td>2.012</td>
<td>2.002</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td>1.966</td>
<td>1.954</td>
<td>99.4</td>
</tr>
<tr>
<td>p-Nitrobenzaldehyde</td>
<td>2.155</td>
<td>2.141</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td>2.026</td>
<td>2.013</td>
<td>99.4</td>
</tr>
<tr>
<td>p-Hydroxybenzaldehyde</td>
<td>1.964</td>
<td>1.952</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td>2.053</td>
<td>2.037</td>
<td>99.2</td>
</tr>
<tr>
<td>Benzaldehyde</td>
<td>2.423</td>
<td>2.415</td>
<td>99.7&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1.970</td>
<td>1.958</td>
<td>99.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Salicylaldehyde</td>
<td>1.908</td>
<td>1.885</td>
<td>98.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.261</td>
<td>2.23&lt;sup&gt;b&lt;/sup&gt;</td>
<td>98.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Furfural</td>
<td>2.270</td>
<td>2.258</td>
<td>99.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.440</td>
<td>2.420</td>
<td>99.2&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>n-Butyraldehyde</td>
<td>2.558</td>
<td>2.523</td>
<td>98.6&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1.902</td>
<td>1.872</td>
<td>98.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Purified by distillation.

<sup>b</sup>60 minutes reaction time used.
Fig. 27 Potentiometric Curves for Sample Titrations
less reactive samples such as acetophenone became occluded within the precipitate and low results were obtained.

2. **Ketones**

Quantitative data for the analysis of ketones are given in Table 7. With the exception of dibenzylketone, good percent recoveries were obtained.

Table 7. Determination of ketones

<table>
<thead>
<tr>
<th>Compound</th>
<th>Millimoles taken</th>
<th>Millimoles found</th>
<th>Per cent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tridecanone</td>
<td>1.972</td>
<td>1.966</td>
<td>99.7</td>
</tr>
<tr>
<td></td>
<td>2.149</td>
<td>2.135</td>
<td>99.4</td>
</tr>
<tr>
<td>Cyclopentanone</td>
<td>2.606</td>
<td>2.567</td>
<td>98.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.329</td>
<td>2.289</td>
<td>99.3&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Methyl isobutyl ketone</td>
<td>2.215</td>
<td>2.177</td>
<td>98.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.325</td>
<td>2.281</td>
<td>98.1&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Cyclohexanone</td>
<td>2.222</td>
<td>2.187</td>
<td>98.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.000</td>
<td>1.970</td>
<td>98.5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Dibenzyl ketone</td>
<td>1.975</td>
<td>1.889</td>
<td>95.7&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1.952</td>
<td>1.866</td>
<td>95.6&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.053</td>
<td>1.970</td>
<td>96.0&lt;sup&gt;b,c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Purified by distillation.

<sup>b</sup>Technical grade sample used.

<sup>c</sup>60 minutes reaction time used.
Some aromatic ketones were also analyzed. By using a reaction time of 2 hours, 97.5 ± 0.3 and 97.9 ± 0.2 per cent recoveries were observed for acetophenone and 2-acetonaphthone respectively. Benzoin showed approximately 84 per cent reaction under these conditions. Further work on the analysis of aromatic and sterically hindered ketones is now in progress.

C. Investigation of Interferences

Samples of vanillin were analyzed in the presence of carboxylic acids, esters and amines. The results of this study are tabulated in Table 8.

Moderate concentrations of benzoic acid, methylsalicylate and ethylacetate apparently do not interfere significantly. Theoretical results were obtained for vanillin in the presence of up to equimolar quantities of these compounds. A similar behavior was expected for phenylacetic acid-vanillin samples. However, considerably higher results were obtained. At a benzoic acid to vanillin ratio of 5 to 1, the potentiometric break was not as sharp. In addition, the equivalence point was shifted to more positive potentials and low results were obtained.

The presence of amines results in serious errors. However, by initially neutralizing the amines with hydrochloric acid to a potential of +295 millivolts and subsequently ti-
Table 8. Analysis of vanillin in the presence of equimolar amounts of carboxylic acids, esters and amines

<table>
<thead>
<tr>
<th>Compound added</th>
<th>Millimoles vanillin taken</th>
<th>vanillin found</th>
<th>Per cent recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>-</td>
<td>99.4&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Benzoic acid</td>
<td>2.102</td>
<td>2.088</td>
<td>99.3&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>1.950</td>
<td>1.946</td>
<td>99.8&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.249</td>
<td>2.238</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td>2.161</td>
<td>2.147</td>
<td>99.4</td>
</tr>
<tr>
<td></td>
<td>1.932</td>
<td>1.913</td>
<td>99.0&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>2.193</td>
<td>2.169</td>
<td>98.9&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Phenylacetic acid</td>
<td>1.782</td>
<td>1.781</td>
<td>99.9</td>
</tr>
<tr>
<td></td>
<td>1.879</td>
<td>1.881</td>
<td>100.1</td>
</tr>
<tr>
<td>Methylsalicylate</td>
<td>1.969</td>
<td>1.960</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td>2.153</td>
<td>2.141</td>
<td>99.4</td>
</tr>
<tr>
<td>Ethyl acetate</td>
<td>2.041</td>
<td>2.031</td>
<td>99.5</td>
</tr>
<tr>
<td></td>
<td>1.993</td>
<td>1.986</td>
<td>99.6</td>
</tr>
<tr>
<td>Tribenylamine</td>
<td>Interferes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n-Butylamine</td>
<td>Interferes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Average of 6 determinations.

<sup>b</sup>Benzoic acid to vanillin ratio = 1 to 5.

<sup>c</sup>Benzoic acid to vanillin ratio = 5 to 1.
trating the excess hydroxylamine to the same potential, 97 to 99 per cent recoveries were obtained.
VI. SUMMARY

A comprehensive review of hydroxylamine procedures has been presented along with a brief survey of other chemical methods for the analysis of carbonyl compounds.

Aldehydes and ketones can be analyzed rapidly and accurately by using a 1 to 1 mixture of hydroxylamine and hydroxylamine hydrochloride in absolute isopropanol as the reagent. The reagent is prepared in situ by the addition of appropriate quantities of 2-dimethylaminoethanol and hydroxylammonium chloride to the sample. After a suitable reaction time, the excess hydroxylamine is titrated potentiometrically with alcoholic hydrochloric acid using a glass-calomel electrode system. A blank is determined simultaneously and from the difference, a measure of the carbonyl compound is obtained.

Numerous aldehydes and ketones were analyzed by this procedure with remarkable precision and accuracy. In most cases, better than 98 per cent recoveries were obtained. The very sharp potentiometric break at the equivalence point is also a definite improvement over earlier methods.

The effect of carboxylic acids, esters and amines on the analysis of carbonyl compounds was studied by analyzing samples of vanillin in the presence of varying amounts of these substances. No significant deviation was observed in the presence of equimolar quantities of benzoic acid, methyl-
salicylate and ethylacetate. The presence of phenylacetic acid produced high results. At a 5 to 1 benzoic acid to vanillin ratio, somewhat lower results were obtained. Amines interfered as expected but by initially neutralizing the amines with hydrochloric acid, 97 to 99 per cent recoveries were obtained.
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VIII. ACKNOWLEDGMENTS

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