

Reaction of Arylmethanes and Heteroarylmethanes with the *tert*-Butoxy Radical¹

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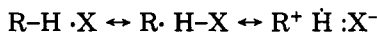
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The relative rates of hydrogen atom abstraction from a series of 13 homoaryl- and heteroarylmethanes by the *tert*-butoxy radical were determined at 70 °C. The attacking radical was photochemically generated from di-*tert*-butyl peroxide. A relatively small range of relative rates (factor of 7) has been found among the compounds studied; however, significant position variation among isomers is noted. The relative reactivities of the homoaryl- and heteroarylmethanes can be correlated with various calculated energy differences obtained from both HMO and standard semiempirical SCF-MO methods. Fairly good correlations were obtained by use of a carbocation model for the transition state (correlation coefficient 0.92). Much poorer correlations were obtained when a radical model was used for the transition state with either the HMO or SCF-MO approach (maximum correlation coefficient 0.49). This suggests that considerable charge development must be associated with the transition state of this reaction.

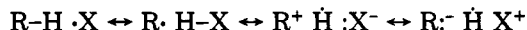
The *tert*-butoxy radical is a fairly reactive species that has been shown to be capable of abstracting hydrogen atoms from a wide range of organic substrates.² This species can be generated via the thermal decomposition of a variety of precursors. These include *tert*-butyl hypochlorites,³ di-*tert*-butyl peroxalate,⁴ di-*tert*-butyl hypodinitrite,⁵ and di-*tert*-butyl peroxide.⁶

On the basis of Hammett-type studies involving the relative ease of hydrogen atom abstraction from substituted toluenes, the *tert*-butoxy radical is recognized as an electrophilic species.^{3,7-11} Originally, a disparity in ρ values for hydrogen atom abstraction from substituted toluenes was observed between those studies that utilized *tert*-butyl hypochlorite as the source of *tert*-butoxy radical^{3,10,11} and investigations in which the same radical was generated from other precursors.⁷⁻⁹ Walling and McGuinness demonstrated that this was due to the presence of a competing hydrogen atom abstraction pathway involving chlorine when *tert*-butyl hypochlorite is the radical source.⁸ This competing mechanism can be suppressed if alkenes, which act as chlorine atom traps, are present in the reacting system.

Other, related, systems such as substituted benzaldehydes also undergo hydrogen atom abstraction with the *tert*-butoxy radical.¹² As expected, electron-donating substituents enhance reactivity toward the electrophilic abstracting agent. The majority of these negative ρ values showed optimum correlation with σ^+ parameters. This has traditionally been regarded as indicative of charge development in the transition state for the hydrogen atom abstraction.¹³ This is shown below:



The substituted toluene-*tert*-butoxy radical system was also investigated by Zavitsas and Pinto.¹⁴ These workers argued that their data did not require the contribution of charge-separated canonical forms to the hybrid description of the transition state. Subsequent studies have not supported this view. In the absence of charge development in the transition state, Zavitsas and Pinto's approach would lead to negative ρ values for all hydrogen atom abstractions from substituted toluenes. Positive ρ values have been observed, however, if nucleophilic alkyl radicals are the abstracting agents.¹⁵⁻¹⁸ As a result of these findings, the resonance description of the transition state for hydrogen atom abstraction is given as the hybrid of the four canonical structures shown below:



As a complement to typical Hammett studies, it has been noted that studies that utilize polycyclic aromatic substrates rather than substituted phenyl groups can allow for separation of inductive and conjugative effects in free-radical reactions.¹⁹ Literature examples include hydrogen atom abstraction from methylarenes using radicals generated from bromotrichloromethane²⁰ and molecular bromine,²¹ the addition of phenylthiyl radical to the exocyclic double bond of vinylarenes,²² vinylarenes, and chlorine atom abstraction from (chloromethyl)arenes using triphenyltin radicals.²³ Until recently, the results of similar hydrogen atom abstraction by the *tert*-butoxy radical from a series of methylarenes of widely differing reactivities were not available for discussion. A few systems, however, had been investigated. The reactivity of 1-methylnaphthalene was shown to be approximately 70% greater than 2-methylnaphthalene toward the *tert*-butoxy radical generated from the hypochlorite.²⁴ Unruh and Gleicher

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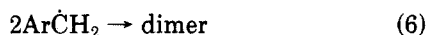
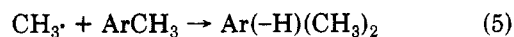
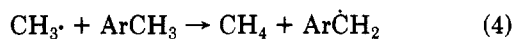
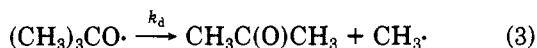
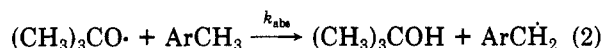
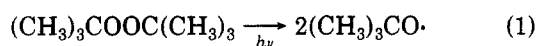
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studied nine methylarenes under similar conditions.^{20b} A reactivity range of 5 was found between the most and least reactive systems. Unfortunately, isomers of methylpyrenes and methylanthracenes could not be included among the compounds investigated. These systems, which should have greatly expanded the total reactivity range, apparently effectively compete with added alkene as chlorine atom traps. Recently, Lissi, Collados, and Olea studied the reactivities of methylanthracenes and less reactive systems toward the *tert*-butoxy radical generated from di-*tert*-butyl peroxide.²⁵ Unlike the results of previous studies, these workers reported that only the identity of the arene and not the point of attachment of the methyl group affects the relative ease of hydrogen atom abstraction.

It should also be pointed out that while polycyclic substrates of the type mentioned above are amenable to simple molecular orbital correlations,¹⁹ they provide no particular insight into the points raised by Zavitsas and Pinto. This is a result of the alternant nature of the benzenoid species usually employed and the parallelism of calculated energies for the carbocations, radicals, and carbanions derived from such systems.²⁶

The present work concerns the reaction of the *tert*-butoxy radical with some methylarenes and methylheteroarenes. The inclusion of heteroaromatic systems within these studies can provide information on the question of possible charge development in the transition state for hydrogen atom abstraction. The parallelism of energies for the reactive intermediates of benzenoid systems is *not* found for the pyridylmethyl and quinolylmethyl intermediates formed in the present case. The *tert*-butoxy radical is formed by the photolysis of di-*tert*-butyl peroxide at 70 °C. Scheme I illustrates the possible reactions encountered.

Scheme I



All studies were carried out at 70 °C to allow for comparison with prior results obtained in these laboratories. At this temperature, direct thermolysis of di-*tert*-butyl peroxide to generate the *tert*-butoxy radical is unsuitable. The radical precursor has a half-life of over 1 year at 70 °C.²⁷ Fortunately, it is possible to expeditiously generate the *tert*-butoxy radical photolytically. At 70 °C, di-*tert*-butyl peroxide has a half-life of approximately 6 h.²⁸ It has also been shown that the products obtained from the *tert*-butoxy radical so generated with various substrates are equivalent to those obtained from thermally generated *tert*-butoxy radical.²⁸

The relative reactivities of the arylmethanes and heteroarylmethanes were evaluated by the traditional ap-

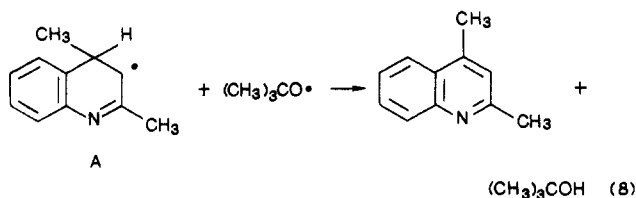
proach of determining the ratio of *tert*-butyl alcohol to acetone. This ratio must be corrected for the molarity of the substrate since eq 2 is a second-order process, while eq 3 is first-order. The standard form of the expression is shown in eq 7. As the rate constant of the β -scission reaction that produces acetone is known,²⁹ it is possible to convert these relative reactivities to absolute rates of hydrogen atom abstraction.

$$k_{\text{abs}}/k_d = [\textit{tert}\text{-butyl alcohol}]/[\text{acetone}][\text{substrate}] \quad (7)$$

Because the *tert*-butoxy radical may react with a variety of substrates, it was decided to run all reactions in the absence of solvent. Solutions of di-*tert*-butyl peroxide in substrate were prepared in an approximate ratio of 1:500. This would ensure that other potential sources of abstractable hydrogen atoms such as dimethylated substrates (eq 5) or dimers (eq 6) would be present in no greater abundance than 0.4% and 0.2% of starting substrate, respectively. As the hydrogen atom lability of these possible products is comparable to that of substrate, the presence of so small a concentration should not affect the *tert*-butyl alcohol to acetone ratio within experimental uncertainties. Standard reaction times correspond to 9–12 half-lives of di-*tert*-butyl peroxide. Such relatively long reaction times ensured against appreciable radical precursor being present that might decompose during the gas chromatographic determination of *tert*-butyl alcohol and acetone.

As no common solvent was employed in these studies, variance in solvent properties among the substrates themselves might be considered. Early studies suggested that reactions of the *tert*-butoxy radicals at 70 °C showed very small solvent dependence.³ Later investigations indicated somewhat larger differentiation between solvents that could or could not exhibit hydrogen bonding.³⁰ In these investigations, however, *tert*-butyl hypochlorite was the radical precursor. In the absence of a chlorine atom trap, it is difficult to assess the roles played by complexation of chlorine atoms with π systems or hydrogen bonding with the hydrogen chloride formed by hydrogen atom abstraction by this species.³¹ Overall, the possible solvent effects are still rather small. Differences among isomeric systems should be negligible in view of the minor positional effect a methyl group has on partial electron transfer, which is necessary for π complex formation.³² The corresponding effect on base strength, which affects the ability to hydrogen bond, is also small. The seven isomers of methylquinoline used in this study, for example, show a variation of only 0.4 pK unit at 25 °C.³³

It was mentioned above that potential hydrogen atom abstraction from systems other than substrate can lead to a high value for *tert*-butyl alcohol concentration. While secondary products should be present in too low a concentration to appreciably contribute to the total *tert*-butyl alcohol formed, hydrogen abstraction from the intermediate σ complexes leading to dimethylated aromatics (such as A, for example) may compete (eq 8). While the con-



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Table I. Ratios of *tert*-Butyl Alcohol to Acetone Formed in the Photolytic Reaction of Di-*tert*-butyl Peroxide with Arylmethanes and Heteroarylmethanes at 70 °C^a

system	<i>tert</i> -butyl alcohol ^b / acetone	rel react.
1-methylnaphthalene	0.702 ± 0.026 ^c	1.654 ± 0.053 ^c
2-methylnaphthalene	0.516 ± 0.003	1.210 ± 0.008
5-methylquinoline	0.504 ± 0.020	1.182 ± 0.042
toluene	0.427 ± 0.012	1.00
8-methylquinoline	0.395 ± 0.001	0.927 ± 0.003
7-methylquinoline	0.356 ± 0.003	0.835 ± 0.007
3-methylquinoline	0.353 ± 0.005	0.828 ± 0.012
3-methylpyridine	0.271 ± 0.005	0.635 ± 0.011
6-methylquinoline	0.234 ± 0.020	0.548 ± 0.042
2-methylpyridine	0.137 ± 0.001	0.321 ± 0.003
2-methylquinoline	0.124 ± 0.001	0.290 ± 0.003
4-methylquinoline	0.100 ± 0.002	0.234 ± 0.005
4-methylpyridine	0.097 ± 0.001	0.228 ± 0.003

^a Number of runs = 5. ^b Corrected for concentration of substrate. ^c Standard deviations.

centration of A is no greater than that of dimethylated product, the lability of the hydrogen atom shown may be orders of magnitude greater than those found in substrate. This is due to the driving force of completely rearomatizing the system. In order to determine how serious a problem this might be, unsubstituted quinoline was allowed to react with the *tert*-butoxy radical, and the *tert*-butyl alcohol to acetone ratio was monitored as a function of time. Quinoline, rather than pyridine, benzene, or naphthalene, was chosen for study since it exhibits the greatest affinity for the methyl radical.³⁴ Since a mixture of methylquinolines is being generated, the *tert*-butyl alcohol to acetone ratio must be extrapolated to zero time to obtain an estimate of the inherent ability of this system to function as a source of alcohol. It was found that this potential side reaction could account for less than 2% of the *tert*-butyl alcohol found in the least reactive of the systems studied. As this is within the experimental uncertainty of most of the data obtained, no corrections were made.

Both the values of *tert*-butyl alcohol to acetone and the relative reactivity for the substrates utilized are presented in Table I. All systems were run in replicate. A reasonably high precision (average standard deviation of under 2%) was found for all systems. Although the total reactivity range comprised only a factor of 7, substantial differences among positional isomers are apparent. A very striking example of this is the fivefold difference between 5-methylquinoline and 4-methylquinoline. In this respect, our findings significantly differ from those reported by Lissi et al.²⁵ This difference may be experimental in nature, as these workers refer to an "estimated error of ±15%" in their data. They also carried out their measurements at a temperature 50 °C higher than that employed in the present study. The relative reactivity ratio of 1-methylnaphthalene to 2-methylnaphthalene (1.37) agrees reasonably well with the values previously obtained with *tert*-butyl hypochlorite.^{20b,24} A relative reactivity ratio of 1.33 (110 °C) has been reported for 3-methylpyridine to 2-methylpyridine.³⁵ This compares favorably with the present value of 1.98 (70 °C).

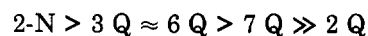
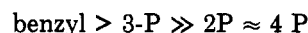
Relatively simple π electron molecular orbital techniques have proven to be successful not only in correlating rates of benzylic radical formation^{19,23} but also in treating the

Table II. Correlation Coefficients of Linear Regression Analyses of Logarithms of Relative Rate Data vs. Various Molecular Orbital Treatments

approach		correl coeff
PMO		0.83
HMO ΔE_r	carbocation intermediate	0.91
	radical intermediate	0.14
	carbanion intermediate	0.69
SCF-PPP ΔE_T	carbocation intermediate	0.92
	radical intermediate	0.49
	carbanion intermediate	0.39
four	$\Delta E_T(\text{radical})$ plus charge density	0.08
parameters	$\Delta E_T(\text{carbocation})$ plus charge density	0.92
	$\Delta E_T(\text{carbocation})$ plus $\Delta E_T(\text{radical})$	0.92

corresponding benzylic carbocations and carbanions as well.^{26,36-38} Correlations of the logarithms of relative reactivities with the results of PMO,³⁶ HMO,³⁷ and SCF-PPP³⁸ calculations are discussed below. The coefficients for all correlations are summarized in Table II.

PMO theory may be used to evaluate the effect of replacing a carbon-hydrogen unit in an odd alternant system with an isoelectronic nitrogen atom. The nitrogen may affect the energy of the system by either a direct conjugative effect or an, presumably less important, inductive effect.³⁹ By standard parameterization, the following ordering of the systems' stability was found:



Only as regards the relative positions of 6- and 7-quinolylmethyl is a serious discrepancy found with the experiment. While a single linear regression analysis of all data points yields a poor correlation (0.83), the results are qualitatively encouraging. The calculated trends clearly show that conjugation destabilization of the system by nitrogen is far more important than any adverse inductive effects. It should be pointed out that the inductive differences among the isomeric heteroaryl groups are small. Elderfield and Siegel, for example, have shown that of the seven possible quinoline carboxylic acids six have nearly equivalent $\text{p}K_a$ values (4.53–4.98 at 25 °C in methanol).⁴⁰ The exceptional compound is 8-quinolinecarboxylic acid with a $\text{p}K_a$ value of 7.20. This must be due to intramolecular hydrogen bonding. The relative reactivities presented herein do not correlate (0.21) with these small inductive differences.

HMO calculations were based on π energy differences between the appropriate arylmethyl intermediate and starting materials, which were taken as being equivalent to that of the parent, unmethylated system. Correlations based on arylmethyl carbanion or radical intermediates are virtually nonexistent. The correlation coefficients are, respectively, 0.69 and 0.14. The use of the corresponding arylmethyl carbocation intermediates led to a reasonable correlation (0.91).

A similar approach was adopted for the SCF-PPP calculations. However, as the iterative approach employed allows for reevaluation of bond length, a difference in "total

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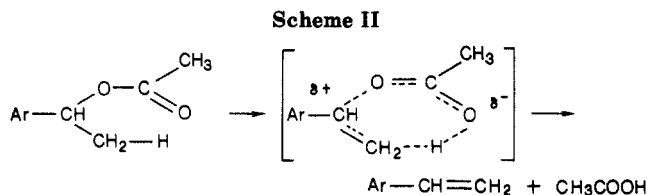
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energy" (π energy plus σ energy of bonds comprising the conjugated portion of the molecule) was employed. The overall method has been described.^{38,41} Improved parameters for the nitrogen atom have subsequently been developed and were used in the present calculations.⁴² As in the case of the HMO correlations, the only reasonable correlation obtained was that based on a carbocation intermediate (0.92). Tables of computed values for both HMO and SCF-PPP calculations may be obtained as supplementary material.

The fact that both HMO and SCF-PPP correlations yield optimum results with a carbocation intermediate illustrates the importance of charge development in the transition state for hydrogen atom abstraction by the *tert*-butoxy radical. The Zavitsas-Pinto observation that in certain systems equally good correlations of rate data for hydrogen atom abstraction from substituted toluenes are obtained with σ , σ^+ , or σ^- parameters¹⁴ is not valid for the present case.

In view of the modest nature of the best correlations obtained to this point, various four-parameter approaches were attempted to improve this situation. These were based on suggestions in the literature.^{23b,43} The results are also presented in Table II. In no case did the inclusion of a second parameter statistically increase the precision of the correlation. One such approach was a modified Yukawa-Tsuno equation⁴⁴ that included both SCF-PPP carbocation and radical intermediate parameterization. The carbocation contribution was appreciably greater than that of the radical structure.

The moderate nature of the correlations need not be attributable solely to experimental error. It is also possible that the calculations employed do not take certain factors such as peri or through-space interactions into account. Correlations of the present relative reactivities with extant data in the literature might prove valuable. Unfortunately, the amount of such pertinent data dealing with the formation of heteroarylmethyl intermediates is rather limited. One very good example, however, does exist. Taylor, Smith, and co-workers have published a series of papers on the pyrolysis of 1-homoaryl and 1-heteroarylethyl acetates.⁴⁵⁻⁴⁷ The transition state for this reaction also involves generation of appreciable carbocation character at the benzylic position. This is shown in Scheme II.

When the logarithms of the relative reactivities for this reaction are plotted against those obtained in the present study, a good correlation is obtained. The value of the correlation coefficient is 0.97. This is the best correlation we have obtained and is graphically shown in Figure 1. The fact that optimum agreement is obtained when the data for hydrogen atom abstraction are correlated with that for another reaction, rather than some theoretical model, underscores the suggestion that factors not taken

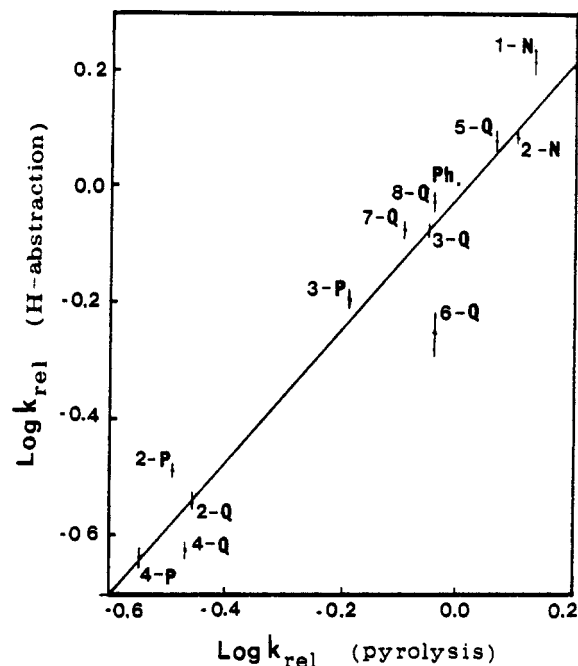


Figure 1. Logarithms of the relative rates of formation of homo- and heteroarylmethyl radicals vs. logarithms of the relative rates of pyrolysis of the corresponding 1-arylethyl acetates.

into account by the calculations may play some small role in determining hydrogen atom labilities.

Experimental Section

Reagents. All compounds used in this study were commercially available except for 5-methylquinoline. This compound was prepared from 8-chloro-5-methylquinoline (using the procedure of Yoshikawa)⁴⁸ which, in turn, was synthesized by the Skraup reaction described by Gatterman and Kaiser.⁴⁹ The purity of all compounds was determined by gas chromatography and in all cases was greater than 99%.

Procedure for the Determination of Relative Rates of Hydrogen Atom Abstraction from Substrates by the *tert*-Butoxy Radical. Solutions of the arylmethanes and di-*tert*-butyl peroxide were prepared in the approximate molar ratio of 500:1. These solutions were equally divided into ampoules. After a series of freeze-thaw cycles, the ampoules were sealed under a reduced pressure of nitrogen. They were then placed horizontally just below the surface of a constant-temperature oil bath maintained at $70 \pm 1^\circ\text{C}$. Kinetic runs were initiated photochemically with a Ken-Rap 275-W sun lamp placed 22.5 cm from the surface of the oil. Reaction times were as great as 72 h and corresponded to between 9 and 12 half-lives of the di-*tert*-butyl peroxide. After completion of the reaction, the ampoules were cooled and opened. The material was then transferred rapidly to a vial equipped with a serum septum. The reaction mixture was analyzed for the formation of acetone and *tert*-butyl alcohol. All determinations were run in replicate.

Gas-liquid chromatographic analyses were carried out with a Hewlett-Packard 5880A gas chromatograph equipped with a flame-ionization detector. The capillary column used in this investigation was a 12 m \times 0.2 mm column of dimethyl cross-linked silicone. The carrier gas was hydrogen.

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public of Algeria, which has provided support for B.M. at Oregon State University.

Registry No. 1-Methylnaphthalene, 90-12-0; 2-methylnaphthalene, 91-57-6; 5-methylquinoline, 7661-55-4; 8-methylquinoline, 611-32-5; 7-methylquinoline, 612-60-2; 3-methylquinoline, 612-58-8; 3-methylpyridine, 108-99-6; 6-methylquinoline,

91-62-3; 2-methylpyridine, 109-06-8; 2-methylquinoline, 91-63-4; 4-methylquinoline, 491-35-0; 4-methylpyridine, 108-89-4; *tert*-butoxy radical, 3141-58-0; toluene, 108-88-3; H₂, 1333-74-0.

Supplementary Material Available: Tables of computed energy terms from HMO and SCF-PPP calculations (4 pages). Ordering information is given on any current masthead page.

Conformational Change Occasioned by Complexation: "Contra-Anomeric-Effect" Epimerization of 2-Methoxy-1,3-dioxanes in the Presence of Magnesium Bromide^{1†}

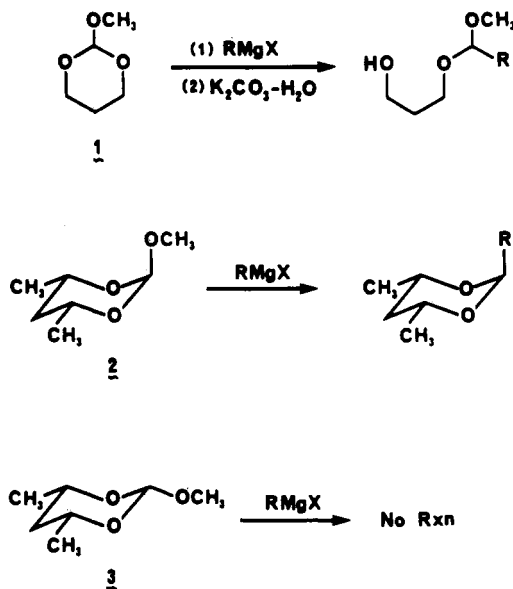
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The complexation of 2-methoxy-1,3-dioxanes with MgBr₂ has been investigated in an effort to assess the conformational consequences of binding acidic reagents to small, basic molecules with well-defined conformational minima. Anhydrous MgBr₂ has been found to catalyze the epimerization of anancomeric 2-methoxy-1,3-dioxanes and form a 1:1 complex with the ortho esters containing a preponderance (>91%) of the thermodynamically less stable, equatorially substituted 2-methoxy-1,3-dioxane. Preferential coordination of MgBr₂ with the "contra-anomeric-effect" epimer having an equatorial 2-OCH₃ provides at least 1.7 kcal/mol of driving force for conformational change. These observations suggest that reagent-substrate complexation can affect the outcome of reactions subject to stereoelectronic control.

Several years ago we reported² that the reaction of 2-methoxy-1,3-dioxane (1) with Grignard reagents does not follow the course suggested by the reactions of anancomeric models for the conformational isomers of 1.³ The failure



of the biased models 2 and 3 to reflect the behavior of the conformationally mobile substrate in this prototypical example of a stereoelectronically controlled reaction⁴ was attributed to complexation between 1 and the Grignard reagent to give a species having the 2-OCH₃ group effectively "locked" in an equatorial orientation.^{2,5}

The results of these studies suggested that dramatic conformational change occasioned by reagent-substrate complexation may have a profound effect on the outcome

of reactions subject to stereoelectronic control. In an effort to assess the conformational consequences of binding acidic reagents to small, basic substrates with well-defined conformations, we have explored the behavior of cyclic ortho esters in the presence of Mg²⁺ species.

The ability of ethers to solvate Mg²⁺ ions has been known for more than 80 years.⁶ Much of the pioneering work on complex formation between alkaline earth cations and Lewis-type bases was reported by Menschutkin in a remarkable series of papers published at the beginning of this century.⁷ Due to the reactivity of RMgX with ortho esters, we have employed MgBr₂ in our model studies and have, perforce, repeated much of this early work on "etherates" (a term coined by Menschutkin to describe solvates that involve ether-like oxygen atoms)⁷⁻¹⁰ of Mg²⁺

(1) Taken in part from: Rivera, A. D. Ph.D. Dissertation, University of Connecticut, Storrs, CT, 1983.

(2) Bailey, W. F.; Croteau, A. A. *Tetrahedron Lett.* 1981, 454.

(3) Eliel, E. L.; Nader, F. W. *J. Am. Chem. Soc.* 1970, 92, 584.

(4) Deslongchamps, P. *Stereoelectronic Effects in Organic Chemistry*; Pergamon: New York, 1983.

(5) The fact that model compound 3 is inert to RMgX under conditions leading to endocyclic cleavage of the C(2)-O bond in 1 led to the suggestion² that equatorial methyl substituents at C(4) and C(6) in 3 shield the ring oxygens from the approach of the Grignard reagent. This scenario finds support in the observation that *cis*-2-methoxy-4-methyl-1,3-dioxane undergoes cleavage of the endocyclic C(6)-O bond when treated with RMgX: Bailey, W. F.; Croteau, A. A., manuscript in preparation. For a related example, indicating the importance of steric interactions in determining the course of endocyclic C-O bond cleavage in similar systems, see: Bailey, W. F.; Rivera, A. D. *J. Org. Chem.* 1984, 49, 4958.

(6) (a) Grignard V. *Ann. Chim. Phys. (Paris)* 1901, 24, 433. (b) Zelinsky, N. D. *J. Russ. Phys.-Chem. Soc.* 1903, 35, 399; *J. Chem. Soc., Abstr.* 1903, 84i, 802.

(7) Menschutkin, B. N. *J. Russ. Phys.-Chem. Soc.* 1906, 38, 1317; *Chem. Abstr.* 1907, 1, 2090; *J. Russ. Phys.-Chem. Soc.* 1907, 39, 1548; *Chem. Abstr.* 1908, 2, 1265; *Z. Anorg. Chem.* 1909, 62, 45.

(8) (a) Post, H. W. *Chemistry of the Aliphatic Orthoesters*; ACS Monograph Series 92; Reinhold: New York, 1943; Chapter 3. (b) More recently, complexes of MgBr₂ with alkoxy-substituted carbonyl compounds have been investigated. See, for example: Keck, G. E.; Castellino, S. *J. Am. Chem. Soc.* 1986, 108, 3847 and references therein.

[†]Dedicated to Professor Ernest L. Eliel on the occasion of his 65th birthday.