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Reaction Progress at the Transition State for Nucleophilic Attack on Esters[1]

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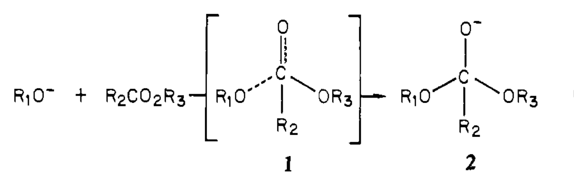
Abstract: β-Deuterium isotope effects (k_{CH_3}/k_{CD_3}) at 25 °C in aqueous solution for reaction of the following nucleophiles and substrate acetate esters are as follows: $CH_3CO_2^-$, 2,4-$(NO_2)_2C_6H_3O_2CCL_3$ (L = H, D), 0.950 ± 0.008; $C_6H_5O^-$, 4-$NO_2C_6H_4O_2CCL_3$, 0.971 ± 0.020; $C_6H_5O^-$, 2,4-$(NO_2)_2C_6H_4O_2CCL_3$, 0.968 ± 0.009; HO^-, 4-$NO_2C_6H_4O_2CCl_3$, 0.970 ± 0.009; HO^-, $C_6H_5O_2CCL_3$, 0.980 ± 0.009. These are consistent with fractions of reactant progress at the transition state of 0.37, 0.21, 0.22, 0.22, and 0.15, respectively. Agreement is reasonably good with fractions of reaction progress estimated from α-deuterium isotope effects in formate ester reactions, measured by Cordes et al. For the nucleophilic reaction of water with $C_6H_5O_2CCL_3$, protolytically catalyzed by $CH_3CO_2^-$, the β-D effect is 0.914 ± 0.023 (fraction of reaction progress 0.65). This corresponds well with fractions of reaction progress of 0.58–0.66 from α-D effects for carboxylate general catalysis of three formate ester hydrolyses, studied by Cordes et al. For very strong bases ($pK > 12$) reacting as nucleophiles, the value of β_{nuc} ($\sim$0.2) is similar to, or smaller than, the fraction of reaction progress estimated from the isotope effects ($\sim$0.2–0.4). The value of β_{nuc} for nucleophilic reactions of weaker bases ($pK \approx 8$–11) is larger than the fractions of reaction progress calculated from isotope effects (0.2–0.4 while $\beta_{nuc} \approx 0.7$). This evidence is consistent with negative deviations both for aryloxide ions and for strongly basic nucleophiles such as alkoxide and hydroxide ions from a hypothetical line of β_{nuc} greater than 0.2 but smaller than 0.7. The major reason for negative deviation of aryloxide ions is probably disproportionate loss of resonance energy and of alkoxide ions is disproportionate loss of solvation energy, upon nucleophilic binding at the transition state. These two factors may be linked and may not be entirely separable.

In the attack of a nucleophile at ester carbonyl (eq 1), the



(1)

transition state **1** can be thought of as a structure intermediate in character between the reactants and the tetrahedral adduct **2**. A naive measure of the structure of the transition state is then a quantity $\hat{\xi}$, expected to lie between zero and unity and to give the fractional progress toward **2** at the transition state.[2] In simple cases, a value of $\hat{\xi}$ might be estimated experimentally. For example, Jencks, Gilchrist, and Hupe[3-5] have determined structure-reactivity slopes β_{nuc} (eq 2). If divided by β_{nuc} for complete

$$\log k_{R_1O^-} = \beta_{nuc} pK_{R_1OH} + \text{constant} \qquad (2)$$

formation of **2**, these quantities would be normalized to $\hat{\beta}_{nuc}$ and might be hoped to estimate $\hat{\xi}$. Similarly, do Amaral, Bastos, Bull, Ortiz, and Cordes[6] have obtained α-hydrogen secondary isotope effects (k_H/k_D for R_2 = H and D in eq 1), which might be related by eq 3 to the equilibrium isotope effect K_H/K_D for complete

$$(k_H/k_D) = (K_H/K_D)^{\hat{I}} \qquad (3)$$

formation of **2**. In eq 3, $\hat{I}$ is a quantity which should vary between zero (when **1** strongly resembles the reactants) and unity (when **1** strongly resembles the adduct **2**). For α-D isotope effects, we label this quantity $\hat{I}_{\alpha L}$. In this paper, we report β-hydrogen secondary isotope effects (for $R_2 = CH_3$ and CD_3 in eq 1). These also yield, from eq 3, a value of $\hat{I}$ which can be denoted $\hat{I}_{\beta L}$. This should also vary from zero to one with reaction progress at the transition state.

Of course, these three quantities ($\hat{\beta}_{nuc}$, $\hat{I}_{\alpha L}$, and $\hat{I}_{\beta L}$) measure progress toward **2** in different aspects, because they arise from different structural characteristics of transition state **1**. Thus $\hat{\beta}_{nuc}$ might be expected to measure the fraction by which the electrical charge in R_1O^- has been reduced toward its value in **2**. This fractional charge alteration is a molecular property of the transition state and can be considered a *normalized reaction variable*[2] $\hat{Q}_1$. The value of $\hat{I}_{\alpha L}$, in turn, is expected[7] to measure the fractional alteration in **1** of the force constants binding the α-hydrogen atom. The corresponding normalized reaction variable is $\hat{F}_\alpha$. Quite similarly, $\hat{I}_{\beta L}$ should[7] be related to $\hat{F}_\beta$, the normalized reaction variable giving the fractional alteration of the force constants at the β-hydrogenic sites, on the carbon adjacent to the carbonyl group.

The normalized reaction variables $\hat{Q}_1$, $\hat{F}_\alpha$, and $\hat{F}_\beta$ themselves are not expected to be equal to each other in general.[2] Only in the unusual circumstance that charge alteration in the R_1O moiety and force-constant alterations at both α-L and β-L sites are precisely coupled to one another should an equality of $\hat{Q}_1$, $\hat{F}_\alpha$, and $\hat{F}_\beta$ arise. Even if this were so, the derived quantities $\hat{\beta}_{nuc}$, $\hat{I}_{\alpha L}$, and $\hat{I}_{\beta L}$ would be equal to each other only if they were equal to the corresponding normalized reaction variables throughout their respective ranges. Here there is cause for optimism. Model calculations[7] suggest that $\hat{I}_{\alpha L}$ and $\hat{I}_{\beta L}$, derived from relations like eq 3, will not be far from $\hat{F}_\alpha$ and $\hat{F}_\beta$. Similar theoretical work for $\hat{\beta}_{nuc}$ is still lacking but the assumption that $\hat{\beta}_{nuc} \approx \hat{Q}_1$ seems better than any other at the current time. In the present paper, we shall go still further and assume that β_{nuc} for formation of the tetrahedral adduct **2** is approximately unity. This is a quite reasonable assumption since, at the tetrahedral-intermediate structure, the nucleophilic atom has become bonded only to a saturated carbon atom. Such a process should have $\beta_{nuc} \approx 1$, with larger values arising only after leaving-group expulsion has set in, when the incipient carbonyl group will draw further electron density away from the nucleophilic atom. For this reason, we will use the experimental values of β_{nuc} directly, taking them as normalized and thus equal to $\hat{\beta}_{nuc}$.

A comparison among $\hat{\beta}_{nuc}$, $\hat{I}_{\alpha L}$, and $\hat{I}_{\beta L}$ may therefore be hoped to illuminate the ways in which the corresponding aspects of transition-state structure respond to structural and environmental

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[1] This research was supported by the National Institutes of Health through Research Grant No. GM 20198 from the National Institute of General Medical Sciences.

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[3] Jencks, W. P.; Gilchrist, M. *J. Am. Chem. Soc.* **1962**, *84*, 2910.

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[5] Hupe, D. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 451.

[6] do Amaral, L.; Bastos, M. P.; Bull, H. C.; Ortiz, J. J.; Cordes, E. H. *J. Am. Chem. Soc.* **1979**, *101*, 169–73.

[7] Hogg, J. L.; Rodgers, J.; Kovach, I.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 79–85.

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Table I. β-Deuterium Secondary Isotope Effects for Reactions of Oxyanions with CH_3CO_2Ar and CD_3CO_2Ar at 25.00 ± 0.01 °C in Water[a]

oxyanion	ester (L = H, D)	k_{CH_3}, M^{-1} s^{-1}	k_{CD_3}, M^{-1} s^{-1}	k_{CH_3}/k_{CD_3}
HO^-	$C_6H_5O_2CCL_3$	1.309 ± 0.009	1.336 ± 0.009	0.980 ± 0.009
HO^-	$4\text{-}NO_2C_6H_4O_2CCL_3$	8.496 ± 0.063	8.762 ± 0.054	0.970 ± 0.009
$C_6H_5O^-$	$4\text{-}NO_2C_6H_4O_2CCL_3$	1.093 ± 0.018	1.126 ± 0.014	0.971 ± 0.020
$C_6H_5O^-$	$2,4\text{-}(NO_2)_2C_6H_3O_2CCL_3$	12.24 ± 0.08	12.65 ± 0.08	0.968 ± 0.009
$CH_3CO_2^-$	$2,4\text{-}(NO_2)_2C_6H_3O_2CCL_3$	(5.525 ± 0.025) × 10^{-4}	(5.817 ± 0.040) × 10^{-4}	0.950 ± 0.008
$(CH_3CO_2^-)^b$	$C_6H_5O_2CCL_3$	(3.137 ± 0.069) × 10^{-7}	(3.431 ± 0.045) × 10^{-7}	$(0.914 \pm 0.023)^b$

[a] Total salt concentration maintained at 1 M with KCl. [b] This reaction proceeds by protolytic, rather than nucleophilic, catalysis.[8,9]

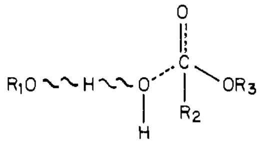
Table II. Measures of Reaction Progress in Acyl-Transfer Transition States[a]

	oxyanion, R_1O^-	pK_{R_1OH}	ester	$k_{\alpha II}/k_{\alpha D}$ $(\hat{I}_{\alpha L})$	k_{CH_3}/k_{CD_3} $(\hat{I}_{\beta L})$	Brønsted slope
1.	HCO_2^-	3.75	$4\text{-}NO_2C_6H_4O_2CL$	0.813 ± 0.007 (0.66 ± 0.11)		$\beta_{pro} \approx 0.4$
2.	$CH_3CO_2^-$	4.76	$4\text{-}NO_2C_6H_4O_2CL$	0.833 ± 0.007 (0.58 ± 0.10)		
3.	$CH_3CO_2^-$	4.76	$4\text{-}CH_3OC_6H_4O_2CL$	0.825 ± 0.002 (0.61 ± 0.10)		
4.	$CH_3CO_2^-$	4.76	$C_6H_5O_2CCL_3$		0.914 ± 0.023 (0.65 ± 0.29)	$\beta_{nuc} \approx 1$
5.	$CH_3CO_2^-$	4.76	$2,4\text{-}(NO_2)_2C_6H_3O_2CCL_3$		0.950 ± 0.008 (0.37 ± 0.15)	
6.	$(CF_3)_2CHO^-$	9.3	$4\text{-}CH_3OC_6H_4O_2CL$	0.876 ± 0.011 (0.42 ± 0.08)		
7.	$C_6H_5O^-$	9.86	$4\text{-}NO_2C_6H_4O_2CCL_3$		0.971 ± 0.020 (0.21 ± 0.17)	$\beta_{nuc} \approx 0.7$
8.	$C_6H_5O^-$	9.86	$2,4\text{-}(NO_2)_2C_6H_3O_2CCL_3$		0.968 ± 0.009 (0.22 ± 0.10)	
9.	$HC{\equiv}CCH_2O^-$	13.5	$4\text{-}CH_3OC_6H_4O_2CL$	0.885 ± 0.009 (0.39 ± 0.07)		
10.	HO^-	15.74	$4\text{-}NO_2C_6H_4O_2CCL_3$		0.970 ± 0.009 (0.22 ± 0.10)	$\beta_{nuc} \approx 0.2$
11.	HO^-	15.74	$C_6H_5O_2CCL_3$		0.980 ± 0.009 (0.15 ± 0.09)	

[a] Values of $k_{\alpha H}/k_{\alpha D}$ are from ref 6, normalized by $K_{\alpha H}/K_{\alpha D}$ = 0.73 ± 0.04. Values of β_{nuc} are from ref 5 and the estimate of β_{pro} from ref 6. Values of k_{CH_3}/k_{CD_3} are from Table I, normalized by K_{CH_3}/K_{CD_3} = 0.87 ± 0.04.

perturbations. Here we consider the effect of perturbing the structure of the nucleophile and of the changes from nucleophilic reaction to protolytically catalyzed attack of water.

Nucleophilic attack by R_1O^- (as in eq 1) is the dominant mode of reaction when R_3OH is a substantially stronger acid than R_1OH, but when the reverse is true, a protolytically catalyzed hydrolysis with a transition-state structure like **3** emerges as the major route.[8,9] Here R_1O^- may be regarded as accelerating water attack by protolytic general-base catalysis, or, in kinetically equivalent but physically different processes (not shown), R_1OH may be regarded either as accelerating hydroxide ion attack by protolytic general-acid catalysis or as assisting R_3O^- departure from a preformed tetrahedral intermediate. The relation of reactivity to R_1 structure is still governed by an equation of the form of eq 2, but its slope should now be denoted β_{pro}, for protolytic catalysis. The value of β_{pro} is automatically normalized.



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Results

The rate constants and β-D isotope effects for acyl transfer from various aryl acetates to various oxyanion nucleophiles (eq 4, L = H or D) are shown in Table I. The rates were measured spectrophotometrically as described in the Experimental Section.

$$R_1O^- + CL_3CO_2Ar \rightarrow R_1OCOCL_3 + ArO^- \qquad (4)$$

Discussion

Normalization of Isotope Effects. In order to estimate the magnitude of the equilibrium β-deuterium isotope effect for formation of the tetrahedral intermediate **2** and thus to calculate values of $\hat{I}_{\beta L}$, we shall (a) make use of the effect K_{4H}/K_{4D} for equilibrium hydration[11] of $ClCL_2COCL_2Cl$ (0.83 ± 0.02), (b) assume equal contributions of all deuteriums in order to generate an estimate K_{CH_3}/K_{CD_3} = 0.87 ± 0.02, and (c) assume that electrostatic contributions are small enough[12] so that if we increase the error estimate to ±0.04, they will be included. This limiting value for ketone hydration could be more inverse than the proper limiting value for ester-carbonyl hydration, because the amount of hyperconjugation of the β-CH electrons in a ketone is expected to be greater than in an ester. Whether this actually changes the limiting isotope effect depends on how much influence the difference in hyperconjugation has on the β-CH force constants, and this unknown. There is some indication that no real change in the limit is produced: Küllertz, Fischer, and Barth[10] found a *kinetic* isotope effect (probably closer to unity than the limiting equilibrium effect) of 0.89 ± 0.02 for the nucleophilic reaction of hydroxide ion with an anilide, where the amount of hyperconjugation should have been reduced even more than in an ester. It seems likely then that any difference of this kind will fall within the quite generous error limit of ±0.04. Therefore the values of k_{CH_3}/k_{CD_3} from Table I have been used together with eq 3 and a value K_{CH_3}/K_{CD_3} = 0.87 ± 0.04 to obtain estimates of $\hat{I}_{\beta L}$. These are given, with other information, in Table II.

Faced with the same kind of normalization problem for the α-deuterium isotope effect, do Amaral, Bastos, Bull, Ortiz, and Cordes[6] considered two possible limiting values of $K_{\alpha H}/K_{\alpha D}$. We

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(9) Gold, V.; Oakenfull, D. G.; Riley, T. *J. Chem. Soc. B* **1968**, 515.

(10) Küllertz, G.; Fischer, G.; Barth, A. *Tetrahedron* **1976**, *32*, 759–61.

(11) Kovach, I. M.; Hogg, J. L.; Raben, T.; Halbert, K.; Rodgers, J.; Schowen, R. L. *J. Am. Chem. Soc.* **1980**, *102*, 1991–9.

(12) Barnes, D. J.; Goldring, P. J.; Scott, J. M. W. *Can. J. Chem.* **1974**, *52*, 1966.

have decided to use only the estimate $K_{\alpha H}/K_{\alpha D} = 0.73$, which is based on four independent experimental studies, and thus to set aside the value of about 0.87 based on theoretical calculations. To include conceivable electrostatic effects, we have included ±5% error, for a final estimate $K_{\alpha H}/K_{\alpha D} = 0.73 \pm 0.04$. This was employed in eq 3 to generate from the data of Cordes et al.[6] the values of $\hat{I}_{\alpha L}$ presented in Table II.

Values of β_{nuc} from Hupe and Jencks[5] and the estimate of β_{pro} by Cordes et al.[6] are included for the appropriate sets of reactions in Table II.

Correlation of α-D and β-D Isotope Effects. Table II contains 11 examples of closely related formate ester and acetate ester reactions from which values of $\hat{I}_{\alpha L}$ and $\hat{I}_{\beta L}$, respectively, have been calculated. The comparison of α-D and β-D effects leads to the following conclusions.

(1) For reactions probably subject to protolytic general-base catalysis[6,8,9] (examples 1–4), the mean values of $\hat{I}_{\alpha L}$ are 0.66, 0.58, and 0.61 and the single value for $\hat{I}_{\beta L}$ is 0.65. Thus for this small sample, excellent agreement of the two probes is observed.

(2) For reactions which are probably nucleophilic in character (examples 5–11), the mean values of $\hat{I}_{\alpha L}$ are 0.42 and 0.39, while the mean values of $\hat{I}_{\beta L}$ are 0.37, 0.21, 0.22, 0.22, and 0.15 (in order of increasing pK_a of R_1OH in each set). If comparisons of nucleophiles with similar pK's are made, the closest agreement is expected for example 6 ($\hat{I}_{\alpha L} = 0.42$) with example 7 and 8 ($\hat{I}_{\beta L} = 0.21, 0.22$) and for example 9 ($\hat{I}_{\alpha L} = 0.39$) with examples 10 and 11 ($\hat{I}_{\beta L} = 0.22, 0.15$). The discrepancies are not large, considering the likely errors, but insofar as discrepancies do exist, the α-D effect indicates a greater degree of progress toward the tetrahedral adduct **2** than does the β-D effect.

For the entire data set, one concludes that α-D and β-D effects yield qualitatively similar conclusions about reaction progress at the transition state. For protolytic catalysis, the results are also in quantitative agreement. Semiquantitatively, α-D effects may, for nucleophilic attack by more basic nucleophiles, indicate higher degrees of reaction progress than β-D effects. This might logically arise either because the smaller degree of steric repulsion at the formate center than at the acetate center actually permits a greater degree of bond formation (a "perpendicular effect[13]" on transition-state structure) or because the two probes offer some differential response to reaction progress even if the transition-state structures are identical for acetate and formate esters.[14]

Lack of Correlation of Isotope Effects and Brønsted Slopes. Table II exhibits a gross failure of general correlation between values of β_{nuc} and β_{pro} and values of $\hat{I}_{\alpha L}$ or $\hat{I}_{\beta L}$. For very basic nucleophiles (p$K > 12$), the correlation appears fair ($\hat{I}_{\alpha L} \approx 0.4$, $\hat{I}_{\beta L} \approx 0.2$, $\beta_{nuc} \approx 0.2$). A serious breakdown appears for nucleophiles of pK = 8–11 ($\hat{I}_{\alpha L} \approx 0.4$, $\hat{I}_{\beta L} \approx 0.2$, $\beta_{nuc} \approx 0.7$) and continues for one example of nucleophilic catalysis at p$K < 8$ ($\hat{I}_{\beta L} \approx 0.4$, $\beta_{nuc} \approx 1$) and four examples of protolytic catalysis ($\hat{I}_{\alpha L} \approx \hat{I}_{\beta L} \approx 0.6$–$0.7$, $\beta_{pro} \approx 0.4$).

Clearly the isotope effects and Brønsted slopes are not providing similar information about the transition states. Furthermore, the discrepnacies can hardly arise from failure to normalize β_{nuc}. In order to bring the values of β_{nuc} = 0.7–1 into agreement with $\hat{I}$'s of 0.2–0.4, the magnitude of the equilibrium β_{nuc} for formation of **2** would have to be around 2, while in fact it cannot be far from unity.

Thus for very basic nucleophiles (p$K > 12$) rough agreement of fractional reaction progress as measured by β_{nuc}, $\hat{I}_{\alpha L}$, and $\hat{I}_{\beta L}$ is observed, with all around 0.2–0.4. Nucleophiles of lower basicity (pK = 8–11) continue to exhibit $\hat{I} \approx 0.2$–0.4 while β_{nuc} rises to 0.7–1. Around nucleophile pK values of 5–6, the mechanism for these substrates changes to protolytic catalysis of water attack. Now β_{pro} is relatively small (~0.4–0.5) and both $\hat{I}_{\alpha L}$ and $\hat{I}_{\beta L}$ are ~0.6–0.7. No general agreement between isotope effects and Brønsted slopes is seen.

Origin of the Nonlinearity in Brønsted Relations for Basic Nucleophiles. As noted in Table II, the Brønsted plot of log $k_{R_1O^-}$ vs. pK_{R_1OH} breaks sharply downward in the range of p$K_{R_1OH} \approx$ 11–12, with $\beta_{nuc} \approx 0.7$ in the range pK = 8–11 and $\beta_{nuc} \approx 0.2$ above pK = 12. The break is not connected with a change from rate-determining decomposition to rate-determining formation of the tetrahedral intermediate **2** because formation of **2** is rate limiting throughout the range of interest.[5] The nonlinearity must arise from some other source.

All three measures of reaction progress, $\hat{I}_{\alpha L}$, $\hat{I}_{\alpha L}$, and β_{nuc}, agree at ~0.2–0.4 in the range p$K > 12$, while in the range pK = 8–11, the values of $\hat{I}_{\alpha L}$ and $\hat{I}_{\beta L}$ remain ~0.2–0.4 but β_{nuc} rises to 0.7. We interpret this to mean that the average reaction progress at the transition state throughout the entire pK range 8–16 is about 0.2–0.4, that $\beta_{nuc} \approx 0.2$ measured for p$K > 12$ roughly reflects this (but is probably somewhat low), and that $\beta_{nuc} \approx 0.7$ for pK = 8–11 is unusually *large* for some reason.

A possible explanation for the unusually large value of β_{nuc} for nucleophiles pK = 8–11 could be the necessity for localizing charge and substantially reorganizing nearby solvent structure upon nucleophilic attack by aryloxide nucleophiles of pK = 8–11, an effect not expected to be so important with alkoxide nucleophiles (p$K > 12$). Alkoxide nucleophiles already have their charge localized on the nucleophilic atom and can be envisioned in the reactant state with bound solvent molecules in a roughly tetrahedral array about the negative oxygen. Replacement of one of these solvent molecules by the electrophile and the initiation of covalent bonding may be accomplished with little other structural, electronic or solvent reorganization in or near the alkoxide molecule. The removal of the first solvent molecule and its replacement by electrophile will involve, however, an unknown, basicity-related cost in energy (see below). An aryloxide nucleophile, by contrast, may be considered as having one of the three oxygen electron pairs delocalized throughout the aryl ring and the other two lying in the plane of the ring (sp^2 configuration of the nucleophilic atom). There should exist a nearby solvent structure appropriate to this disposition of electronic charge. The ortho substituents of the ring should strongly inhibit electrophile binding to the in-plane electron pairs, forcing the delocalized pair to form the new bond. Formation of this bond would thus be accompanied by a strong localization of electron density, electronic reorganization at the nucleophilic atom, structural reorganization in the phenyl ring, and much associated solvent-structural reorganization. The work associated with such processes could produce negative deviations from the Brønsted plot (as extended downward from that for strongly basic nucleophiles) and thus an artificially *large* value of β_{nuc} (perhaps 0.7) for aryloxide nucleophiles. This argument will apply in general to nucleophiles with highly delocalized electrons which must be localized for nucleophilic attack. It is not limited to nitrophenoxides, a situation considered by Hupe and Jencks,[5] and indeed the effect may not even be especially intense for phenoxides with strongly delocalizing substituents. The major energy loss may come from the requirement to bring electron density generally out of the ring to the nucleophilic atom; perturbations by substituent may not alter the situation to a sensible degree. Similar arguments about localization energies have long been adduced to explain the slow protonation rates of carbon bases (which are nearly always highly delocalized) compared to oxygen or nitrogen bases of similar basicity.[15] The present argument suggests that a rate reduction, smaller in magnitude, may also be seen when delocalized oxyanions are compared with localized oxyanions.

Hupe and Jencks[5] have earlier proposed that the value $\beta_{nuc} \approx$ 0.7, seen for p$K \approx$ 8–11, is a more realistic indicator of the transition-state structure than the value of $\beta_{nuc} \approx 0.2$, seen for p$K > 12$. Certainly ideas like Hammond's postulate[13] are in accord with a quasi-tetrahedral transition state for formation of

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(13) Thornton, E. K.; Thornton, E. R. In "Transition States of Biochemical Processes"; Gandour, R. D.; Schowen, R. L., Eds.; Plenum: New York, 1978.

(14) Indeed the situation may be even more complicated. Data published after submission of this paper (Pohl, E. R.; Hupe, D. J. *J. Am. Chem. Soc.* **1980**, *102*, 2763–8), of which Professor Hupe was kind enough to inform us at an earlier point, indicate still larger values of $\hat{I}_{\alpha L}$ than those of ref 6. These discrepancies remain to be resolved.

(15) Bell, R. P. "The Proton in Chemistry", 2nd ed.; Chapman and Hall: London, 1973; pp 208–14. Kresge, A. J. *Acc. Chem. Res.* **1975**, *8*, 354–60.

the unstable adduct **2**, which is then consistent with the large magnitude of β_{nuc}. While considerable sophistication[13] in mechanistic thinking has come about since Hammond put forward this idea and it might be rejected out of hand by many at the present time, its pervasive success (even in cases where it ought not to apply) has been such that it ought still to carry a good deal of weight. To explain the downward break at p$K \approx 11-12$, Hupe and Jencks note that such strongly basic nucleophiles are doubtless heavily solvated in the reactant state and that considerable work of desolvation must be accomplished to liberate the nucleophilic electron pair for attack upon the substrate carbonyl group. If such work reduces the rate, it could produce a negative deviation from the Brønsted plot, and if the required work, and thus the deviation, were to increase—as expected—with nucleophile basicity, then a lower value of β_{nuc} (such as 0.2) could result. Such a view would predict that in the pK range 8–11, all measures of reaction progress at the transition state (β_{nuc}, $\hat{I}_{\alpha\mathrm{L}}$ and $\hat{E}_{\beta\mathrm{L}}$) would agree, at a value of about 0.7. In the range of p$K > 12$, the $\hat{I}$'s should remain about 0.7 while β_{nuc} drops to 0.2. Since the opposite is observed, we consider that some hypothesis like that offered above, concentrating on localization energies, must also be included in the picture and perhaps be given a dominant place.

It is worth noting that our argument, based on an unusual work term for aryloxides resulting mainly from localization energies, and the argument of Hupe and Jencks,[5] based on an unusual work term for alkoxides resulting mainly from desolvation energies, share a common feature. In both cases, the localization of charge and the desolvation contribute to the equilibrium free energy of neutralization of the oxyanions, as well as to the free energy of activation. Thus they affect the pK as well as log k and—since neutralization is complete at equilibrium—they doubtless affect the pK more greatly. Such effects can therefore induce nonlinearity in Brønsted plots *only* when log k is affected *disproportionately*: at the transition state, the desolvation or charge localization must have occurred to a greater extent than anticipated merely from the degree of neutralization. This point is considered below and was treated in detail by Hupe and Jencks,[5] who offered persuasive arguments that disproportionate desolvation of highly basic nucleophiles is both highly likely and energetically costly.

In our view, it is most probable that both effects, desolvation and change localization, are involved to some degree in generating the nonlinear Brønsted relations. The values of $\hat{I}_{\alpha\mathrm{L}}$ and $\hat{I}_{\beta\mathrm{L}}$ are 0.2–0.4 for nucleophiles of p$K > 12$ while β_{nuc} is not more than 0.2. Hydroxide ion also has an extraordinary negative deviation, even from this Brønsted line. We would attribute the possibly smaller value of β_{nuc} than $\hat{I}_{\alpha\mathrm{L}}$ and $\hat{I}_{\beta\mathrm{L}}$ and possibly the unreactive character of the hydroxide ion to disproportionate desolvation. The unreactive character of hydroxide ion presents an unusual, perhaps unique, problem. The studies of Gold and Grist[16] suggest a quite similar nature for the solvation shells of hydroxide and methoxide ions, while the latter is very commonly more reactive as a nucleophile by as much as 1 or 2 orders of magnitude. It is conceivable that part of this lack of hydroxide reactivity is apparent and results from overestimation of the basicity of hydroxide ion in water. The pK value of 15.74, which is commonly used, results from reducing the autoprotolysis constant of water by a factor of 55.5, the presumed molar concentration of pure water, to arrive at a standard state in common with other ionizing acids. Few would disagree that this factor probably overestimates the effective concentration of water species. A further consideration, however, may be much more important. It is well-known that individual water molecules are greatly stabilized in aqueous solution by the extensive hydrogen-bonded structure of this solvent. No other solute such as the conjugate acid of another oxyanion nucleophile will be so stabilized. Thus the tendency of hydroxide ion to combine with a proton to form a water molecule in aqueous solution will be extraordinary, not because of any inherent property of the hydroxide ion, but because of the unusual stabilization of the product water molecule. This means that the expected nucleophilicity of hydroxide ion will be greatly overestimated by its apparent basicity, in comparison to any other nucleophile. Such an effect may contribute to the negative deviation of the hydroxide ion point from Brønsted relations.

At pK = 8–11, the values of $\hat{I}_{\alpha\mathrm{L}}$ and $\hat{I}_{\beta\mathrm{L}}$ remain at 0.2–0.4 while the Brønsted slope rises to 0.7. This effect we attribute to negative deviations of the delocalized aryloxides, occasioned by disproportionate localization of charge. Possibly a nucleophile like $(CF_3)_3CHO^-$ (Table II) will show a positive deviation from the Brønsted line for aryloxides, when enough data are available to test the question with precision. Even with this nucleophile, however, the negative charge may be delocalized by σ-bond resonance.

The discussion above has emphasized the *distinction* of desolvation events in preparing alkoxide ions for nucleophilic binding, on the one hand, and the localization of electron density in preparing aryloxide ions for nucleophilic binding, on the other hand. It is very likely that these two processes are strongly linked physically and that such an attempted distinction is artificial and unrealistic. The dominating effect in determining nucleophilic reactivity may go over smoothly from one to the other, as nucleophile structure is altered.

Early Transition State for Nucleophilic Attack. If a reasonable picture of these transition states for nucleophilic attack by oxyanions of pK = 8–16 is conveyed by magnitudes of $\hat{I}_{\alpha\mathrm{L}}$ and $\hat{I}_{\beta\mathrm{L}}$, then the average fractional reaction progress is only 0.2–0.4. The transition states are *early*, resembling the planar reactants, which have the carbonyl carbon in the sp^2 configuration, more nearly than they resemble the tetrahedral intermediate of sp^3 configuration. This result is not generally anticipated;[13] instead the transition state for conversion of a stable carbonyl compound to an unstable adduct is expected to resemble the adduct.

A possible explanation has to do with the disproportionate progress of solvent reorganization and other reorganization processes alluded to above. The mechanism of carbonyl addition may require the production of a highly reactive nucleophilic species, desolvated, possibly with localized charge and otherwise fully prepared for bond formation, in an independent, uncoupled reaction step preceding the step in which the carbon–nucleophile bond is joined and by which the rate is principally limited near 25 °C. Such a species might well exceed in energy the tetrahedral adduct; if so, formation of the adduct from this preceding species with planar carbonyl would be exergonic. Then one would expect a transition-state structure closer to the structure of the high-energy complex of reactive nucleophile with planar carbonyl compound than to the structure of the tetrahedral adduct. This would be fully consistent with $\hat{I}_{\alpha\mathrm{L}}$ and $\hat{I}_{\beta\mathrm{L}} \approx 0.2-0.4$.

Late Transition State for Protolytic Catalysis. The values of $I_{\alpha\mathrm{L}}$ and $\hat{I}_{\beta\mathrm{L}}$ for cases of protolytic catalysis of water attack (transition state **3** above; examples 1–4 of Table II) are around 0.6–0.7, suggesting a transition state closer in structure to the tetrahedral adduct than to the original reactants. This is in complete contrast to the situation with direct nucleophilic reaction of the oxyanion bases.

Such a result is understandable in view of the fact that the species now forming a bond to carbonyl is a water molecule, bridging through one of its hydrogens to a general base. This aggregate, scarcely altered in structure from the reactant-state solvated general base, can perform addition with no requirement for generation of high-energy, reactive species of the sort discussed above. Instead as the water oxygen binds to carbonyl, the hydrogen bridge may adjust its character for optimal transition-state stabilization. This adjustment can in principle occur either along a reaction pathway for concerted proton transfer and heavy-atom reorganization or along one of the various nonconcerted alternative routes involving solvation catalysis.[14]

Protolytic vs. Nucleophilic Catalysis. One substrate, phenyl acetate, was studied under conditions where its hydrolysis was nucleophilically catalyzed by hydroxide ion and under other conditions where its hydrolysis was subject to protolytic general-base catalysis by acetate ion. Scheme I (free-energy changes for 1 M standard states calculated from the data of Table I)

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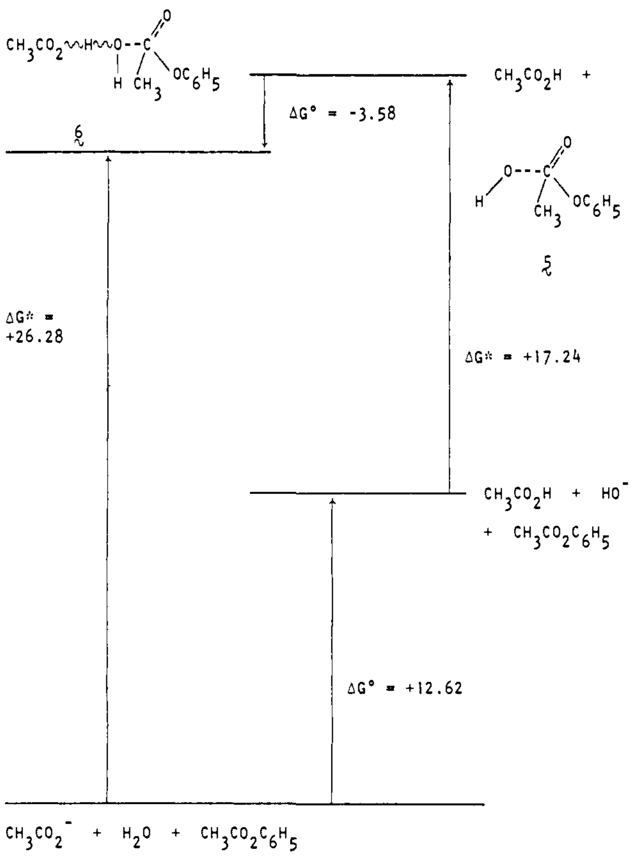
(16) Gold, V.; Grist, S. *J. Chem. Soc., Perkin Trans 2*, **1972**, *32*, 759–61.

(17) Schowen, R. L. *Prog. Phys. Org. Chem.* **1972**, *9*, 275–332.

Scheme I



illustrates that when acetic acid binds to the nucleophilic-catalysis transition state **5** to form the protolytic-catalysis transition state **6**, the binding is accompanied by the liberation of 3.58 kcal mol^{-1} of free energy. The reaction-progress estimates of Table II suggest that this binding of acetic acid to **5** to form **6** is also accompanied by an internal structural change from a structure of $\hat{I}_{\beta L} \approx 0.2$ to one of $\hat{I}_{\beta L} \approx 0.6$.

This is a rather drastic internal structural reorganization upon complexation with a hydrogen donor molecule (a change in bond order from 0.2 to 0.6 corresponds, by Pauling's rule,[18] to a decrease in carbon–oxygen partial bond length of 0.33 Å). It contrasts with hydrogen-bonding complexation of stable molecules, where internal structures of donor and acceptor are commonly little changed by complexation. This emphasizes the high plasticity of transition-state structure compared with the structure of stable molecules which have stronger bonds.

The structural reorganization also indicates that the free-energy change of -3.58 kcal mol^{-1} upon binding of acetic acid is deceptively small as a measure of the true interaction energy between acetic acid and the remainder of the transition state. A more revealing way of viewing the situation is to imagine the conversion of **5** to **6** as a formal, two-step process. In the first step (eq 5),

$$\mathbf{5}\ (\hat{I}_{\beta L} \approx 0.2) \xrightarrow{\Delta G_{\mathrm{dis}}} \text{poised structure}\ (\hat{I}_{\beta L} \approx 0.6) \qquad (5)$$

$$\text{poised structure}\ (\hat{I}_{\beta L} \approx 0.6) + \mathrm{CH_3CO_2H} \xrightarrow{\Delta G_{\mathrm{bin}}} \mathbf{6} \qquad (6)$$

5 is distorted to the "poised" structure which it will have as a fragment of **6**, with a free-energy cost ΔG_{dis} which may be considerable. In the second step (eq 6), the poised structure binds acetic acid with the liberation of the binding energy ΔG_{bin} to produce **6**. The expressed catalytic free energy, -3.58 kcal mol^{-1}, is thus the algebraic sum $\Delta G_{\mathrm{dis}} + \Delta G_{\mathrm{bin}}$. ΔG_{bin} may therefore be a very substantially exergonic term. Many readers will recognize the resemblance of this argument to the views of Jencks[19] on "intrinsic binding energy" and enzyme catalysis.

Experimental Section

Materials. Inorganic salts were reagent grade materials and were dried before use. Organic liquids were distilled. Water was distilled from a copper-bottom still, passed through a Barnstead mixed-bed ion-exchange column, distilled in glass, boiled for 20 min, and cooled suddenly. Sodium hydroxide solutions were diluted from Fisher 0.1000 N certified standard with 0.5 M or 1.0 M KCl solution. Acetate buffers of 0.1–0.5 M concentrations were prepared at pH 5.22 (1.0 M total salt concentration maintained with KCl), conjugate base fraction 0.80, and at 0.5–1.0 M concentrations at pH 5.96 (1.0 M total salt also maintained with KCl), conjugate base fraction 0.96. Phenol buffers were prepared in 0.06 M concentration at pH 9.05 (conjugate base fraction 0.127, total salt 1.0 M with KCl), were stored in the dark in tightly sealed containers and were discarded after 10 days.

Substrates. Phenyl acetate and 4-nitrophenyl acetate, in protiated and deuterated forms (>98% labeled and 99.5% labeled, respectively) were prepared from the isotopic forms of acetyl chloride and the appropriate phenol as previously described.[11] 2,4-Dinitrophenyl acetate was prepared from 2,4-dinitrophenol (Aldrich) and either $\mathrm{CH_3COCl}$ or $\mathrm{CD_3COCl}$ (the latter from $\mathrm{CD_3CO_2H}$ supplied by Diaprep, Inc.) in dry benzene containing pyridine. After 3–4 h of reflux, the organic layer was successively washed with 0.1 M HCl, 0.1 M $\mathrm{NaHCO_3}$, and water and dried over anhydrous $\mathrm{MgSO_4}$. The solvent was evaporated and the product recrystallized several times from hot petroleum ether. The degree of deuteration of the labeled ester was 99.5% (NMR).

Kinetics. With the exception of the reaction of acetate buffers with phenyl acetate, procedures like those previously described[11] were employed. All rates were measured spectrophotometrically with automatic data acquisition, with a Cary 118-microprocessor system[20] or a Cary 16-Hewlett-Packard minicomputer system.[21] Reaction temperatures were controlled by a Lauda K4/RD circulating bath connected to cell compartment, cuvet holder, and the jacket of a syringe used to inject substrate stock solutions when reactions were reasonably fast. Temperatures were monitored by a thermistor device with digital readout and electronic recording. Substrate injections were performed either with a long syringe needle or with a polyethylene tube. Slow reactions were studied by using a multiple-sample sample changer. Except for the phenyl acetate, acetate buffer system, rates were determined under first-order conditions. First-order rate constants were obtained by weighted, nonlinear least-squares analysis, commonly of 1000 data points. Second-order rate constants were calculated by dividing the slope of a plot of k_{obsd} vs. total buffer concentration by the fraction of base in the buffer.

The reaction of phenyl acetate with acetate buffers was studied under zero-order conditions. Phenyl acetate at somewhat less than 0.01 M concentrations was mixed with acetate buffers in a 3-mL cuvet, and absorbances at 275 nm were collected for a 3–7-h period, corresponding to about 0.4% reaction (absorbance change ≈ 0.08). A linear least-squares fit of absorbance vs. time gave $\mathrm{d}A/\mathrm{d}t$. Exact values of initial substrate concentration E_0 were obtained by 25-fold dilution of an aliquot of reaction solution with 0.1 M NaOH and spectrophotometric measurement of liberated phenoxide ion (286.9 nm (ϵ 2544 $\mathrm{M}^{-1}\ \mathrm{cm}^{-1}$), 275 nm ($\epsilon$ 1595 $\mathrm{M}^{-1}\ \mathrm{cm}^{-1}$)). With use of the extinction coefficients of phenol (1356 $\mathrm{M}^{-1}\ \mathrm{cm}^{-1}$ at pH 5.96, 275 nm) and phenyl acetate (15 $\mathrm{M}^{-1}\ \mathrm{cm}^{-1}$, pH 5.96, 275 nm) and the acetate ion concentration B, the second-order rate constant was then calculated by

$$k_2 = (\mathrm{d}A/\mathrm{d}t)/E_0B(1356 - 15)$$

In all studies, rates for protiated and deuterated substrates were measured simultaneously or were measured in alternation.

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