Proton Inventories of Transition States for Solvation Catalysis and Proton-Transfer Catalysis. Decomposition of the Tetrahedral Intermediate in Amide Methanolysis[1,2]

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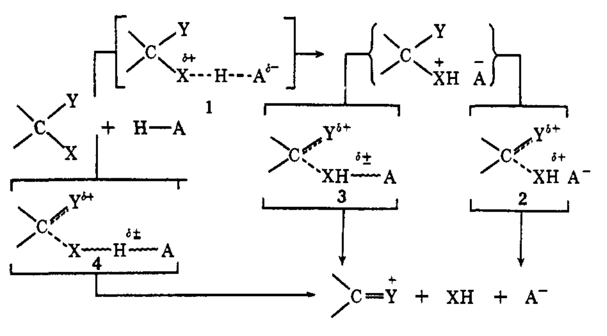
Abstract: The second-order rate constants, k_n, for methoxide-catalyzed methanolysis of $CF_3CON(CH_3)C_6H_4X$ in binary mixtures of CH_3OD (mole fraction n) and CH_3OH (mole fraction $1 - n$) are described by the equation, $k_n = k_0(1 - n + \phi^* n)(1 - n + 1.2n)^2/(1 - n + 0.74n)^8$, where $\phi^* = 0.39$ (X = *m*-NO_2), 0.29 (X = *p*-Cl), and 0.13 (X = *p*-OCH_3). The tetrahedral intermediate decomposes with proton-transfer catalysis in the *p*-OCH_3 case ($k_H/k_D = 7.4\ [\equiv(\phi^*)^{-1}]$) and with solvation catalysis in the *m*-NO_2 case ($k_H/k_D = 2.6$), the isotope effects referring solely to the proton bridging the core, or substrate portion, of the transition state to the catalytic entity. The latter may contain two "gas-like" methanol molecules ($\phi_m = 1.2$) deriving from nonequilibrium solvation of the transition state.

We have earlier given arguments and evidence that proton transfer and heavy-atom reorganization processes are not concerted (*i.e.*, do not occur as common components of the reaction coordinate of a single transition state) in reactions where proton motion is between two electronegative atoms, *e.g.*, general acid catalyzed cleavage of C–O and C–N bonds (eq 1) in such systems as amide hydrolysis, acetal and hemiacetal decomposition, and ester hydrolysis.[4] The various plausible transition states[4b] for nonconcerted paths are shown in eq 1.



(1)

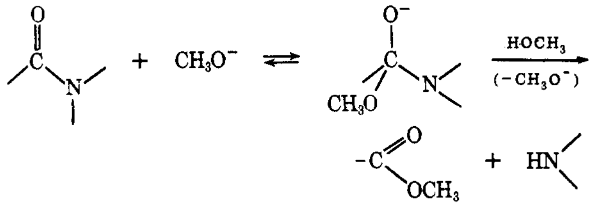
1 is a simple-proton-transfer transition state and will be favored when X is capable of supporting positive charge; it is observed in the hydrolysis and methanolysis of anilides with electron-donor substituents in the ring.[4b,5]

2 is a spectator-catalysis transition state in which A⁻ is trapped in the solvent cage as the C–N bond breaks. It may be under observation in the specific base–general acid catalyzed hydrolysis of some amides.[2]

3 is similar to **2**, but A⁻ is envisioned as actively supporting C–N bond fission through solvation catalysis.[4a]

4 represents solvation catalysis of C–N bond fission without prior transfer of the proton to N and is observed in the hydrolysis and methanolysis of anilides with electron-acceptor substituents in the ring, and in various reactions in which X is an oxygen center.[4a,b;5]

Part of the evidence for structures **1** and **4** consists of kinetic isotope effects, which are expected to be large for the bridging hydrogen in proton-transfer catalysis and small in solvation catalysis. A degree of ambiguity generally intrudes on the interpretation of these effects, however, because the hydrogens involved are exchangeable and the isotope effects are usually measured by complete isotopic substitution of the solvent, *e.g.*, D_2O *vs.* H_2O. Concern then arises whether the observations are complex mixtures of effects not easily understandable in terms of the properties of the catalytic proton bridge in the transition state. Such concern is intensified when the reactants are not equally stable in light and heavy solvents, as in the methoxide-catalyzed methanolysis of amides[5] (eq 2). The methoxide ion is known[6] to be up to 2.5 times more reactive in CH_3OD than in CH_3OH, so that the isotope effects from transition-state structural characteristics are doubtless different from the observed effects in methoxide-consuming reactions.



(2)

These ambiguities can be removed by conducting a *proton inventory* of the transition state, using rates in mixtures of light and heavy solvent.[7] If we consider a

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[1] This research was supported by grants from the National Science Foundation and the National Institutes of Health. Data reduction was carried out in the Computation Center of the University of Kansas. Further information is available in C. R. Hopper, M.S. Thesis in Chemistry, University of Kansas, 1971.

[2] Amide Hydrolysis. VII. For part VI, see D. Drake, H. Jayaraman, and R. L. Schowen, *J. Amer. Chem. Soc.*, **95**, 454 (1973).

[3] Holder of a Research Career Development Award of the National Institute of General Medical Sciences.

[4] (a) C. G. Swain, D. A. Kuhn, and R. L. Schowen, *J. Amer. Chem. Soc.*, **87**, 1553 (1965); (b) L. D. Kershner and R. L. Schowen, *ibid.*, **94**, 2014 (1971); (c) R. L. Schowen, *Progr. Phys. Org. Chem.*, **9**, 275 (1972).

[5] R. L. Schowen, C. R. Hopper, and C. M. Bazikian, *J. Amer. Chem. Soc.*, **94**, 3095 (1972).

[6] (a) F. M. Menger, *ibid.*, **88**, 5356 (1966); (b) R. A. More O'Ferrall, *Chem. Commun.*, 114 (1969); (c) V. Gold and S. Grist, *J. Chem. Soc. B*, 1665, 2282 (1971); (d) C. G. Mitton, M. Gresser, and R. L. Schowen, *J. Amer. Chem. Soc.*, **91**, 2045 (1969).

[7] A. J. Kresge, *Pure Appl. Chem.*, **8**, 243 (1964); V. Gold, *Advan. Phys. Org. Chem.*, **7**, 259 (1969).

mixture of CH_3OD (mole fraction n) and CH_3OH (mole fraction $1 - n$), the rate constant k_n in this mixture should be equal to the rate constant in pure CH_3OH, k_0, times a series of correction factors (eq 3). There should be

$$k_n = k_0 \prod_i^{\nu} J_i^n \tag{3}$$

one factor J_i^n for each of the ν exchangeable isotopic sites which contribute to the solvent isotope effect. The value of J_i^n will be determined by the amount of deuterium in the solvent (n) and the relative condition of the ith hydrogen in reactant and transition states. In fact it will be equal to the equilibrium fraction (X) of protium present in the ith reactant-state site, divided by the similar fraction for the ith transition-state site (eq 4a). Thus if the ith site prefers protium to a greater

$$J_i^n = [X_H^{Ri}/(X_H^{Ri} + X_D^{Ri})]_n / [X_H^{Ti}/(X_H^{Ti} + X_D^{Ti})]_n \tag{4a}$$

extent in the reactant than in the transition state ($J_i^n > 1$), addition of deuterium will favor the transition state and $k_n > k_0$. Equations 4b–d show that J_i^n also

$$J_i^n = \frac{1 + (X_D^{Ti}/X_H^{Ti})_n}{1 + (X_D^{Ri}/X_H^{Ri})_n} \tag{4b}$$

$$X_D^i/X_H^i = \phi_i n/(1 - n) \tag{4c}$$

$$J_i^n = \frac{1 - n + n\phi_i^T}{1 - n + n\phi_i^R} \tag{4d}$$

has a more familiar form involving the isotopic fractionation factor ϕ_i, which measures the deuterium preference (and thus the tightness of binding) of the ith site. These considerations finally result in the well-known eq 5 for $k_n(n)$. Equation 5 also shows that k_n

$$k_n = k_0 \prod_i^{\nu} \frac{(1 - n + n\phi_i^T)}{(1 - n + n\phi_i^R)} = k_0 \frac{\prod_i^{\nu}(1 - n + n\phi_i^T)}{\prod_i^{\nu}(1 - n + n\phi_i^R)} = k_0 \frac{TSC(n)}{RSC(n)} \tag{5}$$

contains a transition-state contribution $TSC(n) = \Pi_i^{\nu}(1 - n + n\phi_i^T)$ and a similar reactant-state contribution $RSC(n)$. $RSC(n)$ is frequently available experimentally, *e.g.*, from nmr or solubility measurements. Thus $TSC(n)$ can be evaluated from $k_n(n)$ and $RSC(n)$ and in a fortunate case all the ϕ_i^T can be tabulated. This we term a *proton inventory* of the transition state. The ϕ_i^T are each larger as the tightness of binding of the ith transition-state hydrogen increases relative to a solvent hydrogenic site. In fact, ϕ_i^T is just the equilibrium inverse isotope effect for conversion of a solvent hydrogen into the ith transition-state hydrogen (eq 4c).

This article reports proton inventories of transition states for reactions subject to solvation catalysis and proton-transfer catalysis. The methanolysis of p-$CH_3OC_6H_4N(CH_3)COCF_3$ proceeds[5] with rate-determining breakdown of its methoxide adduct, 89% by proton-transfer catalysis as in **1** and 11% by solvation catalysis as in **4**, as calculated from the two-term Hammett equation which describes the methanolysis reactions of these compounds.[5] The methanolysis of m-$NO_2C_6H_4N(CH_3)COCF_3$ (99% through **4**, 1% through **1**) provides an example of solvation catalysis in breakdown of the methoxide adduct,[5] while p-$ClC_6H_4N(CH_3)COCF_3$ reacts with sizable contributions of both pathways (22% through **1**, 78% through **4**).

Results

Second-order rate constants in binary mixtures of CH_3OH and CH_3OD were obtained for the sodium methoxide catalyzed methanolyses of p-$CH_3OC_6H_4N(CH_3)COCF_3$, p-$ClC_6H_4N(CH_3)COCF_3$, and m-$NO_2C_6H_4N(CH_3)COCF_3$. The constants are presented in Table I.

Table I. Second-Order Rate Constants for the Sodium Methoxide Catalyzed Methanolysis of $XC_6H_4N(CH_3)COCF_3$ in Binary Mixtures of CH_3OH and CH_3OD (Mole Fraction n) at 25.00 ± 0.02°

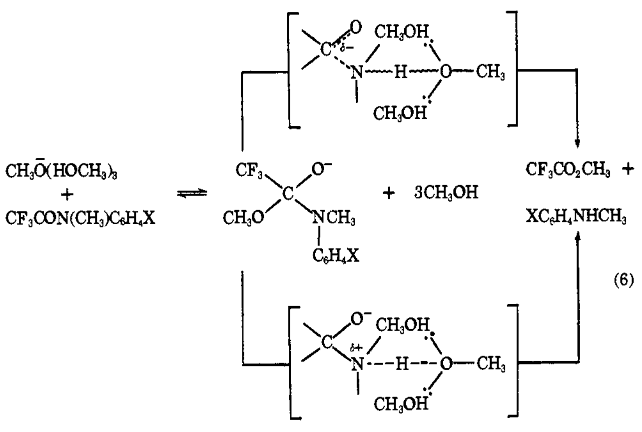
X	$10^2k_n(n)$, M^{-1} sec^{-1}	N (R)[a]
p-OCH_3	5.64 ± 0.06 (0.00)	4 (0.01–0.20)
	5.68 ± 0.04 (0.097)	4 (0.64–2.40)
	5.77 ± 0.03 (0.338)	4 (0.30–2.13)
	5.66 ± 0.12 (0.484)	4 (0.08–0.40)
	5.56 ± 0.07 (0.580)	4 (0.11–0.35)
	5.17 ± 0.03 (0.725)	4 (0.08–0.22)
	4.87 ± 0.03 (0.774)	4 (0.03–0.11)
	3.87 ± 0.10 (0.870)	4 (0.08–0.25)
	3.22 ± 0.08 (0.967)	4 (0.25–0.65)
p-Cl	26.5 ± 1.2 (0.000)	4 (0.02–0.20)
	27.4 ± 0.1 (0.193)	4 (0.20–0.40)
	28.1 ± 0.1 (0.338)	4 (0.17–0.36)
	28.8 ± 0.1 (0.491)	4 (0.08–0.40)
	28.5 ± 0.3 (0.629)	4 (0.20–1.00)
	27.9 ± 0.2 (0.725)	4 (0.35–2.00)
	28.5 ± 0.6 (0.885)	4 (0.08–0.50)
	27.4 ± 1.3 (0.983)	9 (0.01–0.20)
m-NO_2	575 ± 7 (0.000)	4 (0.002–0.02)
	678 ± 8 (0.194)	4 (0.001–0.006)
	735 ± 6 (0.387)	4 (0.001–0.004)
	756 ± 20 (0.483)	4 (0.0008–0.004)
	789 ± 3 (0.725)	4 (0.001–0.007)
	795 ± 5 (0.774)	4 (0.001–0.008)
	824 ± 2 (0.967)	4 (0.001–0.007)

[a] N is the number of first-order rate constants measured; R is the approximate range of sodium methoxide concentrations (M) used. Quite large concentrations are permissible because of the surprising absence of salt effects in these reactions.[5]

Discussion

The most plausible mechanisms[5] for the reactions studied are shown in eq 6. Each of the transition states contains three protons: a bridging proton (solvation

5, X = m-NO_2



6, X = p-OCH_3

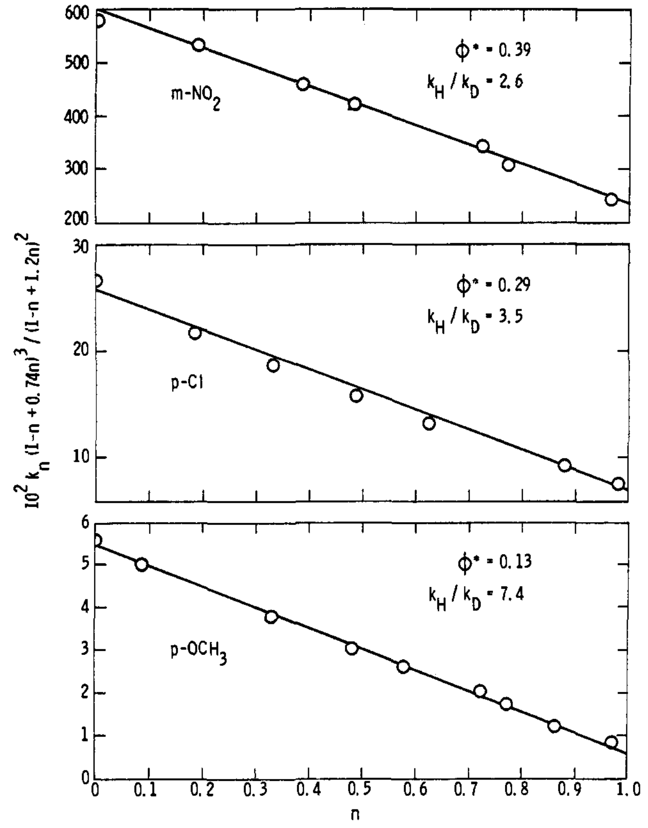


Figure 1. The left-hand side of eq 8, with $\phi_m = 1.2$, is plotted *vs.* n for reactions of the m-NO$_2$, p-Cl, and p-OCH$_3$ substrates. The circles are rough maximum error limits. The slopes of the lines determine the ϕ^* and k_H/k_D ($\equiv[\phi^*]^{-1}$) values shown.

bridge in **5**, proton-transfer bridge in **6**) and two others, occupying the lone-pair positions of the electrophilically active solvent molecule. More complex structures may also be imagined but would be difficult to support experimentally at this stage. The reactant state consists of the triply solvated methoxide ion, each solvating molecule[6b,c] with $\phi_B = 0.74$, and the substrate which we take as essentially insensitive to solvent isotopic composition. Thus RSC(n) = $(1 - n + 0.74n)^3$ for all compounds; TSC(n) will be given experimentally by eq 7a and theoretically by eq 7b, where ϕ^* is the isotopic

$$\text{TSC}(n) = k_n(1 - n + 0.74n)^3/k_0 \qquad (7a)$$

$$\text{TSC}(n) = (1 - n + n\phi^*)(1 - n + n\phi_m)^2 \qquad (7b)$$

fractionation factor for the bridging proton and ϕ_m is for each of the other two methanolic protons.

Several cases in which methanol molecules are forming proton bridges of either the solvation or proton-transfer variety have now come under our study.[8] In all of these cases it has been necessary to assume that $\phi_m \sim 1.2$ in order to fit experimental data to theoretical expressions like eq 7b. The molecular significance of this factor will be considered later, but it is easy immediately to test whether $\phi_m = 1.2$ in the reactions under discussion here. Combination of eq 7a and 7b to form eq 8 illustrates that if ϕ_m is known, then the left-hand side of eq 8 contains only known quantities

$$k_n(1 - n + 0.74n)^3/(1 - n + n\phi_m)^2 = k_0(1 - n + n\phi^*) \qquad (8)$$

and is a linear function of n. From the slope of such a plot ϕ^* can be evaluated. If the wrong value of ϕ_m is used, however, the plot should not be linear.

Figure 1 shows plots of eq 8 for the three reactions which we have studied here. For both the m-NO$_2$ and p-OCH$_3$ substrates, the plots are satisfactorily linear. The plot for the p-Cl substrate shows some departure from linearity, probably reflecting the mechanistic inhomogeneity of its reaction.[9] We conclude that $\phi_m \sim 1.2$ for these reactions also and that the values of ϕ^* derived from these plots correctly represent the bridging-proton isotope effects for the m-NO$_2$ and p-OCH$_3$ transition states ($\phi^* = 0.39$, $k_H/k_D = 2.6$ and $\phi^* = 0.13$, $k_H/k_D = 7.4$, respectively). Since the p-Cl substrate reacts about 22% by the p-OCH$_3$ pathway and about 78% by the m-NO$_2$ pathway, we expect[9] the apparent isotope effect for its bridge to be about the weighted average of the other two, as is observed ($\phi^* = 0.29$, $k_H/k_D = 3.5$ *vs.* average values of 0.33 and 3.0).

Bridging Protons. The most striking of these results is the large isotope effect of 7.4 for the proton bridge in decomposition of the p-OCH$_3$ tetrahedral intermediate. Because the transition-state nitrogen bears a small positive charge ($\rho \sim 0$ so the charge is about the same as in the reactant amide), we earlier suggested[5] that this is a case of proton-transfer catalysis with the C–N bond not breaking (transition state **6**). This is fully substantiated by this large, apparently primary effect.

The bridge isotope effect of 2.6 for the m-NO$_2$ reaction, where the substituent effect[5] ($\rho \sim 2.9$) indicates the C–N bond *is* breaking, is one of a growing class of bridge effects in the range 2.2 ± 0.5, observed when other evidence favors heavy-atom reorganization in the *core*, or substrate portion, of the catalytic transition state.[10] We have denoted[10] such bridges "one-proton solvation bridges" and we consider the catalytic mechanism to involve strong hydrogen-bond formation in the transition state[4] (structure **5**).

The Other Two Methanols. The linearity of the plots in Figure 1 supports the propriety of setting $\phi_m = 1.2$ in eq 7b and 8. This value is surprising because we expect the methoxy group of the proton-donor molecule in both **5** and **6** to be intermediate in character between the corresponding group of a bulk-solvent methanol molecule and a methoxide ion. Thus the fractionation factor for its solvation shell should be between 1 and 0.74. In fact, the value of 1.2, *if* it could be assigned unambiguously to these solvating molecules, would mean that the force field about their OH protons had increased—that the protons were more tightly bound in the transition state than in bulk solvent. Since the inverse isotope effect of 1.2 could correspond to an increase in the OH stretching frequency from 3400 to 3600 cm^{-1}, it is tempting to imagine that as the proton-donor molecule moves toward the substrate to form either a solvation or proton-transfer bridge, it severs its bonds to its two lone-pair solvators and that these are

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(8) C. R. Howie, R. Bacon, and A. Modro, unpublished investigations.

(9) The simple expression of eq 5 should not in principle be used for this reaction which proceeds by two parallel pathways, with a reasonable fraction of substrate going by each. For our purposes, we assume that by using eq 5, we will derive a ϕ^* which approximates the weighted average of the ϕ^*'s for the two parallel paths. No substantive changes may be expected from use of the more exact expression.

(10) S. S. Minor and R. L. Schowen, *J. Amer. Chem. Soc.*, **95**, 2279 (1973).

trapped in a nonequilibrium,[11] "gas-like" state during the existence of the transition state.

Such a conclusion from this work would be premature. We have not adequately dealt with isotopic "medium effects" on the stabilities of reactants and transition state nor have we exhaustively explored other fits to these data than that used here. Until this is completed, detailed interpretation of these small secondary effects must be deferred.

A Note on the Technique of Proton Inventory. In conducting a proton inventory, one successively isolates contributions to the n-dependence of the rate constant k_n until a satisfactory account of the shape of the function $k_n(n)$ is obtained. This is in some degree a subjective procedure and therefore questions arise about the uniqueness and validity of any inventory. In the future, when improvements in the technology of rate measurements (particularly the introduction of computers for experimental control and data acquisition) permit the collection of very extensive data sets of $k_n(n)$, more objective methods such as general least-squares fitting will be feasible. At present, however, attempts at such fits lead to rapid discouragement and suggest that rules of thumb such as the "Nine Rules" of Albery and Davies[12] are of greater utility. Our procedure has been as follows. First, $k_n\text{RSC}(n)$ calculated from the formula given above was plotted *vs.* n. The resulting curve (a) is nonlinear, showing that TSC(n) contains contributions from more than one proton; (b) decreases sharply in value as n increases, showing that TSC(n) contains a major normal-isotope-effect contribution ($\phi^* < 1$), tending to cause slower reaction in more highly deuterated solvent; (c) is slightly dome-shaped (*i.e.*, its nonlinearity takes the form of upward convexity), indicating that the large normal effect is opposed by one or more small inverse effects, which distort the curve toward faster rates in deuterated solvent. The only way these small inverse effects can enter from the transition state is if $\phi > 1$ for the sites involved. Since structural considerations suggest two such sites and other experience[8] suggests $\phi \sim 1.2$, we divided the corresponding contributions out of $k_n \cdot \text{RSC}(n)$, plotting the left-hand side of eq 8 *vs.* n. At this point, as Figure 1 shows, the plots were linear which indicated that only a single-proton contribution remained in TSC(n). The values of ϕ^* for this contribution are fixed by the slopes and intercepts of these plots. The only ambiguity in this procedure lies in the number and ϕ values of the sites which produce the small upward convexity mentioned in (c) above.[13] Therefore we have adopted a conservative attitude toward their significance. The magnitudes of ϕ^* (thus the isotope effects for the bridging protons) are not in any doubt.

Experimental Section

Materials. Substrate anilides were available from previous work.[4b,5] Solutions of sodium methoxide in methanol[6d] and mixtures[14] of CH_3OH and CH_3OD were prepared as described before.

Kinetics. The spectrophotometric method already described[5] was employed.

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(11) Ideas and evidence on this subject are discussed by J. L. Kurz and L. C. Kurz, *J. Amer. Chem. Soc.*, **94**, 4451 (1972).

(12) W. J. Albery and M. H. Davies, *J. Chem. Soc., Faraday Trans. 1*, 167 (1972).

(13) We are, of course, absolutely unable to specify the *location* of the unusual sites in the transition state. Although we have placed them in the solvation shell of the incipient methoxide ion, it is at least equally probable that they are in the solvation shell of the alkoxide position (the former carbonyl function) of **5** or **6**, which might be expected to be triply solvated as well. We cannot really distinguish two sites with $\phi_m = 1.2$ from three sites with $\phi_m = 1.13$.

(14) K. O'Donnell, R. Bacon, K. L. Chellappa, R. L. Schowen, and J. K. Lee, *J. Amer. Chem. Soc.*, **94**, 2500 (1972).