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Kinetics and Some Equilibria of Transacylation between Oxy Anions in Aprotic Solvents[1]

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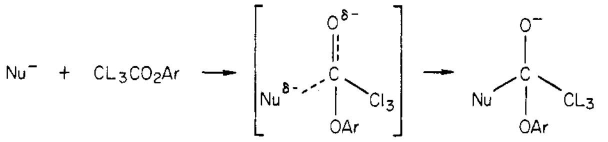
β-Deuterium isotope effects (β-DIE) determined in acetonitrile for the following reactions are: $CH_3COO^- + 4\text{-}NO_2C_6H_4O_2CCL_3$ (L = H, D) (PNPA-L_3), 0.958 ± 0.007 (5–45 °C); $CH_3COO^- + 2,4\text{-}(NO_2)_2C_6H_3O_2CCL_3$ (DNPA-L_3), 0.964 ± 0.011 (5–20 °C); OH^- + PNPA-L_3, 0.972 ± 0.028 (25 °C); $4\text{-}NO_2C_6H_4O^-$ (PNP^-) + $CL_3COOCOCL_3$, 1.00 ± 0.02 (20 °C); $4\text{-}NO\text{-}C_6H_4O^-$ ($PNOP^-$) + $CL_3COOCOCL_3$, 1.00 ± 0.03 (20 °C). β-DIEs in benzene for two of these reactions are: CH_3COO^- + PNPA-L_3, 0.957 ± 0.045 (10–20 °C); CH_3COO^- + DNPA-L_3, 0.985 ± 0.050 (5–10 °C). The fraction of tetrahedral character at the transition state (TS) deduced from β-DIEs for reactions of CH_3COO^- + PNPA is 0.32 in both CH_3CN and benzene, of CH_3COO^- + DNPA is 0.28 in CH_3CN and 0.12 in benzene, and of OH^- + PNPA is 0.21 in CH_3CN. These values are similar to what is found in water and indicate TSs of essentially trigonal geometry. Isotope effects ($k^{(CH_3)_2}/k^{(CD_3)_2}$) of unity for ester formation from $CL_3COOCOCL_3$ with phenoxides might be interpreted by two contributing factors to the observed effect; one of the usual hyperconjugation source and the other from electrostatic effect of the label in the departing CL_3COO^-. An equilibrium isotope effect ($K^{(CH_3)_2}/K^{(CD_3)_2}$) of 1.03 in the direction of ester formation is calculated. A Hammett correlation of reactions of substituted phenoxides with $CH_3COOCOCH_3$ in CH_3CN yielded $\rho = -2.54$. The reaction of CH_3COO^- in CH_3CN could not be effected with phenyl acetate. The reaction was endergonic ($\Delta G° = +2.59$ kcal/mol) with PNPA and exergonic ($\Delta G° = -7.61$ kcal/mol) with DNPA. Activation enthalpies of these reactions decrease from H_2O to CH_3CN to benzene, whereas activation entropies increase in this order.

Since the initial work of Bender,[2] β-deuterium secondary isotope effects have been employed in both nonenzymic and enzymic acyl-transfer reactions, as diagnostic probes, much to the analogy of nucleophilic substitution reactions at saturated carbon.[3] Considerable experience has accumulated in the use of this technique lately.[4] The appeal of investigating acyl-transfer transition-state (TS) structures by means of β-DIEs lies in the premise that the effect arises almost completely from changes in hyperconjugation of the electrons of the β-CH bonds into the carbonyl p orbital.[5] This results in a physical change in the β-CH force constants. For example, upon nucleophilic interaction at the carbonyl carbon (eq 1) hyperconjugation should decrease, thus increasing the force constant and resulting in an inverse isotope effect ($k_H < k_D$).[6,7] A reasonable estimate of the limit of "inverseness" may be made from equilibrium isotope effects on tetrahedral carbonyl-adduct formation. Such a limiting value, 0.87/CD_3, has been adopted from the equilibrium hydration of 1,3-dichloroacetone,[8] but very similar values are obtained from most comparable equilibria.[9,10]



(1)

TS TI

Indicators of reaction progress at the TS such as Brønsted correlations[11,12] and α-[13] and β-DIEs[14] for reac-

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[1] This research was supported by the National Institutes of Health through Grant No. 26006 from the National Institute of General Medical Sciences.

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[3] Hogg, J. L. In "Transition States in Biochemical Processes"; Gandour, R. D., Schowen, R. L., Eds.; Plenum Press: New York, 1978, Chapter 5.

[4] Shiner, V. J., Jr. In "Isotope Effects in Chemical Reactions"; Collins, C. J., Bowman, N. S., Eds.; Van Nostrand-Reinhold: Princeton, NJ, 1970; Chapter 2 and references therein.

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[8] Kovach, I. M.; Hogg, J. L.; Raben, T.; Halbert, K.; Rodgers, J.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 1991.

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[13] do Amaral, L.; Bastos, M. P.; Bull, H. C.; Ortiz, I. J.; Cordes, E. H. *J. Am. Chem. Soc.* **1979**, *101*, 169.

[14] (a) Kovach, I. M.; Elrod, J. P.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 7530. (b) The concept of the "virtual" transition state has been developed by R. L. Schowen in ref 3, Chapter 2 and applied in ref 8 and also in R. L. Stein *J. Org. Chem.* **1981**, *46*, 3328.

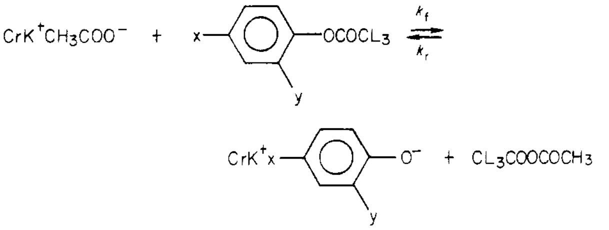
0022-3263/82/1947-2235$01.25/0

tions of some oxy anion nucleophiles such as alkoxide ions,[11,12,14] phenoxide ions,[13,14] and acetate ion[14] with aryl acetates have showed earlier TSs in protic solvents than would have been expected from a straightforward (and perhaps simplistic) application of ideas like Hammond's postulate. One explanation offered[11,12] is the manifestation in protic solvents of a "virtual"[14a] TS that comprises several contributing high-energy structures. These contributors may be, for example, the TSs of solvent reorganization processes and covalent-rearrangement processes. The anomalous temperature dependence of the β-DIE of reactions of esters with oxy anions in protic solvents can be explained similarly.[8]

To expose the bond breaking and formation step to closer scrutiny, one might study acyl transfer TSs in nonpolar or dipolar aprotic media, by means of β-DIEs. In aprotic media, solvent reorganization around reactant ion pairs and polar TSs is expected to be of a different nature and, presumably, energetically less costly. Relatively few attempts have been made[15,16] toward the investigation of acyl-transfer reactions in aprotic media and absolutely none with β-DIEs, in great contrast to the vast information about aqueous solutions. This trend could be rapidly reversed now. The difficulty of studies of ionic reactions in aprotic solvents have become greatly alleviated recently with the availability of macrocyclic polyethers[17,18] and other macrocycles[19] for solubilization of alkali salts of nucleophiles.

It may go without saying that the comparison of acyl-transfer TSs in aprotic media to enzymic acyl-transfer TSs arising at the active site of enzymes that contain hydrophobic regions[20] might be illuminating at worst and very useful at best. The benefits of understanding the role of the medium in assisting or inhibiting catalytic interactions are equally enormous in enzymic and organic acyl transfer.

Out of concern for the points raised above, β-DIEs of the reactions of aryl acetates with acetate ion in dry acetonitrile and 18-crown-6 were studied and reported recently.[21] The nucleophilic reaction of acetate ion in aprotic solvents proceeds with the reversible formation of acetic anhydride (eq 2). A study of the rates and β-DIEs of the forward and reverse reactions for the first time in any medium is reported here.



(2)

Results

Table I. Temperature Dependence of the Second-Order Rate Constants[a] and of the β-DIEs of PNPA-L_3 (L = H, D) with KOAc Solubilized with 18-Crown-6

temp, °C	k^{CH_3}, M^{-1} s^{-1}	k^{CD_3}, M^{-1} s^{-1}	k^{CH_3}/k^{CD_3}
	A. CH_3CN[b]		
5	0.02995 ± 0.00043	0.03121 ± 0.00089	0.960 ± 0.030
10	0.04847 ± 0.00089	0.05108 ± 0.00119	0.949 ± 0.028
15	0.07137 ± 0.00160	0.07575 ± 0.00162	0.951 ± 0.027
20	0.1137 ± 0.00062	0.1184 ± 0.0010	0.960 ± 0.010
20[c]	0.1128 ± 0.0019	0.1179 ± 0.0016	0.957 ± 0.020
25	0.1685 ± 0.0030	0.1753 ± 0.0039	0.957 ± 0.027
30	0.2567 ± 0.0039	0.2689 ± 0.0075	0.956 ± 0.030
35	0.3422 ± 0.0050	0.3585 ± 0.0086	0.955 ± 0.027
40	0.5339 ± 0.0158	0.5500 ± 0.0164	0.97 ± 0.04
45	0.6816 ± 0.0119	0.7070 ± 0.0143	0.964 ± 0.026
	B. Benzene[d]		
10	0.1500 ± 0.0034	0.1580 ± 0.0065	0.950 ± 0.045
20	0.0453 ± 0.0014	0.0469 ± 0.0018	0.964 ± 0.048

[a] Determined from initial rates (See Experimental Section). [b] Data in CH_3CN is taken from ref 21. [c] Determined with KOAc-d_3 in this study. [d] Values of the rate constants are subject to 20–30% systematic error due to uncertainties in the value of the molar absorptivity in benzene.

Table II. Temperature Dependence of the Second-Order Rate Constants[a] and of the β-DIEs for Reaction of DNPA-L_3 (L = H, D) with KOAc Solubilized with 18-Crown-6

temp, °C	k^{CH_3}, M^{-1} s^{-1}	k^{CD_3}, M^{-1} s^{-1}	k^{CH_3}/k^{CD_3}
	A. CH_3CN[b]		
5	45.33 ± 0.131	47.61 ± 1.007	0.952 ± 0.020
10	60.96 ± 1.175	62.78 ± 1.764	0.971 ± 0.022
15	87.46 ± 1.353	91.11 ± 1.234	0.960 ± 0.020
20	124.21 ± 2.86	127.8 ± 2.56	0.972 ± 0.030
	B. Benzene		
5	114.57 ± 4.33	117.00 ± 4.40	0.98 ± 0.05
10	138.87 ± 5.33	140.00 ± 5.00	0.99 ± 0.05

[a] Determined under pseudo-first-order conditions (See Experimental Section). [b] Data in CH_3CN taken from ref 21.

Table III. Activation Parameters

compd	solvent	$\Delta H^{\ddagger}$, kcal/mol	$\Delta S^{\ddagger}$, eu
PNPA	CH_3CN	13.29 ± 0.18	5.35 ± 0.11
DNPA	CH_3CN	10.38 ± 0.34	9.32 ± 0.33
DNPA[a]	benzene	5.49	19.4

[a] Calculated from two values.

Reaction of Potassium Acetate (KOAc) with Aryl Acetates. Second-order rate constants and β-DIEs on the acyl transfer from PNPA to acetate ion as a function of temperature in acetonitrile and in benzene are tabulated in Table I. Similar data for DNPA appear in Table II. The rapidity of the reactions and limited solubility of

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(20) Bender, M. L. *Bioorg. Chem.* **1978**, *1*, 19.

(21) Kovach, I. M. *Tetrahedron Lett.* **1980**, *21*, 4309.

Table IV. Second-Order Rate Constants for the Reaction of Acetic-L_6 Anhydride (L = H, D) with Potassium Salts of Substituted Phenols Solubilized with 18-Crown-6 in CH_3CN at 20 °C[a]

reagent	k^{CH_6}, $M^{-1}\,s^{-1}$	k^{CD_6}, $M^{-1}\,s^{-1}$	k^{CH_6}/k^{CD_6}
KDNP	2.5×10^{-4}[b]		
KPNP	9.84 ± 0.156[c]	9.82 ± 0.165[c]	1.00 ± 0.02[d]
KPNOP	58.00 ± 1.063[c]	58.05 ± 1.34[c]	1.00 ± 0.03[d]
HPFP	109.0 ± 5.1[b]		

[a] Measured rate constants were divided by two to correct for a twofold greater probability of acyl transfer from $CL_3COOCOCL_3$. [b] Calculated from slopes of k_{obsd} vs. [N] plots with four-five [N] concentrations. [c] Calculated from slopes of k_{obsd} vs. [N] plots with three [N] concentrations. [d] The same isotope effects are observed at each [N] with better precision [<±1.5%].

KOAc in benzene (even with a large excess of 18-crown-6) necessitated the use of dilute solutions. This circumstance and the volatility of benzene imposed limitations on the precision of the technique and on the range of temperature for feasible kinetic studies. Addition of water in 1–10-fold excess of KOAc retarded the rates as reported earlier[21] for PNPA and DNPA in acetonitrile. The activation parameters are given in Table III. Phenyl acetate did not react with solubilized KOAc in acetonitrile.

Reactions of Potassium Salts of Substituted Phenols with Acetic Anhdyride. Table IV exhibits the second-order rate constants and β-DIEs for the reactions of potassium salts of *p*-formylphenol (KPFP), of *p*-nitrosophenol (KPNOP), of *p*-nitrophenol (KPNP), and of 2,4-dinitrophenol (KDNP) with acetic-L_6 anhydride in acetonitrile at 20 °C.

Reaction of Potassium Hydroxide (KOH) with PNPA. Rates were measured in a 10^{-3} M solution of KOH in acetonitrile–18-crown-6 in 100% excess in the presence of perhaps as much as 3×10^{-3} M water. KOH is insoluble in acetonitrile under completely dry conditions even in 5-fold excess of 18-crown-6; however, finely ground, analytical grade KOH which contains 10% water gave a 10^{-3} M solution. The second-order rate constants for PNPA-H_3 and PNPA-D_3 at 25 °C were 8.511 ± 0.024 $M^{-1}\,s^{-1}$ and 8.759 ± 0.005 $M^{-1}\,s^{-1}$, respectively, which yields $k^{CH_3}/k^{CD_3} = 0.972 \pm 0.025$. All rates and the isotope effect are in excellent agreement with data measured in water.[14]

Relative Basicities of Potassium Phenolates and KOAc. The higher reactivity of KPNOP than that of KPNP toward acetic anhydride brought the need to measure relative basicities of the two phenolates in acetonitrile. Contrary to expectations, acetic acid was reported[22] to be a weaker acid than PNP in acetonitrile. It has also been mentioned[22] that most phenolate ions form homoconjugates and heteroconjugates with the conjugate acid (and, presumably, with other acids) in acetonitrile. For HPNP, the following homoconjugation scheme (eq 3) has been described:

$$2\mathrm{HPNP} + \mathrm{PNP}^- \xrightleftharpoons{K_2} [\mathrm{HPNP}]_2\mathrm{PNP}^- \qquad K_2 = 10^5\ \mathrm{M}^{-2} \tag{3}$$

Spectrometric measurements of the equilibria in acetonitrile, thus, were complicated by the task of determining concentrations of three absorbing species simultaneously. Since the homoconjugate could be produced only in the presence of the phenol and not in total absence of phenolate ion (a very good chromophor), its molar absorptivity could not be determined precisely. $K_2 \sim 10^6\ M^{-2}$ was measured under these circumstances. After correcting for the homoconjugation equilibrium by $K_2 = 10^6$, we measured K_{eq} described in eq 4 to be 0.05 in dilute solutions (lit.[22] value = 0.025). However, the value of K_{eq} rose with

$$K_{eq} = [\mathrm{HPNP}][\mathrm{CH_3COO^-}]/[\mathrm{PNP^-}][\mathrm{CH_3COOH}] \tag{4}$$

increasing reactant concentrations, indicating the occurrence of other equilibria for conjugation of PNP^- with acetic acid or HPNP, in other proportion of acid to base than 2:1.

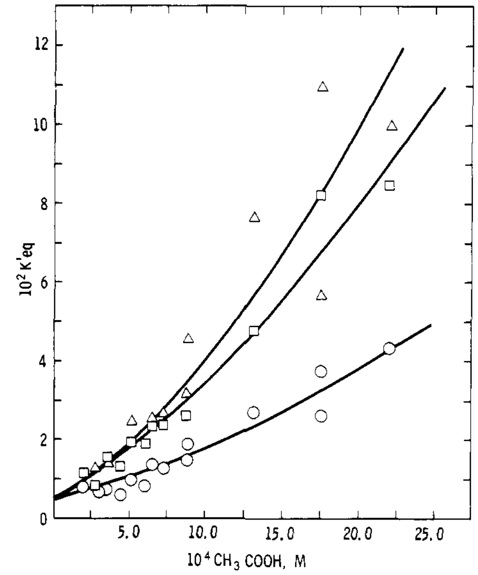

Figure 1. Dependence of the apparent equilibrium constant (K'_{eq}) between KPNOP and CH_3COOH in CH_3CN on the concentration of CH_3COOH at 20 °C: (△) 411 nm, (□) 400 nm, (○) 380 nm.

To avoid the interference of such unknown equilibria, we determined K_{eq} for KPNOP by extrapolation to zero acetic acid concentration of a plot of apparent K'_{eq} values in their dependence on acetic acid concentration. Figure 1 shows that apparent K'_{eq} values measured at three different wavelengths depend on acetic acid concentration in a parabolic fashion and deviate from the true value of K_{eq} to the extent of the absorbance of the homoconjugate contributes to the absorbance and reduces the absorbance of the anion and the phenol at a particular wavelength. All three curves intersect the *y* axis at zero acetic acid concentration, at 5×10^{-3}, which, in the light of what is known about the other substituted phenols and acetic acid in acetonitrile, seems to be a very reasonable value for this equilibrium.

Discussion

Acyl Transfer from Aryl Acetates to Acetate Ion and Hydroxide Ion in Aprotic Solvents. The most salient features of the results here are pointed out through a comparison of rates and β-DIEs of a particular reaction in the aprotic solvent to those of the same reaction in water. Table V provides such a comparative overview along with a measure of reaction progress ($\hat{I}$) at the TS given in the last column. In a previous paper,[14] the idea of a measure of the structure of the TS as a quantity that lies between zero and unity to give the fractional progress toward a TI at the TS has been developed. β-DIEs yield such a measure of reaction progress at the TS, $\hat{I}$, when related to the equilibrium isotope effet, K^H/K^D, for the complete formation of a tetrahedral adduct (eq 5). Model

$$k^H/k^D = (K^H/K^D)^{\hat{I}} \tag{5}$$

calculations[24] suggest that $\hat{I}$, so derived, is closely reated

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[22] Kolthoff, I. M.; Chantooni, M. K., Jr.; Bhowmik, S. *J. Am. Chem. Soc.* **1968**, *90*, 23.

Table V. Comparison of Rates and β-DIEs in CH_3CN, Benzene, and H_2O

solvent	system	$\frac{k_2(\text{solv})}{k_2(H_2O)}$	β-DIEs	temp range, °C	$\hat{I}^a$
CH_3CN	KOAc + PNPA	2.7×10^4	0.958 ± 0.007	5-45	0.32
CH_3CN	KOAc + DNPA	2.7×10^5	0.964 ± 0.011	5-20	0.28
CH_3CN	KOH + PNPA	1	0.972 ± 0.028	25	0.21
benzene	KOAc + PNPA	2.7×10^4	0.957 ± 0.045	10-20	0.32
benzene	KOAc + DNPA	6.0×10^5	0.985 ± 0.050	5-10	0.12
H_2O^b	KOAc + DNPA	1	0.950 ± 0.009	25	0.37

^{a} $I = \log(k^H/k^D)/\log 0.87$. ^{b} Reference 14.

to the normalized reaction variable giving the fractional change of the force constants at the β-hydrogenic sites on the carbon adjacent to the carbonyl group. Thus, values of β-DIEs are normalized by 0.87 ± 0.04[25] for CD_3 from the β-DIE of the equilibrium hydration of $ClCL_2COCL_2Cl$ (0.83 ± 0.02)[8] and with the assumptions[14] given earlier.

Impressive rate acceleration is observed in aprotic solvents, which is attributed to the liberation from intervening hydrogen-bonding solvent, of ionic and polar reactants and TSs. Despite of this difference, TSs of all these acyl-transfer reactions as reflected in β-DIEs show more nearly trigonal than tetrahedral character regardless of the protic/aprotic nature of the solvent. The indicator of the fraction of reaction progress is 0.28–0.32 in acetonitrile and 0.12–0.32 in benzene with KOAc in comparison to 0.37 in water. Neither the rate nor the extent of reaction progress at the TS seems to be influenced by alteration of the bulk medium of the reaction of solvated[26] (it is the most unlikely that more than three water molecules, which can be accommodated in the first solvate shell, were present per hydroxide ion) hydroxide ion with PNPA. Hydroxide ion apparently exists mostly in the same hydrogen-bonded primary solvate shell of water in acetonitrile as in bulk water. Surprisingly, regardless of the difference in the more distant environment, the energy requirement for removal of all or at least one molecule of solvate water in order to have contact occur between the nucleophile and substrate seems to remain the same.

In protic solvents, all β-DIEs measured for nucleophilic reactions of oxy anions, such as hydroxide,[13] methoxide,[8] phenoxide,[14] and acetate[14] ions with aryl acetates studied are less inverse than anticipated for TSs that resemble the tetrahedral intermediate. Instead, the fractions of reaction progress are 0.15–0.2, ~0.2, 0.2–0.4, and 0.37, respectively. These estimates come alike from both β-DIEs and α-DIEs for reactions of the same nucleophiles with aryl formates.[13] A Brønsted plot[11,12] of the reaction of aryl acetates with oxy anions resulted in β_{nuc} values of 0.2 for strong bases ($pK > 12$) and 0.7 for weak bases ($pK = 8$–11), mostly supporting the conclusions from isotope effects. The lower value (0.2) than that for weaker bases was explained by ground-state solvation effects.[12] Lately, it has also been suggested,[14] however, that 0.7 might be too large due to losses of resonance energy in the TS. Thus, the nature and extent of the involvement of solvent reorganization in the reaction coordinate dynamics are not answered by studies in water alone.

Notice is made of the apparent trigonal character of the TSs to be more reactant and/or productlike than adductlike in disagreement with Hammond's postulate. Moreover, it seems likely that all reactions in Table V go through early TSs with carbonyl bond order ~1.6–1.8, since even acetate ion shows greater basicity than the substituted phenol leaving groups in CH_3CN and, perhaps, similarly in benzene, contrary to water. This reversed relative basicity in CH_3CN, shown in Table VI, had been reported earlier[22] and has also been confirmed in this study for HPNP and HPNOP. In Table V, the only partial exception is the reaction of DNPA with acetate ion in water, which may constitute a precedent of a symmetrical TS in as much as the pK_a values of attacking and leaving groups are nearly identical in water.

Table VI. pK_a Values of Substituted Phenols and Acetic Acid in H_2O and in CH_3CN

reagent	pK_a H_2O^a	pK_a CH_3CN
PFP	7.60	
PNP	7.20	20.70[22]
PNOP	6.70	20.00
2,4-DNP	4.11	16.00[22]
CH_3COOH	4.70	22.30[21]

^{a} From ref 27.

Whether or not the rate-determining step is the same in the different solvents, perturbation of the medium does not affect the geometric character of the TS. Therefore, requirements for desolvation of the nucleophile, unique to protic solvents are unlikely causes for structural features of the TS. For interpretations of anomalous temperature dependence of β-DIEs[8] and of anomalous structure–reactivity behavior,[12] the concept of a "virtual"[14a] TS being observed in these experiments was raised. This is an argument for partial rate-determining solvent reorganization that has a normal isotope effect contribution to cancel out partially the inverse effect arising from covalent rearrangements. The near equality of β-DIEs in different environments would necessitate the conclusion that such solvent reorganization bears the same isotope effect component in a broad variety of systems from water through CH_3CN to benzene. Such commonality among these solvents is not persuasive and could only be attributed to fortuitous circumstances.

It is the *most consistent* with all results reported here to propose that generation of unsolvated ionic reactants or leaving groups perhaps in a common solvent cage with the trigonal aromatic ester, as high-energy precursors, precedes and succeeds covalent rearrangement in all cases. These unstable ionic precursors may lie *above* the tetrahedral aromatic adduct in energy in the same way in *all* solvents. Then the difficulty in forming these from solvated reactants is expected to be dependent on the strength of the specific solute–solvent interaction and be reflected in rates, while at the TSs, structural characteristics of the trigonal electrophile (or product) would be preserved in the high-energy, desolvated complexes regardless of what the components of the encasing solvent cage may be. The pictorial representation in Scheme I might be envisioned, with AB and CD representing the

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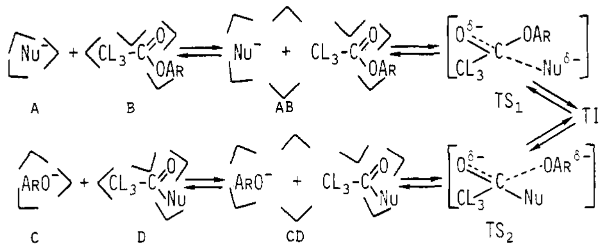
(24) Hogg, J. L.; Rodgers, J.; Kovach, I. M.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 79.

(25) Medium effect on the β-DIE of tetrahedral adduct formation equilibrium can be assumed to be negligible. References 8 and 9 substantiate this claim.

Scheme I



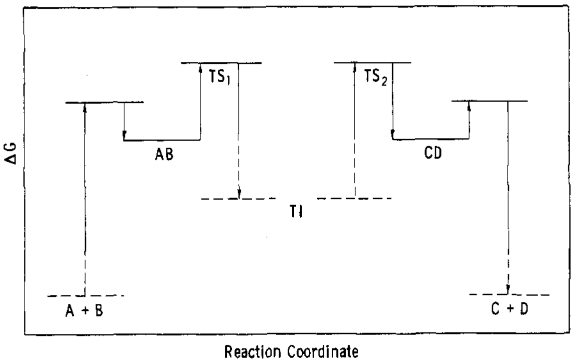


Figure 2. Free-energy profile with A + B, C + D, and TI at different energy levels in different solvents for a reaction outlined in Scheme I.

“naked” ions in a common solvent cage with the trigonal reactant or product, respectively. Figure 2 gives the corresponding free-energy profile.

β-DIEs of the reactions of acetate ion with PNPA and DNPA in the two solvents and in the indicated temperature range were indistinguishable within experimental error (Table I, II, and V) as expected from only zero-point energy changes. The change in activation parameters in increasingly aprotic solvents is in the direction of reduced $\Delta G^{\ddagger}$ and $\Delta H^{\ddagger}$ and increased $\Delta S^{\ddagger}$ values. One may consider the values $\Delta H^{\ddagger} = 15.7$ kcal and $\Delta S^{\ddagger} = -28.7$ kcal reported[28] for PNPA and acetate ion in water for comparison. It has to be remembered, however, that the nucleophilic reaction of acetate ion in water contributes only 50% to the rate; the other 50% is accountable from general-base catalysis by acetate ion.[29] The more conspicuous change occurs in $\Delta S^{\ddagger}$ that reaches sizable positive values in aprotic solvents. Even if one disregards a large part of the negative entropy that is associated with aqueous solvent reorganization, only the cost of bringing two reactants together is expected to be at least ~−8 eu.[30] At least two models might be discernible in concurrence with the positive activation entropy in aprotic solvents. (a) It can stem from both more dissociated ion pairs at the TS than at the reactant state and yet some solvent release upon bringing the two polar reactants into the vicinity of one another for stronger anionic (nucleophilic) interactions with the electrophilic carbonyl center. (b) The alternative situation is a large solvent release at the TS if, for example, a tighter ion pair were formed. Both propositions, especially the first one, would be reconciliable with a decrease in activation enthalpy between reactions in acetonitrile and benzene if the enthalpy cost of breaking solute–solvent interactions was made up for, more in benzene than in acetonitrile, by a vanishing difference in internal enthalpy between “naked” ionic reactants and TSs. Should the TI become stabilized in the aprotic solvents relative to the “naked” ionic precursor, the TS would be earlier and more trigonal as the covalent rearrangement step in Figure 2 becomes more exergonic, the internal activation enthalpy would become smaller, and the internal entropy would increase as the forming bond becomes longer.

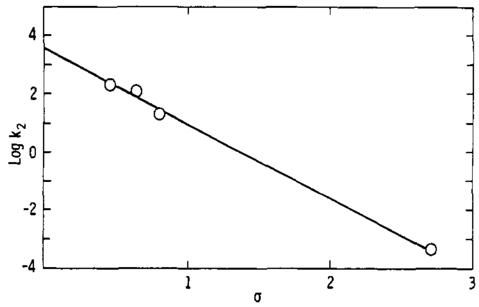


Figure 3. Hammett correlation for the reaction of acetic anhydride with substituted phenols in CH_3CN.

Reactions of Potassium Salts of Phenols with Acetic Anhydride in Acetonitrile. Since these reactions have not been studied in any solvent yet, they are of special interest. β-DIEs of reactions of both KPNP and KPNOP and KPNOP with acetic-L_6 anhydride were found to be unity within experimental error, in contrast to the ~0.96 value observed for the forward reaction between PNPA and KOAc. This inevitably gives an equilibrium β-DIE of 0.96 in the direction of anhydride formation and 1.04 in the direction of ester formation, which is not readily justified. Relevant to an interpretation of this strange finding is the equilibrium β-DIE of 1.03 observed[31] for acetic acid ionization in water. To account for this effect, differences in isotopically sensitive frequencies observed in species like CH_3F and CD_3F[32] were used[31] in terms of charge–dipole interactions. The average dipole moment was deduced to be smaller for CD than for CH, which is resultant of a nonlinear variation of the dipole moment with internuclear distance and of anharmonicity of the CH bonds.[33] We may consider a TS of our reactions, represented by TS_1, which follows from earlier arguments for an early TS in the direction of anhydride formation, i.e., a late TS for ester formation. The effect of label, H or D, in the approaching or leaving acetate ion through this electrostatic effect manifested in slightly enhanced leaving tendency of the H-labeled acetate over the D-labeled one seems probable. Thus the apparent effects on k_r, the rate constant for ester formation, can be a composite of two ingredients, k_r^{β} for the β-DIE and k_r^{ϵ}, for the electrostatic effect, whereas the β-DIE in the direction of anhydride formation has only the β-effect component (k_f^{β}). The electrostatic effect on the later reaction (k_f^{ϵ}) was also determined by studying rates of the reactions of PNPA and KOAc-L_3 at 20 °C (Table I), which yielded $k_f^{\epsilon} = 1.008 \pm 0.018$. The secondary isotope effect on the equilibrium formation of ester

$$K^{(\mathrm{CH_3})_2}/K^{(\mathrm{CD_3})_2} = K^{\beta}K^{\epsilon} = (k_r^{\beta}k_r^{\epsilon})/(k_f^{\beta}k_f^{\epsilon}) = 1.000/(0.96 \times 1.008)$$

is then 1.03. It is certainly tempting to attribute this value to an electrostatic contribution (K^{ϵ}); however, one cannot exclude the possibility of an anomaly, such as a breakdown

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Table VII. Equilibrium Constants for the Formation of Acetic Anhydride from Aryl Acetates and KOAc in CH_3CN at 20 °C and Ratios of Equilibrium and Rate Constants for DNPA/PNPA

		ratios of constants for DNPA/PNPA		
compd	K	K	k_f	k_r
DNPA	4.97×10^5	4.30×10^7	1.1×10^3	2.54×10^{-5}
PNPA	1.155×10^{-2}			

of the rule of geometric means, occurring in β-DIEs (K^β).

A Brønsted correlation of the log of the second-order rate constants for the reactions of three potassium phenolates with acetic anhydride from Table IV[34] vs. the pK_a values in acetonitrile as given in Table VI yielded β_{nuc} value of ~1.0. A seemingly more precise correlation is obtained (Figure 3) for all the four phenolates[35] with σ_p values, $\rho = -2.54$ (±0.08), and a fair correlation with σ_p^- values, $\rho^- = -3.31$ (±0.51). These, on the other hand, might be compared to analogous Hammett correlations of the log K_b values of substituted phenolates in acetonitrile. Such calculation from the data in Table VI and appropriate values for phenol gave $\rho = -3.38$ (±0.96) with σ_p substituent constants and $\rho = -3.93$ (±0.27) with σ_p^- substituent constants. Using these values, we calculated β_{nuc} values of 0.75 (2.54/3.38) and 0.84 (3.31/3.93). A $\beta_{nuc} = 0.75$–1.00 is exactly the range where β_{nuc} values were observed for rate-determining breakdown of the tetrahedral intermediate in the reactions of aryl acetates with oxy anions[11] and in the reaction of substituted pyridines with acetic anhydride.[36] The acetyl moiety of acetic anhydride and other acetyl derivatives demonstrated greater sensitivity toward polar effects in the nucleophiles than the proton, which was indicated by $\beta_{nuc} = 1.6$ measured for complete transfer of an acetyl group between oxygen and nitrogen nucleophiles.[30,36] Therefore, a β_{nuc} value of ~0.75–1.00 would correspond to a charge loss of 0.5–0.63 ($\bar{I} \sim 0.5$–0.63) on the phenoxide ion at the TS. This again is consistent with a structure like TS_1, proposed earlier for the rate-limiting step of the reversible reaction (or with a late TS with extensive bond formation of a synchronous S_N2 displacement).

The larger (negative) values of ρ in acetonitrile than those for corresponding ionic equilibria (~2.0) and for rates (~1.5–1.8)[30] in water may arise from two major factors; a greater susceptibility of the reaction center to change in charge density and the low dielectric constant, i.e., the consequent low ion solvating power of acetonitrile.[37,38]

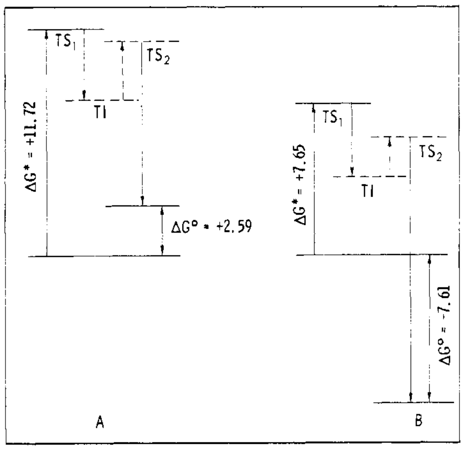

Figure 4. Free-energy profile for the equilibrium formation of acetic anhydride from KOAc and (A) PNPA and (B) DNPA in CH_3CN at 20 °C.

Equilibria in Acetonitrile. Equilibrium constants for the formation of acetic anhydride from PNPA and DNPA in acetonitrile at 20 °C were calculated from the second-order rate constants for the forward (k_f) and reverse (k_r) reactions, as shown in Table VII. Ratios of the equilibrium constants and rate constants are also shown. Anhydride formation was not observable from phenyl acetate but was endergonic ($\Delta G° = +2.59$ kcal/mol) from PNPA and very exergonic ($\Delta G° = -7.61$ kcal/mol) from DNPA. Comparable ester hydrolysis equilibria in water yield relative values of the equilibrium constants (K_X/K_H): 1:60:6000 for (X = Y = H)/(X = NO_2, Y = H)/(X = Y = NO_2). The much more pronounced substituent effect on these equilibria in acetonitrile than in water is ostensible, although it might have been expected to some extent since removal of strongly interacting solvent from polar substituents and from reaction centers should promote inductive and resonance interactions. Free-energy changes for the reactions and for overall equilibria, calculated from the data, are portrayed in Figure 4.

Summary. The resemblance of the TSs of the reaction of aryl esters with oxy anions in aprotic solvents to those in water is a *new feature* of the acyl-transfer process. Earlier notions of solvent reorganization involved in limiting the rate do not adequately explain this finding; however, a proposition for the *transient* existence of *high-energy* precursors in a solvent cage formed on stripping off solvent from electrophiles and nucleophiles, which then form the tetrahedral intermediate in a rate-determining covalent rearrangement step, is consistent with activation parameters and with commonality of the TSs in all solvents. β-DIEs on the reaction of acetate ion and aryl esters in acetonitrile are temperature independent.

β-DIEs on the reverse reaction between acetic anhydride (L_6) and potassium phenolates are unity, apparently due to opposing trends at the TS, between rehydridization and an "electrostatic" differentiation of the leaving tendencies of H and D labeled acetate ion. Rates and the equilibrium for formation of acetic anhydride from aromatic esters in acetonitrile exhibit a much higher sensitivity to substituents in the phenolates than the respective hydrolysis equilibrium.

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(34) Interestingly enough, while the order of basicity among the phenolates does not change from water to acetonitrile, there is an inversed nucleophilicity of KPNP and KPNOP, for example, in acetonitrile. A differential solvation by acetonitrile of the delocalized negative charge of the phenolates in the ground state could favor the more dispersed negative charge (Parker, A. J. *Chem. Rev.* **1969**, *69*, 1) on the *p*-nitro derivative than on the *p*-nitroso derivative. This would result in an increase in the activation free energy of the former vs. the latter if solvation of the higher charge density at the TSs were about equal.

(35) Acquisition of additional points between that for KPNP and that for KDNP is very difficult due to the rareness of phenols with nucleophilicity in this range. The σ_p and σ_p^- values were taken from Exner, O. In "Correlation Analysis in Chemistry"; Chapman, N. B., Shorter, J., Eds.; Plenum Press: New York, 1978; Chapter 10, Table 10.1, except for the value for the 2,4-dinitro substituent. This latter value (2.7) was estimated from the plot of log (K/K_0) for ionization of phenols vs. log (K/K_0) for ionization of benzoic acids from Taft, R. W., Jr.; Lewis, I. C. *J. Am. Chem. Soc.* **1958**, *80*, 2436. (It could not be generated in any inequivocal manner.) Given the circumstance and the lack of such information on anhydrides, this correlation, although limited, might be considered a worthwhile preliminary assessment of substituent effects in the action of phenolate ions on acetate anhydride in aprotic media.

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Experimental Section

Materials. Reagents were all reagent grade materials and were dried before use. KOAc was recrystallized from absolute methanol. The purification of 18-crown-6 and CH_3CN was reported earlier.[20] Benzene was distilled from sodium ribbons and stored over 3-Å molecular sieves. Acetic acid was dried by shaking it with P_2O_5 for 30 min prior to distillation from P_2O_5. Acetic anhydride was dried over sodium ribbons for several days followed by drying it over magnesium turnings for days and then it was refluxed and distilled. Acetic-d_6 anhydride was purchased from Aldrich (99% D) and was used without purification.

Syntheses. Ester substrates of this study in protiated and deuterated forms (>99.5% labeled) were prepared from the appropriate purified phenol and acetyl-L_3 chloride as previously described.[8,14] Potassium salts of the substituted phenols were prepared from the appropriate pure phenol and potassium hydroxide in methanol. They were recrystallized from hot methanol and/or acetone 2–3 times. KOAc–d_3 was prepared similarly from acetic-d_6 anhydride via hydrolysis with potassium hydroxide in slightly aqueous methanol. The salt was forced out of solution with acetone and ethyl ether. All potassium salts of oxy anions were then dried over $CaSO_4$ at 80–100 °C (0.5 mm) for 2–3 days and characterized by melting point, elemental analysis, and acid titrations in some cases. All reagents and substrates were stored over P_2O_5 under vacuum.

Kinetics and Equilibria. Solutions of potassium salts of oxy anions were prepared with an excess of 18-crown-6 in 40% over KOAc and potassium phenolates in CH_3CN, 100% over KOH in CH_3CN, and 100% over KOAc in benzene.[36] All solutions were made in predried glassware, and stored in desiccators in 0.02–0.08 M concentration, and all transfers were made in airtight syringes. Dilutions were made daily. Solutions for kinetic studies: KOAc was used in $\sim 3 \times 10^{-3}$ concentration in CH_3CN and in $\sim 2 \times 10^{-3}$ M in benzene. Potassium salts of phenoxides were used in $2–5 \times 10^{-3}$ M concentration except for KDNP that was used in 5×10^{-5} M with acetic anhydride in 10^3-fold excess. Other substrates were employed in $2–5 \times 10^{-5}$ M in pseudo-first-order processes and 5×10^{-4} M PNPA-L_3 was used for initial rates. The very rapid opposing reaction in case of PNPA-L_3 with KOAc necessitated the determination of rates under zero-order conditions, below 2% completion of the reactions.

Equilibria between acetic acid and KPNP or KPNOP were studied in $1–2 \times 10^{-4}$ M solutions of the phenolate with a series of 6–14 concentrations of acetic acid ($1–30 \times 10^{-4}$ M) in acetonitrile. The homoconjugation constant (K_2) for KPNP was estimated from dilutions of a solution of KPNP 10^{-4} M and HPNP 0.5×10^{-4} M.

The details of spectrophotometric measurements are given in Table VIII for kinetics and equilibria. Automated data acquisition with a Cary 118 microprocessor system[14] or a Cary 16–Hewlett-Packard minicomputer system[14] was employed for rate determinations from 200–1000 data points. Temperature control was maintained from a Lauda K4/RD circulating bath connected to the cuvette holder in the cell compartment. Temperatures were monitored by a digital thermometer and electronic recording with a thermistor probe.

Acetonitrile or benzene solutions of 18-crown-6 did not give any absorbance change when any of the substrates was added.

Table VIII. Experimental Details

reactions in benzene	λ_{max}	ϵ_λ
PNPA + KOAc	419	22970 ± 290[a]
DNPA + KOAc	360	

reactions in CH_3CN	λ
KPFP + $(CH_3CO)_2O$	265 (min)
KPNOP + $(CH_3CO)_2O$	278 (max)
KPNP + $(CH_3CO)_2O$	270 (sh)
KDNP + $(CH_3CO)_2O$	330 (sh)

equilibria in CH_3CN	λ	ϵ_λ	
		anion	phenol
KPNP + CH_3COOH	427 (max)	32110 ± 150	1.68 ± 0.05
	400 (sh)	16620 ± 40.64	33.63 ± 0.15
	380 (sh)	5334 ± 1.36	221.5 ± 0.89
KPNOP + CH_3COOH	411 (max)	29242 ± 340	
	400 (sh)	26458 ± 222	
	380 (sh)	13254 ± 101	

[a] This value may be 20–30% low due to the difficulties in obtaining stable absorbance readings in dilute basic solutions of phenoxides in benzene.

First-order-rate constants were obtained by weighted nonlinear least-squares analysis of absorbance data. Second-order rate constants were calculated from the slope of k_{obsd} vs. nucleophile concentration $[N^-]$ with the exception of very rapid reactions of DNPA with KOAc where 10–15 measurements of k_{obsd} were averaged at a low concentration of KOAc and divided by [KOAc]. Initial rates (dA/dt) were evaluated by a linear least-squares fit of absorbance vs. time. The second-order rate constant was then calculated by

$$k = (dA/dt)/[E_0][\text{KOAc}]\Delta\epsilon_h$$

where E_0 is the initial substrate concentration and $\Delta\epsilon_h$ is the difference in molar absorptivity between product and reactant at a particular wavelength.

Protiated and deuterated substrates were measured in alteration in all kinetic studies.

Acknowledgment. The most generous support of facilities and extremely stimulating discussions that have improved this paper are acknowledged with gratitude to Professor Richard L. Schowen.

Registry No. PNPA-H_3, 830-03-5; PNPA-D_3, 81408-98-2; DNPA-H_3, 4232-27-3; DNPA-D_3, 81408-99-3; KDNP, 14314-69-3; KPNP, 1124-31-8; KPNOP, 81409-00-9; KPFP, 58765-11-0; PNOP, 104-91-6; $CH_3COOCOCH_3$, 108-24-7; $CD_3COOCOCD_3$, 16649-49-3; AcO^-, 71-50-1; OH^-, 14280-30-9.