1,5- and 1,9-Hydrogen atom abstractions. Photochemical strategies for radical cyclizations

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1,5- and 1,9-Hydrogen atom abstractions. Photochemical strategies for radical cyclizations

Abstract
0.1 mM in dichloromethane. *The source phase, Aq I, contained a 1:1:1 ratio of AMP, CMP, and GMP at a 10 mM concentration in each. The initial pH was adjusted by the careful addition of NaOH(aq). †Transport experiments were performed in a manner similar to those reported in refs 5 and 7. Values reported are the average of three independent measurements; estimated error <5%. “Not determined. eControl experiment using 3,8,12,13,17,22-hexaethyl-2,7,18,23-tetramethylsapphyrin (0.1 mM) as the putative carrier.

Disciplines
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neuralizable) species in the organic membrane phase.17

Although the model of Figure 1 is by no means proved, it is clear from the present study that the transport of a normally organic-insoluble species, namely GMP, can be effected by preparing and using an appropriate nucleobase-expanded porphyrin conjugate. This leads us to suggest that a similar designed receptor approach could be used to achieve the into-cell delivery of Xylo-GMP and other nucleotide drugs in vivo. We are currently exploring this possibility.

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Supplementary Material Available: Listings of synthetic experimental data and time plots for nucleotide transport studies (13 pages). Ordering information is given on any current masthead page.

1.5- and 1,9-Hydrogen Atom Abstractions. Photochemical Strategies for Radical Cyclizations

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The use of radical reactions in organic synthesis is now well established.1 Current topics of research in radical chemistry include the development of nonreductive radical cyclization reactions,2 the study of acyclic stereochemical control in radical reactions,3 and the development of new methods for the generation of radicals.4 Although the action of halides or selenides with tributylstannyl radicals is still the predominantly used method for generating radicals, the expense, toxicity, and operational difficulties associated with the organometallic reagents have prompted the evaluation of alternate methods. Photochemistry has long been used to generate biradical intermediates; however, few of these reactive biradicals are useful in the generation of new radicals. Notable exceptions include the biradicals derived from benzophenones and certain quinones, which undergo efficient intermolecular hydrogen atom abstraction reactions.5 The trapping of 1,4-biradicals (whose short lifetimes necessitate intramolecular


(15) The 2:1 complex formed between monobasic phenyl phosphate and diprotonated sapphyrin has been analyzed in the solid state by X-ray diffraction. One phenyl phosphate is bound on the "top" face of the macrocycle to each of three pyrroles, while the other phosphate is bound to two pyrroles on the "bottom" side. Furuta, H.; Sessler, J. L.; Lynch, V. Unpublished results.
(17) Charge neutralization as a requirement for efficient carrier-mediated transport is known as Fick's first law. See ref 12, p 78.
traps) to generate new biradicals which can cyclize is almost unknown. In a classic experiment, Wagner and co-workers irradiated 2-allylpropiophenone and isolated only 4% of 2-phenyl-2-norbornanol.

\[
\begin{align*}
\text{Ph} & \xrightarrow{hv} \text{Ph} \xrightarrow{hv} \text{HO} \\
\end{align*}
\]

4%

In the context of developing new radical cyclization methods, we examined the interception of the biradicals produced by the photolysis of α-keto esters. The photolysis of α-keto esters has been well studied and has been employed in a mild procedure for the oxidation of alcohols by Binkley. We initially examined the interception of the 1,4-biradicals derived from the photolysis of α-keto esters with an alkene. Acylation of 5-hexen-1-ol with benzoylformic acid (I) and DCC followed by irradiation afforded a good yield of 5-hexenal. We did not isolate any products resulting from the intramolecular trapping of the biradical by the alkene.

\[
\begin{align*}
\text{PhCOOC}_2\text{H} (1) & \xrightarrow{DCC} \xrightarrow{DMAP} \\
\end{align*}
\]

We next examined the cyclopropyl carbinyl radical rearrangement as a way to intercept the biradical. Compound 2a was synthesized from cyclohexanone by the method of Murai. Irradiation of 2a provided a quantitative yield of ketone 3 (X = H) with no trace of products resulting from cleavage of the cyclopropane. Newcomb has demonstrated that phenyl substitution on a methylene carbon of the cyclopropane increases the rate of the cyclopropyl carbinyl radical opening by a factor of 100.

\[
\begin{align*}
2a: & \ x = H, R = \text{Ph} \\
2b: & \ x = \text{R}, R = \text{Ph} \\
2c: & \ x = \text{Ph}, R = \text{Me} \\
2d: & \ x = \text{Me}, R = \text{Ph} \\
2e: & \ x = \text{Ph}, R = \text{Me} \\
\end{align*}
\]

In order to extend the scope of the cyclopropyl carbinyl opening, ester 9 was prepared by reduction of the known cyclopropyl ester with LAH in ether at 0 °C followed by esterification with 1. Surprisingly, irradiation of 9a afforded only the eight-membered-ring lactone 10 in 51% yield. Lactone 10 may have been formed from the 1,4-biradical shown below by a 1,5-hydrogen transfer followed by cyclization.

However, lactone 10 could also have been formed from a direct 1,9-hydrogen atom abstraction. Such long-range hydrogen atom abstractions are rare. All of the cases involve amino ketones, amino imides, or sulfide imides and proceed via an electron-transfer reaction. In order to differentiate between the two mechanisms, the deuterated ester 9b was prepared and subjected to the photolysis conditions. Lactone 11 was isolated in 62% yield, demonstrating that in this case a 1,9-hydrogen abstraction reaction had indeed occurred. The NMR spectrum of the product from photolysis of 9b before purification showed no trace of product derived from the 1,5-hydrogen atom abstraction followed by a 1,5-hydrogen transfer. This remarkable selectivity may reflect photoreaction via the favored syn rotamer of the ester. The 1,5-hydrogen abstraction must occur from the anti rotamer.

Several systems have been evaluated to identify structural features necessary for the formation of eight-membered-ring lactones. The production of aldehyde 12 from keto ester 13 indicates that some degree of conformational rigidity is required.

Both the aromatic analog 14 and the ketal 15 provided eight-membered-ring lactones 16 and 17 in 74% and 22% yields, respectively. Lactate 16 was a single stereoisomer as evidenced by

\[
\begin{align*}
9a: & \ x = \text{H} \\
9b: & \ x = \text{D} \\
10: & \ x = \text{H} \\
11: & \ x = \text{D} \\
10b: & \ x = \text{D} \\
\end{align*}
\]

Communications to the Editor

(12) This phenomenon may be related to the observation by Gellman that certain dipeptides have conformations with 10-membered hydrogen-bonded rings. See: Liang, G.-B.; Rito, C. J.; Gellman, S. H. J. Am. Chem. Soc. 1992, 114, 4440. We thank a referee for bringing this paper to our attention.
Regioselective and Endo-Stereoselective $[3+2]$ Cycloaddition of Dipolar Trimethylenemethane to Electron-Deficient Olefin

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Stereoselective synthesis of five-membered carbocycles continues to attract the interest of organic chemists.1,2 We report that the thermal $[3+2]$ cycloaddition of a substituted dialkoxymethylenemethane (TMM, 2) to an electron-deficient olefin proceeds endo-stereoselectively with retention of the olefin geometry, providing a single-step synthesis of substituted cyclopentanes (Scheme I). Some examples of successful regiocontrol in the cycloaddition to unsaturated olefins are also described. The present cycloaddition of a 4$\pi$-electron TMM to an olefin3 shares an important characteristic with the Diels–Alder reaction in that the reaction proceeds under predictable regio- and stereocontrol.

We have previously shown4 that thermolysis of (E)-ethylidenecyclopentane 1a at 60–100 °C reversibly and stereospecifically generates a dipolar, 4$\pi$-electron (E)-TMM 2a, which is stereochemically stable under the conditions of its $[3+2]$ cycloaddition to olefins (vide infra).5 In order to investigate the stereochemical behavior of 2a in the cycloaddition, we examined its reaction with dimethyl maleate. When a 1 M CdD$_2$ solution of an equimolar mixture of 1a and the maleate was heated at 80 °C for 24 h under nitrogen, the ketene acetals (4a and 5a) were formed in 88% yield with a ratio of 95:5. By $^1$H NMR analysis of $\Delta^{2,3}$-NOE, and COSY) combined with chemical derivatization,4 the major isomer was assigned to be 4a. In no case did we note isomerization of either the starting olefin or the product under the reaction conditions. The stereochemistry of the product in conjunction with the $E$ geometry of 2a strongly suggested that the major cycloaddition pathway involves an endo transition state (3), wherein the acetal and the ester groups are located close to each other.7 Various other observations (vide infra) are also consistent with the endo transition state. The olefin 5a may be due to an alternative exo transition state.

Several important observations were made. The endo:exo isomer ratio (4a:5a) exhibited notable dependence on the solvent polarity (Table I, entry 1), decreasing dramatically from 97:3 to 73:27 as the polarity of the solvent was increased from octane ($\epsilon$ = 1.9) to DMSO-d$_6$ ($\epsilon$ = 46.6). The results suggest that polar interactions between the directing groups control the stereochemistry. This solvent dependency stands in contrast to the very small solvent effects in the Diels–Alder reaction.5 Polar solvent also accelerated the cycloaddition, which may be in part due to accelerated cycloaddition and in part due to accelerated TMM formation, which is about 100 times faster in DMSO than in an alkane solvent.4 The product yield was little influenced by the solvent variation, however. The cycloadditions to methyl trans-crotonate (entry 2) and methacrylate (entry 3) proceeded with virtually complete endo selectivity, but with poor regioselectivity. However, a high level of regiocontrol was achieved with the aid of substituent steric effects. Thus, the isopropyl TMM 1b reacted with methyl trans-crotonate to give a single endo adduct, with other isomers accounting for only 4% of the cycloadducts (entry 4). On the other hand, a cis olefin reacts regio-randomly even with 1b (entry 5), and a bulky cis substituent on the olefin acceptor severely retards the cycloaddition (entry 7). These observations are also in agreement with the endo transition state 3. Alternatively, methyl (E)-4,4-dimethyl-2-pentenoate, bearing a bulky olefinic substituent, reacted with 1a to give a single cycloadduct (>97% isomeric purity, entry 6). In general, an olefin substituent trans to the ester group appears to ensure high endo selectivity.