Oxygen Exchange as a Function of Racemization in 1-Phenyl-1-ethanol. Kinetic Evidence for Ion-Dipole Pair Intermediates†

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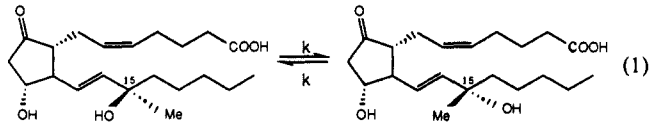
Abstract: The rate constants for three competing processes at the chiral center in the acid-catalyzed racemization of both (*R*)- and (*S*)-1-phenyl-1-ethanol in 50% ^{18}O-enriched water at 64.5 °C have been determined by chiral HPLC and GC/MS methods: oxygen exchange without inversion, $k_E = (5.9 \pm 0.6) \times 10^{-4}$ M^{-1} s^{-1}, inversion without oxygen exchange, $k_I = (4.1 \pm 0.2) \times 10^{-4}$ M^{-1} s^{-1}, and oxygen exchange with inversion, $k_{EI} = (7.6 \pm 0.7) \times 10^{-4}$ M^{-1} s^{-1}. The fact that k_I is comparable to the other rate constants indicates that, in some cases, the departing water molecule bonds to the intermediate carbocation from the opposite face. The smaller value of k_E relative to k_{EI} indicates that the departing water shields the front side from attack by the bulk solvent. To account for the observed rate constants, a mechanism is proposed in which the initially formed carbocation intermediate is present as a tightly solvated ion-dipole with a finite lifetime. The water molecules within the solvation sphere exchange at a rate comparable to their exchange with the bulk solvent to form a randomly solvated carbocation. These proposed intermediates are analogous to the intimate and solvent separated ion pairs of solvolysis reactions.

A study of the relative rates of ^{18}O-incorporation into each epimer as a function of epimerization revealed the presence of an asymmetric carbocation intermediate during the acid-catalyzed epimerization of 15(*R*)-methylprostaglandin E_2 and 15(*S*)-methylprostaglindin E_2 in ^{18}O-enriched water.[1] The relative rates



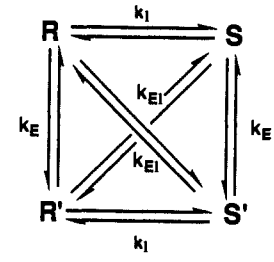
(1)

15(R)-methyl PGE_2 15(S)-methyl PGE_2

of these processes indicated that the exchange at the C-15 hydroxyl group was more rapid than the change in configuration at this site. In addition, a significant percentage of the initially formed epimerized product did not exchange with the ^{18}O-enriched water. This latter result indicated that, in some cases, the departing water molecule ultimately bonds to the carbocation from the opposite face. These data were shown to be consistent with a mechanism for epimerization in which the departing water molecule remains associated with the positively charged carbocation intermediate as an ion-dipole pair which formally retains the configuration of the starting material.

Although the apparent symmetry of these carbocation intermediates may be unique to the prostaglandins, the more limited nature of earlier kinetic studies of oxygen exchange as a function of racemization of other optically active alcohols would not have revealed similar asymmetric intermediates. Grunwald's detailed analysis of the racemization of 1-phenyl-1-ethanol in ^{18}O-enriched water in 1957 is typical of these studies in that the mechanistic

Scheme I



conclusions were based, in part, on the oxygen isotopic composition of the the unresolved racemic products.[2] To probe the stereochemistry and solvation of the carbocation intermediate in the racemization of 1-phenyl-1-ethanol, we have taken advantage of the progress in separation techniques to determine the oxygen exchange rates of each isomer in this reaction as was done in the (15)-methylprostaglindin E_2 epimerization. Specifically, we report here the rate constants for the following processes as a function of racemization of 1-phenyl-1-ethanol in ^{18}O-enriched water:

$$R \overset{k_E}{\rightleftharpoons} R'$$

oxygen exchange without inversion (2)

$$R \overset{k_I}{\rightleftharpoons} S$$

inversion without oxygen exchange (3)

$$R \overset{k_{EI}}{\rightleftharpoons} S'$$

oxygen exchange with inversion (4)

$$R \overset{k_{tot\,ex}}{\rightleftharpoons} R' + S'$$

oxygen exchange into racemic product (5)

The oxygen exchange processes all involve the incorporation of the isotopically distinct solvent oxygen into the specified alcohol isomer(s). R symbolizes the optically pure starting material; R', the same isomer in which the original oxygen has been replaced with that of the solvent. Similarly, S and S' symbolize the isomer

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‡ National Science Foundation Research Experiments for Undergraduate Participants, 1988.

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⊥ Wellesley College Chemistry Department Early Opportunities Research Participants, Summer 1987.

(1) Merritt, M. V.; Bronson, G. E.; Baczynskyj, L.; Boal, J. R. *J. Am. Chem. Soc.* **1980**, *102*, 346-351.

(2) Grunwald, E.; Heller, A.; Klein, F. S. *J. Chem. Soc.* **1957**, 2604-2613.

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with inverted configuration relative to the starting material and contain either the oxygen of the starting material or that of the solvent, respectively. In this report, we have followed the extent of oxygen exchange between the alcohol and the solvent by examining the reactions of unlabeled 1-phenyl-ethanol in water enriched in ^{18}O. Consequently, R, R′, S, and S′ are $R^{16}OH$, $R^{18}OH$, $S^{16}OH$, and $S^{18}OH$, respectively. The interrelationship of these four equilibrating species is shown diagrammatically in Scheme I.

The determination of the rate constants of eqs 2–4 for the (15)-methylprostaglandin E_2 study required the separation of two diastereomers, whereas their evaluation for 1-phenyl-1-ethanol involves the more difficult resolution of compounds isomeric at a single chiral center. In general, chromatographic separation of enantiomers can be achieved by employing either chiral or achiral stationary phases.[3] The latter approach requires the formation of diastereomeric derivatives prior to chromatography. The former achieves the desired separation via in situ formation of transient diastereomers. In our evaluation of GC and HPLC chiral stationary phases, we found that the commercially available cellulose tribenzoate adsorbed on macroporous silica developed by Okamoto et al.[4,5] provided resolution optimum for the separation and isolation of the phenethanol isomers in kinetic samples for subsequent mass spectral determination of the oxygen isotopic composition. Our kinetic results reported here show that, as with the prostaglandins, a significant portion of the inverted product is formed by bonding of the leaving water to the opposite face of the initially formed carbocation. The importance of this process is reflected in a value of k_I comparable to both k_{EI} and k_E in Scheme I. The relative sizes of the rate constants, $k_E < k_{EI} < k_I$, are consistent with a tightly solvated carbocation intermediate, in which the rate of change of position of the waters within the solvation sphere is comparable to the rate of movement of the departing water into the bulk solvent. This tightly solvated carbocation, an ion–dipole pair, is analogous to the intimate ion pair of solvolysis reactions.

Materials and Methods

Chemicals. Racemic 1-phenyl-1-ethanol (phenethanol), (*R*)-(+)-1-phenyl-1-ethanol, (*S*)-(−)-1-phenyl-1-ethanol, styrene, anhydrous pyridine, and acetophenone were purchased from Aldrich Chemical Company, Milwaukee, WI, and used as received. All solvents were HPLC grade and used as received. The (−)-menthyl chloroformate reagent [(2% (+) isomer)], 0.1 M in toluene, was obtained from Regis Chemical Company, Morton Grove, IL; water 50%-enriched in ^{18}O, from Cambridge Isotope Laboratories, Woburn, MA.

Glassware. All glassware used in these experiments was washed with methanol and dried at 100 °C, 2 h. The kinetic studies and derivatization reactions were done in 1- or 2-mL cone-shaped reaction vessels (Reactivials, Supelco, Inc., Bellefont, PA) with Teflon-lined caps.

Kinetic Samples and Analysis. Samples of the pure isomeric alcohols (0.5–5 μL) were weighed to the nearest microgram into tared 1- or 2-mL Reactivals. An accurately weighed 1- or 2-mL aliquot of water enriched in ^{18}O was then added to these samples. In expt 7 (Table I), a weighed portion of dried sodium chloride was also added. The vials were sealed with a Teflon-lined closure (Miniinert Valve, Supelco) and sonicated overnight to ensure complete dissolution of the alcohol. Following equilibration of the samples to 64.5 ± 0.1 °C in a circulating water bath, the isomerization reaction was initiated by adding an aliquot of standardized $HClO_4$ or HCl. At predetermined times, 100-μL aliquots were removed and quenched by mixing with 400 μL of hexane and a few mg of $NaHCO_3$. Following centrifugation, the hexane layer was transferred to a clean container and divided for analyses of the isomeric and oxygen isotopic composition. At least eight samples taken during the first 2 half-lives were examined in each kinetic run in addition to two equilibrium aliquots taken at 10–12 half-lives. At the end of the run, 100-μL aliquots were titrated with standardized base to check the acid concentration.

Analysis of Isomeric Composition. Isomeric Composition via GC of (−)-Menthyl Carbonate Derivatives. In expt 1 (Table I), the isomeric composition was determined by both HPLC and GC of the diastereomeric (−)-menthyl carbonate derivatives.[6] To duplicate 50-μL aliquots ([alcohol] = ca. 1×10^{-2} M) from each sample, 500 μL of (−)-menthyl chloroformate reagent and 125 μL of pyridine were added; the samples were mixed and heated overnight at 100 °C. To the cooled solutions were added 600 μL of water. After mixing and centrifugation of the samples, the solvent was evaporated with N_2 from a 200-μL aliquot of the organic layer. The residue was dissolved in 200 μL of hexane; 1-μL aliquots were examined by GC by using a Hewlett-Packard 5890A gas chromatograph equipped with a flame ionization detector and a 10 m × 0.530 mm i.d. HP methyl silicone column. Peak areas were measured with a Hewlett-Packard 3329A computing integrator. He was the carrier gas; the initial oven temperature of 100 °C was raied to 200 °C at a rate of 10 °C/min to detect unreacted alcohol. None of the derivatized samples contained more than 1% unreacted alcohol. Isomeric composition was determined isothermally at 165 °C. Under these latter conditions, retention times of the diastereomeric (*S*)- and (*R*)-derivatives were 13.7 and 14.7 min, respectively. Standards of known isomeric composition were prepared in duplicate from weighed amounts of the two pure isomers, derivatized, and examined by GC to establish the precision and accuracy of this assay.

HPLC Determination of Isomeric Content and Separation of Isomers. The isomeric composition of all kinetic samples was determined by the following HPLC method: 50- or 100-μL aliquots of the quenched kinetic samples (ca. 0.7×10^{-2} M in hexane) were analyzed for the isomeric composition, and the isomers were separated and collected by using a chiral HPLC column. All HPLC was done by using a Varian 5600 HPLC pump along with a Valco fixed sample loop injector and a 25 cm × 0.46 cm Chiralpack OB column (Daicel, Inc., Japan, distributed by J.T. Baker Chemical Company, Vineland, NJ). The column effluent was monitored via a Kratos Spectraflow 773 variable wavelength UV/vis absorbance detector at 258 nm. The HPLC peak areas were measured by using a Varian Vista 401 integrator. These areas were shown to be proportional to the relative amount of each isomer present by analysis of standards prepared from weighed portions of the alcoholic isomers. A mobile phase of 6% isopropyl alcohol in hexane, flow rate of 0.5 mL/min [experiments 1–4 (Table I)] or 1.0 mL/min [experiments 5–7 (Table I)], was used to separate the phenethanol isomers from one another as well as from the trace impurities of styrene (generated in the kinetic samples) and acetophenone (found in the starting alcohols). The starting isomeric alcohols contained ca. 0.5% acetophenone and less than 0.1% styrene. The acetophenone content was invariant over the kinetics run. Styrene was produced as a minor product during this reaction; final equilibrium samples contained no more than 1% styrene.

The HPLC-separated isomers were collected from the detector by using a 1-in. piece of 0.012-in. stainless steel tubing connected to 1-mL glass containers. Samples not examined the same day by GC/MS were stored at 4 °C. Repeated MS examination of samples stored for several weeks showed no change in oxygen isotopic composition. A single determination was done on each kinetic sample because of the high reproducibility of this HPLC assay. Replicate analyses of standards, covering the range of 10–90% *R*, had a relative standard deviation of 0.3% and indicated that the isomer composition measured in this fashion is accurate to 1–2%. Reinjection of each isomer collected from the HPLC effluent of these standards showed <1% of contamination with the other isomer. Observed inaccuracies in composition may be partially attributed to isomeric impurities in the "pure" *R* and *S* isomers used to prepare the standards. Repeated assays of racemic alcohol gave values of 50.0 ± 0.2% of each isomer.

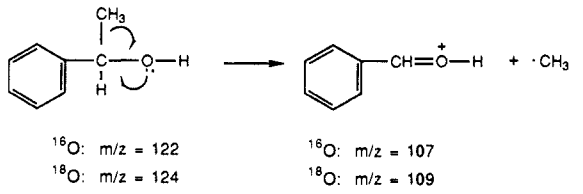
Determination of Oxygen Isotopic Composition. The oxygen isotopic composition assays, required for the evaluation of $k_{total\,ex}$, k_E, k_{EI}, and k_I, were done by using GC/electron impact MS. The values of total ^{18}O content [$\Sigma(^{18}O)$] needed to evaluate $k_{total\,ex}$ were determined from the unresolved alcohol (or TMS derivative) of each kinetic sample. The relative amounts of R, R′, S, and S′ needed to determine the microscopic rate constants of Scheme I were derived from assaying the isotopic composition of the pure isomers isolated via HPLC.

a. Underivatized Alcohols. Kinetic samples were either diluted with hexane, examined directly following HPLC separation, or concentrated by evaporating the HPLC mobile phase with a stream of N_2 to yield concentrations of $1–10 \times 10^{-4}$ M so that 1-μL injections yielded 0.1–1 nmol on column for GC/MS analysis. All MS data were obtained by using a Hewlett-Packard Model 5995 GC/MS with a 59970B workstation. The phenethanol was separated from the solvent and introduced into the MS with a 12 m × 0.20 mm (i.d.) × 0.33 μm film HP-1 cross-linked methyl silicon fused silica column by using He as a carrier

(3) Lochmuller, C. H.; Souter, R. W. *J. Chromatogr.* **1975**, *113*, 283–302.
(4) Ichida, A.; Shibata, T.; Okamoto, I.; Yuki, Y.; Namikoshi, H.; Toga, Y. *Chromatographia* **1984**, *19*, 280.
(5) Okamoto, Y.; Kawashima, M.; Hatada, K. *J. Am. Chem. Soc.* **1984**, *106*, 5357–5359.

(6) Preliminary kinetics experiments including the use of the (−)-menthyl carbonate derivatives of the phenethanols were done by Lincoln J. McBride, Senior Independent Project, Kalamazoo College, 1980.

Scheme II



gas with splitless injection. The alcohol isomers were resolved from the solvent but not from one another with this achiral column by using the following oven temperature program: An initial temperature of 50 °C was programmed at 0.5 °C/min to a final temperature of 130 °C. Under these conditions, the unresolved phenethanols had a retention time of 4.0 min. The MS data were collected by using the selected ion mode (SIM) in which the ion fragments at the mass/charge ratios of 122 and 107 (reflecting the ^{16}O content) and 124 and 109 (reflecting the ^{18}O content) were monitored. Approximately 20 measurements were made and averaged across the alcoholic peak. These fragments correspond to the parent ion and a C_7H_7O fragment resulting from the loss of a methyl group as shown in Scheme II.

b. Trimethylsilyl Ether (TMS) Derivatives of Phenylethanol. The TMS derivatives of the alcohols gave more symmetrical peaks in the gas chromatogram than the underivatized alcohol and, hence, yielded more reproducible peak areas. The derivatives were prepared in the following manner: aliquots of standards, unresolved kinetic samples, or those isolated from the HPLC column effluent (ca. 10–100 nmol of alcohol) were transferred to 1-mL Reactivials. After addition of 100 μL each of pyridine and Deriva-sil (Regis), the vials were heated at 100 °C, 1 h. The samples were cooled to room temperature; 400 μL each of water and hexane were added to each vial and mixed. The hexane layer was transferred to a clean vial; 1-μL aliquots were examined by GC/MS by using the same conditions as for the underivatized alcohols except that the final oven temperature was 160 °C. In the SIM mode, the mass fragments at 179 and 181, corresponding to the loss of a methyl group, contain the oxygen of interest. Although a few additional peaks were observed in the chromatograms, particularly those of m/z = 179, of the kinetic samples as well as in reagent blanks, none had the retention time of the alcohol TMS derivative. Integration of the peak areas of each of the ion chromatograms yielded the relative amount of each fragment present and, consequently, the amount of each oxygen isotope present in the alcohol sample examined. For the kinetic data collected from the TMS derivatives, correction of isotopic composition was made due to the 4.55% observed (4.11% theoretical) abundance of the (M + 2) ion found in the TMS derivative ion fragments at 181. For the underivatized alcohols, no correction was made for the natural abundance of the (M + 2) ion because its intensity (0.5%) was comparable to the error in the integrated peak areas.

Preparation of ^{18}O-Labeled Racemic 1-Phenylethanol. The accuracy and precision of isotopic composition assays were determined by examining samples of ^{18}O-enriched 1-phenyl-1-ethanol prepared as follows: To approximately 1.0 g of 97% ^{18}O-enriched water in a 2-mL Reactivial was added 100 mg of racemic phenethanol. Following sonication for several hours to dissolve and disperse the alcohol, 50 μL of 2.0 M perchloric acid was added; the samples were then heated at ca. 55 °C for 24 h. The cooled sample was neutralized with solid sodium bicarbonate and extracted 3× with 400-μL aliquots of hexane. The combined hexane extracts were diluted to 5 mL and examined by the HPLC method outlined above. This assay showed a total alcohol concentration of ca. 0.5 M, equal amounts of the R and S isomers, and ca. 1% styrene. The oxygen isotopic composition of this racemic sample and of its TMS derivative was determined by the MS methods outlined above.

Replicate assays of the underivatized racemic alcohol, monitoring the 107/109 and 122/124 pairs, gave the ^{18}O content as 55.8 ± 1.6%. No significant difference in the isotopic composition was obtained from monitoring these two different pairs of ions. Assays of each isomer, separated and collected from the chiral HPLC column, yielded an ^{18}O content of 56.4 ± 0.8%. The MS data of the TMS derivative of the racemic alcohol indicated, corrected for ^{30}Si and ^{13}C natural abundance, an ^{18}O content of 59.3 ± 0.3%, significantly higher than that of the underivatized alcohols. We consistently observed this same unidentifiable bias in our kinetic samples as well. Consequently, we did not average the isotopic composition data but used each set of composition data to obtain separate rate constants. There was no significant difference between the rate constants obtained by using the TMS derivative data and those from the underivatized alcohols.

A second labeled standard (prepared by diluting ^{18}O-enriched racemic alcohol with a known amount of the unlabeled S isomer) was separated via HPLC, and the underivatized alcohols were analyzed by GC/MS. The calculated isomeric composition of this sample was 20% R and 80% S; found by HPLC, 19.3% R and 80.7% R. The separated S isomer was shown to contain 12.4% ^{18}O vs the expected value of 12.9% based on dilution. The purified R isomer, expected to have 56% enrichment if the racemate were the only source labeled R, gave an assay value of 48.4%. This lower value was consistent with an appropriate 3% impurity of this isomer in the "pure" S isomer used in preparing this sample. HPLC analysis of this lot of S indicated the presence of 2.3% R. The results of the assays of these two isotopically labeled standards indicate the combined HPLC–GC/MS technique for obtaining the isotopic composition of each alcohol is accurate within 2–3%.

Calculation with Kinetic Sample Composition. The percentage of each isomer in the kinetic sample was determined from its HPLC peak area, A:

$$\%\sum R = [A_R/(A_R + A_S)] \times 100\%,\ \%\sum R = \%R + \%R' \quad (6a)$$

$$\%\sum S = [A_S/(A_R + A_S)] \times 100\%,\ \%\sum S = \%S + \%S' \quad (6b)$$

Similarly, the relative amount of each oxygen isotope was determined from integrated MS ion chromatograms. For example, the enrichment of ^{18}O from the 107 and 109 ion chromatograms was calculated as shown in eq 7

$$E = [A_{109}/(A_{107} + A_{109})] \quad (7)$$

where E is the ^{18}O enrichment, A_{109} is the peak area of the ion containing ^{18}O, and A_{107} is the peak area of the ion containing ^{16}O. Two additional measures of the ^{18}O composition of each kinetic sample were obtained from the 122/124 fragments of the underivatized alcohols and the 179/181 fragments of the TMS derivatives. The relative amounts of the four species, R, R′, S, S′, in each sample were determined by combining the HPLC isomeric and the MS isotopic composition data:

$$\%R = (1 - E_R) \times \%\sum R \quad (8)$$

$$\%R' = E_R \times \%\sum R \quad (9)$$

$$\%S = (1 - E_S) \times \%\sum S \quad (10)$$

$$\%S' = E_S \times \%\sum S \quad (11)$$

Calculation of Rate Constants. The inversion and oxygen exchange processes of Scheme I were assumed to be pseudo-first-order in $[H^+]$. Grunwald et al. had previously demonstrated that the k_{rac} and $k_{iol\ ex}$ depend linearly on $[H^+]$.[2] All experiments of this study were carried out in ca. 0.1 M acid. The set of differential equations (see Appendix) showing the time dependence of R, R′, S, and S′ derived from the model of Scheme I and including the dependence on solvent oxygen composition were solved to express the experimentally measured quantities as a function of the rate constants of Scheme I and f_{16} and f_{18} (fractions of water containing ^{16}O and ^{18}O, respectively):

$$\%\sum R_t = (R + R')_t = C_1 - 2\alpha C_3 e^{-\mu[H^+]t} - 2(f_{16} - f_{18})\cdot k_{EI} C_4 e^{-\tau[H^+]t} \quad (12)$$

$$\%(R' + S)_t = C_1 + 2(f_{16} - f_{18})\cdot C_3 k_E e^{-\mu[H^+]t} - 2\alpha C_4 e^{-\tau[H^+]t} \quad (13)$$

$$\%(R' + S')_t = \%\sum {}^{18}O = 2f_{18}\cdot C_1 - 2C_2 e^{-(k_E + k_{EI})[H^+]t} \quad (14)$$

where C_1, C_2, C_3, and C_4 are constants evaluated from initial and equilibrium conditions

$$\alpha = (k_E - k_{EI} + \sqrt{\Theta})/2;\ \Theta = k_E^2 + k_{EI}^2 + 2(1 - 8f_{16}\cdot f_{18})k_E\cdot k_{EI}$$

$$\mu = [(k_E + k_{EI} + 4k_1) + \sqrt{\Theta}]/2$$

$$\tau = [(k_E + k_{EI} + 4k_1) - \sqrt{\Theta}]/2$$

Under the conditions of our experiments in which the solvent was ca. 50% ^{18}O-labeled water ($f_{16} \approx f_{18} \approx 0.5$), $\Theta \approx (k_E - k_{EI})^2$. Therefore,

$$\alpha \approx (k_E - k_{EI}),\ \mu \approx (k_E + 2k_1),\ \text{and}\ \tau \approx (k_{EI} + 2k_1)$$

Equations similar to (12–14) describe the time dependence of $\%\sum S$, $\%(R' + S)$, and $\%(R + S)$ in terms of the rate constants and the solvent isotopic composition. Under our experimental conditions in which $f_{16} \approx f_{18} \approx 0.5$, eqs 12–14 can be approximated by the following expressions, each containing a single exponential function relating k_E, k_{EI}, and k_1 to the experimentally measured quantities:

$$\%(\sum R_t - \sum R_{eq}) = \%(\sum R_0 - \sum R_{eq})e^{-(k_{EI}+2k_1)[H^+]t} \quad (15a)$$

$$\%(\sum S_{eq} - \sum S_t) = \%(\sum S_{eq} - \sum S_0)e^{-(k_{EI}+2k_1)[H^+]t} \quad (15b)$$

$$\%[(\sum {}^{18}O)_t - (\sum {}^{18}O)_{eq}] = \%[(\sum {}^{18}O)_{eq} - (\sum {}^{18}O)_0]e^{-(k_E+k_{EI})[H^+]t} \quad (16)$$

$$\%[(R' + S)_t - (R' + S)_{eq}] = \%[(R' + S)_{eq} - (R' + S)_0]e^{-(k_E+2k_1)[H^+]t} \quad (17a)$$

$$\%[(R + S')_t - (R + S')_{eq}] = \%[(R + S')_{eq} - (R + S')_0]e^{-(k_E+2k_1)[H^+]t} \quad (17b)$$

Here, $\%\sum R$, $\%\sum S$, $\%(\sum {}^{18}O)$, $\%(R' + S)$, and $\%(R + S')$ represent the percentage of these materials at time t, at equilibrium (eq), and the initial time ($t = 0$). The values of $\%\sum R$ [(R + R')] and $\%\sum S$ [(S + S')] are thoseof the alcohol present as each isomer as determined via HPLC. The term $\%(\sum {}^{18}O)$ represents the $\%{}^{18}O$ in the unresolved alcohol obtained from MS isotopic composition measurements on the unresolved alcohol. The values of R, R', S, and S' [and subsequent values for $\%(R' + S)$ and $\%(R + S')$] were obtained by the combined isotopic and isomeric composition assays as shown in eqs 8–11.

Linear least-squares analyses of the experimental composition data as a function of time were used to obtain three rate constants (k_{rac}, $k_{lol\ ex}$, and k_{cross}) from which the microscopic rate constants of Scheme I were calculated.

$$(k_{EI} + 2k_1) = k_{rac} \quad (18)$$

$$(k_E + k_{EI}) = k_{lol\ ex} \quad (19)$$

$$(k_E + 2k_1) = k_{cross} \quad (20)$$

$$k_{rac} = 2k \text{ for the process } \sum R \underset{k}{\overset{k}{\rightleftharpoons}} \sum S$$

We have used k_{rac},[7] typically measured by loss of optical activity, to compare our results with Grunwald et al.[2] In those kinetic runs in which the *R* isomer was the starting material, the slopes of the following linear least-squares plots were used to obtain k_{rac}, $k_{lol\ ex}$, and k_{cross}:

$$\ln[\%(R)_t - 50.0\%] \text{ vs time, } k_{rac} = \text{slope}/[H^+]\ M^{-1}\ \text{min}^{-1} \quad (21)$$

$$\ln(\%\sum {}^{18}O_{eq} - \%\sum {}^{18}O_t) \text{ vs time, } k_{lol\ ex} = \text{slope}/[H^+]\ M^{-1}\ \text{min}^{-1} \quad (22)$$

$$\ln[50.5\% - \%(R' + S)_t] \text{ vs time, } k_{cross} = \text{slope}/[H^+]\ M^{-1}\ \text{min}^{-1} \quad (23a)$$

$$\ln[(R + S')_t - \%50.0] \text{ vs time, } k_{cross} = \text{slope}/[H^+]\ M^{-1}\ \text{min}^{-1} \quad (23b)$$

Correlation coefficients for these plots were ≥0.98; most were >99%. Values for k_{cross} reported are the mean of those obtained from plots of $\ln[50.5\% - \%(R' + S)_t]$ and $\ln[(R + S')_t - \%50.0]$. Nonlinear least-squares fit of some of our data using eqs 12–14 indicated that the approximations expressed in eqs 21–23 introduced ≤10% in the rate constants obtained.

The values of $\%(\sum {}^{18}O)$ could have been obtained from $\%(R' + S')$ rather from the isotopic composition of unresolved alcohol samples. The former requires two separate measurements rather than the single one obtained from examining the unresolved alcohol and, hence, doubles the relative error. Determinations of $k_{lol\ ex}$ and k_{cross} [eqs 16 and 17] were, therefore, based on independent measurements. The values for $\sum {}^{18}O_{eq}$ in each kinetic run were obtained from replicate measurements of equilibrium samples and agreed within experimental error to those calculated from the dilution of the 50.0% ^{18}O-enriched water with the acid (in unlabeled water) used to initiate the reactions.

The ^{18}O content of the solvent varied from 45–48% for experiments 2–7 (Table I); that for experiment 1 was 42.2%. This choice of ca. 50% for the ^{18}O content of the solvent water was made both to simplify the data analysis (see above) and to produce a minimum and consistent error in each of the variables changing with time: $\%\sum {}^{18}O$, R, R', S, and S'. The use of 50% ^{18}O-enriched water yielded the following range variations for these variables: for %R, 100–25%; R', 0–25%; S, 0–25%; S', 0–25%; and $\%\sum {}^{18}O$, 0–50%.

Results

Table I tabulates the rate constants for the racemization and the processes of eqs 2–5 of the 1-phenyl-1-ethanol isomers under a variety of experimental conditions: *R* or *S* isomer as the starting material, a range of alcohol concentrations from 19.9 (expt 4) to 64.2 mM (expt 7), $HClO_4$ (expt 1–4), or HCl (expt 5–7) as the source of H^+, and in the presence of 1.0 M chloride ion (expt 7). In all experiments, except for 6 and 7, k_{rac} was the same, within experimental error, as that determined by Grunwald et al. in 1957 via monitoring the loss of optical activity.[2] The slightly lower value for this constant in expt 6 is probably attributable to an error in the acidity of the medium. In contrast, the increased rate of racemization of expt 7 reflects the increased ionic strength of the media and may be considered a neutral salt effect since all the rate constants increase by the same magnitude (ca. 40%).

Comparison of the rate constants obtained in expt 1 and 2 (Table I) in which the *S* isomer was used as the starting material with those using the *R* isomer (expt 3 and 4) indicate, as expected, no difference between isomers. Various lots of the two isomers, from commercial sources, contained different amounts of the second isomer (1–3% via HPLC) along with differing trace (≤1%) amounts of styrene and acetophenone. The identity of the rate constants and their ratios (Table III, below), regardless of starting material, indicates that the impurities do not alter the rates measured and do reflect the processes of eqs 2–4. Because the *R* isomer was more strongly retained by the chiral HPLC column, assays using this isomer as starting material were less time-consuming and more precise. Consequently, this isomer was used as the starting material in the majority of the kinetic experiments.

Isomeric composition of expt 1 samples was determined both by GC of the (−)-menthyl carbonate derivatives and by chiral HPLC: k_{rac} (GC) = $(14.7 \pm 0.4) \times 10^{-4}\ M^{-1}\ s^{-1}$; k_{rac} (HPLC) = $(16.5 \pm 0.2) \times 10^{-4}\ M^{-1}\ s^{-1}$. The (−)-chloroformate reagent used to prepare derivatives for GC analysis contained ca. 2% of the (+)-isomer. The isomer composition of standards assayed by GC gave a consistently higher value for the *S* isomer than that obtained by HPLC, although both agreed within ±1–2% of that calculated from the weights of the standards. The GC assay of equilibrium sample of exp 1 sample found 50.8% of the *S* isomer, whereas the HPLC assay yielded a value of 50.2%. The apparent bias of the assay to overestimate the *S* content leads to an erroneously low value for k_{rac} in exp 1. Nonetheless, the relatively good agreement of values for k_{rac} determined by GC and HPLC in exp 1 served as validation of the HPLC assay for accurate and precise measurements of isomer composition.

Table II contains the isomer and oxygen composition data based on the 107/109 mass spectral fragments of exp 5 in Table I. These data are typical of this study. The ^{18}O content of the unresolved alcohol ($\%\sum {}^{18}O$) should be identical with that based on the sum of the ^{18}O content of the HPLC-isolated isomers (%R' + %S'). Comparison of these data, the last two columns of Table II, suggests that the combination of HPLC isolation and mass spectral analysis provides accurate values for the four species required for this kinetic study: R, R', S, and S'. The largest absolute difference in these separate measures of the ^{18}O content of unseparated alcohol is observed for 80-min samples: $\%\sum {}^{18}O = 22.9\%$ vs (%R' + %S') = 22.0%; relative error = 4%.

Table III contains the ratios of $k_{lol\ ex}/k_{rac}$ as well as the microscopic rate constants, k_E, k_{EI}, and k_1, relative to k_{rac} for the experiments of Table I. The value of $k_{lol\ ex}/k_{rac}$ was the same within experimental error in all experiments and significantly less than unity: 0.84 ± 0.05. Our value is in good agreement with that previously reported by Grunwald et al.: 0.82. Since the rate constants for oxygen exchange into each isomer are derived, in part, from the data used to determine k_{rac}, they are not independent of k_{rac}. Differences in the absolute rates of these reactions from one experiment to another may reflect differences both in the oxygen exchange rates and k_{rac}, whereas the ratios with respect to k_{rac} reported in Table III reflect only the former. The invariance of all the rate constants, normalized to k_{rac} in Table III, to starting isomer, concentrations of alcohol, acid used to initiate the reaction, and added NaCl suggest that the mechanism is invariant to these changes in reaction conditions.

In every experiment, the rate constant of oxygen exchange of the starting isomer with the solvent, k_E, was significantly less than that for the reaction involving both a change in stereochemistry at the chiral center and exchange with the solvent, k_{EI}; mean values (Table I) are as follows: $k_E = (5.9 \pm 0.6) \times 10^4\ M^{-1}\ s^{-1} < k_{EI} = (7.6 \pm 0.7) \times 10^4\ M^{-1}\ s^{-1}$; $k_E/k_{EI} = 0.77 \pm 0.11$. The most unusual result is that the rate constant for inversion at the chiral center without exchange of oxygen with the solvent, k_1, was comparable to those for the other processes of Scheme I: k_1 =

Table I. Rate Constants of Racemization and ^{18}O Exchange of 1-Phenyl-1-ethanol at 64.5 °C in 50% ^{18}O-Enriched Water

expt & starting isomer	alcohol, mM	acid	rate constants × 10^4, M^{-1} s^{-1} [a,b]					
			k_{rac}	$k_{tot\ ex}$ [c]	k_{cross} [c]	k_E [d]	k_I [d]	k_{EI} [d]
1 *S*	36.6	$HClO_4$	16.6 ± 0.1 [e]	14.0 ± 0.6	14.6 ± 0.2	5.7 ± 0.3	4.1 ± 0.3	7.6 ± 0.3
2 *S*	39.0	$HClO_4$	16.2 ± 0.7	14.3 ± 1.4	16.0 ± 1.2	7.0 ± 0.7	4.5 ± 0.7	7.3 ± 0.7
3 *R*	39.7	$HClO_4$	16.9 ± 0.7	14.4 ± 0.3	13.8 ± 0.3	5.7 ± 0.4	4.1 ± 0.4	8.7 ± 0.4
4 *R*	19.9	$HClO_4$	16.4 ± 0.2	12.5 ± 0.5	13.7 ± 0.2	5.1 ± 0.3	4.3 ± 0.3	7.8 ± 0.3
5 *R*	44.3	HCl	16.0 ± 0.7	13.6 ± 0.3	14.0 ± 0.2	5.8 ± 0.3	4.1 ± 0.3	7.8 ± 0.3
6 *R*	42.4	HCl	14.1 ± 0.2	11.7 ± 0.1	12.8 ± 0.2	5.2 ± 0.1	3.8 ± 0.1	6.5 ± 0.1
7 *R*	64.2	HCl 0.90 M NaCl	20.5 ± 0.3	16.1 ± 1.2	18.1 ± 0.2	6.8 ± 0.6	5.7 ± 0.6	9.2 ± 0.6
mean values (run 7 omitted)			16.0 ± 1.0	13.4 ± 1.1	13.9 ± 1.1	5.9 ± 0.6	4.1 ± 0.2	7.6 ± 0.7
f	40	$HClO_4$	16.7	13.7				

[a] $k_{rac} = k_{racemization}$, $k_{tot\ ex}$ = rate constant for ^{18}O exchange into racemic product. k_{cross} = rate constant obtained from the slope/$[H^+]$ of the linear least-squares fit of ln[50% − (R′ + S)] vs time or ln[(R + S′) − 50%] vs time. k_E = rate constant for ^{18}O exchange with starting material. k_{EI} = rate constant for ^{18}O exchange with isomer of inverted configuration relative to starting material. k_I = rate constant for formation of isomer with inverted configuration relative to starting material with no ^{18}O exchange. [b] Acid used to initiate reaction; in all cases, $[H^+]$ = 0.10 ± 0.02 M. In kinetic run 7, 0.90 M NaCl was also present in the solution. [c] The relative amounts of R, R′, S, and S′ in runs 1 and 4 were determined from the mean of the isotopic composition based on the 107/109 and 122/124 mass fragments of the underivatized alcohols; the precision is expressed as the standard deviation of rate constants from the least-squares analyses of eqs 21–23. For all other runs the isotopic composition was determined both from these underivatized alcohols and from the 179/181 fragments of the TMS derivatives. In these cases, the rate constants are expressed as the mean ± standard deviation of the rate constants obtained by these three different measures of isotopic composition. [d] k_E, k_I, and k_{EI} are calculated from k_{rac}, $k_{total\ ex}$, and k_{cross} as shown in eqs 18–20. [e] Isomer composition determined by HPLC and GC. The isomer composition needed to determine this constant for other experiments was detd. only by HPLC. [f] Grunwald, Heller, and Klein, ref 2.

Table II. Isomer and Isotopic Composition of 1-Phenyl-1-ethanol Based on 107/109 Mass Spectral Fragments in Expt 5 *R*[a]

time, min	%∑R[a]	%R[b]	%R′[b]	%S[b]	%S′[b]	%∑^{18}O[c]	%R′ + %S′[d]
10.0	93.4	91.5	1.88	4.63	2.00	4.11	3.88
20.1	89.2	85.9	3.25	6.90	3.90	7.48	7.15
30.0	85.6	81.0	4.64	8.51	5.89	10.1	10.5
45.0	81.8	75.4	6.45	11.1	7.91	14.5	14.5
60.0	76.5	68.7	7.80	13.6	9.89	18.3	17.7
80.0	71.8	62.0	9.84	16.0	12.2	22.9	22.0
100	68.0	56.0	12.0	18.1	13.9	26.2	25.9
120	64.8	51.3	13.8	19.7	15.5	28.9	29.3
25 h	49.9	27.3	22.7	27.1	23.0	45.4	45.7

[a] %∑R was determined by HPLC analysis. [b] %R = %R^{16}OH, %R′ = %R^{18}OH, %S = %S^{16}OH, %S′ = %S^{18}OH. These values were obtained by combining HPLC isomer composition with the mass spectral isotopic composition data based on the 107/109 fragments in samples of isolated *R* and *S*. The values based on the molecular ion fragments, 122/124, were identical within experiment error, with the reported data. [c] %∑^{18}O was determined from mass spectral data based on the 107/109 fragments of unresolved alcohol from the kinetic samples. [d] %R′ + %S′ = %R^{18}OH + %S^{18}OH as determined in *b*. [e] Expt 5 *R* (Table I): *T* = 64.5 °C; [HCl] = 0.102 M; [alcohol] = 44.3 mM.

Table III. Relative Rates of Racemization, Isomerization, and ^{18}O-Exchange Reactions of 1-Phenyl-1-ethanol at 64.5 °C in 50% ^{18}O-enriched Water at 64.5 °C[a–d]

expt & starting isomer	alcohol, mM	acid	$k_{tot\ ex}/k_{rac}$	k_E/k_{rac}	k_I/k_{rac}	k_{EI}/k_{rac}
1 *S*	36.6	$HClO_4$	0.90 ± 0.04[e]	0.34 ± 0.02	0.25 ± 0.02	0.45 ± 0.02
2 *S*	39.0	$HClO_4$	0.89 ± 0.08	0.43 ± 0.05	0.28 ± 0.05	0.45 ± 0.02
3 *R*	39.7	$HClO_4$	0.85 ± 0.04	0.34 ± 0.02	0.24 ± 0.02	0.51 ± 0.02
4 *R*	19.9	$HClO_4$	0.76 ± 0.06	0.31 ± 0.02	0.26 ± 0.02	0.48 ± 0.02
5 *R*	44.3	HCl	0.85 ± 0.04	0.36 ± 0.02	0.26 ± 0.02	0.49 ± 0.02
6 *R*	42.4	HCl	0.83 ± 0.04	0.37 ± 0.01	0.27 ± 0.01	0.46 ± 0.01
7 *R*	64.2	HCl 0.90 M NaCl	0.78 ± 0.06	0.33 ± 0.02	0.28 ± 0.02	0.45 ± 0.02
mean values			0.84 ± 0.05	0.35 ± 0.02	0.26 ± 0.01	0.47 ± 0.01
f	40	$HClO_4$	0.82			

[a–f] Same as *a–f* in Table I.

(3.8 ± 0.4) × 10^4 M^{-1} s^{-1}. This result suggests that the departing water molecule remains a part of the solvation sphere of the intermediate and reattaches to the opposite face of that intermediate. The relative amounts of S and S′ as a function of time, presented in Table II, illustrates the relative importance of this process. If the intermediate carbocation completely equilibrated with the solvent, one would expect the ratio of S/S′ to match that of the solvent and be equal to that observed for the sample taken at equilibrium (25 h): S/S′ = 27.1%/23.0% = 1.18. The observed ratios of S/S′ are all much larger ranging from 2.32 (4.63%/2.00% = 2.32) at 10 min to 1.27 at 120 min. These results illustrate our finding that the rate constant for inversion with retention of the original oxygen (k_I) is of the same magnitude as that for inversion with exchange with the solvent (k_{EI}): k_I/k_{EI} = 0.54 ± 0.06.

Discussion

The rate of ^{18}O exchange between water and optically active alcohols as a function of racemization has been extensively used as a criterion for distinguishing between the S_N2 and S_N1 mechanisms for nucleophilic substitution by water on a saturated carbon atom. The expected ratio of $k_{tot\ ex}/k_{rac}$ is 0.5 for the S_N2 mechanism and 1.0 for a pure S_N1 process.[8] The unity value in this latter case is based on the assumption that the leaving water molecule rapidly equilibrates with the solvent on both sides of a planar or rapidly rotating cation so that each ionization of the

(7) Moore, J. W.; Pearson, R. G. *Kinetics and Mechanisms*, 3rd ed.; John Wiley & Sons, Inc.: 1981; p 304.

(8) For a review, see: Samuel, D.; Silver, B. *Adv. Phys. Org. Chem.* **1965**, *3*, 128–144.

Table IV. Observed and Expected Values of Rate Constants for Alcohol Oxygen Exchange Reactions Relative to Racemization

	$k_{tot\,ex}/k_{rac}$	k_E/k_{rac}	k_1/k_{rac}	k_{EI}/k_{rac}	k_E/k_{EI}
obsd for phenethanol[a]	0.84 ± 0.05	0.35 ± 0.02	0.26 ± 0.01	0.47 ± 0.01	0.78 ± 0.11
			Expected Values		
S_N2	0.5	0	0	0.5	0
S_N1 (model of Scheme III)					
case A: $k_s > k_{is} \gg k_{-1}$	1.0	0.5	0	0.5	1.0
case B: $k_{-1} > k_s > k_{is}$	<1.0	<0.5	0	0.5	<1.0
case C: $k_{-1} > k_{is} > k_s$	<1.0	<0.5	>0	<0.5	1.0
case D: $k_{-1} > k_{is} \approx k_s$	<1.0	<0.5	>0	<0.5	<1.0

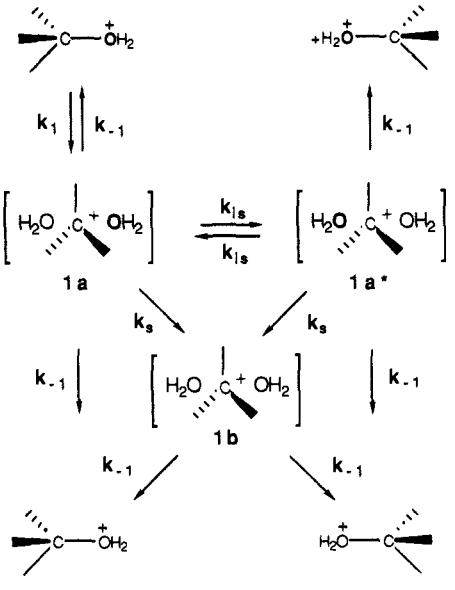
[a] Data taken from Table III.

C–O bond results both in exchange and in racemization. In the racemization of a number of optically active secondary and tertiary alcohols involving carbocation intermediates, however, oxygen exchange studies have provided evidence that the departing water does not rapidly equilibrate with the solvent but remains closely associated with the positively charged carbocation as an ion–dipole pair in analogy to the ion pairs of solvolysis reactions.[2,9-15]

The detailed study of oxygen exchange as a function of racemization of 1-phenyl-1-ethanol by Grunwald, Heller, and Klein[2] is representative both of these kinetic results and methods used in establishing the close association of a carbocation with its leaving water. They determined $k_{tot\,ex}/k_{rac}$ by monitoring the loss of the ^{18}O isotope to the aqueous solvent of ^{18}O-enriched, optically active 1-phenyl-1-ethanol as a function of the loss in optical activity. The product mixture of isomers was not resolved; consequently, the loss of ^{18}O represents exchange from a mixture of the two interconverting isomers. The effect of high perchloric acid concentrations on k_{rac} was interpreted as supporting a mechanism including a carbocation. Consequently, the observed value of $k_{tot\,ex}/k_{rac} = 0.82 \pm 0.04$, less than unity, was attributed to shielding by the departing water. These authors further suggested that racemization occurs through a solvated carbocation. More recent studies have provided evidence for phenethyl ion pairs in solvolysis reactions.[16,17] The kinetic results of the present study can be accounted for by expanding the mechanistic scheme of Grunwald et al. to include a process in which the waters within the solvation sphere change position with a rate constant of k_{is}. That expanded mechanism is shown in Scheme III. For simplicity, only two waters are shown within the solvation sphere; the mechanistic conclusions drawn here are not altered by changing the number of solvated water molecules. In this scheme, **1a–1a*** and **1b** are similar to the intimate and solvent-separated ion pairs, respectively, of the solvolysis scheme. In the present case, however, these species have thermodynamic stability which differ only by entropy of mixing of the labeled and unlabeled water. These intermediates will be referred to here as intimate ion–dipole pairs, **1a–1a***, and a randomly solvated carbocation, **1b**.

Although a mixed mechanism in which a portion of the racemic product is formed through an S_N2 mechanism cannot be completely excluded, the present results strongly support Grunwald's earlier conclusion that the racemization of 1-phenylethanols occurs predominantly through the carbocation intermediates of Scheme III. In the S_N2 mechanism, each displacement yields an exchange reaction resulting in inversion of configuration at the chiral carbon atom. Consequently, the rate of production of inverted product incorporating the solvent water should be half that of racemization:

Scheme III



$k_{EI}/k_{rac} = 0.5$. We found the relative value of k_{EI} for the 1-phenylethanols to be less than 0.5: $k_{EI}/k_{rac} = 0.47 \pm 0.01$ (Table III). More significantly, bimolecular substitution would yield neither noninverted, exchanged product nor inverted product with the original oxygen, $k_E = k_1 = 0$, whereas both these rate constants are comparable to k_{EI} (Tables I and III) and, hence, are inconsistent with a major S_N2 mechanistic component.

The mechanism of Scheme III can account for the wide variety of observed values for $k_{tot\,ex}/k_{rac}$ in the racemization of alcohols involving carbocation intermediates by changes in the relative values of k_{is}, k_s, and k_{-1} as shown in Table IV. Examination of this table also indicates that the relative values of k_E, k_{EI}, and k_1 give considerable insight regarding mechanistic details. For example, measured values of $k_{tot\,ex}/k_{rac} = 1.0$, $k_E/k_{rac} = k_{EI}/k_{rac} = 0.5$, $k_1/k_{rac} = 0$ are consistent with an S_N1 mechanism in which the departing water rapidly equilibrates with the surrounding medium such that the lifetime of **1a** and **1a***, the intimate ion dipole pairs, is very short (Table IV, S_N1-case A). The predominant reacting species is the randomly solvated species **1b**. The rapid departure of the leaving water would yield none of the inverted product containing the original oxygen so that $k_1 = 0$.

Other values of k_E, k_{EI}, and k_1 (relative to k_{rac}) indicate that bond formation occurs more rapidly than equilibration with the bulk solvent and motion within the solvation sphere of **1a–a*** (Table IV, S_N1-cases B–D). An increase in the magnitude of k_{is} relative to k_s of Scheme III leads to the prediction of the formation of some inverted product with no exchange, $k_1 > 0$ (Table IV, S_N1-cases C–D). In other words, both **1a** and **1a*** become significant contributors in the mechanism of Scheme III. The formation of product resulting from recombination of the partners formed in the dissociation is analagous to ion pair return in solvolysis reactions.[18] This result, involving an ion–dipole pair,

(9) Bunton, D. A.; Konaseiwica, A.; Llewellyn, D. R. *J. Chem. Soc.* **1955**, 604–607.
(10) Bunton, D. A.; Llewellyn, D. R. *J. Chem. Soc.* **1957**, 3402–3405.
(11) Goering, H. L.; Dilgren, R. E. *J. Am. Chem. Soc.* **1960**, *82*, 5744–5749.
(12) Bunton, C. A.; Henderson, R. B. *Tetrahedron Lett.* **1964**, 1829–1832.
(13) Mannassen, J.; Klein, F. S. *J. Chem. Soc.* **1960**, 4203–4213.
(14) Boyd, R. H.; Taft, R. W.; Wolf, A. P.; Christman, D. R. *J. Am. Chem. Soc.* **1960**, *82*, 4729–4736.
(15) Herlihy, K. P. *Aust. J. Chem.* **1982**, *35*, 2221–2228.
(16) Allen, A. D.; Kanagasabapathy, V. M.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 4513–4519.
(17) Richard, J. P.; Rothenberg, M. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1984**, *106*, 1361–1372.
(18) Winstein, S.; Clippinger, E.; Fainberg, A. H.; Heck, R.; Robinson, G. C. *J. Am. Chem. Soc.* **1956**, *78*, 328–335.

has been noted in the irreversible rearrangement of ^{18}O-labeled τ-phenylallyl alcohol to give α-phenyallyl alcohol containing a slightly greater ^{18}O abundance than the water in the solvent.[11] This excess indicated that some of the α-phenylallyl alcohol resulted from recombination.

The observed experimental results obtained in this study for 1-phenyl-1-ethanol, $k_E < k_{EI}$ and $k_1 > 0$ are consistent with the mechanism of Scheme III in which $k_{-1} > k_{is} \approx k_s$ (Table IV, S_N1-Case D). If the rates at which the waters move within the solvation sphere, k_{is}, are comparable to their equilibration with the bulk solvent, k_s, one expects our observation of inverted, unexchanged product ($k_1 > 0$) and unequal portions of the two isomers exchanging with the surrounding water. Protection of the front side of **2a** by the leaving water is consistent with our finding that $k_E < k_{EI}$. The mechanism of Scheme III differs from that proposed by Grunwald in that it explicitly requires significant reorganization of the solvation sphere in the intimate ion–dipole pairs **1a–a***. We have here described that reorganization as movement of water molecules. This reorganization could also result from rotation of the carbocation itself.

The lack of a specific effect by added sodium chloride as well as the identical rate constants obtained by using either HCl or $HClO_4$ to initiate the reaction provides further evidence that a significant portion of the exchange reactions occur within the solvation sphere of the intimate ion dipoles **1a–a*** (Tables I and III). Furthermore, these results indicate that the important association with the carbocation is that with its departing water not with an anion.

It should be noted that the carbocations themselves in the mechanism of Scheme III are achiral; i.e., racemization occurs on ionization. This mechanism cannot account for the observed oxygen exchange rate constants in the epimerization of the 15-methylprostaglindins E_2 in which $k_{1ol\ ex}/k_{rac} > 1$ and $k_E/k_{EI} > 1$.[1] Asymmetric carbocation intermediates must be invoked to account for the relative rates of the oxygen exchange reactions of the prostaglandins. It should be noted that the rate of prostaglandin epimerization is much more rapid than the rate of racemization of the 1-phenyl-1-ethanols: $k_{epim} = 7 \times 10^{-2}$ M^{-1} s^{-1} at 37 °C[1] vs 1.6×10^{-3} M^{-1} s^{-1} at 65 °C (Table I), respectively. These rate constants suggest that the lifetimes of the prostaglandin carbocation intermediates are much shorter than those derived from the phenethanols. We, consequently, might expect to detect asymmetric carbocations in the racemization of other optically active alcohols yielding short-lived intermediate carbocations: those not stabilized by an α-phenyl ring or in which the phenyl ring contains an electron-withdrawing substituent. A chiral carbocation may result from segregation of the waters of solvation about the leaving water on the hydrophilic side of the carbocation. Increasing the bulk of the alkyl substituent at the chiral center might be expected to lead to this asymmetric solvation of 1-phenyl secondary alcohols; these studies are in progress.

Determination of the rate constants k_E, k_{EI}, and k_1 may give insight into the mechanism for the racemization of other alcohols such as butan-2-ol for which Bunton et al.[9,10] found $k_{1ol\ ex}/k_{rac} = 0.5$, suggesting a direct displacement mechanism. The linear dependence of the exchange reaction on the H_0 acidity function indicated, however, that the water molecule is not present in the transition state and led Bunton et al. to propose a carbocation intermediate similar to **1a–a*** of Scheme III. Although Manassen and Klein also postulated a similar planar carbocation, partially covalently bonded to one water molecule on each side of the plane, as the common intermediate in the acid-catalyzed conversion of but-1-ene to but-2-ene, hydration of but-1-ene, isomerization of [4-^{14}C]butan-2-ol to [1-^{14}C]butan-2-ol, and oxygen exchange of [^{18}O]-butan-2-ol with water,[13] more recent work of Dietz and Jencks has shown these processes to be more complicated.[19]

In summary, we have used chiral HPLC and GC/MS methods to reveal three competing processes of comparable rates in the change of configuration at the chiral carbon in a secondary alcohol: (1) substitution (^{18}O exchange) with inversion, (2) substitution (^{18}O exchange) with retention, and (3) inversion without substitution. The observed rate constants for these processes can be accounted for by a mechanism general for the S_N1-type acid-catalyzed racemization of optically active alcohols. In the proposed mechanistic scheme, the initially formed carbocation is present in tight association with its departing water. This scheme can account for only for the rate constants of this study but about for the wide range of reported values for oxygen exchange reactions into racemic products. The observed rates of the oxygen exchange reactions as a function of racemization depend on the relative rates of bond formation, motion of water molecules within the solvation sphere of the initially formed ion–dipole pair, and escape of the departing water into the bulk solvent.

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Appendix: Rate Equations

The rate laws for the interconverting species R, R′, S, S′ of the kinetic model of Scheme I include a dependence on the solvent oxygen isotopic composition. In this model the rates of formation of the species involving oxygen exchange (R′ and S′ from R as the starting material) are dependent on the oxygen isotopic composition of the solvent:

$$R \underset{k_E f_{16}}{\overset{k_E f_{18}}{\rightleftharpoons}} R' \qquad \text{(A1a)}$$

$$R \underset{k_{EI} f_{16}}{\overset{k_{EI} f_{18}}{\rightleftharpoons}} S' \qquad \text{(A1b)}$$

where f_{16} and f_{18} represent the fractions of the solvent water present as each oxygen isotope. In contrast, inversion without exchange is independent of solvent isotopic composition. To simplify the notation and provide more generally applicable equations, let $f_{18} = p$ and $f_{16} = q$. The rate laws for the four species of Scheme I are as follows:

$$d[R]/dt = -(pk_E + k_1 + pk_{EI})[R] + qk_E[R'] + k_1[S] + qk_{EI}[S'] \qquad \text{(A2)}$$

$$d[R']/dt = pk_E[R] - (qk_E + k_1 + qk_{EI})[R'] + pk_{EI}[S] + k_1[S'] \qquad \text{(A3)}$$

$$d[S]/dt = k_1[R] + qk_{EI}[R'] - (pk_E + k_1 + pk_{EI})[S] + qk_E[S'] \qquad \text{(A4)}$$

$$d[S']/dt = pk_{EI}[R] + k_1[R'] + pk_E[S] - (qk_E + k_1 + qk_{EI})[S'] \qquad \text{(A5)}$$

These form a system of first-order linear equations with constant coefficients. The solutions were obtained by using standard methods (α, μ, and τ are defined above):

$$[R]_t = qC_1 + C_2e^{-(k_E+k_{EI})[H^+]t} + [(p-q)k_E - \alpha]C_3e^{-\mu[H^+]t} + [(p-q)k_{EI} + \alpha]C_4e^{-\tau[H^+]t} \qquad \text{(A6)}$$

$$[R']_t = pC_1 - C_2e^{-(k_E+k_{EI})[H^+]t} + [(q-p)k_E - \alpha]C_3e^{-\mu[H^+]t} + [(p-q)k_{EI} - \alpha]C_4e^{-\tau[H^+]t} \qquad \text{(A7)}$$

$$[S]_t = qC_1 + C_2e^{-(k_E+k_{EI})[H^+]t} + [(q-p)k_E + \alpha]C_3e^{-\mu[H^+]t} + [(q-p)k_{EI} - \alpha]C_4e^{-\tau[H^+]t} \qquad \text{(A8)}$$

$$[S']_t = pC_1 - C_2e^{-(k_E+k_{EI})[H^+]t} + [(p-q)k_E + \alpha]C_3e^{-\mu[H^+]t} + [(q-p)k_{EI} + \alpha]C_4e^{-\tau[H^+]t} \qquad \text{(A9)}$$

(19) Dietze, P. E.; Jencks, W. P. *J. Am. Chem. Soc.* **1987**, *109*, 2057–2061.