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Effect of Solvation on β Values for Formyl, Acetyl, and Pivaloyl Transfer between Sulfur and Oxygen Nucleophiles

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Abstract: Second-order rate constants were measured in aqueous solution for the reaction of a series of oxy anions and thiol anions with the formate and pivalate esters of *p*-nitrophenol and *p*-nitrothiophenol. These data, along with literature data, provide a picture of the effect of alkyl substitution on the rates of uncatalyzed acyl transfer between sulfur and oxygen nucleophiles. Evidence is provided in support of the proposal that β values for oxy anions are altered by solvation, whereas those for thiol anions are not. The change of rate-determining step from formation to breakdown of tetrahedral intermediate occurs for formate and pivalate esters in the same manner that this occurs for acetate esters. The greater kinetic reactivity of formate esters compared to acetate esters is not a function of the entering or leaving nucleophile but is an inherent difference in the esters reflecting the relative ease of formation of the tetrahedral intermediates.

Introduction

Because the β value for the attack of a nucleophile on an electrophile must reflect the loss of charge upon reaching the transition state,[1] interpretation of these slopes in terms of transition-state bond order is reasonable. Other factors can influence β values, however, and make such an interpretation difficult. For example, nucleophilic attack by oxy anions on esters shows large values of β for phenoxides and small values of β for alkoxides.[1,2] Thus, β values suggest substantially different degrees of bond formation for these two classes of nucleophiles, whereas other indexes of transition-state structure (such as β values for leaving groups) suggest identical degrees of bond formation.

The Brønsted plot for proton abstraction from carbon by oxy anions shows substantial curvature.[3] We have proposed that this curvature is due to an effect of solvation stabilizing oxy anions in the transition state for attack on the proton. Since the curves for proton abstraction and nucleophilic attack on acetate esters are similar, it was proposed that the β values for both reactions were influenced similarly by solvation.[4] Consistent with this interpretation was the fact that the curvature was substantially diminished for pivalate esters, presumably because of the steric inhibition of this solvation effect. The literature data for oxy anion attack on acetate[1] and pivalate[4] esters are included in Figures 1 and 2.

We have recently shown that thiol anions are much poorer catalysts for proton abstraction from carbon than are comparably basic oxy anions.[5] Thus, even though the equilibrium constant for proton transfer from carbon to sulfur may be identical with that for transfer to oxygen, the latter may occur 50 times faster. These facts are also consistent with the solvation argument discussed above since thiol anions are less well solvated than oxy anions and thiols do not hydrogen bond readily. The rates of thiol anions are therefore not enhanced (and β values not altered) by solvation as are oxy anions. Ritchie has shown[6] that in Me_2SO, where this solvation difference should be absent, equally basic thiol anions and oxy anions have equal rates for proton transfer from carbon, as expected. A plot of rate constants for proton transfer from carbon to sulfur or oxygen bases vs. the equilibrium constants for the same process in the same medium was fit by a single correlation line.

The following general picture, therefore, begins to emerge. Oxy anions are assisted by solvation in the transition state for attack on an electrophile. This solvation effect results in a

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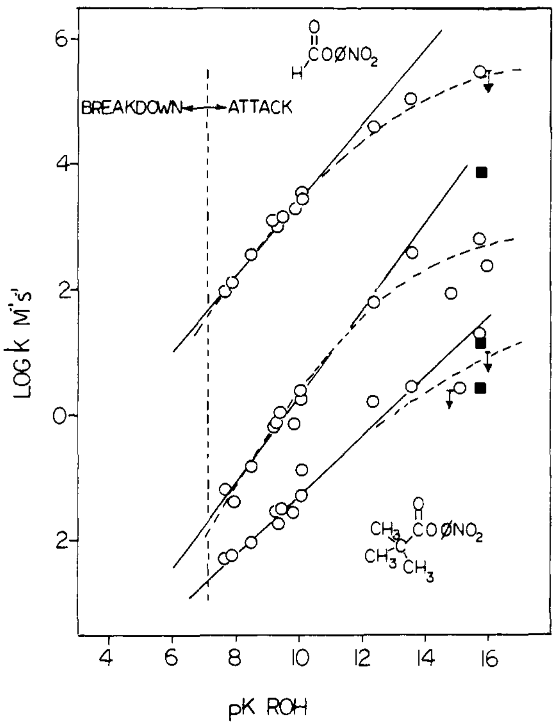

Figure 1. A Brønsted-type plot for the reaction of oxy anions with the oxy esters PNPF, PNPA, and PNPP in order of decreasing rate. The solid lines are the least-squares slopes through the points for phenoxides with values of 0.61 (0.99), 0.69 (0.96), and 0.48 (0.87). The points of hydroxide are indicated by filled squares. All of the data shown involve rate-determining attack to form tetrahedral intermediate.

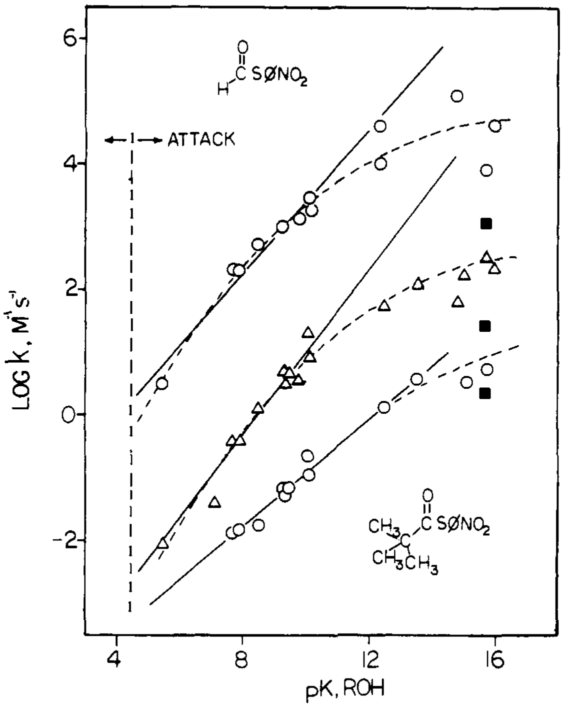

Figure 2. A Brønsted-type plot for the reaction of oxy anions with the thioesters PNPTF, PNTPA, and PNTPP, in order of decreasing rate. The solid lines are the least-squares slopes through the points for phenoxides with values of 0.57 (0.95), 0.66 (0.97), and 0.44 (0.88). The points for hydroxide are indicated by filled squares. All of the data shown involve rate-determining attack to form tetrahedral intermediate.

curved Brønsted plot characterized by a large β for phenoxides and a small β for alkoxides. This curvature can be diminished by sterically restricting solvation. β values for thiol anions are not influenced in this manner by solvation and therefore show no curvature and presumably more closely reflect the transition-state bond order than do oxy anions.

In order to further test this hypothesis, we have measured the rates of reaction of oxy anions and thiol anions with *p*-nitrophenyl formate (PNPF) and *p*-nitrothiophenyl formate (PNTPF), and thiol anions with *p*-nitrophenyl pivalate (PNPP) and *p*-nitrothiophenyl pivalate (PNTPP). The conditions chosen were identical with those used previously[1,4] to measure the rates of reaction of oxy anions with PNPP[1] and PNTPP[4] and oxy and thiol anions with *p*-nitrophenyl acetate (PNPA) and *p*-nitrothiophenyl acetate (PNTPA).[1]

If the solvation arguments presented above are correct, then the lower β for phenoxide attack on pivalate vs. acetate esters (reflecting a loss of curvature) should *not* be found for thiol anions. The data for formate esters was sought because these esters are less hindered than acetates and therefore might show larger effects due to solvation. These data would also provide insight into why formate esters are so much more reactive than acetate esters. In addition, these collected data would allow the determination of whether a given formyl or pivaloyl transfer involved rate-determining attack to form tetrahedral intermediate or rate-determining breakdown of the intermediate to form product. This determination would be particularly useful for formate esters since they are used in studies of secondary deuterium isotope effects[7] and a change in rate-determining step could alter the isotope effect substantially.

Experimental Section

Materials. The 4-nitrophenyl formate and 4-nitrothiophenyl formate were synthesized from formic-acetic anhydride and the corresponding phenol according to published procedures.[8,9] Other reagents employed in this study were obtained commercially or prepared as previously described[1,3,4] and either distilled, sublimed, or recrystallized prior to use. Glass-distilled water was employed throughout.

Kinetic Measurements. A Radiometer TTT2 titrator equipped with a pH meter (combined glass electrode, Type GK2321C), ABU 12 T Auto Burette, SBR3 titrigraph, TTA3 titration assembly, and Haake constant-temperature bath was used to follow the alkaline hydrolysis reactions and the formyl transfer to ethoxide and methoxide. The measurements were made at pH values between 7 and 8. The electrode was standardized before and after hydrolysis with pH 7.00 buffer. Solutions consisting of 25 mL of glass-distilled water or serial dilutions of catalyst maintained at an ionic strength of 1.0 with KCl were placed into a thermostated 35-mL glass vessel with a mechanical stirrer. The electrode, the nitrogen line, and the capillary tube from the microburet were inserted into the reaction mixture. The reaction mixture was first brought to a pH slightly higher than that desired by addition of 0.01 N NaOH, which served as the titrant. After temperature equilibrium, the experiment was initiated by the addition of 20 μL of 9×10^{-1} M solution of ester in acetonitrile from a microsyringe to yield a solution of 7×10^{-4} M ester and less than 1% acetonitrile. pH fluctuations during the reaction did not exceed 0.05 pH units.

All other reactions were monitored spectrometrically using a McPherson automated double-beam spectrophotometer equipped with a thermostated cuvette holder, a slave recorder, and a mechanical stirrer for rapid stirring of the solution. Procedures and precautions for the prevention of oxidation or volatilization of thiols were the same as those described previously.[1,4,5] Values of pH were determined at the temperature of the kinetic runs using a Radiometer Model PHM 26 pH meter equipped with a GK2321C combination electrode. Serial dilutions of catalyst were done so as to maintain constant pH and ionic strength. In all cases, the rate constant obtained was independent of the concentration of the substrate used. The concentrations of the nucleophile were at least 100 times greater than the concentration of ester and the reactions were routinely followed to 10 half-lives.

The pH control during the reactions was usually maintained by having the catalyst act as the buffer for the reactions. For the reactions of very basic oxy anions, however, 0.002 M KH_2PO_4 was used to buffer the solutions. Control experiments showed that no rate enhancement due to buffer was detectable under the conditions of the experiment. All stock solutions were kept under argon.

The values of k_{obsd} were determined from the least-squares slope of $\ln(1 - A/A_\infty)$ vs. time with a correlation coefficient ≥ 0.99. These

Table I. Second-Order Rate Constants for the Reaction of Formate Esters with Oxy Anions in Aqueous Solution at 25 °C, μ = 1.0[a]

			PNPF			PNTPF	
ROH	pK_a[b]	pH	max RO$^-$ concn	k_2, M^{-1} s^{-1}	pH	max RO$^-$ concn	k_2, M^{-1} s^{-1}
OH$^-$(H$_2$O)	15.75		5.0×10^{-7}	7.16×10^3		3.16×10^{-6}	1.09×10^3
CH_3CH_2OH	16.0	7.50	2.7×10^{-9}	$<3 \times 10^5$	8.30	1.8×10^{-8}	$<4 \times 10^4$
CH_3OH	15.7	7.50	7.0×10^{-9}	3.5×10^5	8.30	5.0×10^{-8}	7.7×10^4
$CH_3OCH_2CH_2OH$	14.8				7.95	2.4×10^{-7}	1.25×10^5
$HC{\equiv}CCH_2OH$	13.55	7.70	7.0×10^{-7}	1.16×10^5			
F_3CCH_2OH	12.37	7.70	5.8×10^{-6}	3.82×10^4	7.81	1.5×10^{-5}	9.31×10^3
4-CH_3PhOH	10.07	7.40	9.3×10^{-5}	2.76×10^3	7.47	1.1×10^{-4}	1.79×10^3
4-CH_3OPhOH	10.06	7.58	1.6×10^{-4}	3.01×10^3	7.72	8.6×10^{-5}	2.91×10^3
PhOH	9.86	7.58	1.8×10^{-4}	2.00×10^3	7.28	1.4×10^{-4}	1.30×10^3
4-AcNHPhOH	9.49	7.60	3.6×10^{-4}	1.40×10^3	6.98	3.2×10^{-5}	1.12×10^3
3-AcNHPhOH	9.38	7.74	5.3×10^{-4}	1.13×10^3	7.63	2.6×10^{-4}	8.91×10^2
4-ClPhOH	9.28	7.10	1.7×10^{-4}	1.24×10^3	7.61	3.0×10^{-4}	9.58×10^2
3,4-Cl_2PhOH	8.51	7.34	1.3×10^{-3}	3.65×10^2	7.56	1.1×10^{-3}	5.07×10^2
3,5-Cl_2PhOH	7.92	7.26	2.0×10^{-3}	1.35×10^2	7.28	2.5×10^{-3}	1.90×10^2
3,4,5-Cl_3PhOH	7.69	7.33	2.4×10^{-3}	9.83×10^1	7.19	6.6×10^{-2}	2.17×10^2
F_5PhOH	5.49	7.13	5.3×10^{-2}	4.43×10^{-1}	5.66	3.9×10^{-2}	3.16

[a] Eight to ten runs at various concentrations of RO$^-$ were measured to determine each k_2 value. [b] Taken from ref 1 and 2.

Table II. Second-Order Rate Constants for the Reaction of Formate Esters with Thiol Anions in Aqueous Solution at 25 °C, μ = 1.0[a]

			PNPF			PNTPF	
RSH	pK_a[b]	pH	RS$^-$ concn	k_2	pH	max RS$^-$ concn	k_2
$HOCH_2CH_2CH_2SH$	10.19	7.39	5.3×10^{-6}	7.27×10^4	7.12	1.7×10^{-6}	3.48×10^5
$HOCH_2CH_2SH$	9.61	7.43	2.2×10^{-5}	2.92×10^4	7.04	4.0×10^{-6}	1.95×10^5
CH_3OOCCH_2-CH_2SH	9.33	7.56	8.8×10^{-6}	1.66×10^4	7.03	2.5×10^{-6}	1.51×10^5
CH_3OOCCH_2SH	7.91	7.40	9.1×10^{-5}	8.91×10^3	6.20	4.8×10^{-6}	8.75×10^4
CF_3CH_2SH	7.30	7.40	1.4×10^{-4}	2.26×10^3	5.08	3.1×10^{-6}	4.80×10^4
PhSH	6.43	7.36	4.4×10^{-4}	3.84×10^2	5.57	1.5×10^{-5}	2.72×10^4
4-FPhSH	6.20	7.42	2.8×10^{-4}	6.14×10^2	5.20	2.1×10^{-5}	3.91×10^4
4-AcNHPhSH	6.08	7.76	6.4×10^{-4}	4.24×10^2	5.26	2.0×10^{-5}	2.75×10^4
4-ClPhSH	5.97	7.83	1.0×10^{-3}	2.04×10^2	7.57	8.3×10^{-5}	1.43×10^4
3,4-Cl_2PhSH	5.48	7.47	3.9×10^{-3}	4.10×10^1	7.63	7.8×10^{-5}	1.21×10^4
3,5-Cl_2PhSH	4.94	7.82	3.5×10^{-3}	3.73×10^1	7.55	7.2×10^{-5}	8.35×10^3
3,4,5-Cl_3PhSH	4.89	7.56	2.4×10^{-4}	3.68×10^{-1}	7.83	9.1×10^{-5}	8.35×10^3
2,3,5,6-F_4PhSH	2.75	6.58	2.6×10^{-2}	3.59×10^{-1}	6.98	3.0×10^{-3}	1.08×10^2
F_5PhSH	2.68	7.68	5.3×10^{-2}	3.80×10^{-1}	6.74	2.7×10^{-3}	9.75×10^1

[a] Eight to ten runs at various concentrations of RS$^-$ were done to determine each k_2 value. [b] Taken from ref 1-3.

Table III. Second-Order Rate Constants for the Reactions of Pivalate Esters with Thiol Anions in Aqueous Solution at 25 °C, μ = 1.0[a]

			PNPP			PNTPP	
RSH	pK_a[b]	pH	max RS$^-$ concn	k_2, M^{-1} s^{-1}	pH	max RS$^-$ concn	k_2, M^{-1} s^{-1}
$CH_3CH_2CH_2SH$	10.53	10.21	1.5×10^{-3}	2.15	10.84	1.9×10^{-3}	2.97×10^1
CH_3CH_3SH	10.35	10.48	2.8×10^{-3}	3.10	10.21	4.0×10^{-3}	5.97×10^1
$HOCH_2CH_2CH_2SH$	10.19	8.96	5.6×10^{-4}	2.76	9.36	1.3×10^{-3}	6.58×10^1
$HOCH_2CH_2SH$	9.61	9.09	3.0×10^{-2}	1.63	7.52	7.5×10^{-4}	3.03×10^1
$CH_3O_2CCH_2$-CH_2SH	9.33	9.16	6.7×10^{-4}	1.68	8.72	5.1×10^{-4}	2.89×10^1
$CH_3O_2CCH_2SH$	7.91	8.10	8.0×10^{-3}	3.74×10^{-1}	7.72	3.8×10^{-3}	1.98×10^1
CF_3CH_2SH	7.30	8.12	1.5×10^{-2}	1.21×10^{-1}	10.02	7.2×10^{-3}	9.81
4-FPhSH	6.20	9.43	3.9×10^{-2}	1.39×10^{-2}	10.00	1.8×10^{-2}	8.37×10^{-1}
4-AcNHPhSH	6.08				9.85	2.7×10^{-2}	1.25
4-ClPhSH	5.97	9.73	5.3×10^{-2}	1.01×10^{-2}	9.53	2.9×10^{-2}	6.63×10^{-1}
3,4-Cl_2PhSH	5.48				10.01	2.1×10^{-2}	5.84×10^{-1}
3,5-Cl_2PhSH	4.94				10.03	1.8×10^{-2}	3.60×10^{-1}
3,4,5-Cl_3PhSH	4.89				10.00	1.2×10^{-2}	3.84×10^{-1}

[a] Eight to ten runs at various concentrations of RS$^-$ were measured to determine each k_2 value. [b] Taken from ref 1-3.

values of k_{obsd} were plotted vs. the concentration of phenoxide, alkoxide, or thiol anion in order to obtain the values listed in Tables I-III.

Results

The rate of formation of *p*-nitrophenoxide or *p*-nitrothiophenoxide from PNPF, PNTPF, PNPP, or PNTPP in the presence of oxy anions or thiol anions is described by the equation

$$k_{obsd} = k^{OH}[OH^-] + k_2[B] + k_{H_2O} \qquad (1)$$

where [B] is the concentration of alkoxide or phenoxide calculated from the pH, pK_a, and total concentration. The values of k_{H_2O} were 1.13×10^{-3} s^{-1} for PNTPF and 9.1×10^{-4} s^{-1} for PNPF. The values of k_2 for each nucleophile are shown in Tables I-III, which also show the conditions under which the

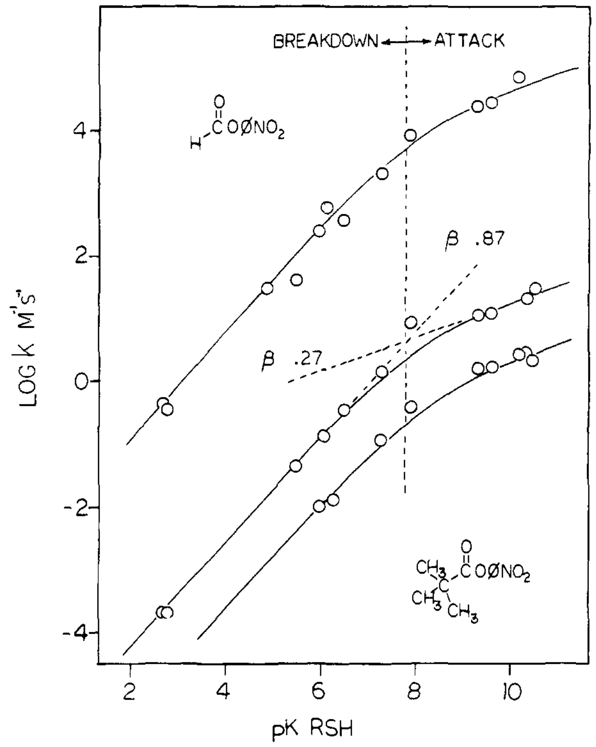

Figure 3. A Brønsted-type plot for the reaction of thiol anions with the oxy esters PNPF, PNPA, and PNPP, in order of decreasing rate. The curved line through the PNPA points was calculated using β values of 0.27 and 0.87 because these values fit data for a series of esters of varying reactivity. Parallel curves provide a reasonable fit for the PNPF and PNTPF data points shown.

rate constants were determined. As was the case for acetate esters,[1] control experiments at several pH values showed that k_{obsd} depended only upon the concentration of the thiol anion or oxy anion and not upon the concentration of the protonated form of the nucleophile. Other control experiments showed that the observed rate constants were independent of the concentration of phosphate buffer used in several of the experiments.

Brønsted-type plots for these data are shown in Figures 1-4. Also included in these figures are literature data for some of the reactions of pivalate[4] and acetate[1] esters.

Discussion

The structure-reactivity correlations for acetyl exchange between sulfur and oxygen nucleophiles show a clear break consistent with a change from rate-determining attack for high pK_a nucleophiles to rate-determining breakdown of the tetrahedral intermediate for low pK_a nucleophiles.[1] The break in the slopes occurs when the pK_a of the attacking and leaving nucleophile are equivalent, regardless of whether they are thiol or oxy anions.

The data for formyl and pivaloyl transfer shown in Figures 1-4 exhibit similar behavior. For example, the data in Figure 3 are fit with a calculated[1] curve using a $\beta_{attack} = 0.27$ and a $\beta_{breakdown} = 0.87$. (These β values were chosen to fit rate data for a series of esters of varying reactivity.[1]) The break occurs at a pK_a value of ~7. The data for PNPF and PNPP are fit by similar curves which differ only by a constant term. The data in Figure 4 for thiol anion attack on thiol esters are similar also. Using the same criteria that were established for acetyl transfer, therefore, each of the curves in Figures 1-4 was divided by a dashed line into the regions which pertain to rate-determining attack or rate-determining breakdown.

All of the data shown in Figures 1 and 2 pertain to rate-determining attack of oxy anions on esters. The curves for the formate esters differ by a constant factor but are otherwise very similar to those of the acetate esters. As an index of curvature, the least-squares line through the phenoxide points is larger than that for pivalates and the negative deviations of alkoxides from this line are similar to those found for acetates. The point for hydroxide is exceptionally low for formates and acetates but not for pivalates. The change from acetate to formate does not alter the contribution of solvation to the curvature of the plot.

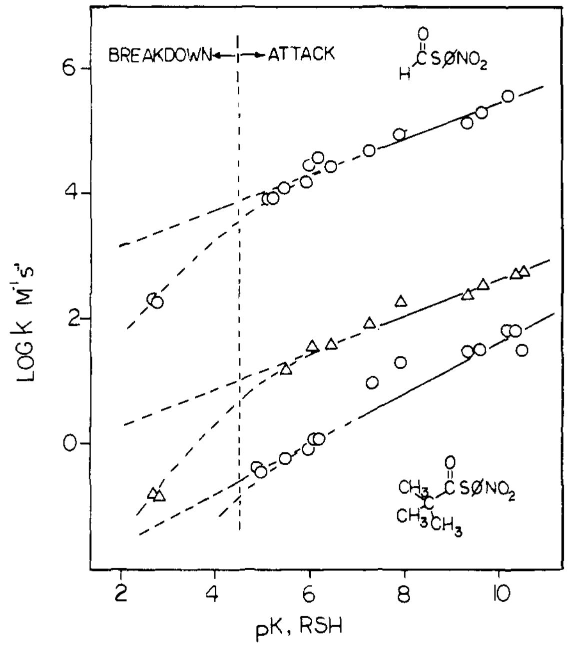

Figure 4. A Brønsted-type plot for the reaction of thiol anions with the thioesters PNTPF, PNTPA, and PNTPP, in order of decreasing rate. The solid lines represent the least-squares slopes for those points above $pK = 4.5$, which represent rate-determining attack. These have values of 0.29 (0.96), 0.29 (0.96), and 0.41 (0.95) in order of decreasing rate.

The data in Figures 3 and 4 are for the reaction of thiol anions with the esters. The formate esters and acetate esters are again identical except for a constant difference. With thiol anions as nucleophiles, there is no decrease in slope attributable to solvation with a change from acetates to pivalates. The limited data for PNPP can be fit by a line similar to that for PNPA except for a constant term. The change from PNTPA to PNTPP actually produces an increase in slope rather than the decrease found with oxy anions. It is likely that this is caused by a constant difference in the steric interaction of aryl and alkyl thiol anions with the pivalate group.

There is a relative reactivity of about 1:12:20 000 for an oxy anion ($pK_a = 7$) with pivalates:acetates:formates. The corresponding ratio for thiol anions is similar, 1:8:10 000. The relatively high kinetic reactivity of formate esters is independent of the nucleophile and an intrinsic property of the ester. A lower energy of formation of the tetrahedral intermediate of the formates is apparently reflected in their rates of formation and breakdown. The small change from *tert*-butyl to methyl and the large change from methyl to hydrogen mimic the equilibrium constants measured for addition of hydrogen cyanide to *tert*-butyl methyl ketone, acetone, and acetaldehyde.[10]

We draw the following conclusions from the data presented in this study. The decrease in β_{nuc} for attack by phenoxides with a change from acetate to pivalate is not found for thiol anions. This result is consistent with the contention that β_{nuc} values for oxy anions are influenced by solvation in a way that thiol anions are not. The curvature in β_{nuc} due to solvation is the same for formate and acetate esters with the formates faster by a factor of ~10^3 regardless of the nucleophile. The break in slopes due to a change in rate-determining step from formation to breakdown of tetrahedral intermediate occurs in the same manner for formates as had been found for acetates. For a formyl transfer between oxygen and sulfur nucleophiles, it is therefore possible to predict the rate-determining step.

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Secondary Deuterium Isotope Effects on Formyl Transfer Reactions between Sulfur and Oxygen Nucleophiles

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Abstract: Secondary deuterium isotope effects have been measured for formyl and deuterioformyl transfer between oxygen and sulfur nucleophiles at 25 °C in aqueous solution. Most data were obtained on *p*-nitrophenyl formate and deuterioformate, and on *p*-nitrothiophenyl formate and deuterioformate. The nucleophiles that were used are a series of aromatic and aliphatic thiol anions and oxy anions having a broad range of pK_a values. The value of k_D/k_H is larger for oxy anion attack (~1.22) on esters than for thiol anion attack (~1.00). The effects on k_D/k_H of changing from an aryl to an alkyl anion nucleophile are discussed. No measurable effect on k_D/k_H is observed with changing nucleophile basicity, suggesting little "Hammond postulate" type of change in transition-state structure. This lack of change is found even in regions where β_{nuc} varies substantially for oxy anions. Data are presented which suggest that the use of absolute values of k_D/k_H for determining transition-state bond orders can give values much different than other indexes of transition-state structure. The possibility that changes in frequencies other than C–H stretching and bending modes may result in a variation in k_D/k_H is considered.

Introduction

In the preceding paper,[1] we demonstrated that the structure–reactivity correlations for formyl transfer between oxygen and sulfur nucleophiles indicate that these reactions are faster by a constant factor than the corresponding acetyl transfers but otherwise are virtually identical. By extrapolation of more extensive data obtained for acetate esters,[2] it was therefore possible to identify those reactions of formate esters that involved rate-determining attack to form tetrahedral intermediate and those that involved rate-determining breakdown of the intermediate. It was also proposed that the curvature found in the plots of log k vs. pK_a for oxy anions (but not for thiol anions) was due to an effect of solvation rather than a change in the degree of bond formation between the nucleophile and carbon.[3-5]

The formate esters present an opportunity to probe transition-state structure by measuring the secondary deuterium isotope effect on reaction rates which arises when the formyl hydrogen is replaced with deuterium.[6] Although a considerable amount of work has been done on the subject of ester reaction isotope effects,[6-9] some ambiguities do remain. No study has yet been done, for example, in which the value of k_D/k_H is measured as a function of nucleophile basicity using a series of nucleophiles of the same type but having a wide range of pK_a values. This is the type of data which would be most useful in detecting a Hammond postulate type of change in transition-state structure. The changing value of β_{nuc} for oxy anions with esters, were it caused by a change in the degree of bond formation between oxygen and carbon, would presumably be reflected in a changing value of k_D/k_H.

Cordes has found values for k_D/k_H of about 1.22 for the reaction of several oxy anions with deuterated and nondeuterated *p*-nitrophenyl formate,[8] whereas Kirsch has determined a value of 1.05 for hydroxide ion with methyl formate.[9] We wanted to be able to determine, therefore, the importance of changing from an aryl to an alkyl entering or leaving group in determining the value of k_D/k_H.

Kirsch has shown also that changing the identity of the nucleophile can have a profound effect on the value of k_D/k_H.[9] Hydrazinolysis of methyl formate has a value of 1.35 for k_D/k_H, whereas that for hydroxide ion is 1.05, as mentioned above. It would, therefore, be interesting to see if attack by thiol anions produces a substantially different value than that of oxy anions. Since rate-determining step changes were defined for formyl transfer between sulfur and oxygen nucleophiles,[1] it was also of interest to see if a change in rate-determining step was paralleled by a change in isotope effect.

With these objectives in mind we have determined the secondary deuterium isotope effects on the reactions of oxy anions and thiol anions with *p*-nitrophenyl formate (PNPF) and *p*-nitrothiophenyl formate (PNTPF) along with the deuterioformate analogues (PNPF-*d* and PNTPF-*d*).

Experimental Section

Thiols, phenols, and alcohols used in this study were obtained and purified as previously described.[1-5,10,11] Procedures and precautions

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