

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 ( $\sim 1.22$ ) than for thiol anion attack ( $\sim 1.00$ ). 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  $\beta_{nuc}$  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,<sup>1</sup> 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,<sup>2</sup> 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.<sup>3-5</sup>

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.<sup>6</sup> Although a considerable amount of work has been done on the subject of ester reaction isotope effects,<sup>6-9</sup> 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  $\beta_{nuc}$  for oxy anions with esters, were it caused by a change in the degree of bond for-

mation between oxygen and carbon, would presumably be reflected in a changing value of  $k_D/k_H$ .

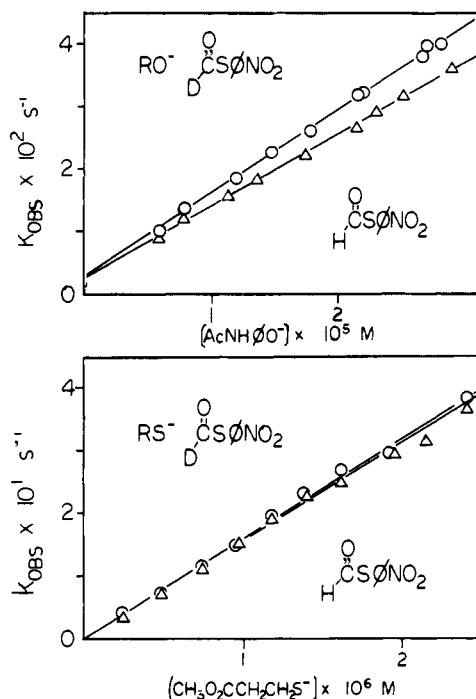
Cordes has found values for  $k_D/k_H$  of about 1.22 for the reaction of several oxy anions with deuterated and nondeuterated *p*-nitrophenyl formate,<sup>8</sup> whereas Kirsch has determined a value of 1.05 for hydroxide ion with methyl formate.<sup>9</sup> We wanted to be able to determine, therefore, 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  $k_D/k_H$ .<sup>9</sup> 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,<sup>1</sup> 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.<sup>1-5,10,11</sup> Procedures and precautions



**Figure 1.** A typical plot of  $k_{\text{obsd}}$  vs. oxy anion concentration for PNTPF and PNTPF-*d* showing a substantial value of  $k_D/k_H$  (1.22). The corresponding value for thiol anion attack on the same esters exhibits a much smaller value of  $k_D/k_H$  (1.02). Each of the uncircled numerical values of  $k_D/k_H$  shown in Figures 3 and 4 represents an experiment of this type, with approximately the same number of data points.

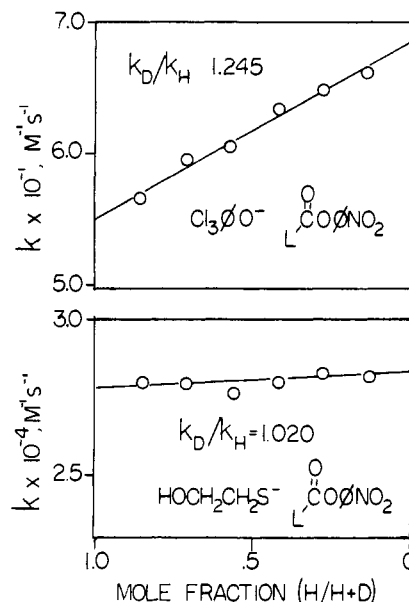
for working with dilute solutions of thiols were also the same as those used previously. PNPf-*d* and PNTPF-*d* were prepared in a manner identical with that used for the nondeuterated esters<sup>1</sup> but the starting material was deuterated with sodium formate obtained from Merck. Analysis by NMR showed >99% deuterium incorporation at the formyl position.

The rates of reaction of the esters with nucleophiles were usually determined by spectrophotometric measurement of *p*-nitrophenoxide or *p*-nitrothiophenoxide as previously described.<sup>1-5</sup> Several of the rate constants for high  $pK_a$  alkoxides and for hydroxide ion were determined using a pH-stat method as described previously.<sup>1</sup> This method was also used in this study to measure the rate of reaction of hydroxide ion with methyl formate and methyl deuterioformate.

The values of  $k_D/k_H$  were determined from the nucleophile concentration dependence of  $k_{\text{obsd}}$  values for both deuterated and non-deuterated ester so that any difference in background rates could be accounted for, as shown in Figure 1. Several cases were selected where conditions could be obtained with little background rate. With these conditions fixed, values of the rate constants were obtained with varying ratios of deuterated and nondeuterated ester as shown in Figure 2. These experiments gave more precise values of  $k_D/k_H$  which were very similar to those values measured by the other method.

2-Carbomethoxyethyl thioformate and the corresponding deuterioformyl ester were prepared from methyl 3-mercaptopropionate and acetic-formic anhydride (or acetic-deuterioformic anhydride) using a literature procedure.<sup>12,13</sup> To 5.9 mmol of acetic-formic anhydride were added 4 mmol of methyl 3-mercaptopropionate and 2 drops of pyridine followed by stirring for 1 h at room temperature. A pure sample of the ester was obtained by extraction into ether, drying, removal of solvent, and preparative VPC on a  $\frac{1}{4}$  in.  $\times$  5 ft SE-30 column, 121 °C,  $t_R = 2.7$  min. NMR:  $\delta$  2.60 (t, 2H), 3.17 (t, 2H), 3.62 (s, 3H), 10.0 (s, 1H). Analysis was satisfactory. The NMR of the deuterated analogue showed >99% deuterium at the formyl position.

The experimental procedure used for measuring the rate constants for the reaction of 2-carbomethoxyethyl thioformate-*d* with 3,4,5-trichlorophenol follows. A solution was prepared by adding 0.136 g of potassium dihydrogen phosphate to an argon-filled 100-mL volumetric flask. To this was added enough potassium chloride to bring the ionic strength to  $\mu = 2.0$  and the pH was adjusted to 7.4. The dipotassium salt of 5,5'-dithiobis(2-nitrobenzoic acid)<sup>11</sup> (213 mg) was



**Figure 2.** Plots of second-order rate constants vs. mole fraction of PNPf in a mixture of PNPf and PNPf-*d*. These experiments give more precise values of  $k_D/k_H$  which support the values determined by the method shown in Figure 1. Conditions were chosen so that the background rate was negligible. Values obtained by this method are circled in Figures 3 and 4.

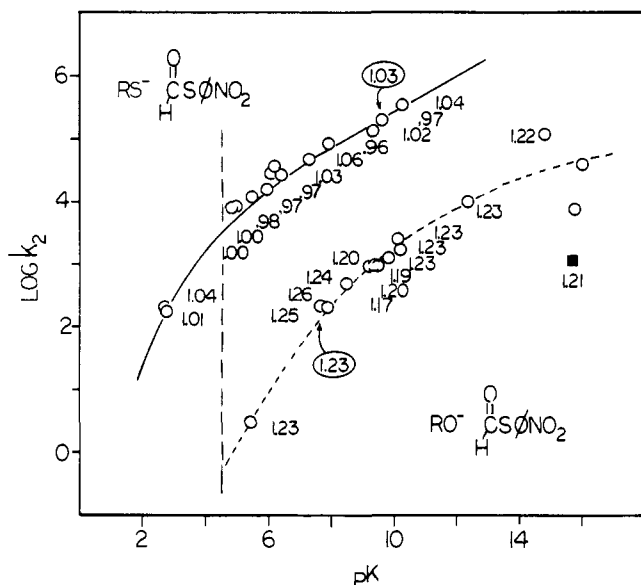
added and the flask was then filled to the mark with water to give a  $4.51 \times 10^{-3}$  M solution of Ellman's reagent. Another solution was prepared by dissolving 0.06497 g of 3,4,5-trichlorophenol in a 100-mL flask and adjusting the pH to 8.9. Stock solutions of 0.02 M 2-carbomethoxyethyl thioformate and 2-carbomethoxyethyl thioformate-*d* in acetonitrile were prepared. Phenolic solutions of varying concentrations were prepared by mixing 1.0 mL of the Ellman's solution with different ratios of the stock solution and water to give a total volume of 2 mL in a 3-mL cuvette that was fitted with a Teflon stopper. The cuvette was thermostated at 25 °C in a McPherson GCA ultraviolet-visible spectrometer. The reaction was initiated by injecting 2  $\mu$ L of the stock solution of ester into the cuvette, the solution was mixed,<sup>10</sup> and then the reaction was monitored by following the formation of  $ES^-$  at 412 nm. The rate of attack of methyl 3-mercaptopropionate on ESSE was much faster ( $>10^3$ ) than the attack of phenoxide on the thioester.<sup>10,11</sup> The reaction was monitored for >10 half-lives. Good first-order kinetics were obtained by subtracting out the slow, linear increase in absorbance due to the slow side reaction of Ellman's reagent under these conditions.

Infrared spectra were taken neat or in carbon tetrachloride solution on a Beckman IR 4240 spectrophotometer. Raman spectra were taken on a SPEX 1401 Raman spectrophotometer using a Spectra Physics Model 125 He-Ne laser. Freshly sublimed solid samples were used for the Raman spectra.

## Results

Two methods were used to determine  $k_D/k_H$  for the reaction of nucleophiles with formate esters as demonstrated in Figures 1 and 2. The more precise method shown in Figure 2 gives values which are similar to those measured in the manner shown in Figure 1. In several cases the value of  $k_D/k_H$  differed from those measured for similar cases and so repeat determinations were made. For example, 3,4,5-trichlorothiophenoxide gave a value of 1.07 with PNTPF, whereas other similar thiophenoxides gave values close to 1.01. Upon repeating the experiment twice, values of 1.07 and 1.06 were obtained. Some of the apparently random variation within a group of similar nucleophiles may not be due to experimental error, therefore. The values of  $k_D/k_H$  are listed in Tables I and II and are shown in Figures 3 and 4 also.

The values of  $k_D/k_H$  may be grouped according to type of nucleophile or ester and according to whether there is rate-determining attack or rate-determining breakdown of inter-



**Figure 3.** A plot of  $\log k$  vs.  $pK$  for the reaction of PNTPF with thiol anions and with oxy anions. The dashed line indicates where the change from rate-determining attack to rate-determining breakdown of tetrahedral intermediate occurs. The numbers indicate individual values of  $k_D/k_H$ . Those encircled are more precisely measured values of  $k_D/k_H$  obtained by varying the ratio of deuterated to nondeuterated substrate under identical experimental conditions, as shown in Figure 2.

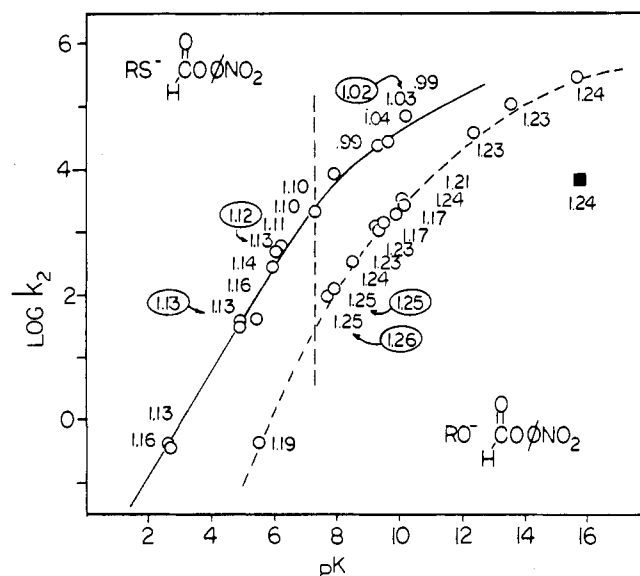
**Table I.** Values of  $k_D/k_H$  for the Reaction of Thiol Anions with Formyl and Deuterioformyl Esters at 25 °C,  $\mu = 1.0$ , in Aqueous Solution<sup>a</sup>

thiol	$pK_a^b$	$k_D/k_H$ , PNTPF	$k_D/k_H$ , PNTPF
HOCH <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> SH	10.19	0.99	1.04
HOCH <sub>2</sub> CH <sub>2</sub> SH	9.61	1.03 (1.02) <sup>c</sup>	0.97 (1.03) <sup>c</sup>
CH <sub>3</sub> O <sub>2</sub> CCH <sub>2</sub> CH <sub>2</sub> SH	9.33	1.04	1.02
CH <sub>3</sub> O <sub>2</sub> CCH <sub>2</sub> SH	7.91	0.99	0.96
CF <sub>3</sub> CH <sub>2</sub> SH	7.30	1.10	1.06
C <sub>6</sub> H <sub>5</sub> SH	6.43	1.10	1.04
4-FC <sub>6</sub> H <sub>4</sub> SH	6.20	1.11 (1.12) <sup>c</sup>	0.96
4-AcNHC <sub>6</sub> H <sub>4</sub> SH	6.08	1.13	0.97
4-ClC <sub>6</sub> H <sub>4</sub> SH	5.97	1.14	0.98
3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SH	5.48	1.16	1.00
3,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> SH	4.94	1.13 (1.13) <sup>c</sup>	1.00
3,4,5-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub> SH	4.89	1.12	1.07
F <sub>4</sub> C <sub>6</sub> HSH	2.75	1.16	1.04
F <sub>5</sub> C <sub>6</sub> SH	2.64	1.13	1.01

<sup>a</sup> The rate constants for the reactions of the nondeuterated esters and the conditions under which they were obtained are listed in ref 1. <sup>b</sup> Reference 1. <sup>c</sup> Value in parentheses measured under constant conditions with varying ratios of deuterated and nondeuterated ester.

mediate. These average values are listed in Table III along with the number of individual  $k_D/k_H$  values that were averaged. Those that are the average of five or more values are italicized in Table III and underlined in Figures 5 and 6 in order to indicate that they are more certain than those that are not italicized (or underlined).

The data in Figures 3 and 4 have more data for rate-determining attack than for rate-determining breakdown since the esters were chosen because of their good leaving groups. As a result, no data were available for rate-determining breakdown with an oxy anion attacking a thiol ester. In order to obtain a value of  $k_D/k_H$  for this case, the reaction of 3,4,5-trichlorophenoxide with 2-carbomethoxyethyl thioformate (and the deuterioformyl analogue) was studied. Since this reaction did not generate a chromophore, the thiol was allowed to react with Ellman's reagent,<sup>14</sup> which was also present in solution. This



**Figure 4.** A plot of  $\log k$  vs.  $pK_a$  for the reaction of PNTPF with thiol anions and with oxy anions similar to that shown in Figure 3.

**Table II.** Values of  $k_D/k_H$  for the Reaction of Oxy Anions with Formyl and Deuterioformyl Esters at 25 °C,  $\mu = 1.0$ , in Aqueous Solution<sup>a</sup>

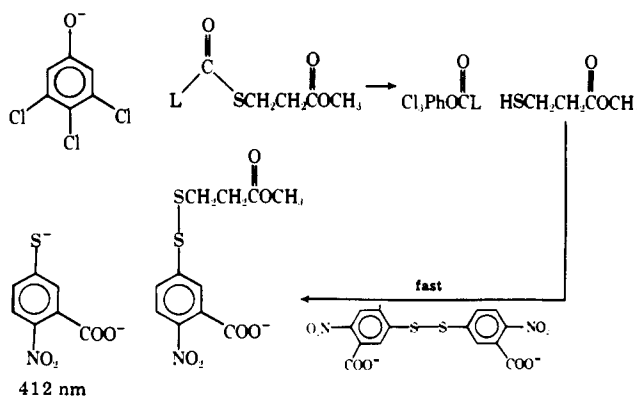
ROH	$pK_a^b$	$k_D/k_H$ , PNTPF	$k_D/k_H$ , PNTPF
H <sub>2</sub> O(HO <sup>-</sup> )	15.75	1.24	1.21
CH <sub>3</sub> OH	15.7	1.24	
CH <sub>3</sub> OCH <sub>2</sub> CH <sub>2</sub> OH	14.8		1.22
HC≡CCH <sub>2</sub> OH	13.55	1.23	
CF <sub>3</sub> CH <sub>2</sub> OH	12.37	1.23	1.23
CH <sub>3</sub> C <sub>6</sub> H <sub>5</sub> OH	10.07	1.21	1.23
CH <sub>3</sub> OC <sub>6</sub> H <sub>4</sub> OH	10.06	1.24	1.23
C <sub>6</sub> H <sub>5</sub> OH	9.86	1.17	1.19
4-AcNHC <sub>6</sub> H <sub>4</sub> OH	9.49	1.17	1.20
3-AcNHC <sub>6</sub> H <sub>4</sub> OH	9.38	1.23	1.17
4-ClC <sub>6</sub> H <sub>4</sub> OH	9.28	1.22	1.20
3,4-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> OH	8.51	1.24	1.24
3,5-Cl <sub>2</sub> C <sub>6</sub> H <sub>3</sub> OH	7.92	1.25 (1.25) <sup>c</sup>	1.25 (1.23) <sup>c</sup>
3,4,5-Cl <sub>3</sub> C <sub>6</sub> H <sub>2</sub> OH	7.69	1.25 (1.26) <sup>c</sup>	1.25 (1.23) <sup>c</sup>
F <sub>5</sub> C <sub>6</sub> OH	5.49	1.19	1.23

<sup>a</sup> The rate constants for the nondeuterated esters and the conditions under which they were obtained are listed in ref 1. <sup>b</sup> Reference 1. <sup>c</sup> Value in parentheses measured under constant conditions with varying ratios of deuterated and nondeuterated ester.

coupled reaction, shown in Scheme I, in which the second step is much faster than the formyl transfer step,<sup>10,11</sup> generates a chromophore which can be easily measured at 412 nm.

In Table IV are shown infrared and Raman data for deuterated and nondeuterated formate esters and thiol esters. Also

**Scheme I**



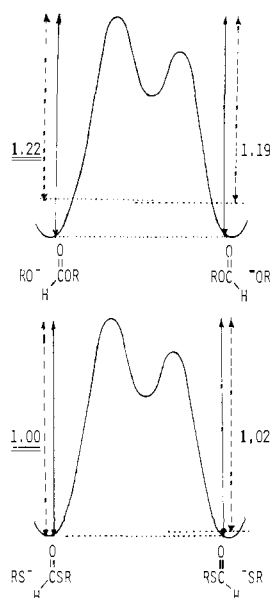


Figure 5. A free-energy profile for the reaction of oxy anions with oxyformate esters and their deuterioformate analogs. A comparable plot for the reaction of thiol anions with thiol esters is also shown.

Table III. Average Values of  $k_D/k_H$  (Standard Deviation) for the Reaction of Oxy Anions and Thiol Anions with Formate Esters

	rate-det attack	no. of determi- nations	rate-det breakdown	no. of determi- nations
RO <sup>-</sup> ROC- (=O)L	1.22 (±0.02)	15	1.19	1
RS <sup>-</sup> ROC- (=O)L	1.02 (±0.02)	5	1.12 (±0.02)	12
RO <sup>-</sup> RSC- (=O)L	1.22 (±0.02)	14	1.12	1
RS <sup>-</sup> RSC- (=O)L	1.00 (±0.03)	13	1.02 (±0.02)	2

computed are the frequency changes that occur upon deuteration for some of the peaks exhibiting the largest shifts. The data for methyl formate were taken from the literature,<sup>15,16</sup> and the spectral assignments for the other esters in Table IV were made by analogy to these. Although the kinetic data were obtained in aqueous solution, the IR data were obtained on carbon tetrachloride solutions and the Raman data on the pure solids. It was presumed that the effect of the medium on the frequency shifts caused by deuteration would be small.

### Discussion

Several interesting features are apparent from the collected isotope effects displayed in Figures 3 and 4. There is no apparent dependence upon basicity of the value of  $k_D/k_H$  within

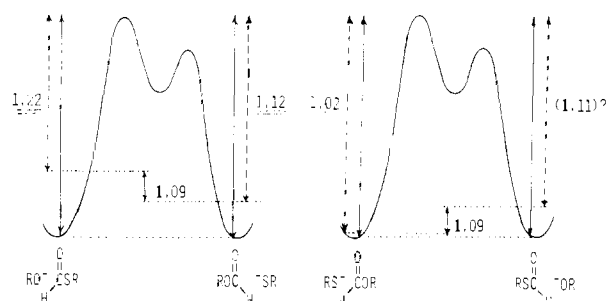


Figure 6. Free-energy profiles for the reaction of thiol anions with formate or deuterioformate esters and for the reverse reaction of oxy anions with thioformate and deuteriothioformate esters.

any group of measurements. For example, the values for rate-determining attack by oxy anions do not increase or decrease with changing  $pK_a$  even though there is a substantial change in  $\beta_{nuc}$  in this region. One possible explanation for the fact that  $\beta$  values for esters with alkoxides are small whereas those with phenoxides are large is that this reflects a dramatic change in transition-state bond order.<sup>2,17</sup> To the extent that  $k_D/k_H$  values reflect changes in transition-state bond order, there seems to be no variation measurable. This supports the hypothesis that the variation in  $\beta$  values for nucleophilic reactions arises because of an effect due to solvation rather than because of a change in transition-state bond order.<sup>2-4</sup> The same constancy of  $k_D/k_H$  values was also found for the thiol anions studied.

Another interesting result demonstrated by the data is that the value of  $k_D/k_H$  is apparently independent of whether the attacking nucleophile is an alkyl or aryl anion. For example, rate-determining attack by either phenoxides or alkoxides on PNPf gave essentially identical values of  $k_D/k_H$  of about 1.22. This seemed to be inconsistent with values published by Kirsch<sup>9</sup> of  $k_D/k_H$  for the attack of hydroxide ion on methyl formate (1.05) and ethyl formate (1.10) but consistent with the larger values found by Cordes<sup>8</sup> for the reaction of hydroxide with PNPf. We therefore repeated the experiment with methyl formate and found a value of  $k_D/k_H = 1.08$ , which is essentially identical with Kirsch's result. Apparently  $k_D/k_H$  is lower when neither the entering or leaving group is an aromatic anion. The reason for this behavior is not known.

Hydroxide ion, even though its rate with esters is anomalously low relative to comparably basic alkoxides,<sup>1,2,4</sup> gives a  $k_D/k_H$  value identical with those of other oxy anions. This suggests that the rate difference between hydroxide and alkoxides does not reflect a difference in the degree of bond formation between oxygen and carbon. It is likely that a solvation effect is responsible for the anomalously low rate of hydroxide ion, therefore.

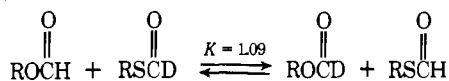
Shown in Figures 5 and 6 are free-energy profiles for formyl transfer between oxygen and sulfur nucleophiles. The average values for  $k_D/k_H$  from Table III are listed in these figures also.

Table IV. Infrared and Raman Spectral Data for Some Aromatic and Aliphatic Formate and Deuterioformate Esters<sup>a</sup> (cm<sup>-1</sup>)

	CH <sub>3</sub> OC(=O)L <sup>c</sup>			CH <sub>3</sub> OC(=O)CH <sub>2</sub> CH <sub>2</sub> SC(=O)L <sup>d</sup>			O <sub>2</sub> NPhOC(=O)L <sup>e</sup>			O <sub>2</sub> NPhSC(=O)L <sup>e</sup>		
	H	D	Δ	H	D	Δ	H	D	Δ	H	D	Δ
C—H str	2932-2219		723	2840-2140		700	2954-2228		726	2838-2135		703
C—H bend	1371-1048		323	1352-1030 <sup>b</sup>		322	1332-1009 <sup>b</sup>		323	1340-1019 <sup>b</sup>		321
C=O	1754-1731		23	1678-1648		30	1760-1740		20	1702-1672		30
C—O	925-878		47				1191-1113		78			
							1088-1098		-10			
C—S				740-700		40				718-684 <sup>b</sup>		34
C—O—C	325-304		21									
total			1137			1092			1137			1088

<sup>a</sup> IR frequencies unless otherwise indicated. <sup>b</sup> Raman frequencies. <sup>c</sup> IR spectra obtained in CCl<sub>4</sub> solution. <sup>d</sup> IR and Raman spectra obtained on the neat liquid. <sup>e</sup> IR spectra obtained in CCl<sub>4</sub> solution. Raman spectra obtained on pure solid.

Scheme II



The dashed lines illustrate schematically the fact that the barriers for deuterated esters are generally lower than those for nondeuterated esters. These diagrams essentially represent a subtraction process in which the transition-state energies have been matched so that differences in relative energies of deuterated and nondeuterated ground states may be clearly seen. (For example, Figure 5 is not intended to imply that deuteration raises the ground-state energy of PNPf, but rather that the ground state is lowered less than the transition state by the amount shown.) The numerical values refer not to energies but to the ratios of  $k_D/k_H$  (or  $K_D/K_H$ ) that these changes in energy produce. For simplicity, all of the diagrams have been drawn as though the reactions were isoenergetic. Since  $k_D/k_H$  is independent of basicity, as discussed above, this will have no bearing on the isotope-effect arguments.

Figure 5 shows the profile for oxy anions with oxy esters. The average value of 1.22 for  $k_D/k_H$  for rate-determining attack is similar to the single value of 1.19 determined for rate-determining breakdown (in the opposite direction). The similarity of the values for the forward and reverse reactions gives the required lack of an isotope effect on the ground-state equilibrium. A similar situation, with much smaller values of  $k_D/k_H$ , is found for thiol anions reacting with thiol esters, as shown in Figure 5 also.

In Figure 6 is shown the case of formyl transfer between sulfur and oxygen nucleophiles. The values of 1.22 and 1.12 in the curve on the left require an isotope effect of 1.09 on the equilibrium constant (essentially a fractionation factor) for the reaction shown in Scheme II in which deuteration stabilizes the oxy ester slightly more than deuteration of the thiol ester. Since both of the numbers used were averages of several kinetic measurements, the equilibrium constant therefore reflects the behavior of a broad series of reactants. The value of  $k_D/k_H$  for rate-determining attack on an oxy ester shown on the right-hand side of Figure 6 is 1.02 and along with the equilibrium value of 1.09 this predicts a value of 1.11 for the oxy anion reaction with a thiol ester which involves rate-determining breakdown. The reaction of 2-carbomethoxyethyl thioformate with 3,4,5-trichlorophenoxide was studied since the leaving group in this reaction is more basic ( $pK = 9.33$ ) than the attacking oxy anion ( $pK = 7.69$ ).<sup>2</sup> The rate-determining step would therefore be a breakdown of the tetrahedral intermediate. The experimental value of 1.12 for  $k_D/k_H$  is close to the predicted value of 1.11 based on the cycle described above.

It is instructive to consider the infrared and Raman spectral data for these esters to see if the equilibrium constant of 1.09 in Scheme II is consistent with them. In Table IV are listed the frequency shifts encountered upon deuteration of alkyl and aryl esters or thioesters. The equilibrium constant for the reaction in Scheme II of 1.09 is equivalent to 0.06 kcal or 20  $\text{cm}^{-1}$ . Thus the oxy esters would be expected to be shifted by a total of 20  $\text{cm}^{-1}$  more than the corresponding thiol ester. The data from Table IV demonstrate how difficult it would be to make accurate prediction of  $K_D/K_H$  (or  $k_D/k_H$ ) from infrared data. A measurable change in rate or equilibrium constant isotope effect can be caused by a 0.2% difference in the total change in zero-point vibrational energy. Streitwieser's<sup>6,18</sup> formulation attempts to approximate values of  $k_D/k_H$  by presuming that the major contributions to the isotope effect arise from changes in the carbon-hydrogen stretching and bending modes. Whereas it is certainly true that these shifts are the largest, it is also true that the loss or appearance of changes in frequency in other bonds (C=O, C—O, C—S, etc.) could be contributing substantially to the isotope effect. A simplifying assumption relying on C—H/C—D changes alone automatically

presumes that these other frequency changes (totaling  $>100 \text{ cm}^{-1}$ ) are matched very precisely in starting material and in product (or transition state). It is quite possible that the apparently unpredictable variations of  $k_D/k_H$  such as found for hydroxide ion with methyl formate (1.08), PNPf (1.22), and *p*-methoxyphenyl formate (1.14)<sup>8</sup> arise because of differences in the frequency changes of bonds other than C—H upon deuteration.

The attack of thiol anions on esters gives values of  $k_D/k_H$  of  $\sim 1.00$ , whereas the oxy anions have values of 1.22. If the usual translation of isotope effects into transition-state bond orders is made,<sup>6-9</sup> this would require a substantial degree of bond formation for oxy anion attack but no bond formation for thiol anion attack. This conclusion contrasts dramatically with the identical values of  $\beta_{\text{lg}}$  for leaving groups from esters when either thiol anions or oxy anions are the attacking nucleophile.<sup>2</sup> This particular index of transition-state structure suggests identical degrees of bond formation, whereas isotope effects suggest vastly different values. This means that the use of absolute values of  $k_D/k_H$  as determinants of transition-state bond order (even in those rare cases where the equilibrium  $K_D/K_H$  value is known accurately) may give results that are very different from those obtained using other indexes of transition-state structure.

The lesser isotope effects for the sulfur-bearing compounds could be due to the differences in the deformation frequency of the C—H bond of the tetrahedral intermediate. Literature data<sup>19</sup> for the IR spectra of compounds of the type  $(\text{RO})_2\text{CLPh}$  and  $(\text{RS})_2\text{CLPh}$  reveal the fact that deuterium substitution lowers the frequency of the ketal C—H deformation ( $1360$  to  $980 \text{ cm}^{-1} = 380 \text{ cm}^{-1}$ ) more than the dithioacetal ( $1230$  to  $975 \text{ cm}^{-1} = 255 \text{ cm}^{-1}$ ). By analogy the tetrahedral intermediate bearing oxygen may be expected to be stabilized more than the one bearing sulfur (by  $125 \text{ cm}^{-1} = 0.36 \text{ kcal}$ ;  $K = 1.9$ ). If this is the case, however, it is not clear why the change from oxy esters to thiol esters causes no change in isotope effect. It is only a change in the attacking nucleophile that produces this difference.

Recently obtained data of Knier and Jencks for the attack of nucleophiles on substrate showing an "open"  $\text{S}_{\text{N}}2$  type mechanism provide an interesting comparison. A range of secondary isotope effects from  $k_D/k_H = 0.85$  for  $\text{F}^-$  to 1.01 for  $\text{I}^-$  was found, including  $\text{RO}^- = 0.93$  and  $\text{RS}^- = 0.88$ . The direction and relative magnitude of isotope effects found in this study involving an  $\text{sp}^3$  to  $\text{sp}^2$  type of conversion are consistent with the ester reactions above which involve an  $\text{sp}^2$  to  $\text{sp}^3$  conversion. Both sets of isotope effects suggest that the larger, softer nucleophiles give transition states in which the carbon appears (by this criterion, at least) to be more  $\text{sp}^2$ -like than  $\text{sp}^3$ -like.

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## Chiral Secondary Amides. 2. Molecular Packing and Chiral Recognition

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**Abstract:** A molecular model which accounts for stereoselective interactions within the series of chiral secondary amides  $RCONHCH(CH_3)Ar$  is proposed. It assumes that a guest molecule intercalates between two host molecules in their 5-Å translation H-bonded array to form diastereomeric arrangements for the two enantiomers, differing in stability. The model explains various aspects of chiral recognition: (1) the gas chromatographic separation of enantiomers achieved with *N*-acyl- $\alpha$ -arylethylamines as chiral phases; (2) the difference in solubility of (*R*)- and (*S*)-*N*-trifluoroacetyl- $\alpha$ -(1-naphthyl)ethylamine in solid (*R*)-*N*-lauroyl- $\alpha$ -(1-naphthyl)ethylamine. The packing arrangement of certain diamide molecules was examined in order to reinforce the assumptions on which the explanation of the stereoselective effects was based. Energy computations support the stability relationships which follow from the model.

### I. Introduction

The interactions between chiral secondary amides  $RCONHCH(CH_3)Ar$  were analyzed in terms of their molecular packing in both the solid and the liquid states in part 1.<sup>1</sup> The analyses demonstrated a preference for the formation of stacks in which the molecules are hydrogen bonded along a 5-Å translation axis (Figure 1). The detailed geometry and contacts in this packing motif were revealed by several crystal-structure determinations.<sup>1</sup> The 5-Å translation mode fulfills the requirements for linear hydrogen bonds and for close packing between the aromatic residues whose planes are separated by 3.4 Å. It also generates favorable contacts between the R groups, especially for long hydrocarbon chains. The high stability of this packing mode is further manifested by its retention in the melt.<sup>1</sup>

The compounds in this series, when serving as chiral stationary phases in gas-liquid chromatography, separate optical isomers.<sup>2</sup> Resolution is particularly good when the optical isomers are of the same type ( $RCONHCH(CH_3)Ar$ ) as the chiral phase, with higher retention times for the enantiomer of the same absolute configuration as that of the stationary phase.

It is our purpose to explain on a molecular level the GLC resolutions, as well as other phenomena involving chiral recognition which were found to occur with these amides. The spatial arrangement of the molecules and the contacts between atoms, as observed in the crystal structures, are used to describe the diastereomeric association complexes assumed to be responsible for stereoselectivity.

This approach has been adopted previously. Crystal structure data have been used successfully by Yoneda and co-workers<sup>3</sup> to interpret the resolution of racemic metal-coordination compounds by sodium *d*-tartrate solutions. The crystal structures<sup>4</sup> of the host-guest complexes formed by crown ethers, synthesized by Cram and co-workers,<sup>5</sup> have been determined to examine the host-guest geometry so as to account for observed stereoselectivity.

### II. Molecular Model of Chiral Recognition

Having demonstrated the stability of the 5-Å translation array in the chiral amides  $RCONHCH(CH_3)Ar$ , both in the solid and in the melt,<sup>1</sup> we now propose a model which will account for the discrimination in the interactions of these amides with pairs of enantiomers. It is based on the 5-Å translation H-bonding motif, as found in the crystal, and assumes that a guest molecule intercalates within the H-bonded array of the host matrix. The intercalated enantiomers lead to two diastereomeric arrangements, the different stabilities of which account for the stereoselectivity. Within each arrangement, the molecules implement their potential for optimal contacts.

The intercalation model is presented for the particular case of (*R*)-*N*-lauroyl- $\alpha$ -(1-naphthyl)ethylamine (host) and *N*-trifluoroacetyl- $\alpha$ -phenylethylamine (guest). It is seen (Figure 2a) that the guest molecule with a configuration identical with that of the host intercalates in a manner such that the original motif of H bonding is preserved, the aromatic groups make plane-to-plane contacts, and the hydrogen atom linked to the chiral atom of the guest is wedged between two aromatic rings as in the original stack. The methyl group, linked to the chiral carbon atom of the guest, points away from the stack and does not participate in any intrastack contacts. Let us now consider the insertion of a guest molecule of configuration opposite to that of the host while maintaining the host structure, H bonds, and aromatic overlap between host and guest (Figure 2b). This would demand that the methyl group and the hydrogen atom linked to the chiral carbon atom of the guest be interchanged. The methyl group, thus wedged between two naphthyl planes, would lead to severe overcrowding. Another argument against the likelihood of this structure is based on conformational stabilities. The most stable conformation of the isolated molecule according to energy calculations—and also observed in the crystalline state—corresponds to  $\phi = 135^\circ$  and  $\psi = 109^\circ$  (see Figure 1).<sup>6</sup> Interchange of the hydrogen atom and methyl group would lead to a conformation in which  $\phi = -135^\circ$  and  $\psi = -109^\circ$ , which is distinctly less stable by about 12 kcal/mol