C4'-H), 8.00 (d, 1 H, J = 8.5 Hz, C4''-H), 7.38 (d, 1 H, J = 8.5 Hz, C5'-H), 7.24 (d, 1 H, J = 8.5 Hz, C5''-H), 7.22 (d, 1 H, J = 9.0 Hz, C6-H), 7.14 (s, 1 H, C1'-H), 6.99 (s, 1 H, C3-H), 6.95 (s, 1 H, C1''-H), 6.45 (d, 1 H, J = 9.0 Hz, C5-H), 6.17 (s, 2 H, NH_2), 4.66 (m, 2 H, C1-H_2), 4.12 (t, 2 H, J = 8.5 Hz, C7'-H_2), 4.09 (t, 2 H, J = 8.5 Hz, C7''-H), 3.43 (t, 2 H, J = 8.5 Hz, C8'-H_2), 3.58 (apparent t, 1 H, J = 6.0 Hz, C7''-H), 3.29 (t, obscured by H_2O, J = 8.5 Hz, C8''-H_2), 2.27 (m, 1 H, C7-HH), 1.92 (m, 1 H, C7-HH); IR (KBr) ν_{max} 3416, 2959, 2928, 2854, 1636, 1611, 1580, 1507, 1503, 1431, 1403, 1364, 1285, 1113 cm^{-1}; UV (*N*,*N*-dimethylformamide) 328 (ϵ 35 000), 304 (ϵ 32 000), 278 nm (ϵ 25 000); positive FABMS (triethanolamine), m/e 559 ($M + H^+$); negative FABMS (triethanolamine), m/e 557 ($M - H^+$); FABHRMS (triethanolamine), m/e 559.2091 ($C_{32}H_{26}N_6O_4 + H^+$ requires 559.2096); HPLC (0.5 mg of **8**/0.01 mL of DMF, solvent = THF, flow rate = 3.1 mL/min, R_t = 14 min) purity ≥95%.

(−)-**8**: $[\alpha]^{25}_D$ −19.6° (c = 0.046, *N*,*N*-dimethylformamide).

(+)-**8**: $[\alpha]^{25}_D$ +19.5° (c = 0.041, *N*,*N*-dimethylformamide).

Aqueous Solvolytic Reactivity of CI Agents 7-10. Stock solutions (25-100 μL, 2.0 mM concentration) of the agents in *N*,*N*-dimethylformamide (**1**, **3**), tetrahydrofuran (**6**), or dioxane (**10**) were diluted with a 1:1 mixture of methanol and water (pH 7) or a mixture of 1:1 methanol and aqueous buffer (pH 3) to prepare the solvolysis solution (30-100 μM). In selected instances, an aqueous *N*,*N*-dimethylformamide solution (**7**, **8**) or aqueous tetrahydrofuran solution (**9**) was used as solvolysis solvent instead of aqueous methanol (2.5 μM). The buffer contained 4:1:20 (volumes) of 0.1 M aqueous citric acid, 0.2 M aqueous Na_2HPO_4, and water, respectively. The UV spectrum of each solution was recorded immediately after mixing with water or aqueous buffer, the control and aqueous solutions were stoppered, protected from light, and allowed to stand at room temperature. The UV spectrum of each solution was recorded periodically (every 15 s for **10**, pH = 3) until no further change was detectable in the spectra. The residual absorbance at the long-wavelength absorbance (352 nm for **6**, 280 nm for **10**) was subtracted from the measured absorbances. Linear regression analysis ($r > 0.998$) of the linear plots of log (A/A_0) versus time revealed solvolysis rate constants of 3.67 ± 0.02 × 10^{-5} s^{-1} (pH = 7, $t_{1/2}$ = 5.24 h) and 1.98 ± 0.06 × 10^{-2} s^{-1} (pH = 3, $t_{1/2}$ = 35 sec) for **10**. The spent reaction mixture from the acidic or neutral solvolysis of **10** was extracted with ethyl acetate and analyzed by thin-layer chromatography (TLC). Two major products were detectable on TLC (50% hexane/tetrahydrofuran), which presumably correspond to the water and methanol addition products, respectively.

Acknowledgment. We gratefully acknowledge the financial support of the National Institutes of Health (CA 41986, D.L.B.) and the Alfred P. Sloan Foundation. We thank Dr. B. J. Invergo, Dr. M. Yasuda, and Dr. R. S. Coleman for early experimental contributions to the work.

Supplementary Material Available: General experimental details, details of the preparation and/or diagnostic characterization of **28**, **29**, and **31-35**, details of computational studies (ref 34), and a summary of the in vitro cytotoxic activity of the agents (Table II) (9 pages). Ordering information is given on a current masthead page.

Oxygen Scrambling and Stereochemistry during the Trifluoroethanolysis of Optically Active 2-Butyl 4-Bromobenzenesulfonate

Paul E. Dietze* and Marek Wojciechowski

Contribution from the Department of Chemistry and Biochemistry, University of Maryland Baltimore County, Baltimore, Maryland 21228. *Received October 27, 1989. Revised Manuscript Received March 5, 1990*

Abstract: It is shown that during the trifluoroethanolysis of 2-butyl 4-bromobenzenesulfonate, containing ^{18}O in the nonbridging oxygens, scrambling of the oxygen label occurs. When enantiomerically enriched 2-butyl 4-bromobenzenesulfonate is subjected to the same solvolysis conditions, racemization of the starting ester is not observed. Therefore 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. The possibility that the oxygen scrambling may be a concerted reaction and not involve an ion-pair intermediate is discussed.

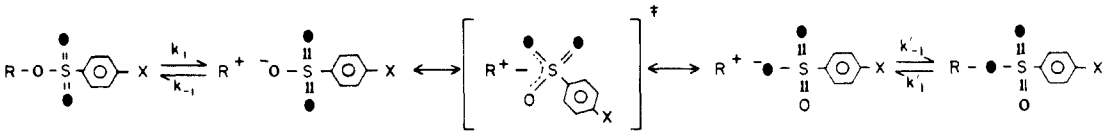
Although the mechanism of substitution at carbon centers has been studied extensively, there is still disagreement concerning the existence of intermediates in the solvolysis of simple secondary carbon centers. The solvolysis of simple secondary carbon compounds is generally thought to proceed by a stepwise mechanism that involves the formation of an intermediate ion pair.[1-7] The observation that oxygen isotope scrambling occurs in the substrate during solvolysis of benzenesulfonate[7-15] and carboxylate esters[16] is usually interpreted according to a mechanism that involves an ion-pair intermediate and is often cited as evidence for the existence of an ion-pair intermediate.[7,9-11,16] Isotope scrambling in benzenesulfonate esters according to an ion-pair mechanism presumably involves formation of a carbocation-benzenesulfonate ion pair, with sufficient lifetime to allow rotation of the benzenesulfonate anion followed by collapse of the ion pair to regenerate covalently bonded sulfonate ester as depicted in Scheme I and by the solid line of Figure 1.

Recent results have led to the suggestion that the solvolysis of simple secondary carbon compounds may actually be one-step

(1) Bentley, T. W.; Schleyer, P. v. R. *Adv. Phys. Org. Chem.* **1977**, *14*, 1-67.
(2) Harris, J. M. In *Progress in Physical Organic Chemistry*; Streitweiser, A., Jr., Taft, R. W., Eds.; Wiley: New York, 1974; Vol. 11, pp 89-173.
(3) Raber, D. J.; Harris, J. M.; Schleyer, P. v. R. In *Ions and Ion Pairs in Organic Reactions*; Szwarc, M., Ed.; Wiley: New York, 1974; Vol. 2, Chapter 3.
(4) Shiner, V. J., Jr.; Dowd, W.; Fisher, R. D.; Hartshorn, S. R.; Kessick, M. A.; Milakofsky, L.; Rapp, M. W. *J. Am. Chem. Soc.* **1969**, *91*, 4838-4843.
(5) Shiner, V. J., Jr.; Nollen, D. A.; Humshi, K. *J. Org. Chem.* **1979**, *44*, 2108-2115.
(6) Doering, W.; Zeiss, H. *J. Am. Chem. Soc.* **1953**, *75*, 4733-4738.
(7) Paradisi, C.; Bunnett, J. *J. Am. Chem. Soc.* **1985**, *107*, 8223-8233.
(8) Paradisi, C.; Bunnett, J. *J. Am. Chem. Soc.* **1981**, *103*, 946-948.
(9) Diaz, A. F.; Lazdins, I.; Winstein, S. *J. Am. Chem. Soc.* **1968**, *90*, 1904-1905.
(10) Goering, H. L.; Thies, R. W. *J. Am. Chem. Soc.* **1968**, *90*, 2967-2968, 2968-2970.
(11) Goering, H. L.; Jones, B. E. *J. Am. Chem. Soc.* **1980**, *102*, 1628-1633.
(12) Denny, D. B.; Goldstein, B. *J. Am. Chem. Soc.* **1957**, *79*, 4948-4951.
(13) Norlander, S. E.; Kelly, W. J. *J. Org. Chem.* **1967**, *32*, 4122-4124.
(14) Chang, S.; le Noble, W. J. *J. Am. Chem. Soc.* **1983**, *105*, 3708-3709.
(15) Fujio, M.; Futoshi, S.; Yuho, T.; Sawada, M.; Tukan, Y. *Tetrahedron Lett.* **1988**, *29*, 93-96.
(16) Goering, H. L.; Pombo, M. M. *J. Am. Chem. Soc.* **1960**, *82*, 2515-2521 and references within.

0002-7863/90/1512-5240$02.50/0

Scheme I



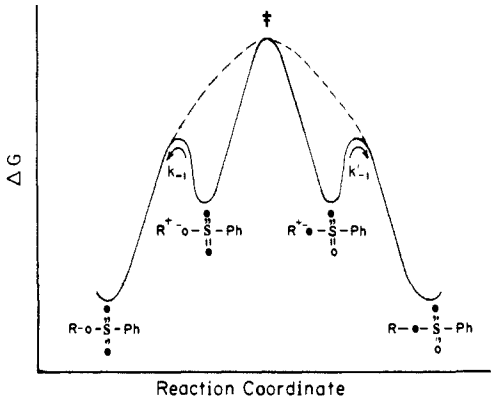


Figure 1. A free energy diagram depicting oxygen scrambling in a labeled benzenesulfonate ester. The solid line depicts scrambling by a stepwise mechanism involving an ion-pair intermediate as described in Scheme I. The dotted line depicts oxygen scrambling by a concerted mechanism.

concerted reactions and not involve intermediates.[17-19] The conclusion that the solvolysis of secondary carbon compounds does not involve an intermediate is consistent with the notion that the reaction is concerted since the carbocation has too short a lifetime to exist as a discrete intermediate in the presence of the surrounding nucleophiles.[17] Indeed Jencks has suggested that the observed scrambling of the oxygens may also be a concerted process.[20] If there is no activation barrier for collapse of the ion-pair intermediate (k_{-1} of Figure 1) then there is no intermediate and the scrambling of the oxygen label will occur by a concerted mechanism as shown by the dotted line in Figure 1.

If an ion pair does exist and has a significant lifetime such that rotation of the anion is possible, rotation of the carbocation might also be possible. Rotation of the carbocation followed by collapse of the ion pair would lead to racemization of the substrate. Partial racemization of 2-octyl 4-methylbenzenesulfonate has been observed during acetolysis.[21,22] The observed racemization of the starting sulfonate ester was attributed to a reaction of the 2-octyl 4-methylbenzenesulfonate with product sulfonic acid generated during solvolysis. It is also possible that some of the racemization may have occurred from rotation of the octyl group in an ion-pair intermediate followed by collapse of the ion pair. In fact, partial racemization in an ion pair derived from enantiomerically enriched 2-butyl 4-methylbenzenesulfonate was proposed to occur during the trifluoroacetolysis of this compound.[23] However, the trifluoroacetolysis is complicated by an elimination to form 2-butene followed by readdition of the 4-methylbenzenesulfonic acid, which also results in racemization.[23,24] Racemization in an ion pair has also been proposed to occur during the solvolysis of several 4-methylbenzenesulfonate esters of substituted 1-phenethyl alcohols.[25]

Table I. The ^{18}O Content of the Bridging Oxygen in Unsolvolyzed 2-Butylbrosylate Isolated at Various Times during the Trifluoroethanolysis at 30 °C of 2-Butylbrosylate Initially Containing ^{18}O (93%) in the Nonbridging Oxygens

time, min^{-1}	% ^{18}O
0	1.7
1100	3.1
2200	5.5
3300	6.9
4400	9.0

In order to test clearly the possibility of racemization due to formation of an ion-pair intermediate we have studied the stereochemical purity of enantiomerically enriched 2-butyl 4-bromobenzenesulfonate (2-butylbrosylate) that has been subjected to solvolytic conditions that lead to scrambling of an oxygen label and presumably involve an ion pair. Partial racemization of starting 2-butylbrosylate would provide evidence for the existence of an ion-pair intermediate.

Results and Discussion

The rate constant for solvolysis of 2-butylbrosylate in trifluoroethanol containing 1 equiv of 2,6-lutidine at 30 ± 0.3 °C is (5.3 ± 0.5) × 10^{-6} s^{-1} and was determined by monitoring the disappearance of 2-butylbrosylate as a function of time with high-pressure liquid chromatography as described in the Experimental Section. The addition of a molar equivalent of 2,6-lutidine prevents the readdition of 4-bromobenzenesulfonic acid generated during solvolysis to the 2-butene formed from elimination.[7,26]

The rate constant for scrambling of ^{18}O was determined by subjecting a sample of 2-butylbrosylate (5 × 10^{-3} M) having ^{18}O in the nonbridging oxygens to the same solvolysis conditions as were used to determine the rate of solvolysis. The scrambling reaction was conducted at a lower initial concentration of 2-butylbrosylate in order to minimize ^{18}O incorporation as a result of external attack by brosylate anion generated during solvolysis (see below). Aliquots of the reaction mixture were removed at five equally spaced time intervals covering two solvolysis half-lives. The unsolvolyzed ester was recovered and reduced with sodium in liquid ammonia following the procedure of Paradisi and Bunnett with slight modification.[7,8] The reduction selectively cleaves the 2-butylbrosylate to give 2-butanol such that the bridging oxygen of the ester is found in the alcohol product. Following the reduction the alcohol was derivatized with (*S*)-2-acetoxypropionyl chloride as described in the Experimental Section. The (*S*)-2-acetoxypropionic esters of 2-butanol were analyzed by gas chromatography/mass spectrometry in order to determine the ^{18}O content of the isolated alcohol. The rate constant for equilibration of the ^{18}O label between the bridging and nonbridging positions was found to be (4.9 ± 0.4) × 10^{-7} s^{-1} by using standard kinetic analysis for a system going to equilibrium.[7] In Table I is given the percent of ^{18}O found in the bridging oxygen for each time point.

It was demonstrated that the incorporation of ^{18}O was not a result of attack by brosylate anion generated during solvolysis by the following experiment: a solution of 2-butylbrosylate (5.0 × 10^{-3} M) was solvolyzed in trifluoroethanol containing 4-methylbenzenesulfonic acid (3.75 × 10^{-3} M) and 2,6-lutidine (5.0 × 10^{-3} M). The amount of 2-butyl 4-methylbenzenesulfonate formed was determined at various times with use of high-pressure liquid chromatography. After a time period corresponding to 2 half-lives for solvolysis of the 2-butylbrosylate there was less than 2% of the 2-butyl 4-methylbenzenesulfonate present. This value

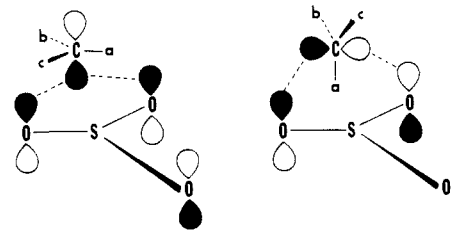
(17) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1986**, *108*, 4549–4555.
(18) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 2057–2062.
(19) Dietze, P. E.; Harlri, R.; Khattak, J. *J. Org. Chem.* **1989**, *54*, 3317–3320.
(20) Jencks, W. P. *Chem. Soc. Rev.* **1981**, *10*, 345–375.
(21) Streitwieser, A., Jr.; Walsh, T. D.; Wolfe, J. R., Jr. *J. Am. Chem. Soc.* **1965**, *87*, 3682–3685.
(22) Streitwieser, A., Jr.; Walsh, T. D. *J. Am. Chem. Soc.* **1965**, *87*, 3686–3691.
(23) Allen, A. D.; Ambidge, C. I.; Tidwell, T. T. *J. Org. Chem.* **1983**, *48*, 4527–30. Also see: Dannenberg, J. J.; Barton, J. K.; Bunch, B.; Goldberg, B. J.; Kawalski, T. *J. Org. Chem.* **1983**, *48*, 4524–4527.
(24) Dannenberg, J. J.; Goldberg, B. J.; Barton, J. K.; Kill, B.; Weinworzel, D. H.; Longas, M. O. *J. Am. Chem. Soc.* **1981**, *103*, 7764–7768.
(25) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513–4519.
(26) Yamataka, H.; Tamura, S.; Hanafusa, T.; Ando, T. *J. Am. Chem. Soc.* **1985**, *107*, 5429–5434.

of 2% is certainly an upper limit on the amount of reaction with brosylate anion generated during solvolysis, since the 4-methylbenzenesulfonate is present in a higher concentration than would occur in a solvolysis experiment and it is also expected to be more nucleophilic than a brosylate anion. This observation that reaction with external brosylate anion generated during solvolysis is not significant is in agreement with the results of others.[7]

The optical purity of unsolvolyzed 2-butylbrosylate after two solvolysis half-lives was determined by solvolyzing a sample of enantiomerically enriched (*R*)-2-butylbrosylate and recovering the unsolvolyzed ester. The solvolysis conditions were identical with those used in the experiments that measured oxygen scrambling. The optical purity of the 2-butylbrosylate before solvolysis was determined by electrochemical reduction of the ester to yield 2-butanol.[27] Electrochemical techniques have been used previously to reduce benzenesulfonate esters.[28] The resulting 2-butanol was derivatized with (*S*)-2-acetoxypropionyl chloride to produce the diasteriomeric (*S*)-2-acetoxypropanoic esters of (*R*)- and (*S*)-2-butanol. Gas chromatographic analysis of the (*RS*)-2-butyl-(*S*)-2-acetoxypropionate was employed to determine the optical purity of the derivatized alcohol, which is the same as the optical purity of the 2-butylbrosylate. The optical purity of the starting 2-butylbrosylate was found to be 88 ± 2% and was the same as that of the alcohol used for its synthesis (89 ± 2%). Derivatization of racemic 2-butanol followed by gas chromatographic analysis demonstrated that there was no stereoselectivity in the derivitization reaction. A sample of the enantiomerically enriched (*R*)-2-butylbrosylate was subjected to the same solvolysis conditions as described above. After two solvolysis half-lives the unsolvolyzed ester was recovered, reduced electrochemically, derivatized with (*S*)-2-acetoxypropionyl chloride, and analyzed by gas chromatography. The optical purity of the isolated 2-butylbrosylate was found to be 86 ± 2%, the same as that of the starting 2-butylbrosylate. All experiments to determine optical purity were repeated in duplicate.

The above results demonstrate that during the trifluoroethanolysis of 2-butylbrosylate oxygen scrambling can occur, but racemization of the butyl group is not observed. If the trifluoroethanolysis of 2-butylbrosylate does involve an ion-pair intermediate, the activation energy for rotation of the butyl group in the ion pair to give inversion of configuration is too large for it to compete with reaction with solvent.

These results are also consistent with scrambling occurring by a concerted mechanism. If there is no barrier to collapse of the ion-pair intermediate (k_{-1} of Figure 1) then the intermediate cannot exist and the observed scrambling will occur by a one-step concerted mechanism as shown by the dotted line of Figure 1. The concerted reaction can be viewed as a 1,3-sigmatropic shift of the butyl group and would be expected to follow orbital symmetry rules.[29] Since the sulfonate group has a 3-fold axis of symmetry, the highest occupied molecular orbitals exist as a degenerate pair.[30] A 1,3-sigmatropic shift suprafacial on the π system is therefore allowed with retention of configuration or inversion of configuration, as depicted in structures **1a** and **1b**, respectively. (Structures **1a** and **1b** represent only the π molecular orbitals of the sulfonate ester and omit the phenyl ring and the orbitals on sulfur for clarity.[31]) The observation of complete retention of configuration indicates that if the mechanism for oxygen scrambling is concerted the lowest energy path is a 1,3-sigmatropic shift suprafacial with respect to the migrating group and proceeds with retention of configuration of the migrating group. An ion-pair intermediate that permits rotation of the anion



1a 1b

but not the cation cannot be definitively ruled out. Since the sulfonate anion of the ion pair is tetrahedral with bond angles of approximately 110° it only needs to rotate 55° in order to make the unlabeled oxygen that was originally the bridging oxygen of the ester equivalent to one of the ^{18}O labeled, nonbridging oxygens. The 2-butyl cation, however, is planar and requires a 90° rotation in order to make the two faces of the cation equivalent. Rotation of the cation may also lead to an unfavorable steric interaction between the hydrogen on the cationic carbon and the benzenesulfonate anion. This interaction does not occur for rotation of the benzenesulfonate anion. The greater amount of rotation required for the cation of the ion pair, as well as the unfavorable steric interaction associated with this rotation, may make cation rotation more difficult than rotation of the anion. A free energy diagram depicting oxygen scrambling according to a mechanism involving an ion-pair intermediate is shown by the solid line in Figure 1. Clearly, if the ion pair does exist it is an extremely tight ion pair.

The above results are therefore consistent with oxygen scrambling occurring by a concerted mechanism that is suprafacial with respect to the migrating group or by a mechanism involving an ion pair that is so "tight" that it does not allow for inversion of configuration of the butyl group. In as much as other experimental results suggest that the secondary carbocation cannot exist in the presence of weakly nucleophilic solvents such as trifluoroethanol,[17-19] we feel it is not unreasonable to prefer the operation of a concerted mechanism in order to explain the observed oxygen scrambling. If indeed the secondary carbocation cannot exist in the presence of a trifluoroethanol molecule, it will not exist in the presence of the more nucleophilic sulfonate anion.[32] In view of the high stereospecificity for oxygen scrambling in secondary alkyl systems, oxygen scrambling, contrary to current dogma, is not proof for the existence of ion-pair intermediates. In these cases the alternative and self-consistent concerted mechanism may be in effect.

Most of the other evidence for an ion-pair intermediate in the solvolysis of simple secondary carbon compounds is based on characterization of the transition state for the solvolysis reaction. Although it is true that a carbocation-like transition state exists in the solvolysis of secondary carbon compounds, there is no evidence that this transition state leads to a carbocation intermediate. The experimental results that characterize the solvolytic transition state of secondary substrates are fully consistent with a one-step concerted mechanism that involves a large amount of positive charge development on the carbon undergoing substitution (an "open" or "exploded" transition state). There is good precedence for this type of transition state in concerted reactions.[33-35] Phosphoryl transfer reactions[33] and the reaction of nucleophiles

(27) We chose to use electrochemical reduction in order to determine optical purity since this procedure was reproducible and did not lead to any detectable racemization of the 2-butylbrosylate. We found that in our hands reduction with sodium in liquid ammonia did lead to some racemization and optical purity measurements were not as reproducible. However, reductions with sodium in liquid ammonia did give accurate and reproducible results for determining the ^{18}O content. We are currently investigating the chemistry involved with these reductions.

(28) Yousefzadeh, P.; Mann, C. K. *J. Org. Chem.* **1968**, *33*, 2716–2720.

(29) Woodward, R. B.; Hoffmann, R. *The Conservation of Orbital Symmetry*; Verlag Chemie, Academic Press: New York, 1971.

(30) (a) Borden, W. T. *Modern Molecular Orbital Theory for Organic Chemists*; Prentice-Hall: Englewood Cliffs, NJ, 1975. (b) Streitwieser, A., Jr. *Molecular Orbital Theory for Organic Chemists*; Wiley: New York, 1961.

(31) A 1,3-sigmatropic rearrangement antarafacial on the π system is not likely due to required distortion of the π system.[29]

(32) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 5880–5886.

(33) (a) Skoog, M. T.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 7597–7606. (b) Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7579–7586. (c) Herschlag, D.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 7587–7596.

(34) Richards, J. P.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1383–1396.

(35) Knier, B. L.; Jencks, W. P. *J. Am. Chem. Soc.* **1980**, *102*, 6789–6798.

with 1-phenethyl substrates[34] and methoxymethyl derivatives[35] are examples of concerted reactions with "exploded" transition states.

In summary, the oxygen-scrambling experiments reported here are consistent with a concerted mechanism or a mechanism involving a very tight ion pair in which rotation of the cation is not possible. In view of previous results[17-19] that suggest that the carbocation does not exist in the presence of weak nucleophiles and the high stereospecificity observed for oxygen scrambling we conclude that these reactions are best viewed as one-step concerted reactions having an "exploded" transition state.

Experimental Section

Methods. High-pressure liquid chromatography was performed on a Shimadzu HPLC system equipped with a Model SPC-6A variable-wavelength detector and a Model C-R6A electronic integrator. NMR spectra were recorded on an IBM NR/80 spectrometer. Gas chromatographic analysis was performed on a Varian Model 3300 gas chromatograph with a 1075 split/splitless capillary injector and a flame ionization detector. The gas chromatograph was interfaced to a chart recorder and a Varian Model CDS-111 integrator. Mass spectral analysis was performed on a Hewlett Packard Model 5988A GC/MS/DS. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected.

Materials. 2,2,2-Trifluoroethanol (99+% Gold Label grade, Aldrich) and 1,1,1,3,3,3-hexafluoro-2-propanol (Aldrich) were dried over 4A molecular sieves for several days before use. 2,6-Lutidine (99%, Aldrich) was distilled from aluminum chloride and stored in an amber bottle. Racemic 2-butanol (Aldrich), enantiomerically enriched (*R*)-2-butanol (99+%, Aldrich), 4-bromobenzenethiol (Aldrich), acetonitrile (HPLC grade, Fischer), and tetraethylammonium perchlorate (polarographic grade, Kodak) were used without further purification. Water containing 97–98% ^{18}O was purchased from ICN Biomedicals Inc.

(*S*)-2-Acetoxypropionyl chloride was synthesized from L-(+)-lactic acid (Chemical Dynamics Corp.) according to published procedure.[36] The product exhibited the following ^1H NMR, δ 1.6 (d, 3 H), 2.2 (s, 3 H), 5.3 (q, 1 H) ppm, and showed no indication of a hydroxylic proton.

4-Bromobenzenesulfonyl chloride of natural isotopic abundance was commercially available from Aldrich and before use was recrystallized from ethyl ether with cooling to −78 °C.

4-Bromobenzenesulfonyl chloride containing ^{18}O was prepared from 4-bromobenzenethiol and 97–99% ^{18}O-enriched water according to the procedure of Oae et al.[37] except that 1,1,1,3,3,3-hexafluoro-2-propanol was used as the solvent.[38] The ^{18}O-labeled 4-bromobenzenesulfonyl chloride was purified by dissolving the solid in ethyl ether and washing twice each with cold 10% NaOH and cold water. The ether layer was dried ($MgSO_4$) and the ether removed under reduced pressure. The resulting solid was recrystallized from ethyl ether with cooling to −78 °C. The isolated material was shown to be better than 98% pure by HPLC and had a mp of 74–75 °C (lit. mp 76–76 °C).[39] Mass spectral analysis demonstrated the ^{18}O content of the 4-bromobenzenesulfonyl chloride was 95%.

2-Butylbrosylate was prepared according to published procedure[38] to give a pale yellow oil that was purified by trituration with petroleum ether and cooling to −78 °C before decanting. The isolated ester showed only one spot on thin-layer chromatography (silica gel with methylene chloride) having an R_f value of 0.7 and was shown to be better than 98% pure by HPLC analysis. The NMR spectrum also indicated the correct product. 2-Butylbrosylate containing ^{18}O was prepared in the same way, using ^{18}O-labeled 4-bromobenzenesulfonyl chloride. Mass spectral analysis indicated the percent ^{18}O incorporated into the ester was 93%.

2-Butyl 4-methylbenzenesulfonate was prepared according to published procedure[40] and was purified by trituration with petroleum ether and cooling to −78 °C before decanting. The purified material was a pale yellow oil that was shown to be better than 99% pure by HPLC.

4-Methylbenzenesulfonic acid was prepared in anhydrous form by drying the monohydrate (Aldrich) by azeotropic distillation from benzene; after removal of the remaining organic solvent under reduced pressure the 4-methylbenzenesulfonic acid was placed in a vacuum oven at 100 °C for 4 h. The sample was allowed to cool in a desiccator to give a purple solid [mp 35–38 °C (lit. mp 38 °C)].[41] Integration of the NMR spectrum (in dimethyl sulfoxide d-6) gave a ratio of 3:1 for the methyl protons (δ 2.2 ppm) relative to the acidic proton (δ 13.8 ppm), indicating that the sample was anhydrous.

Kinetics. The rate of solvolysis of 2-butylbrosylate was determined by measuring the disappearance of 2-butylbrosylate as a function of time with HPLC. A 3-mL solution of trifluoroethanol containing 2-butylbrosylate (0.6 M), 2,6-lutidine (0.6 M), and *p*-dichlorobenzene (0.4 M) as an internal standard was placed in a 30.0 ± 0.2 °C constant-temperature bath. At various time intervals a 50-μL aliquot of the reaction mixture was removed and quenched in 1 mL of cold 0.1 N HCl, 1 mL of ethyl ether was than added to the HCl solution, and the mixture was shaken well. After separation of the two layers, a 20-μL aliquot of the ether layer was analyzed by HPLC. Components of the reaction mixture were separated on a 4.6 × 25 cm C-18 column with a mobile phase of 62.5:37.5 methanol–water and a flow of 2 mL/min. The peak areas of the 2-butylbrosylate and of the *p*-dichlorobenzene internal standard were obtained by electronic integration of their UV absorbances at 265 nm. Each data point was calculated as the average of three injections. The rate constant for solvolysis was obtained from the slope of a semilogarithmic plot of 2-butylbrosylate area relative to internal standard against time. The semilogarithmic plot was linear and contained 17 data points covering more than 5 half-lives. The rate constant for solvolysis is estimated to be better than ±10%.

HPLC analysis was also used to determine the amount of 2-butyl 4-methylbenzenesulfonate produced when the solvolysis reaction was run in the presence of 4-methylbenzenesulfonate anion. The 4-methylbenzenesulfonate and the 4-bromobenzenesulfonate esters of 2-butanol were separated on a Waters 8NVC184 HPLC column in a Waters RCM 8 × 10 radial compression module with a mobile phase of 50:50 acetonitrile–water and a flow of 2 mL/min. The peak areas of the esters were obtained by electronic integration of their UV absorbances at 265 nm. It was shown that in an equimolar mixture of 2-butyl 4-bromobenzenesulfonate and 2-butyl 4-methylbenzenesulfonate that the integrated area of the 2-butyl 4-bromobenzenesulfonate was 1.2 times larger than the peak corresponding to the 2-butyl 4-methylbenzenesulfonate. Appropriate corrections were made to account for this difference in absorbance at 265 nm when determining the percent of each ester present in the reaction mixture.

Oxygen-Scrambling Experiments. A trifluoroethanol solution (150 mL) of 2-butylbrosylate (5×10^{-3} M) with ^{18}O in the nonbridging oxygen and 2,6-lutidine (5×10^{-3} M) was placed in a constant-temperature bath at 30 ± 0.2 °C. At various time intervals a volume of the reaction mixture was removed and quenched in a 3- to 4-fold excess of ice-cold water. Enough of the reaction mixture was removed such that ca. 0.02 g of the substrate could be recovered. The unsolvolyzed ester was recovered by extraction with 4–5 portions of diethyl ether according to published procedure,[7] except that the combined ether layers were washed once with 5% $NaHCO_3$, once with 1:1 HCl/H_2O, and then with water until the aqueous layer was neutral to litmus paper. After the ether layer was dried ($MgSO_4$) the ether was removed under reduced pressure at room temperature and the residual oil placed under vacuum for 12 h. The isolated 2-butylbrosylate obtained at each time point was weighed and reduced with sodium in liquid ammonia according to published procedure,[7,8] except that a larger excess of sodium metal was used (ca. 5 equiv). The reduction selectively cleaves the 2-butylbrosylate to give 2-butanol such that the bridging oxygen of the ester is found in the alcohol product. After the reduction was complete the ammonia was allowed to evaporate at °C; a pale orange residue remained. To the residue was added, at 0 °C, 65 μL of pyridine for each 10 mg of 2-butylbrosylate reduced, followed by 180 μL of a 2 M methylene chloride solution of (*S*)-2-acetoxypropionyl chloride per 10 mg of 2-butylbrosylate reduced. The resulting solution was warmed to room temperature and 3 drops of 0.1 N HCl added. The solution was swirled, 1 mL of hexane was added, and the solution was dried ($MgSO_4$) and filtered. The resulting hexane solution contained the (*S*)-2-acetoxypropanoic esters of (*R*)- and (*S*)-2-butanol.[42] The ^{18}O content of the derivatized alcohol was determined by gas chromatographic–mass spectral analysis. Derivatization of the 2-butanol before gas chromatographic–mass spectral analysis provides a simple way of separating the 2-butanol from the solvent peak. A 0.6–1.0 μL volume of the hexane solution was injected onto a 30 m × 0.257 mm J&W fused silica DB-5 capillary column operated at 70 °C. This effectively separated the (*S*)-2-acetoxypropionic esters from other components. The mass spectrometer was operated in chemical ionization mode with isobutane as the reagent gas. The peaks of interest in the mass spectrum are the parent peaks of the derivatized

(36) Julia, S.; Zurbano, M. *Affinidad* **1978**, 150–153.
(37) Oae, S.; Kitao, T.; Kitaoka, Y. *Tetrahedron* **1963**, *19*, 827–832.
(38) This procedure was made available to us in a personal communication from Dr. V. J. Shiner.
(39) *Handbook of Chemistry and Physics*, 48th ed.; CRC Press: Cleveland, 1968.
(40) Tipson, R. S. *J. Org. Chem.* **1944**, *9*, 235–241.
(41) *Beilstein*, 4th ed., 11, 44.
(42) The derivatization procedure is a modification of that employed by: Doolittle, R. E.; Heath, R. R. *J. Org. Chem.* **1984**, *49*, 5041–5050.

2-butanol (m/z of 189 and 191 for ^{16}O and ^{18}O, respectively). The intensities of these peaks were measured by single ion monitoring of m/z 189 and 191 using the average of scans taken over each entire GC peak after appropriate background correction. The ratio of 191/(189 + 191) gives the percent ^{18}O in each sample. Repeat injections were reproducible to better than ±0.5%.

Stereochemical Experiments. A sample of enantiomerically enriched (*R*)-2-butylbrosylate (optical purity 88 ± 2%) was subjected to solvolysis conditions identical with those described above for the ^{18}O scrambling experiments. After two solvolysis half-lives the unsolvolyzed 2-butylbrosylate was recovered as described above and was reduced electrochemically. The recovered 2-butylbrosylate was reduced at a mercury pool electrode with use of controlled-potential electrolysis (CPE). Acetonitrile was used as the solvent and tetraethylammonium perchlorate (TEAP) served as the supporting electrolyte. CPE was conducted in a sealed electrochemical cell (IBM Instruments). Three milliliters of triply distilled mercury (Bethlehem Apparatus Co.) was used to form the mercury pool that served as the working electrode (surface area ca. 25 cm^2). A Pt wire was inserted into the pool to make contact. During CPE the mercury pool was stirred by a magnetic stirring bar. The auxillary electrode (Pt wire) compartment was a glass cylinder with a large Vycor tip, inset in the top of the cell. The Ag/Ag^+ reference electrode (a silver wire submerged in the 0.01 M $AgNO_3$–0.1 M TEAP acetonitrile solution) was separated from the electrolyzed solution by means of a salt bridge. The auxillary electrode compartment and the reference bridge were both filled with 0.1 M TEAP acetonitrile solution.

CPE of 2-butylbrosylate was carried out in 5-mL volumes of solutions prepared by dissolving approximately 15 mg of the compound in 0.1 M TEAP acetonitrile solution. Prior to CPE the solution was purged with argon for 20 min and then was kept under an argon blanket during CPE. Argon was purified from traces of moisture and oxygen and saturated with acetonitrile vapors by passing through a molecular sieve column, a copper catalyst column (Labclear), and two washing bottles filled with acetonitrile.

The progress of CPE was monitored coulometrically and by means of linear scan voltammetry (LSV) at a small mercury electrode (mercury coated platinum wire; surface area ca. 0.05 cm^2). The CPE and LSV measurements were conducted with a BAS-100 electrochemical analyzer (Bioanalytical Systems). The LSV voltammograms obtained for 2-butylbrosylate in 0.1 M TEAP in acetonitrile exhibited two peaks with peak potentials of −2.25 V and −2.53 V vs Ag/Ag^+. All of the CPE reductions of 2-butylbrosylate in this work were carried out at −2.80 V potential, which our preliminary CPE experiments had shown was sufficient to completely reduce the compound.

When the electrochemical reduction was complete the acetonitrile solution containing the 2-butanol was separated from the mercury pool and cooled to 0 °C. To the cooled acetonitrile solution was added, with stirring, 30 μL of pyridine and 150 μL of a 2 M solution of (*S*)-2-acetoxypropionyl chloride. The solution was warmed to room temperature, and stirring was continued for 2 h. The acetonitrile solution containing the derivatized alcohol was evaporated at room temperature under reduced pressure. To the resulting solid was added 1 mL of hexane followed by 10 drops of 0.1 N HCl; the hexane layer was separated and the HCl washed again with 1 mL of hexane. The combined hexane layers were dried ($MgSO_4$) and filtered, and the hexane was removed under reduced pressure at room temperature. After evaporation to dryness, 0.5 mL of hexane was added to the flask and the resulting solution used for gas chromatographic analysis. Gas chromatographic analysis was performed by injecting 1–2 μL of the hexane solution onto a 15 m × 0.25 mm J&W DB-1 fused silica capillary column operated at 70 °C. The linear flow velocity was 18 cm/min, and the split ratio was 100:1. The percent of each diasteriomer was determined by electronic integration of the peak areas. Several injections of each sample were made, and the average deviation was better than ±1.3%. Electrochemical reduction and derivatization of the starting 2-butylbrosylate and of 2-butylbrosylate isolated after two solvolysis half-lives was repeated twice and the results agreed within ±2%.

Acknowledgment. This work was supported in part by an institutional DRIF grant from the University of Maryland. We thank Dr. G. R. Underwood (New York University) and Dr. J. F. Liebman, Dr. M. R. Hulce, and Dr. R. M. Pollack (University of Maryland Baltimore County) for helpful discussions and Dr. V. J. Shiner (Indiana University) for communicating some of his results with us. We thank Dr. P. Callery (University of Maryland at Baltimore) for preliminary mass spectral analyses and Michael Greisman for assistance with the electrochemical reductions.

Synthesis and Reactions of Phosphine–Boranes. Synthesis of New Bidentate Ligands with Homochiral Phosphine Centers via Optically Pure Phosphine–Boranes

Tsuneo Imamoto,* Toshiyuki Oshiki, Takashi Onozawa, Tetsuo Kusumoto, and Kazuhiko Sato

Contribution from the Department of Chemistry, Faculty of Science, Chiba University, Yayoi-cho, Chiba 260, Japan. *Received August 28, 1989*

Abstract: Secondary and tertiary phosphine–boranes were synthesized in one-pot from phosphine oxides or substituted chlorophosphines without isolation of the intermediate phosphines. Phosphine–boranes having a methyl group were metalated with *sec*-butyllithium. The generated carbanions reacted with alkyl halides or carbonyl compounds to yield various phosphine–borane derivatives. The carbanions underwent copper(II)-promoted oxidative coupling without impairment of the borane functionality. Secondary phosphine–boranes reacted with alkyl halides, aldehydes, or α,β-unsaturated carbonyl compounds to give phosphine–borane derivatives having a functional group. The boranato group of phosphine–boranes was removed in a stereospecific manner with retention of configuration by treatment with a large excess of amine such as morpholine. A new route to bidentate ligands with homochiral phosphine centers has been explored by utilizing these characteristic reactivities of phosphine–boranes. Thus, optically pure (*S,S*)-1,2-bis(*o*-anisylphenylphosphino)ethane, (*R,R*)-1,2-bis(*tert*-butylphenylphosphino)ethane, and (*S,S*)-1,4-bis(*o*-anisylphenylphosphino)butane have been synthesized via phosphine–boranes.

Phosphine–boranes, adducts of phosphines and boranes, constitute a unique class of organophosphorus compounds. These compounds have attracted the attention of chemists, and a number of preparative and physicochemical studies have been made so far, revealing their peculiar chemical properties as well as the inherent P–B bond nature.[1,2] In addition, it has been demon-

0002-7863/90/1512-5244$02.50/0