When Does an Intermediate Become a Transition State? Degenerate Isomerization without Competing Racemization during Solvolysis of (S)-1-(3-Nitrophenyl)ethyl Tosylate

ARTICLE *in* JOURNAL OF THE AMERICAN CHEMICAL SOCIETY · DECEMBER 2006

Impact Factor: 12.11 · DOI: 10.1021/ja066235d · Source: PubMed

2 AUTHORS, INCLUDING:

John P. Richard
University at Buffalo, The State University of …

219 PUBLICATIONS **6,863** CITATIONS

SEE PROFILE

J|A|C|S
ARTICLES
Published on Web 12/06/2006

When Does an Intermediate Become a Transition State? Degenerate Isomerization without Competing Racemization during Solvolysis of (*S*)-1-(3-Nitrophenyl)ethyl Tosylate

Yutaka Tsuji[†] and John P. Richard*[,‡]

Contribution from the Department of Biochemistry and Applied Chemistry, Kurume National College of Technology, Komorinomachi, Kurume 830-8555, Japan, and Department of Chemistry, University at Buffalo, SUNY, Buffalo, New York 14260

Received August 28, 2006; E-mail: jrichard@chem.buffalo.edu

Abstract: (*S*)-1-(3-Nitrophenyl)ethyl tosylate [**(*S*)-2-OTs**] was prepared in >99% enantiomeric excess and the change in the chiral purity of this compound was monitored during solvolysis in 50:50 trifluoroethanol/water. The barely detectable formation of 0.5% **(*R*)-2-OTs** after two half times for the solvolysis reaction was used to calculate a rate constant of $k_{rac} \approx 4 \times 10^{-6}$ s^{-1}. This is 80-fold smaller than $k_{iso} = 3.2 \times 10^{-4}$ s^{-1} for the isomerization that exchanges oxygen-16 and oxygen-18 of **3-NO$_2$C$_6$H$_4$^{13}CH(Me)OS(^{18}O)$_2$Tos** during solvolysis and 10-fold smaller than the minimum value of $k_{rac} = 4.6 \times 10^{-5}$ s^{-1} predicted if isomerization and racemization products form by partitioning of a common ion-pair intermediate of a stepwise reaction. It is concluded that the isomerization reaction proceeds mainly by a pathway that avoids formation of this putative intermediate. It is suggested that the solvolysis reaction of **2-OTs** may proceed by a stepwise preassociation mechanism where solvent "reorganization" precedes substrate ionization to form an ion-pair intermediate.

Introduction

Nucleophilic substitution at aliphatic carbon may occur either by a stepwise mechanism through a carbocation intermediate (S_N1 or $D_N + A_N$ reaction mechanism) or by a concerted mechanism in which two steps take place in a single reaction stage (S_N2 or A_ND_N reaction mechanism).[1] The imperatives for reaction by stepwise nucleophilic substitution through a stable carbocation intermediate and for concerted bimolecular substitution that avoids formation of an unstable intermediate are relatively clear.[2−4] A more difficult question is how to model the transition across the borderline between stepwise and concerted mechanisms where the carbocation intermediate is very unstable, but the advantage of a concerted substitution is only beginning to become significant.[5,6]

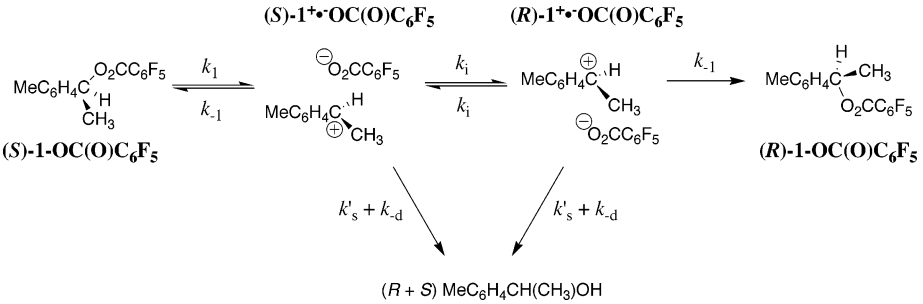
There are several examples of "borderline" thermal reactions for which there is no intermediate with a vibrational lifetime, but there is no significant energetic advantage to formation of the transition state for a coupled−concerted mechanism that avoids formation of the intermediate. These include the stereomutation of cis and trans disubstituted cyclopropanes,[7,8] the thermal deazetization of 2,3-diazabicyclo[2.2.1]hept-2-ene,[9] and the thermal interconversion of bicyclo[3.2.0]hept-2-ene and bicyclo[2.2.1]hept-2-ene.[10] Each of these reactions proceed through unstable biradical species that lie at flat plateaus on energy landscapes in which substrate bonds undergo rotation to form a second biradical species that collapses to products. To a first approximation, the borderline region for polar reactions might also be described using unstable ionic species that lie at flat plateaus on energy landscapes where they partition to form different reaction products.[5]

The observation of racemization and/or degenerate isomerization reactions of neutral substrates during solvolysis may provide evidence for the formation of very unstable ion-pair reaction intermediates that partition between addition of solvent and "reorganization" followed by internal return to regenerate neutral reactant.[11,12] It is also possible that the degenerate isomerization proceeds by a mechanism that avoids formation of a very reactive carbocation intermediate,[6,13] but there are no well documented examples of such concerted-type rearrangement reactions in polar solvents.[14]

[†] Kurume National College of Technology.
[‡] University at Buffalo, SUNY.

(1) Guthrie, R. D.; Jencks, W. P. *Acc. Chem. Res.* **1989**, *22*, 343−349.
(2) Ingold, C. K. *Structure and Mechanism in Organic Chemistry*; 2nd ed.; Cornell University Press: Ithaca, NY, 1969.
(3) Jencks, W. P. *Acc. Chem. Res.* **1980**, *13*, 161−169.
(4) Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383−1396.
(5) Amyes, T. L.; Toteva, M. M.; Richard, J. P. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jr., M. J., Eds.; John Wiley & Sons: Hoboken, NJ, 2004, pp 41−68.
(6) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345−375.
(7) Doubleday, C., Jr.; Bolton, K.; Hase, W. L. *J. Am. Chem. Soc.* **1997**, *119*, 5251−5252.
(8) Hrovat, D. A.; Fang, S.; Borden, W. T.; Carpenter, B. K. *J. Am. Chem. Soc.* **1997**, *119*, 5253−5254.
(9) Reyes, M. B.; Carpenter, B. K. *J. Am. Chem. Soc.* **2000**, *122*, 10163−10176.
(10) Carpenter, B. K. *J. Am. Chem. Soc.* **1996**, *118*, 10329−10330.
(11) Harris, J. M. *Prog. Phys. Org. Chem.* **1974**, *11*, 89−173. Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; John Wiley & Son: New York, 1974; Vol. 2.
(12) Richard, J. P.; Amyes, T. L.; Toteva, M. M.; Tsuji, Y. *Adv. Phys. Org. Chem.* **2004**, *39*, 1−26.
(13) Dietze, P. E.; Wojciechowski, M. *J. Am. Chem. Soc.* **1990**, *112*, 5240−5244.
(14) Tsuji, Y.; Richard, J. P. *Chem. Rec.* **2005**, *5*, 94−106.

Scheme 1



The chiral ester **(*S*)-1-OC(O)C$_6$F$_5$** undergoes racemization to form **(*R*)-1-OC(O)C$_6$F$_5$** in 50/50 (v/v) trifluoroethanol/water (I = 0.50, $NaClO_4$) with a rate constant of $k_{rac} = 8.5 \times 10^{-7}$ s^{-1}, which is 12 times smaller than $k_{solv} = 1.06 \times 10^{-5}$ s^{-1} for the solvolysis reaction[15] and 2 times smaller than $k_{iso} = 1.6 \times 10^{-6}$ s^{-1} for degenerate isomerization, which exchanges the position of the ester bridging and nonbridging oxygens of **1-OC(O)C$_6$F$_5$** (Scheme 1).[16] These data were used to calculate a rate constant of $k_i = 1.5 \times 10^{10}$ s^{-1} for inversion of the chiral ion pair that is about 7-fold smaller than $k_r = 1 \times 10^{11}$ s^{-1} for simple reorganization of ions within a solvent cage that, for example, would exchange the positions of the oxygens of a carboxylate anion leaving group.[15] This work provides an estimate for the relative rates of reorganization and inversion of the chiral ion-pair intermediates of solvolysis of neutral ring-substituted 1-phenylethyl derivatives in 50/50 (v/v) trifluoroethanol/water, since the rate constants for the physical reorganization of these ion pairs (k_i and k_r) should be nearly independent of the ring substituent at the 1-phenylethyl carbocation intermediate and the leaving group anion.

The 1-(4-methylphenyl)ethyl carbocation intermediate of solvolysis of **1-OC(O)C$_6$F$_5$** has a very short, but finite, lifetime of 10^{-10} s in 50/50 (v/v) trifluoroethanol/water.[17] By comparison, a lifetime of $\approx 10^{-13}$ s has been estimated for the putative 1-(3-nitrophenyl)ethyl carbocation intermediate of solvolysis of 1-(3-nitrophenyl)ethyl derivatives in the same solvent.[4,17] The "lifetime" for this *hypothetical* reaction intermediate suggests it may not exist in a potential energy well in the presence of a properly oriented solvent molecule.[4]

There is substantial isomerization ($k_{iso} = 0.32 \times 10^{-3}$ s^{-1}) that exchanges oxygen-16 and oxygen-18 of **3-NO$_2$C$_6$H$_4$^{13}CH(Me)OS(^{18}O)$_2$Tos** during solvolysis ($k_{solv} = 1.04 \times 10^{-3}$ s^{-1}) in 50/50 trifluoroethanol/water, but it is not known whether these reactions proceed by partitioning of a common intermediate of a stepwise reaction or by competing *"concerted"* processes.[18] We report here the results of a study of the racemization of (*S*)-1-(3-nitrophenyl)ethyl tosylate during solvolysis in 50/50 (v/v) trifluoroethanol/water using analytical methods that would have detected the presence of <1% of the (*R*)-enantiomer. Our results provide strong evidence that most of the isomerization reaction of **3-NO$_2$C$_6$H$_4$^{13}CH(Me)OS(^{18}O)$_2$Tos** during solvolysis does not proceed through an ion-pair intermediate, because almost none of the expected product of *inversion* in the configuration of a chiral intermediate is detected.

Experimental Section

All organic and inorganic chemicals were reagent grade from commercial sources and were used without further purification. Water for kinetic studies and HPLC analyses was distilled and passed through a Milli-Q water purification system. ^{1}H NMR spectra were recorded on a JEOL AL-400 FT-NMR spectrometer operating at 400 MHz.

(*S*)-1-(3-Nitrophenyl)ethyl alcohol was prepared by reduction of *m*-nitroacetophenone with a chiral borane.[19] *m*-Nitroacetophenone (11.9 g, 72 mmol) was dissolved in 50 mL of dry THF and was added dropwise under N_2 to [(−)-*B*-chlorodiisopinocampheylborane] (25 g, 78 mmol) in 56 mL of dry THF at −25 °C. The solution was stirred overnight at −25 °C. The solvent was removed under vacuum (ca. 10 mM Hg) at room temperature and the α-pinene produced in the reaction was removed under high vacuum and collected in a cold trap. The residue was dissolved in 30 mL of ether, 18 g of diethanolamine (171 mmol, 2.2 equiv) was added, and the mixture was stirred for 2 h. The solid precipitate was collected and washed with 120 mL of ether. The product was purified by silica gel column chromatography eluting with hexane/ether and then by recrystallization from benzene/ether/hexane: yield 56%; mp 84−85 °C; ^{1}H NMR (400 MHz, C_6D_6) 7.98, (s, 1H, Ar), 7.75 (d, 1H, J = 7.2 Hz, Ar), 7.09 (d, 1H, J = 8.4 Hz, Ar), 6.74 (t, 1H, J = 8.0 Hz, Ar), 4.22 (dq, 1H, J = 6.4 Hz, 2.8 Hz, CH), 1.08 (d, 1H, J = 3.6 Hz, OH), 1.01 (d, 3H, J = 6.0 Hz, CH_3). The spectrum determined in the presence of 1 M of the chiral shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol showed that the enantiomeric purity of this alcohol was >99%. (*S*)-1-(3-Nitrophenyl)ethyl tosylate was prepared from (*S*)-1-(3-nitrophenyl)ethyl alcohol as described in earlier studies of racemic compounds.[18]

Solvolysis of (*S*)-1-(3-Nitrophenyl)ethyl Tosylate. The compound (140−250 mg) was dissolved in 5 mL of acetonitrile, and this solution was diluted with 50/50 (v/v) TFE/H_2O (I = 0.5, $NaClO_4$) to give a final substrate concentration of 0.4 mM. The reaction was kept at 25 °C for up to 20 min. The unreacted substrate and products were then extracted into 800 mL of toluene at 0 °C. The extract was washed with water and dried over $MgSO_4$ and the toluene was removed by evaporation. The solvolysis reaction products were separated from the remaining substrate by HPLC using a JAIGEL-1H column (styrene polymer) and eluting with $CHCl_3$.

Optical Purity of 1-(3-Nitrophenyl)ethyl Tosylate. The following procedure was used to convert samples of 1-(3-nitrophenyl)ethyl tosylate into the thiobenzoate ester. The tosylate (50−100 mg) was added to 100 mL of acetonitrile that contained 1 g of thiobenzoic acid and 6.6 mL of 1 M NaOH. The solution was stirred overnight at room temperature and then poured into ca. 1 L of water. The products were extracted into diethyl ether, the ether extract was washed with water

(15) Tsuji, Y.; Mori, T.; Toteva, M. M.; Richard, J. P. *J. Phys. Org. Chem.* **2003**, *16*, 484−490.
(16) Tsuji, Y.; Mori, T.; Richard, J. P.; Amyes, T. L.; Fujio, M.; Tsuno, Y. *Org. Lett.* **2001**, *3*, 1237−1240.
(17) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361−1372.
(18) Tsuji, Y.; Toteva, M. M.; Amyes, T. L.; Richard, J. P. *Org. Lett.* **2004**, *6*, 3633−3636.
(19) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539−1546.

and dried over $MgSO_4$, and the ether was removed using a rotary evaporator. 1-(3-Nitrophenyl)ethyl thiobenzoate was purified by chromatography over silica gel, eluting with benzene, and then further purified by HPLC using a JAIGEL-1H column (styrene polymer) and eluting with $CHCl_3$: ^{1}H NMR (400 MHz, C_6D_6) 8.17 (s, 1H, Ar), 7.88 (d, 2H, $J = 8.0$ Hz, Ar), 7.82 (d, 1H, $J = 8.0$ Hz, Ar), 6.85−7.07 (m, 4H, Ar), 6.66 (t, 1H, $J = 8.0$ Hz, Ar), 4.78 (q, 1H, $J = 7.2$ Hz, CH), 1.32 (d, 3H, $J = 7.2$ Hz, CH_3).

The isolated 1-(3-nitrophenyl)ethyl thiobenzoate (10 mg) was dissolved in 0.6 mL of C_6D_6, and 160 mg of the chiral shift reagent (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol was added. ^{1}H NMR spectra were obtained using a sweep width of 4000 Hz, a 60 s relaxation delay time, a 90° pulse angle, and with the collection of 32 000 data points (0.12 Hz/point). The α-CH_3 protons of the thiobenzoate were irradiated in order to cause the quartet for the benzylic methine proton to collapse to a singlet. The spectra were recorded after 300−700 transients, depending upon the sample.

Results

(*S*)-1-(3-Nitrophenyl)ethyl tosylate [**(*S*)-2-OTs**] was synthesized in >99% enantiomeric excess (see below) using published procedures.[15,19] The chiral shift reagents used in previous work to resolve the signals for the enantiotopic benzylic proton of **2-OH**,[18] **1-OH**,[15] and **1-OC(O)C$_6$F$_5$**[15] using ^{1}H NMR failed to give separate signals for the ^{1}H NMR spectrum of **2-OTs**. Therefore, **2-OTs** was converted to the thiobenzoate ester **2-SC(O)Ph** by a concerted bimolecular displacement reaction of thiobenzoate at **2-OTs**. The ^{1}H NMR signals for the enantiotopic proton for **2-SC(O)Ph** (ca. 50 mM) were resolved in C_6D_6 that contains (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol (ca. 1 M). Figure 1A shows the partial ^{1}H NMR spectrum, determined in the presence of (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, of the benzylic proton for **(*R*)-2-SC(O)Ph** prepared by concerted bimolecular nucleophilic displacement of thiobenzoate anion at **(*S*)-2-OTs**. Parts B and C of Figure 1 show the ^{1}H NMR spectra in the presence of chiral shift reagent of **2-SC(O)Ph**, prepared by mixing measured amounts of **(*R*)-2-SC(O)Ph** with the racemic thioester to give 90:10 and 99:1 ratios, respectively, of the (*R*)- and (*S*)-enantiomers. These spectra show that the (*S*)-enantiomer can be detected in a sample of 98% enantiomeric excess. Integration of the spectrum in Figure 1A is consistent with the presence of ca. 0.3% **(*S*)-2-SC(O)Ph**, which is just at our detection limits. This may arise in the enantioselective synthesis of **(*S*)-2-OH** or from partly nonstereospecific nucleophilic substitution at **(*S*)-2-OTs**.

The unreacted tosylate was reisolated after a 15 min solvolysis reaction and after a 20 min solvolysis reaction ($t_{1/2} = 11$ min)[18] of **(*S*)-2-OTs** at 25 °C in 50:50 (v:v) trifluorethanol/water ($I = 0.50$, $NaClO_4$) and converted to **2-SC(O)Ph**. Figure 1D shows the partial ^{1}H NMR spectrum, determined in the presence (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)ethanol, of the benzylic proton of **2-SC(O)Ph** prepared from **2-OTs** reisolated after a 20-min reaction time of **(*S*)-2-OTs**. Integration gives a ratio of 99.2:0.8 for **(*R*)-** and **(*S*)-2-SC(O)Ph**. These data show that the fraction of the (*R*)-enantiomer in **2-OTs** increases from 0.3% to 0.8% during the 20-min reaction time. This corresponds to 0.5% racemization during solvolysis. We have not carried out experiments to determine the uncertainty in this result. However, the data from Figure 1 show clearly that there is <1% racemization during nearly two half times for solvolysis of **(*S*)-2-OTs**. The chiral purity of **2-SC(O)Ph** determined by ^{1}H NMR analysis of the compound prepared from **2-OTs** reisolated after a 15-min reaction time of **(*S*)-2-OTs** was not detectably different from **2-SC(O)Ph** prepared from authentic **(*S*)-2-OTs**.

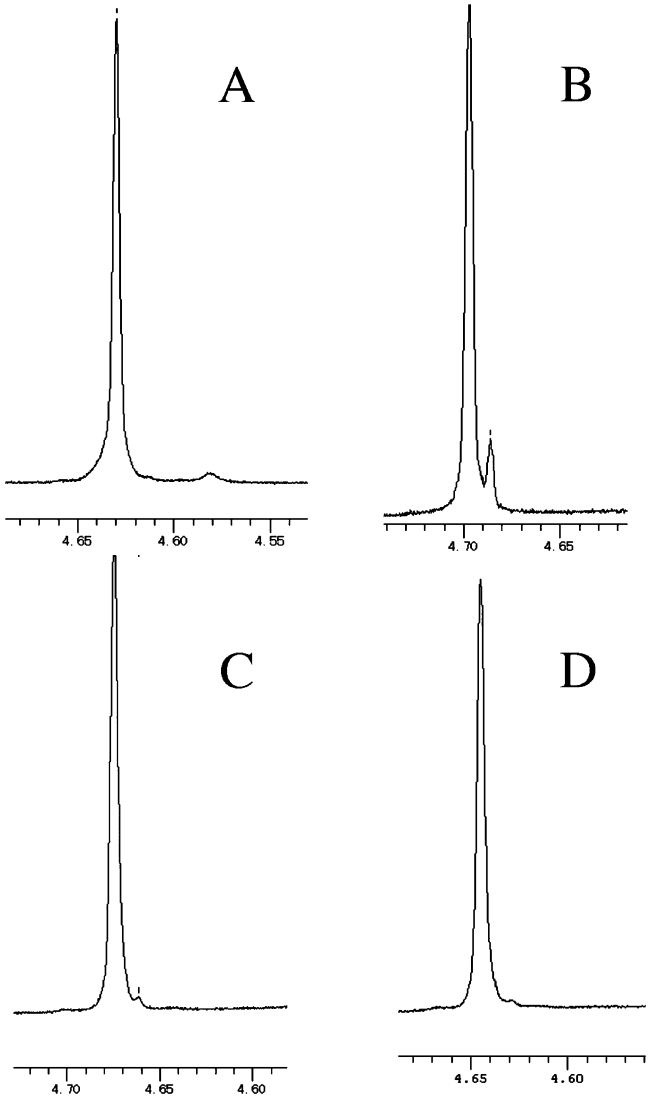
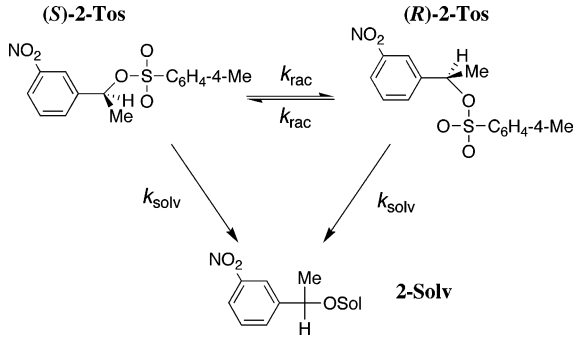


Figure 1. Partial ^{1}H NMR spectra for the enantiotopic proton of **2-SC(O)Ph** in C_6D_6 that contains (*S*)-(+)-2,2,2-trifluoro-1-(9-anthryl)-ethanol. (A) Synthetic **(*R*)-2-SC(O)Ph**. (B) A 90:10 mixture of **(*R*)-2-SC(O)Ph:(*S*)-2-SC(O)Ph**. (C) A 99:1 mixture of **(*R*)-2-SC(O)Ph:(*S*)-2-SC(O)Ph**. (D) **2-SC(O)Ph** recovered after a 20-min solvolysis reaction of **(*S*)-2-OTs** in 50:50 (v:v) trifluorethanol/water ($I = 0.50$, $NaClO_4$) at 25 °C.

These data allow for an estimate of the rate constant k_{rac} for racemization of **(*S*)-2-OTs** during solvolysis using eq 1, derived for Scheme 2,[15] where; (i) $(A_R)_{nor}$ is the area for the peak for the benzylic proton of **(*R*)-2-OTs** normalized relative to a value of 1.00 for the area of the benzylic proton of substrate **(*S*)-2-OTs** at $t = 0$, (ii) k_{solv} is the observed rate constant for the solvolysis reaction, and (iii) t is the reaction time. Substitution of $(A_R)_{nor} = 0.0014$, $k_{solv} = 1.04 \times 10^{-3}$ s^{-1},[18] and $t = 1200$ s into eq 1 gives a value of $k_{rac} \approx 4 \times 10^{-6}$ s^{-1} for the racemization of **(*S*)-2-OTs**.

$$(A_R)_{nor} = 0.5\{\exp(-k_{solv}t) - \exp[-(2k_{rac} + k_{solv})t]\} \quad (1)$$

Scheme 2



Discussion

In 1990, Dietze and Wojciechowski reported that there is scrambling of the brosylate oxygens in enantiomerically enriched 2-butyl 4-bromobenzenesulfonate containing ^{18}O in the nonbridging oxygens in the absence of detectable racemization of the starting ester during solvolysis in trifluoroethanol.[13] It was concluded that "if an ion-pair intermediate is involved in the trifluoroethanolysis reaction, the ion pair has a sufficient lifetime to permit rotation of the anion leading to oxygen scrambling. However, rotation of the cation, which would lead to racemization, does not occur".[13] The results of this earlier study are similar in some respects to data reported here. However, they do not exclude the possibility that ^{18}O-scrambling proceeds through an ion-pair reaction intermediate because of the following limitations of the earlier experiments, which are addressed in the present work.

(1) The optical purity of the starting brosylate ester (88% ± 2%) and the sensitivity of the analysis of chiral purity in the previous work were both low, so that it would not have been possible to detect what might be considered a significant extent of racemization during solvolysis. We report here the synthesis of **(*S*)-2-OTs** in ≥99.7% chiral purity and analytical methods that allow for the detection of ca. 0.5% racemization during solvolysis in 50/50 (v/v) trifluoroethanol/water.

(2) Racemization during solvolysis in water will normally be slower than isomerization for reactions that proceed through a common ion-pair intermediate.[15] Therefore, it is important to have estimates of the relative rates of these processes and to show that the analytical methods used are adequate to exclude racemization through an ion-pair intermediate. We have shown that **(*S*)-1-OC(O)C$_6$F$_5$** undergoes racemization to form **(*R*)-1-OC(O)C$_6$F$_5$** in 50/50 (v/v) trifluoroethanol/water at 25 °C (Scheme 1) with a rate constant of $k_{rac} = 8.5 \times 10^{-7}$ s^{-1}, which is 12 times smaller than $k_{solv} = 1.06 \times 10^{-5}$ s^{-1} for stepwise solvolysis and 2 times smaller than $k_{iso} = 1.6 \times 10^{-6}$ s^{-1} for degenerate isomerization, which exchanges the position of the ester bridging and nonbridging oxygens.[15] These data are used here to estimate the rate constant expected for racemization of **(*S*)-2-OTs**, if isomerization and racemization of this tosylate were to proceed through a common intermediate.

Racemization of (*S*)-2-OTs. The partial ^{1}H NMR spectra, determined in the presence of a chiral shift reagent, of the benzylic proton for authentic **(*R*)-2-SC(O)Ph** (Figure 1A) and for **2-SC(O)Ph** prepared from **(*S*)-2-OTs** recovered after a 20-min solvolysis reaction in 50/50 trifluoroethanol/water (Figure 1D) show that the chiral purity of the ester is almost completely maintained during solvolysis. Only ca. 0.5% of the remaining **2-OTs** has been converted to the (*R*)-enantiomer. After solvolysis under the same conditions and for the same time, 30% (!) of remaining **3-NO$_2$C$_6$H$_4$^{13}CH(Me)OS(^{18}O)$_2$Tos** was converted to **3-NO$_2$C$_6$H$_4$^{13}CH(Me)^{18}OS(^{16}O,^{18}O)Tos** ($k_{iso} = 3.2 \times 10^{-4}$).[18] We conclude that degenerate isomerization of **(*S*)-2-OTs** is much faster than racemization to form **(*R*)-2-OTs**. Table 1 shows a comparison of the rate constants determined in studies of the racemization and degenerate isomerization of chiral and ^{18}O-labeled **(*S*)-1-OC(O)C$_6$F$_5$** and **(*S*)-2-OTs**.

Table 1. First-Order Rate Constants for the Solvolysis (k_{solv}), Racemization (k_{rac}), and Degenerate Isomerization (k_{iso}) Reactions of **(*S*)-1-OC(O)C$_6$F$_5$** and **(*S*)-2-OTs** in 50:50 (v:v) Trifluoroethanol/Water[a]

rate constant	(*S*)-1-OC(O)C$_6$F$_5$[b]	(*S*)-2-OTs
k_{solv}/s^{-1}	1.06×10^{-5}	1.04×10^{-3} [c]
k_{iso}/s^{-1}	1.6×10^{-6}	3.2×10^{-4} [c]
k_{rac}/s^{-1}	8.5×10^{-7}	$\approx 4 \times 10^{-6}$ [d]
k_{iso}/k_{rac}	2	≈80

[a] At 25 °C and $I = 0.50$ maintained with $NaClO_4$. [b] Reference 15. [c] Reference 18. [d] This work.

Is the Isomerization Reaction Stepwise? Consider the following limiting and intermediate cases for partitioning of ion-pair intermediates of solvolysis (e.g., solvolysis of **2-OTs**) to form the products of isomerization and racemization of neutral substrate.

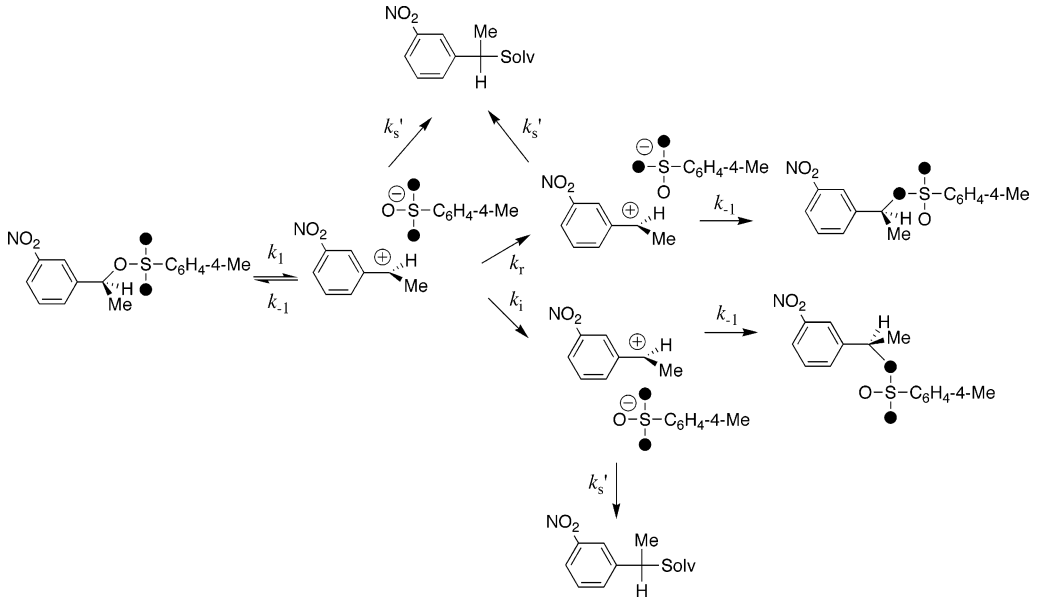
(1) The ion-pair intermediate has a long lifetime that allows complete equilibration of the now equivalent oxygen and of the (*R*)- and (*S*)-enantiomeric ion-pair forms to occur. If these species reach chemical equilibrium faster than the ion pair returns to neutral reactant, then this return step will give a racemic reactant in which there is an equal distribution of label between the bridging and nonbridging positions. At this limit, the rate constants for the isomerization and racemization of reactions of a chiral, specifically oxygen-18 labeled substrate will be the same ($k_{iso}/k_{rac} = 1$).[6,15]

(2) The lifetime of the ion-pair is too short to allow for equilibration to occur for both reactions. At this point the intrinsic difference in the rates of isomerization and racemization of the ion-pair will begin to be expressed as a difference in the observed rate constants for the degenerate isomerization and racemization reaction of neutral substrate.[20] This is the case for the reactions of **(*S*)-1-OC(O)C$_6$F$_5$**, for which a value of $k_{iso}/k_{rac} = 2$ was determined (Table 1).[15]

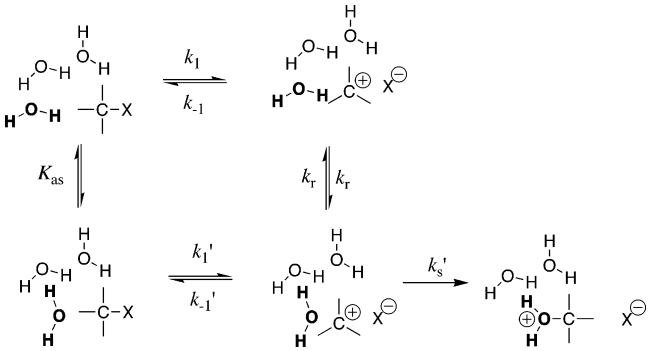
(3) Scheme 3 shows a limiting case where the putative carbocation intermediate is so unstable that its different reactions of addition of solvent ($k_{s'}$), reorganization that scrambles the tosylate oxygens (k_r), and inversion (k_i) are effectively irreversible so that the yields of the products of the different reactions reflect their relative rates. In this case, the ion pair has only a single "opportunity" to partition between reorganization (k_r) and inversion (k_i). Now, the ratio of these microscopic rate constants for reactions of the ion pair will be equal to the ratio of the rate constants for formation of products of isomerization and racemization: $k_r/k_i = k_{iso}/k_{rac} = 7$, where $k_r = 10^{11}$ s^{-1} [21] and $k_i = 1.5 \times 10^{10}$ s^{-1}.[15] In other words, the rapid addition of solvent to a very reactive ion-pair intermediate will cause the same

(20) Goering, H. L.; Briody, R. G.; Sandrock, G. *J. Am. Chem. Soc.* **1970**, *92*, 7401−7407.
(21) Richard, J. P.; Tsuji, Y. *J. Am. Chem. Soc.* **2000**, *122*, 3963−3964.

Scheme 3



Scheme 4



proportional decrease in the product yields for reaction of the ion pair, but it cannot affect the relative rate at which these products are formed. The estimated upper limit of $k_{iso}/k_{rac} \approx 7$ for a reaction that proceeds through a short-lived ion-pair intermediate is much smaller than $k_{iso}/k_{rac} = 80$ observed here for degenerate isomerization and racemization of **(*S*)-2-OTs** (Table 1).

Single-Stage (Concerted) Reaction. If there is 0.5% racemization of **(*S*)-2-OTs** during a 20-min solvolysis reaction through an ion-pair intermediate, then during the same reaction time the intermediate would react to give a ca. 7-fold larger (3.5%) yield of isomerization product ($k_{iso}/k_{rac} \approx 7$).[15] We conclude that most of the 30% conversion of **3-$NO_2C_6H_4{}^{13}$CH(Me)OS(^{18}O)$_2$Tos** to **3-$NO_2C_6H_4{}^{13}$CH(Me)^{18}OS(^{16}O,^{18}O)Tos** observed during this time proceeds by a mechanism that avoids formation of a simple ion-pair intermediate. We suggest that isomerization proceeds by a mechanism in which bond cleavage and bond formation occur in a single reaction step in which (i) The bond to the tosylate oxygen stretches to give an ionic species, **[2^{+}·$^{-}$OTs]†**, whose structure is similar to an ion pair but with the oxygen positioned to return to substrate without passage over a significant barrier. (ii) The sulfonate group moves across a flat energy surface that exchanges the position of initially carbon-bridging and nonbridging oxygens. (iii) The high-energy ionic species collapses to form the isomerization reaction product.[6,13] This pathway for the isomerization reaction will be observed when there is no vibrational barrier for conversion of an ion-pair "intermediate" to neutral reactant.[3,6] Such an isomerization reaction of **2-OTs** might be viewed as a symmetry-allowed, suprafacial, 1,3-sigmatropic shift of the 1-(3-nitrophenyl) ethyl group.[13] However, these orbital symmetry considerations may not be relevant to reactions that proceed through transition states that closely resemble the putative intermediate of a stepwise reaction.[22−26]

The ionic transition state proposed for the degenerate isomerization of **2-OTs**, **[2^{+}·$^{-}$OTs]†**, is similar conceptually to biradical-like transition states for thermal cis−trans isomerization reactions of disubstituted cyclopropanes[7,8] and related reactions,[27] because it resembles the putative intermediate of a stepwise reaction, but does not lie in a potential energy-well. Both the radical-type and ionic reactions are proposed to proceed with initial bond cleavage to give an intermediate-like species that rearranges on a flat potential energy surface and then collapses to form product.

The observation of exchange of isotopically labeled nitrogens of benzene diazonium ion during solvolysis in water has been cited as evidence that this reaction proceeds with reversible formation of a benzene cation intermediate.[28] However, the formation of this intermediate might be avoided in a concerted reaction similar to that proposed to occur for isomerization of **3-$NO_2C_6H_4{}^{13}$CH(Me)OS(^{18}O)$_2$Tos**.[29,30] It has been proposed that an accurate description of solvolysis and rearrangement reactions of aryldiazonium ions in water requires a consideration of dynamic effects.[29] Any full theoretical treatment of the

(22) Baldwin, J. E.; Shukla, R. *J. Am. Chem. Soc.* **1999**, *121*, 11018−11019.
(23) Baldwin, J. E.; Samuel, J.; Bonacorsi, J. *J. Am. Chem. Soc.* **1996**, *118*, 8258−8265.
(24) Baldwin, J. E.; Fedé, J.-M. *J. Am. Chem. Soc.* **2006**, *128*, 5608−5609.
(25) Baldwin, J. E.; Burrell, R. C. *J. Am. Chem. Soc.* **2003**, *125*, 15869−15877.
(26) Baldwin, J. E.; Burrell, R. C. *J. Am. Chem. Soc.* **2001**, *123*, 6718−6719.
(27) Carpenter, B. K. In *Reactive Intermediate Chemistry*; Moss, R. A., Platz, M. S., Jr., M. J., Eds.; John Wiley & Sons: Hoboken, NJ, 2004, pp 925−960.
(28) Insole, J. M.; Lewis, E. S. *J. Am. Chem. Soc.* **1963**, *85*, 122.
(29) Ussing, B. R.; Singleton, D. A. *J. Am. Chem. Soc.* **2005**, *127*, 2888−2899.
(30) Glaser, R.; Horan, C. J. *J. Org. Chem.* **1995**, *60*, 7518−7528.

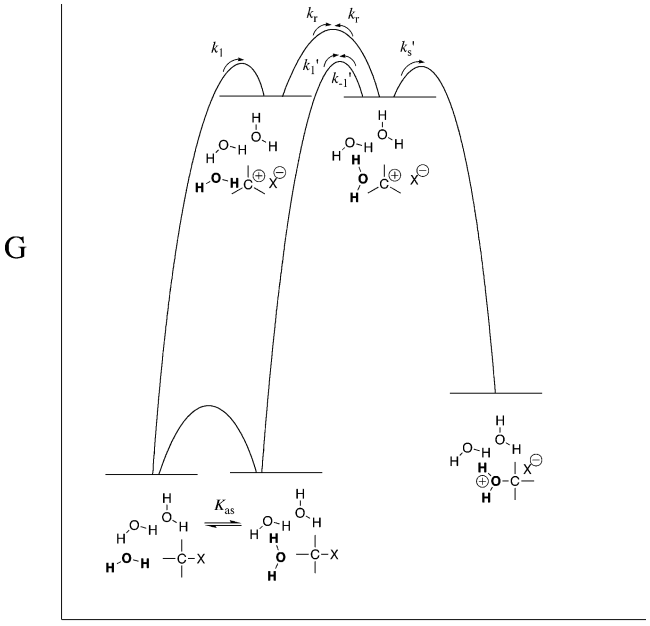


Figure 2. Free-energy reaction profiles for the solvolysis reaction of an alkyl halide by a simple stepwise pathway (k_1, k_r, $k_{s'}$) and by a stepwise preassociation pathway (K_{as}, $k_{1'}$, $k_{s'}$). The figure shows the case where $k_{-1'} > k_r$ and reaction by the preassociation pathway is favored.

reactions of **2-OTs** should also take into account a variety of dynamic effects.[31,32]

Solvolysis Reaction Mechanism. The slow rate of racemization of **(*S*)-2-OTs** compared with solvolysis ($k_{solv}/k_{rac} = 260$, Table 1) requires that $k_{s'}$ be ca. 260-fold times greater than $k_i = 1.5 \times 10^{10}$ s^{-1}, if the solvolysis and racemization products form by partitioning of a common intermediate (Scheme 3). However, the limiting rate constant for addition of solvent to an ion-pair intermediate is expected to be $\approx 10^{11}$ s^{-1}, which is the rate constant for reorganization of the solvent shell that moves water into a reactive position.[5,33] This suggests that solvent reorganization at the ion-pair intermediate may not be a step in the solvolysis reaction of **(*S*)-2-OTs**.

Scheme 4 shows competing stepwise pathways for nucleophilic substitution at an aliphatic carbon. The top pathway proceeds with heterolytic bond cleavage (k_1), solvent reorganization ($k_r = 10^{11}$ s^{-1}),[34,35] and collapse of the intermediate to product ($k_{s'}$). The bottom pathway for a preassociation mechanism[36−38] proceeds with solvent reorganization to place the water into a reactive position (K_{as}), substrate ionization ($k_{1'}$), and collapse of the intermediate to product ($k_{s'}$). When there is no nucleophilic assistance to substrate ionization, the preferred reaction pathway is determined by the relative barriers to $k_{-1'}$ and k_r.[36−38] The preassociation reaction will be observed in the case of very rapid internal return of the ion-pair to substrate ($k_{-1'} > k_r \approx 10^{11}$ s^{-1}), as shown in Figure 2. The advantage to reaction by the preassociation pathway over a conventional stepwise reaction where substrate ionization occurs before solvent reorganization arises from (1) avoiding the "slow" step of reorganization of the solvation shell of the carbocation reaction intermediate (k_r) [The rate acceleration from the preassociation reaction pathway when $k_1 = k_{1'}$ (Figure 2) cannot be larger than $k_{-1'}/k_r$ (Figure 2). The advantage may approach 100-fold if $k_r \approx 10^{11}$ and $k_{-1'}$ approaches the vibrational limit of $\approx 10^{13}$ s.] and (2) nucleophilic solvent assistance that would favor ionization after solvent reorganization ($k_{1'} > k_1$).[39,40] The small product selectivity $k_{MeOH}/k_{TFE} = 2.4$ determined from the ratio of the yields of **2-OMe** and **2-OTFE** from the reaction of 1-(4-nitrophenyl)ethyl tosylate[41] in 45/5/50 (v/v/v) trifluoroethanol/methanol/water shows that there is little stabilization of the product-determining step by nucleophilic participation of methanol compared with trifluoroethanol,[4,42] consistent with the conclusion that there is not strong nucleophilic participation of solvent in this reaction.

We suggest that $k_{-1'} > k_r$ for solvolysis of **(*S*)-2-OTs** and that solvent reorganization precedes substrate ionization for the reaction in 50:50 trifluoroethanol/water (Figure 2). The solvolysis of **(*S*)-2-OTs** proceeds mainly with inversion of configuration and gives only a 17% yield of **(*S*)-2-OH**.[18] The preference for backside displacement is generally explained by the leaving group anion acting to shield the carbocation reaction intermediate from reaction with solvent. The results might be rationalized for a preassociation reaction by a preference for backside "solvation" of the reactant in the preassociation complex that forms by K_{as} (Scheme 4 and Figure 2).

Scheme 4 shows solvent reorganization that places solvent in a position to react directly with the carbocation intermediate. More realistically, solvent reorganization will include other changes that lead to stabilization of charge at the ion pair. Therefore, while the simple energy profile shown in Figure 2 is supportive of the notion that solvent reorganization to form the solvation shell for the ion-pair reaction intermediate will precede substrate ionization when *relaxation* of solvent to the reactant shell is slower than internal return of the ion pair to reactant, $k_r < k_{-1'}$, the proposal requires a consideration of questions that are outside the scope of this paper. For example, it is assumed without justification for Figure 2 that $K_{as} = 1.0$. It is also assumed that the rate constants for solvent reorganization around the ion-pair intermediate are the same for the reactions in either direction. This will not be the case on moving from the solvation shell favored for the neutral reactant to the shell for the ionic intermediate, which is presumably highly ordered and strongly stabilized by hydrogen-bonding and electrostatic interactions between the solvent and ions.

Hynes and co-workers have considered in theoretical studies the timing of solvent reorganization and carbon−halide bond cleavage during the solvolysis reactions of *tert*-butyl halides

(31) Peters, K. S.; Gasparrini, S.; Heeb, L. R. *J. Am. Chem. Soc.* **2005**, *127*, 13039−13047.
(32) Zwan, G. v. d.; Hynes, J. T. *J. Chem. Phys.* **1982**, *76*, 2993−3001.
(33) Toteva, M. M.; Richard, J. P. *J. Am. Chem. Soc.* **1996**, *118*, 11434−11445.
(34) Kaatze, U.; Pottel, R.; Schumacher, A. *J. Phys Chem.* **1992**, *96*, 6017−6020.
(35) Kaatze, U. *J. Chem. Eng. Data* **1989**, *34*, 371−374.
(36) Jencks, W. P. *Acc. Chem. Res.* **1976**, *9*, 425−432.
(37) Gilbert, H. F.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 7931−7947.
(38) Cox, M. M.; Jencks, W. P. *J. Am. Chem. Soc.* **1978**, *100*, 5956−5957.
(39) Harris, J. M.; McManus, S. P.; Sedaghat-Herati, M. R.; Neamati-Mazraeh, N.; Kamlet, M. J.; Doherty, R. M.; Taft, R. W.; Abraham, M. H. In *Nucleophilicity (Advances in Chemistry Series)*; Harris, J. M., McManus, S. P., Eds.; American Chemical Society: Washington, DC, 1987; Vol. 215, pp 247−254.
(40) Richard, J. P.; Toteva, M. M.; Amyes, T. L. *Org. Lett.* **2001**, *3*, 2225−2228.
(41) A similar selectivity should be observed for the reaction of **2-OTs**, because the effect of moving the nitro group from the 3- to the 4-position on reactivity of 1-phenylethyl derivatives towards solvolysis will be small [Richard, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1373−1383.]
(42) Kim, H. J.; Hynes, J. T. *J. Am. Chem. Soc.* **1992**, *114*, 10508−10528.

but do not consider the model in Scheme 4 and Figure 2.[42−44] We suggest that QM-MM-type calculations to model the barriers to the reactions shown in Figure 2 and to determine the magnitude of ion-pair stabilization that occurs upon solvent reorganization from the substrate to ion-pair solvation shell might also provide insight into the timing of substrate ionization and solvent reorganization during solvolysis.

Acknowledgment. We acknowledge the National Institutes of Health (GM 39754) for generous support of this work.

JA066235D

(43) Kim, H. J.; Hynes, J. T. *J. Am. Chem. Soc.* **1992**, *114*, 10528−10537.
(44) Mathis, J. T.; Kim, H. J.; Hynes, J. T. *J. Am. Chem. Soc.* **1993**, *115*, 8248−8262.