Notes

Proton Inventories of the Basic Methanolysis of Phenyl Methyl Carbonate and Diphenyl Carbonate

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Introduction

The addition of nucleophiles to a carbonyl group is an important biochemical reaction. Hydroxide and methoxide ions are highly solvated in polar protic solvents, and the extent of desolvation of these ions as they attack the carbonyl group to form the transition state is an important question in organic reaction mechanisms. Also the desolvation of the serine alkoxide ion by some of the active site groups of the serine proteases may be partially responsible for the unusual reactivity of the serine hydroxyl group in these enzymes as suggested by Kollman and his co-workers.[1] The solvent reorganization that accompanies the desolvation of these anionic nucleophiles can be probed by the proton inventory technique, which involves measuring reaction rates in pure light and heavy isotopic solvents and in mixtures of the two. The utility of this technique in obtaining information of transition-state structures is well documented.[2]

In the basic methanolysis of phenyl acetate, the addition of heavily solvated methoxide ion to the ester carbonyl proceeds with a substantial solvent reorganization but with little bond formation between the methoxide ion and the carbonyl group.[3] Aryl carbonates have been shown to undergo basic methanolysis with rate-limiting addition of methoxide ion.[4] In these methoxide-catalyzed reactions, fractionation in the reactant state is confined to the three solvent sites around the nuclephilic oxygen. In the transition state, the solvation is likely to be confined to sites around the methoxide oxygen and possibly around the carbonyl oxygen. Here we report our results on the proton inventory of the basic methanolysis of phenyl methyl carbonate and diphenyl carbonate.

Results

The pseudo-first-order rate constants obtained for the methanolysis of phenyl methyl carbonate are plotted against methoxide concentrations in Figure 1. Four representative plots in solutions containing different atom fractions of deuterium are shown. The slopes provide the second-order rate constants for phenyl methyl carbonate. These data are collected in Table I. The second-order rate constant at 25.1 °C in pure nondeuterated methanol was determined to be 0.690 M^{-1} s^{-1}, and this compares favorably with the value 0.70 M^{-1} s^{-1} reported by Mitton and Schowen.[4] The second-order rate constant at 25.1 °C in pure methanol-*d* was found to be 1.26 M^{-1} s^{-1}, which also compares favorably with the literature value of 1.30 M^{-1} s^{-1}.[4] Table I lists these second-order rate constants at 25.1 °C for 10 different solutions containing varying atom fractions of deuterium.

The methanolysis of diphenyl carbonate proceeds with an initial rapid release of the first phenoxide followed by a slower release of the second phenoxide. A typical first-order plot for the methanolysis of diphenyl carbonate shows a break confirming the occurrence of two consecu-

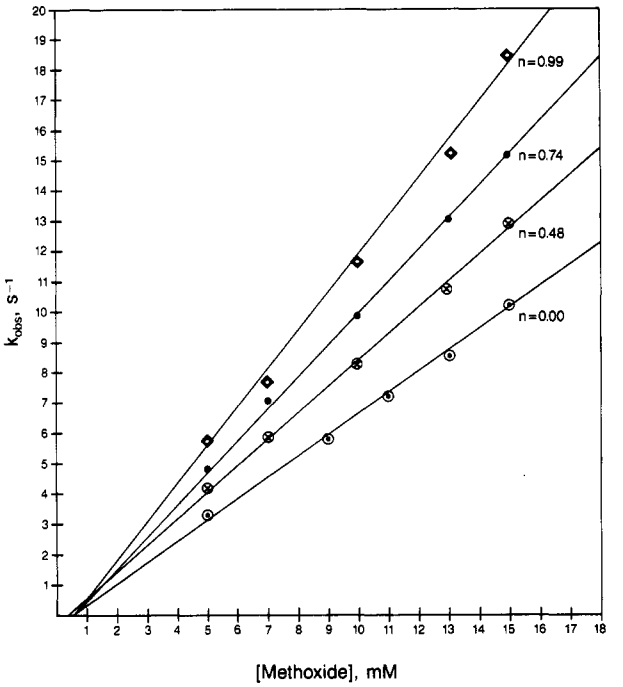

Figure 1. Representative plots used to determine the second-order rate constants for the basic methanolysis of phenyl methyl carbonate at 25.1 °C and 0.4 M ionic strength. The atom fraction of deuterium present in solution is *n*. Individual first-order rate constants are reproducible to within 2%.

Table I. Second-Order Rate Constants, k_n,[a,b] for Methoxide-Catalyzed Methanolysis of Phenyl Methyl Carbonate and Diphenyl Carbonate as a Function of *n*, the Atom Fraction of Deuterium at 25.1 °C

	k_n, M^{-1} s^{-1}	
n	phenyl methyl carbonate	diphenyl carbonate
0.99	1.26 (0.03)	1.24 (0.03)
0.80	1.10 (0.02)	
0.74	1.06 (0.02)	
0.65	0.987 (0.020)	
0.59	0.946 (0.024)	
0.48	0.880 (0.018)	0.886 (0.022)
0.35	0.823 (0.021)	
0.22	0.752 (0.015)	
0.15	0.733 (0.018)	
0.00	0.690 (0.010)	0.693 (0.014)

[a] Error limits (shown in parentheses) are standard deviations. [b] Ionic strength maintained at 0.40 M using lithium perchlorate.

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(2) (a) Alvarez, F. J.; Schowen, R. L. *Isot. Org. Chem.* **1987**, *7*, 1. (b) Venkatasubban, K. S.; Schowen, R. L. *CRC Crit. Biochem.* **1984**, *17*, 1–44.
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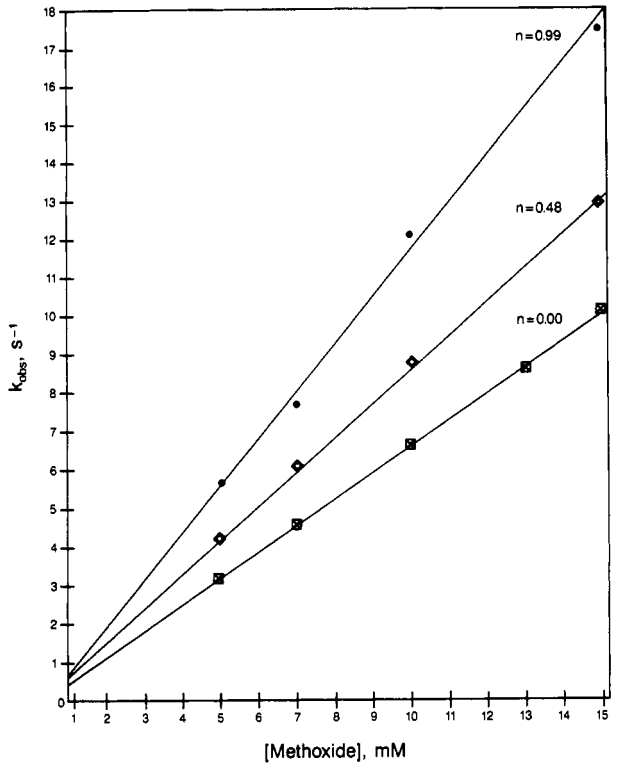

Figure 2. Representative plots used to determine the second-order rate constants for the basic methanolysis of diphenyl carbonate at 25.1 °C and 0.4 M ionic strength. The atom fraction of deuterium present in solution is n. The first-order rate constants were obtained from the later half of the time vs absorbance curves.

tive reactions. The first-order rate constants, computed from the slower second reaction obtained at 25.1 °C, are plotted against methoxide concentrations in Figure 2. The second-order rate constants generated from these first-order rate constants are also collected in Table I as a function of the atom fraction deuterium of the solvent. These second-order rate constants are identical (within experimental error) to the ones obtained for the methanolysis of phenyl methyl carbonate.

The second-order rate constant, k_n, in a solution of a given atom fraction deuterium n, is related to k_0, the rate constant in pure nondeuterated methanol by the Gross–Butler equation shown below.

$$k_n = k_0\frac{(\mathrm{TSC})}{(\mathrm{RSC})}$$

Here TSC and RSC are transition-state and reactant-state contributions to the measured isotope effect. In evaluating the reactant-state contributions to the isotope effect we need to assess the contribution of the methanol molecules solvating the methoxide ions. The magnitude of the deuterium solvent isotope effects for several reactions involving methoxide and hydroxide ions are consistent with three solvent molecules (corresponding to the three lone pair of electrons) solvating each of these ions.[5] Some recent theoretical calculations suggest that aqueous hydroxide ion may be solvated by six hydrogen-bonded water molecules,[1,6] but it is unlikely that methoxide ion is solvated by more than three methanol molecules in its primary solvation shell. This is partly because of the steric effect due to the larger size of the methoxide ion. Also, the methyl group is more hydrophobic compared to hydrogen, which probably precludes more extensive hydrogen bonding for the methoxide ion. Thus we assume here that there are only three sites corresponding to three methanol molecules solvating the reactant-state methoxide ion that contribute to the isotope effect. The fractionation factor for these three reactant-state sites is 0.72–0.74.[7] We have used an average value of 0.73 for these three reactant-state fractionation factors in the analysis of our data. The Gross–Butler equation now takes the form represented by eq 1.

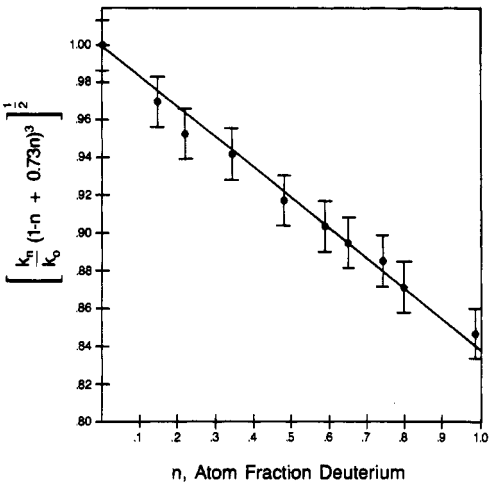

Figure 3. Plot of the left hand side of eq 2 against n, the atom fraction or deuterium. The intercept was forced through a value of 1. The error limits were estimated based on the errors in k_0 and k_n given in Table I. The slope of the line is −0.160 from which ϕ_2 is calculated to be 0.84.

$$k_n = k_0\frac{(\mathrm{TSC})}{(1-n+0.73n)^3} \qquad (1)$$

We fitted our data to a polynomial regression after correcting for the reactant-state contributions to determine the number of transition-state sites that contribute to the measured isotope effect. Our analysis reveals that the linear and quadratic terms are significant at 99.9% confidence level and the addition of the cubic term did not improve the fit at any significant confidence level. This strongly suggests that there are at least two transition-state protons that contribute to the observed isotope effect. Hence, we have fitted our data to a model involving two-site fractionation in the transition state. For this two-proton model, eq 1 can be rearranged to eq 2. In eq 2,

$$\left[\frac{k_n}{k_0}(1-n+0.73n)^3\right]^{1/2} = 1-n(1-\phi_2) \qquad (2)$$

ϕ_2, represents the identical fractionation factor for each of the two transition-state sites. A plot of the left-hand side of eq 2, against n, should be linear with an intercept of unity. The transition-state fractionation factor can be evaluated from the slope of this plot. Figure 3 represents the plot of eq 2.[8] It is linear, and ϕ_2 is determined to be 0.84 from this plot. The ϕ_2 value for phenyl acetate is 0.879.[3] Figure 4 represents the best-fit curve for a two-site transition-state model with the experimental second-order rate constants plotted on it. The fit of the experimental points to the theoretical curve is satisfactory.

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(8) A nonlinear fit our data gave a value of 0.843 for ϕ_2 in good agreement with the value of 0.84 obtained from the linear transformation of our data. We thank one of the reviewers for this suggestion.

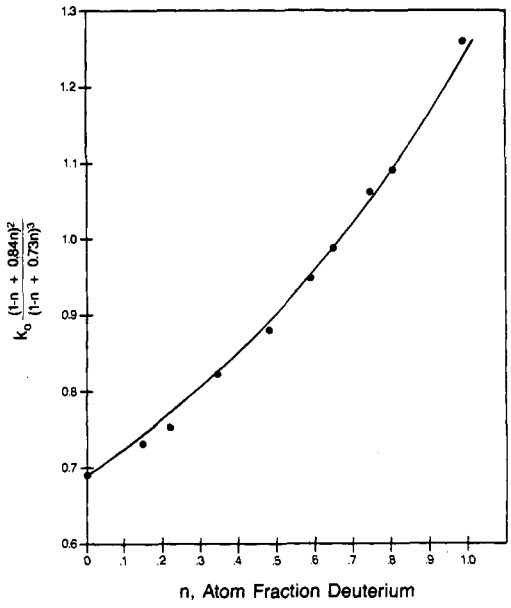

Figure 4. The complete proton inventory of the basic methanolysis of phenyl methyl carbonate. The solid curve is generated using the equation $k_n = k_0[(1 - n + 0.84n)^2/(1 - n + 0.73n)^3]$.

Discussion

The addition of methoxide to methyl-tritiated aryl methyl carbonates proceeded with no methoxide exchange, confirming that the addition of methoxide to carbonyl group is rate limiting in the methanolysis of these carbonates.[4] The proton inventory experiments in this study should thus provide information on the transition state leading to the formation of the tetrahedral intermediate. The observed inverse isotope effect of 1.83 clearly suggests that there is considerable solvent reorganization as the transition state is formed. For a transition state resembling the tetrahedral intermediate, the limiting inverse isotope effect should be $1/(0.73)^3 = 2.57$. This limiting value, along with the experimental value of 1.83, suggests that the solvent reorganization has proceeded to about 64% completion.

In the proposed two-site transition-state model, it is assumed that the nucleophilic methoxide ion loses one of its solvating methanol molecules before the transition state is reached. The fractionation factor for this methanol molecule has thus changed from an initial value of 0.73 to a final value of 1.0 corresponding to bulk methanol. The methoxide oxygen is partially bonded to the carbonyl carbon and carries a partial negative charge. It is assumed that this methoxide oxygen with its partial negative charge still carries two solvating methanol molecules. This constitutes the proposed two-site model with each site having a fractionation factor of 0.84. Thus for each of these two sites, the fractionation factor has changed from an initial value of 0.73 to a final value of 0.84. The degree of reaction progress for each of these sites can be estimated to be 0.45.[9] Overall, one of three solvating methanols has undergone total solvent reorganization and the other two have undergone roughly 46% reorganization. This averages to an overall 64% solvent reorganization. A similar model for the transition-state structure has been proposed for the methanolysis of phenyl acetate.[3] In the above model, it was assumed that the solvation in the transition state is essentially centered around the attacking methoxide ion. It is very likely that the solvation is centered around the carbonyl oxygen or at both oxygens at the same time.

(9) $1 - \log 0.84/\log 0.73 = 0.45$.

Comparison to Models Based on Theoretical Calculations. On the basis of their theoretical calculations for the addition of hydroxide ion to formamide, Kollman and co-workers have noted that of the original six hydrogen bonds solvating the hydroxide ions only two still exist in the transition state.[1] This amounts to a two-proton transition-state model for the addition of the hydroxide ion to the carbonyl group. This agreement with the transition-state structure proposed here for the methoxide addition to carbonates may be fortutious but all the same rather comforting. For the hydroxide addition to formaldehyde in aqueous solutions, Madura and Jorgensen suggest that all the six hydrogen bonds solvating the hydroxide ion in the reactant state are still present in the transition state but they are about 40% weaker.[6] Our data here may also be consistent with a model similar to this where all the three hydrogen-bonding sites originally present in methoxide ion are still present in the transition state but in a considerably weaker state. This apparently means that the rate-limiting event in the addition of these nucleophiles to a carbonyl group is predominantly one of a solvent reorganization around the nucleophile.

Methanolysis of Diphenyl Carbonate. We pointed out earlier that the methoxide-catalyzed methanolysis of diphenyl carbonate exhibited biphasic kinetics. We concluded from this biphasic kinetics that the addition of the first methoxide and the release of the first phenoxide is relatively rapid, in comparison to the addition of the second methoxide and the release of the second phenoxide. We were somewhat surprised by this result, because we anticipated that the addition of methoxide ion to diphenyl carbonate would be slower than the addition of methoxide ion to phenyl methyl carbonate based on the larger size of the phenoxy group compared to the methoxy group. The second-order rate constant for the basic methanolysis of dimethyl carbonate is about 1.6×10^{-2} M^{-1} s^{-1}.[10] Using this value and the second-order rate constant of 1.25 M^{-1} s^{-1} for phenyl methyl carbonate, we estimated the second-order rate constant for the addition of methoxide ion to diphenyl carbonate to be about 98 M^{-1} s^{-1}. This means that even for the lowest methoxide concentration used by us (0.005 M) the half-life is about 1–2 s. Thus the addition of the first methoxide ion will be too fast to be measured by conventional spectrophotometry. This is exactly what we observe experimentally. Also the proton inventory of this slower second half of the reaction is identical to the proton inventory of phenyl methyl carbonate studied independently (see Table I).

Why is the methoxide-catalyzed methanolysis of diphenyl carbonate faster than that of phenyl methyl carbonate? For both compounds the addition of methoxide ion to form the tetrahedral intermediate is rate limiting. On the basis of steric factors, we would expect phenyl methyl carbonate to add methoxide ion faster than diphenyl carbonate, since the phenoxy group is larger than the methoxy group. On the other hand, electronic effects would favor the addition of methoxide to diphenyl carbonate over phenyl methyl carbonate, since phenoxy group is more electronegative than the methoxide group.[11] The electronic effects seem to be in control here.

Experimental Section

The phenyl methyl carbonate was prepared by using a slight modification of the method reported by Caprino et al.[12] Phenyl

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chloroformate was treated with methanol in the presence of quinoline using methylene chloride as solvent. The mixture was stirred and cooled in an ice bath for about 2 h. The mixture was washed with aqueous acid and bicarbonate and water successively. The organic layer was dried by sodium sulfate, and the solvent was removed by evaporation. Vacuum distillation of the remaining liquid yielded phenyl methyl carbonate [bp 210 °C (760 mm); lit.[12] bp 212–215 °C (760 mm)]. The IR spectrum was consistent with what is expected for the pure compound (IR bands at 3020, 2960, 1765, 1600, 1500, 690, and 760 cm^{-1}). Diphenyl carbonate was obtained from Aldrich, the purity was checked by melting point determination, and the material was was used as obtained. Methanol-*d* (99% D) was purchased from MSD isotopes and used as such. The atom fraction of deuterium of individual solutions was based on the deuterium content of this stock methanol-*d*.

Kinetics. The methanolysis was followed by monitoring the release of phenoxide ion at 240 nm using a DMS-90 UV–visible spectrophotometer fitted with a thermostated cell holder. Three milliliters of the base solution was allowed to equilibrate to the required temperature in a cuvette, and 20 μL of a stock solution of the carbonate in acetonitrile was rapidly mixed with the base. The time vs absorbance data was collected using a Varian DS-15 data station interfaced to the spectrophotometer. The first-order rate constants were calculated from the time vs absorbance data using a kinetics calculation program available with the data station.

The methoxide solution was prepared by treating clean pieces of sodium metal with methanol cooled in an ice bath. The concentration of the methoxide solution was determined by titrating against potassium hydrogen phthalate. Methoxide in methanol-*d* was prepared by the same technique using pure methanol-*d*. The atom fraction of deuterium for individual solutions was calculated on the basis of the fact that the stock methanol-*d* has 99% deuterium. All operations using methanol-*d* were done in a drybox flushed with nitrogen.

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Registry No. Methyl phenyl carbamate, 13509-27-8; deuterium, 7782-39-0; diphenyl carbamate, 102-09-0.

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A New High-Yielding Method for the Preparation of 2-Alkyl- and 1,2-Dialkyl-4-nitro-5-bromoimidazoles

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2-Alkyl-4(5)-nitro-5(4)-bromoimidazoles and 1,2-dialkyl-4-nitro-5-bromoimidazoles have considerable synthetic and pharmacological significance. They are useful as chemotherapeutic agents[1] and potential radiosensitizers.[2] These compounds are also intermediates in the synthesis of a variety of biologically important nitroimidazole derivatives because of the ease of replacement of bromine. The corresponding 5-thio derivatives have antitumor activity.[3] Azoxymethyl nitroimidazoles with antitrichomonal and antiviral properties have also been synthesized from these intermediates.[4] A series of mercaptopurine derivatives known for their immunosuppressive and cytostatic action has been prepared from 4-nitro-5-bromoimidazoles.[5] The corresponding mercaptopyrazolopyrimidine derivatives have antigout properties.[6] 4-Nitro-5-cyanoimidazole derivatives having coccidostatic activity,[7] and novel heterocyclic systems like imidazo-, dihydroimidazo-, and tetrahydroimidazotriazines have been synthesized from 4-nitro-5-bromoimidazoles.[8]

We recently reported high-yielding methods for the preparation of 1,2-dialkyl-4-nitroimidazoles.[9-11] To extend our work to the preparation of potentially useful 5-substituted 4-nitroimidazoles, a suitable method for preparation of 5-bromo compounds without affecting the sensitive functional groups of the N-alkyl side chain was required. Reaction of bromine with a DMF solution of the substrate in the presence of potassium bicarbonate has been found to be a mild brominating system which provides the required bromo compounds in nearly quantitative yields (Table I).

Application of the Br_2–DMF–$KHCO_3$ method for the bromination of a number of 4-nitroimidazoles revealed that acid- and base-sensitive functionalities like ester, nitrile, and ketone present on N'-side chain remain intact under the conditions employed. Also, no side-chain bromination in the substrates carrying acetate, propionate, and propionitrile groups (entries 9, 7, and 5 of Table I) and ring bromination of aryl groups were observed (entries 10 and 11 of Table I). The N-unsubstituted, 2-alkylimidazoles also could be brominated in high yields with no detectable N-bromination (entries 1 and 2, Table I). The yields were practically quantitative, and the products were pure enough to be employed directly in further reactions.

In the methods described in the literature, bromination of 4-nitroimidazoles was carried out by reagents like Br_2–AcOH–$KBrO_3$,[1] Br_2–NaOH,[12] Br_2–NaOAc,[13] Br_2–H_2O,[14] and Br_2–$CHCl_3$–AcOH.[15] The superiority of the

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