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Registry No. Azide, 14343-69-2; quinuclidine, 100-76-5; 2-nitropropane anion, 20846-00-8; α,p-dintrocumene, 3276-35-5; p-nitrocumyl chloride, 14500-58-4; α-nitroisobutyrate, 5342-77-8; 2-nitropropane lithium salt, 3958-63-2; sodium azide-α,p-dinitrocymene charge-transfer complex, 108592-01-4; sodium azide-p-nitrocumyl chloride charge-transfer complex, 108592-02-5; quinuclidine-p-nitrocumyl chloride charge-transfer complex, 108617-76-1; α-nitroisobutyrate-HMPA charge-transfer complex, 108592-03-6.

Modification of Photochemical Reactivity by Cyclodextrin Complexation: Consequences of Restricted Rotation of Norrish Type II 1,4-Diradicals from Aryl Alkyl Ketones

G. Dasaratha Reddy, B. Jayasree, and V. Ramamurthy*

Department of Organic Chemistry, Indian Institute of Science, Bangalore-560 012, India

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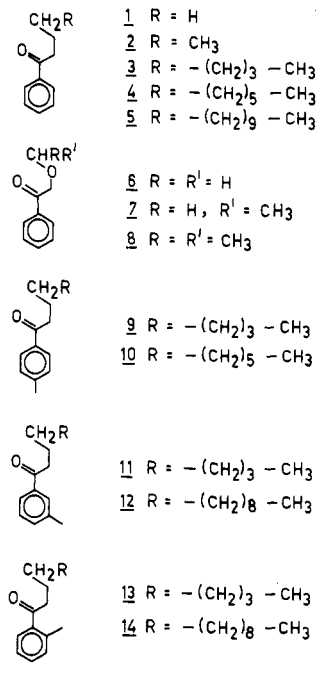
Photochemical behavior of aryl alkyl ketones complexed to β-cyclodextrin both in aqueous solution and in the solid state have been investigated. Comparison of the above behavior with that in isotropic solvents reveals that cyclodextrin inclusion provides an environment wherein photoreactions may be carried out with consequences different from those observed in homogeneous solution. Products of elimination and cyclization resulting from the Norrish type II hydrogen abstraction were monitored. The ratio of these products was dependent on the length but not on the bulkiness of the alkyl substituent. These observations are rationalized on the basis of the steric constraints by the cyclodextrin cavity on the rotational motions of the 1,4-diradical.

Introduction

The past decade has witnessed an ever-increasing interest in the effects of organized assemblies on photochemical reactions.[1] Reactants accommodated in molecular assemblies such as micelles, microemulsions, liquid crystals, and organic crystals often achieve a greater degree of organization compared to homogeneous solution, a feature which may promote unique reaction features. A specific subarea that has attracted recent interest concerns the reactivity of molecules incorporated into "host-guest" systems. Cyclodextrin, which is a cyclic oligosaccharide containing six or more D-(+)-glucopyranose units, is one of the most important host systems. Each cyclodextrin molecule has a toroidal, hollow, truncated cone with primary and secondary hydroxyl groups crowning the narrower and wider rims, respectively. The interior of each cyclodextrin cavity contains two rings of C-H groups and a ring of glucose oxygen atoms. Hence, the interior is relatively hydrophobic, whereas the exterior is relatively hydrophilic. It is this feature that enables cyclodextrins to extract, hold, and protect hydrophobic molecules from aqueous solutions. The application of cyclodextrins as an organizing microenvironment in photochemical reactions has been initiated recently and has revealed selectivity in product distributions.[2] During the last few years, our group has been investigating the influence of cyclodextrin cavity on photochemical reactions.[3] The goal is to achieve selectivity in photochemical reactions using this unusual

Chart I



(1) Ramamurthy, V. Tetrahedron **1986**, *42*, 5753.

(2) Ohara, M.; Watanabe, M. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 820. Chenevert, R.; Voyer, N. *Tetrahedron Lett.* **1984**, *25*, 5007. Chenevert, R.; Plante, R. *Can. J. Chem.* **1983**, *61*, 1092. Liu, J. H.; Weiss, R. G. *J. Photochem.* **1985**, *38*, 303. Liu, J. H.; Weiss, R. G. *Isr. J. Chem.* **1985**, *25*, 228. Tamaki, T.; Kokubu, T. *J. Inclusion Phenom.* **1984**, *2*, 815. Tamaki, T. *Chem. Lett.* **1984**, 53. Neckers, D. C.; Paczkowski, J. *J. Am. Chem. Soc.* **1986**, *108*, 91. Neckers, D. C.; Paczkowski, J. *Tetrahedron* **1986**, *42*, 4671. Yumoto, T.; Hayakawa, K.; Kawase, K.; Yamokita, H.; Taode, H. *Chem. Lett.* **1985**, 1021. Vekama, K.; Irie, T.; Hirayama, F. *Chem. Lett.* **1978**, 1109.

(3) (a) Arjunan, P.; Ramamurthy, V. *J. Photochem.* **1986**, *33*, 123. (b) Syamala, M. S.; Devanathan, S.; Ramamurthy, V. *J. Photochem.* **1986**, *34*, 219. (c) Sharat, S.; Usha, G.; Tung, C. H.; Turro, N. J.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 941. (d) Nageswara Rao, B.; Turro, N. J.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 460. (e) Dasaratha Reddy, G.; Usha, G.; Ramanathan, K. V.; Ramamurthy, V. *J. Org. Chem.* **1986**, *51*, 3085. (f) Syamala, M. S.; Dasaratha Reddy, G.; Nageswara Rao, B.; Ramamurthy, V. *Curr. Sci.* **1986**, *55*, 875. (g) Devanathan, S.; Dasaratha Reddy, G.; Ramamurthy, V. In *Surfactants in Solution: Modern Aspects*; Mittal, K. L. Ed.; Plenum: New York, in press.

0022-3263/87/1952-3107$01.50/0

Table I. Norrish Type II Reactions of Phenyl Alkyl Ketones: Effects of the Medium on the Elimination to Cyclization Ratio (E/C)[a,d]

medium	ketone				
	butyrophenone	valerophenone	octanophenone	decanophenone	tetradecanophenone
benzene	6.5	3.0	1.2	2.5	1.6
tert-butyl alcohol	8.5	4.2	2.5	3.3	2.9
β-cyclodextrin (aq soln)	3.8	3.8	1.8	1.6	1.4
β-cyclodextrin (solid)	3.5	2.7 (1:0.9)[b]	0.8 (1:0.8)[b]	0.7 (1:0.85)[b]	0.4 (1:0.86)[b]
E/C[*t*-BuOH/CD (solid)]	2.4	1.6	3.1	4.7	7.3
10^3K_d,[e] M L^{-1}	1.1	0.77	0.6	0.17	*c*

[a] Products were identified by GC: error limit; ±5%; conversion, 20%. [b] Host:guest ratio as measured by GC and gravimetry. [c] Complex poorly soluble in water. [d] Irradiations were conducted after bubbling samples with N_2 for 45 min. [e] Dissociation constant in water.

Table II. Norrish Type II Reactions of α-Alkoxyacetophenones: Effect of the Medium on the Elimination to Cyclization Ratio (E/C)[a,b]

medium	ketone		
	α-methoxyacetophenone	α-ethoxyacetophenone	α-isopropoxyacetophenone
benzene	1.9	0.8	1.6
tert-butyl alcohol	2.9	1.1	2.1
β-cyclodextrin (aq soln)	3.6	1.0	2.7
β-cyclodextrin (solid)	1.7 (1:0.91)[c]	0.4 (1:0.85)[c]	1.1 (1:0.90)[c]
E/C[*t*-BuOH/β-CD(solid)]	1.7	2.8	1.9

[a] Products were identified by GC: error limit, ± 5%; conversion, 20%. [b] All solution irradiations were carried out after passing nitrogen through the solution for 45 min. [c] Host:guest ratio as measured by GC and gravimetry.

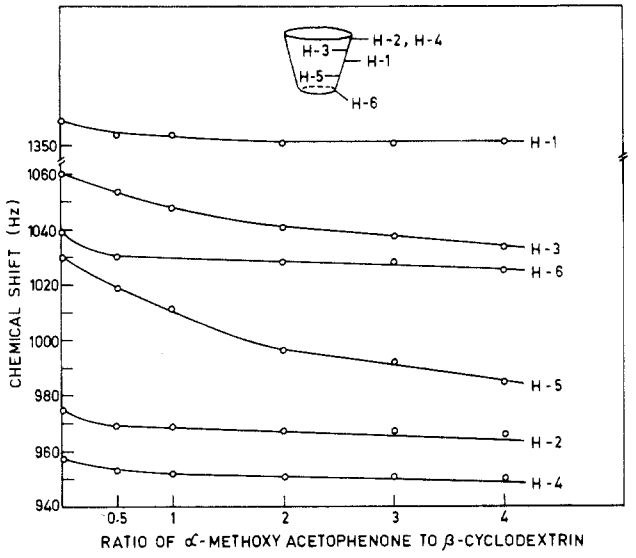


Figure 1. ^1H NMR chemical shift differences of β-cyclodextrin protons as a function of α-methoxyacetophenone to cyclodextrin ratio.

environment and to understand the features controlling such selectivity. In continuation of such studies, we have investigated the photochemical behavior of a large number of aryl alkyl ketones (Chart I). It was anticipated that the cyclodextrin cavity would impose certain constraints on product formation from the Norrish type II process which these ketones undergo. Three sets of aryl alkyl ketones have been chosen as guests (Chart I), whose photochemical behavior in host cyclodextrin we anticipated, would provide considerable information regarding the restrictions imposed by the cyclodextrin cavity on the guest molecules or the intermediates derived therefrom. Such information is vital for utilizing cyclodextrin to control or modify the photochemical behavior of not only the aryl alkyl ketones investigated here but also of many other reactions of a wide variety of substrates.

Results

Addition of aryl alkyl ketones **1**–**14** to saturated aqueous solutions of β-cyclodextrin precipitates a white solid which is soluble in excess of water. These ketones did not form stable complexes with α-cyclodextrin, and therefore the effect of α-cyclodextrin on the photobehavior of **1**–**14** could not be pursured. The X-ray powder pattern of the precipitated solid differed from that of β-cyclodextrin. The solid-state ^{13}C NMR of the isolated precipitate, in cases where recorded, exhibited peaks corresponding to both the ketone and the β-cyclodextrin. Both of these results indicated the inclusion of the guest ketones in the cyclodextrin cavity. The molar ratio of ketone to β-cyclodextrin was calculated by estimating (GC analysis and gravimetrically) the amount of ketone extracted from a known amount of the solid complex. The molar ratios of ketone to β-cyclodextrin for all the solid complexes were ~1:1 (Tables I–III).

Table III. Norrish Type II Reactions of *o*-, *p*-, and *m*-Methylphenyl Alkyl Ketones: Effect of the Medium on the Elimination to Cyclization Ratio (E/C)[a,b]

medium	compound					
	o-Me Oct[c]	*o*-Me Tridec[c]	*m*-Me Oct[c]	*m*-Me Tridec[c]	*p*-Me Oct[c]	*p*-Me Dec[c]
benzene	3.53	3.24	1.86	3.07	2.60	2.48
tert-butyl alcohol	5.06	4.92	3.40	4.65	4.65	3.57
β-CD (aq soln)	2.33	2.08	2.52	2.05	2.54	2.44
β-CD (solid)	2.15 (1:0.90)[d]	0.80 (1:0.92)[d]	1.30 (1:0.86)[d]	0.70 (1:0.9)[d]	2.24 (1:0.89)[d]	1.60 (1:0.92)[d]
E/C [*t*-BuOH/β-CD (solid)]	2.4	6.2	2.6	6.6	2.1	2.2
K_d	2.07×10^{-3}		4.81×10^{-3}		0.52×10^{-3}	

[a] Products were analyzed by GC: error limit, ±5%; conversion, 20%. [b] Irradiations were conducted after bubbling samples with N_2 for 45 min. [c] Oct, octanophenone; Tridec, Tridecanophenone; Dec, decanophenone; Me, Methyl. [d] Host:Guest ratios were measured by GC and gravimetry.

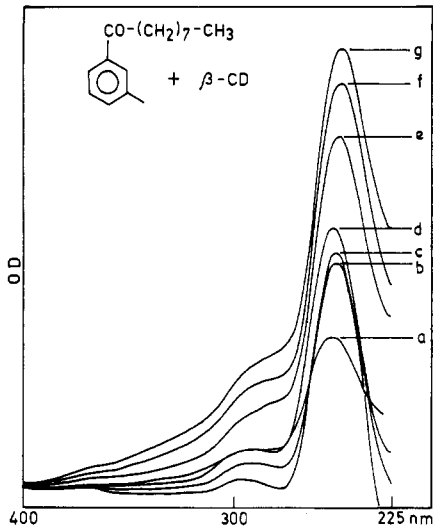


Figure 2. Absorption spectra of *m*-methyloctanophenone (1.37×10^{-5}) in water with varying concentrations of β-CD: (a) 0 M; (b) 5.36×10^{-4} M; (c) 1.07×10^{-3} M; (d) 1.60×10^{-3} M; (e) 3.75×10^{-3} M; (f) 5.90×10^{-3} M; (g) 8.04×10^{-3} M.

The existance of an inclusion complex in aqueous solution was conceived on the basis of ^{1}H NMR studies[4] and the measurement of dissociation constants using UV–vis absorption shifts. The complexes of β-cyclodextrin with valerophenone and α-methoxyacetophenone were chosen as model systems for the structural analysis in aqueous solution. The 270-MHz ^{1}H NMR spectra of aqueous solutions of β-cyclodextrin and solutions containing various ratios of the host to the guest were recorded. The chemical shifts of β-cyclodextrin protons in the presence and in the absence of the guest were utilized for drawing conclusions regarding the complexation. Figure 1 gives a plot of the chemical shift difference for β-cyclodextrin protons as a function of the ratio of α-methoxyacetophenone to β-cyclodextrin. Similar results were obtained with valerophenone and other ketones. Inclusion of the guest in the cavity of β-cyclodextrin is evident from the upfield shifts of the inside protons (H_3, H_5, and H_6) and from the absence of change in the chemical shifts of outside protons (H_1, H_2, and H_4) of cyclodextrin.

UV–vis absorption spectroscopy has been used as an effective tool in determining the stability constants for various cyclodextrin complexes. Aqueous solution of ketones **1–14** experienced an increase in spectral intensity but no discernible change of the spectral shape upon addition of β-cyclodextrin. Figure 2 illustrates one such example. The dissociation constants of the complexes of ketones **1–4**, **6–9**, **11**, and **13** with β-cyclodextrin were determined by using the approach of Benesi and Hilderbrand.[5] The poor solubility of ketones **5**, **10**, and **14** in water does not allow estimation of K_d. The dissociation constants are in the range of 10^{-3}–10^{-4} M L^{-1} implying that the above complexes are fairly stable in aqueous solution (Tables I–III). It is interesting to note that the stability of the complexes increases with the length of the alkyl chain in ketones **1–4** (Table I). Such a behavior has recently been reported for alkyl benzoates.[6] Furthermore, the observed variation in stability between *o*-, *p*-, and *m*-methyloctanophenone complexes is consistent with the behavior of a number of similarly disubstituted aromatics;[7] *p*-methyloctanophenone forms the most stable complex, while *m*-methyloctanophenone forms the least stable complex.

All the ketones investigated here (Chart I) undergo Norrish type II hydrogen abstraction reaction upon irradiation either in benzene or in *tert*-butyl alcohol solutions. Generally, in the absence of α-alkyl substitution, the rate of α-cleavage is low, and therefore the cleavage process does not compete with the γ-hydrogen abstraction. Thus the occurence of Norrish type II alone in **1–14** is consistent with the expectation. Cyclobutanols (or oxetanols) and acetophenone were obtained as the products of cyclization and elimination processes, respectively, of the primary 1,4-diradical. The ratio of acetophenone to cyclobutanols (E/C) measured by GC analysis are provided in Tables I–III. Photolysis in cyclodextrin media brought about a significant difference in behavior. Photolyses of aqueous solutions of β-cyclodextrin complexes as well as those of solid complexes were conducted. In all the cases, the effect of the cyclodextrin cavity was more pronounced in the solid state than in aqueous solution.

Table I summarizes the results on simple aryl alkyl ketones **1–5**. In all the cases, cyclodextrin complexation reduces the yield of the elimination products (in other words enhances the cyclization product) with respect to *tert*-butyl alcohol as the solvent. Furthermore, a clear trend in the E/C ratio is visible when going from butyrophenone to tetradecanophenone, the gradual decrease correlating well with the length of the alkyl chain. A dramatic decrease in the ratio of E/C is seen in the case of tetradecanophenone. Results on the α-alkoxyacetophenones **6–8** are tabulated in Table II. As in the case of the aryl alkyl ketones (Table I), cyclodextrin complexation enhances the cyclization process. But no trend was obvious with respect to the bulkiness of the alkoxy substituent. In order to unravel the effect of the geometry of the complex on the product distribution, the photobehavior of ortho-, meta- and para-methylated phenyl alkyl ketones **9–14** was investigated. Once again it is clear from Table III that cyclodextrin complexation enhances the yield of cyclobutanol with respect to acetophenone. The effect of the alkyl chain length is also evident when one compares the results between octanophenones and tridecanophenones. But no obvious effect of the difference in aryl substitution (*o*-, *p*-, and *m*-methyl) was seen.

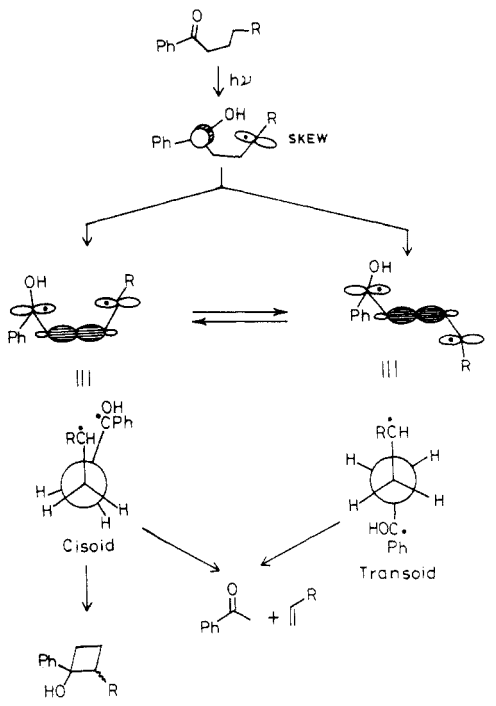
In order to assess the use of cyclodextrin in controlling the stereochemistry of the cyclobutanols, those obtained from valerophenone and tetradecanophenone were examined in detail. While valerophenone gave both the isomeric cyclobutanols, tetradecanophenone gave only one, upon complexation to cyclodextrin. But no optical induction in the product cyclobutanols was obtained in any of these cases.

Discussion

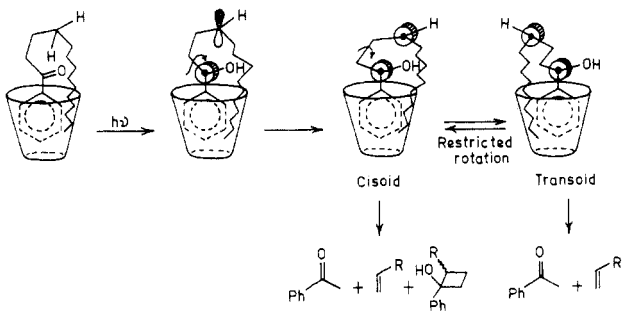
General Photochemical Behavior. The Norrish type II hydrogen abstraction reaction of aryl alkyl ketone possessing γ-hydrogen has been extensively investigated.[8]

(4) Demarco, P. V.; Thakkar, A. L. *J. Chem. Soc., Chem. Commun.* **1970**, 2.
(5) Benesi, H. A.; Hilderbrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703.
(6) Ueno, A.; Suzuki, I.; Hino, Y.; Suzuki, A.; Osa, T. *Chem. Lett.* **1985**, 159.
(7) Matsui, Y.; Nishioka, T.; Fujita, T. *Top. Curr. Chem.* **1985**, *128*, 61. Bergeron, R. J. In *Inclusion Compounds*; Atwood, J. L., Davies, J. E. D., Mac Nicol, D. D., Eds.; Academic: New York, 1984; Vol. 3, pp 391–443.
(8) Wagner, P. J. *Acc. Chem. Res.* **1971**, *4*, 168. Turro, N. J.; Dalton, J. C.; Dawes, K.; Farrington, G.; Hautala, R.; Morton, D.; Niemczyk, M.; Schore, N. *Acc. Chem. Res.* **1971**, *5*, 92. Scaiano, J. C. *Acc. Chem. Res.* **1982**, *15*, 252. Scaiano, J. C. *Tetrahedron* **1982**, *38*, 819.

Scheme I



Scheme II



They undergo γ-hydrogen abstraction exclusively from the $n\pi^*$[3] triplet state to yield the triplet 1,4-diradical as the primary intermediate (Scheme I). Intersystem crossing of the triplet 1,4-diradical generates the corresponding singlet, and hence the ensuing products reflect the conformation of the precursor triplet 1,4-diradical. The triplet diradical that is generated in the skew form from the excited ketone readily equilibrates (via bond rotations) between the cisoid and the transoid forms (Scheme I), the transoid being more favored in isotropic solvents and more so in protic solvents. It may be noted that the transoid form can undergo only fragmentation while the cisoid form can also cyclize to give the cyclobutanols.

On the basis of our earlier studies on the geometric isomerization of stilbenes[3b] and the Norrish type I and type II reactions of benzoinalkyl ethers,[3e] we anticipated that the cyclodextrin complexation of the aryl alkyl ketones might impose considerable restriction on the rotational motions of the type II diradical and thus alter the equilibrium distributions of the cisoid and the transoid conformers in comparison to isotropic solvents. Further, it appeared probable that the equilibrium can be shifted in favor of the cisoid form in β-cyclodextrin by the introduction of a long alkyl chain on the ketone, that would anchor the diradical present in the cavity in the cisoid conformation (Scheme II). These changes, we thought, should reflect in the ratio of products resulting from the elimination (transoid form) and the cyclization (cisoid form) processes. It is in this context that the ketones **1–5**

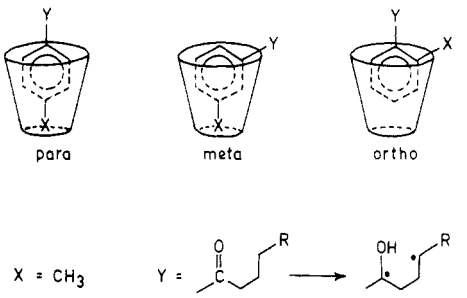
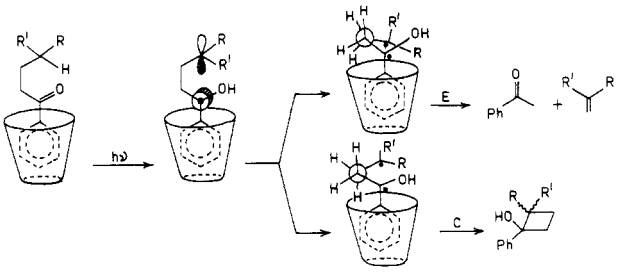


Figure 3. Proposed geometries of the disubstituted benzenes as guests in cyclodextrin cavity.

Scheme III



were chosen for investigation.

In addition to the above factor, the elimination to cyclization ratio is also controlled by the orbital overlap requirements. It is widely accepted that efficient cleavage requires a 1,4-diradical conformation in which both the singly occupied p orbitals can overlap significantly with the central σ bond being broken; failing this, cyclization occurs from a conformation involving small nonbonded interactions and only partial orbital overlap.[9] We believed that the cyclodextrin cavity would impose certain restrictions on the diradical's motions in achieving these conformations suitable for orbital overlap and that they might vary with the bulkiness of the alkyl substituent (Scheme III). Ketones **6–8** appeared as suitable substrates for investigating the above phenomenon.

It is well-known that the ortho, meta, and para isomers of aromatic compounds form inclusion compounds with cyclodextrin of different strengths.[7] Figure 3 illustrates the geometry of these three complexes. We speculated that such a gemetrical variation in complexation of appropriately substituted aryl alkyl ketones might reflect in the product distribution. Such effects have already been established in thermal reactions. For example the catalytic effect of cyclodextrin on ester hydrolysis is dependent on the structures of the substrate.[10] The rate accelerations for the meta-substituted phenyl acetates were always larger than for the corresponding para-substituted phenyl acetates. It was our hope that the diradicals generated from *o*-, *p*-, and *m*-methyl-substituted aryl alkyl ketones would experience different amounts of restriction to conformational interchange and to the requirement of orbital overlap, which would reflect in the E/C ratio. This speculation led us to investigate the photobehavior of ketones **9–14** in the cyclodextrin cavity. Thus, three sets of aryl alkyl ketones have been chosen as guests, whose photochemical behavior in host cyclodextrin would provide

(9) Wagner, P. J.; Kelso, P. A.; Kemppainen, A. E.; McGrath, J. M.; Schott, H. N.; Zepp, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 7506. Lewis, F. D.; Hillard, T. A. *J. Am. Chem. Soc.* **1972**, *94*, 3852.

(10) van Etten, R. L.; Sebastian, J. F.; Clowes, G. A.; Bender, M. L. *J. Am. Chem. Soc.* **1967**, *89*, 3242. Griffiths, D. W.; Bender, M. L. *Adv. Catal.* **1973**, *23*, 209.

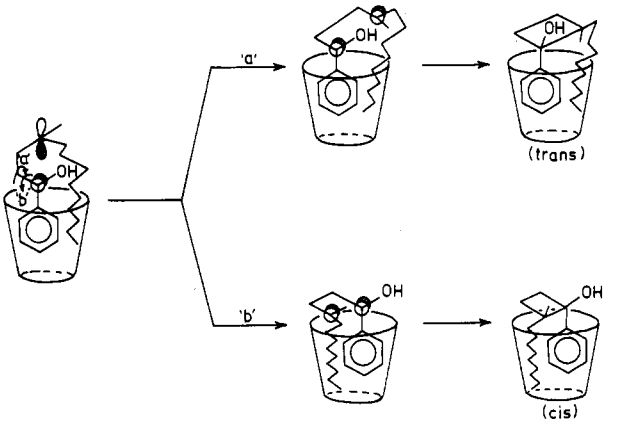
considerable information regarding the restrictions imposed on the guest molecules or intermediates derived therefrom by the host matrix.

Choice of Scale for Comparison. Cyclodextrin's influence on the type II reaction needs to be examined at least in terms of three factors, namely, solvent effects on the excited-state reactivity, solvent hydrogen-bonding effects, and the influence of encapsulation on biradical partitioning. The polarity of cyclodextrin interior in aqueous solution has been measured through several physical techniques.[11] They all indicate that the polarity inside the cavity is similar to ethanol. Further, the cavity of cyclodextrin consists of ether linkages and peripheral hydroxyl groups capable of hydrogen bonding to the intermediate 1,4-diradical. Therefore, in order to delineate the role of encapsulation effect of the cyclodextrin it is appropriate to compare the E/C ratio measured in cyclodextrin with that in *tert*-butyl alcohol as solvent. To make this comparison meaningful, it is necessary to make an assumption that the association constants for the intermediate biradical and the excited ketone are virtually the same as that for the ketone in the ground state. Although information on these are highly desirable they are not presently available. Examination of Tables I–III reveals that the effect of the cavity on the product distribution is much less in aqueous solution than in the solid state. This raises a question—where does the reaction occur when photolysis is conducted in aqueous solution? Is it from the bound substrates or from the unbound free ketones? On the basis of the following observations we assume that the reaction originates from the included ketone: (a) the measured stability constants are fairly high; (b) the product distribution is independent of an excess of cyclodextrin (more than a molar ratio); (c) all the ketones investigated are fairly insoluble in water.

The Role of Cyclodextrin. The following conclusions can be readily made on examining Tables I–III. (1) the elimination to cyclization (E/C) ratio is always lower in cyclodextrin media than in *tert*-butyl alcohol as solvent; (2) the extent of decrease of E/C ratio in cyclodextrin with respect to *tert*-butyl alcohol is much dependent on the length of the alkyl chain—the longer the chain the larger the influence; (3) the ratio is independent of the bulkiness of the alkyl substituent; (4) the influence of cyclodextrin on the product ratio is normally more predominant in the solid state than in aqueous solution.

The factors that control the partitioning of the 1,4-diradical to the elimination and cyclization products can be visualized with the help of Schemes I–III. In order to understand the role of the cyclodextrin cavity in sterically inhibiting the guest diradicals achieving the required orbital overlap for elimination and cyclization, ketones **6–8** having alkoxy substituents of differing bulkiness were examined. We speculated that the larger the size of the alkoxy group, more would be the hindrance for achieving the parallel alignment required for elimination (Scheme IV). On this basis, we predicted that the variation of E/C ratio in the cyclodextrin cavity (both in aqueous solution and in the solid state) should be related to the size of the alkoxy group. Perusal of Table II reveals that this is not the case. Therefore, it is clear that the influence of the cyclodextrin cavity on the orbital overlap/alignment criteria is not the major force behind the reduction of the

Scheme IV



E/C ratio. This conclusion is further supported by the results on ketones **9–14**. As illustrated in Figure 3, the three isomeric ketones were expected to generate diradicals with different geometries. Therefore, the steric influence by the rim of the cavity upon the diradical achieving the orbital overlap/alignment requirement is expected to be different and consequently, the reduction in the E/C ratio. Once again in agreement with the above conclusion this was not the case. These negative observations led us to conclude that the general effect of a decrease in the E/C ratio in cyclodextrin cavity can be understood on the basis of the host influence on the interconversion between the cisoid and the transoid diradicals.

As illustrated in Scheme II, excitation of the aryl alkyl ketone included in the cyclodextrin cavity would result in a 1,4-diradical in which the two singly occupied p orbitals are perpendicular to each other. Since the phenyl group is locked inside the host cavity, the rotations required for further reaction have to occur only on the alkyl side. Rotation of the central σ bond would result in the cisoid–transoid interconversion. It is well established that in a medium where the 1,4-diradical is hydrogen bonded, the diradical prefers a transoid geometry, and therefore elimination products dominate.[8] This is reported to be the case in *tert*-butyl alcohol. Although, the internal polarity and the hydrogen-bonding ability of the cyclodextrin cavity would favor the transoid conformation, the hydrophobic effect of the medium would influence the molecule to adopt the cisoid conformation for the following reasons. We postulate that in the ground state, a part of the alkyl group is buried inside the hydrophobic cavity along with the phenyl group. A similar structure for the diradical, would require the alkyl group to move out of the cavity during the cisoid to transoid conformational change. Such a change would be restricted since the hydrophobic alkyl chain would prefer to stay in the cavity. On the basis of this model, the contribution of the cisoid conformation in yielding products would increase with the length of the alkyl chain. This is indeed the case as reflected in the observed E/C ratios for **1–5** (Table I). This effect is also reflected in the behavior of *m*- and *p*-methyloctanophenones and *m*- and *p*-methyltridecanophenones. The severe constraints imposed by the solid matrix should attenuate the barrier for the cisoid to transoid conversion, and therefore, the effect observed in aqueous solution could only be the lower limit of the cavity influence. It is evident from Tables I–III that the influence of cyclodextrin on the product distribution is much more in the solid complex than in the aqueous solution.

From the above discussion it is clear that the cyclodextrin cavity does not tolerate the rotational motions of the central σ bond (2,3-bond) of the diradical from the

(11) Heredia, A.; Requena, G.; Garcia Sanchez, F. *J. Chem. Soc., Chem. Commun.* **1985**, 1814. Cox, G. S.; Turro, N. J. *Photochem. Photobiol.* **1984**, *40*, 185. Cox, G. S.; Hauptman, P. J.; Turro, N. J. *Photochem. Photobiol.* **1984**, *39*, 597. Cox, G. S.; Turro, N. J.; Yang, N. C.; Chen, M. J. *J. Am. Chem. Soc.* **1984**, *106*, 422.

cisoid to transoid geometry. It is of interest to check whether any preference exists for rotation around the 1,2-bond of the diradical having the skew geometry. As illustrated in Scheme IV, the rotation to the left would give the *trans*-cyclobutanol whereas to the right would yield the cis isomer. In this context cyclobutanols from valerophenone and tetradecanophenone were examined in detail. While β-cyclodextrin-complexed valerophenone gave cyclobutanols of both the geometry in ratios similar to benzene, tetradecanophenone complexed to cyclodextrin in the solid state gave only the trans isomer, whereas in benzene both the isomers were formed. Although the above results suggests that there exists a preference for the rotational motion around the 1,2-bond of the skew diradical, the reasons behind such a preference are not obvious.

Thus, the results presented here clearly illustrate that cyclodextrin cavity can impose restrictions on the rotational motions of various single bonds. Such restrictions can often result in selectivity in product distribution. Examples discussed here is a testimony to such a phenomenon and provide an optimistic outlook for future activities in this field.

Experimental Section

Materials. β-Cyclodextrin, butyrophenone, and valerophenone (Aldrich) were used as received. Octanophenone, decanophenone, and tetradecanophenone, all known compounds, were prepared by the Friedel–Crafts acylation on benzene[12] with the corresponding acid chloride. These were purified by repeated column and preparative thin-layer chromatography (silica gel, hexane/benzene), and the purity was checked by GLC. As per GLC, these compounds were ~99% pure. These compounds showed intense carbonyl stretching at 1670 cm^{-1} and had melting and boiling points identical with the literature values[12] [**3**, bp 110 °C (10 mm); **4**, mp 35–36 °C; **5**, mp 52 °C]. α-Methoxy-, α-ethoxy-, and α-isopropoxyacetophenones were prepared by following the reported procedures of Newman and Beal[13] from α-diazoacetophenone[14] and the corresponding alcohol. These compounds were purified by column and thin-layer chromatography (silica gel, hexane/chloroform) and were >98% pure according to analytical GLC and had boiling points close to the reported values [**6**, 125–128 °C (20 mm); **7**, 130–132 °C (15 mm); **8**, 90 °C (5 mm)]. The spectral data (IR and NMR) of **6** are consistent with the reported values.[15] The compounds **7** and **8** were further confirmed by their IR and ^1H NMR spectra. *p*-Methyloctanophenone and *p*-methyldecanophenone were prepared by the Friedel–Crafts acylation on toluene with the corresponding acid chloride. *o*- and *m*-methyl-substituted aryl alkyl ketones **11–14** were prepared by the Grignard reaction of the respective alkylmagnesium iodides with the corresponding tolunitriles (Aldrich). All the above ketones (**9–14**) were purified by column and preparative thin-layer chromatography (silica gel, hexane/chloroform). Analytical GLC showed all to be >98% pure. The spectral and elemental analysis data for ketones **9–14** are provided below.

***p*-Methyloctanophenone (9)**: IR (Nujol) 2930, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t), 1.36 (8 H, br s), 1.70 (2 H, m), 2.38 (3 H, s), 2.80 (2 H, t), 7.40 (4 H, AB q). Anal. Found: C, 83.05; H, 10.42. Calcd: C, 82.51; H, 10.16.

***p*-Methyldecanophenone (10)**: IR (Nujol) 2935, 1760, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t), 1.35 (12 H, br s), 1.75 (2 H, m), 2.38 (3 H, s), 2.80 (2 H, t), 7.40 (4 H, AB q). Anal. Found: C, 82.12; H, 10.75. Calcd: C, 82.87; H, 10.64.

***m*-Methyloctanophenone (11)**: IR (neat) 2940, 2800, 1680, 1600 (d) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t), 1.25 (8 H, br s), 1.60 (2 H, m), 2.30 (3 H, s), 2.78 (2 H, t), 7.10–7.60 (4 H, m). Anal. Found: C, 83.10; H, 10.42. Calcd: C, 82.51; H, 10.16.

***m*-Methyltridecanophenone (12)**: IR (neat) 2940, 2800, 1680, 1600 (d) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.90 (3 H, t), 1.25 (2 OH, br s), 1.60 (2 H, m), 2.30 (3 H, s), 2.80 (2 H, t), 7.10–7.60 (4 H, m). Anal. Found: C, 82.62; H, 10.32. Calcd: C, 82.51; H, 10.16.

***o*-Methyloctanophenone (13)**: IR (neat) 2920, 2840, 1660, 1600 (d) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, t), 1.55 (8 H, br s), 1.62 (2 H, m), 2.46 (3 H, s), 2.80 (2 H, t), 6.90–7.65 (4 H, m). Anal. Found: C, 82.62; H, 10.32. Calcd: C, 82.51; H, 10.16

***o*-Methyltridecanophenone (14)**: IR (neat) 2920, 2840, 1660, 1600 (d) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.85 (3 H, t), 1.55 (2 OH, br s), 1.60 (2 H, m), 2.46 (3 H, s), 2.80 (2 H, t), 6.90–7.60 (4 H, m). Anal. Found: C, 82.93; H, 11.31. Calcd: C, 83.27; H, 11.18.

Preparation of Cyclodextrin Complexes. To a saturated solution of β-cyclodextrin in distilled water, equimolar amounts of ketones were added and stirred for 24 h. The white microcrystalline solid that precipitated was collected by filtration, washed repeatedly with diethyl ether to remove the uncomplexed ketone, and dried at 50 °C for 10 h. The aqueous solutions of the complexes were prepared by dissolving the microcrystalline complex (100 mg) in 100 mL of distilled water for solution irradiations, and the microcrystalline material was used as such for solid irradiations.

Determination of Dissociation Constants (K_d). A stock solution (1.0×10^{-2} M) of β-cyclodextrin was prepared by dissolving 1 g in 100 mL of distilled water. Solutions (10 mL) containing differing amounts of β-cyclodextrin stock solution and a constant amount of ketone (the concentration of the ketone is $\simeq 1.5 \times 10^{-5}$ M) were prepared in 10-mL flasks and stirred well. The concentration of β-cyclodextrin was maintained far higher (range 10^{-4}–10^{-2} M) than that of the ketone. UV absorption spectra of these solutions were recorded with a Shimadzu UV-180 spectrophotometer, and optical densities were monitored at various wavelengths ranging between 250 and 300 nm. A plot of $a_o b_o/\Delta OD$ vs. $a_o + b_o$ was linear with the slope and intercept being equal to $1/\Delta\epsilon$ and $K_d/\Delta\epsilon$, respectively (a_o and b_o being the concentrations of β-cyclodextrin and the ketone, respectively). The values of K_d were obtained from these linear plots according to the Benesi–Hilderbrand method.[5] The dissociation constants thus calculated for various ketones are listed in Tables I–III.

Identification of Cyclodextrin Complexes. (a) Solid Complexes. The X-ray powder patterns of β-cyclodextrin and β-cyclodextrin complexes with various ketones were recorded with a Phillips powder diffractometer employing monochromated Cu Kα radiation. Since the ketones were generally liquid at room temperature no spectra were recorded for pure guests. Powder patterns of the complexes were compared with the β-cyclodextrin in the absence of ketone. The substantial difference between them is attributed to the formation of complex of β-cyclodextrin with the ketones.

(b) Aqueous Complexes. To confirm the formation of β-cyclodextrin complexes in aqueous solution, the ^1H NMR spectra of β-cyclodextrin complexes in D_2O were recorded with a Bruker WH 270-MHz NMR spectrometer. The upfield chemical shifts of β-cyclodextrin protons (H-3, H-5, and H-6) in the presence of guest ketone suggest the inclusion of the aromatic guest in the cyclodextrin cavity. The UV spectra of the ketone(s) in the presence of β-cyclodextrin shows slight hypsochromic shift, providing an additional evidence for the complex formation.

Host–Guest Ratio. A known amount of the solid complex was dissolved in a minimum amount of distilled water, and the guest ketone was reextracted with warm chloroform. The amount of the recovered ketone was estimated by GLC using an internal standard (either biphenyl or acenaphthylene) as well as by gravimetry. On the basis of the knowledge of the weight of the complex and the recovered ketone, the host–guest ratios were calculated.

Photolysis and Identification of Photoproducts. The aqueous solutions of the complexes prepared by dissolving the microcrystalline complex (100 mg) in 100 mL of distilled water (the concentration of the complex ~10^{-3} M) were irradiated with a Rayonet reactor fitted with RPR-3000 lamps in Pyrex vessels after purging with nitgrogen gas for about 45 min. After the irradiation (60–90 min), the products were extracted from aqueous solution with warm chloroform. Microcrystalline cyclodextrin

(12) Gilman, H.; Meals, R. N. *J. Org. Chem.* **1943**, *8*, 126.
(13) Newman, M. S.; Beal, P. F. *J. Am. Chem. Soc.* **1950**, *72*, 4339.
(14) Newman, M. S.; Beal, P. F. *J. Am. Chem. Soc.* **1949**, *71*, 1506.
(15) *The Aldrich Library of NMR Spectra*, 2nd ed.; Pouchert, C. J., Ed.; Aldrich: Milwaukee, 1983; Vol. 2, p 234. *The Aldrich Library of IR Spectra*, 3rd ed.; Pouchert, C. J., Ed.; Aldrich: Milwaukee, 1981, Vol. 3, p 866F.

complexes in Pyrex tubes were degassed, sealed, and irradiated (48 h) with a Hanovia 450-W medium-pressure mercury arc lamp. To obtain an uniform exposure of light the sample tubes were rotated periodically.

The photoproducts were extracted with a chloroform–water mixture. The products were analyzed with a Chemito gas chromatograph fitted with either 5% or 10% SE-30 columns (adsorbed on chromosorb P 5 ft × $^1/_8$ in.) and characterized by their spectral properties. Among the photoproducts from **1–8**, acetophenone was a commonly available one, and the other product, the cyclobutanol, from **1**, **2**, and **6–8** has already been reported and has been characterized.[15] The IR and ^{1}H NMR spectra of the cyclobutanols derived from **1**, **2**, and **6–8** in this study match well with the reported values.[16] The photoproducts derived from **9–14** are substituted acetophenones and aryl-substituted cyclobutanols. The substituted acetophenones were identified by comparison with authentic samples obtained from Aldrich. The cyclobutanols derived from **9–14** were spectrally characterised after obtaining pure samples (as per GLC) via preparative photolysis followed by preparative TLC. The IR and ^{1}H NMR spectra of cyclobutanols derived from **5** and **9–14** are provided below.

1-Phenyl-2-decylcyclobutan-1-ol: IR (neat) (a) 3600–3250, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) [cis] δ 0.86 (3 H, t), 1.00–1.40 (18 H, m), 1.62 (2 H, m), 2.00–2.28 (2 H, m), 2.65 (1 H, m), 7.20–7.50 (5 H, m), [trans] 0.87 (3 H, t), 1.20–1.25 (18 H, m), 1.85 (1 H, m), 1.97 (1 H, m), 2.17 (1 H, m), 2.40 (1 H, m), 2.63 (1 H, m), 7.15–7.50 (5 H, m).

1-(4-Methylphenyl)-2-butylcyclobutan-1-ol: IR (neat) 3620–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (3 H, t), 1.09–1.32 (6 H, m), 2.01–2.23 (3 H, m), 2.35 (3 H, s), 2.60–2.69 (2 H, m), 7.26 (4 H, AB q).

1-(4-Methylphenyl)-2-hexylcyclobutan-1-ol: IR (neat) 3625–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.76 (3 H, t), 1.09–1.40 (10 H, m), 2.01–2.23 (3 H, m), 2.35 (3 H, s), 2.60–2.70 (2 H, m), 7.26 (4 H, AB q).

1-(3-Methylphenyl)-2-butylcyclobutan-1-ol: IR (neat) 3640–3250, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, t), 1.35 (6 H, m), 1.60 (1 H, m), 2.20 (1 H, m), 2.40 (3 H, s), 2.53 (1 H, t), 2.85 (1 H, m), 3.27 (1 H, t), 7.20–7.91 (4 H, m).

1-(3-Methylphenyl)-2-nonylcyclobutan-1-ol: IR (neat) 3640–3250, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.93 (3 H, t), 1.35 (16 H, m), 1.60 (1 H, m), 2.20 (1 H, m), 2.40 (3 H, s), 2.52 (1 H, t), 2.85 (1 H, m), 3.25 (1 H, t), 7.20–7.90 (4 H, m).

1-(2-Methylphenyl)-2-butylcyclobutan-1-ol: IR (neat) 3630–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t), 1.05–1.60 (6 H, m), 2.0–2.25 (3 H, m), 2.45 (3 H, s), 2.60–2.70 (2 H, m), 6.9–7.5 (4 H, m).

1-(2-Methylphenyl)-2-nonylcyclobutan-1-ol: IR (neat) 3630–3300, 1600 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.85 (3 H, t), 1.05–1.60 (16 H, m), 2.0–2.28 (3 H, m), 2.45 (3 H, s), 2.60–2.75 (2 H, m), 6.9–7.50 (4 H, m).

Analytically pure samples (>98%) of cyclobutanols could not be obtained for elemental analysis.

(16) Lewis, F. D.; Turro, N. J. *J. Am. Chem. Soc.* **1970**, *92*, 311.

Effects of Cyclonucleoside Formation on the Rates of Glycosidic Hydrolyses in Purine Ribonucleosides

Lee-Gin Lin, V. Bakthavachalam, X. M. Cherian, and Anthony W. Czarnik*

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

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Syntheses of several carbon-bridged purine cyclonucleosides are reported, along with kinetic data on their rates of glycosidic hydrolysis. We find that 5′,8-bridged nucleosides hydrolyze less than 10 times more slowly than analogous nucleoside models, but that the 3,5′-bridged adenosine hydrolyzes 29 000 times more slowly than does 3-methyladenosine at 25 °C in 0.1 N HCl. This surprising stability can be rationalized on the basis of (1) an electrostatic effect resulting from the presence of an ammonium group at the 5′-carbon and (2) the existence of a nonideal geometry for lone-pair stabilization of the transition structure. On the basis of these results, the previously reported slow rates of hydrolysis in 3,5′-cycloguanosine and 3,5′-cyclowyosine can be rationalized.

Glycosidic hydrolysis (glycolysis, depurination) of purine deoxyribonucleosides is a fundamental process in the chemistry of DNA both in vivo[1] and in vitro.[2-10] In vivo depurination of methylated nucleotides is accomplished with the DNA glycosylases, which are important in a major pathway by which damaged or misreplicated DNA is repaired.[11] We have recently proposed a mechanism for glycosylase enzymes that involves the repulsion of lone-pair electrons on the substrate and the enzyme.[12a] In order to test our hypothesis under conditions that model the enzymatic reaction as we suggest, we have looked first to glycolysis in cycloribonucleosides. The use of *ribo*nucleosides allows us to take advantage of the vicinal diol group for the positioning of catalytic groups;[12b] mechanistically, acid-catalyzed ribonucleoside hydrolysis (Scheme I)[13] is identical with that of deoxyribonucleoside hydrolysis, albeit slower. The rationale for the use of *cyclo*ribonucleosides is shown in Scheme II. While adenosine (or guanosine) can relieve a potential electrostatic repulsion via a ribose "envelope inversion" (**1a** → **1b**), the corresponding cyclonucleoside (**2**) cannot. This, coupled with the fact that forming a ring between C-8 and C-5′ does not introduce a large electronic perturbation of the sugar or base rings, makes cyclonucleosides appropriate models for

(1) Lindahl, T.; Nyberg, B. *Biochemistry* **1972**, *11*, 3610.
(2) Brown, D. M. In *Basic Principles in Nucleic Acid Chemistry*; Ts'o, P. O. P., Ed.; Academic Press: New York, 1974; Vol. II, Chapter 1.
(3) Walker, R. T. *Annu. Rep. Chem. Soc.* **1972**, *69B*, 531.
(4) Romero, R.; Stein, R.; Bull, H. G.; Cordes, E. H. *J. Am. Chem. Soc.* **1978**, *100*, 7620.
(5) Garrett, E. R.; Mehta, P. J. *J. Am. Chem. Soc.* **1972**, *94*, 8532.
(6) Parkin, D. W.; Leung, H. B.; Schramm, V. L. *J. Biol. Chem.* **1984**, *259*, 9411.
(7) Cordes, E. H.; Bull, H. G. In *Transition States of Biochemical Processes*; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978; pp 429–465 (especially pp 456–458).
(8) Zoltewicz, J. A.; Clark, D. F. *J. Org. Chem.* **1972**, *37*, 1193.
(9) Zoltewicz, J. A.; Clark, D. F.; Sharpless, T. W.; Grahe, G. *J. Am. Chem. Soc.* **1970**, *92*, 1741.
(10) Panzica, R. P.; Rousseau, R. J.; Robins, R. K.; Townsend, L. B. *J. Am. Chem. Soc.* **1972**, *94*, 4708.
(11) For a recent review, see: Pegg, A. E.; Bennett, R. A. In *Enzymes of Nucleic Acid Synthesis and Modification*; Jacob, S. T., Ed.; CRC Press: Boca Raton, FL, 1983; Vol. I, Chapter 6.

(12) (a) 191st Meeting of the American Chemical Society, New York, April 13–18, 1986, abstract 200 (organic division); *Tetrahedron Lett.*, in press. (b) Bakthavachalam, V.; Lin, L.-G.; Cherian, X. M.; Czarnik, A. W. *Carbohydr. Res.*, in press.
(13) Although the first site of protonation in adenosine is N^1, N^1-methyladenosine does not hydrolyze much faster than does adenosine itself (cf. ref 44). The site of protonation that leads to productive glycosidic cleavage is not known; we have arbitrarity depicted hydrolysis via N7 protonation in Scheme I.

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