β-Deuterium kinetic isotope effects for identity processes: bromide ion substitution at 1-bromo-1-arylethanes and 2-bromooctane

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While deuterium kinetic isotope effects for solvolyses have been extensively studied, other nucleophilic substitutions have received less attention, and identity processes, that is, substitutions where the nucleophile and leaving group are the same, have rarely been examined. Identity reactions must pass through a truly symmetrical stage, a transition state or an intermediate, so that data will be of interest to both theoretical and experimental chemists. Values of k_H/k_D have been determined by polarimetry for bromide exchange– racemization at $ArCHBrCH_3/CD_3$ (Ar = C_6H_5, 4-Br- and 4-Me-C_6H_4, and 3,4,-dimethyl-C_6H_3) in acetone, acetonitrile, and nitromethane. Observed values are analogous to values seen in solvolyses. They range from 1.01 to 1.35 and, in some cases, increase markedly as the concentration of Bu_4NBr decreases. Solvolyses are either first order or pseudo first order whereas plotting observed racemization rate versus [Bu_4NBr] allows separation of first- and second-order components; those species giving more stable carbocations in the more dipolar solvents, the systems showing k_H/k_D variation with Br^- concentration, alone show an appreciable first-order component. The second-order k_H/k_D ratio averages 1.062 ±–0.018 at temperatures ranging from 25 to 50°C for all substrates in the three solvents, very analogous to the values seen for racemization of 1,1,1-d_3-2-bromooctane or solvolysis of ethyl substrates but considerably lower than the typical solvolysis values of 1.15–1.25 for *secondary*, and 1.35–1.5 for *tertiary* substrates. The first-order k_H/k_D values obtained are higher, 1.1–1.5. These and other results are discussed.

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Les effets isotopiques cinétiques du deutérium sur les solvolyses ont fait l'objet de nombreuses études; toutefois, d'autres substitutions nucléophiles ont reçu beaucoup moins d'attention et les processus d'identité, les réactions de substitutions dans lesquelles le nucléophile et le nucléofuge sont les mêmes, ont rarement été examinés. Les réactions d'identité doivent nécessairement passer par une étape, un état de transition ou un intermédiaire, vraiment symétrique; ces données devraient donc présenter de l'intérêt pour les chimistes tant expérimentaux que théoriques. Faisant appel à la polarimétrie, on a déterminé les valeurs des k_H/k_D pour la réaction d'echange – racémisation des $ArCHBrCH_3/CD_3$ (Ar = C_6H_5, 4-Br-, 4-Me-C_6H_4 et 3,4-diméthyl-C_6H_3) dans l'acétone, l'acétonitrile et le nitrométhane. Les valeurs observées sont semblables à celles obtenues lors des solvolyses. Elles varient de 1,01 à 1,35 et, dans quelques cas, elles augmentent beaucoup avec une diminution de la concentration de Bu_4NBr. Les solvolyses sont soit du premier ordre ou du pseudo premier ordre alors que, dans notre cas, la courbe de la racémisation en fonction de la concentration de Bu_4NBr permet de séparer les composantes du premier et du deuxième ordre; seules les espèces conduisant à carbocations les plus stables dans les solvants les plus dipolaires, les systèmes présentant une variation du k_H/k_D en fonction de la concentration du Br^-, présentent une portion importante des réaction du premier ordre. Pour tous les substrats, dans les trois solvants, à des températures allant de 25 à 50°C, le valeur du rapport k_H/k_D des réactions du deuxième ordre rend une moyenne de 1,062 ± 0,018 et elles sont très semblables à celles observées lors de la racémisation du 1,1,1-d_3-2-bromoéthane ou de la solvolyse des substrats avec des groupes éthyles; elles sont toutefois beaucoup plus basses que les valeurs typiques de 1,15 à 1,25 ou 1,35 à 1,5 observées lors de solvolyses de substrats *secondaires* ou *tertiaires*. Les valeurs des k_H/k_D du premier ordre sont plus élevées (1,1–1,5). On discute de ces valeurs et d'autres résultats.

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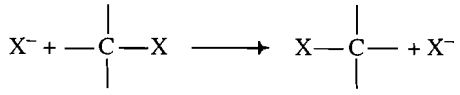
A continuing research interest of ours has been the ion-pair mechanism for nucleophilic substitutions, especially bimolecular substitutions at saturated carbon (1,2). As part of the mechanistic evidence, β-deuterium kinetic isotope effects were desired. The empirical β-deuterium isotope effects reported here are apparently the first measured for an "identity process," which, in the case of a nucleophilic substitution, Scheme 1,



SCHEME 1. An identity process.

requires that the nucleophile and the leaving group are identical species. Such processes can, in principle, be followed by either of two methods: by isotopic exchange using *radio* or stable isotopes of the nucleophile/leaving group if they are available, or by optical activity changes, racemization, if the substrate has a chiral centre at the site of substitution. Both approaches have been used.

Radio-tracer studies were an essential part of the early evidence for the S_N2 reaction mechanism first proposed by Hughes and Ingold. Hughes et al. (3) followed *radio*-iodide exchange with 2-iodooctane, and *radio*-bromide exchanges with 1-bromo-1-phenylethane and 2-bromopropanoic acid in the mid-1930s. Others have also used *radio* tracers to follow exchanges (4–9). We employed the electrodeposition of silver halide at a silver anode, a method developed and extensively used by Beronius (5), to follow *radio*-halide exchanges (6, 7).

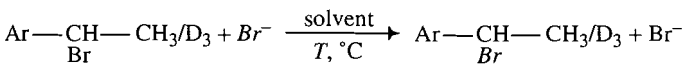
Racemization kinetics of chiral alkyl halides, together with halide exchanges, were used by Hughes to show that bimolecular nucleophilic substitutions are accompanied by inversion of stereochemistry (3). These studies were a major, if not *the* major, bulwark of the S_N2 mechanistic proposal. While isotopic exchange methods can, in principal, be used for any substrate, racemizations are limited to species that can show chirality, substrates such as those used in this study.

For the studies reported here, racemizations of chiral *protio* and *deutero* substrates were used. The principal system studied is indicated in Scheme 2. β-Deuterium kinetic isotope effects were determined in acetone, acetonitrile, and nitromethane over

TABLE 1. Observed inversion rate constants and apparent k_H/k_D for 1-phenyl-1-bromoethanes; 40°C, [Bu_4NBr] = 0.00500 M[a]

Solvent	Substrate	k_H[a] ($\times 10^{-3}$ L m^{-1} s^{-1})	k_H/k_D[b]
Acetone	4′-Bromo	9.521 ± 0.073	1.037 ± 0.010
	Unsubstituted	4.440 ± 0.055	1.046 ± 0.011
	4′-Methyl	9.905 ± 0.066	1.014 ± 0.009
	3′,4′-Dimethyl	11.43 ± 0.12	1.076 ± 0.011
Acetonitrile	4′-Bromo	9.634 ± 0.003	1.047 ± 0.009
	Unsubstituted	7.866 ± 0.009	1.066 ± 0.004
	4′-Methyl	25.809 ± 0.069	1.054 ± 0.024
	3′,4′-Dimethyl	40.502 ± 0.004	1.211 ± 0.008
Nitromethane	4′-Bromo	6.909 ± 0.003	1.059 ± 0.002
	Unsubstituted	6.455 ± 0.004	1.065 ± 0.006
	4′-Methyl[c]	40.218 ± 0.043	1.149 ± 0.023[c]
	3′,4′-Dimethyl	74.682 ± 0.068	1.172 ± 0.019

[a]In acetone, [Bu_4NBr] = 0.0200 M, T = 25.0°C.
[b]Average of 2–6 runs. Error limits are one standard deviation.
[c]Observed k_H/k_D at the concentration of Bu_4NBr indicated: 0.0200 M, 1.082 ± 0.021; 0.0100 M, 1.129 ± 0.003; 0.00500 M, 1.149 ± 0.006; 0.00100 M, 1.270 ± 0.012.



SCHEME 2. The identity process studied.

a range of temperatures and as a function of bromide ion concentration (as the tetrabutylammonium salt).

Results

The β-D_3-labelled 1-phenylethanols were made with *deutero*-methyl magnesium iodide and the corresponding benzaldehyde, where that was commercially available, or by metal hydride reduction of the β-*deutero*-acetophenone, which was either commercially available (acetophenone itself) or prepared by exchange using basic D_2O and a phase transfer agent (PTA). For such exchanges, the procedures of Starkes (11), modified as indicated, was used. Racemic alcohols with isotopic purities of 99.7–99.9% (by nmr) were obtained. These alcohols were converted to the corresponding $ArCHBrCH_3/D_3$ substrates used in these studies by procedures analogous to those already described (10, 12).

Racemizations with *protio* and *deutero* substrates, using the same batch of electrolyte solution, were alternated to minimize any effects due to variation in experimental conditions upon the measured isotope effects. Similarly, if one of the pair of unlabelled and labelled bromides had significantly greater optical activity than the other, it was diluted with racemic material to keep substrate concentrations approximately equal while using near full-scale deflections of the recorder at the same recorder and instrument settings. Two to seven runs were done at each temperature and ionic bromide concentration reported. Standard deviations within a run, from the weighted least-squares analysis of rotation versus time, were always considerably smaller than the differences between duplicate runs.

Second-order rate constants reported in this paper are for inversion (or substitution), that is, they are one half the observed racemization rate constants because substitution with inversion in an identity process results in the loss of two units of enantiomeric excess. First-order rate constants are those for racemization; there is no analogous factor of two here (16).

Actual, directly measured, rate constants and the calculated kinetic isotope effects are reported in Table 1 for 0.0200 M Bu_4NBr in acetone at 25°C and 0.00500 M Bu_4NBr in acetonitrile and nitromethane at 40°C.

Previous studies established that, in acetone, racemizations of all substrates examined are cleanly second order; a plot of observed racemization rate versus the concentration of added halide salt has a zero, or very near zero, intercept (7). The plot, however, is nonlinear because ion pairing of the bromide ion with its cation reduces the activity coefficient of the nucleophile as its concentration, a salt, is increased. The plot of rate versus the activity of the bromide ion was, thus, linear with a zero or very nearly zero intercept for all substrates. Consequently, deuterium kinetic isotope effect determinations were done at only a single concentration of tetrabutylammonium bromide in acetone.

In acetonitrile and nitromethane, in contrast to acetone, there is no evidence of ion pairing of the Bu_4NBr over the concentration ranges employed yet, especially those substrates giving more stable carbocations (i.e., 4′-methyl- and 3′,4′-dimethylphenyl-1-bromoethanes) show a marked dependence of the measured k_H/k_D upon the concentration of Bu_4NBr. Typical values for the methyl-substituted substrates in nitromethane are shown as a footnote to Table 1. A change in Bu_4NBr concentration from 0.02 to 0.001 M increases the observed isotope effect from 1.08 to 1.27! Even larger variations are seen for the 3′4′-dimethyl substrate in nitromethane, lower ones for these two substrates in acetonitrile.

As Fig. 1 clearly indicates, this apparent concentration dependence arises from mixed kinetics (1, 6). For such cases first- and second-order components of the reaction can be separated by plotting the observed rate versus the concentration of the nucleophile, or its salt. First- and second-order components were obtained by linear regression analysis of all data, Table 3 the activation parameters determined, Table 2, and used to recalculate the rate constants and kinetic isotope effects at 30.00°C included in Table 3. A comparison of the kinetic isotope effects in Tables 1 and 3 confirms the necessity of such a separation of the rate components. Note that, except for 4′-methyl and 3′,4′-dimethyl substrates in acetonitrile and nitromethane, the first-order component is very small, Table 3

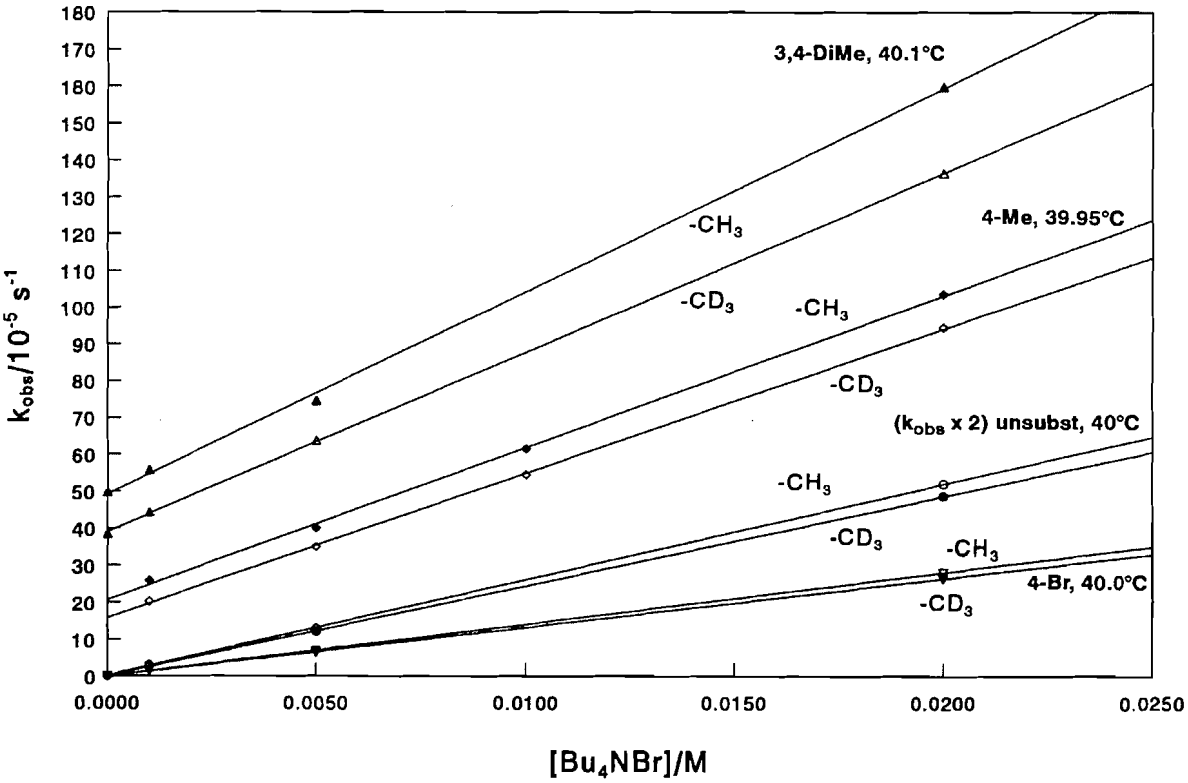


FIG. 1. Observed rate of racemization versus [Bu_4NBr]; separation of unimolecular (intercept) and bimolecular (slope) contributions in CH_3NO_2 at 40°C.

Uncertainties in these small rate constants are relatively large and the corresponding k_H/k_D is even more uncertain. Obviously, care must be exercised in attaching significance to such results.

For comparison, β-deuterium kinetic isotope effects for an identity process at a non-benzylic secondary carbon were desired. Chiral 1,1,1-d_3-2-bromooctane, and its *protio* analog, were prepared. In acetonitrile, a linear plot, with a zero intercept, for observed rate of racemization versus concentration of bromide ion was obtained so that a single Bu_4NBr concentration, 0.02500 M, was used for isotope effect measurements. Racemizations have, to date, only been done in acetonitrile at 60°C, giving $k_H = (5.923 \pm 0.040) \times 10^{-4}$ L mol^{-1} s^{-1} and $k_H/k_D = 1.084 \pm 0.006$.

Discussion

Deuterium kinetic isotope effects have commonly been determined and were the basis for much mechanistic discussion over the years. β-Deuterium effects are generally rather small secondary effects because the isotopically substituted atom is not directly involved in reaction progress. For the hydrolysis of *tert*-butyl chloride, presumedly a reaction through a carbocation, Robertson and co-workers (13) obtained an isotope effect of 2.387, or 1.101 per D. In our case, with three deuteriums, values of $(1.10)^3$ or 1.34 might be expected if the reactions were unimolecular. Such normal effects are usually attributed to hyperconjugative overlap of the C—H (or C—D) bond orbital with the empty, or electron deficient, developing *p*-orbital on the carbon undergoing the substitution. As such, the amount of overlap should reflect the degree of charge on the central carbon at the transition state. Isotope effects for reactions through a carbocation thus are larger than those following a concerted substitution, that is, the bimolecular mechanism. Consequently, the value of 1.34 per CD_3 group would represent a near-maximum value for substitution.

Shiner and Humphrey have confirmed that there is also an inductive effect, by using bridgehead deuteration where hyperconjugation is prohibited by stereochemistry. Inductive effects lead to smaller, inverse, effects, in Shiner's case about 0.986 per D (14). Of course, for a methyl group adjacent to the carbon undergoing substitution, only one of the C—D bonds can be appropriately orientated for hyperconjugation; the other two deuteriums on the methyl carbon exert inductive effects. Thus the measured k_H/k_D is the product of the normal hyperconjugative and inverse inductive contributions.

Almost all, or at the very least the vast majority, of k_H/k_D measurements for nucleophilic substitutions have been for solvolysis reactions. In fact, we have been unsuccessful in finding any reports of β-deuterium kinetic isotope effect measurements for identity processes. Unfortunately, in solvolysis, all reactions are kinetically first order, whether they are in fact first or actually pseudo first order. If first- and second-order processes are in competition and there is no way to determine the individual contributions, interpretation of the results is bound to be fraught with difficulty! Conversely, the lack of deuterium isotope effect data for identity processes, and the individual first- and second-order components for systems other than those reported here for the 1-phenylethyl system, makes interpretation of our results more difficult.

In fact the only published β-deuterium effects for identity processes have been obtained through force field calculations by McKenna et al. (15). Some of his results, those for the reaction RBr + Br^-, are presented in Table 4 along with the hydrolysis data of Robertson quoted in the paper. To facilitate comparison, both the calculated and measured effects are con-

TABLE 2. Activation parameters for uni- and bimolecular components of racemization of 1-phenyl-1-bromoethanes

Solvent	Substrate	Bimolecular racemization		Unimolecular racemization	
		$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J deg^{-1} mol^{-1})	$\Delta H^{\ddagger}$ (kJ mol^{-1})	$\Delta S^{\ddagger}$ (J deg^{-1} mol^{-1})
Acetone	4′-Bromo, *protio*	69.49 ± 0.30	−50.6 ± 1.0		
	deutero	69.36 ± 0.33	−51.3 ± 1.1		
	Unsubstituted, *protio*	69.42 ± 0.41	−57.1 ± 1.3		
	deutero	69.55 ± 0.28	−57.08 ± 0.90		
	4′-Methyl, *protio*	65.60 ± 0.25	−63.28 ± 0.83		
	deutero	66.23 ± 0.23	−61.30 ± 0.77		
	3′,4′-DiMe, *protio*	64.36 ± 0.43	−66.3 ± 1.4		
	deutero	66.06 ± 0.41	−61.2 ± 1.5		
Acetonitrile	4′-Bromo, *protio*	71.93 ± 0.12	−54.26 ± 0.37	90.0 ± 29.0	−74.0 ± 91.0
	deutero	71.67 ± 0.14	−55.58 ± 0.45	105.0 ± 19.0	−24.0 ± 61.0
	Unsubstituted, *protio*	70.73 ± 0.39	−60.0 ± 1.3	106.0 ± 27.0	−20.0 ± 88.0
	deutero	70.41 ± 0.17	−61.46 ± 0.55	118.0 ± 29.0	14.0 ± 93.0
	4′-Methyl, *protio*	64.7 ± 1.7	−69.9 ± 5.6	80.8 ± 3.7	−71.0 ± 12.0
	deutero	65.79 ± 0.39	−66.9 ± 1.2	80.4 ± 2.6	−73.0 ± 8.4
	3′,4′-DiMe, *protio*	64.8 ± 2.6	−67.5 ± 8.4	77.9 ± 4.4	−71.0 ± 14.0
	deutero	67.2 ± 2.2	−60.1 ± 7.2	60.2 ± 1.2	−132.8 ± 4.0
Nitromethane	4′-Bromo, *protio*	70.59 ± 0.06	−61.14 ± 0.19	0.5 ± 12.0	−365.0 ± 38.0
	deutero	70.6 ± 1.4	−61.6 ± 4.3	12.9 ± 3.0	−328.2 ± 9.4
	Unsubstituted, *protio*	68.6 ± 1.3	−68.3 ± 4.1	92.0 ± 29.0	−61.0 ± 92.0
	deutero	68.6 ± 1.3	−68.9 ± 4.3	106.0 ± 34.0	−18.0 ± 108.0
	4′-Methyl, *protio*	62.52 ± 0.58	−78.1 ± 1.9	82.1 ± 2.8	−52.9 ± 8.8
	deutero	64.3 ± 1.1	−72.9 ± 3.4	80.7 ± 2.1	−60.3 ± 6.9
	3′,4′-DiMe, *protio*	64.62 ± 0.81	−68.6 ± 2.6	69.5 ± 4.7	−87.0 ± 15.0
	deutero	65.09 ± 0.76	−68.2 ± 2.5	75.4 ± 2.9	−69.8 ± 9.4

verted to the contribution for d_3 that is for one CD_3 group. McKenna's and Robertson's data (15) are somewhat more consistent with the values reported in Table 1 than with those in Table 3. Thus, in the more dipolar acetonitrile and nitromethane solutions, 4′-methyl- and 3′4′-dimethylphenyl-1-bromoethanes follow mixed kinetics with observed net isotope effects similar to an "ordinary" secondary substrate, isopropyl bromide, in the even more ionizing media, water. Does that imply that the latter reaction also has mixed kinetics?

Solvolyses data abound in the literature. A cross section of typical results is tabulated in Table 5 for comparison with the results reported in this paper. These studies are grouped according to the type of system studied. On a per CD_3 basis, for aqueous and mixed aqueous solvents, primary substrates show k_H/k_D values similar to those for the second-order component of the identity reaction reported here, that is about 1.03–1.04. Secondary substrates, that is isopropyl, 1-arylethyl, and other substrates, give hydrolysis isotope effects of about 1.15–1.26, more in line with those substrates showing mixed kinetics prior to separation of first- and second-order components as reported in Table 1. The effects reported for hydrolysis of *tert*-butylsubstrates, about 1.35 per CD_3, are more comparable to the unimolecular components of this study.

For racemizations of 2-bromooctane and 1,1,1-d_3-2-bromooctane in acetonitrile, a plot of observed rate versus nucleophile concentration is linear with a zero intercept. This identity process is cleanly second order. At 60°C, $k_H = (5.923 \pm 0.040) \times 10^{-4}$ L mol^{-1} s^{-1} and $k_H/k_D = 1.084 \pm 0.006$, which is not far from the average second-order component value for all the 1-phenyl-1-bromoethanes in acetonitrile as reported in Table 3, 1.065 ± 0.031 for the recalculated values at 30°C or 1.062 ± 0.012 for the actual values at various temperatures (25–50°C).

If the current results for identity processes give representatives values for "pure bimolecular" and "pure unimolecular" nucleophilic displacements at secondary carbon, then it appears that ethyl substrates alone hydrolyse by bimolecular substitution, *tertiary* substrates by unimolecular, and *secondary* substrates such as isopropyl and phenylethyl follow mixed kinetics apparently with a large first-order component. A number of the authors whose data are presented in Table 5 have reached conclusions that are not at variance with these observations.

For the phenylethyl substrates in the presence of the base lutidine, we have shown that the loss of optical activity could contain nucleophilic substitution and elimination components (6). Elimination, even in the presence of added base, was a relatively small component of the process except for 4-methyl and 3,4-dimethyl substrates at the lower Bu_4NBr concentrations especially in nitromethane. Except for an apparent solvent effect, the elimination rate was independent of lutidine concentration. Without added base, no elimination, as seen by increase in bromide concentration, was observed for any of the substrates in any of the solvents examined. Nor was the elimination rate with added lutidine affected by the initial bromide ion concentration. Thus, no second-order elimination component was detected. However, a first-order elimination–readdition process could contribute to the first-order isotope effect component reported in this paper. While deprotonation of the carbocation intermediate would, presumedly, show a primary kinetic isotope effect, that deprotonation is occurring *after* the transition state for the overall process and should contribute comparatively little to the observed isotope effects.

As is possible for our first-order component, part of the solvolytic isotope effect reported for some of the compounds in Table 5 is likely due to the much larger primary isotope effect associated with elimination rather than with substitution processes. The Sridharan and Vitullo (20) and the Humski, Sendi

TABLE 3. Uni- and bimolecular rate constants and deuterium kinetic isotope effects for racemization of 1-phenyl-1-bromoethanes[a]

Solvent	Substrate and temperature (°C)	Unimolecular		Bimolecular	
		k_H ($\times 10^{-5}$ s^{-1})	k_H/k_D	k_H, ($\times 10^{-3}$ L m^{-1} s^{-1})	k_H/k_D
Acetone	4′-Bromo, 32.5	—	—	19.326 ± 0.0011	1.037 ± 0.006
	25.0	—	—	9.5571 ± 0.0009	1.037 ± 0.010
	20.0	—	—	5.7803 ± 0.0003	1.035 ± 0.008
	Recalculated at 30[b]	—	—	15.341	1.037
	Unsubstituted, 40.0	—	—	17.880 ± 0.020	1.036 ± 0.019
	32.5	—	—	9.178 ± 0.008	1.066 ± 0.006
	25.0	—	—	4.4398 ± 0.0055	1.046 ± 0.011
	Recalculated at 30[b]	—	—	7.194	1.052
	4′-Methyl, 32.55	—	—	19.5481 ± 0.0015	1.012 ± 0.008
	25.0	—	—	9.9421 ± 0.0009	1.014 ± 0.009
	15.2	—	—	2.8906 ± 0.0003	1.027 ± 0.009
	Recalculated at 30[b]	—	—	15.551	1.013
	3′,4′-DiMe, 32.6	—	—	22.2665 ± 0.0017	1.059 ± 0.022
	25.0	—	—	11.3099 ± 0.0015	1.076 ± 0.011
	14.95	—	—	4.4411 ± 0.0006	1.103 ± 0.011
	Recalculated at 30[b]	—	—	17.730	1.064
Acetonitrile	4′-Bromo, 50.0	0.268 ± 0.071	—	23.261 ± 0.029	1.062 ± 0.003
	40.0	0.048 ± 0.021	—	9.611 ± 0.009	1.058 ± 0.002
	30.0	0.027 ± 0.032	—	3.731 ± 0.013	1.055 ± 0.004
	Recalculated at 30[b]	0.022[a]	0.733[a]	3.734	1.055
	Unsubstituted, 50.0	0.37 ± 0.10	1.60 ± 0.54	18.354 ± 0.044	1.063 ± 0.002
	40.0	0.183± 0.057	1.79 ± 0.84	7.608 ± 0.026	1.054 ± 0.004
	30.0	0.026 ± 0.014	2.2 ± 1.8	3.031 ± 0.006	1.054 ± 0.006
	Recalculated at 30[b]	0.031[a]	2.07[a]	3.023	1.053
	4′-Methyl, 50.0	12.2 ± 1.6	1.17 ± 0.17	51.68 ± 0.64	1.036 ± 0.013
	40.0	4.18 ± 0.99	1.02 ± 0.20	24.10 ± 0.43	1.099 ± 0.020
	30.0	1.57 ± 0.31	1.15 ± 0.20	9.91 ± 0.14	1.066 ± 0.013
	Recalculated at 30[b]	1.531	1.105	10.029	1.081
	3′,4′-DiMe, 40.0	12.6 ± 1.3	1.84 ± 0.43	30.30 ± 0.55	1.038 ± 0.029
	30.0	4.85 ± 0.44	1.42 ± 0.18	12.43 ± 0.20	1.064 ± 0.018
	25.0	2.62 ± 0.34	1.29 ± 0.13	8.32 ± 0.14	1.089 ± 0.017
	Recalculated at 30[b]	4.619	1.486	12.779	1.069
Nitromethane	4′-Bromo, 50.0	0.05 ± 0.13	—	16.742 ± 0.054	1.058 ± 0.003
	40.0	0.04 ± 0.20	—	7.020 ± 0.085	1.060 ± 0.010
	30.0	0.047 ± 0.028	—	2.775 ± 0.012	1.058 ± 0.004
	Recalculated at 30[b]	0.043[a]	1.593[a]	2.776	1.059
	Unsubstituted, 50.0	0.810 ± 0.069	1.07 ± 0.17	14.659 ± 0.031	1.067 ± 0.004
	40.0	0.14 ± 0.11	1.4 ± 1.3	6.461 ± 0.049	1.065 ± 0.007
	30.0	0.079 ± 0.014	1.52 ± 0.46	2.553 ± 0.007	1.066 ± 0.003
	Recalculated at 30[b]	0.065[a]	1.585[a]	2.576	1.066
	4′-Methyl, 49.95	61.5 ± 1.8	1.392 ± 0.042	43.36 ± 0.73	1.026 ± 0.016
	40.0	21.49 ± 0.87	1.350 ± 0.059	19.96 ± 0.33	1.011 ± 0.016
	29.95	7.74 ± 0.09	1.341 ± 0.038	8.82 ± 0.04	1.069 ± 0.008
	Recalculated at 30[b]	7.639	1.336	8.823	1.057
	3′,4′-DiMe, 40.1	47.8 ± 1.1	1.227 ± 0.034	28.31 ± 0.46	1.138 ± 0.021
	32.5	22.2 ± 1.2	1.142 ± 0.057	15.11 ± 0.41	1.144 ± 0.033
	25.0	11.75 ± 0.38	1.373 ± 0.044	7.67 ± 0.19	1.148 ± 0.027
	Recalculated at 30[b]	18.50	1.267	12.04	1.145

[a]The unimolecular component for these reactions was very small; uncertainties in the rate constants and the isotope effects are thus comparatively large.
[b]Recalculated values were obtained using the thermodynamic activation parameters reported in Table 2.

jarevevic, and Shiner (21) results make that most obvious. Unfortunately, the current study is the only one that allowed separation of uni- and bimolecular components — solvolyses and, under solvolysis conditions, also competing eliminations are first or pseudo first order.

Unfortunately, substituent, solvent, and temperature effects on the isotope effects are largely masked because the imperfect reproducibility of the kinetic data and the manipulation required to separate the first- and second-order components result in quite large standard deviations. Other approaches such as the differential methods (31), while they might improve the precision in measuring the observed k_H/k_D, would not allow separation of the first- and second-order components of the racemization. Consequently, any detailed discussion of identity kinetic isotope effects should await completion of the much more extensive study currently in progress.

However, it is apparent that the contribution of a β-CH_3/CD_3 in a bimolecular nucleophilic substitution is very nearly the same whether the reaction is hydrolysis of a primary substrate or bromide exchange at an aryl-substituted, or other secondary,

TABLE 4. β-Deuterium isotope effects predicted from force field calculations;[a] RBR + Br^-

R	Predicted	k_H/k_D hydrolysis[b]
Ethyl β-d_3	1.039	1.033
Propyl β-d_2	1.004 (d_3, 1.006)	1.054 (d_3, 1.082)
Isopropyl β-d_6	1.237 (d_3, 1.112)	1.366 (d_3, 1.169)
tert-Butyl β-d_9	1.508 (d_3, 1.147)	3.387 (d_3, 1.336)

[a]Reference 15.
[b]Results of R.E. Robertson, as quoted by McKenna for the corresponding hydrolysis.

centre. Solvolyses at secondary (and tertiary) centres give larger β-D_3 k_H/k_D effects, likely because the reactions are mixtures of substitution and elimination processes, either or both of which can have uni- and (or) bimolecular components.

Experimental

All solvents used for kinetics were HPLC or reagent grade, dried by final distillation from calcium hydride under nitrogen, which was dried with a train of concentrated H_2SO_4 and molecular sieves. Commercial anhydrous ether was used for Grignard reactions. Tetrahydrofuran (THF) was dried by shaking and storing over KOH, followed by refluxing over, then distillation from, $LiAlH_4$, again under dried nitrogen. The polarimeter cell was oven dried at about 60°C, other glassware used for the kinetics, at 125°C. Kinetics solutions were prepared, and all transfers made, in a nitrogen-flushed glove box.

Kinetics of racemization were followed with a Perkin Elmer model 141MC polarimeter fitted with a retransmitting potentiometer and a recorder. Actual rotations due to the solutions were not recorded; the rate of change alone was required. Temperature control was better than ±0.05° with a thermostated circulating constant temperature bath and a jacketed 10-cm quartz polarimeter cell. Times and rotations, as voltages, were read from the recorder trace and processed using standard weighted linear regression analysis. Generally 3–5 half-lives were used except for those cases with a significant first-order component, where the reaction accelerated with time due to increasing bromide ion concentration as competing elimination occurred (1, 6). Initial slopes from, generally, about a single half-life were used for such runs. Error limits, where reported, are one standard deviation. Standard deviations of one part in 5 000–40 000 were normal for individual kinetic runs and agreement between duplicate runs was generally better than one percent. For each solvent, at each temperature and nucleophile concentration, two to seven runs were averaged.

Preparation of substrates

Achiral alcohols and esters

Protio. Except for 1-phenylethanol, which was commercially avail-

TABLE 5. Representative β-deuterium kinetic isotope effects for solvolyses

Alkyl	Leaving group	Solvent	k_H/k_D (per CD_3)	References
Primary				
Ethyl	Br	H_2O	1.033	23
	I	H_2O	1.037	
	OTos	H_2O	1.018	
	$MeSO_3$	H_2O	1.027	
	OTf	HOAc	1.11	24
		TFE	1.09	
Secondary				
2-Propyl	Br	H_2O	1.148	23
	I	H_2O	1.146	
	OTos	H_2O	1.245	
	$MeSO_3$	H_2O	1.243	
	OBros	TFA	1.169	25
	$NaphSO_3$	EtOH to 97% F_6*i*PrOH	1.10–1.49	27
(2-Ad)Me	Cl	TFE	1.48	29
1-(1-Ad)Et	OBros	70–97% TFE	1.151	18
		79% EtOH	1.256	
	Me_5PhSO_3	90% F_6*i*PrOH	1.135	18
1-(1-Ar)Ethyl[a]	Cl, Br	Various aqueous	1.212 ± 0.011	25
Tertiary				
tert-Butyl	Cl	Various aqueous	1.35 ± 0.02	13, 23, 26
	$NaphSO_3$	EtOH	1.10	27
		TFE	1.33	
		97% HFIP	1.49	
2-(2-Bz)Pr	Cl	MeOH	1.30	22
2-(2-(*p*-FPh))Pr	Cl	60% EtOH	1.21	26
2-(2-CN)Pr	OTf	TFE	1.48	28
2-(2-CF_3)Pr	OTf	Various	~1.78	19
1-(1,1-Ph_2)Ethyl	Cl	MeOH/MeCN	0.84–0.96	17[b]
1-(1-Ph-1-CF_3)Ethyl	OTos	TFA to 80% EtOH	1.63–2.110	30

[a]Ar = *p*-Me, *p*-F, *p*-NO_2, *p*-PhO, *m*-Br, and unsubstituted phenyl in aqueous EtOH, acetone.
[b]Value quoted is for methanolysis; elimination gave 2.2–3.2 for a combined k_H/k_D of 1.81–1.58 with 1.96–9.09 vol% MeOH.

TABLE 6. Observed optical rotations[a] and boiling points[b]

Substrate	bp, °C/Torr	CH_3, at nm			CD_3, at nm		
		365	435	579	365	435	579
4′-Bromophenylethanol	118/5.0	25.70	15.09	7.31	25.90	15.15	7.28
4′-Bromophenylbromoethane	104/2.6	−43.5	−23.0	−10.2	−45.4	−24.0	−10.7
Phenylethanol	85.5/~8	14.23	8.84	4.47	13.13	8.19	4.18
Phenylbromoethane	73/5.3	−41.7	−22.0	−9.68	−52.4	−27.6	−22.2
4′-Methylphenylethanol	93/5.4	13.5	7.98	4.05	14.04	8.56	4.25
4′-Methylphenylbromoethane	83/3.9	−7.70	−3.98	−1.72	−20.3	−10.6	−4.35
3′,4′-Dimethylphenylethanol	85/1.4	12.76	7.38	3.91	13.76	8.45	4.24
3′,4′-Dimethylphenylbromoethane	85/1.6	4.65	2.40	1.01	1.63	0.82	0.34
2-Octanol	70/~6	−2.04	−1.36	−0.72	−1.93	−1.28	−0.63
2-Bromooctane	49/3.2	12.22	7.70	3.94	11.48	7.22	3.30

[a]Measured rotation for 1.00 cm of neat liquid at 25°C at the wavelength indicated for the material from the (+)-1-amino-1-phenylethane salt of the corresponding biphthalate.
[b]Boiling points for the *protio* material; those for the *deutero* materials were almost identical.

able (Aldrich), these were made, under dry nitrogen, from the corresponding ketone (Aldrich) by reduction, at reflux for several hours in THF, with 1.05 equivalents of $LiAlH_4$. The alcohol was not isolated. Phthalic anhydride (Fisher), which had been recrystallized from chloroform, 1.02 equivalents, was added to the cooled solution and reflux, with magnetic stirring, was continued overnight. The solution was concentrated and taken up in ether and ice-cold, approximately 2 M, HCl. The ethereal layer was washed 2–4 times with cold aqueous acid, water, and saturated brine. The ethereal solution was concentrated on a rotovac and the biphthalate allowed to crystallize. If desired, the half-ester was recrystallized from heptane but, generally, it was resolved directly.

1-Phenylethanol was converted to the lithium salt by refluxing with 1.1 equivalents of LiH in THF, phthalic anhydride was added, and the solution subsequently treated analogously.

Deutero. D_3-Acetophenone, which is commercially available (Aldrich), was treated analogously to the *protio* ketones.

To 4-bromobenzaldehyde (Aldrich), *p*-tolualdehyde (Anachemia), or heptanal (Aldrich) in anhydrous ether, 1.01 equivalents of CD_3MgI in ether (Aldrich) was added over 30 min at ice temperatures. The solution was refluxed for several hours and the acidified, washed several times with cold dilute acid, water, dilute Na_2CO_3 solution, and saturated brine. After drying over K_2CO_3, the ether was removed and the alcohol vacuum distilled: β-D_3-4′-bromophenylethanol, bp 100–102°C/2.0 Torr (1 Torr = 133.3 Pa); 4′-methylphenylethanol, bp 93–93.5°C/5.4 Torr; 2-octanol, bp 84–86°C/14.5 Torr. No, or at most a minute amount of, CD_2H group was detectable in the nmr. Yields were greater than 90%, and isotopic purities, as measured by nmr, were 99.7% or greater.

The β-D_3-alcohols were converted to their lithium salts by refluxing with 1.1 equivalents of LiH in THF and the biphthalate ester was prepared as for the *protio* equivalent above.

β-D_3-3′,4′-Dimethylacetophenone was made from the corresponding *protio* material by exchange (11). Under dry nitrogen, 25.0 g of 3′,4′-dimethylacetophenone and 1.95 g of tricaprylmethylammonium chloride was stirred at 30°C for about 30 min with four 15-mL batches of D_2O (99.95%) approximately 1.5 M in NaOD (Aldrich). After standing briefly to permit phase separation, each of the aqueous phases was removed from the pear-shaped flask by pipet. After exchange, three washes of the organic phase with 5-mL portions of D_2O saturated in KCl for anion exchange,[1] were followed by vacuum distillation of the product, bp 79–81.5°/1.6 Torr, 91.5%, greater than 99.7% CD_3 by nmr. The biphthalate ester was prepared, using LiH, as described above.

Optical resolutions

Using (+)- and (−)-1-amino-1-phenylethanes (Eastman), procedures analogous to those already described were used for both *protio* and *deutero* substrates (10). Ether was used as solvent for all but the 4′-bromo material, where acetone was used. With the *deutero* material, when difficulty was experienced in obtaining diastereomeric salt crystals in the resolutions, a small-scale sample was seeded with *protio* salt crystals and the resulting crystals used as seeds to initiate crystallization for the full-scale resolution. Combined yields of the two diastereomeric salts were greater than 80%, generally over 90%, based upon starting alcohol or ketone. The resolved materials were stored as the salts until required for kinetics.

Preparation of chiral bromides

Chiral alcohols were recovered from their diastereomeric salts by partition between ice-cold aqueous hydrochloric acid and ether, followed by base-catalyzed hydrolysis of the biphthalate esters as previously described (10).

Except for 3′,4′-dimethylphenyl-1-bromoethane, which was prepared using gaseous HBr in benzene as previously described (10), all of the chiral alcohols were converted to the bromides with diphos and bromine (12). (The dimethyl alcohol gave almost totally racemic product with the diphos procedure.) The clear, colourless bromides very slowly racemize and discolour even in the freezer, where they were stored between kinetic runs at −12°C. The 4′-methyl- and 3′,4′-dimethylphenyl-1-bromoethanes were prepared freshly every 7–10 days; the others, while much more stable, were prepared every 3 or 4 weeks.

Measured optical rotations for neat alcohol, and the resulting bromide, from the (+)-1-amino-1-phenylethane salt of the corresponding biphthalate, are reported in Table 6 together with the appropriate boiling points. All nmr and ir spectra were as expected. No OH was present in the ir of the bromides and the CD_2H signal in the nmr was, at most, barely detectable by nmr, generally representing >99.7% isotopic purity.

Kinetics of racemization

Bu_4NBr (Eastman) was dried at ~1 Torr and 50–60°C for 5–6 h and

[1]In initial runs, 3,4-dimethylacetophenone, about 87.5% CD_3-, 12.5% CD_2H-, as determined by nmr, was obtained whereas, based upon the amount of deuterium to hydrogen in the exchange cycles, the product should have been about 99.8% isotopically pure. The composition was essentially unchanged by recycling the substrate with fresh batches of D_2O and PTA. The counterion was no longer chloride, but rather deuteroxide, and heating for vacuum distillation caused Hoffman elimination of HOD from the tricaprylmethylammonium deuteroxide. Under the basic conditions, the HOD back-exchanges with the acetophenone to equilibrium. The ratio of D_2- to D_3-acetophenone was, in fact, almost exactly that expected after such equilibrium back-exchange. Anion exchange by washing the product several times with D_2O saturated in KCl before vacuum distillation solved the problem.

weighed and transferred in the glove box. Stock solutions, usually 0.0200 or 0.0500 M in electrolyte, were made, sealed in hypo vials with Teflon-lined caps, and diluted as required. Such stock solutions gave reproducible results for several months but were generally prepared freshly every few weeks. Diluted solutions were stored in volumetrics with glass stoppers and freshly prepared daily or, when the reactions were especially slow, after each pair of *protio* and *deutero* runs.

In the glove box, 25 mL of the diluted Bu_4NBr solution was prepared, 5.0 mL was pipetted into the polarimeter cell, and a weighted amount of chiral substrate added by syringe. The amount of substrate used was determined by the rotation of the resultant solution. A rotation of 0.4° gives near full-scale deflection on the recorder at moderate amplification. When rotations of a pair of substrates differed markedly, racemic material was added to the more active substrate so that similar total concentrations for the *protio* and *deutero* materials were used. The Teflon stoppers were inserted, the cell transferred to the circulating, constant temperature bath, and the contents of the cell thoroughly mixed while equilibrating to the pre-set temperature before the cell was inserted into the Perkin Elmer model 141MC polarimeter. Time was measured from the recorder trace, zero being when the pen crossed a dark time line. Runs with *protio* and *deutero* substrates, using the same solutions, were alternated.

About 60 data pairs of rotations, as recorder pen displacements or voltages, and times were read from the recorder chart and treated with standard weighted linear regression analysis routines. Half-lives ranged from about 12 min to several days. A linear regression of observed rate of racemization versus concentration of Bu_4NBr gave the first-order rate constant as the intercept, the second-order constant as the slope.

1. A.R. Stein. Can. J. Chem. **67**, 297 (1989).
2. D.J. McLennan, A.R. Stein, and B. Dobson. Can. J. Chem. **64**, 1201 (1986).
3. E.D. Hughes, F. Juliusburger, S. Masterman, B. Topley, and J. Weiss. J. Chem. Soc. 1525 (1935); E.D. Hughes, F. Juliusburger, A.D. Scott, B. Topley, and J. Weiss. J. Chem. Soc. 1173 (1936); W.A. Cowdrey, E.D. Hughes, T.P. Nevell, and C.L. Wilson. J. Chem. Soc. 209 (1938).
4. A. Ceccon, I. Papa, and A. Fara. J. Am. Chem. Soc. **88**, 4643 (1966).
5. P. Beronius. K. Tek. Hoegsk. Handl. no. 213 (1963); P. Beronius and R.P. Gupta. Acta Chem. Scand. Ser. A: **A30**, 477 (1976).
6. A.R. Stein. Can. J. Chem. **65**, 363 (1987); Tetrahedron Lett. 4145 (1974).
7. A.R. Stein and E. A. Moffatt. Can. J. Chem. **63**, 3433 (1985).
8. H.L. Goering and R.P. Anderson. J. Am. Chem. Soc. **100**, 6469 (1978).
9. M. Fujio, F. Sanematsu, Y. Tsuno, M. Sawada, and Y. Takai. Tetrahedron Lett. 93 (1988).
10. A.R. Stein, R.D. Dawe, and J.R. Sweet. Can J. Chem. **63**, 3442 (1985).
11. C.M. Starkes. J. Am. Chem. Soc. **93**, 195 (1971).
12. S.P. Schmidt and D.W. Brooks. Tetrahedron Lett. 767 (1987).
13. L. Hakka, A. Queen, and R.E. Robertson. J. Am. Chem. Soc. **87**, 161 (1965).
14. V.J. Shiner and J.S. Humphrey. J. Am. Chem. Soc. **85**, 2416 (1963).
15. J. McKenna, L.B. Sims, and I.H. Williams. J. Am. Chem. Soc. **103**, 268 (1981).
16. A.R. Stein. J. Org. Chem. **41**, 519 (1976).
17. A. Thibblin and H. Sidhu. J. Am. Chem. Soc. **114**, 7403 (1992).
18. V.J. Shiner, T.E. Neumann, and R.D. Fisher. J. Am. Chem. Soc. **104**, 354 (1982).
19. M.P. Jansen, K.M. Koshy, N.N. Mangru, and T.T. Tidwell. J. Am. Chem. Soc. **103**, 3863 (1981).
20. S. Sridharan and V.P. Vitullo. J. Am. Chem. Soc. **99**, 8093 (1977).
21. K. Humski, V. Sendijarevevic, and V.J. Shiner, Jr. J. Am. Chem. Soc. **95**, 7722 (1973).
22. A. Thibblin. J. Am. Chem. Soc. **111**, 5412 (1989).
23. K.T. Leffek, J.A. Llewellyn, and R.E. Robertson. Can. J. Chem. **38**, 2171 (1960).
24. A. Streitwieser, Jr., C.L. Wilkins, and E. Kiehlmann. J. Am. Chem. Soc. **90**, 1598 (1968); Tetrahedron Lett. 3159 (1970).
25. V.J. Shiner, Jr., W.E. Buddenhaum, B.L. Murr, and G. Lamty. J. Am. Chem. Soc. **90**, 418 (1968).
26. V.J. Shiner, Jr. ACS Monogr. **167**, 90 (1970).
27. H. Yamataka, S. Tamura, T. Hanafusa, and T. Ando. J. Am. Chem. Soc. **107**, 5429 (1985).
28. P.G. Gassman and J.T. Talley. J. Am. Chem. Soc. **102**, 1214 (1980).
29. D.E. Sunoko, I. Szele, and W.J. Hehre. J. Am. Chem. Soc. **99**, 5000 (1977).
30. A.D. Allen, M.P. Jansen, K.M. Koshy, N.N. Mangru, and T.T. Tidwell. J. Am. Chem. Soc. **104**, 207 (1982).
31. M. Tencer and A.R. Stein. Can. J. Chem. **56**, 2994 (1978); G. Bergson, O. Matsson, and S. Sjoberg. Chem. Scr. **11**, 25 (1977).