Solvent Isotope Effects and Transition-State Solvation in the Basic Methanolysis of Esters[1,2]

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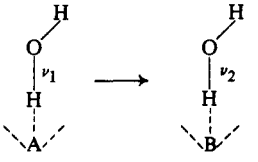
Abstract: Aryl methyl carbonates and aryl acetates undergo methoxide-catalyzed methanolysis in CH_3OD 1.5–2.1 times faster than in CH_3OH. The magnitudes of isotope effects and entropies of activation indicate that the gross isotope effects originate in an increase in structure of the solvent as methoxide ion partially adds to the substrate carbonyl groups, probably accompanied by an increase in solvent librational frequencies. The substituent-induced variations in the isotope effects and entropies of activation are most easily interpreted as involving changes in hydrogen-bonding strength for solvent molecules.

As a medium for the application of solvent isotope effects to reaction mechanism, methanol has some advantages over water.[5] The methoxide ion, CH_3O^-, for example, is not isotopically substituted so that isotope effects observed for its reactions with other species having no exchangeable protons must come from changes in solvation character, with no contribution from internal reactant or activated-complex vibration frequencies. Menger[6] recently noted that the basic methanolysis of *p*-nitrophenyl acetate proceeds more rapidly in CH_3OD by a factor of 2.4 at $-78°$, confirming some earlier indications that reactions of alkoxide ions are faster in the heavier solvent.[7]

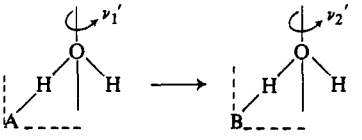
We have found that the enthalpies and entropies for methoxide-catalyzed methanolysis of aryl acetates and carbonates[1] are accounted for by Hepler's model[8] of substituent effects, according to which remote substituent effects on the entropy of activation ($\delta_x\Delta S^*$) are determined entirely by solvation changes on activation. We believe a comparison of this probe of solvation changes on activation with that offered by solvent isotope effects may be especially fruitful for the following reason.

Two basically different views of the origin of solvent isotope effects in water have been offered. Bunton and Shiner[9] emphasized the role of internal-frequency changes in solvent molecules, due to variations in hydrogen bond strength. For example, if A → B such that B becomes more basic, then $\nu_2 < \nu_1$, and a normal isotope effect ($k_{H_2O} > k_{D_2O}$) results. Notice that the increase in hydrogen-bond strength should lead to greater restriction of the solvent molecules, so that this normal solvent isotope effect should be associated with a decrease in entropy: conversely, an *inverse solvent isotope effect* should be



associated with an *increase in entropy*. Swain, Bader, and Thornton[10] have, on the other hand, stressed librational-frequency changes of solvent molecules as the origin of solvent isotope effects. In this view, the internal-frequency change is neglected. Now, if A → B such that (for any reason) solvent structure is decreased and librational motion facilitated ($\nu'_1 > \nu'_2$), a normal isotope effect will be observed. This normal isotope effect will, however, be associated with loss of structure and increase in entropy; conversely, on this model, an *inverse solvent isotope effect* should be associated with a *decrease in entropy*.

We therefore report here a comparison of solvent isotope effects with $\delta_x\Delta S^*$ for basic methanolysis of ten aryl acetates and carbonates.



Results

Table I gives the rate constants (these reactions are devoid of salt effects[1]) and isotope effects for methoxide-catalyzed methanolysis of *p*-$XC_6H_4OCO_2CH_3$ and *p*-$XC_6H_4O_2CCH_3$ in CH_3OH and CH_3OD. Free energies, enthalpies, and entropies of activation for the same series, are given in the accompanying paper.[1]

Discussion

The fact that methoxyl exchange from tritium-labeled aryl methyl carbonates (CH_2TOCO_2Ar) is indetectable in the course of basic methanolysis shows that the addition

(1) Catalysis in Ester Cleavage III. For part II, see C. G. Mitton, R. L. Schowen, M. Gresser and J. Shapley, *J. Am. Chem. Soc.*, **91**, 2036 (1969).

(2) This work was supported by the National Science Foundation and the General Research Fund of the University of Kansas and was carried out in part at the Computation Center of the University of Kansas.

(3) Predoctoral Fellow of the National Institutes of Health.

(4) Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

(5) V. Gold in "Physico-Chemical Processes in Mixed Aqueous Solvents," F. Franks, Ed., American Elsevier Publishing Co., Inc., New York, N. Y., 1967, p 146, has commented on this point.

(6) F. M. Menger, *J. Am. Chem. Soc.*, **88**, 5356 (1966).

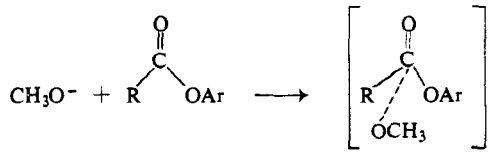
(7) *E.g.*, S. Andreades, *ibid.*, **86**, 2003 (1964); D. J. Cram and R. T. Uyeda, *ibid.*, **86**, 5466 (1964).

(8) L. G. Hepler, *ibid.*, **85**, 3089 (1963).

(9) C. A. Bunton and V. J. Shiner, Jr., *ibid.*, **83**, 42, 3207, 3214 (1961).

(10) (a) C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 182 (1960); (b) C. G. Swain, R. F. W. Bader, and E. R. Thornton, *ibid.*, **10**, 200 (1960); (c) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **83**, 3884, 3890 (1961).

of methoxide ion to the carbonyl group is rate determining for these substrates.[1] The same is likely to be true for aryl acetates. We shall therefore discuss these results in terms of the activation process of eq 1.



The interpretation of the data is made much easier by the recent measurement by Dr. R. A. More O'Ferrall of the isotopic fractionation factor for methoxide ion in CH_3OH–CH_3OD mixture.[11] He found $\phi \equiv [(D/H)_{CH_3O^-}]/[(D/H)_{CH_3OL}]$ to be 0.72 by the nmr method of Gold.[12] This shows that the complete conversion of a methoxide ion to a species having a fractionation factor of unity (the same preference for deuterium as the solvent) would lead to an inverse solvent isotope effect of $(1.39 = 1/0.72)^n$, where n is the number of methanol molecules associated with methoxide ion, having an average fractionation factor of 0.72. It seems doubtful that n will exceed three, the number of free electron pairs possessed by the methoxide ion. This leads to a postulated maximum isotope effect from "destruction" of a methoxide ion of 2.68. All of the isotope effects reported in Table I are smaller than this value, consistent with the view that the activated-complex fractionation factor should be intermediate between that for methoxide ion and the probably nearly unit factor for the neutral substrate esters.

The simplest comparison of ΔS^* and k_D/k_H that we can make is of their rough, general magnitudes. The isotope effect is inverse in all cases (k_D/k_H between 1.6 and 2.1), while the entropies of activation given in Table III of ref 1, ranging from -12 to -22 eu, are rather more negative than is expected for the simple loss of translational and rotational degrees of freedom in a bimolecular reaction in solution. The latter contribution[13] is probably in the neighborhood of about -10 eu. Thus it would appear that conversion of reactants (ester plus methoxide ion) to activated complex (a modified alkoxide ion) is accompanied by a decrease in entropy of up to about 12 eu from sources other than translation and rotation of ester and methoxide ion. These sources are presumably translational–rotational degrees of freedom of solvent molecules. So the gross picture is that an *inverse isotope effect* due to solvation changes is associated with a *decrease in entropy* due to solvation changes. As we argued above, this is more easily understood by ascribing the isotope effect to an increase in the librational frequencies of solvent molecules, on formation of the activated complex, than in terms of changes in the internal vibration frequencies of the solvent molecules.

Table I.[a,b] Rate Constants and Isotope Effects for Methoxide-Catalyzed Methanolysis of p-$XC_6H_4O_2CR$ in CH_3OH and CH_3OD at 25.0°

R	X	$k_2^{CH_3OD}$, M^{-1} sec^{-1}	$k_2^{CH_3OH}$, M^{-1} sec^{-1}	k^{CH_3OD}/k^{CH_3OH}
CH_3	CH_3O	3.36 ± 0.04	1.92 ± 0.05	1.75 ± 0.08
CH_3	CH_3	3.32 ± 0.02	1.96 ± 0.02	1.69 ± 0.02
CH_3	H	4.36 ± 0.01	2.66 ± 0.03	1.43 ± 0.02
CH_3	Br	14.9 ± 0.5	8.85 ± 0.12	1.69 ± 0.06
CH_3	CO_2CH_3	29.1 ± 1.2	14.2 ± 0.9	2.05 ± 0.15
CH_3O	CH_3O	1.06 ± 0.02	0.53 ± 0.01	2.00 ± 0.06
CH_3O	H	1.30 ± 0.02	0.708 ± 0.006	1.84 ± 0.03
CH_3O	Br	4.60 ± 0.25	2.48 ± 0.04	1.85 ± 0.10
CH_3O	$COCH_3$	8.94 ± 0.12	4.94 ± 0.11	1.81 ± 0.05
CH_3O	CHO	12.01 ± 0.35	6.14 ± 0.19	1.96 ± 0.09

[a] The error limits are standard deviations. [b] The temperature is accurate to ±0.2° and precise to ±0.01°.

A more detailed comparison may be made of the substituent effects on the solvent isotope effect and on the activation parameters. There is no very clearly discernible relation between reactivity, as measured by ΔG^*, and the solvent isotope effect. The same is true for ΔH^*. Plots (not shown) of these two quantities *vs.* solvent isotope effect exhibit only scatter. In Figure 1, we see the putative solvation effects of substituents on ΔS^* compared with isotope effects. While one certainly could have hoped for a more definitive result, it is quite clear that *if* these two measures of substituent effects on solvation of reactants *vs.* activated complex correlate in any way, it is such that a more positive ΔS^* (thus an *increase in entropy*) is associated with more *inverse isotope effects*. This is the kind of correlation to be expected if the isotope effects originate in hydrogen-bonding effects on internal solvent stretching frequencies, as suggested by Bunton and Shiner. Since this detailed effect of structure shows an opposite character to the gross changes observed, the simplest picture seems to require the invocation of both interaction mechanisms, librational and internal-frequency changes, to account for the results.

In summary, these results are consistent with the following model of solvation changes on activation in this system. First, conversion of the reactant methoxide ion to the partially formed alkoxide ion of the activated complex causes an increase in solvent structure as indi-

(11) We are much indebted to Dr. More O'Ferrall for kindly providing this datum in advance of publication.

(12) V. Gold, *Proc. Chem. Soc.*, 141 (1963). This method uses the solute concentration dependence of the proton chemical shift in an isotopically mixed solvent, compared to the same quantity for the purely protiated solvent, to derive the mole fraction of protium in the solvation sphere relative to mole fraction of protium in the solvent at large. If a reaction involves "destruction" of a methoxide ion (conversion to a species the solvation shell of which is identical in isotopic composition with bulk solvent), then its isotope effect will be given by ϕ^n where n is the solvation number of the methoxide ion.

$$[CH_3O^-n(CH_3OH)_{CH_3O^-}] \xrightarrow{K_H} P + nCH_3OH$$

$$[CH_3O^-n(CH_3OD)_{CH_3O^-}] \xrightarrow{K_D} P + nCH_3OD$$

$$K_H/K_D = \left[\frac{(CH_3OH)/(CH_3OD)}{(CH_3OH)_{CH_3O^-}/(CH_3OD)_{CH_3O^-}}\right]^n = \phi^n$$

(13) Support for this view is furnished by such examples as the following. L. J. Andrews and R. M. Keefer ("Molecular Complexes in Organic Chemistry," Holden-Day, Inc., San Francisco, Calif., 1964, p 106) cite thermodynamic data for formation of charge-transfer complexes of iodine and hexamethylbenzene with various aromatic compounds in carbon tetrachloride and alkane solvents. The slightly polar reactants here form a weakly polar complex, so that ΔS° should be only slightly more negative than the translation–rotation contributions. For 13 reactions, ΔS° is -13 eu with an average deviation of 3 eu after conversion to concentration units. Schaleger and Long (*Advan. Phys. Org. Chem.*, **1**, 1 (1963)) cite equilibrium thermodynamic data of T. Stewart and B. Fontana, *J. Am. Chem. Soc.*, **62**, 3281 (1940), for cyanohydrin formation from HCN and acetone in solvents as different as benzene and water. For four solvents, ΔH° and ΔS° are almost invariant, indicating little involvement of solvation. $\Delta S^\circ = -9.4$ eu with an average deviation of 0.6 eu.

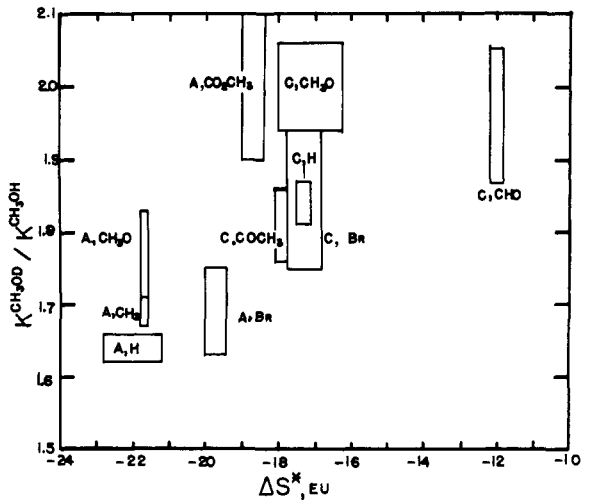


Figure 1. Solvent isotope effects *vs.* entropies of activation for the basic methanolysis of p-$XC_6H_4OCO_2CH_3$ (labeled C, X) and p-$XC_6H_4OCOCH_3$ (labeled A, X). In a general sense, the isotope effect becomes more inverse as ΔS^* becomes more positive.

cated by a decrease in entropy and by an increase in librational frequencies of solvent, thus giving an inverse solvent isotope effect. Second, such substituent effects on charge distribution in the activated complex as give rise to an increase in solvation entropy also, roughly speaking, produce a more inverse isotope effect. These effects apparently come from changes in hydrogen bonding and thus internal vibration frequencies of solvent molecules. The roughness of the second correlation may be due to the fact that, in reality, substituents act by means of both mechanisms. Another point worth noting is that, while entropy changes are (almost by definition) a good criterion of solvent–structure variations, solvent isotope effects may give less clear-cut indications about solvent structure.

Experimental Section

Materials. Esters were prepared as described previously.[1] Methanol-O-*d* was made from deuterium oxide (BioRad Laboratories), according to Streitwieser, Verbit, and Stang's procedure[14] for the acid-catalyzed hydrolysis of dimethyl carbonate. Manipulations were conducted in a glove box.

Kinetics. All measurements were made spectrophotometrically and data were reduced by a GE 625 computer as described before. Rates in CH_3OH and CH_3OD were determined successively within a 2-hr interval for each compound.

(14) A. Streitwieser, Jr., L. Verbit, and P. Stang, *J. Org. Chem.*, **29**, 3706 (1964).

The Synthesis and Solvolysis of 4,7,7-Trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane[1,2]

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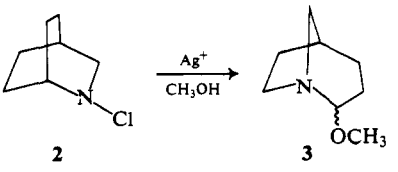
Abstract: 4,7,7-Trimethyl-2-chloro-2-azabicyclo[2.2.1]heptane (**1**) has been prepared *via* an eight-step synthesis starting with *d*-camphor, in 43% over-all yield. In methanol at 70° **1** solvolyzed with a half-life of *ca.* 83 min. In the presence of silver perchlorate, **1** solvolyzed in methanol at room temperature with a half-life of less than 1 min demonstrating that silver ion catalysis could account for a rate acceleration of at least 2×10^3. Both the thermal and silver ion catalyzed methanolysis of **1** produced a mixture of *exo*-2-chloro-3,3,4-trimethyl-1-azabicyclo-[2.2.1]heptane and *exo*-2-methoxy-3,3,4-trimethyl-1-azabicyclo[2.2.1]heptane with the chlorine-containing product being formed in 77 and 59% yields in the silver ion catalyzed and thermal reactions, respectively. The mechanism of this unprecedented silver ion catalyzed internal return of chlorine is discussed.

The facile rearrangements which occur in bicyclic molecules made these systems excellent substrates for the study of alkyl migrations to trivalent electron-deficient carbon.[4] By analogy, certain azabicyclics should serve equally well as models for alkyl migration to a divalent electron-deficient nitrogen (nitrenium ion). The usefulness of this analogy has already been demonstrated by the silver ion catalyzed rearrangement of N-chloroisoquinuclidine (**2**) to 2-methoxy-1-azabicyclo[3.2.1]octane (**3**).[5] This rearrangement provided the first unequivocal evidence for the intermediacy of a divalent electron-deficient nitrogen species. In order to expand our sphere of knowledge in this area we next chose to study the fate of



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(1) Paper VII in a series on the chemistry of nitrenium ions. For the previous paper in this series see P. G. Gassman and D. K. Dygos, *J. Am. Chem. Soc.*, **91**, 1543 (1969).

(2) A preliminary communication describing part of this work has appeared; P. G. Gassman and R. L. Cryberg, *ibid.*, **90**, 1355 (1968).

(3) Alfred P. Sloan Foundation Research Fellow, 1967–1969.

(4) For a review of some of the rearrangements which occur in carbocyclic systems see J. A. Berson, "Molecular Rearrangements," P. de Mayo, Ed., Interscience Publishers, New York, N. Y., 1963, pp 111–232.

(5) P. G. Gassman and B. L. Fox, *J. Am. Chem. Soc.*, **89**, 338 (1967).