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Dynamics for Reaction of an Ion Pair in Aqueous Solution: Reactivity of Carboxylate Anions in Bimolecular Carbocation–Nucleophile Addition and Unimolecular Ion Pair Collapse

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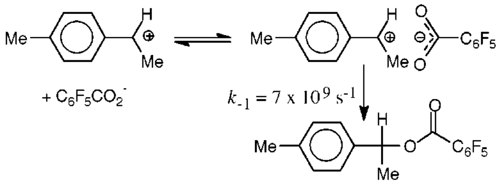
ABSTRACT



The sum of the rate constants for solvolysis and ^{18}O-scrambling of 4-MeC$_6$H$_4$^{13}CH(Me)^{18}OC(O)C$_6$F$_5$ in 50/50 (v/v) trifluoroethanol/water, $k_{solv} + k_{iso} = 1.22 \times 10^{-5}$ s^{-1}, is larger than $k_{solv} = 1.06 \times 10^{-5}$ s^{-1} for solvolysis of the unlabeled ester. This shows that the ion pair intermediate undergoes significant internal return. The data give $k_{-1} = 7 \times 10^9$ s^{-1} for internal return by unimolecular collapse of the ion pair, which is significantly larger than $k_{Nu} = 5 \times 10^8$ M^{-1} s^{-1} for bimolecular nucleophilic addition of carboxylate anions to 4-MeC$_6$H$_4$CH(Me)$^+$.

Although the experimental protocols for detection of the reactions of carbocation−anion ion pairs are well developed,[1] there is substantial unrealized potential for the utilization of these methods in the estimation of *absolute* rate constants for the very fast reactions of ion pairs.[2,3]

We report here an examination of ^{18}O-scrambling that accompanies solvolysis of the ^{18}O-labeled ester 4-MeC$_6$H$_4$^{13}CH(Me)^{18}OC(O)C$_6$F$_5$ (**1-^{18}OC(O)C$_6$F$_5$**, Scheme 1) and a determination of the relative rates of reaction of the ion pair intermediate to form the ^{18}O-scrambeled isomerization product **1-OC(^{18}O)C$_6$F$_5$** (k_{-1}') and the solvent adducts ($k_s' + k_{-d}$, Scheme 1). The results of these experiments allow for an estimate of the *absolute* rate constant $k_{-1} \approx k_{-1}'$ for unimolecular carbocation−anion collapse (Scheme 1) and a comparison of the reactivity of carboxylate anions toward

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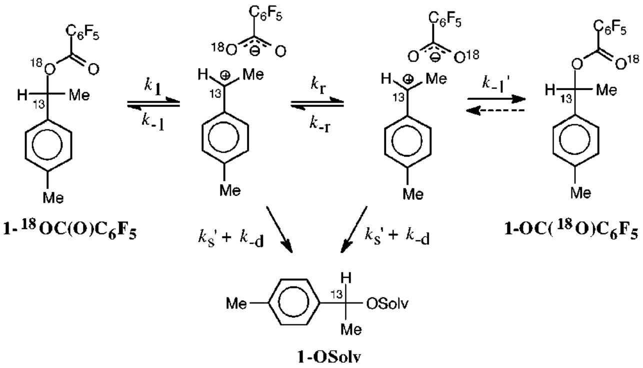
Scheme 1



the 1-(4-methylphenyl)ethyl carbocation $\mathbf{1}^+$ in unimolecular and bimolecular reactions.

1-(4-Methylphenyl)ethyl pentafluorobenzoate labeled with carbon-13 at the benzylic carbon and oxygen-18 at the bridging benzoate oxygen was prepared by the following sequence of reactions: (1) Reaction of 4-MeC_6H_4MgBr with $^{13}CO_2$ to give $4\text{-MeC}_6H_4{}^{13}CO_2H$;[4] addition of MeLi by adaptation of a published procedure to give $4\text{-MeC}_6H_4{}^{13}COMe$;[5,6] reduction with sodium borohydride to give $4\text{-MeC}_6H_4{}^{13}CH(Me)OH$. (2) Perchloric acid-catalyzed exchange of the hydroxyl group of the alcohol in $H_2{}^{18}O$ to give a mixture of $4\text{-MeC}_6H_4{}^{13}CH(Me)^{18}OH$ and $4\text{-MeC}_6H_4{}^{13}CH(Me)OH$.[7] (3) Esterification of this isotopic mixture of alcohols with pentafluorobenzoyl chloride.[8]

The ^{13}C NMR spectrum of the final ester product showed peaks at 75.520 and 75.481 ppm due to the carbon-13-enriched benzylic carbons of **1-OC(O)C$_6$F$_5$** and **1-^{18}OC(O)C$_6$F$_5$**, respectively.[9] The ^{18}O perturbation of the chemical shift of the benzylic carbon, 0.039 ppm upfield, is similar to that observed in earlier work for related sulfonate esters.[1c−e] The ratio of the integrated areas of the two peaks for the benzylic carbons was 1.21:1, which shows that the ^{18}O enrichment of the bridging ester oxygen was 45%.

The reaction of the mixture of **1-OC(O)C$_6$F$_5$** (55%) and **1-^{18}OC(O)C$_6$F$_5$** (45%) in 50/50 (v/v) TFE/H_2O (TFE = trifluoroethanol) (80 mol % water) at 25 °C ($I = 0.50$, $NaClO_4$) was monitored by quantitative ^{13}C NMR spectroscopy.[9] A low substrate concentration (0.3 mM) was used because of its low solubility in this predominantly aqueous solvent.[10] This solvent allows for an examination of the reactions of the carbocation−anion ion pair intermediate under conditions where it is particularly unstable and undergoes very fast diffusional separation to give the free ions.[2b]

Table 1 gives the decreases with time in the normalized areas, A_{nor}, of the ^{13}C NMR signals due to the benzylic carbon of the starting esters **1-OC(O)C$_6$F$_5$** (75.520 ppm) and **1-^{18}OC(O)C$_6$F$_5$** (75.481 ppm) and the ^{18}O-scrambeled isomerization product **1-OC(^{18}O)C$_6$F$_5$** (75.514 ppm) (Scheme 1). The latter signal is partly resolved from the signal for **1-OC(O)C$_6$F$_5$**. The solvolysis of unlabeled **1-OC(O)C$_6$F$_5$** under the same reaction conditions has been shown to proceed by a stepwise mechanism through the 1-(4-methyphenyl)ethyl

Table 1. Normalized Areas of the ^{13}C NMR Signals Due to the Benzylic Carbon during Reaction of an Isotopic Mixture of **1-OC(O)C$_6$F$_5$** and **1-^{18}OC(O)C$_6$F$_5$** in 50/50 (v/v) Trifluoroethanol/Water at 25 °C ($I = 0.50$, $NaClO_4$)

		A_{nor}		
		1-OC(O)C$_6$F$_5$	**1-OC(^{18}O)C$_6$F$_5$**	**1-^{18}OC(O)C$_6$F$_5$**
time (s)	$(A_{\text{nor}})_T$[a]	75.520 ppm	75.514 ppm	75.481 ppm
0	1.00	0.55[b]		0.45[b]
81 000	0.42	0.23[c,d]	0.026[c,e]	0.17[f]
172 800	0.16	0.088[c,d]	0.010[c,e]	0.055[f]

[a] Normalized sum of the ^{13}C NMR peak areas due to the benzylic carbon of all isotopic forms of the ester, calculated as $(A_{\text{nor}})_T = e^{-kt}$, where $k = k_{\text{solv}} = 1.06 \times 10^{-5}\ s^{-1}$ for solvolysis of the unlabeled ester determined by HPLC analysis. [b] Calculated from the overall 45% ^{18}O enrichment of the starting ester (^{16}O:^{18}O = 1.21:1) determined by ^{13}C NMR (see text). [c] The ^{13}C NMR signals for the benzylic carbons of **1-OC(O)C$_6$F$_5$** and **1-OC(^{18}O)C$_6$F$_5$**, both of which contain ^{16}O at the bridging position, are partly resolved (see text). [d] Calculated from $(A_{\text{nor}})_o = 0.55$ at zero time using the relationship $A_{\text{nor}} = (A_{\text{nor}})_o e^{-kt}$, where $k = k_{\text{solv}} = 1.06 \times 10^{-5}\ s^{-1}$ for solvolysis of the unlabeled ester determined by HPLC analysis. [e] Calculated as the difference between $(A_{\text{nor}})_T$ and the sum of the values of A_{nor} for the other two isotopic forms of the ester. [f] Calculated from $(A_{\text{nor}})_T$ and the experimental ratio of the integrated areas of the combined signals due to the two esters containing ^{16}O at the bridging position and the signal due to the ester containing ^{18}O at the bridging position.

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(4) 4-Methylphenylmagnesium bromide was prepared by reaction of 2.5 g of magnesium with 17 g (99 mmol) of 4-bromotoluene in 200 mL of ether. This solution was stirred overnight at room temperature in the presence of 1 L of $^{13}CO_2$ (99% enrichment, Aldrich). The reaction was quenched with 10% HCl (200 mL), the product was extracted into ether, and the ethereal layer was washed with saturated brine. The acid was extracted into 10% NaOH which was then carefully neutralized with concentrated HCl. The product was collected by filtration, dried in vacuo, and used without further purification (58% yield).

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(6) $4\text{-MeC}_6H_4{}^{13}CO_2H$ (7.9 g, 58 mmol) was dissolved in 400 mL of dry tetrahydrofuran at 0 °C, and 200 mL of a 1.4 M solution (0.28 mol) of methyllithium in pentane (Kantoh) was added. The mixture was stirred at 0 °C for 2 h. The reaction was quenched by the addition of trimethylchlorosilane (116 g, 1.1 mol), and stirring was continued for 2 h. Then 10% HCl (200 mL) was added, and the product was extracted into ether and purified by chromatography on silica gel to give $4\text{-MeC}_6H_4{}^{13}COMe$ (64% yield).

(7) $4\text{-MeC}_6H_4{}^{13}CH(Me)OH$ (1 g) was suspended in 1 g of $H_2{}^{18}O$ (98% enrichment, Shoko Ltd.), and 0.10 mL aqueous 1 M $HClO_4$ was added. The mixture was stirred at room temperature for 1 week. The alcohol was extracted into ether, and the ethereal solution was washed with saturated brine, dried over $MgSO_4$, and evaporated to give the oxygen-18 enriched alcohol which was esterified without further purification.

(8) Oxygen-18 enriched $4\text{-MeC}_6H_4{}^{13}CH(Me)OH$ (0.34 g, 2.5 mmol) was reacted with 1.7 molar equiv of pentafluorobenzoyl chloride with stirring at 0 °C for 0.5 h followed by 1 h at room temperature. The reaction was quenched with ice-cold $NaHCO_3$ (30 mL). Recrystallization from ether/hexane gave the ester (52% yield): mp 62−63 °C (lit. mp 63−64 °C).[2a] The carbon-13 enrichment of the ester (99%) was determined by comparison of the integrated ^1H NMR (500 MHz) peak areas of the quartets due to the methine protons attached to carbon-12 and to carbon-13 ($J_{CH} = 150$ Hz).

(9) Proton-decoupled ^{13}C NMR spectra were recorded on a JNM-A500 FT NMR spectrometer operating at 126 MHz. Spectra used to determine the oxygen-18 enrichment at the bridging and nonbridging positions of the ester were acquired using a sweep width of 250 Hz, 8192 data points (0.03 Hz/pt), and an 8 s relaxation delay.

(10) The ester substrate (20 mg) was dissolved in 1 mL of acetonitrile, and this solution was added to 200 mL of 50/50 (v/v) TFE/H_2O ($I = 0.50$, $NaClO_4$) to give a final substrate concentration of 0.3 mM. At specified reaction times of 22.5 or 48 h, the remaining substrate and reaction products were extracted into 400 mL of ether, the ethereal extract was washed with water, dried over $MgSO_4$, and evaporated. The resulting residue was dissolved in $CDCl_3$ and analyzed by ^{13}C NMR.

carbocation intermediate **1**$^+$ which has a significant lifetime in 50/50 (v/v) TFE/H$_2$O and undergoes solvent addition with $k_s = 6 \times 10^9$ s^{-1}.[2] Any isomerization of this substrate by intramolecular ^{18}O-scrambling should also proceed through this moderately stabilized carbocation, because there is no significant driving force for a concerted reaction that avoids its formation.[11]

The data in Table 1 are governed by two first-order rate constants. (1) Values of $(A_{\mathrm{nor}})_{\mathrm{T}}$, which is the normalized sum of the ^{13}C NMR peak areas due to the benzylic carbon of all isotopic forms of the ester, were calculated from $k_{\mathrm{solv}} = 1.06 \times 10^{-5}$ s^{-1} for solvolyses of both the ^{16}O- and ^{18}O-labeled forms of substrate that were determined by following the disappearance of the unlabeled substrate under the same reaction conditions by HPLC. (2) A larger value of $k_{\mathrm{obsd}} = (k_{\mathrm{solv}} + k_{\mathrm{iso}}) = 1.22 \times 10^{-5}$ s^{-1} for the disappearance of **1-^{18}OC(O)C$_6$F$_5$** to give both the solvolysis products **1-OSolv** and the isomerization product **1-OC(^{18}O)C$_6$F$_5$**. This rate constant was determined from the changes in A_{nor} for **1-^{18}OC(O)C$_6$F$_5$** with time. The difference in these rate constants, $(k_{\mathrm{obsd}} - k_{\mathrm{solv}})$, gives $k_{\mathrm{iso}} = 1.6 \times 10^{-6}$ s^{-1}, the rate constant for isomerization of **1-^{18}OC(O)C$_6$F$_5$** to give **1-OC(^{18}O)C$_6$F$_5$**.[12]

The fraction of **1-^{18}OC(O)C$_6$F$_5$** that undergoes isomerization to give **1-OC(^{18}O)C$_6$F$_5$**, $k_{\mathrm{iso}}/k_{\mathrm{obsd}} = 0.13$, is much smaller than the observed 73% isomerization of the corresponding thionobenzoate ester **1-OC(S)C$_6$F$_5$** to give the thiolbenzoate ester **1-SC(O)C$_6$F$_5$** under the same reaction conditions.[3] This reflects the greater nucleophilic reactivity of sulfur at an ion pair containing the thiobenzoate anion than of oxygen at an ion pair containing the pentafluorobenzoate anion.[13]

Scheme 1 shows a minimal mechanism for the observed solvolysis and isomerization reactions of **1-^{18}OC(O)C$_6$F$_5$** in 50/50 (v/v) TFE/H$_2$O. Values of $k_s' = 6 \times 10^9$ s^{-1} for the direct nucleophilic addition of solvent to, and $k_{-d} = 1.6 \times 10^{10}$ s^{-1} for the irreversible diffusional separation of, 1-(4-methylphenyl)ethyl carbocation−anion ion pairs have been reported in earlier work.[2b] Both of these reactions result, eventually, in formation of the solvent adducts **1-OSolv** (Scheme 1). We have shown in previous work that reorganization of the ion pair intermediate of the reaction of **1-OC(S)C$_6$F$_5$**, $k_r = k_{-r} = 10^{11}$ s^{-1}, is significantly faster than nucleophilic addition of solvent to and diffusional separation of the ion pair, $k_r > (k_s' + k_{-d}) = 2.2 \times 10^{10}$ s^{-1}.[3] Therefore, the observation that the isomerization of **1-^{18}OC(O)C$_6$F$_5$** is slower than its solvolysis requires that reaction of the ion pair to form **1-OSolv** be faster than unimolecular collapse of the ion pair, $(k_s' + k_{-d}) > k_{-1}'$ (Scheme 1). This shows that isomerization of **1-^{18}OC(O)C$_6$F$_5$** to give **1-OC(^{18}O)C$_6$F$_5$** takes place by reorganization of the first-formed ion pair intermediate (k_r) followed by rate-limiting ion pair collapse (k_{-1}').

Equations 1−3 give the relationships between the experimental rate constants k_{solv} and k_{iso} and the microscopic rate constants for the individual steps in Scheme 1. These rate laws were derived by making the assumptions that $k_{-1} = k_{-1}'$ for unimolecular collapse of the two equivalent ion pairs and that the degenerate reorganization of the ion pair that exchanges the two equivalent benzoate oxygens ($k_r = k_{-r}$) is much faster than the other reactions of the ion pair, so that $k_r \gg (k_s' + k_{-d})$, k_{-1}'. Under these conditions both the steady-state concentrations and the rates of internal return of the two ion pairs to give the neutral esters will be equal.

$$k_{\mathrm{solv}} = \frac{k_1(k_s' + k_{-d})}{k_s' + k_{-d} + k_{-1}} \tag{1}$$

$$k_{\mathrm{iso}} = \frac{k_1 k_{-1}'}{2(k_s' + k_{-d} + k_{-1})} \tag{2}$$

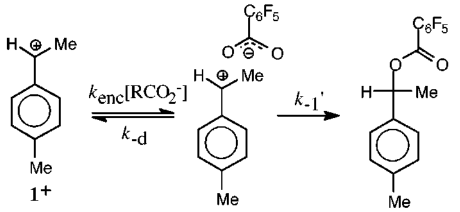
$$\frac{k_{\mathrm{iso}}}{k_{\mathrm{solv}}} = \frac{k_{-1}'}{2(k_s' + k_{-d})} \tag{3}$$

$$k_{\mathrm{Nu}} = \frac{k_{\mathrm{enc}} k_{-1}'}{k_{-d} + k_{-1}'} \tag{4}$$

A value of $k_{-1}' = 7 \times 10^9$ s^{-1} for unimolecular ion pair collapse can be calculated from the ratio of experimental rate constants $k_{\mathrm{iso}}/k_{\mathrm{solv}} = 0.15$ using eq 3 with $k_s' = 6 \times 10^9$ s^{-1} and $k_{-d} = 1.6 \times 10^{10}$ s^{-1}.[2b] The magnitude of this rate constant for internal ion pair return provides the vital "missing link" in the analyses of the reactions of ion pairs **1$^+\cdot{}^-$O$_2$CR** reported in earlier work.[2b]

The value of $k_{-1}' = 7 \times 10^9$ s^{-1} for unimolecular ion pair collapse of **1$^+\cdot{}^-$O$_2$CC$_6$F$_5$** is substantially larger than the pK_a-independent values of $k_{\mathrm{Nu}} = 5 \times 10^8$ M^{-1} s^{-1} for bimolecular addition of a series of alkyl carboxylate anions to **1**$^+$ in 50/50 (v/v) TFE/H$_2$O (Scheme 2 and eq 4).[2b] The difference in

Scheme 2



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[12] (a) Our analysis makes the assumption that formation of the rearranged ester **1-OC(^{18}O)C$_6$F$_5$** represents the irreversible formation of a reaction product. This is reasonable because the very small replenishment of **1-^{18}OC(O)C$_6$F$_5$** by a second ^{18}O-scrambling of the small amount of **1-OC(^{18}O)C$_6$F$_5$** that is formed will not lead to a significant deviation from first-order kinetics or to a significant decrease in the rate constant for the disappearance of **1-^{18}OC(O)C$_6$F$_5$**. For example, after 1 halftime, less than (0.5)(0.13)(0.13)/0.5 = 1.7% of the remaining **1-^{18}OC(O)C$_6$F$_5$** can be attributed to the occurrence of consecutive ^{18}O-scrambling. (b) Competing solvolysis and oxygen-18 equilibration was observed in an earlier study of the reactions of oxygen-18 labeled 1-(4-methoxyphenyl)ethyl and 1-phenylethyl 4-nitrobenzoates in 70% and 90% aqueous acetone.[1f] These data provide a qualitative description of the partitioning of the ion pair intermediates of these reactions but not the absolute rate constant for ion pair return reported here.

[13] The reaction of thiobenzoate anion with the 1-(4-thiomethylphenyl)-ethyl carbocation in 50/50 (v/v) TFE/H$_2$O to form the thiol ester is diffusion-limited[3] and is ca. 80-fold *faster* than addition of the more basic acetate ion to the same carbocation.[2b]

this observed second-order rate constant for reaction of carboxylate anions in bulk solvent and the first-order rate constant for collapse of the carbocation−carboxylate anion ion pair provides direct evidence that the reactivity of free carboxylate anions is “suppressed” by aqueous solvation. A value of $k_{enc} = 1.5 \times 10^9$ M^{-1} s^{-1} for formation of an ion pair encounter complex between carboxylate anions and the carbocation $\mathbf{1}^+$ can be calculated using eq 4 derived for Scheme 2, with $k_{-1}' = 7 \times 10^9$ s^{-1} determined here and $k_{-d} = 1.6 \times 10^{10}$ s^{-1}.[2b] This is significantly smaller than the values of $k_{az} = (5-7) \times 10^9$ M^{-1} s^{-1} determined for the diffusion-limited reactions of azide ion with unstable carbocations.[14] It is consistent with the earlier conclusion that the formation of encounter complexes between $\mathbf{1}^+$ and carboxylate anions is slower than a simple diffusional encounter as a result of a requirement for desolvation of the carboxylate anion.[2b]

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