



Table I.  $\beta$ -Deuterium Secondary Isotope Effects for Reactions of Oxyanions with  $\text{CH}_3\text{CO}_2\text{Ar}$  and  $\text{CD}_3\text{CO}_2\text{Ar}$  at  $25.00 \pm 0.01^\circ\text{C}$  in Water<sup>a</sup>

oxyanion	ester (L = H, D)	$k_{\text{CH}_3}, \text{M}^{-1} \text{s}^{-1}$	$k_{\text{CD}_3}, \text{M}^{-1} \text{s}^{-1}$	$k_{\text{CH}_3}/k_{\text{CD}_3}$
$\text{HO}^-$	$\text{C}_6\text{H}_5\text{O}_2\text{CCL}_3$	$1.309 \pm 0.009$	$1.336 \pm 0.009$	$0.980 \pm 0.009$
$\text{HO}^-$	$4\text{-NO}_2\text{C}_6\text{H}_4\text{O}_2\text{CCL}_3$	$8.496 \pm 0.063$	$8.762 \pm 0.054$	$0.970 \pm 0.009$
$\text{C}_6\text{H}_5\text{O}^-$	$4\text{-NO}_2\text{C}_6\text{H}_4\text{O}_2\text{CCL}_3$	$1.093 \pm 0.018$	$1.126 \pm 0.014$	$0.971 \pm 0.020$
$\text{C}_6\text{H}_5\text{O}^-$	$2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{O}_2\text{CCL}_3$	$12.24 \pm 0.08$	$12.65 \pm 0.08$	$0.968 \pm 0.009$
$\text{CH}_3\text{CO}_2^-$	$2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{O}_2\text{CCL}_3$	$(5.525 \pm 0.025) \times 10^{-4}$	$(5.817 \pm 0.040) \times 10^{-4}$	$0.950 \pm 0.008$
$(\text{CH}_3\text{CO}_2^-)^b$	$\text{C}_6\text{H}_5\text{O}_2\text{CCL}_3$	$(3.137 \pm 0.069) \times 10^{-7}$	$(3.431 \pm 0.045) \times 10^{-7}$	$(0.914 \pm 0.023)^b$

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

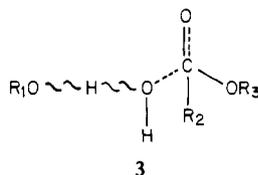
Table II. Measures of Reaction Progress in Acyl-Transfer Transition States<sup>a</sup>

	oxyanion, $\text{R}_1\text{O}^-$	$\text{p}K_{\text{R}_1\text{OH}}$	ester	$k_{\alpha\text{H}}/k_{\alpha\text{D}} (\hat{I}_{\alpha\text{L}})$	$k_{\text{CH}_3}/k_{\text{CD}_3} (\hat{I}_{\beta\text{L}})$	Brønsted slope
1.	$\text{HCO}_2^-$	3.75	$4\text{-NO}_2\text{C}_6\text{H}_4\text{O}_2\text{CL}$	$0.813 \pm 0.007$ ( $0.66 \pm 0.11$ )		
2.	$\text{CH}_3\text{CO}_2^-$	4.76	$4\text{-NO}_2\text{C}_6\text{H}_4\text{O}_2\text{CL}$	$0.833 \pm 0.007$ ( $0.58 \pm 0.10$ )		
3.	$\text{CH}_3\text{CO}_2^-$	4.76	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{O}_2\text{CL}$	$0.825 \pm 0.002$ ( $0.61 \pm 0.10$ )		$\beta_{\text{pro}} \approx 0.4$
4.	$\text{CH}_3\text{CO}_2^-$	4.76	$\text{C}_6\text{H}_5\text{O}_2\text{CCL}_3$		$0.914 \pm 0.023$ ( $0.65 \pm 0.29$ )	
5.	$\text{CH}_3\text{CO}_2^-$	4.76	$2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{O}_2\text{CCL}_3$		$0.950 \pm 0.008$ ( $0.37 \pm 0.15$ )	$\beta_{\text{nuc}} \approx 1$
6.	$(\text{CF}_3)_2\text{CHO}^-$	9.3	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{O}_2\text{CL}$	$0.876 \pm 0.011$ ( $0.42 \pm 0.08$ )		
7.	$\text{C}_6\text{H}_5\text{O}^-$	9.86	$4\text{-NO}_2\text{C}_6\text{H}_4\text{O}_2\text{CCL}_3$		$0.971 \pm 0.020$ ( $0.21 \pm 0.17$ )	$\beta_{\text{nuc}} \approx 0.7$
8.	$\text{C}_6\text{H}_5\text{O}^-$	9.86	$2,4\text{-(NO}_2)_2\text{C}_6\text{H}_3\text{O}_2\text{CCL}_3$		$0.968 \pm 0.009$ ( $0.22 \pm 0.10$ )	
9.	$\text{HC}\equiv\text{CCH}_2\text{O}^-$	13.5	$4\text{-CH}_3\text{OC}_6\text{H}_4\text{O}_2\text{CL}$	$0.885 \pm 0.009$ ( $0.39 \pm 0.07$ )		
10.	$\text{HO}^-$	15.74	$4\text{-NO}_2\text{C}_6\text{H}_4\text{O}_2\text{CCL}_3$		$0.970 \pm 0.009$ ( $0.22 \pm 0.10$ )	$\beta_{\text{nuc}} \approx 0.2$
11.	$\text{HO}^-$	15.74	$\text{C}_6\text{H}_5\text{O}_2\text{CCL}_3$		$0.980 \pm 0.009$ ( $0.15 \pm 0.09$ )	

<sup>a</sup> Values of  $k_{\alpha\text{H}}/k_{\alpha\text{D}}$  are from ref 6, normalized by  $K_{\alpha\text{H}}/K_{\alpha\text{D}} = 0.73 \pm 0.04$ . Values of  $\beta_{\text{nuc}}$  are from ref 5 and the estimate of  $\beta_{\text{pro}}$  from ref 6. Values of  $k_{\text{CH}_3}/k_{\text{CD}_3}$  are from Table I, normalized by  $K_{\text{CH}_3}/K_{\text{CD}_3} = 0.87 \pm 0.04$ .

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  $\text{R}_1\text{O}^-$  (as in eq 1) is the dominant mode of reaction when  $\text{R}_3\text{OH}$  is a substantially stronger acid than  $\text{R}_1\text{OH}$ , but when the reverse is true, a protolytically catalyzed hydrolysis with a transition-state structure like **3** emerges as the



major route.<sup>8,9</sup> Here  $\text{R}_1\text{O}^-$  may be regarded as accelerating water attack by protolytic general-base catalysis, or, in kinetically equivalent but physically different processes (not shown),  $\text{R}_1\text{OH}$  may be regarded either as accelerating hydroxide ion attack by protolytic general-acid catalysis or as assisting  $\text{R}_3\text{O}^-$  departure from a preformed tetrahedral intermediate. The relation of reactivity to  $\text{R}_1$  structure is still governed by an equation of the form of eq 2, but its slope should now be denoted  $\beta_{\text{pro}}$ , for protolytic catalysis. The value of  $\beta_{\text{pro}}$  is automatically normalized.

## Results

The rate constants and  $\beta$ -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.



## Discussion

**Normalization of Isotope Effects.** In order to estimate the magnitude of the equilibrium  $\beta$ -deuterium isotope effect for formation of the tetrahedral intermediate **2** and thus to calculate values of  $\hat{I}_{\beta\text{L}}$ , we shall (a) make use of the effect  $K_{4\text{H}}/K_{4\text{D}}$  for equilibrium hydration<sup>11</sup> of  $\text{ClCL}_2\text{COCL}_2\text{Cl}$  ( $0.83 \pm 0.02$ ), (b) assume equal contributions of all deuteriums in order to generate an estimate  $K_{\text{CH}_3}/K_{\text{CD}_3} = 0.87 \pm 0.02$ , and (c) assume that electrostatic contributions are small enough<sup>12</sup> so that if we increase the error estimate to  $\pm 0.04$ , 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  $\beta$ -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  $\beta$ -CH force constants, and this unknown. There is some indication that no real change in the limit is produced: Küllertz, Fischer, and Barth<sup>10</sup> found a kinetic isotope effect (probably closer to unity than the limiting equilibrium effect) of  $0.89 \pm 0.02$  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  $\pm 0.04$ . Therefore the values of  $k_{\text{CH}_3}/k_{\text{CD}_3}$  from Table I have been used together with eq 3 and a value  $K_{\text{CH}_3}/K_{\text{CD}_3} = 0.87 \pm 0.04$  to obtain estimates of  $\hat{I}_{\beta\text{L}}$ . These are given, with other information, in Table II.

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

(8) Oakenfull, D. G.; Riley, T.; Gold, V. *Chem. Commun.* **1966**, 385.

(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  $K_{\alpha\text{H}}/K_{\alpha\text{D}} = 0.73$ , 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  $\pm 5\%$  error, for a final estimate  $K_{\alpha\text{H}}/K_{\alpha\text{D}} = 0.73 \pm 0.04$ . This was employed in eq 3 to generate from the data of Cordes et al.<sup>6</sup> the values of  $\hat{I}_{\alpha\text{L}}$  presented in Table II.

Values of  $\beta_{\text{nuc}}$  from Hupe and Jencks<sup>5</sup> and the estimate of  $\beta_{\text{pro}}$  by Cordes et al.<sup>6</sup> are included for the appropriate sets of reactions in Table II.

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

(1) For reactions probably subject to protolytic general-base catalysis<sup>6,8,9</sup> (examples 1–4), the mean values of  $\hat{I}_{\alpha\text{L}}$  are 0.66, 0.58, and 0.61 and the single value for  $\hat{I}_{\beta\text{L}}$  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  $\hat{I}_{\alpha\text{L}}$  are 0.42 and 0.39, while the mean values of  $\hat{I}_{\beta\text{L}}$  are 0.37, 0.21, 0.22, 0.22, and 0.15 (in order of increasing  $\text{p}K_{\text{a}}$  of  $\text{R}_1\text{OH}$  in each set). If comparisons of nucleophiles with similar  $\text{p}K_{\text{a}}$ 's are made, the closest agreement is expected for example 6 ( $\hat{I}_{\alpha\text{L}} = 0.42$ ) with example 7 and 8 ( $\hat{I}_{\beta\text{L}} = 0.21, 0.22$ ) and for example 9 ( $\hat{I}_{\alpha\text{L}} = 0.39$ ) with examples 10 and 11 ( $\hat{I}_{\beta\text{L}} = 0.22, 0.15$ ). The discrepancies are not large, considering the likely errors, but insofar as discrepancies do exist, the  $\alpha$ -D effect indicates a greater degree of progress toward the tetrahedral adduct **2** than does the  $\beta$ -D effect.

For the entire data set, one concludes that  $\alpha$ -D and  $\beta$ -D effects yield qualitatively similar conclusions about reaction progress at the transition state. For protolytic catalysis, the results are also in quantitative agreement. Semiquantitatively,  $\alpha$ -D effects may, for nucleophilic attack by more basic nucleophiles, indicate higher degrees of reaction progress than  $\beta$ -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"<sup>13</sup> 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.<sup>14</sup>

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

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

Thus for very basic nucleophiles ( $\text{p}K > 12$ ) rough agreement of fractional reaction progress as measured by  $\beta_{\text{nuc}}$ ,  $\hat{I}_{\alpha\text{L}}$ , and  $\hat{I}_{\beta\text{L}}$  is observed, with all around 0.2–0.4. Nucleophiles of lower basicity ( $\text{p}K = 8$ –11) continue to exhibit  $\hat{I} \approx 0.2$ –0.4 while  $\beta_{\text{nuc}}$  rises to 0.7–1. Around nucleophile  $\text{p}K$  values of 5–6, the mechanism for these substrates changes to protolytic catalysis of water attack. Now  $\beta_{\text{pro}}$  is relatively small ( $\sim 0.4$ –0.5) and both  $\hat{I}_{\alpha\text{L}}$  and  $\hat{I}_{\beta\text{L}}$  are

$\sim 0.6$ –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  $\log k_{\text{R}_1\text{O}^-}$  vs.  $\text{p}K_{\text{R}_1\text{OH}}$  breaks sharply downward in the range of  $\text{p}K_{\text{R}_1\text{OH}} \approx 11$ –12, with  $\beta_{\text{nuc}} \approx 0.7$  in the range  $\text{p}K = 8$ –11 and  $\beta_{\text{nuc}} \approx 0.2$  above  $\text{p}K = 12$ . 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.<sup>5</sup> The nonlinearity must arise from some other source.

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

A possible explanation for the unusually large value of  $\beta_{\text{nuc}}$  for nucleophiles  $\text{p}K = 8$ –11 could be the necessity for localizing charge and substantially reorganizing nearby solvent structure upon nucleophilic attack by aryloxide nucleophiles of  $\text{p}K = 8$ –11, an effect not expected to be so important with alkoxide nucleophiles ( $\text{p}K > 12$ ). 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 ( $\text{sp}^2$  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  $\beta_{\text{nuc}}$  (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,<sup>5</sup> 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.<sup>15</sup> 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<sup>5</sup> have earlier proposed that the value  $\beta_{\text{nuc}} \approx 0.7$ , seen for  $\text{p}K \approx 8$ –11, is a more realistic indicator of the transition-state structure than the value of  $\beta_{\text{nuc}} \approx 0.2$ , seen for  $\text{p}K > 12$ . Certainly ideas like Hammond's postulate<sup>13</sup> are in accord with a quasi-tetrahedral transition state for formation of

(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  $\hat{I}_{\alpha\text{L}}$  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  $\beta_{\text{nuc}}$ . While considerable sophistication<sup>13</sup> 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  $\text{p}K \approx 11$ –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  $\beta_{\text{nuc}}$  (such as 0.2) could result. Such a view would predict that in the  $\text{p}K$  range 8–11, all measures of reaction progress at the transition state ( $\beta_{\text{nuc}}$ ,  $\hat{\lambda}_{\text{al}}$  and  $\hat{E}_{\text{BL}}$ ) would agree, at a value of about 0.7. In the range of  $\text{p}K > 12$ , the  $\hat{\lambda}$ 's should remain about 0.7 while  $\beta_{\text{nuc}}$  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,<sup>5</sup> 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  $\text{p}K$  as well as  $\log k$  and—since neutralization is complete at equilibrium—they doubtless affect the  $\text{p}K$  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,<sup>5</sup> 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 charge localization, are involved to some degree in generating the nonlinear Brønsted relations. The values of  $\hat{\lambda}_{\text{al}}$  and  $\hat{\lambda}_{\text{BL}}$  are 0.2–0.4 for nucleophiles of  $\text{p}K > 12$  while  $\beta_{\text{nuc}}$  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  $\beta_{\text{nuc}}$  than  $\hat{\lambda}_{\text{al}}$  and  $\hat{\lambda}_{\text{BL}}$  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<sup>16</sup> 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  $\text{p}K$  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 nu-

cleophilicity 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  $\text{p}K = 8$ –11, the values of  $\hat{\lambda}_{\text{al}}$  and  $\hat{\lambda}_{\text{BL}}$  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  $(\text{CF}_3)_3\text{CHO}^-$  (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  $\sigma$ -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  $\text{p}K = 8$ –16 is conveyed by magnitudes of  $\hat{\lambda}_{\text{al}}$  and  $\hat{\lambda}_{\text{BL}}$ , 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  $\text{sp}^2$  configuration, more nearly than they resemble the tetrahedral intermediate of  $\text{sp}^3$  configuration. This result is not generally anticipated;<sup>13</sup> 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  $\hat{\lambda}_{\text{al}}$  and  $\hat{\lambda}_{\text{BL}} \approx 0.2$ –0.4.

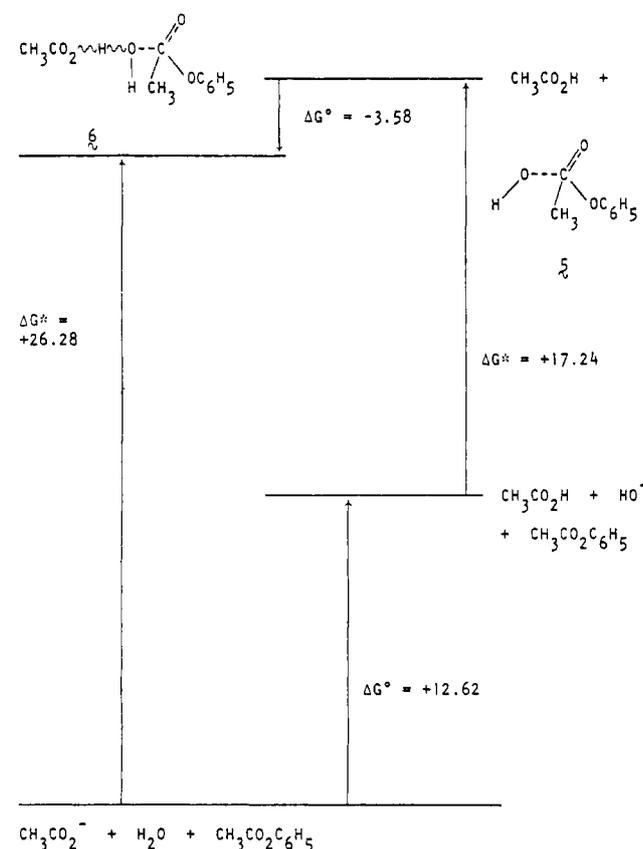
**Late Transition State for Protolytic Catalysis.** The values of  $\hat{\lambda}_{\text{al}}$  and  $\hat{\lambda}_{\text{BL}}$  for cases of protolytic catalysis of water attack (transition state **3** above; examples 1–4 of Table II) are around 0.6–0.7, suggesting a transition state closer in structure 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.<sup>14</sup>

**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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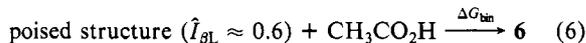
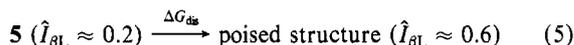
Scheme I



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<sup>-1</sup> 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  $\hat{I}_{\beta\text{L}} \approx 0.2$  to one of  $\hat{I}_{\beta\text{L}} \approx 0.6$ .

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,<sup>18</sup> 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<sup>-1</sup> 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),



**5** is distorted to the "poised" structure which it will have as a fragment of **6**, with a free-energy cost  $\Delta G_{\text{dis}}$  which may be considerable. In the second step (eq 6), the poised structure binds acetic acid with the liberation of the binding energy  $\Delta G_{\text{bin}}$  to

produce **6**. The expressed catalytic free energy, -3.58 kcal mol<sup>-1</sup>, is thus the algebraic sum  $\Delta G_{\text{dis}} + \Delta G_{\text{bin}}$ .  $\Delta G_{\text{bin}}$  may therefore be a very substantially exergonic term. Many readers will recognize the resemblance of this argument to the views of Jencks<sup>19</sup> 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.<sup>11</sup> 2,4-Dinitrophenyl acetate was prepared from 2,4-dinitrophenol (Aldrich) and either CH<sub>3</sub>COCl or CD<sub>3</sub>COCl (the latter from CD<sub>3</sub>CO<sub>2</sub>H 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 NaHCO<sub>3</sub>, and water and dried over anhydrous MgSO<sub>4</sub>. 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<sup>11</sup> were employed. All rates were measured spectrophotometrically with automatic data acquisition, with a Cary 118-microprocessor system<sup>20</sup> or a Cary 16-Hewlett-Packard minicomputer system.<sup>21</sup> 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  $k_{\text{obsd}}$  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  $\approx 0.08$ ). A linear least-squares fit of absorbance vs. time gave  $dA/dt$ . 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 ( $\epsilon$  2544 M<sup>-1</sup> cm<sup>-1</sup>), 275 nm ( $\epsilon$  1595 M<sup>-1</sup> cm<sup>-1</sup>)). With use of the extinction coefficients of phenol (1356 M<sup>-1</sup> cm<sup>-1</sup> at pH 5.96, 275 nm) and phenyl acetate (15 M<sup>-1</sup> cm<sup>-1</sup>, pH 5.96, 275 nm) and the acetate ion concentration  $B$ , the second-order rate constant was then calculated by

$$k_2 = (dA/dt) / E_0 B (1356 - 15)$$

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

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