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Base Catalyzed Hydrolysis and $^{18}O{=}C$ Exchange of Ethyl and Isopropyl Toluoate in H_2O and D_2O Media. The Anionic Tetrahedral Intermediates Are Protonically Equilibrated

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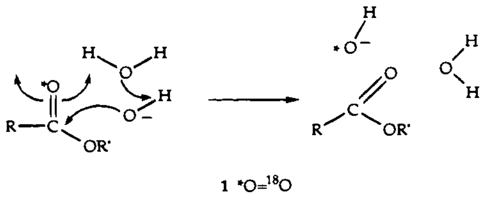
Abstract: To answer the question of whether the anionic tetrahedral intermediates produced from base hydrolysis of esters are in protonic equilibrium, ^{18}O exchange studies of the esters ethyl toluoate (**2**) and isopropyl toluoate (**3**) recovered from the basic hydrolysis medium in H_2O and D_2O at 25 °C were undertaken. The observed deuterium solvent kinetic isotope effects on $(k_{hyd})_{H_2O/D_2O}$ are 0.75 and 0.81 for **2** and **3**, respectively. For the $^{18}O{=}C$ exchange process, the DSKIEs are $(k_{ex})_{H_2O/D_2O} = 0.97$ and 0.86 for **2** and **3**. Overall $(k_{ex}/k_{hyd})_{H_2O} = 0.068$, $(k_{ex}/k_{hyd})_{D_2O} = 0.052$ for **2**; for **3** these values are $(k_{ex}/k_{hyd})_{H_2O} = 0.15$, $(k_{ex}/k_{hyd})_{D_2O} = 0.14$. On the basis of these results there is no compelling evidence for a process limiting the exchange where there is a proton in flight generating a strong primary deuterium kinetic isotope effect.

Base promoted hydrolysis of carboxylic acid esters is a well-studied process that adheres to the accepted mechanism depicted in Scheme 1.[1] That the reaction proceeds in most cases through the reversible formation of anionic tetrahedral intermediates (To^-) has largely been evidenced by seminal ^{18}O-exchange studies of Bender[2] and Shain and Kirsch.[3] Thus, the simple alkyl esters of benzoic acid exhibit $^{18}O{=}C$ exchange concurrent with alkaline hydrolysis, the k_{ex}/k_{hyd} ratios (defined according to Scheme 1 as $k_{hyd} = k_1k_2\,[OH^-]/(k_{-1} + k_2)$; $k_{ex} = k_1\,k_{-1}\,[OH^-]/2(k_{-1} + k_2)$; $k_{ex}/k_{hyd} = k_{-1}/2k_2$) ranging from ~0.4–0.04.

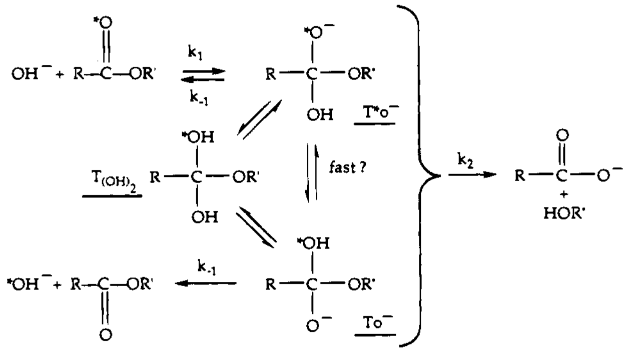
That the k_{ex}/k_{hyd} ratios provide an accurate assessment of the partitioning of the intermediate rests on two necessary assumptions, namely (1) that the intermediates leading to exchange and hydrolysis lie on the same reaction pathway, and (2) that protonic equilibration between the two anionic To^- intermediates (either directly or through the conjugate acid $T_{(OH)_2}$) is rapid relative to either C−(OH) or C−(OR) cleavage. The first assumption, as discussed by Jencks[4] seems eminently reasonable unless one envisions a concerted $^{18}O{=}C$ exchange mechanism involving several proton transfers (as in **1**) that occur in a side reaction at a rate that is fast relative to the lifetime of To^-.



1 *O=^{18}O

The second assumption allows considerable simplification of the expression for the exchange rate constant; thus the factor of 2 in k_{ex} stems from the expectation that only half of the k_{-1} reversal events lead to ^{18}O loss. In the case of esters, several authors have expressed reservations about the validity of this assumption.[2d,3,5–7] The earliest of these reservations were based on such experimental observations as (a) the large effect of a para substituent on the k_{ex}/k_{hyd} ratios for OH^- promoted hydrolysis of methyl benzoates[2d] (subsequently shown not to be reproducible by Shain and Kirsch[3]); (b) the differing behavior of the rates of acid and base hydrolysis of certain alkyl trifluoroacetates to small increases in the [H_2O] using aqueous acetone as a solvent;[5] and (c) the observation that k_{ex}/k_{hyd} is decreased by 2–3-fold in the neutral hydrolysis of ethyl trifluoroacetate when the reaction is run in D_2O.[6] In each of the above cases, reasonable estimates of the lifetimes of the tetrahedral intermediates and protonic exchange rate constants were presented which convincingly argued that assumption (2) might be invalid, at least in some cases. More recently, McClelland and coworkers[7] have directly determined the

Scheme 1



[a] *O = ^{18}O.

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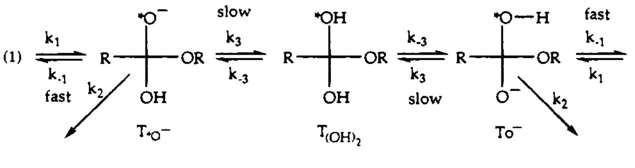
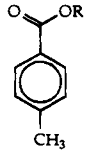
kinetics for breakdown of $PhC(O^-)(OCH_3)_2$ to $PhC(O)(OCH_3) + OCH_3^-$ as a function of pH. The observed maximal rate constant at high pH for breakdown of 9×10^6 s^{-1} is clearly comparable to that for reprotonation of this anionic tetrahedral intermediate. Assuming that this dynamic system represented a reasonable model for the analogous ester hydrolysis tetrahedral intermediates in Scheme 1 leads one to believe that protonic interconversion of the two To^- intermediates, if proceeding through $T_{(OH)_2}$, is competitive with the various C−O bond cleavage reactions.

We have recently undertaken detailed ^{18}O exchange and deuterium solvent kinetic isotope effect (DSKIE) studies of the base catalyzed hydrolysis of certain oxy and thio esters[8] and toluamides[9] to address the question of the partitioning of anionic tetrahedral intermediates. The DSKIE studies, as previously noted,[6,9] provide unique information concerning the validity of assumptions (1) and (2) above. A process such as that in **1** is expected to exhibit a large, normal DSKIE because of the number of protons in flight,[10] so the $(k_{ex})_{H_2O/D_2O}$ is expected to be >1 if **1** represented an important exchange pathway. Similarly, if protonic equilibration were in some way limiting the exchange process (k_3/k_{-3} in eq 1,[7,11] leading to $T_{(OH)_2}$, or some equivalent process directly interconverting $T{*}o^-$ and To^-), then a strong normal DSKIE on k_{ex} is also anticipated.



In order to test the validity of these two assumptions for the basic hydrolysis of esters known to exhibit appreciable ^{18}O exchange, we have undertaken detailed hydrolysis and exchange experiments of the ethyl and isopropyl toluoates **2** and **3** in H_2O and D_2O. The following account of this study indicates that in both cases, there is no strong DSKIE on the exchange process, so that the two assumptions are probably correct, at least for these esters.



2 $R=CH_2CH_3$
3 $R=CH(CH_3)_2$

Experimental Section

(a) Materials. Ethyl toluoate (**2**) and isopropyl toluoate (**3**) were obtained by dropwise treatment of excess alcohol with neat toluoyl chloride followed by heating to reflux for 7 h (in the case of **2**) and 21 h (in the case of **3**). After standard workup procedures, the esters were purified by distillation.

The ^{18}O labeled esters were obtained by the following procedure below described for labeled **3**. To 0.855 mL (0.0065 mol) of toluoyl chloride in a 25-mL flask was added 0.14 mL (0.0077 mol) of 97% $H_2{}^{18}O$. This mixture was allowed to stand at room temperature for 17 h, cooled, and then treated with 25 mL of $SOCl_2$. After heating at 70 °C for 2 h, the excess thionyl chloride was removed by distillation. The ^{18}O labeled toluoyl chloride was distilled (Kugelrohr) and then treated with 3 mL of isopropyl alcohol followed by heating at reflux for 48 h. The excess alcohol was removed, and 25 mL of ether was added to the residue. This solution was extracted with 2 × 5 mL of 5% K_2CO_3, and then 5 mL of saturated NaCl. The solution was dried ($MgSO_4$) and filtered, and the residue was purified by microdistillation: IR ($CHCl_3$ cast) 2981, 1715 ($^{16}O{=}C$), 1685 ($^{18}O{=}C$), 1612, 1276 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.95 (d, 2 H), 7.21 (d, 2 H), 5.23 (m, 1 H), 2.41 (s, 3 H), 1.39 (d, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.63, 21.99, 68.09, 76.64, 77.06, 77.48, 128.30, 128.99, 129.57, 143.28, 166.18 ($^{18}O{=}C$), 166.22 ($^{16}O{=}C$), exact mass calcd for $C_{11}H_{14}{}^{18}O_1{}^{16}O_1$ 180.10362, found 180.10348.

The spectral parameters for ^{18}O labeled **2** are as follows: IR ($CHCl_3$ cast) 2982, 1719 ($^{16}O{=}C$), 1688 ($^{18}O{=}C$), 1613, 1276 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 8.96 (d, 2 H), 7.24 (d, 2 H), 4.48 (q, 2 H), 2.42 (s, 3 H), 1.40 (t, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.93, 21.09, 60.24, 127.54, 128.80, 129.53, 142.91, 166.05 ($^{18}O{=}C$), 166.10 ($^{16}O{=}C$); exact mass calcd for $C_{10}H_{12}{}^{18}O_1{}^{16}O_1$ 166.08797, found 166.08811.

(b) Kinetics. (i) **H_2O.** All base solutions were made by dilution of 19 M NaOH under CO_2 free conditions (drybox) using CO_2 free H_2O (Osmonics-Aries water purification system). Ionic stength was maintained at 0.1 (NaCl). NaOH solutions were titrated with standardized 0.0997 M HCl (Aldrich) using bromothymol blue as an indicator, or with potassium hydrogen phthalate solution using phenolphthalien indicator.

The hydrolysis kinetics of **2** and **3** were monitored at 25 °C, μ = 0.1 (NaCl) by observing the rate of diminution of the UV bands at 248 (**2**) and 250 (**3**) nm using an OLIS modified Cary 17 spectrophotometer. Cuvettes were charged with 3 mL of the appropriate base solution under CO_2 free conditions and allowed to thermally equilibrate in the spectrometer cell holder for 15 min. Reactions were initiated by injecting 125 μL of a 1.75 (for **2**) or 1.85 mM (for **3**) solution of the ester in DME into the aqueous base (final concentration of esters 6 and 5×10^{-4} M, respectively). Reactions were followed in triplicate to at least 5 half times at base concentrations of ~0.01 and 0.1 M.

(ii) **D_2O.** NaOD solutions of 0.0103 and 0.0960 M were made by adding Na metal to D_2O, μ = 0.1 (NaCl). Exact base concentrations were determined by titration against standardized HCl (0.0997 N) using bromothymol blue as an indicator or against potassium hydrogen phthalate using phenolphthalein. Hydrolysis kinetics in D_2O were performed as above.

(c) ^{18}O Exchange. These were conducted following protocols established before[8] for ^{18}O exchange accompanying base promoted amide hydrolysis. Care was taken to ensure that the esters (particularly **3**) were soluble in the medium, and a typical experiment is described below for **3**.

To 700 mL of the appropriate base solution (0.0102 and 0.095 M NaOH, μ = 0.1 (NaCl)) in a 1000 mL volumetric flask (equilibrated in a 25 °C thermostated bath) was aded 30 mL of a 0.0125 M solution of **3** in DME. The flask was inverted several times and allowed to stand in the 25 °C bath for the appropriate time (up to 3 half-times of hydrolysis during which 100-mL fractions of the reaction mixture were removed at various times and quenched with 88 μL (or 0.86 mL for 0.095 M NaOH) of 7.35 M H_3PO_4. The final pH was 6−7. The solution was extracted with 3 × 30 mL of distilled CH_2Cl_2. The combined CH_2Cl_2 extracts were dried and filtered, and the volatiles were removed. To the residue were added 10 drops of CH_2Cl_2; this was then transferred to a vial for low resolution mass analysis.

The ^{18}O exchange for **2** and **3** was also conducted in D_2O solutions (0.0960 M NaOD, μ = 0.1 (NaCl) for **3**; and 0.0103 M NaOD, μ = 0.1 (NaCl) for **2**) using the above protocol.

In each of the above cases, ^{18}O analyses were conducted in duplicate at 5 to 6 times up to $3t_{1/2}$ hydrolysis. The ^{18}O content in recovered

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Table 1. Rate Constants for Hydrolysis of **2** and **3** in Base, T = 25 °C, $\mu = 0.1$ (NaCl)

ester	[NaOL] (M)	k_{obs} (s^{-1})[a]	k_{hyd} (M^{-1} s^{-1})[b]
2	0.00979	$(1.42 \pm 0.01) \times 10^{-4}$	0.015 ± 0.001
2	0.00912	$(1.39 \pm 0.03) \times 10^{-3}$	
2	0.00989 (D_2O)	$(1.39 \pm 0.06) \times 10^{-4}$	0.020 ± 0.007
2	0.0922 (D_2O)	$(1.81 \pm 0.07) \times 10^{-3}$	
3	0.00956	$(3.1 \pm 0.1) \times 10^{-5}$	$(3.37 \pm 0.12) \times 10^{-3}$
3	0.0922	$(3.10 \pm 0.04) \times 10^{-5}$	
3	0.00989 (D_2O)	$(4.64 \pm 0.09) \times 10^{-5}$	$(4.17 \pm 0.64) \times 10^{-3}$
3	0.0922 (D_2O)	$(3.87 \pm 0.09) \times 10^{-4}$	

[a] Pseudo-first-order rate constant; average of 3–4 determinations, error are ±1 SD of average k_{obsd}; contains 4% DME. [b] k_{hyd} is second-order rate constant computed from linear regressions of plots of k_{obsd} vs [OH^-]; quoted errors are ±2 SD of the slope.

Table 2. Rate Constants for ^{18}O Exchange Accompanying Base Hydrolysis of ^{18}O-Labeled **2** and **3**, T = 25 °C, $\mu = 0.1$ (NaCl)

ester	[NaOL] (M)	k_{obs} (s^{-1})[a]	k_{ex} (M^{-1} s^{-1})[b]
2	0.00981	$(1.07 \pm 0.07) \times 10^{-5}$	1.09×10^{-3}
2	0.00981	$(1.02 \pm 0.09) \times 10^{-5}$	1.04×10^{-3}
2	0.00927	$(8.9 \pm 1.1) \times 10^{-6}$	9.6×10^{-4}
			av = $(1.02 \pm 0.14) \times 10^{-3}$
2	0.00989 (D_2O)	$(1.04 \pm 0.02) \times 10^{-5}$	$(1.05 \pm 0.04) \times 10^{-3}$
3	0.0913	$(4.82 \pm 0.25) \times 10^{-5}$	5.28×10^{-4}
3	0.092	$(4.33 \pm 0.15) \times 10^{-5}$	4.71×10^{-4}
			av = $(4.99 \pm 0.80) \times 10^{-4}$
3	0.0922 (D_2O)	$(5.37 \pm 0.07) \times 10^{-5}$	$(5.82 \pm 0.16) \times 10^{-4}$

[a] Pseudo-first-order rate constant; k_{obsd} determined from linear regression of ln (% ^{18}O) *vs* time; 6–8 data points; error is ±1 SD of the slope; contains 4% DME for solubility. [b] Average k_{ex} is the mean of the individual k_{obsd}/ [OL^-] values. For **2** and **3** in H_2O, errors in k_{ex} are given as ±2 SD from the mean. In D_2O, since k_{ex} is a single number, the errors are given ±2 SD of the linear regression of ln ^{18}O *vs* time.

ester was determined as percent $^{18}O = 100 \times I_{M^{+}+2}/(I_{M^{+}} + I_{M^{+}+2})$ where I is the intensity of the M^+ and M^++ 2 peaks: 20–25 scans of these peaks were taken for each sample. The percent ^{18}O vs time data are given in Tables 1S–9S, supplementary material.

Results

Given in Table 1 are the hydrolysis rate constants for **2** and **3** in H_2O and D_2O media at 25 °C. The solutions contained 4% DME for solubility of the esters so that the hydrolysis and ^{18}O exchange experiments (the latter require higher [ester]) could be directly compared. In comparing the hydrolytic data in H_2O and D_2O, inverse DKIE for the hydrolysis of **2** and **3** are observed, $(k_{hyd})_{H_2O/D_2O}$ = 0.75 ± 0.27 and 0.81 ± 0.13, respectively.

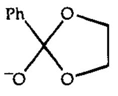
^{18}O exchange accompanying the hydrolysis was determined by low resolution mass analysis of ester recovered from the hydrolytic media at various times up to $3t_{1/2}$ hydrolysis. The k_{ex} rate constants for **2** and **3** in basic media are given in Table 2. In the case of the exchange studies in D_2O, the low solubility of the esters required large volumes of D_2O, so only a single base concentration was investigated for each ester. Using the average values for the k_{ex} and k_{hyd} data given in Tables 2 and 1, the following ratios can be computed: for **2** $(k_{ex}/k_{hyd})_{H_2O} = 0.068 \pm 0.005$, $(k_{ex}/k_{hyd})_{D_2O} = 0.052 \pm 0.009$; for **3** $(k_{ex}/k_{hyd})_{H_2O} = 0.15 \pm 0.01$, $(k_{ex}/k_{hyd})_{D_2O} = 0.14 \pm 0.01$.

Discussion

Bender and coworkers[2a,c] originally investigated ^{18}O exchange accompanying the basic hydrolysis of ethyl benzoate and isopropyl benzoate in H_2O and 33% dioxane/H_2O at 25 °C. The k_{ex}/k_{hyd} ratios found in H_2O were; ethyl benzoate $(k_{ex}/k_{hyd})_{H_2O} = 0.21$; isopropyl benzoate $(k_{ex}/k_{hyd})_{H_2O} = 0.37$. In 33% dioxane/$H_2O$ the reported values were 0.09[2a,c] and 0.27,[2a] the latter value being determined at 62.5 °C. Kirsh and Shain also report a $(k_{ex}/k_{hyd})_{H_2O} = 0.08$ for ethyl benzoate at 25 °C. The values reported for H_2O compare favorably with those we have determined for the toluoyl derivatives **2** ($k_{ex}/k_{hyd} = 0.068$) and **3** ($k_{ex}/k_{hyd} = 0.15$).

In subsequent studies with para substituted methyl benzoates in 33% dioxane/H_2O, Bender and Thomas[2d] reported that the para substituent has a large effect on the k_{ex}/k_{hyd} ratio. They interpreted this as signifying that the assumption of complete protonic equilibration of the tetrahedral intermediates may be incorrect. However, subsequent studies by Shain and Kirsch[3] failed to detect any ^{18}O depletion in the p-CH_3, p-H, or p-NO_2 derivatives accompanying the base hydrolysis in 33% dioxane/H_2O. While these latter findings cast doubt on the experimental underpinnings for questioning the assumption of protonic equilibration of the tetrahedral intermediates, both Kirsch[3] and Bender[2d] presented reasonable arguments that the lifetime of the tetrahedral intermediates was sufficiently short that protonic equilibration of the intermediates was incomplete. At best, they concluded, only lower limits for the k_{-1}/k_2 partitioning ratios could be ascertained from the experimental k_{ex}/k_{hyd} ratio.

More recently, McClelland has investigated the breakdown of the hemiorthoester anion **4** and has given an estimate of ~10 ns for its lifetime.[11] That value compares favorably with the 10–100 ns lifetime quoted for anion **5**.[12] Accordingly, it was suggested[11] that if the expulsion of alkoxide can occur with a rate constant of 10^7–10^8 s^{-1}, the situation could easily be reached with small variations in leaving group abilities where the lifetime of the anionic tetrahedral intermediate could be shorter than proton switches through water bridges, these having rate constants on the order of 5×10^7–5×10^8 s^{-1}.[13]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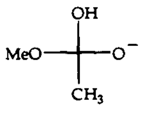
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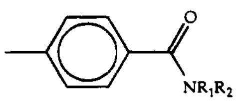
6a $R_1 = R_2 = CH_3$
b R_1,R_2 = $\left(CH_2CH_2\right)$
c R = Et, R_2 = $-CH_2CF_3$

This may well be the case for To^- intermediates produced from benzyl benzoates,[2e] phenyl benzoate,[14] pthalide,[7,15] thiophthalide,[8] and ethyl thiobenzoate[8] for which no ^{18}O exchange is observed to accompany base hydrolysis. Unfortunately, since no ^{18}O exchange is observed in these cases, one cannot probe the question of protonic equilibration using DSKIE studies.[8]

The question still remains as to whether the To^- produced from esters with simple alkoxy leaving groups are in protonic equilibrium. The present study aims to provide an answer to this long standing and fundamental problem by determining whether a solvent DKIE exists on the ^{18}O exchange accompanying base hydrolysis of esters **2** and **3**. Similar earlier studies of the base hydrolysis of toluamides **6a-c**[9c,d] revealed that there

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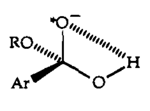
was no solvent DKIE on the ^{18}O exchange: accordingly protonic equilibration of the intermediates was suggested to be complete prior to their breakdown. In the case of esters **2** and **3**, k_{hyd} shows slightly inverse DKIEs of 0.75 ± 0.27 and 0.81 ± 0.13, respectively which is consistent with what is observed for OH^- attack on related esters[8] and toluamides.[9c,d] Important for our purposes is the fact that the exchange process shows almost no dependence on the isotopic composition of the solvent, $(k_{ex})_{H_2O/D_2O}$ being 0.97 ± 0.14 for **2** and 0.86 ± 0.14 for **3**. For these two esters, the most easily interpretable values to address the isotopic effect on the partitioning of the intermediates is $(k_{ex}/k_{hyd})_{H_2O/D_2O}$ since this compares the two breakdown transition states directly. For **2**, $(k_{ex}/k_{hyd})_{H_2O/D_2O} = 1.31 \pm 0.25$, while for **3** this value is 1.07 ± 0.10. Given the inherent errors in the rate constants, and those propagated in the computation of the $(k_{ex}/k_{hyd})_{H_2O/D_2O}$ ratios,[16] we cannot say that these values are significantly different from unity. Thus, whatever the mechanism is for equilibration of $T^{\cdot}o^-$ and To^-, we find no compelling evidence for a rate determining step that would involve protons in flight leading to a strong normal solvent DKIE.

Mechanistic Possibilities. The lack of an observable isotope effect on k_{ex} or k_{ex}/k_{hyd} for these two esters is consistent with a number of possibilities listed below in increasing order of acceptability. There are three plausible models, **7**–**9**, for the proton transfer required to equilibrate $T^{\cdot}o^-$ and To^-. These involve, respectively, a concerted proton switch through a four membered T. S.; a stepwise protonation of $T^{\cdot}o^-$ or To^- by H_2O followed by deprotonation by OH^-, and a fully concerted proton shift through one (or more) bridging waters. We have assumed that, if rate limiting, the proton switch required to equilibrate the two oxygens in To^- should show a large and normal solvent DKIE. This is a reasonable assumption,[10] particularly if the proton transfers proceed through bridging waters which is generally the case for O or N acids and bases.[17] A cyclic concerted mechanism as in **9** would have a large primary kinetic isotope effect because there are two or more protons in flight: this assumption was made by Bell et al.[18] in their analysis of ketone hydration which bears a formal similarity to the $T^{\cdot}o^- \rightleftharpoons To^-$ equilibration. In the case of the N to C proton shift required to convert $10^{\pm}$ into **10** Bernasconi and co-workers[19] have found a large solvent DKIE of 3.3–3.7, the value depending upon whether the amine portion is glycine or morpholine. Although proton transfer between acids and carbon bases normally occurs directly,[20] proton inventory studies[19] indicated that the $\mathbf{10}^{\pm} \rightleftharpoons \mathbf{10}$ interconversion involved one or two intervening waters: apparently direct $N-H \rightarrow C$ transfer through a four membered T.S. analogous to that in model **7** is energetically unfavorable. Hence we conclude that if the rate limiting steps proceeded through model **9**, a large normal primary DKIE is expected. Similarly, if the proton transfer is stepwise, proceeding through $T_{(OH)_2}$ as in model **8**, one anticipates a normal primary DKIE albeit possibly smaller than for **9**, since there is only one proton in flight.



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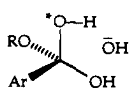

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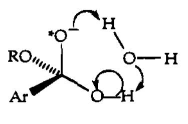

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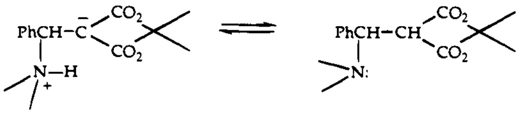

$10^{\pm}$ 10

There are reasons that the $T^{\cdot}o^- \rightleftharpoons To^-$ equilibration could involve rate limiting proton transfer, but the DKIE would be smaller than maximal. These reasons have been discussed in relation to the 4-membered $N-H \rightarrow C$ proton shift transition state for $\mathbf{10}^{\pm} \rightleftharpoons \mathbf{10}$ by Bernasconi et al.[19] These include nonlinearity of the possible transition states or highly asymmetric ones.[21] The former would certainly have bearing for ester hydrolysis if the proton transfer proceeded intramolecularly as in the highly bent model **7**. Nevertheless, such a strained four-membered T.S. would probably be too high in energy to be a viable one for the proton transfer in H_2O,[22] particularly since proton transfers between oxygen usually occur through bridging waters.[13d,20] Accordingly, we tentatively reject **7** as being a viable candidate for the oxygen equilibration.

This leaves us with the more palatable conclusion that the DKIE experiments rule out a rate limiting step for the exchange process involving proton transfers. One must first consider a case where the two oxygens in To^- become equilibrated by some rate limiting physical process such as conformational change within the solvent cage having prior or subsequent fast proton transfer. Deslongchamps has considered this sort of conformational change is required for ^{18}O exchange to occur during the hydrolysis of carboxylic acid derivatives.[23] The above solvent DKIE on k_{ex} does not point to which of a heavy atom bond cleavage or conformational change is rate limiting for k_{-1}. We can however state the expected DKIE for exchange if conformational isomerization is rate limiting. The latter should have an isotope effect similar to that for diffusion[9c] because it involves a similar displacement of the solvent molecules with disruption of the hydrogen bond network. Ridd[24] calculates on the basis of the viscosity differences between H_2O and D_2O that a diffusion limited process should exhibit a (k_{H_2O}/k_{D_2O}) of ~1.21 at 19°; the value at 25 °C cannot be much different. Such a value is not inconsistent with what we observe for $(k_{ex})_{H_2O/D_2O}$. However, the fact that exchange is more prevalent for the more highly sterically encumbered isopropyl ester **3** than for **2** leads us to believe that any conformational changes required for exchange are fast relative to the bond cleavage reactions.

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(16) For propagated error in a ratio, where $z = x/y$, the standard error is given as

$$\delta z = |z|\sqrt{(\delta x/x)^2 + (\delta y/y)^2}$$

(17) (a) Eigen, M. *Angew. Chem., Int. Ed. Engl.* **1964**, *1*, 3. (b) Grunwald, E.; Eustace, D. In *Proton Transfer Reactions*; Caldin, E.; Gold, V., Eds.; Chapman & Hall: London, 1975, pp 103–120.

(18) Bell, R. P.; Millington, J. P.; Pink, J. M. *Proc. Roy. Soc. London A* **1968**, *303*, 1.

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(20) (a) Hibbert, F. *Compr. Chem. Kinet.* **1977**, *8*, 97. (b) Albery, W. J. In *Proton Transfer Reactions*; Caldin, E., Gold, U., Eds.; Chapman and Hall: London, 1975; p 285. (c) Bednar, R. A.; Jencks, W. P. *J. Am. Chem. Soc.* **1985**, *107* and references therein.

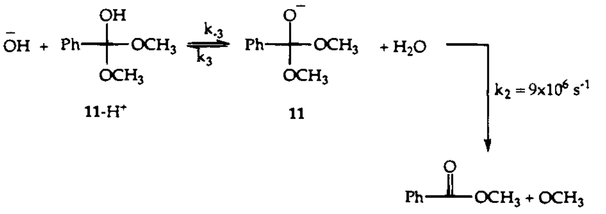
(21) (a) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 785. (b) Melander, L.; Saunders, W. H. *Reaction Rates of Isotopic Molecules*; Wiley-Interscience: New York, **1980**, p 42. (c) More O'Ferrall, R. A. In *Proton Transfer Reactions*; Caldin, E.; Gold, V., Eds.; Wiley: New York, **1975**, p 201. (d) Westheimer, F. H. *Chem. Rev.* **1961**, *61*, 265.

(22) A recent computational study considered the gas phase intramolecular proton transfer between the oxygens in the monoanion of oxalic acid and concluded that the shift occurs through a strained five-membered T. S. having a strong 1° DKIE due to the inplane stretch and various binding modes of the H. Truong, T. N.; McCammon, J. A. *J. Am. Chem. Soc.* **1991**, *113*, 7504.

(23) Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Pergamon: London, 1983.

(24) Ridd, J. H. *Adv. Phys. Org. Chem.* **1978**, *16*, 1.

Finally, we consider our preferred mechanism where the anionic tetrahedral intermediates are at protonic equilibrium viaa fast concerted proton switch through bridging water followed by rate limiting heavy atom bond cleavages (k_2 and k_{-1}). McClelland and co-workers[7] have recently presented compelling evidence that methoxide cleavage from **11** occurs with a rate constant of 9×10^6 s^{-1}. Their work allows one to accurately determine the p*K*a for the conjugate acid of **11** (**11-H**$^+$) as 11.08. This value is similar to the value computed by Guthrie and Cullimore[25] for the p*K*a of $PhC(OH)_2OCH_3$ (11.01). That value is certainly close to the hydrates of the ethyl and isopropyl toluoates studied here, and we accept the k_2 value for cleavage of **11** as being appropriate for breakdown of To^- to product. With a p*K*a of roughly 11, and assuming that OH^- deprotonation of the ester hydrates in the thermodynamically favored direction occurs at the diffusion limit, k_{-3} in eq 2 must be $\sim 10^{10}$ M^{-1} s^{-1} and k_3 is $\sim 10^7$ s^{-1}. As McCelland argues,[7] the fact that k_2 and k_3 are on the same order of magnitude indicates that **11-H**$^+$ and **11** (and by inference $T_{(OH)_2}$ and To^- of eq 1) are not in full protonic equilibrium. Unfortunately, it is not possible to put exact values on the rate constants in eq 2 that are germane to $T_{(OH)_2}$ and To^- since these are slightly different from the hemiorthoester system. Nevertheless, the unit isotope effect on k_{ex} for both esters studied here suggests that if the pathway for equlibration involves $T^*o^- \rightleftharpoons T_{(OH)_2} \rightleftharpoons To^-$ as in eq 1, then the k_3/k_2 ratio is sufficiently larger than 1 to satisfy the observed DKIE. Alternatively we suggest a rapid, concerted interconversion of $T^*o^- \rightleftharpoons To^-$ via a bridging H_2O which avoids the formation of $T_{(OH)_2}$. Such processes have been suggested earlier to be operative in the protonic equilibration of the oxygens in carboxylic acids[13b,c] and in the case of equlibration of the CH_3CO_2H oxygens the proton switch through bridging H_2O has a value of 4.8×10^7 s^{-1}. The analogous process in the case of To^- could easily have a larger rate constant which would be consistent with the DSKIE experiments herein.

(2)


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Supplementary Material Available: Tables of ^{18}O content *vs* time for esters **2** and **3** recovered from the hydrolytic media (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(25) Guthrie, J. P.; Cullimore, P. A. *Can. J. Chem.* **1980**, *58*, 1281.