NIH GM-27029 with the assistance of Dr. J. C. Cook and Professor K. S. Suslick; the ZAB mass spectrometer was purchased in part by grants from the Division of Research Resources, NIH (RR01575), and from the NSF (PCM-8121494).

Registry No. $K_6HSiW_9V_3O_{40}\cdot 3H_2O$, 101056-07-9; $K_4H_3SiW_9V_3O_4$, 91523-04-5; $H_7SiW_9V_3O_{40}$, 101056-06-8; $TBA_4H_3SiW_9V_3O_{40}$, 92816-61-0; $TBA_5H_2SiW_9V_3O_{40}$, 101033-41-4; $TBA_6HSiW_9V_3O_{40}$, 101033-39-0; $TBA_7SiW_9V_3O_{40}$, 101033-40-3; $K_8HP_2W_{15}V_3O_{62}\cdot 9H_2O$, 101165-00-8; $TMA_6H_3P_2W_{15}V_3O_{62}\cdot 6H_2O$, 101164-99-2; $TBA_5H_4P_2W_{15}V_3O_{62}$, 101164-94-7; $TBA_6H_3P_2W_{15}V_3O_{62}$, 101164-95-8; $TBA_7H_2P_2W_{15}V_3O_{62}$, 101164-96-9; $TBA_8HP_2W_{15}V_3O_{62}$, 101164-97-0; $TBA_9P_2W_{15}V_3O_{62}$, 101078-21-1; $Na_{12}P_2W_{15}O_{56}$, 84750-84-5; A-β-$Na_9HSiW_9O_{34}$, 91686-50-9; $Na_{12}P_2W_{16}O_{59}$, 65046-52-8; $Na_2SiO_3\cdot 9H_2O$, 13517-24-3; $Na_2WO_4\cdot 2H_2O$, 10213-10-2; $NaVO_3$, 13718-26-8; H^+, 12408-02-5; ^{29}Si, 14304-87-1; V, 7440-62-2; ^{183}W, 14265-81-7; pyridine, 110-86-1.

Supplementary Material Available: Four figures showing the following: Figure 1, plots of the ultracentrifugation molecular weight measurements for $(Bu_4N)_4H_3SiW_9V_3O_{40}$ in CH_3CN and $(Me_4N)_6H_3P_2W_{15}V_3O_{62}$; Figure 2, IR spectra while monitoring the deprotonation of $(Bu_4N)_4H_3SiW_9V_3O_{40}$ with $Bu_4N^+OH^-/MeOH$; Figure 3, sample potentiometric titration of $(Bu_4N)_4H_3SiW_9V_3O_{40}$ with $Bu_4N^+OH^-/MeOH$; and Figure 4, IR spectra while monitoring the deprotonation of $(Bu_4N)_6H_3P_2W_{15}V_3O_{62}$ with $Bu_4N^+OH^-/H_2O$ (5 pages). Ordering information is given on any current masthead page.

Evidence for a Rate-Determining Solvation Change in Methyl Transfer to Water. Solvent Dependence of H_2O/D_2O Kinetic Isotope Effects

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Abstract: When H_2O is a dilute (<1 M) solute in CH_3CN or sulfolane, the rate of methyl transfer from CH_3X to H_2O is first order both in $[CH_3X]$ and in $[H_2O]$, but H_2O and D_2O react at the same rate ($k_H/k_D = 1.00 \pm 0.01$ for $X^- = OClO_3^-$ or thiophene). The analogous methyl transfers in CH_3CN at 25 °C from the same X^-'s to CH_3OH have $k_H/k_D = 1.07$ and 1.05 and to $(CH_3)_3COH$ have 1.12 and 1.07. In CH_3CN/H_2O (or ROH) solvent mixtures, as the H_2O (or ROH) content is increased to mole fractions >0.5, k_H/k_D for five of these six reactions increases sharply to the values observed in near H_2O or ROH: at 25 °C for $X^- = OClO_3^-$ and thiophene, respectively, $k_H/k_D = 1.20$ and 1.13 for H_2O, 1.22 and 1.15 for CH_3OH, and 1.08 and 1.12 for $(CH_3)_3COH$. Comparison of these k_H/k_D values to known values of deuterium fractionation factors for CH_3OH, H_3O^+, and $CH_3OH_2^+$ suggests the following: (a) for $CH_3X + H_2O$, there is little or no positive charge ($\delta = 0.00 \pm 0.04$) on the nucleophilic oxygen in the transition state. (b) For $CH_3X + CH_3OH$ or $(CH_3)_3COH$, that charge is larger than for H_2O. (c) The activation process in these methyl transfers (except for $CH_3OClO_3 + (CH_3)_3COH$) is predominantly a change in solvation of a preassociated H_2O (or ROH), CH_3X pair and, in the transition state, the solvation is more product-like than is the internal charge distribution. These inferences are consistent with a partly coupled mechanism for methyl transfer to H_2O.

Aliphatic nucleophilic substitutions in solution constitute one of the most exhaustively studied sets of organic reactions. However, several anomalous observations exist which imply that one of the most studied subsets of those reactions, nucleophilic attack by H_2O on methyl or primary alkyl groups (eq 1), does

$$H_2O + RCH_2X \rightarrow H_2O^+CH_2R + X^- \qquad (1)$$

not take place via the generally accepted S_N2 mechanism or its ion pair variant. Those observations recently have been reviewed;[1] they suggest that the activation process is almost entirely a fluctuation in *solvent* configuration and does *not* involve significant H_2O–C bond formation or C–X bond cleavage.

The H_2O/D_2O kinetic isotope effect (KIE) on the rate of such a displacement by water provides a direct probe of the extent of H_2O–C bond formation during the activation process.[2] If this KIE is measured by changing the solvent from H_2O to D_2O, then the resulting k_{H_2O}/k_{D_2O} rate constant ratio is a product of two factors: the desired secondary deuterium KIE on the nucleophilicity of water and an isotopic *solvent effect* on the rate. The presence of that solvent effect renders uncertain any estimation of the extent of H_2O–C bonding present in the transition state which is based on the observed value of that k_{H_2O}/k_{D_2O} ratio. Prior to the work discussed here,[3] published values of k_{H_2O}/k_{D_2O} referred to such a combined change in solvent and in nucleophile.

The purpose of the work presented here was to reduce that uncertainty. Methyl transfers to H_2O and D_2O from three CH_3X compounds with two different charges were studied in two aprotic solvents: rate laws were determined and H_2O/D_2O KIE's were measured for reactions of 1-methylthiophenium ion ($MeTh^+$), methyl perchlorate ($MeOClO_3$), and methyl trifluoromethanesulfonate (MeOTf) with *dilute* solutions of water in acetonitrile (MeCN) and tetrahydrothiophene 1,1-dioxide ($TMSO_2$; tetramethylenesulfone or sulfolane), and alkyl substituent effects on the KIE's were explored via the reactions of ROL [R = CH_3 or $(CH_3)_3C$ (*t*-Bu); L = H or D] with $MeTh^+$ and $MeOClO_3$ and of L_2O with ethyl perchlorate ($EtOClO_3$). Also, the magnitudes of the isotopic *solvent* effects were measured by varying the solvent compositions over the full range from dilute solutions of the three nucleophiles (ROL or L_2O) in MeCN to pure ROL and L_2O. All of the observations are consistent with a mechanism in which the activation process is primarily a solvation change, and many of the observations are *not* consistent with the traditional S_N2

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[3] Preliminary reports of some of the observations discussed here were presented in ref 4 and 5. Small differences between rate constants and KIE's given here and in those references reflect the results of later measurements or of reanalysis of the original data; qualitative conclusions in those references remain unchanged.

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Table I. Rate Constants[a] for Displacements by Dilute ROL in Aprotic Solvents (from Linear Eq[b] for k_ψ^L)

rxn no.	rxn	T (°C)	solvent	range of [ROL] (M)	n[c]	$10^5 k_0$ (s^{-1})	$10^5 k_1^L$ ($M^{-1} s^{-1}$)	$10^5 r$[d] (s^{-1})
1	$MeTh^+ + H_2O$	25	MeCN	0.09–0.9	12	4.5 ± 0.4	20.8 ± 0.8	0.37
	$MeTh^+ + D_2O$				12	4.7 ± 0.4	19.8 ± 0.8	0.35
2	$MeTh^+ + H_2O$	40	MeCN	0.09–0.9	9	23.4 ± 0.2	85.5 ± 2.2	0.79
	$MeTh^+ + D_2O$				9	23.4 ± 0.2	85.5 ± 2.2	0.80
3	$MeTh^+ + H_2O$	55	MeCN	0.09–0.9	9	111 ± 6	318 ± 14	4.6
4	$MeTh^+ + H_2O$	30	$TMSO_2$	0.09–0.9	9	0.3 ± 0.4	43.6 ± 0.8	0.33
	$MeTh^+ + D_2O$				9	0.1 ± 0.4	43.8 ± 1.0	0.35
5	$MeTh^+ + H_2O$	50	$TMSO_2$	0.09–0.9	9	7 ± 2	265 ± 4	1.4
6	$MeOClO_3 + H_2O$	35	MeCN	0.09–0.7	8	2.6 ± 0.2	12.5 ± 0.6	0.16
	$MeOClO_3 + D_2O$				8	2.6 ± 0.2	12.7 ± 0.6	0.15
7	$MeOClO_3 + H_2O$	55	MeCN	0.09–0.7	8	16.9 ± 0.8	50.7 ± 1.6	0.47
8	$MeOClO_3 + H_2O$	35	$TMSO_2$	0.09–0.7	8	0.9 ± 0.8	68.6 ± 2.0	0.55
	$MeOClO_3 + D_2O$				8	0.6 ± 0.8	69.8 ± 1.6	0.47
9	$MeOClO_3 + H_2O$	55	$TMSO_2$	0.09–0.7	8	7 ± 4	294 ± 10	2.6
10	$MeOTf + H_2O$	25	MeCN	0.09–0.9	18	13.4 ± 2.0	95.6 ± 4.2	2.1
	$MeOTf + D_2O$				19	13.8 ± 2.0	97.8 ± 4.0	2.1
11	$MeOTf + H_2O$	45	MeCN	0.04–0.9	11	95 ± 6	370 ± 13	11
12	$EtOClO_3 + H_2O$	35	MeCN	0.09–0.7	6	1.6 ± 0.4	12.2 ± 0.6	0.18
	$EtOClO_3 + D_2O$				6	1.6 ± 0.2	12.2 ± 0.6	0.16
13	$MeTh^+ + MeOH$	25	MeCN	0.08–0.8	8	3.8 ± 0.2	63.8 ± 0.6	0.19
	$MeTh^+ + MeOD$				8	4.0 ± 0.2	60.4 ± 0.6	0.17
14	$MeOClO_3 + MeOH$	25	MeCN	0.04–0.6	8	1.2 ± 0.1	12.4 ± 0.3	0.10
	$MeOClO_3 + MeOD$				5	1.1 ± 0.6	11.7 ± 1.4	0.28
15	$MeTh^+ +$ *t*-BuOH	25	MeCN	0.03–0.3	9	4.4 ± 0.4	34.6 ± 0.8	0.14
	$MeTh^+ +$ *t*-BuOD				7	4.5 ± 0.2	31.8 ± 1.1	0.16
16	$MeOClO_3 +$ *t*-BuOH	25	MeCN	0.03–1.4	6	1.1 ± 0.2	7.21 ± 0.20	0.16
	$MeOClO_3 +$ *t*-BuOD				5	1.2 ± 0.1	6.40 ± 0.10	0.08

[a] Uncertainties given for k_0 and k_1^L are *twice* the standard deviations (approximate 95% confidence limits). [b] Equation 2. [c] Number of runs used to evaluate k_0 and k_1. [d] Standard deviation of the observed k_ψ^L values from the least squares lines, $[\sum \Delta_i^2/(n-2)]^{1/2}$.

mechanism in which the activation process involves extensive bond formation and bond cleavage.

Experimental Section

Materials. Some, but not all, commercial samples of MeCN (Aldrich spectrophotometric grade or MCB OmniSolv) were found to contain between 10^{-5} and 10^{-4} M of a basic impurity (presumably NH_3) which interfered with the indicator method (vide infra) used to follow reactions of perchlorate and triflate esters. When present, this impurity was removed by distillation from freshly activated 3-Å molecular sieve, using the vacuum line procedure previously described[6] for removing traces of H_2O from MeCN. Samples of MeCN which were free from this impurity were used as received; rate constants measured by using this MeCN as solvent were identical, within the experimental uncertainty, with those for which the purified MeCN was used. Aldrich $TMSO_2$ was purified as described.[7,8] Most samples of deionized H_2O and of D_2O (Aldrich, Bio-Rad, or Merck; 99.7 or 99.8 atom % D) were used without further purification; distillation from $KMnO_4$ before use did not change values of rate constants within experimental error. All samples of MeOH (Fisher Certified or MCB OmniSolv) and MeOD (Aldrich or Merck, >99.5 or >99 atom % D) were distilled on the vacuum line from $Mg(OCH_3)_2$, and all samples of *t*-BuOH (Fisher certified) and *t*-BuOD (Merck, >99 atom % D) were distilled on the vacuum line from freshly calcined CaO; these purifications were required to avoid errors in the measured KIE's. Some samples of 2,4,6-trimethylpyridine (Eastman or Aldrich) were suitable for use as received (observed rate constants for reactions of $MeOClO_3$ or MeOTf were independent of the concentration of 2,4,6-trimethylpyridine), while one contained a nucleophilic impurity; that impurity was removed by vacuum distillation from boron trifluoride etherate[9] through an annular Teflon spinning-band column. A sample of 2,6-di-*tert*-butylpyridine (PCR) was found to be suitable for use as received. $MeTh^+$ was prepared and used as the PF_6^- salt;[10] this salt was stable when stored in a −85 °C freezer. Aldrich 99+% Gold Label MeOTf was used without purification. $MeOClO_3$ and $EtOClO_3$ were prepared as solutions in pentane,[11] which were converted into solutions in CH_3CN (by adding CH_3CN and evaporating under an N_2 jet) for use in kinetic runs. These perchlorate esters are explosive and shock-sensitive when pure; they always were handled as solutions with concentrations <1 M. Their stock solutions in MeCN were assayed by the procedure described below for rate measurements, by using the known difference (3.89×10^3 M^{-1} cm^{-1} at 265 nm) between the extinction coefficients of protonated and free base 2,4,6-trimethylpyridine; injection into an aqueous solution of that indicator gives an initial "instantaneous" ΔOD, which measures the content of solvolysis products in the stock solution, followed by a slow ΔOD which measures the $ROClO_3$ content.

Rate Measurements. All reactions were followed by UV spectroscopy. For measurements of KIE's, pairs of reactions using equal volume fractions of ROH and ROD (e.g., 20.0 μL each of H_2O and D_2O in 3.00-mL portions of MeCN) were followed simultaneously to facilitate cancellation of errors in the isotopic rate constant ratio. In a typical set of runs, the thermostated (±0.05 °C) carousel of a Cary 16 K or Cary 219 spectrophotometer was loaded with four stoppered 3-mL cells (two ROH/ROD pairs), each containing all components except the MeX; the fifth carousel position was occupied by a dummy cell containing solvent and a thermistor temperature probe. After temperature equilibration, all four reactions were initiated by injection 10 μL of a stock solution of the MeX in MeCN into each and mixing the cell contents without removal of the cell from the carousel. For those few reactions which were too fast for both runs in a ROH/ROD pair to be followed simultaneously, the reactions (after initial temperature equilibration) were initiated and run sequentially, alternating the ROH and ROD systems. Reactions were followed for ≥3 $t_{1/2}$, and the absorbance changes obeyed a first-order rate law. Pseudo-first-order rate constants, k_ψ^L, were evaluated either by using the observed "infinity" absorbance (read at >10 $t_{1/2}$) or, more commonly, by a least-squares fit of the absorbance during the first 3 $t_{1/2}$ to $A = A_\infty + (A_0 - A_\infty)\exp(-k_\psi^L t)$, where A_∞, $A_0 - A_\infty$, and k_ψ^L are adjustable parameters. Reactions of $MeTh^+$ usually were followed at 267 nm, the λ_{max} for $MeTh^+$; at this λ, product thiophene has negligible absorbance. Reactions of $MeOClO_3$, $EtOClO_3$, and MeOTf were run in the presence of a nonnucleophilic indicator base, and the absorbance change resulting from protonation of that base usually was followed at 265 nm (for 2,4,6-trimethylpyridine) or 270 nm (for 2,6-di-*tert*-butylpyridine). The concentration of MeX was usually in the range, 10^{-5}–10^{-4} M, and the concentration of the indicator base, when used, was

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Table II. Rate Constants[a] for Displacements by Dilute ROL in Aprotic Solvents (from Quadratic Equation[b] for k_ψ^L)

rxn no.[c]	10^5k_0 (s^{-1})	$10^5k_1^L$ (M^{-1} s^{-1})	$10^5k_2^L$ (M^{-2} s^{-1})	10^5r^d (s^{-1})	ρ^e	r(quad)[f]/r(linear)	$k_2^L/k_1^{L\,g}$ M^{-1}
1	4.7 ± 0.6	19.4 ± 3.6	1.6 ± 3.6	0.38	−0.967	1.03	0.08 ± 0.20
	4.6 ± 0.8	20.5 ± 3.4	−0.7 ± 1.8	0.36	−0.967	1.03	−0.03 ± 0.18
2	24.4 ± 1.8	79 ± 8	6 ± 8	0.73	−0.970	0.92	0.08 ± 0.10
	24.0 ± 2.0	82 ± 5	4 ± 10	0.82	−0.970	1.03	0.05 ± 0.12
3	121 ± 8	264 ± 38	58 ± 40	3.3	−0.970	0.72	0.22 ± 0.18
4	0.7 ± 0.4	40 ± 2	4.7 ± 1.8	0.18	−0.970	0.55	0.12 ± 0.06
	0.9 ± 0.4	38 ± 2	6.6 ± 1.0	0.18	−0.970	0.51	0.17 ± 0.06
5	8 ± 4	261 ± 16	4 ± 16	1.47	−0.970	1.05	0.01 ± 0.06
6	3.0 ± 0.2	9.9 ± 1.4	3.2 ± 1.6	0.09	−0.976	0.56	0.32 ± 0.20
	3.0 ± 0.2	10.0 ± 1.0	3.4 ± 1.2	0.06	−0.976	0.40	0.34 ± 0.16
7	17.9 ± 1.0	43.6 ± 5.4	9.1 ± 6.8	0.33	−0.976	0.70	0.42 ± 0.18
8	2.2 ± 1.0	59.6 ± 5.2	11.1 ± 6.2	0.32	−0.976	0.58	0.19 ± 0.06
	1.6 ± 1.0	63.1 ± 5.4	8.3 ± 6.6	0.34	−0.976	0.72	0.13 ± 0.12
9	13. ± 2.	253 ± 26	51 ± 32	1.61	−0.976	0.62	0.20 ± 0.14
10	19.0 ± 0.7[h]	62.3 ± 3.8	36.3 ± 4.0	0.44	−0.971	0.21	0.58 ± 0.10
	18.9 ± 0.6[h]	65.2 ± 3.4	36.6 ± 3.8	0.43	−0.970	0.20	0.56 ± 0.09
11	114 ± 4	232 ± 26	158 ± 30	3.0	−0.966	0.27	0.68 ± 0.20
12	2.0 ± 0.3	9.6 ± 1.6	3.3 ± 2.0	0.09	−0.977	0.52	0.34 ± 0.26
	2.0 ± 0.2	9.8 ± 1.2	3.0 ± 1.6	0.08	−0.977	0.48	0.31 ± 0.20
13	4.2 ± 0.4	61.4 ± 1.8	2.7 ± 2.0	0.14	−0.974	0.74	0.04 ± 0.04
	4.1 ± 0.4	59.4 ± 2.4	1.1 ± 1.3	0.17	−0.974	1.00	0.02 ± 0.04
14	1.2 ± 0.2	12.0 ± 1.5	0.7 ± 2.2	0.10	−0.970	1.00	0.06 ± 0.38
	1.5 ± 0.9	8.2 ± 6.2	6 ± 10	0.26	−0.970	0.93	0.7 ± 1.3
15	4.5 ± 0.4	34.1 ± 4.4	1 ± 10	0.15	−0.977	1.07	0.04 ± 0.32
	4.5 ± 0.4	32.6 ± 5.6	−2 ± 14	0.18	0.975	1.13	−0.06 ± 0.22
16	1.0 ± 0.5	8.2 ± 4.1	−0.6 ± 2.6	0.18	−0.989	1.13	−0.07 ± 0.56
	1.0 ± 0.1	7.8 ± 1.0	−0.9 ± 0.6	0.04	−0.989	2.0	−0.12 ± 0.12

[a] Uncertainties given for k_0, k_1^L, k_2^L, and k_1^L are *twice* the standard deviations (approximate 95% confidence limits). [b] Equation 3. [c] See Table I for identity of the reaction, solvent and temperature. [d] Standard deviation of the observed k_ψ^L values from the least-squares curve, $[\sum \Delta_i^2/(n-3)]^{1/2}$. [e] Correlation coefficient between k_i^L and k_2^L. [f] If this ratio is not significantly less than 1.00, then the k_2^L term in eq 3 is not significant. [g] If this ratio is not positive and greater than its uncertainty, then the k_2^L term in eq 3 is not greater than its uncertainty, and then the k_2^L term in eq 3 is not significant. The listed uncertainty is *twice* the standard deviation; since errors in k_1^L and k_2^L are correlated, the standard deviation of their ratio is calculated, by using ρ, as $[(s_2/k_1)^2 + k_2^2s_1^2/k_1^4 - 2k_2s_1s_2\rho/k_1^3]^{1/2}$. [h] Reference 27 gives 20.3 × 10^{-5} s^{-1}.

usually 2–4 times the concentration of the MeX.

Results

Dilute Solutions of ROL. For all the reactions described here, k_ψ^L becomes linear in the molarity of ROL (including L_2O) as that molarity decreases. Tables I and II present parameters resulting from least-squares fits of observed k_ψ^L values to linear (eq 2) and quadratic (eq 3) functions of [ROL] in the range,

$$k_\psi^L = k_0 + k_1^L[\mathrm{ROL}] \tag{2}$$

$$k_\psi^L = k_0 + k_1^L[\mathrm{ROL}] + k_2^L[\mathrm{ROL}]^2 \tag{3}$$

[ROL] <1 M. The k_2^L term is not significant for reactions of MeOL or *t*-BuOL; for reactions of L_2O, it is significant when the other reactant is $MeOClO_3$, $EtOClO_3$, or MeOTf (contributing up to ca. $^1/_3$ of the observed k_ψ^L at 1 M L_2O) but not, in most cases, when the other reactant is $MeTh^+$. Figure 1 illustrates this behavior of k_ψ^L for two reactions, one in which k_2^L is significant and one in which it is not.

The assumption that the k_0 and k_1^L terms correspond respectively to reactions of MeX with solvent (MeCN or $TMSO_2$) and with ROL was verified by ^1H NMR. During solvolysis of CH_3Th^+ in dry CD_3CN, the reactant resonance intensities (δ 3.19 and δ 7.59)[12] decrease smoothly as the product resonances at δ 3.72 ($CD_3CNCH_3^+$)[14] and δ 7.3 (C_4H_4S) increase. During reaction of 0.05 M CH_3Th^+ with 1.00 M D_2O in CD_3CN at 35 °C, no $CD_3CNCH_3^+$ signal is observed, but the intensity of a resonance at δ 2.97 ($CD_3CONDCH_3$ from reaction of $CD_3CNCH_3^+$ with D_2O) increases smoothly as the C_4H_4S signal increases and the CH_3Th^+ signals decrease. The observation that the CH_3Th^+ resonances retained their relative intensities (3:4) while decreasing in absolute intensity and also that the product signals at δ 3.32 (CH_3OD) plus δ 2.97 ($CD_3CONDCH_3$) and δ 7.3 (C_4H_4S) kept their intensity ratio constant (3:4) while increasing in intensity shows that there is no deuterium exchange between CH_3Th^+ and D_2O. When this reaction was complete, the ratio of peak areas of the CH_3OD and $CD_3CONDCH_3$ products was 3.9, in agree-

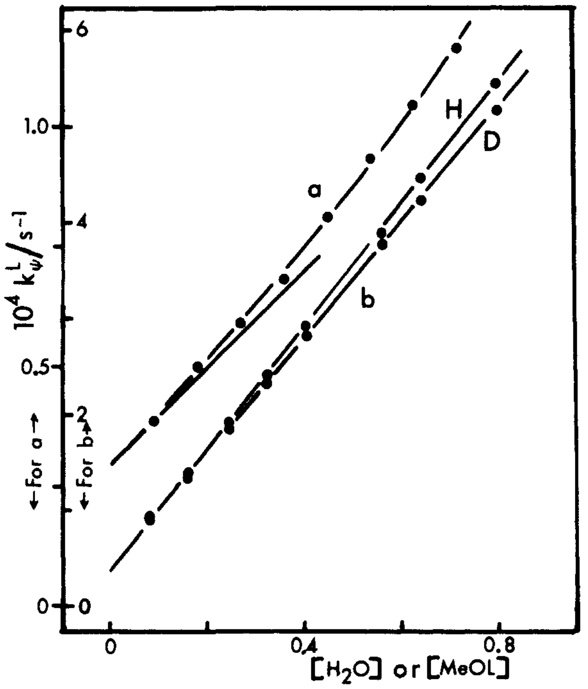

Figure 1. Examples of fits of k_ψ^L to eq 2 and 3. (a) $MeOClO_3$ + H_2O in MeCN at 35 °C (reaction no. 6); the points for D_2O are not shown since on this scale most are not resolved from the points shown for H_2O. The curve is from eq 3 and the parameters in Table II; the initial slope shown is k_1^H from Table II. (b) $MeTh^+$ + MeOH (and MeOD) in MeCN at 25 °C (reaction no. 13). The lines are from eq 2 and the parameters in Table I.

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[12] Since TMS reacts with $MeTh^+$,[13] the CHD_2CN peak in the CD_3CN was used as the internal standard (assumed 1.95 ppm downfield from TMS).

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Table III. KIE's[a] on Displacements by Dilute ROL in Aprotic Solvents

reaction	T (°C)	solvent	n^b	$\langle k_l^H/k_1^D\rangle^{a,c}$
$MeTh^+ + L_2O$	25	MeCN	10	1.004 ± 0.010
	40	MeCN	9	0.998 ± 0.006
	30	$TMSO_2$	9	1.001 ± 0.005
$MeOClO_3 + L_2O$	35	MeCN	7	0.989 ± 0.004
	35	$TMSO_2$	8	0.995 ± 0.012
$MeOTf + L_2O$	25	MeCN	18	0.969 ± 0.006
$EtOClO_3 + L_2O$	35	MeCN	6	0.994 ± 0.004
$MeTh^+ + MeOL$	25	MeCN	8	1.046 ± 0.004
$MeOClO_3 + MeOL$	25	MeCN	5	1.070 ± 0.013
$MeTh^+ + t\text{-}BuOL$	25	MeCN	7	1.071 ± 0.010
$MeOClO_3 + t\text{-}BuOL$	25	MeCN	5	1.118 ± 0.016

[a] The listed uncertainties are *twice* the standard deviations of the means (approximate 95% confidence limits). [b] Number of k_1^L pairs used to evaluate the KIE. [c] Mean of the n values of k_1^H/k_1^D calculated from eq 4. For reactions of L_2O with $MeOClO_3$, $EtOClO_3$, and MeOTf, $\langle k_0\rangle$ in eq 4 is based on fits of k_ψ^L to eq 3; for all other reactions, $\langle k_0\rangle$ is based on fits to eq 2.

ment with the product ratio predicted from the rate constants in Table I: $k_1^D[D_2O]/k_0 = 3.8$ at 35 °C. A similar identification of products from the k_0 and k_1^D plus k_2^D terms was made for the reaction of CH_3OTf with D_2O in CD_3CN.

It has been reported that nucleophilic substitution reactions of alkyl sulfonium ions can be catalyzed by anions.[15,16] Although PF_6^- at these low concentrations ($\leq 10^{-4}$ M in most runs) would be expected to be a poor candidate for such a role, the possibility that the reactions of $MeTh^+PF_6^-$ discussed here could proceed via such catalysis was excluded experimentally. Values of k_ψ^H observed for one set of reactions of 0.92 M H_2O in MeCN with $MeTh^+PF_6^-$ in concentrations of 0.5, 1, 2, and 4 × 10^{-4} M were, respectively, 2.57, 2.49, 2.50, and 2.47 × 10^{-4} s^{-1}. These values show that no such catalysis occurs, and they suggest the possible existence of a small negative salt effect, as would be anticipated for a reaction of this charge type.

Values of the desired KIE, k_1^H/k_1^D, could be obtained simply from ratios of pairs of k_1^L values in Table I or II. That, however, would not take advantage of the fact that pairs of k_ψ^L values for reactions with approximately equal concentrations of ROH and ROD were measured concurrently. More precise values of k_1^H/k_1^D were obtained from an analysis which recognizes that pairing.[17] For reactions which obey eq 2, each pair of runs yields a value of k_1^H/k_1^D from eq 4, where $\langle k_0\rangle$ is the mean of the k_0

$$\frac{k_1^H}{k_1^D} = \left(\frac{k_\psi^H - \langle k_0\rangle}{k_\psi^D - \langle k_0\rangle}\right)\frac{[ROD]}{[ROH]} \qquad (4)$$

values obtained from least-squares fits of k_ψ^H and k_ψ^D to eq 2. Since the ROH and ROD members of each pair were present at equal volume fractions, the nucleophile molarity ratio in eq 4 is given by $(MW_H/MW_D)(d_D/d_H)$, where MW and d denote molecular weights and densities of liquid ROH and ROD. Values of [ROD]/[ROH] are 0.9964,[18] 0.9954,[19] and 0.9978[18] for L_2O, MeOL, and t-BuOL, respectively.

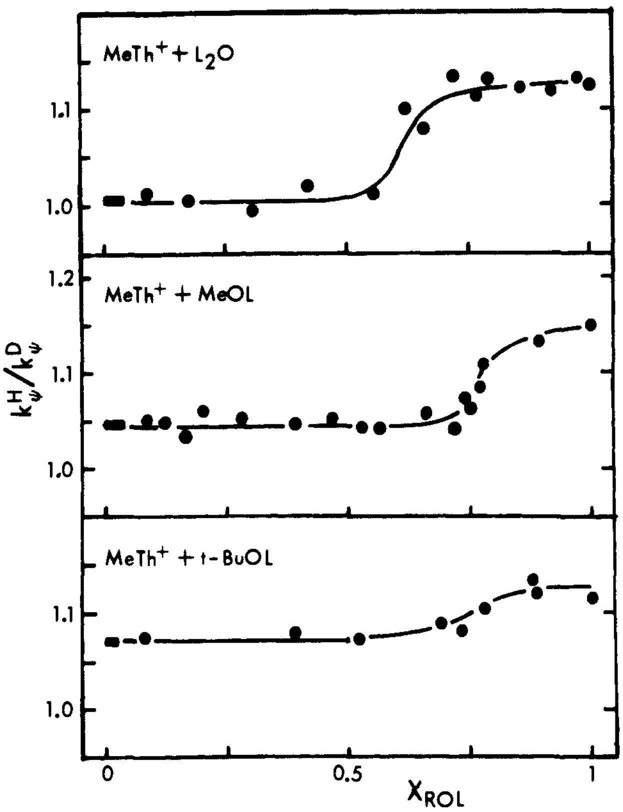

Figure 2. KIE's for reactions of $MeTh^+$ at 25 °C. The horizontal bars at $X_{ROL} = 0$ are $\langle k_1^H/k_1^D\rangle$ from Table III; the length of the bar shows the range of X_{ROL} used in measurements of k_1^H/k_1^D. KIE's at $X_{ROL} = 1$ are from Table IV. Each point at other values of X_{ROL} represents k_ψ^H/k_ψ^D from a single pair of runs. The diameter of each point is ca. 1% of its value. Curves are drawn to guide the eye; they have no assumed theoretical functional form.

Table IV. KIE's and Rate Constants for Displacements by ROL when ROL is the Solvent[l]

reaction	T (°C)	n^a	$10^4 k_\psi^{H\,b}$ (s^{-1})	$k_\psi^H/k_\psi^{D\,b,c}$
$MeTh^+ + L_2O$	25	5	7.44 ± 0.05	1.128 ± 0.002
	40	4	34.7 ± 0.2	1.122 ± 0.002
$MeOClO_3 + L_2O$	25	5	17.44 ± 0.04[d]	1.20 ± 0.01
	45	3	175 ± 1[e]	
$EtOClO_3 + L_2O$	25	4	34.6 ± 0.1[f]	1.15 ± 0.01
$MeOTf + L_2O$	1	3	47.4 ± 0.03[g]	
	15	4	251 ± 1	1.24 ± 0.02
$EtOTf + L_2O$	15	3	273 ± 1	1.22 ± 0.01
$MeTh^+ + MeOL$	25	4	232 ± 3	1.15 ± 0.01
$MeOClO_3 + MeOL$	25	3	7.42 ± 0.06[h]	1.22 ± 0.01
$MeTh^+ + t\text{-}BuOL$	25[i]	2	15.1 ± 1.0	1.12 ± 0.01
$MeOClO_3 + t\text{-}BuOL$	25[i]	1	1.75[j,k]	1.08[j]

[a] Number of k_ψ^L pairs used to evaluate the KIE. [b] Listed uncertainties are *twice* the standard deviations of the means (approximate 95% confidence limits). [c] Values in this column do not contain the [ROD]/[ROH] factor and thus differ slightly from the right hand intercepts in Figures 2 and 3. [d] References 20, 21, 22, and 23 give 17.3, 17.9, 15.4, and 15.8, respectively. [e] Reference 20 gives 170. [f] Reference 22 gives 19.3. [g] Reference 24 gives 43.8 at 0.3 °C. [h] References 25 and 26 give 6.00 and 6.80, respectively, for MeOH containing 3.2% cyclohexane and 2% benzene. [i] The MeCN depressed the freezing point of t-BuOL below 25 °C. [j] Single value, but consistent with values at lower t-BuOL mole fractions; see Figures. [k] Reference 26 gives 1.29. [l] The ROL contains 0.3–0.6% MeCN (0.06–0.13 M).

For reactions in which the k_2^L term is significant, the value of k_2^H/k_2^D does not differ from that of k_1^H/k_1^D within the experimental uncertainty. This can be seen both from the k_ψ^H/k_ψ^D values measured at higher [ROL] discussed below and from the observation that the right hand side (rhs) of eq 4 does not change as [ROL] increases. For example, consider the reaction of MeOTf with L_2O in MeCN at 25 °C; Table II shows this to be the reaction for which k_2^L is most significant. Linear extrapolation of values of the rhs of eq 4 (with $\langle k_0\rangle$ from fits to eq 3) to [ROL] = 0 gives a limiting value of 0.966 ± 0.010, in agreement with the value, 0.969 ± 0.005, of the mean of those values. Thus no significant

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(15) Knipe, J. O.; Vasquez, P. J. Coward, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 3202–3209.

(16) (a) Hyne, J. B.; Jensen, J. H. *Can. J. Chem.* **1962**, *40*, 1394–1398. (b) Hyne, J. B.; Abrell, J. W. *Can. J. Chem.* **1961**, *39*, 1657–1669.

(17) For reactions run at different times, the k_ψ^H/k_ψ^D ratios from concurrent pairs were significantly more reproducible than the individual k_ψ^L values. Compare the r values and confidence limits listed in Tables I and II for the k_1^L values derived from the k_ψ^L values to the smaller relative confidence limits for $\langle k_1^H/k_1^D\rangle$ in Table III.

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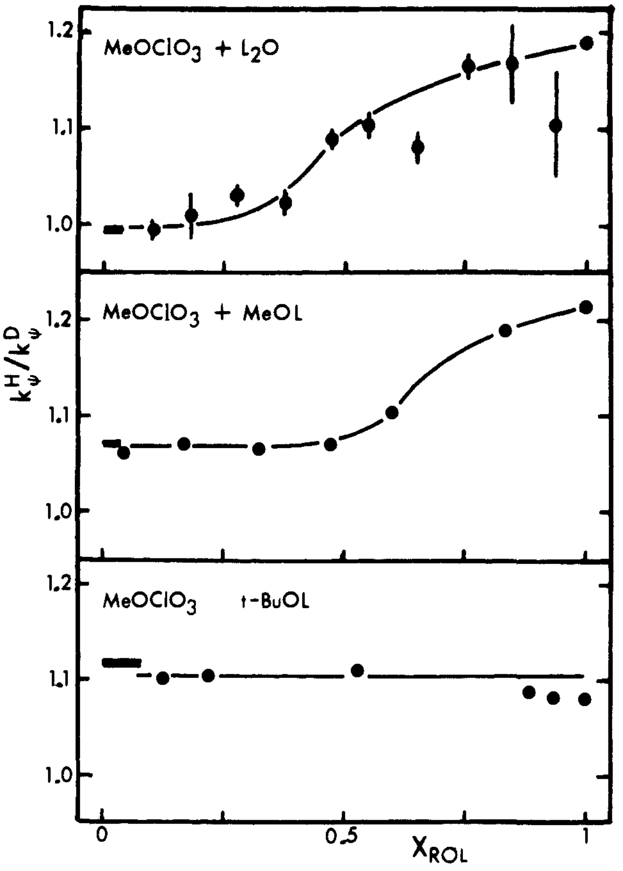


Figure 3. KIE's for reactions of $MeOClO_3$. Plots are as described for Figure 2 with one exception: points for L_2O at intermediate values of X_{L_2O} are means of between two and six measurements, and error bars are ± one standard deviation of the mean.

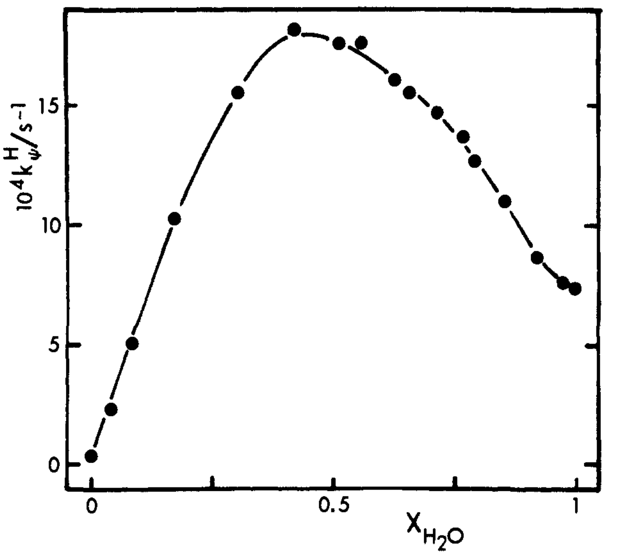


Figure 4. Rate constants for $MeTh^+ + H_2O$ in MeCN at 25 °C. The curves in this figure and in Figures 5–9 are drawn to guide the eye; they have no assumed theoretical functional form.

error results from evaluation of the KIE on k_1^L using eq 4.

Values of KIE are given in Table III. For all of the displacements by L_2O, k_1^H/k_1^D is seen to be very close to 1.00, while for the displacements by MeOL and t-BuOL, k_1^H/k_1^D is clearly greater than 1.00.

Concentrated Solutions of ROL. Figures 2 and 3 show the behavior of the k_ψ^H/k_ψ^D ratios for reactions of $MeTh^+$ and $MeOClO_3$ as the L_2O, MeOL, and t-BuOL contents of the solvents are varied from dilute solutions in MeCN all the way to neat ROL. The behaviors of the corresponding k_ψ^H values are shown in

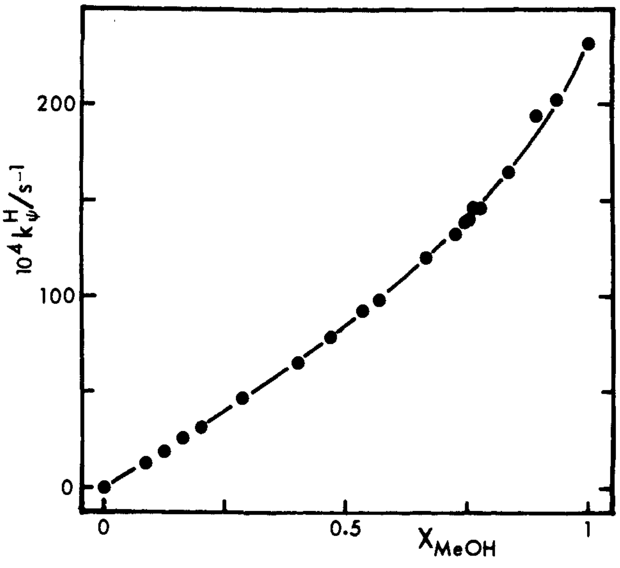


Figure 5. Rate constants for $MeTh^+ + MeOH$ in MeCN at 25 °C.

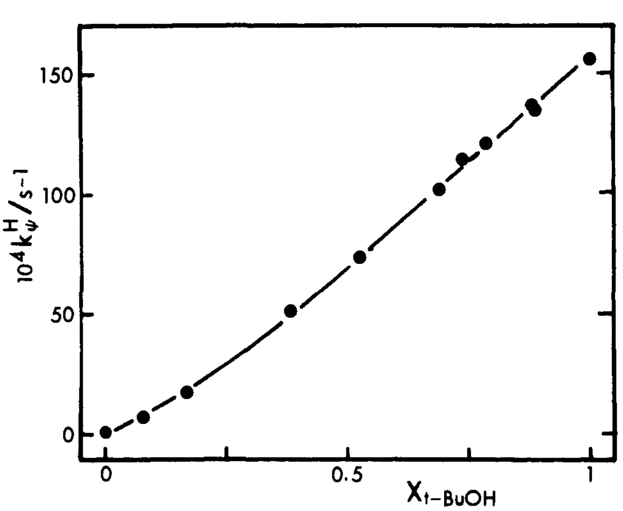


Figure 6. Rate constants for $MeTh^+ + t$-BuOH in MeCN at 25 °C.

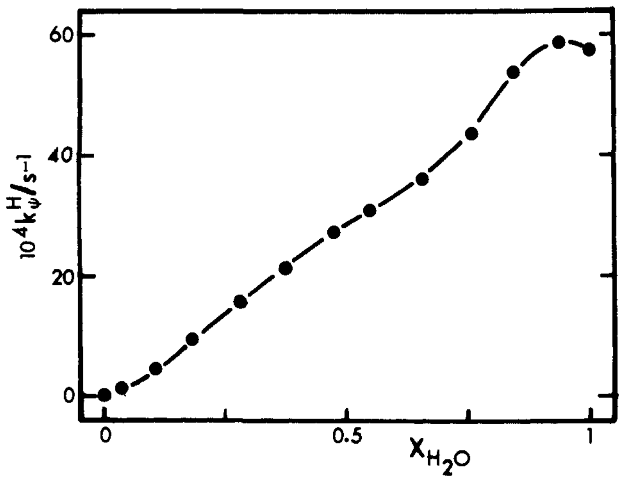


Figure 7. Rate constants for $MeOClO_3 + H_2O$ in MeCN at 25 °C.

Figures 4–9. Numerical values of k_ψ^H/k_ψ^D and k_ψ^H for reactions in the neat ROL limit are given in Table IV.

As the ROL concentrations increase, all six KIE's shown in Figures 2 and 3 remain equal to their dilute solution values until quite high concentrations are reached. Five of the six KIE's finally rise to a higher value as the solvent composition approaches pure ROL; the reaction of $MeOClO_3$ with t-BuOL is the one exception, its KIE is independent of solvent composition within the exper-

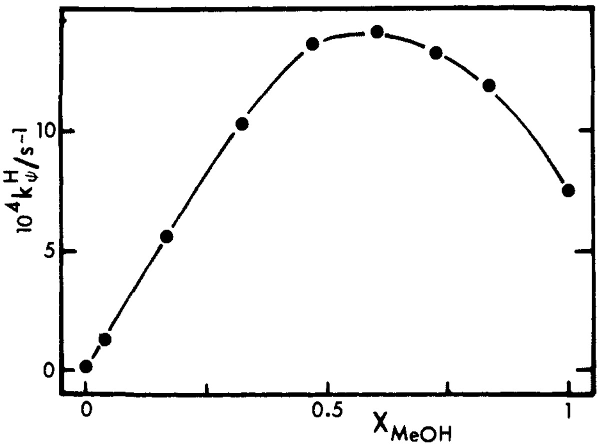


Figure 8. Rate constants for $MeOClO_3$ + MeOH in MeCN at 25 °C.

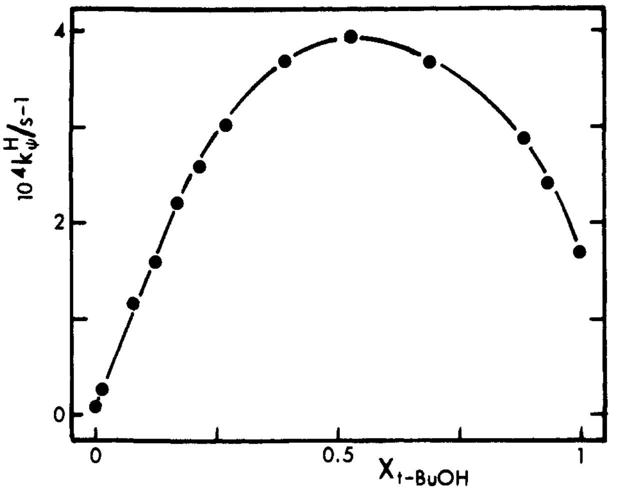


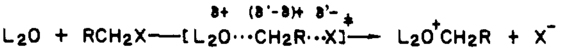
Figure 9. Rate constants for $MeOClO_3$ + *t*-BuOH in MeCN at 25 °C.

imental uncertainty. The rise in KIE is relatively sharp for the three reactions of $MeTh^+$. The rise is more gradual and occurs at lower ROL concentrations for the two reactions of $MeOClO_3$ which have solvent-dependent KIE's.

As is implied by the scatter in Figure 2 and 3, the reproducibility of k_ψ^H/k_ψ^D for all reactions, except $MeOClO_3$ + L_2O, is comparable to the size of the circles (diameter ≈ 1%) which represent the observations, so that the form of the dependence of the KIE on the mole fraction of ROL is well-defined. The reproducibility for the reaction of $MeOClO_3$ with L_2O was much poorer throughout the midrange of solvent composition, and the data for that reaction demonstrate only that the variation in KIE is qualitatively similar to that for the better-behaved reaction of $MeOClO_3$ with MeOL. In the two limits of pure L_2O and dilute L_2O in MeCN, the KIE was much more reproducible (cf. the uncertainties listed in Tables III and IV). The origin of the irreproducibility for some reactions of $MeOClO_3$ is uncertain, but the wide spread of rate constants reported by different groups for the solvolysis of $MeOClO_3$ in H_2O (see Table IV) suggests that it is a commonly encountered phenomenon.

Discussion

The focus of the following discussion is on what our results imply concerning the charge distribution in the transition state and the nature of the activation process. In the traditional S_N2 mechanism (eq 5) for displacements by L_2O, significant positive charge, $\delta+$,



$$L_2O + RCH_2X \longrightarrow [\overset{\delta+}{L_2O}\cdots\overset{(\delta'-\delta)+}{CH_2R}\cdots\overset{\delta'-}{X}]^{\ddagger} \longrightarrow L_2\overset{+}{O}CH_2R + X^- \qquad (5)$$

is expected to be present on the L_2O moiety in the transition state, the activation process and the reaction coordinate through the transition state are described in terms of O–C bond formation and C–X bond cleavage, and the polarization of the surrounding solvent is implicity assumed to remain in equilibrium with the internal charge distribution.

The Dilute Solution Rate Law. The predominant water species present in solutions of water in MeCN is known to be monomeric L_2O when the total water concentration is <1 M.[28-30] Since the k_1^L term in eq 2 or 3 is first order in total $[L_2O]$, it must thus correspond to a reaction in which the rate-determining transition state contains one molecule of L_2O. Since the product from the k_1^L term is MeOL (from MeX), that one L_2O is known to function as a nucleophile, so that k_1^L can be interpreted safely as the rate constant for nucleophilic displacement of X^- from MeX by monomeric L_2O.

The interpretation of the k_2^L term in eq 3 is less certain. It could correspond to a mechanism in which a second H_2O is specifically bound into the rate-determining transition state or it could reflect merely the effect of changing solvent polarity on the value of k_1^L. Since the k_2^L term is kinetically significant only for L_2O (not MeOL or *t*-BuOL) and only when the leaving group is an anion (OTf^- or ClO_4^-), not when the leaving group is uncharged (thiophene), it could reflect hydration of the leaving group. General base-catalysis by one H_2O of nucleophilic attack by the second (H_2O--HOH + MeX → H_2OH^+ + HOMe + X^-) is an unlikely interpretation of the k_2^L term, because strong hydrogen bonding or proton transfer in the transition state should introduce a comparatively large normal KIE ($k_2^H > k_2^D$), and it is observed that the value of k_2^H/k_2^D does not differ significantly from that of k_1^H/k_1^D.

However, the small value of the k_2^L/k_1^L ratio does imply the absence of any large $\delta+$ on the nucleophilic oxygen in the k_1^L transition state (eq 5) since it can be shown that, if such a large δ^+ were present, then general base-catalysis should occur and should lead to a larger value for k_2^L/k_1^L. Consider a k_1^L transition state, $[L_2OMeX]^\ddagger$, for a displacement by L_2O. The virtual equilibrium constant, $K(\ddagger)$, for its association with a second L_2O to form the k_2^L transition state for general base-catalysis (eq 6)

$$[L_2OMeX]^\ddagger + L_2O \overset{K(\ddagger)}{\rightleftharpoons} [L_2OL_2OMeX]^\ddagger \qquad (6)$$

can be shown to be equal to k_2^L/k_1^L.[31] The largest observed value of k_2^L/k_1^L, for L_2O + MeOTf in MeCN, is ca. 0.6 M^{-1}, and most of the values fall in the range, 0.0–0.3 M^{-1} (Table III). These values can be compared to the known association constants for model equilibria in which $\delta+$ is equal to the limiting values of 1 and 0. In MeCN the equilibrium constants for eq 7 and 8 are

$$H_3O^+ + H_2O \rightleftharpoons H_5O_2^+ \qquad (7)$$

$$H_2O + H_2O \rightleftharpoons (H_2O)_2 \qquad (8)$$

50 M^{-1} and 0.18 M^{-1}, respectively.[32,30] After adjustment of the former for the differing numbers of O–H bonds in the k_1^L transition state for H_2O and in H_3O^+, these values suggest that the value of $K(\ddagger)$ for eq 6 would be comparable to 33 M^{-1} if $\delta+$ were near 1 and comparable to 0.2 if $\delta+$ were near 0. The upper end of this range is ca. 500 times as large as the largest $K(\ddagger)$ value while the lower end is quite comparable to most of the observed values. The observed value of the k_2^L/k_1^L ratio thus is consistent with the conclusion which is derived below from the dilute solution of KIE's: that $\delta+ \approx 0$ for displacements by L_2O.

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[32] The value of the equilibrium constant for eq 7 is the ratio of the values given in ref 33 for $K^f_{H2W^+}$ and $K^f_{HW^+}$.

The Dilute Solution KIE's. In the limit of dilute (monomeric) ROL in an aprotic solvent, the only factor which contributes to the ROH/ROD KIE is the secondary deuterium isotope effect on the nucleophilicity of the oxygen. The KIE can be expressed in terms of fractionation factors for the isotopic hydrogens in reactant and transition state, and the transition state fractionation factors can be approximated as weighted geometric means of those for reactants and products.[2,34] If ϕ_{OL} and ϕ_{OL^+} denote the fractionation factors for one deuterium in reactant (L_2O or ROL) and product ($MeOL_2^+$ or $Me(R)OL^+$), respectively, and if both are expressed *relative to L_2O in the particular solvent* used, then the expressions for the dilute solution KIE's become: for reactions of L_2O

$$k_1^H/k_1^D = (\phi_{OL^+})^{-2\delta} \tag{9}$$

and for reactions of MeOH and *t*-BuOH

$$k_1^H/k_1^D = (\phi_{OL}/\phi_{OL^+})^{\delta} \tag{10}$$

In eq 9 and 10, δ is approximately equal to the fractional positive charge on the nucleophilic oxygen in the transition state (eq 5). For the reactions of L_2O, so long as the value of ϕ_{LO^+} differs significantly from 1.00, the observation that $k_1^H/k_1^D \approx 1.00$ (Table III) implies via eq 9 that $\delta \approx 0$.

A comparison of δ values for the reactions of MeOL and *t*-BuOL to that for the reactions of L_2O, or a more quantitative estimation of δ for L_2O, requires knowledge of the values of the fractionation factors in eq 9 and 10. The data of Rolston and Gale[35] imply that $\phi_{OL} = 1.06 \pm 0.04$ for MeOL in L_2O. It has long been known that $\phi_{OL^+} = 0.69$ for L_3O^+ in L_2O,[36] and it has recently been determined that $\phi_{OL^+} = 0.79$ for L_3O^+ in MeCN[6] and 0.58 for $MeOL_2^+$ in L_2O.[37] These few known values demonstrate that ϕ_{OL} and ϕ_{OL^+} are too dependent on solvent and structure to permit precise evaluation of δ, particularly for the reactions of MeOL and *t*-BuOL. However, some tentative limits can be set. The above values suggest that $\phi_{OL^+} < 0.8$ for $MeOL_2^+$ in MeCN, and six of the seven reactions of L_2O in Table III have k_1^H/k_1^D well within the range, 1.00 ± 0.02; substitution of these ranges into eq 9 gives $\delta = 0.00 \pm 0.04$. For the reactions of the alcohols, if it is assumed on the basis of the above known values that $\phi_{OL} = 1.06 \pm 0.04$ and $\phi_{OL^+} = 0.7 \pm 0.1$, then eq 10 together with the KIE's in Table III give $\delta = 0.1 \pm 0.1$ and 0.2 ± 0.1 for the reactions of MeOL with $MeTh^+$ and $MeOClO_3$ and $\delta = 0.2 \pm 0.1$ and 0.3 ± 0.2 for the reactions of *t*-BuOL with $MeTh^+$ and $MeOClO_3$. Unless the assumed ϕ ranges are very wrong, the transition states for methyl transfers to these alcohols have more positive charge on the nucleophilic oxygen than is present in the transition states for methyl transfer to water.

Rates and KIE's in More Concentrated Solutions. The dependences of the rate constants on solvent composition (Figures 4–9) are consistent with what has been reported previously for reactions of these charge types. As has been discussed in detail elsewhere,[1] the response of k_ψ^H to many traditional probes of mechanism, such as a change in solvent polarity, is qualitatively the same for a reaction that follows the partly coupled mechanism, in which the activation process is composed largely of a fluctuation in solvent polarization, as it would be if that reaction followed the commonly accepted S_N2 mechanism. Thus the value of k_ψ^H for reactions of $MeTh^+$ increases monotonically with X_{MeOH} or $X_{t\text{-}BuOH}$ (nucleophile concentration increases; polarity remains constant or decreases), but passes through a maximum as X_{H_2O} increases, reflecting the competing acceleration from increasing nucleophile concentration and deceleration from increasing polarity. Analogously, k_ψ^H for $MeOClO_3$ tends to be increased both by increasing nucleophile concentration and increasing polarity; it passes through a maximum as $X_{t\text{-}BuOH}$ increases and is close to monotonic as X_{H_2O} increases. The k_ψ^H maximum observed for the MeOH/MeCN mixtures and the possible shallow maximum for the H_2O/MeCN mixtures resemble the maxima previously reported[23,25] for $MeOClO_3$ in H_2O/acetone, H_2O/dioxane, MeOH/acetone, and MeOH/dioxane mixtures. Kevill[23] has attributed this behavior to a preferential solvation of the ClO_4^- leaving group by aprotic solvents. Thus the solvent dependences of k_ψ^H shown in Figures 4–9 are smooth within the experiiental scatter and (aside from the puzzling but mechanistically uninformative maxima for $MeOClO_3$ in MeOH/MeCN and H_2O/MeCN) provide no hint that the mechanism may be unconventional.

The solvent dependences of the isotopic k_ψ^H/k_ψ^D ratios shown in Figures 2 and 3 are much more informative. Five of the six show increases in k_ψ^H/k_ψ^D with increasing X_{L_2O} or X_{ROL} which are sufficiently sharp to imply the participation of a large number of L_2O or ROL molecules.

How could such participation increase k_ψ^H/k_ψ^D? Consider the limit of pure L_2O or ROL as solvent. Transfer of the reaction from H_2O (or ROH) to D_2O (or ROD) changes the solvent as well as the nucleophile. In addition to the secondary deuterium KIE on the nucleophilicity of L_2O (or ROL), there is an isotopic solvent effect on k_ψ^L. That solvent effect can contain contributions both from a *static* solvent effect and from a *dynamic* solvent effect.[38] The expressions for k_ψ^H/k_ψ^D thus contain three factors and become: for reaction in L_2O

$$k_\psi^H/k_\psi^D = [(\phi_{OL^+})^{-2\delta}][\exp(\Delta\Delta\bar{G}^\circ_{Tr}/RT)][\tau_D/\tau_H] \tag{11}$$

and for reactions of MeOL or t-BuOL

$$k_\psi^H/k_\psi^D = [(\phi_{OL}/\phi_{OL^+})^{\delta}][\exp(\Delta\Delta\bar{G}^\circ_{Tr}/RT)][\tau_D/\tau_H] \tag{12}$$

In eq 11 and 12, the first factor is the internal secondary KIE which was the sole contributor to the dilute solution KIE's (eq 9 and 10); the second factor is the *static* solvent effect which arises from inequality of the values of $\Delta\bar{G}^\circ$ for transferring reactant and activated complex (without exchange) from ROH into ROD and is analogous to the corresponding factor in a solvent isotope effect on an equilibrium constant; the third factor is the *dynamic* solvent effect which is present when motion along the reaction coordinate through the transition state is composed wholly or partly of reorganization of solvent structure. (For brevity, we shall refer to the condition of the solvent structure in such a transition state as being "in flight".) That third, dynamic factor has no analogue in the solvent isotope effect on an equilibrium constant,[39] and its value is expected[40] to be comparable to the ROD/ROH dielectric relaxation time ratio (~1.2 for undiluted L_2O and ~1.3 for undiluted MeOL).[41,42] Thus k_ψ^H/k_ψ^D in liquid ROL is expected, in general, to differ from k_1^H/k_1^D in dilute solutions of ROL as a result of the static and dynamic solvent effects expressed by the second and third factors in eq 11 and 12.

If the internal structure of the activated complex is very reactant-like ($\delta \approx 0$ in eq 5) as the dilute solution KIE's imply, then $\Delta\Delta\bar{G}^\circ_{Tr} \approx 0$ and the second factor in eq 11 and 12 will be near unity. If the first factor were strongly solvent-dependent, it would be expected to change gradually across the full range of solvent composition. Since the observed KIE remains constant when $X_{ROL} < 0.5$, that first factor can be assumed to be ap-

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proximately solvent-independent. In contrast, for the third factor (τ_D/τ_H, the isotopic ratio of rotational relaxation times for solvent in the neighborhood of the ROL, MeX reacting pair) to differ from unity, the cooperative participation of many ROL molecules is required. Thus the relatively narrow range of X_{ROL} within which most of the observed increase in KIE occurs marks the solvent composition at which the solvent structure around the reacting pair in the transition state changes from a relatively disordered mixture of ROL and MeCN into a structured network with relaxation properties similar to those of pure liquid ROL, and the observed magnitude of that increase in KIE is approximately equal to τ_D/τ_H.

This identification of the observed H_2O/D_2O solvent isotope effects on solvolyses in water with τ_D/τ_H is not new. It first was proposed in 1969 by Robertson and co-workers;[43] they based their proposal on the parallel temperature dependences of H_2O/D_2O solvolysis rate constant ratios and D_2O/H_2O viscosity and dielectric relaxation time ratios. Independent arguments, based on $pK_a(\ddagger)$ and its temperature dependence, that such hydrolyses have transition states with reactant-like internal structures and solvent reorganization as their reaction coordinates appeared soon after.[31b,44,45] However, acceptance of these conclusions has not yet become widespread. We regard the KIE's and their solvent dependences reported here as strong evidence that these conclusions are correct.

Possible Mechanisms. Two conclusions concerning the transition state structure for methyl transfers to L_2O have been derived above from the observed KIE's: there is little or no positive charge on the nucleophilic oxygen, and the surrounding solvent structure is in flight. The conventional S_N2 mechanism (eq 5), in which the reaction coordinate through the transition state is described in terms of bond-making and -breaking, could be consistent with the second conclusion, since these internal bonding changes could be coupled with solvent motion. However, that conventional S_N2 mechanism can *not* account for the first conclusion. These reactions have high barriers ($\Delta G^\ddagger$ in the range, ca. 20–25 kcal/mol) and, if no bonding or charge transfer between L_2O and CH_3X occurs prior to the transition state, what process consistent with that conventional mechanism could be responsible for that barrier? Formally, an ion-pair mechanism in which bond breaking runs far ahead of bond making so that the activated complex is very loosely bound, or "exploded" ($\delta'/\delta \gg 1$ in eq 5), could be consistent with this conclusion. However, convincing evidence from isotope effects,[46] $pK_a(\ddagger)$[44,31b] and other mechanistic probes[26,47] excludes transition states for transfer of methyl or primary aliphatic carbon in which appreciable charge is present on that carbon. If the barrier does not result from changes in internal charge distribution and/or bond orders, there are two other processes which must occur sometime during the transformation of reactant into product, and, in principle, either one could be responsible for the barrier: a change in solvation and an inversion of the transferred carbon. A mechanism in which either is rate-determining can be regarded as a kind of what Jencks[48] has christened an enforced preassociation mechanism but must be distinguished from the mechanism of that type which involves a carbocationic intermediate and which Jencks has discussed explicitly. The rate-determining process is a fluctuation in the structure of the reactant, either a fluctuation in its solvation or in its H–C–X bond angles, to form a transient species with high standard chemical potential. That transient species can relax back to its ground-state reactant structure or, if a preassociated L_2O molecule has the correct location and orientation, that L_2O can be captured by the CH_3X to produce $(L_2O^+CH_3, X^-)$ via a process which has little or no barrier. The rate-determining transition state thus lies at, or barely past, the end of the original structural fluctuation, and changes in O–C and C–X bonding occur after that transition state has been passed.

For three reasons, we choose the fluctuation in solvation as the more probable alternative. First, it has been concluded above that solvent structure in the transition state is in flight, and domination of the entire activation process by solvent motion is the simplest mechanism consistent with that finding. Second, if the activation process were predominantly a rehybridization with a coupled solvation change as a minor contribution, then it would be predominantly a motion of the methyl hydrogens, and if those hydrogens remained in flight along the reaction coordinate through the transition state, the CH_3/CD_3 KIE would have primary character and thus be larger (more normal) than α-D KIE's on alkyl transfers which follow the conventional mechanism. It has been observed[49-51] that coupling of C–H bending motion into a reaction coordinate for hydride transfer does introduce sufficient primary character into what is nominally a secondary D KIE to cause it to be larger than the corresponding equilibrium isotope effect. The corresponding anomaly has not been observed for α-D KIE's on alkyl transfers; all are smaller than the expected equilibrium isotope effect on formation of the alkyl cation.[46b] Moreover, α-D KIE's on methyl transfer to H_2O are among the smallest (most inverse) α-D KIE's known.[52,53] It is possible that some reduction of the H–C–X angles does occur during the activation process for $L_2O + CL_3X$; this could help make the α-D KIE inverse, but it appears that any α-hydrogenic motion which remains in the reaction coordinate through the transition state is no more than that in S_N2 reactions which proceed by the conventional mechanism.

Our third, and most compelling, reason for choosing to regard the activation process as entirely, or almost entirely, a solvation change is that a theoretical analysis based on a simple model for fluctuations of solvation away from equilibrium with the internal structure shows that such a mechanism not only is consistent with the experimental observations but would be particularly favored for alkyl transfer to L_2O.[1] Now consider that mechanism.

The Partly Coupled Mechanism. Uncoupled changes in bonding and in solvent structure occur on different time scales. An unconstrained methyl transfer event would occur on a vibrational time scale, while the cooperative rotational reorganization of the surrounding solvent structure from equilibrium solvation of reactant to equilibrium solvation of product has a much slower natural time scale. Different reactions will have different strengths of coupling between changes in internal structure and changes in solvation, and those differences can result in a range of mechanisms. In the limit of very strong coupling, the internal and solvent structures will be forced to change synchronously during a reaction event, resulting in a "coupled"[40] or "polarization caging"[38b] mechanism. In the opposite limit of very weak coupling, a three-step asynchronous "uncoupled" mechanism will result; solvent structure is free to fluctuate on its natural time scale; whenever that solvent structure becomes sufficiently product-like, the internal structure can jump from reactant to product on its more rapid time scale, and the solvation can then relax the rest of the way to equilibrium with the internal product structure. This uncoupled path is analogous to Marcus' mechanism[54] for outer-sphere electron transfer and is the "first uncoupled" mechanism previously described[40] for proton transfer.

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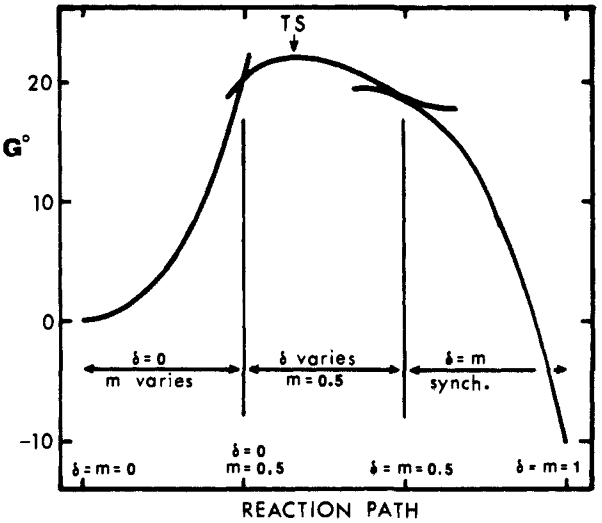

Figure 10. A possible $G°$ profile for the reaction of a preassociated ROH, MeX pair via the partly coupled mechanism. The reaction path is specified by two coordinates: δ (the charge on the nucleophilic oxygen) and m (the absolute value of Marcus' solvent polarization parameter). The profile is calculated as described in ref 1. At the transition state, the internal structure ($\delta = 0.17$) is much more reactant-like than the solvent polarization ($m = 0.5$).

In a methyl transfer to L_2O, the product pair ($L_2O^+CH_3,X^-$) contains the small, strongly hydrogen-bonding, cationic L_2O^+ moiety and thus will have much stronger coupling between its internal charge distribution and its solvent structure than does the much less polar reactant pair (L_2O,CH_3X). If this difference in coupling is sufficiently large, the internal charge distribution and the solvation will be constrained to change synchronously along the final part of the reaction path but will be free to change asynchronously along the initial reactant-like part of the path, resulting in a "partly-coupled" mechanism.

A free energy profile for such a partly-coupled mechanism is shown in Figure 10. This profile is based on our previously described model[1] for the coupling between changes in solvation and internal charge distribution for methyl transfers to L_2O. The model assumes that the coupling forces are electrostatic, uses the charge on the nucleophilic oxygen (δ) as the measure of internal structure, and uses the absolute value of Marcus' polarization parameter[55] (m) as the measure of solvent structure. Thus a reactant pair with equilibrated solvation has $m = \delta = 0$, and a product pair with equilibrated solvation has $m = \delta = 1$. The initial leg of the profile in Figure 10 is a fluctuation (increase) of m from $m = 0$ while δ remains constant at $\delta = 0$, and the transition state has a reactant-like internal structure with nonequilibrium ($m > \delta$) more product-like solvation.

The qualitative reason why the partly-coupled mechanism is favored for methyl transfer to water is more easily seen by considering the *reverse* of the transfer event ($L_2O^+CH_3$, $X^- \rightarrow L_2O,CH_3X$). As $L_2O^+CH_3,X^-$ (at $m = \delta = 1$) starts to react, the strong solvent–solute coupling requires solvent polarization and internal bonding to change synchronously (with $m = \delta$). At $m = \delta = 0.5$ in Figure 10, C–X bond-making and C–O bond-breaking have decreased the charges, and the solvent–solute coupling has consequently become sufficiently weak to allow asynchronous ($m \neq \delta$) changes in bonding and solvation. The intrinsically faster (vibrational time scale) bonding changes then can proceed to give the internal structure of L_2O,CH_3X ($\delta = 0$, $m = 0.5$) before the solvation finally relaxes (rotational time scale) to that proper for L_2O,CH_3X ($m = \delta = 0$).

The small curvature of the barrier along the second leg of the $G°$ profile results from its being a sum of two opposing contributions: as $\delta \rightarrow m$, the internal structure approaches equilibrium with the solvation (so that the contribution to $G°$ from solvent–solute interaction approaches the minimum in a well), and the O–C and C–X bonding approaches that present in the transition state for the hypothetical equilibrated mechanism[1] (so that this contribution to $G°$ approaches the maximum in a barrier). An expected result of this small curvature would be an enhanced sensitivity of the internal structure of the transition state to perturbations resulting from changes in substituents.[56,5] This could account for the increase in δ which was tentatively concluded above to result from replacement of one L in L_2O by Me or *t*-Bu. Transition states for methyl transfers to other nucleophiles (which presumably follow the traditional mechanism) appear to be quite implastic,[52,56] so that a large change in δ would not have been expected to result from such alkyl substituents. The direction of the change is that expected from steric hindrance of solvation by the alkyl group; this would destabilize more product-like (larger δ) internal structures and tend to shift the transition state parallel to the reaction coordinate toward that destabilization.[57] The transition state on the profile depicted in Figure 10 does not have its internal structure at the extreme reactant-like limit ($\delta \approx 0$) which the observed KIE's imply for L_2O; this results from the parabolic functional form assumed[1] for the hypothetical equilibrated barrier. That parabolic form was chosen for its simplicity, and the small curvature of the resulting barrier in the partly-coupled mechanism would allow a small deviation from the assumed equilibrated parabola to shift the maximum very close to $\delta = 0$.

Thus the partly-coupled mechanism is consistent both with theoretical expectation for a reaction which places charge on an L_2O moiety and with the observed dilute solution KIE's. It also can account for the observed transition to a larger KIE in the highly aqueous solvent mixtures. Qualitatively, the larger KIE results from the solvent structure being in flight along the first leg of the partly-coupled path. As the internal structure starts to change along the second leg, those aspects of solvent structure which are characteristic of the "in-flight" condition will relax, but their relaxation is not instantaneous; the τ_D/τ_H contribution to the KIE (eq 11 and 12) will still be present if the transition state lies at, or just slightly past, the transfer from the first (m changing) to the second (δ changing) leg. The absence of an increase in KIE as $X_{t\text{-BuOL}}$ increases from the reaction of *t*-BuOL with $MeOClO_3$ also fits this picture. Of the six methyl transfers studied, this one should have the weakest coupling and, therefore, should be the reaction most likely to follow the completely uncoupled path, for which no τ_D/τ_H factor contributes to the KIE.[40]

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