Enantiomer-Specific Oxygen Exchange Reactions. 2. Acid-Catalyzed Water Exchange with 1-Phenyl-1-alkanols†,[1]

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Abstract: The rate constants for three competing processes at the chiral center in the acid-catalyzed racemization of (*R*)-1-phenyl-1-propanol and (*R*)-1-phenyl-1-butanol at 64.5 ± 1.0 °C have been determined by chiral HPLC and GC/MS methods: oxygen exchange without inversion, k_E, oxygen exchange with inversion, k_{EI}, and inversion without exchange, k_I. These same rate constants, previously determined for natural abundance 1-phenylethanol in 50% ^{18}O-enriched water, have been reevaluated for this compound by following the kinetics of 91% ^{18}O-enriched alcohol in natural abundance water. These latter data strengthen the evidence that, for 1-phenylethanol, the departing water, in some cases, bonds to the opposite face of the intermediate carbocation as indicated by a non-zero value for k_I; this process is also operative in the reactions of the other two alkanols as shown by similar kinetic data. In terms of substitution reactions with the solvent leading to oxygen exchange, phenylpropanol behaves similarly to phenylethanol in that $k_E < k_{EI}$; whereas, for phenylbutanol, $k_E \approx k_{EI}$. A common mechanism in which the initially formed carbocation is present as a complex with the departing water, an ion–molecule pair, can account for the variations in the relative rate constants for the oxygen exchange reactions of these three alcohols. The rate of motion of water molecules within the solvation sphere of these intermediates relative to their exchange with the bulk solvent to form randomly solvated carbocations differs, depending on the substituent at the chiral center. The variations in the rate constants for the oxygen exchange reactions reflect these differences in water mobility.

Introduction

The role of ion pairs in solvolysis is well established. Extensive mechanistic studies have documented the roles of both solvent-separated ion pairs and intimate (contact) ions pairs which can recombine to produce the original substrate in an internal return process.[2] Fewer reports have been made, however, on the role of the intermediates analogous to the intimate ion pairs resulting from the heterolysis of substrates with uncharged leaving groups.[1,3–18] Such intermediates have been described as ion–dipole pairs,[1,3,12] encumbered carbocations,[8,9] or ion–molecule pairs.[13–18] Evidence for intermediates of this type, composed of a cation and an uncharged molecule, has been presented for solution reactions of sulfonium ions with azide,[3] racemization and isomerization reactions of alcohols,[1,4–12] displacement of pyridines from *N*-benzylpyridinium cations,[13] dediazoniation of arenediazonium ions,[14,15] and solvolysis of ethers.[16–18] The term "ion–molecule pair" encompasses the diverse structures of the intermediates observed in all these examples and will be used throughout this report. Recently the role importance of ion–neutral complexes in gas-phase heterolysis chemistry and analogies to ion–molecule pairs have been reviewed.[19]

The majority of reports on ion–molecule intermediates arise from studies of ^{18}O exchange between water and optically active alcohols.[20] In these cases, the species analogous to the intimate ion pair of solvolysis reactions is a carbocation–water complex.[1,4–12] For example, the irreversible rearrangement of ^{18}O-labeled γ-phenylallyl alcohol gives α-phenylallyl alcohol containing a higher ^{18}O-content than the solvent;[10] this excess indicates that some of the α-phenylallyl alcohol was formed from recombination of the carbocation with its aqueous partner in the ion–molecule pair. Similarly, in the acid-catalyzed epimerization of the 15-methylprostaglandins E_2 in ^{18}O-enriched water, it was found that the C15 inversion product contained significantly less ^{18}O than the solvent, indicating some recombination of the tertiary allyl cation with the water molecule formed in the dissociation process.[11] On the other hand, it should be pointed out that recent work of

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Dietze and Jencks[21] on the hydration of 1-butene indicates that the carbocation–water pair postulated earlier in the racemization of butan-2-ol[4] cannot be the common intermediate both in this reaction and in the hydration of 1-butene.[5,7,9]

Although there is rich literature on the solvolysis of compounds yielding intimate 1-phenethyl carbocation ion pairs,[22] relatively few studies have been made on the analogous 1-phenethyl carbocation–molecule pairs.[1,6] Our recent kinetic studies on the oxygen exchange reactions of each enantiomer of 1-phenylethanol as a function of racemization indicate that the resultant enantiomer-specific oxygen exchange rate constants provide evidence for a tightly associated carbocation-water complex and give considerable insight into the nature of the solvation sphere of carbocation intermediates as well.[1] Specifically, we have previously reported the rate constants for three competing processes at the chiral center in the acid-catalyzed racemization of 1-phenyl-1-ethanol in ^{18}O-enriched water: (1) substitution (^{18}O exchange) with retention, k_E, (2) substitution (^{18}O exchange) with inversion, k_{EI} and (3) inversion without substitution, k_1.[1]

$$R \overset{k_E}{\rightleftarrows} R', \quad \text{oxygen exchange with retention} \qquad (1)$$

$$R \overset{k_{EI}}{\rightleftarrows} S', \quad \text{oxygen exchange with inversion} \qquad (2)$$

$$R \overset{k_1}{\rightleftarrows} S, \quad \text{inversion without oxygen exchange} \qquad (3)$$

R symbolizes the optically pure starting material, and R′, the same isomer in which the original oxygen has been replaced with that of the solvent. Similarly, S and S′ symbolize the isomer with inverted configuration relative to the starting material and contain either the oxygen of the starting material or that of the solvent, respectively. The two oxygen exchange reactions (eqs 1 and 2) each involve the incorporation of the isotopically distinct solvent oxygen into the specified alcohol isomer. The relative values of these enantiomer-specific rate constants, k_E, and k_{EI}, for the phenylethanols were invariant to a variety of experimental conditions: *R*- or *S*-isomer as the starting material, variations in alcohol concentration from 20 to 64 mM, the source of H^+, and the presence of 1.0 M NaCl in the medium.

The smaller value of k_E relative to k_{EI} suggested that the departing water shields the front side from attack by the bulk solvent. The observation that k_1, inversion with no exchange, was non-zero indicates that the departing water remains associated with the carbocation intermediate and attacks this species from the opposite face. Interpretation of the rate constants led to a proposed mechanism in which the initially formed achiral carbocation is present as a discrete ion–molecule pair.

In the study described above, the extent of oxygen exchange between the alcohol and the solvent was followed by examining the reactions of unlabeled 1-phenylethanol in water enriched in ^{18}O. Here we report on these same oxygen exchange reactions of ^{18}O-labeled phenylethanol in natural abundance water. These data provide strong confirmatory evidence for the contribution of the internal return process, measured by k_1, in the racemization of this alcohol. Subsequent to our early report, we discovered that our kinetic analysis overestimated the value for k_1. Although this error does not alter the mechanistic conclusions of the initial report, we are pleased to provide here corrected values for k_1 as well as for the rate constants for the oxygen exchange reactions, k_E and k_{EI} for eqs 1 and 2, for phenylethanol.

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Earlier studies of similar isomer-specific oxygen exchange reactions in the epimerization of the 15-methylprostaglandins found that, in contrast to the 1-phenylethanols, oxygen exchange with retention of configuration proceeded more rapidly than exchange with inversion.[11] This observation led to the mechanistic conclusion that the initially formed carbocation formally retained the asymmetry of the starting alcohol. The hairpin-like structure of the prostaglandins can yield an intermediate carbocation with a hydrophobic and a hydrophilic side. It was suggested that the apparent chirality of the prostaglandin intermediates may result from segregation of the waters of solvation about the leaving water on the hydrophilic side of the carbocation. If this hypothesis is correct, an increase in the bulk of the alkyl substituent at the chiral center of 1-phenylalkanols might be expected to lead to a similar asymmetric solvation of the resultant carbocation intermediate. In analogy to the oxygen exchange processes for the prostaglandins, this asymmetry should be reflected in an increase of k_E relative to k_{EI}. With analytical methods similar to those used in obtaining the rate constants of eqs 1–3 for phenylethanol, we report here on the kinetics of the enantiomer-specific oxygen exchange reactions of 1-phenyl-1-propanol and 1-phenyl-1-butanol to evaluate the effect of the 1-alkyl substituent on the solvation sphere of the intermediate carbocation.

Materials and Methods

Chemicals. Racemic and the *R*- and *S*-isomers of 1-phenylbutanol, 1-phenylethanols, and 1-phenylpropanols were purchased from either Aldrich Chemical Co., Milwaukee, WI, or Fluka, Ronknonkoma, NY, and used as received. The enantiomeric purity of the optically active alcohols was evaluated prior to kinetic studies via the HPLC methods given below. The ^{18}O-enriched water was obtained from Cambridge Isotope Laboratories, Woburn, MA, Merck Sharp & Dome/Isotopes, St. Louis, MO, or Isotec, Inc., Miamisburg, OH. All solvents used were HPLC grade.

Glassware. All glassware was washed with methanol and dried at 100 °C for at least 2 h prior to use. The kinetic studies and subsequent derivatization reactions were done in cone-shaped reaction vessels (Reactivials) obtained from Supelco, Bellefont, PA.

Preparation of ^{18}O-Labeled (*R*)-1-Phenyl-1-ethanol. Racemic ^{18}O-enriched phenylethanol was prepared as previously described[1] by equilibrating racemic alcohol with highly enriched ^{18}O-enriched (>95%) water in the presence of 0.1 M $HClO_4$ at 65 °C. The extent of the ^{18}O exchange was monitored by MS. The labeled alcohol was extracted with hexane; any residual acid was neutralized by equilibration of this hexane solution with a small amount of solid $NaHCO_3$. The hexane solution, dried with Na_2SO_4, was diluted to yield a final alcohol concentration of 0.1 M. The two isomeric alcohols were separated from one another, and the styrene was formed in the racemization reaction by chromatography of 50-μL aliquots of this solution on a 25- × 0.46-cm Chiralpak OB column (Daicel, Inc., Japan, distributed by J. T. Baker Chemical Co., Vineland, NJ) using a 97/3 hexane/isopropyl alcohol mobile phase. The separated alcohols were collected in the column effluent in glass centrifuge tubes; the solvent volume was reduced by evaporation with a gentle stream of N_2. Sufficient racemic alcohol was separated to give approximately 5 mg of pure (*R*)-phenylethanol; the concentration was estimated from the HPLC response relative to standards. Examination of the purified material by HPLC on the Chiracel OB column, using the methodology for analysis of the isomeric content in kinetic samples, showed that it contained ≤0.2% of the *S*-isomer.

The ^{18}O-content of labeled alcohol was found to be 90.6 ± 0.3% as measured by the relative intensities of the molecular ions (m/z = 122/124) in the mass spectra of both the racemic and resolved alcohols; the same methodology was used for this isotopic composition assay as for the kinetic samples. For these samples, the relative intensities of the base peaks (m/z = 107/109), resulting from the loss of a methyl radical, yielded an ^{18}O-content of 85.3 ± 0.5%. It should be noted that this same apparent isotopic effect was observed in the kinetic samples for all three alcohols of this study: a significantly larger value for ^{18}O-content was determined from the molecular ions relative to that found from the intensities of the ion fragments resulting from loss of the 1-alkyl radical (m/z = 107/109). The higher ^{18}O-content seen in the molecular ion

relative to the fragment indicates a more facile fragmentation of the ^{16}O-containing species, consistent with $k_{16}/k_{18} > 1$. The source of this apparent isotope effect is unknown but seems much too large for a secondary ^{18}O-isotope effect; typical values for k_{16}/k_{18} when C–O fission is rate-limiting are around 1.06.[23]

Kinetic Samples. (a) Oxygen Exchange Reactions. Samples of the pure *R*-isomers of either 1-phenyl-1-propanol or 1-phenyl-1-butanol, as received, were weighed (±0.01 mg) into tared 2- or 3-mL Reactivials. An accurately weighed portion of ^{18}O-enriched water was then added to these samples. The vials were sealed with Teflon-lined closures (Miniinert Valve, Supelco) and sonicated overnight to ensure complete dissolution of the alcohol. The samples were thermally equilibrated (±0.1 °C) in a circulating water bath. The racemization reactions were initiated by adding a measured aliquot of standardized perchloric acid to give a final concentration of 0.1 M; at the end of the run, an 100-μL aliquot was titrated with standardized base to determine the exact acid concentration. At predetermined times, 100-μL aliquots were removed, quenched, and extracted with hexane as previously described.[1] The hexane solutions were used for subsequent analyses of the isomeric and oxygen isotopic compositions of the alcohols. The rate constants in 50% ^{18}O-enriched water were determined from assaying 10 samples taken during the first two racemization half-lives of each kinetic run and two equilibrium aliquots taken at the end of 10–12 half-lives. The studies done using 91% ^{18}O-enriched water with 1-phenyl-1-propanol and 1-phenyl-1-butanol as well as the ^{18}O-labeled 1-phenylethanol were followed for approximately one racemization half-life during which 10 samples were assayed as well as equilibrium (≥10 half-lives) samples. The time frame of these latter experiments was chosen to optimize the detection of the internal return product and the estimation of the rate constant, k_1. No *S*-isomer was detectable in the (*R*)-1-phenyl-1-butanol sample used in the experiment in 91% ^{18}O-enriched water; approximately 0.2% of (*S*)-1-phenyl-1-propanol was detected via HPLC in the *R*-starting material used in the companion study of this alcohol in 91% ^{18}O-enriched water. The stated isotopic composition of the water used in these experiments is based on MS assays of the oxygen isotopic composition of the molecular ions of the equilibrium samples.

Samples for kinetic studies using ^{18}O-enriched (*R*)-phenylethanol were prepared in a fashion similar to that described for the phenylpropanol and phenylbutanol except that the ^{18}O-enriched phenylethanol was introduced into a tared Reactivial as a hexane solution; the hexane was removed with a stream of dry nitrogen and the amount of alcohol determined by weight. A weighed portion of HPLC-grade water was used as the solvent for these studies. The reaction was initiated by addition of acid and monitored as described above. The rate constants for this study were determined from 12 samples taken during the first half-life of the racemization reaction; two additional equilibrium aliquots were taken at the end of 10–12 half-lives.

(b) Relative Rates of Racemization. Since the racemization reactions show a first-order dependence on $[H^+]$, which was difficult to measure precisely in the experimental procedure described above, the following experiment was done to compare the absolute values of k_{rac} for the three alcohols. Samples of the *R*-isomer of each of the three alcohols were weighed into separate reaction vessels. To each was added a weighed portion of a 0.092 72 M $HClO_4$ stock solution, and the samples were sonicated overnight to ensure dissolution. The three vials were transferred simultaneously to the controlled temperature bath to initiate the racemization reactions. The vials were sampled as described above and assayed for isomeric content via the HPLC method as described below.

Analysis of Isomeric and Isotopic Compositions of Kinetic Samples. HPLC of kinetic samples on a 25- × 0.46-cm Chiralpak OB column (described above) was used both to determine the isomeric composition and, hence, k_{rac} and to separate and collect each isomer for subsequent mass spectral analysis of isotopic composition as previously described for similar studies with 1-phenylethanols with minor modifications.[1] A mobile phase of 2% isopropyl alcohol in hexane at a flow of 1.0 mL/min was used to resolve the phenylbutanol isomers from one another and from trace amounts of propyl phenyl ketone present at ca. 0.4% in the starting material and 1-phenyl-1-butene produced in the reaction. The phenylpropanols were resolved from one another, the ethyl phenyl ketone impurity in the starting material, and 1-phenyl-1-propene using a mobile phase of 6% isopropyl alcohol in hexane (flow rate, 1.0 mL/min). The ketone content did not vary with time in either alcohol reaction. Upon the basis of relative molar absorptivities, we estimate that no more than 3–5% of the dehydration products (1-phenyl-1-propene and 1-phenyl-1-butene) were present at 10 half-lives. Because of these low yields, the dehydration reactions were ignored in the kinetic analysis. We have found that the chromatography conditions optimal for separating the phenylalkanols change gradually with the use of the Chiralpack OB column (hundreds of assays); in this particular set of experiments with 1-phenyl-1-ethanol, a mobile phase of 10% isopropyl alcohol in hexane was used rather than the 6% isopropyl alcohol/hexane mixture used previously.[1]

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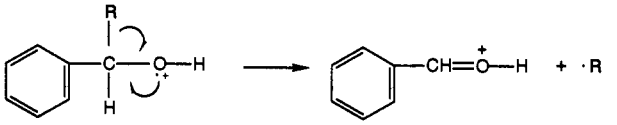
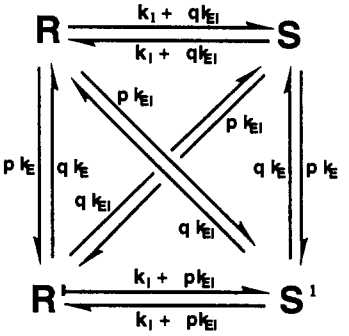
Scheme 1



Scheme 2



The oxygen isotopic composition assays, required for the evaluation of $k_{tot\ ex}$, k_E, k_{E1}, and k_1, were done using GC/electron impact mass spectrometry in the selected ion mode as previously described;[1] $k_{tot\ ex}$ is the rate constant for the reaction in which the solvent oxygen is exchanged into the unresolved product as shown in eq 4. Two pairs of ions were

$$R \xrightarrow{k_{tot\ ex}} R' + S', \quad \text{oxygen exchange into unresolved alcohols} \tag{4}$$

monitored to determine of ^{18}O-content of the alcohols: the molecular ions and those resulting from the loss of the alkyl group as shown in Scheme 1 below; the latter ions are the base peaks in these spectra. The values of total ^{18}O-content $[\Sigma(^{18}O)]$ needed to evaluate $k_{tot\ ex}$ were determined both from the unresolved alcohol of each kinetic sample and from the $\Sigma(R' + S')$ of the HPLC-resolved alcohols. The relative amounts of R, R', S, and S' as a function of time, needed to determine the microscopic rate constants k_E, k_{E1}, and k_1, were derived from assaying the isotopic composition of the pure isomers isolated via HPLC as described previously.[1]

Calculation of Microscopic Rate Constants. The interrelationships between the four interconverting alcohol species, the microscopic rate constants, and the isotopic composition of the solvent are shown schematically in Scheme 2. In Scheme 2, the fraction of the solvent water present with the same oxygen isotope as the starting alcohol is represented by *q*, and with a different isotope, by *p*. Therefore, in the experiments using natural abundance alcohol in ^{18}O-enriched water, *p* equals the fractional amount of ^{18}O in the solvent, whereas, *p* is the fractional amount of ^{16}O in water with experiments done with ^{18}O-labeled alcohol. The rate laws for the four species of Scheme 2 are as follows:

$$d[R]/dt = -(pk_E + k_1 + k_{E1})[R] + (k_1 + qk_{E1})[S] + qk_E[R'] + qk_{E1}[S'] \tag{5}$$

$$d[S]/dt = +(k_1 + qk_{E1})[R] - (pk_E + k_1 + k_{E1})[S] + qk_{E1}[R'] + qk_E[S'] \tag{6}$$

$$d[R']/dt = +pk_E[R] + pk_{E1}[S] - (qk_E + k_1 + k_{E1})[R'] + (k_1 + pk_{E1})[S'] \tag{7}$$

$$d[S']/dt = pk_{E1}[R] + pk_E[S] + (k_1 + pk_{E1})[R'] - (qk_E + k_1 + k_{E1})[S'] \quad (8)$$

These differential equations differ from those previously used in the initial report[1] on the enantiomeric oxygen exchange reactions of phenylethanol in that the bimolecular component involving the solvent was incorrectly omitted for the following processes:

$$R \underset{k_1 + qk_{EI}}{\overset{k_1 + qk_{EI}}{\rightleftarrows}} S \quad (9)$$

$$R' = \underset{k_1 + pk_{EI}}{\overset{k_1 + pk_{EI}}{\rightleftarrows}} S' \quad (10)$$

We are pleased to correct this error here and to report corrected values for the microscopic rate constants of Scheme 2 for phenylethanol. The numerical values for k_{rac} and $k_{tot\ ex}$ were obtained from the HPLC isomeric composition data and the MS oxygen composition data, respectively, as previously described,[1] and are related to the microscopic rate constants as shown in eqs 11 and 12, respectively.

$$2(k_{E1} + k_1) = k_{rac} \quad (11)$$

$$(k_E + k_{E1}) = k_{tot\ ex} \quad (12)$$

A third relationship related to the experimentally measured parameters is required, along with k_{rac} and $k_{tot\ ex}$, to determine k_E, k_{E1}, and k_1 and is dependent upon the isotopic composition of the solvent used in the kinetics experiments. This necessary equation can be readily derived from the following explicit relationships among the equilibrating species where $R(0)$ is the total amount of alcohol present (100%):

$$[(R + S)]_t = qR(0) + \{p[(R + S)_0] - q[(R' + S')_0]\}e^{-(k_E+k_{EI})[H^+]t} \quad (13a)$$

$$[(R' + S')]t = pR(0) - \{p[(R + S)_0] - q[(R' + S')_0]\}e^{-(k_E+k_{EI})[H^+]t} \quad (13b)$$

$$[(R - S)]t = \{p[(R - S)_0] - q[(R' - S')_0]\}e^{-(2k_1+k_E+k_{EI})[H^+]t} + \{q[(R - S)_0] + q[(R' - s)_0]\}e^{-2(k_1+k_{EI})[H^+]t} \quad (13c)$$

$$[(R' - S')]t = \{q[(R' - S')_0] - p[(R - S)_0]\}e^{-(2k_1+k_E+k_{EI})t} + \{p[(R - S)_0] + p[(R' - S')_0]\}e^{-2(k_1+k_{EI})t} \quad (13d)$$

These equations can be further simplified depending on the isotopic labeling of the starting 1-(*R*)-phenylalkanol and solvent.

Case a. Natural Abundance Alcohol in 50% ^{18}O-Enriched Water, $p = q = 0.5$. Equation 13 can be combined to express $[R + S']_t$ and $[R' + S]_t$ in eq 14, containing a single exponential term involving the three microscopic rate constants:

$$[R + S']t = 0.5R(0)[1 - e^{-(2k_1+k_E+k_{EI})[H^+]t}] \quad (14a)$$

$$[R' + S]t = 0.5R(0)[1 - e^{-(2k_1+k_E+k_{EI})[H^+]t}] \quad (14b)$$

$$(2k_1 + k_E + k_{E1}) = k_{cross} \quad (15)$$

The slopes of the following linear least-squares plots were used, consequently, to obtain the rate constants k_{cross} from the alcohol composition data for kinetic studies done in 50% ^{18}O-enriched water: For the experiments done in "50%" ^{18}O-enriched water, the actual ^{18}O composition ranged from 46.5 to 48.6% $H_2{}^{18}O$.

$$\ln[50.0\% - \%(R' + S)_t] \text{ vs time, } k_{cross} = \text{slope}/[H^+]\ M^{-1}\ min^{-1} \quad (16a)$$

$$\ln[\%(R + S')_t - 50.0\%] \text{ vs time, } k_{cross} = \text{slope}/[H^+]\ M^{-1}\ min^{-1} \quad (16b)$$

Case b, 91% ^{18}O-Enriched (*R*)-1-Phenyl-1-ethanol in Natural Abundance Water, and Case c, Natural Abundance Alcohols in ≥90% ^{18}O-Enriched Water. In these experiments, the enantiomeric purity of the starting alcohol was ≥99.8% and $q \approx 0$. Therefore, eq 13c can be approximated as follows:

$$[(R - S)]_t = \{p[(R)_{t=0}]\}e^{-(2k_1+k_E+k_{EI})[H^+]t} \quad (17)$$

$$(2k_1 + k_E + k_{E1}) = k'_{cross} \quad (18)$$

The slope of the following linear plots was used to obtain values for k'_{cross}:

$$\ln[\%(R - S)_t] \text{ vs time, } k'_{cross} = \text{slope}/[H^+]\ M^{-1}\ min^{-1} \quad (19)$$

Correlation coefficients for all least-squares plots were ≥0.99. In those experiments done with ^{18}O-labeled phenylethanol and in 90% ^{18}O-enriched water, the rate constants were determined from the isotopic composition based on the MS base peaks (m/z = 107/109). In the experiments done in 50% ^{18}O-enriched water, data from both the base peak and the molecular ion were used to obtain the relative amount of each species in the kinetic samples; the slope of the plots were averaged to obtain the desired rate constants. The values for $k_{tot\ ex}$ reported are the means of those obtained from plots of $\ln(\%S^{18}O_{eq} - \%S^{18}O_t)$ vs time and $\ln[\%(R' + S')_{eq} - \%(R' + S')_t]$ vs time. The reported values for k_{cross} are the means of those obtained from plots of $\ln[50.0\% - \%(R' + S)_t]$ and $\ln[(R + S')_t - \%50.0]$ for the two sets of ions; for k'_{cross}, the slopes of the plots of $\ln[(R - S)_t]$ vs time for the base peaks were used to obtain this rate constant.

In addition, the microscopic rate constants of Scheme 2 for phenylethanol were obtained by the simultaneous nonlinear fitting of all isotopic composition data (R, S, Σ^{18}O) for the kinetic study of 91% ^{18}O-enriched (*R*)-1-phenylethanol in natural abundance water to the following equations, derived from eqs 13 under the experimental conditions of this experiment, $q \approx 0$ and $(S + S') \approx 0$:

$$\%R_t = Ae^{-Bt} + De^{-Ct} \quad (20)$$

$$\%S_t = Ae^{-Bt} - De^{-Ct} \quad (21)$$

$$\%\Sigma^{18}O = \%[(R' + S')]t = 2Ae^{-Bt} \quad (22)$$

where $A = 0.5(R + S)_0$, $B = (k_E + k_{E1})[H^+]$, $C = (2k_1 + k_E + k_{E1})[H^+]$, and $D = 0.5(R - S)_0$. These kinetic data were fit simultaneously with the program MINSQ (MicroMath Scientific Software, Salt Lake City, UT) to obtain the optimal parameters A, B, C, and D for eqs 20–22.

Results

Exchange of ^{18}O from the aqueous solvent with the 1-phenylalkanols can occur with either retention or inversion of configuration at the chiral center. In the present report, the *R*-enantiomers were used as the starting materials for all experiments; consequently, the two exchange products formed from natural abundance alcohols in ^{18}O-enriched water are R18 (front-side solvent attack, eq 1) and S18 (backside solvent attack, eq 2). Figure 1a–c contains profiles of these two solvent exchange products, R18 and S18, as a function of the total inversion product S, as determined by HPLC, in the racemization of the three (*R*)-1-phenyl-1-alkanols (natural abundance isotopic composition) of this study in 50% ^{18}O-enriched water over approximately two half-lives of the racemization process. The data presented are those determined by combining the HPLC isomeric composition data with the oxygen isotopic composition based on the common m/z 107/109 mass spectral fragments; the results are essentially

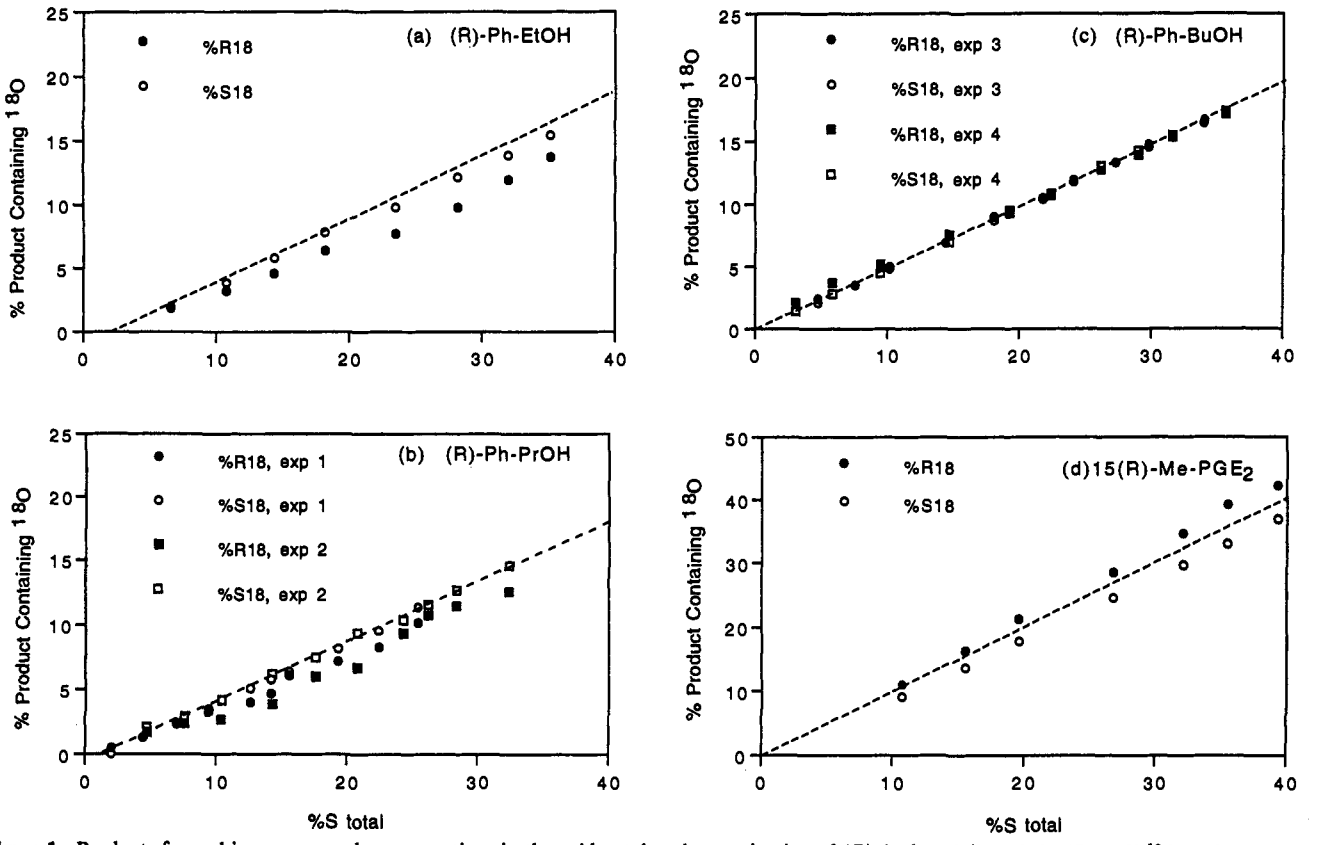


Figure 1. Products formed in oxygen exchange reactions in the acid-catalyzed racemization of (*R*)-1-phenylalkanols in 47 ± 1% ^{18}O-enriched water at 64.5 ± 1.0 °C, 0.1 M $HClO_4$, as a function of the formation of the inverted isomer. The open symbols represent exchange with inversion, the filled symbols, exchange without inversion. The data presented are those determined from the common *m*/*z* 107/109 mass spectral fragments. The dotted line in each figure represents the amount of each exchange product (%R18 = %S18) expected if exchange occurs simultaneous with carbocation formation, based on the initial isomeric composition of the starting alcohol (2.0% S in both the phenylethanol and phenylpropanol samples; 0.2% S in phenylbutanol) and the isotopic composition of the water: (a) 44.3 mM (*R*)-1-phenylethanol, 46% ^{18}O-enriched water, data taken from Table 1, footnote *d*; (b) 34 mM (expt 1, Table 1) and 37 mM (expt 2, Table 1) (*R*)-1-phenylpropanol, 47% ^{18}O-enriched water; (c) 11 mM (expt 3, Table 1) and 13 mM (expt 4, Table 1) (*R*)-1-phenylbutanol, 48% ^{18}O-enriched water; and (d) natural abundance 15(*R*)-Me-PGE_2 in 32.7% ^{18}O-enriched water, data from Table 1, ref 11. The percentages of each product containing ^{18}O were calculated from the published data normalized with respect to the ^{18}O-content of an equilibrium sample in which it was assumed that %R18 = %S18 = 50%.

identical, but less precise, using the isotopic composition derived from the less abundant parent peaks. The results for a single experiment are presented for phenylethanol from published data (Figure 1a); data for two separate experiments are presented for the other two phenylalkanols (Figure 1b,c). For comparison, Figure 1d contains a similar profile of the solvent exchange products of the C-15 hydroxyl group as a function of the change in stereochemistry at this carbon of 15(*R*)-methylprostaglandin E_2 [15(*R*)-Me-PGE_2] using published kinetic data.[11] Although the prostaglandin reaction was carried out in 32.7% ^{18}O-enriched water, the data have been normalized with respect to equilibrium values of %R18 = %S18 = 50%.

If exchange occurs simultaneous with carbocation formation, equal amounts of each exchange product are expected to form: %R18 = %S18. The dotted lines in Figure 1a–d represent this prediction based on the isotopic composition of the water and initial isomeric compositions of the alcohols. (The amount of the *S*-enantiomer present in the natural abundance *R*-starting materials was determined via HPLC for the phenylalkanols: 2.0% S in both the phenylethanol and phenylpropanol samples and 0.2% in phenylbutanol. It was assumed that 15(*R*)-Me-PGE_2 contained none of the *S*-epimer.) The data present in Figure 1a–c are from experiments carried out in approximately 50% ^{18}O-enriched water. Although data are shown from only one experiment for phenylethanol, the same results were found in six similar experiments[1] and one additional experiment each for phenylpropanol and phenylbutanol in 90%^{18}O-enriched water; Table 1 contains a compilation of the rate constants for the racemization and oxygen exchange reactions of the three 1-phenyl-1-alkanols of this study under differing oxygen isotopic labeling regimes. Although the absolute values of the rate constants for the oxygen exchange reactions show some variation from experiment to experiment, reflecting small differences in temperature and acid composition, they are constant for each alcohol, relative to k_{rac}, as shown in Table 2.

Examination of the data in Table 1 leads to the conclusion that the contribution of the internal return process, inversion without exchange measured by k_1, to the change in configuration at the chiral center is small relative to exchange reactions with the solvent, measured by k_E and k_{E1}. The numerical value of this microscopic rate constant is the difference between k_{cross} (or k'_{cross}), eq 15 (or 19), and $k_{tot\ ex}$, eq 12:

$$k_{cross}\ (\text{or } k'_{cross}) - k_{tot\ ex} = (2k_1 + k_E + k_{E1}) - (k_E + k_{E1}) = 2k_1 \quad (23)$$

In fact, the value of k_1 obtained from this difference is not statistically greater than zero for any of the experiments of Table 1. A careful examination of the reactions of the three alcohols under conditions in which the product of the internal return process can be readily detected shows, nonetheless, that this recombination reaction does contribute to the change in stereochemistry at the chiral center in the acid-catalyzed racemization reactions. The oxygen exchange reactions of highly ^{18}O-enriched (*R*)-1-phenylethanol (91%) and of high enantiomeric purity of the starting material (>99.8% *R* > 99.6% enantiomeric excess, %ee) in natural abundance water allowed both the unambiguous detection of the

Table 1. Racemization and Oxygen Exchange Reactions of 1-Phenylalkanols in Water,[a,b] 64.5 ± 0.5 °C

expt no.	1-phenyl-1-alkanol	[alcohol], mM	k_{rac} (×10⁴)	$k_{tot\ ex}$ (×10⁴)	k_{cross} or k'_{cross} (×10⁴)	k_E[c] (×10⁴)	k_{EI}[c] (×10⁴)
		A. Experiments in 50% ^{18}O-Enriched H_2O, 0.10 M $[H^+]$					
d	Ph-Et-OH ($N = 6$)	20–64	16.0 ± 1.0	13.4 ± 1.1	13.9 ± 1.1	5.7 ± 0.9	7.8 ± 0.7
1	(*R*)-Ph-Pr-OH	37[e]	10.2 ± 0.1	8.92 ± 0.16	9.28 ± 0.35	4.0 ± 0.2	4.9 ± 0.2
2	(*R*)-Ph-Pr-OH	34[e]	9.47 ± 0.05	8.01 ± 0.03	8.06 ± 0.04	3.3 ± 0.1	4.7 ± 0.1
3	(*R*)-Ph-Bu-OH	11[e]	11.4 ± 0.1	11.3 ± 0.4	10.9 ± 0.2	5.6 ± 0.2	5.7 ± 0.2
4	(*R*)-Ph-Bu-OH	13[e]	13.0 ± 0.1	12.3 ± 0.3	12.2 ± 0.4	5.8 ± 0.3	6.5 ± 0.3
		B. Experiments in 91% ^{18}O-Enriched H_2O, 0.10 M $[H^+]$[e]					
5	(*R*)-Ph-Pr-OH	13	7.87 ± 0.08	7.10 ± 0.12	7.27 ± 0.13	3.3 ± 0.1	3.8 ± 0.1
6	(*R*)-Ph-Bu-OH	9.7	11.1 ± 0.1	11.2 ± 0.1	11.2 ± 0.2	5.7 ± 0.1	5.6 ± 0.1
		C. 91% ^{18}O-Labeled Alcohol, Natural Abundance H_2O, 0.10 M $[H^+]$[e]					
7	(*R*)-Ph-Et-OH	30[f]	13.8 ± 0.2	11.4 ± 0.1	11.7 ± 0.1	4.6 ± 0.1	6.8 ± 0.1
		D. Racemization in 0.092 72 M $HClO_4$[g]					
8	(*R*)-Ph-Et-OH	11.2	13.9 ± 0.2				
8	(*R*)-Ph-Pr-OH	12.2	7.60 ± 0.08				
8	(*R*)-Ph-Bu-OH	11.4	10.9 ± 0.1				

[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 for experiments done in 50% ^{18}O-enriched H_2O (part A); k'_{cross} = rate constant obtained from the slope/$[H^+]$ of ln[(R − S)] vs time for experiments done in 90% ^{18}O-enriched H_2O (part D) or for 91% ^{18}O-enriched phenylethanol in natural abundance H_2O (part C) (the precision of these rate constants is expressed as the standard deviation of the slope of the least-squares line); k_E = rate constant for ^{18}O-exchange with starting material; k_{EI} = rate constant for ^{18}O-exchange with inverted configuration relative to starting material. [b] For the experiments in part A, the rate constants were determined from the isotopic composition derived from both the molecular ions (M and M + 2) and the 107/109 mass fragments; for parts B and C, the isotopic composition was derived from only the more abundant 107/109 mass fragments. [c] k_E and k_{EI} were determined from k_{rac}, $k_{tot\ ex}$, and k_{cross}) as indicated in eqs 11, 12, and 15 (or 18); the expressed errors are calculated from the errors in k_{rac}, $k_{tot\ ex}$, and k_{cross} (or k'_{cross}). [d] Data taken from Merritt et al., ref 1. [e] The racemization reactions were initiated by the addition of 1 aliquot of concentrated $HClO_4$ to the alcohol solution at 64.5 °C to produce a final concentration of 0.10 M. [f] Estimated concentration. [g] In expt 8, the three alcohols samples were dissolved in 0.092 72 M $HClO_4$ at room temperature and the racemization reactions initiated by simultaneously transferring the alcohol solution to a 64.5 °C temperature bath.

Table 2. Rate Constants for Oxygen-Exchange Reactions of 1-Phenyl-1-alkanols Relative to Racemization in Water, 64.5 ± 0.5 °C[a]

1-phenyl-1-alkanol	expt no.[b]	^{18}O-content of solvent	$k_{tot\ ex}/k_{rac}$	k_E/k_{rac}	k_{EI}/k_{rac}
Ph-Et-OH ($N = 7$)	*c*	50% $[^{18}O]H_2O$	0.84 ± 0.09	0.36 ± 0.06	0.49 ± 0.05
^{18}O-(*R*)-Ph-Et-OH	7	natural abundance	0.83 ± 0.01	0.34 ± 0.03	0.49 ± 0.03
Ph-Pr-OH	1	50% $[^{18}O]H_2O$	0.87 ± 0.02	0.39 ± 0.02	0.48 ± 0.02
Ph-Pr-OH	2	50% $[^{18}O]H_2O$	0.84 ± 0.01	0.35 ± 0.02	0.50 ± 0.02
Ph-Pr-OH	5	90% $[^{18}O]H_2O$	0.86 ± 0.02	0.37 ± 0.01	0.47 ± 0.01
Ph-Bu-OH	3	50% $[^{18}O]H_2O$	1.00 ± 0.04	0.49 ± 0.02	0.50 ± 0.02
Ph-Bu-OH	4	50% $[^{18}O]H_2O$	0.95 ± 0.02	0.45 ± 0.02	0.50 ± 0.02
Ph-Bu-OH	6	90% $[^{18}O]H_2O$	1.02 ± 0.01	0.51 ± 0.02	0.50 ± 0.02

[a] The rate constants are defined in Table 1; data taken from Table 1. [b] Experiment numbers are the same as in Table 1. [c] Data taken from ref 1. The ratios were calculated from mean values of each rate constant, as compiled in Table 1.

internal return process, inversion without exchange, and the most accurate evaluation of k_1 for this alcohol (Table 1, experiment 7). In the absence of the internal return process, the oxygen isotopic composition of the inverted enantiomer, S in this study, would be that of the solvent, ^{16}O. Table 3 contains a compilation of the isomeric and oxygen isotopic composition data for this particular kinetic study. Of particular interest is the $\%^{18}O$ in ΣS, the inversion product as determined by HPLC. At early times in the racemization process, the internal return product is most apparent. For example, at $t = 5.33$ min, the HPLC-isolated inversion product, ΣS, contains 8.62% ^{18}O, whose only source can be from the starting ^{18}O-labeled (*R*)-1-phenyl-1-ethanol. The ^{18}O-content of all the S-samples isolated during this study, encompassing nearly one half-life of the racemization process ($t = 60.3$ min, $\%\Sigma R = 80.5\%$), exceeds that present at equilibrium (0.7%), expected in the absence of any internal return process.

The difference between the equilibrium ^{18}O-content, reflecting the isotopic composition of the solvent, and that found in the HPLC-isolated S-samples in the reaction of ^{18}O-labeled (*R*)-1-phenyl-1-ethanol is designated here as unexchanged oxygen in S and is the experimental measure of the internal return process. Similarly, in kinetic studies carried out with enantimerically pure (>99.6% ee) natural abundance (*R*)-1-phenyl-1-propanol and (*R*)-1-phenyl-1-butanol in 93% ^{18}O-enriched water (experiments 5 and 6, respectively, Table 1), the unexchanged oxygen is the difference in $\%^{16}O$ content of the HPLC-isolated *S*-isomer and that of the solvent, measured by the $\%^{16}O$ content of samples isolated at equilibrium (≥10 half-lives of the racemization reaction). The percent of unexchanged oxygen in the inverted isomer (S) as a function of the inversion reaction for these three kinetic studies is shown in Figure 2. The fact that the data nearly overlap suggests that formation of the inversion product with no exchange with the solvent occurs approximately to the same extent for the three alkanols. Similar profiles (not shown) of the percent of unexchanged oxygen in S as a function of inversion were obtained for the kinetic studies of 1-phenylalkanols conducted using 50% $[^{18}O]H_2O$. These latter results provide less conclusive evidence for the internal return process than those shown in Figure 2 in that the starting material for some of those studies (namely experiments 1 and 2, Table 1) contained as much as 2% of the *S*-enantiomer as an impurity. Consequently, the possibility that the observation of ^{16}O levels higher than those expected at equilibrium originated from the starting material cannot not be completely eliminated.

Because the contribution of the internal return process is small relative to the competing exchange reactions with the solvent, it was difficult to obtain a precise and accurate evaluation of the rate constant, k_1, for this reaction. The best estimate was made from the experiment with 91% ^{18}O-labeled phenylethanol in natural abundance water, experiment 7 of Table 1. Under the conditions of this experiment, eq 17 is an exact expression relating the difference in the exchange products (R16 and S16) to k'_{cross}, the experimental rate constant needed to determine k_1: $0.5(k'_{cross} - k_{tot\ ex}) = k_1 = (0.2 \pm 0.1) \times 10^{-4}\ M^{-1}\ s^{-1}$. Simultaneous nonlinear least-squares fitting of all independent isotopic composition data of this experiment (eqs 20–22) was not possible unless $k_1 >$ zero;

Table 3. Oxygen Exchange Reactions of 91% ^{18}O-Enriched (*R*)-1-Phenyl-1-ethanol in Natural Abundance Water, [$HClO_4$] = 0.10 M, 64.5 °C: Isomer and Isotopic Compositions Based on the 107/109 Mass Spectral Fragments[a]

time, min	%ΣR[b]	% ^{18}O in ΣR[c]	%R18[d]	%R16[d]	% ^{18}O in ΣS[e]	%S18[f]	%S16[f]	%Σ ^{18}O[g]
0	99.8	84.2	84.2	15.6	nd	0.17	0.03	84.2
5.33	97.8	82.7	80.9	16.9	8.62	0.190	2.01	81.4
8.25	96.8	82.1	79.5	17.3	6.62	0.212	2.99	80.4
12.1	95.3	82.1	78.3	17.0	4.93	0.231	4.45	78.1
15.1	94.0	80.6	75.8	18.2	4.16	0.250	5.76	76.3
20.2	92.4	79.3	73.3	19.1	3.43	0.262	7.37	74.5
25.2	90.6	78.0	70.7	19.9	2.93	0.275	9.11	71.5
30.2	88.9	76.4	67.9	21.0	2.45	0.271	10.8	69.0
35.6	87.0	65.7	21.4	21.4	2.25	0.292	12.7	66.7
39.2	85.4	74.1	63.3	22.1	2.01	0.293	14.3	64.2
45.1	84.3	72.7	61.3	23.0	1.90	0.300	15.4	61.9
50.3	83.1	71.6	59.5	23.6	1.88	0.318	16.6	60.4
54.9	81.9	68.9	57.6	25.0	1.75	0.317	17.8	58.3
60.3	80.5	68.9	55.5	25.0	1.70	0.331	19.1	58.3
eq[h]	49.9	0.70	0.5	49.5	0.70	0.350	49.7	0.70

[a] Expt 7, Table 1. [b] ΣR is the percent of *R*-isomers as determined by HPLC. [c] % ^{18}O in ΣR is the percentage determined from the peak area of the m/z = 109 ion chromatogram relative to the sum of the areas of the m/z = 107 and 109 selected ion chromatograms in the HPLC-isolated *R*-isomer. [d] %R18 and %R16 calculated from HPLC isomeric composition (%R) and mass spectral isotopic composition (% ^{18}O in ΣR) data. [e] % ^{18}O in ΣS is the percentage determined from peak area of the m/z = 109 ion chromatogram relative to the sum of the areas of the m/z = 107 and 109 selected ion chromatograms in the HPLC-isolated *S*-isomer. [f] %R18 and %R16 calculated from HPLC isomeric composition (%S) and mass spectral isotopic composition (% ^{18}O in ΣS) data. [g] %Σ ^{18}O is the percentage determined from the peak area of the m/z = 109 ion chromatogram relative to the sum of the areas of the m/z = 107 and 109 selected ion chromatograms of the unfractionated kinetic sample. [h] Equilibrium sample, taken 24 h following initiation of the kinetic experiment.

this fitting gave a value for k_1 identical to that found by the linear least-squares method. In terms of the percent contribution to the reactions of this alcohol, the internal return process occurs approximately 1–3% of the time: $k_1/(k_1 + k_{EI} + k_E) \times 100\% =$ 1–3%. The similar profiles of Figure 2 suggest an equal contribution of the internal return process in the reactions of phenylpropanol and phenylbutanol as well.

Discussion

The previously reported studies of isomer-specific oxygen exchange reactions show that the rate constants for the processes of eqs 1–3 provide considerable detail regarding the structure and dynamics of the solvation of the carbocation intermediates formed during the change in configuration at the α-carbon of optically active alcohols.[1,11] Evaluation of the rate constants for these oxygen exchange reactions in the epimerization of 15(*R*)-Me-PGE_2 and 15(*S*)-Me-PGE_2 indicated that oxygen exchange with retention of configuration proceeded more rapidly than exchange with inversion.[11] In contrast, for 1-phenyl-1-ethanol, the former process, exchange with retention, was found to be more rapid than the latter process.[1] If the reactions proceed through a carbocation intermediate, as shown by Grunwald et al. for phenylethanol,[6] the two exchange reactions represent attack by the bulk aqueous solvent on the carbocation from opposite faces. The data presented in Figure 1 are graphical representations of the two exchange reactions of the three (*R*)-1-phenylalkanols and of 15(*R*)-$MePGE_2$: R18 is a measure of exchange with retention, frontside attack, and S18, exchange with inversion, backside attack, respectively.

For the three 1-phenylalkanols, the products resulting from backside solvent attack, S18, lie either on or within experimental error of the dotted line representing equal probability of front- and backside attack by the bulk solvent on the carbocation intermediate. Figure 1a,b shows that phenylethanol and phenylpropanol behave similarly in that, at all times, the amount of S18 exceeds R18, which results from solvent attack on the front face of the carbocation. In contrast, approximately equal amounts of these two exchange products are formed in the racemization of 1-phenylbutanol as seen in Figure 1c. The profiles of the exchange products in the epimerization of 15-Me-PGE_2 seen in Figure 1d are markedly different from those of the three phenylalkanols of this study in that the product resulting from solvent attack on the front side of the carbocation proceeds more rapidly than exchange from backside attack: R18 > S18. Furthermore, the formation of R18 proceeds more rapidly and that of S18 more slowly than expected if the solvent exchange reactions were to occur simultaneous with carbocation formation (indicated by the dotted line in Figure 1d). (This line would be slightly displaced to the right and have a larger slope if the starting material contained any of the *S*-epimer.). These results, presented in a different fashion, were previously interpreted to indicate that the prostaglandin-derived carbocation formally retained the asymmetry of the starting alcohol; the apparent asymmetry of the carbocation was postulated to arise from asymmetric solvation.[11]

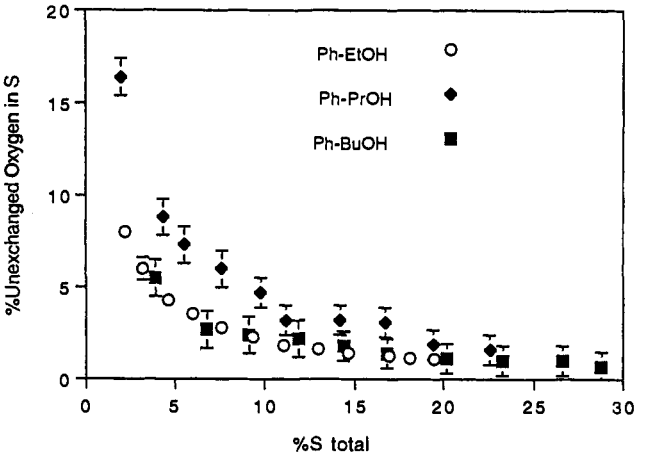
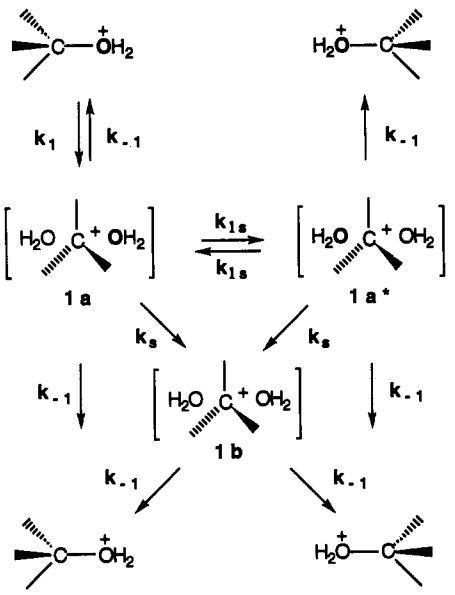


Figure 2. Percent of unexchanged oxygen in the *S*-isomer as a function of formation of the *S*-isomer from 91% ^{18}O-enriched (*R*)-1-phenyl-1-ethanol in natural abundance H_2O, ○ (expt 7, Table 1); from natural abundance (*R*)-1-phenyl-1-propanol in 91% ^{18}O-enriched H_2O, ◆ (expt 5, Table 1); and from natural abundance (*R*)-1-phenyl-1-butanol in 91% ^{18}O-enriched H_2O, ■, (expt 6, Table 1). The unexchanged oxygen is the difference in the percentage of the major oxygen isotope of the starting alcohol (^{18}O for phenylethanol; ^{16}O for phenylpropanol and phenylbutanol)) of each sample and that of the same isotope in the solvent; the latter was determined via mass spectral analysis of alcohol samples isolated at equilibrium (≥10 half-lives for racemization); the isotopic composition was determined from the common m/z 107/109 mass fragments from the HPLC-isolated *S*-isomer for all samples.

The compilation of the rate constants for the oxygen exchange processes in Table 2 is consistent with the pictorial representation of the exchange processes in Figure 1 and can be interpreted as reflecting differences of motion of water molecules within the solvation sphere of the carbocation intermediates. For both 1-phenylethanol and 1-phenylpropanol, $k_{tot\ ex}/k_{rac}$ is less than unity, consistent with the enantiomer-specific oxygen exchange rate constant measuring frontside exchange, k_E, being less than that for exchange with inversion, k_{EI}. The relative size of these rate constants indicates that the departing water protects the carbocation from attack by the solvent as had been suggested by Grunwald's much earlier work on oxygen exchange reactions of 1-phenyl-1-ethanol with isotopically distinct water on the basis of comparisons of loss of optical activity with the oxygen content of the racemate.[6] In contrast, for phenylbutanol, the rate constants for the two exchange processes, k_E and k_{EI}, are approximately equal and are consistent with rapid equilibration of the intermediate carbocation with the bulk solvent. As the bulk of the alkyl substituent at the chiral center increases from methyl to

Scheme 3



propyl, the departing water appears to be less tightly associated with the intermediate carbocation as indicated by the increasing ratio of k_E/k_{rac}: phenylethanol < phenylpropanol < phenylbutanol (Table 2). These rate constants are inconsistent with a major S_N2 mechanistic component for the racemization of the three 1-phenylalkanols. In the S_N2 mechanism, the bimolecular substitution would produce none of the noninverted, exchanged product, R18 of Figure 1 and k_E would be expected to be zero in contrast to our observed results. A major S_N2 component is also inconsistent with the internal return process evidenced in Figure 2. We cannot, however, rule out the possibility of some S_N2 contribution to these reactions. We also cannot exclude a contribution of a dehydration–rehydration process which would lead to equal values for k_E and k_{EI}. The low yield of dehydration products (no more than 3–5% at 10 half-lives) from 1-phenylpropanol and 1-phenylbutanol suggests, however, that the elimination of water from the alcohols, with subsequent readdition of water to the olefin, also does not play a major role in the exchange processes.

Our earlier study of the enantiomer-specific oxygen exchange reactions of natural abundance 1-phenylethanol in ^{18}O-enriched water led to the proposal of a general mechanism, shown in Scheme 3, for the racemization of optically active alcohols involving carbocation intermediates[1] in which **1a–1a*** and **1b**, analogs to the intimate and solvent-separated ion pairs, respectively, of solvolysis reactions can be described as ion–molecule pairs, **1a–1a***, and a randomly solvated carbocation, **1b**. For simplicity, the scheme includes only two waters of solvation; mechanistic conclusions are not varied by altering the number of waters of solvation.

This scheme is an expansion of that proposed by Grunwald, Heller, and Klein[6] in their classic study of the racemization of ^{18}O-enriched, optically active 1-phenylethanol to account for the fact that the rate of the loss of the ^{18}O isotope to the aqueous solvent was less than that of the loss of optical activity; i.e., $k_{tot\,ex}/k_{rac} = 0.82 \pm 0.04$. Our values for $k_{tot\,ex}/k_{rac}$ of 0.84 ± 0.05 and 0.83 ± 0.01 for studies of natural abundance phenylethanol in ^{18}O-enriched water and labeled alcohol in natural abundance water, respectively, are in good agreement with their results. The ability to evaluate the rates of oxygen exchange between water and each enantiomer permitted the expansion of Grunwald's mechanism to that of Scheme 3, which includes a process by which the waters within the solvation sphere change position with a rate constant of k_{is}. This process accounts for the observation of the internal return products seen in Figure 2 for all three phenylalkanols in which the departing water bonds, in some cases, to the intermediate carbocation from the opposite face. Although the original report on the enantiomer-specific oxygen exchange reactions of phenylethanol overestimated the size of the rate constant for this process, k_1,[1] the fact that a portion of the inversion product formed from ^{18}O-enriched phenylethanol contains ^{18}O confirms the contribution of a recombination reaction to the inversion process (Table 3, Figure 2). The similar and non-zero yield of inversion products containing the original oxygen, unexchanged oxygen of Figure 2, suggests that the recombination reaction between members of the initially formed carbocation–water pair contributes to the same small, 1–3%, but significant extent in the change in stereochemistry at the chiral carbon in the three 1-phenylalkanols. This internal return process is represented by reorganization of the solvation sphere in the ion–molecule pairs **1a–1a*** of the mechanism of Scheme 3; this reorganization could also result from rotation of the carbocation within the solvation sphere.

The mechanism of Scheme 3 can account for the variations in the enantiomer-specific oxygen exchange reactions of the 1-phenylalkanols by small variations in the motions of water within the solvation sphere relative to exchange with the bulk solvent. If bond formation is rapid, as measured by k_{-1}, and the rate at which the water molecules move within the solvation sphere, k_{is}, is comparable to their equilibration with the bulk solvent, k_s, one expects to observe some inverted, unexchanged product, $k_1 > 0$, and unequal portions of the enantiomeric products containing the oxygen isotope of the bulk solvent as seen in Figure 1a,b for phenylethanol and phenylpropanol. The behavior of both these alcohols (as previously concluded for phenylethanol[1]) is consistent with the mechanism of Scheme 3 under these conditions: $k_{-1} > k_{is} > k_s$. The departing water protects the front side from attack by bulk solvent: $k_E < k_{EI}$ for both phenylethanol and phenylpropanol. In contrast, our finding that $k_E \approx k_{EI}$ for phenylbutanol (Figure 1c and Tables 2 and 3) along with the observation that $k_1 > 0$ (Figure 2) suggests that the departing water equilibrates with the bulk solvent, k_s, more rapidly than the solvation sphere of **1a–1a*** reorganizes, k_{is}; $k_s > k_{-1} > k_{is}$.

Thibblin has recently compared the rate of solvolysis of (*R*)-1-phenyl-1-methoxyethane in acetonitrile–water mixtures with that for the loss of optical activity.[18] The fact that the rates were identical indicates that racemization of the ether occurs with ionization and that the partners of the intermediate α-methylbenzyl–methanol pair do not recombine in an internal return process such as that seen here in the racemization of all three phenylalkanols. He suggested that the difference between the solvolysis mechanisms of phenylethanol and the corresponding ether is that the inversion of the ion–molecule pair formed from the ether (the process similar to the conversion of **1a** to **1a*** in which the departing water of Scheme 3 is replaced by methanol) is slow, whereas the corresponding process for the intermediate formed from the alcohol is fast. The observed variations in the behavior of α-methylbenzyl carbocation–molecule pairs may arise from differences in the solvation of the two leaving groups, methanol and water.

Both the ion–molecule pairs, **1a–1a***, and the randomly solvated carbocation **1b** of Scheme 3 are themselves achiral. This mechanism cannot account for the observed oxygen exchange reactions in the epimerization of the 15-Me-E_2's in which $k_{tot\,ex}/k_{rac} > 1$ and $k_E > k_1$, as shown diagrammatically by the data in Figure 1d to contrast with the behavior of the phenyl alkanols: the rate of formation of the product resulting from exchange without inversion, R18, is more rapid than that of the exchanged, inverted product, S18. Asymmetric carbocations intermediates must be invoked to account for these latter results; the formal asymmetry of the prostaglandin-derived carbocation was postulated to arise from asymmetric solvation.[11] Our original hypothesis in undertaking the present kinetic studies of phenyl-

propanol and phenylbutanol was that increasing the bulk of the alkyl substituent at the chiral center of 1-phenylalkanols might lead to a similar asymmetric solvation of the carbocation intermediates from these alcohols. The increase in k_E relative to k_{EI}, observed here for phenylbutanol relative to phenylethanol, is consistent with increasing asymmetric solvation of the resultant carbocation in analogy to the behavior of the 15-Me-PGE_2's. In terms of the mechanism of Scheme 3, if the carbocation derived from 1-phenylbutanol is less symmetrically solvated than that from 1-phenylethanol, this asymmetry leads to the postulated more rapid equilibration of the departing water with the bulk solvent.; $k_s > k_{is}$. Recent results support the idea that the observed differences in the relative rates of the exchange reactions, k_E and k_{EI}, reflect the movement of waters within the solvation sphere. In the presence of anionic micelles, 0.1 M sodium docecyl sulfate (SDS), both 1-phenylethanol and 1-phenylbutanol appear to react through carbocations that are formally asymmetric in that $k_E > k_{EI}$;[24] the effect of SDS is much greater on phenylbutanol than on phenylethanol.

The small variation in the rate constants for the racemization of the three 1-phenylalkanols was surprising to us. The most accurate evaluation of the relative rates for the racemization process for these alcohols was obtained in the simultaneous experiments carried out in natural abundance water (Table 1, experiment 8) in which the same acid stock solution was used for each alcohol and the racemization reactions were carried out simultaneously. These data indicate that the rate constants for the racemization process itself, k_{rac}, vary with the alcohol: phenylethanol > phenylbutanol > phenylpropanol. One might expect the variations in the racemization rate constants with the alkyl substituent in the 1-phenylalkanols to be similar to those for S_N1 reactions of other secondary systems with the same variation in alkyl substitents. The rate constants for the S_N1 solvolysis of 2-propyl and 2-butyl tosylates and chlorides in ethanol, corrected for nucleophilic assistance, differ by 1 order of magnitude with the 2-butyl compounds reacting faster.[25] These data predict, in contrast to the observed behavior, that 1-(*R*)-phenylbutanol should racemize most rapidly of the three alkanols and react as much as 10 times more rapidly than 1-phenylpropanol. The small differences in the measured racemization rate constants reflect very small differences in $\Delta G^{\ddagger}$. The largest difference in k_{rac}, for phenylethanol and phenylpropanol (13.9×10^{-4} M^{-1} s^{-1} vs 7.60×10^{-4} M^{-1} s^{-1} at 65 °C), reflects a difference of only 0.4 kcal/mole in $\Delta G^{\ddagger}$, probably arising both from differences from stability of the carbocations and in solvation changes during the heterolysis reaction. In their calorimetric determination of the heats of formation of carbocations, Arnett and Pienta found a monotonic increase in ΔH_f for 2-methyl-2-alkyl carbocations with increasing length of the alkyl chain.[26] In SO_2ClF, however, a reversal in the order of ΔH_f for two members in this series was ascribed to solvation effects. Similar subtle solvation effects may determine the relative rates of racemization of the 1-phenylalkanols.

Few direct observations of internal return products of cation–molecule pair intermediates have been made. In all cases, the cation in the complex is either an aryl-stabilized or allylic carbocation. Such complexes include the phenylallyl carbocation–water pair proposed to account for the irreversible rearrangement of γ-phenylallyl alcohol,[10] nonrearranging tertiary allylic 15-methylprostaglandin E_2 carbocations–water pairs,[11] phenyl and 2,4,6-trimethylphenyl cation–nitrogen molecule pairs detected in dediazoniation reactions carried out in the presence of isotopically distinct N_2 at high pressure,[14,15] aryl-stabilized allyl carbocation–methanol pair in the rearrangement of (2′-methoxyisopropylidene)indan to give 1-(1-methoxy-1-methylethyl)-indene,[16] and α-substituted benzyl carbocation–water pairs from the 1-phenylalkanols of this study. McAdoo and Morton have recently pointed out that the importance of ion–molecule reactions in the gas phase increases with the dipole moment of the neutral to increase the attractive force between it and the ion.[19] It is not surprising, therefore, that the observed recombination products in solution, described above, from the cation–molecule pair intermediates have been found in reactions yielding a polar molecule such as methanol or water. The exception is the nonpolar but highly polarizable nitrogen molecule in the ion–molecule pair of dediazoniation reactions under high pressure.[14,15] Carbocation–water pairs, represented as **1a–1a*** in Scheme 3, may be participants in the racemization of other alcohols via nonresonance-stabilized carbocation intermediates but have not yet been detected.

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