

# Kinetic and Equilibrium Chlorine Isotope Effects in the Cyclization of 2-Chloroethanol in Protic Solvents

Thomas H. Cromartie<sup>1</sup> and C. Gardner Swain\*

Contribution from the Department of Chemistry,  
Massachusetts Institute of Technology, Cambridge, Massachusetts 02139.  
Received May 1, 1975

**Abstract:** Chlorine kinetic isotope effects have been determined for the cyclization of 2-chloroethanol by solvent anion in the solvents H<sub>2</sub>O, D<sub>2</sub>O, ethanol, and *tert*-butyl alcohol at 25°. The first entering group chlorine kinetic isotope effects to be reported were measured in the same solvents for the reverse reaction, ring opening of ethylene oxide by chloride ion. Equilibrium chlorine isotope effects calculated from the ratios of the kinetic isotope effects are essentially identical (1.0053) in H<sub>2</sub>O, D<sub>2</sub>O, and *tert*-butyl alcohol, but larger (1.0060) in ethanol. The variation of equilibrium chlorine isotope effect with solvent is attributed to a chlorine isotope effect on the preequilibrium between 2-chloroethanol and 2-chloroethoxide and to differential solvation of chloride ion in the solvents studied. The degree to which the preequilibrium isotope effect influences the observed equilibrium chlorine isotope effects depends on the relative concentrations of 2-chloroethanol and 2-chloroethoxide. Chlorine isotope effects can thus vary with solvent in complicated ways as a result of both (1) solvent-induced changes in the distribution between different chlorine species in preequilibria and (2) changing strength of solvation bonds to chloride ion.

Two recent reviews of heavy atom isotope effects have emphasized that unique mechanistic information can be expected from determination of these rate ratios for organic reactions.<sup>2,3</sup> The theory of heavy atom isotope effects is well established,<sup>4</sup> and the magnitudes of these effects are known to be related to vibrational changes of bonds to the isotopic atom in passage from the reactant to the transition state. When these vibrational changes can be linked to structural changes, heavy atom isotope effects become a probe for the structure of transition states in organic reactions. The expectation of direct information about the nature of transition states has led to the development of a sizable literature on heavy atom isotope effects.<sup>2-8</sup>

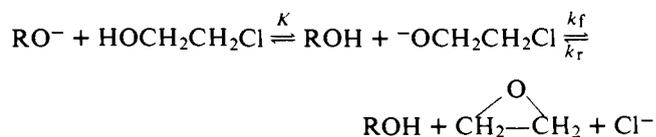
Our recent studies have focused on kinetic chlorine isotope effects.<sup>9-11</sup> Although magnitudes of chlorine isotope effects are small, chlorine isotope effects seemed particularly suited to the study of nucleophilic displacement reactions. Not only is chlorine a convenient leaving group in such displacements, but it also has only one covalent bond, making it useful as the leaving atom for the common three-center S<sub>N</sub>2 transition state model.<sup>12</sup> However, difficulties in the interpretation of chlorine kinetic isotope effects have been noted.<sup>2</sup> For example, leaving group chlorine isotope effects are expected to increase as the carbon-chlorine bond in the transition state becomes more broken.<sup>13</sup> Yet the chlorine kinetic isotope effect for the ethanolysis of *tert*-butyl chloride (1.008),<sup>14</sup> an S<sub>N</sub>1 reaction believed to have a very late transition state,<sup>15</sup> is not much larger than the 1.0074 reported for the S<sub>N</sub>2 reaction of *n*-butyl chloride with methoxide ion in methanol,<sup>16</sup> a reaction that would be expected to retain considerably more carbon-chlorine bonding at the transition state. A similar lack of variation in the chlorine isotope effect among substituted benzyl chlorides has been ascribed to compensating solvation of the incipient chloride ion at the transition state.<sup>17,18</sup>

In an attempt to increase our understanding of the factors that influence the magnitudes of chlorine isotope effects, kinetic chlorine isotope effects for the reaction of 2-chloroethanol with lyate ion (solvent anion) in H<sub>2</sub>O, D<sub>2</sub>O, ethanol, and *tert*-butyl alcohol and for the reaction of ethylene oxide with chloride ion in these same solvents were determined. Equilibrium chlorine isotope effects were then determined from the ratios of the kinetic isotope effects. These reactions have been well studied previously,<sup>19</sup> and it

was hoped that comparison of the chlorine isotope effects with what was already known about these reactions might help elucidate the factors that determine the magnitude of chlorine isotope effects. Additionally, our determination of the first equilibrium chlorine isotope effects for an organic reaction was expected to be useful in relating chlorine isotope effects to carbon-chlorine bond-order changes.

## Isotope Effect Equations

The reaction of 2-chloroethanol with lyate ion in water and in alcohols is known to proceed with a rapidly established preequilibrium between 2-chloroethanol and 2-chloroethoxide, followed by rate-determining cyclization of the anion.<sup>19a</sup>



For the general case in which measurable amounts of both 2-chloroethanol and 2-chloroethoxide are present in solution, the expression for the kinetic isotope effect for the forward reaction (KIE<sub>f</sub>) can be shown to be

$$\text{KIE}_f = \frac{k'_{\text{obsd}}}{k''_{\text{obsd}}} = \left[ \frac{k'_f}{k''_f} \right] \left[ \frac{K'}{K''} \right] \left[ \frac{1 + K''[\text{RO}^-]}{1 + K'[\text{RO}^-]} \right] \quad (1)$$

in which singly primed rate or equilibrium constants refer to the lighter isotope (<sup>35</sup>Cl) and doubly primed constants refer to the heavier isotope (<sup>37</sup>Cl). The expression for the equilibrium isotope effect (EIE) for the same reaction is the ratio of eq 1 to the kinetic isotope effect for the reverse reaction (KIE<sub>r</sub>) and is given by

$$\text{EIE} = \frac{\text{KIE}_f}{\text{KIE}_r} = \left[ \frac{k'_f / k''_f}{k'_r / k''_r} \right] \left[ \frac{K'}{K''} \right] \left[ \frac{1 + K''[\text{RO}^-]}{1 + K'[\text{RO}^-]} \right] \quad (2)$$

The second term in brackets in eq 1 and 2 is the isotope effect on the first or preequilibrium (*K*) step only. On the assumption of no solvent interaction with the covalently bound chlorine,<sup>20,21</sup> this preequilibrium isotope effect should be constant regardless of experimental conditions. When the terms *K*[RO<sup>-</sup>] are large compared to unity, both

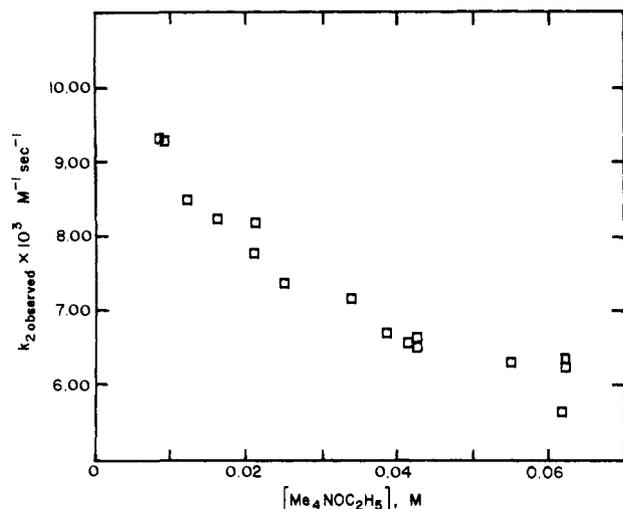


Figure 1. Variation of the second-order rate constant with ethoxide concentration in ethanol at 25.0°. The concentration of 2-chloroethanol was varied over the range 0.0203–0.1218 *M* with no effect on the observed rate constant.

KIE<sub>f</sub> and EIE are independent of the isotope effect on the preequilibrium. When the terms  $K[RO^-]$  are small, however, both will have contributions from the isotope effect ( $K'/K''$ ) on the preequilibrium.

## Results

As a prelude to chlorine isotope effect studies, it is usually necessary to conduct a kinetic investigation of the reaction so that it can be stopped at a small known percentage conversion of reactant chlorine to product chlorine.<sup>22</sup> At such low conversions, the isotopic effect  $k'/k''$ , which is then the ratio of <sup>35</sup>Cl/<sup>37</sup>Cl in the product chlorine to <sup>35</sup>Cl/<sup>37</sup>Cl in the reactant chlorine, can be accurately corrected to its value after essentially no reaction has occurred (see Experimental Section).

The kinetic data for the reactions of 2-chloroethanol and the lyate ions of the protic solvents used in this study are listed in Table I. In agreement with Ballinger and Long,<sup>23</sup> we find that the reaction exhibits good second-order kinetics in water when tetramethylammonium hydroxide is the base, even at high base concentrations. The solvent isotope effect  $k_{D_2O}/k_{H_2O}$  of  $1.51 \pm 0.03$ , calculated from the first and second entries in Table I, agrees favorably with the 1.54 determined earlier.<sup>23,24</sup> The error ( $\pm$ ) limits here and in the tables are standard deviations for the number of experiments listed. In ethanol the cyclization exhibited behavior attributable to significant ion pairing of the reactants. The kinetic data in this solvent are presented in Figure 1. Similar behavior in water has been noted previously with alkali metal hydroxides.<sup>23</sup> A qualitative conductivity study was carried out and the apparent dissociation constant between complexed base and "free" base found to be 0.02. Although separate constants for the complexed base and the free base could be determined, in practice observed or overall rate constants  $k_2$  were obtained by inspection of Figure 1. The rate constant of the reaction of 2-chloroethanol with *tert*-butoxide in *tert*-butyl alcohol was not determined because the reaction was too rapid to follow by conventional chloride titration.

Kinetic results for the reaction of ethylene oxide and chloride ion in the four protic solvents H<sub>2</sub>O, D<sub>2</sub>O, ethanol, and *tert*-butyl alcohol are listed in Table II. The concurrent solvolysis of ethylene oxide can be ignored because a large excess of ethylene oxide was used and the reaction was followed through only two half-lives. GLC product analysis in-

Table I. Kinetic Data for Reaction of 2-Chloroethanol and Me<sub>4</sub>NOR in Protic Solvents at 25.0°

Solvent ROH or ROD	[2-Chloroethanol], <i>M</i>	[Me <sub>4</sub> NOR], <i>M</i>	No. of expts	$k_2 \times 10^3$ , M <sup>-1</sup> sec <sup>-1</sup>
H <sub>2</sub> O	0.0294–0.2735	0.0097–0.0730	8	$1.13 \pm 0.03$
D <sub>2</sub> O	0.0246–0.0757	0.0109–0.0328	6	$1.71 \pm 0.03$
EtOH	0.0203–0.1218	0.0080–0.0615	17	<i>a</i>
<i>t</i> -BuOH				<i>b</i>

<sup>a</sup> Depends on concentration; see Figure 1. <sup>b</sup> Too fast to measure.

indicated that, at the concentrations used in this study in ethanol, 80% of the ethylene oxide that has reacted after 8 half-lives gives 2-chloroethanol and 20% gives 2-ethoxyethanol.

In basic hydroxylic media, the equilibrium between 2-chloroethanol and ethylene oxide favors ethylene oxide, but it can be forced almost completely back to 2-chloroethanol if neutral or acidic conditions are maintained.<sup>19</sup> A buffer system of 1:1 2,6-lutidine–2,6-lutidinium perchlorate was employed to maintain neutral conditions (pH 6.8). 2,6-Lutidine is not a nucleophile toward ethylene oxide,<sup>19c</sup> and neither the concentration of the lutidinium ion nor the buffer ratio has any effect on the rate of the reaction in H<sub>2</sub>O and D<sub>2</sub>O. A small dependence of the rate on the concentration of lutidinium ion in ethanol and in *tert*-butyl alcohol proved to be due to ion-pairing effects, as shown by another conductivity study. Finally, the reaction in water was repeated in the absence of the buffer by using a pH stat to maintain the pH at 6.8. The rate constant in these experiments differed from that determined with the buffer by less than 2%. From the kinetic data in H<sub>2</sub>O and D<sub>2</sub>O in Table II, the solvent isotope effect  $k_{D_2O}/k_{H_2O}$  is  $0.873 \pm 0.036$ . Division of the kinetic solvent isotope effect for the cyclization reaction by the one for the ring-opening reaction gives the equilibrium solvent isotope effect  $K_{D_2O}/K_{H_2O}$ ,  $1.73 \pm 0.05$ .

The chlorine kinetic isotope effects for the cyclization of 2-chloroethanol with base are given in Table III. Reagent concentrations were approximately the same as those for the kinetic studies. The kinetic isotope effects are corrected for the fact that the <sup>35</sup>Cl/<sup>37</sup>Cl ratio of the reactant changes during reaction as the isotopes react at different rates.

Table IV reports the kinetic chlorine isotope effects for the reaction of chloride ion with ethylene oxide. By determining the chlorine kinetic isotope effect for the ring-opening reaction in water in the absence of a buffer by using a pH stat system, it was demonstrated that the presence of the buffer has no effect on the isotope effect for the ring-opening reaction (compare the first and second entries in Table IV). Thus a true value for the ring-opening reactions in the solvents used in this work can be obtained by the use of a buffer system of 2,6-lutidine.

Table V summarizes the equilibrium chlorine isotope effects in the four protic solvents studied. These values were obtained by division of the kinetic isotope effect for the ring closure reaction by that for the ring-opening reaction.

## Discussion

The expression for an equilibrium heavy atom isotope effect derived by Bigeleisen and Mayer<sup>25</sup> is

$$\frac{K'}{K''} = \left[ 1 + \sum_{\text{reactant}}^{3N-6} G(u_i) \Delta u_i - \sum_{\text{product}}^{3N-6} G(u_i) \Delta u_i \right] \quad (3)$$

where  $G(u_i) = \frac{1}{2} - 1/u_i + 1/(\exp(u_i) - 1)$  and  $u_i = h\nu_i/kT$ ;  $\Delta u_i = u'_i - u''_i$ . In eq 3, prime refers to the lighter isotope, double prime refers to the heavier, and  $\nu_i$  is the vibra-

Table II. Kinetic Data for Reaction of Ethylene Oxide and Chloride Ion in Buffered Protic Solvents at 25.0°

Solvent	[C <sub>2</sub> H <sub>4</sub> O], M	[Cl], M	[2,6-Lutidinium ion], <sup>a</sup> M	k <sub>-2</sub> × 10 <sup>5</sup> , <sup>b</sup> M <sup>-1</sup> sec <sup>-1</sup>
H <sub>2</sub> O	0.91–1.30	0.0196–0.0882	0.0606–0.193	0.465 ± 0.012
	1.02–1.35	0.0493–0.0893	<sup>c</sup>	0.474 ± 0.027
D <sub>2</sub> O	0.93–1.15	0.0560–0.0934	0.0560–0.0934	0.406 ± 0.012
EtOH	0.25–1.13	0.0195–0.102	0.0605–0.257	1.19 ± 0.06
<i>t</i> -BuOH	0.79–1.12	0.0197–0.0801	0.0375–0.0801	5.33 ± 0.13

<sup>a</sup> Usually present as a 1:1 buffer with 2,6-lutidine; a fourfold variation of the buffer ratio had no effect on the rate. <sup>b</sup> Determined from the observed first-order rate constant by division by the initial C<sub>2</sub>H<sub>4</sub>O concentration. <sup>c</sup> No buffer present; followed at pH 6.8 with a pH stat.

Table III. Kinetic Chlorine Isotope Effects (k<sub>2</sub>'/k<sub>2</sub>'') for Reactions of 0.08 M 2-Chloroethanol with 0.04 M Me<sub>4</sub>NOR in Protic Solvents at 25.0°

Solvent (HOR)	% reaction <sup>a</sup>	No. of expts	Isotope effect <sup>b</sup>
H <sub>2</sub> O	5–12	7	1.00815 ± 0.00011
D <sub>2</sub> O	7–15	6	1.00810 ± 0.00011
EtOH	8–15	8	1.00831 ± 0.00013
<i>t</i> -BuOH	7.7–13.2	6	1.00779 ± 0.00013

<sup>a</sup> The range of % conversion of 2-chloroethanol to Cl<sup>-</sup>. <sup>b</sup> Corrected for % reaction.

Table IV. Kinetic Chlorine Isotope Effects (k<sub>-2</sub>'/k<sub>-2</sub>'') for Reactions of 1.0 M Ethylene Oxide with 0.1 M Chloride Ion in Protic Solvents at 25.0°

Solvent	% reaction <sup>a</sup>	No. of expts	Isotope effect <sup>b</sup>
H <sub>2</sub> O	8–12	7	1.00280 ± 0.00017
	8–12	4	1.00295 ± 0.00014 <sup>c</sup>
D <sub>2</sub> O	6–14	5	1.00295 ± 0.00014
EtOH	5–15	7	1.00224 ± 0.00018
<i>t</i> -BuOH	7–13.7	6	1.00250 ± 0.00007

<sup>a</sup> The range of % to which Cl<sup>-</sup> has been converted to 2-chloroethanol. <sup>b</sup> Corrected for % reaction. <sup>c</sup> Reaction with no buffer; pH 6.8 maintained by a pH stat.

Table V. Equilibrium Chlorine Isotope Effects for Cyclization of 2-Chloroethanol in Protic Solvents at 25.0°

Solvent	k <sub>2</sub> /k <sub>-2</sub>	Isotope effect <sup>a,b</sup>
H <sub>2</sub> O	2344	1.00533 ± 0.00020
D <sub>2</sub> O	4212	1.00523 ± 0.00018
EtOH	546	1.00606 ± 0.00022
<i>t</i> -BuOH		1.00528 ± 0.00015

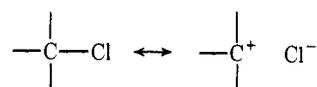
<sup>a</sup> Equal to EIE, the ratio of the kinetic isotope effect for the cyclization of 2-chloroethanol to the kinetic isotope effect for the reaction of ethylene oxide and chloride ion. <sup>b</sup> Standard deviation calculated from the square root of the sum of the variances of the kinetic isotope effects.

tional frequency of the *i*th bond. The G(*u<sub>i</sub>*) function increases as the frequency of vibration *ν<sub>i</sub>* increases.<sup>25</sup> Thus equilibrium isotope effects become larger as the frequencies of vibrations involving the isotopic atom become greater (stronger bonding) in the reactant, but become smaller for a similar change in the product. Interpretation of the equilibrium chlorine isotope effects in Table V requires consideration of solvent-induced changes in both reactant and product summations in eq 3.

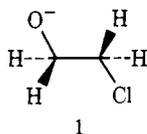
The equilibrium isotope effects in Table V for the cyclization of 2-chloroethanol in water and in *tert*-butyl alcohol are identical within experimental error, while that in ethanol is significantly larger. To demonstrate that our experimental procedures were valid and to obtain some idea of the reliability and precision of our data, the equilibrium isotope effect for the cyclization of 2-chloroethanol in D<sub>2</sub>O was determined. Since the bulk properties of H<sub>2</sub>O and D<sub>2</sub>O are very similar, the equilibrium chlorine isotope effects in these two solvents should also be very similar. Comparison

of the measured isotope effects in H<sub>2</sub>O and D<sub>2</sub>O provides a means of assessing the reproducibility of our isotope effects. The isotope effects in Table V in H<sub>2</sub>O and in D<sub>2</sub>O are in good agreement, within the experimental error. Since we can conclude that our experimental procedures are valid, an explanation of the difference in the equilibrium chlorine isotope effect for the cyclization of 2-chloroethanol in ethanol compared to water and *tert*-butyl alcohol must be found. This unexpected result is understandable in terms of two factors: the effect of the basicity of the lyate ion on the preequilibrium between 2-chloroethanol and 2-chloroethoxide and the effect of hydrogen bonding of the solvent on the chloride ion. Since *equilibrium* chlorine isotope effects are being compared, only the reactants and products, i.e., no transition states, need be considered.

It has been calculated that about 20% of the alcohol in an aqueous solution 1 M in 2-chloroethanol and 1 M in hydroxide ion is in the form of 2-chloroethoxide.<sup>26</sup> In *tert*-butyl alcohol with *tert*-butoxide as the base, the proportion of 2-chloroethoxide will be much higher. The increase in the concentration of the intermediate anion probably accounts for the observation that the cyclization of 2-chloroethanol in *tert*-butyl alcohol catalyzed with *tert*-butoxide is too fast to measure by chloride titration procedures. Thus the term K[RO<sup>-</sup>] in eq 2 will be large in *tert*-butyl alcohol, and the observed equilibrium isotope effect will be the isotope effect for the cyclization of 2-chloroethoxide in *tert*-butyl alcohol with no contribution from an isotope effect for the interconversion of 2-chloroethanol and 2-chloroethoxide. If the reaction is carried out in ethanol with the weaker base ethoxide, less of the 2-chloroethanol reactant will be converted to 2-chloroethoxide at equilibrium. The term K[RO<sup>-</sup>] will no longer be large relative to unity (its exact magnitude has not been determined in this study), and the observed equilibrium isotope effect will be a product of the equilibrium isotope effect for the cyclization of 2-chloroethoxide and some fraction (determined by the exact value of the term K[RO<sup>-</sup>])<sup>27</sup> of the isotope effect for the interconversion of 2-chloroethanol and 2-chloroethoxide. To properly account for the relative magnitudes of the equilibrium isotope effects in *tert*-butyl alcohol and in ethanol, the isotope effect K'/K'' in eq 2 must be normal (greater than unity). This requires that the conversion of 2-chloroethanol to 2-chloroethoxide result in a decrease in bonding to the chlorine. Gerdil<sup>28</sup> has shown that electron-donating groups decrease the infrared stretching frequencies and chlorine nuclear quadrupole resonance frequencies of simple alkyl chlorides when these frequencies are corrected for mass effects. The chlorine nuclear quadrupole resonance frequencies of substituted chlorobenzenes also decrease with electron-donating substituents.<sup>29</sup> In both cases, increasing the electron density appears to lead to decreases in bonding to chlorine, presumably from an increase in ionic character of a carbon-chlorine bond due to stabilization of the incipient positive



charge on carbon by electron-donating groups. A reason for expecting considerable weakening of the carbon–chlorine bond on deprotonation of the alcohol in 2-chloroethanol arises from consideration of the effect of the increased electron density on oxygen in the most probable trans conformation **1** for 2-chloroethoxide. In this conformation, exten-



sion of the carbon–chlorine bond is directly assisted by stabilization of the resultant positive charge on carbon by the negative charge on oxygen.

If the intervention of a normal isotope effect on the preequilibrium between 2-chloroethanol and 2-chloroethoxide accounts for the increased equilibrium isotope effect observed in ethanol compared to *tert*-butyl alcohol, the isotope effect on the overall reaction in water might be expected to be as large or larger than the one in ethanol because the proportion of 2-chloroethanol in water should be about the same as or greater than that in ethanol. However, the equilibrium isotope effect in water (Table V) has a smaller value more like that in *tert*-butyl alcohol. One can account for this, with similar proportions of ethanol and 2-chloroethoxide, if differences in the solvation of chloride ion in water and in ethanol are also considered. An equilibrium chlorine isotope effect ( $K'/K''$ ) of 0.9950 has been reported for the equilibrium<sup>30</sup>  $\text{Cl}^-$  (gas phase)  $\rightleftharpoons$   $\text{Cl}^-$  (solvated by water). An isotope effect differing this much from unity for the solvation of chloride ion is quite striking, for it is of about the same size as the equilibrium isotope effects measured in this work for the cleavage of a carbon–chlorine bond. Although this value clearly represents an upper limit to the effect of solvation on chlorine isotope effects, it is not unreasonable to suppose that the observed lowering of the equilibrium isotope effect from ethanol to water may be due to the differential effects of solvation. A lowering of chlorine kinetic isotope effects upon changing solvent from dipolar aprotic solvents to protic solvents has previously been observed.<sup>31</sup> The interpretation of previous data is clouded by the fact that they are kinetic effects, and the structures of the transition states may change in response to solvent enough to account for the observations. On the other hand, solvation is at a maximum for equilibrium isotope effects in which one of the species is a fully solvated chloride ion.

Table V presents the first equilibrium chlorine isotope effects to be reported for an organic reaction. Evidently the process of breaking a carbon–chlorine bond in protic solvents has an equilibrium isotope effect (due only to changes in bonding) of 1.0052–1.0061. Insofar as 2-chloroethanol is a model for the “typical” carbon–chlorine bond, the largest equilibrium isotope effects in water or alcohols should be on the order of 1.006.

Kinetic chlorine isotope effects are the product of a factor related to bonding changes of the chlorine in passage from the reactants to the transition state (the temperature-dependent factor) and a factor involving the masses of the atoms along the reaction coordinate (the temperature-independent factor).<sup>2,4</sup> Since the observed kinetic isotope effect depends on both, kinetic chlorine isotope effects are inherently more difficult to interpret unambiguously than equilibrium isotope effects. However, examination of the kinetic chlorine isotope effects from which the equilibrium isotope effects were derived does allow some conclusions.

The large values of the isotope effects in Table III for the reactions of 2-chloroethanol with the lyate ions of the four solvents studied suggest that the transition states for these

reactions are late, i.e., resemble ethylene oxide and a chloride ion. This finding agrees with previous conclusions about these reactions based on solvent isotope effect data.<sup>32</sup> In our earlier discussion of equilibrium chlorine isotope effects for the cyclization of 2-chloroethanol, it was suggested that changes in the preequilibrium between 2-chloroethanol and 2-chloroethoxide, brought on by changes in the basicity of the lyate ion of the solvent, influence the observed isotope effect. Kinetic chlorine isotope effects for the ring-closing reaction should be, and apparently are, affected similarly (although changes in the structure of the transition state with changes in solvent are now an additional complication). The kinetic chlorine isotope effect for the cyclization in *tert*-butyl alcohol is again lower than that for either ethanol or water. This is exactly as expected on the basis of no contribution from the isotope effect on the preequilibrium in *tert*-butyl alcohol. It was suggested previously that the preequilibrium isotope effect may contribute about equally to the reactions in ethanol and in water, and kinetic chlorine isotope effects in ethanol and in water are in fact quite similar.

The entering group chlorine kinetic isotope effects listed in Table IV are the first such isotope effects to be reported. They are all greater than unity, which again suggests transition states for the interconversion of 2-chloroethanol and ethylene oxide that are much like chloride ion and ethylene oxide, for the following reason. Since these entering group chlorine isotope effects are products of temperature-independent factors that are greater than unity<sup>33</sup> and temperature-dependent factors that are less than unity, because bonding in the transition state is greater than bonding in the reactant chloride ion, the failure of the latter factors to overbalance the former suggests transition states with little bonding of chlorine to carbon. The only reported entering group carbon isotope effects are also greater than unity.<sup>34–36</sup> The kinetic chlorine isotope effects for the ring-opening reaction have no complication due to the preequilibrium between 2-chloroethanol and 2-chloroethoxide; hence the isotope effects are determined simply by the initial solvation of the chloride ion and the bonding of the chlorine at the transition states. Although transition states for the ring-opening reactions undoubtedly change somewhat with solvent, the fact that the isotope effect for the cyclization in water is the largest shows that the dominant influence on these isotope effects is more effective hydrogen bonding by water than by the other solvents to the reactant chloride ion.

## Conclusions

Heavy atom isotope effects arise from bonding changes to the isotopic atom in passing from reactant to transition state (kinetic isotope effects) or to products (equilibrium isotope effects). Both the kinetic and the equilibrium chlorine isotope effects for the cyclization of 2-chloroethanol in water, ethanol, and *tert*-butyl alcohol suggest that the preequilibrium between 2-chloroethanol and 2-chloroethoxide ion must be taken into account. This effect may well arise in other cases involving preequilibria that change the bonding to the isotopic atom. The use of chlorine isotope effects to investigate reactions in which several kinds of ions or ion pairs may be in equilibrium<sup>37</sup> may be particularly complicated in this respect. Any change of reaction conditions that alters the equilibrium among these ions and ion pairs may lead to observed isotope effects that are complicated functions of both isotope effects for reactions of particular species and isotope effects for preequilibria in which chlorine bonding is changed. Furthermore, equilibrium and kinetic chlorine isotope effects studied in this work have been

found to change with solvent, not only because of effects on this preequilibrium but also because of changes in the solvation of chloride ion. Although changes in chlorine kinetic isotope effects due to changes of the solvation of chlorine in *transition states* have not been directly demonstrated, it seems reasonable to expect that such changes should also occur, at least for those reactions in which chlorine carries a substantial negative charge at the transition state. In view of the two demonstrated kinds of complications, it seems prudent to use chlorine isotope effects in mechanistic studies only in conjunction with other kinds of data. Only after all the factors that determine the magnitudes of chlorine isotope effects have been established will these isotope effects fulfill their promise in the study of organic reaction mechanisms.

## Experimental Section

**Apparatus.** Potentiometric titrations were made with a Radiometer Model 26 pH meter operated in the expanded scale mode. The indicating electrode was Ag-AgCl,<sup>38</sup> and the reference electrode was a Radiometer Type K401 calomel electrode with the KCl electrolyte replaced with a saturated KNO<sub>3</sub> solution. A pH-stat system consisting of a Radiometer Model 25 pH meter equipped with a scale expander, a Radiometer titrator 11, and a Radiometer ABU 1b autoburet was used to maintain a pH of 6.8 (the pH of the 2,6-lutidine buffer system in water) in reactions of ethylene oxide run in the absence of the buffer. Conductivity measurements were made with an Industrial Instruments Co. Model RC 16B1 conductivity bridge using a variety of unplatinized Pt electrode cells.

The mass spectrometer used in this study has been described.<sup>10</sup> A misprint in that description should be corrected to read that amplifier 2 was operated on the 30-mV scale. A Honeywell Elektronik 19 recorder was used to obtain the deviation from true null as described.<sup>10</sup>

**Materials.** Inorganic chemicals were reagent grade used without further purification unless otherwise noted. Distilled water refers to laboratory distilled water redistilled from KMnO<sub>4</sub> and KOH in an aged still with protection from CO<sub>2</sub>. Standard solutions of NaOH were prepared from Acculute NaOH solutions, and standard solutions of Me<sub>4</sub>NOH were prepared from the Eastman pentahydrate or 10% solution in water. Solutions of AgNO<sub>3</sub> were prepared from Mallinckrodt CP AgNO<sub>3</sub> and were standardized against reagent grade NaCl.

Ethanol was purified by treatment with sodium metal followed by ethyl formate.<sup>39</sup> After reflux for 1 hr, the ethanol was distilled and stored with protection from moisture. D<sub>2</sub>O (Thompson-Packard 99.8%) was distilled at 1 atm. *tert*-Butyl alcohol (Eastman) was refluxed with CaH<sub>2</sub> and distilled from CaH<sub>2</sub>. 2-Chloroethanol (Eastman) was treated with a small amount of 2,6-lutidine and distilled through a 12-cm column packed with glass beads, bp 63–64° at 57 mm (lit.<sup>40</sup> 51–52° at 22 mm). This material gave no precipitate with AgNO<sub>3</sub> and was neutral to litmus. These tests were reconfirmed before any use of the alcohol, or it was redistilled. Ethylene oxide (Eastman) was distilled at 1 atm through a 12-cm Vigreux column into a receiver cooled in a dry ice-acetone bath with protection from moisture.

2,6-Lutidine (2,6-dimethylpyridine) was purified by the procedure of Lewis and Allen.<sup>41</sup> After preliminary distillation from CaH<sub>2</sub>, the amine was redistilled from boron trifluoride etherate,<sup>42</sup> bp 141–142° (lit.<sup>41</sup> 145°). GLC on 10% Carbowax 20M on Chromosorb P at 170° indicated that this procedure had removed several impurities in the commercial (Eastman) amine.

2,6-Lutidinium chloride was prepared from the amine and concentrated hydrochloric acid, mp 235–237° (lit.<sup>39</sup> 230–231°) after removal of water and recrystallization from ethanol. 2,6-Lutidinium perchlorate was prepared similarly and recrystallized from ethanol-ether, mp 111–113°.

Solutions of tetramethylammonium ethoxide in ethanol were prepared from equivalent amounts of Me<sub>4</sub>NBr (recrystallized from ethanol) and sodium ethoxide in ethanol. NaBr was filtered out after concentration and cooling to –20°. Titration showed the bromide concentration was less than 1% of the ethoxide concentration.

Tetramethylammonium *tert*-butoxide was prepared similarly and contained a trace of Br<sup>–</sup> (<1% of *tert*-butoxide) and about 4% Na<sup>+</sup> (zinc uranyl acetate).

**Kinetics.** Temperature control of 25.00 ± 0.05° was provided by a large well-stirred water bath. Reactions were followed by the liberation or consumption of chloride ion determined potentiometrically after quenching aliquots of the reaction solution in cold (0–10°) water acidified with HNO<sub>3</sub>. Titrations were carried out to a fixed potential determined for each set of conditions from the inflection point of a chloride titration curve taken under the same conditions. The concentration of 2-chloroethanol was determined from the amount of chloride ion after quantitative hydrolysis with hydroxide. Ethylene oxide was determined by the procedure of Ross<sup>43</sup> as described in Virtanen.<sup>19c</sup> For the reaction employing a pH-stat system, the reaction was followed by the rate of addition of standard HNO<sub>3</sub> required to maintain the pH at 6.8. The reactions of ethylene oxide and chloride ion were carried out under conditions of a large excess of ethylene oxide and followed to only 2 half-lives because of the solvolysis of ethylene oxide. The reactions of 2-chloroethanol and base were conducted under second-order conditions and followed through 90% consumption of the limiting reagent. Rate constants were determined from graphs of the concentration of chloride ion vs. time using the appropriate integrated rate expression.

**Isotope Effects.** For the reaction of 2-chloroethanol with base in H<sub>2</sub>O, D<sub>2</sub>O, and ethanol, reaction was terminated at a known % conversion of 2-chloroethanol to ethylene oxide by the addition of excess aqueous nitric acid. The liberated chloride ion was then precipitated from a solution of high ionic strength (>0.2 M with KNO<sub>3</sub>).<sup>44</sup> It was found that this procedure did not liberate any chloride ion from 2-chloroethanol. The AgCl was washed with dilute nitric acid, filtered, and dried in the dark. Since the reaction in *tert*-butyl alcohol was too rapid to stop in the early stages, only a limiting amount of *tert*-butoxide was used, so that reaction stopped after this base was consumed, liberating only a small amount of chloride from 2-chloroethanol. As long as exchange between the liberated chloride ion and covalently bonded chlorine does not occur, this procedure is as satisfactory as the previously described one. From the fact that the chlorine kinetic isotope effect for this reaction did not change when the liberated chloride ion and unreacted 2-chloroethanol were allowed to remain in contact for varying lengths of time, we assumed that such equilibration did not occur. In both these types of experiments, reactant samples were isolated by complete reaction of a sample of the stock solution of 2-chloroethanol and precipitation of the chloride ion as above.

The isotope effects for the reaction of ethylene oxide and chloride ion were determined from samples of chloride ion isolated in a more complex manner. Although a standard reactant sample could be obtained directly from Ag<sup>+</sup> precipitation of a sample of the stock 2,6-lutidinium chloride solution, the product AgCl samples were isolated by converting the 2-chloroethanol product quantitatively back to chloride ion with excess base after removal of the unreacted chloride as AgCl. Comparison of CH<sub>3</sub>Cl samples (see below) from direct precipitation of part of a sample of 2,6-lutidinium chloride with those from another part which had been completely converted to 2-chloroethanol and completely back again to chloride ion indicated that no fractionation occurred through these manipulations (the samples differed by 6 parts in 10000).

The procedure developed by Hill,<sup>45</sup> as modified by Grimsrud and Taylor,<sup>44</sup> was employed to convert samples of AgCl isolated as described above to methyl chloride for analysis by mass spectrometry. AgCl (0.05–0.15 g) was weighed into a 50- or 100-ml break-seal Pyrex bulb containing a volume of CH<sub>3</sub>I in milliliters equal to twice the weight of AgCl in grams. The CH<sub>3</sub>I was frozen with liquid N<sub>2</sub>, and the bulb evacuated to 10<sup>–4</sup> mm on a vacuum line. The bulb was sealed and heated at 100° for 48–72 hr, and then reattached to the vacuum system. After breaking the break-seal, the CH<sub>3</sub>Cl and CH<sub>3</sub>I were transferred with liquid N<sub>2</sub> to a tube containing crushed KOH to remove any water and HCl. The CH<sub>3</sub>Cl was distilled into a storage bulb cooled with liquid N<sub>2</sub> from the KOH tube cooled in dry ice-acetone. This procedure separated the methyl halides satisfactorily if care was taken not to allow the gases to distill directly from one tube to the other, but if the distillation were carried out from the KOH tube into a vacuum, the KOH tube isolated, and the gas frozen into the receiving tube.

Calculation of the isotope effects from recorder traces has been

discussed previously.<sup>10</sup> In these experiments, greater instrument stability and reproducibility were obtained than in our previous work<sup>9,10</sup> by operating the mass spectrometer only during periods of low variation in the voltage supplied to the instrument (evenings on weekends and holidays). Experimental isotope effects were obtained by division of the average instrument readings for the reactant sample taken before and after the product sample by the reading for the product sample. This procedure compensates for short term drift in the instrument. The observed experimental isotope effects were corrected for % reaction by eq 4

$$\text{CIE} = \text{XIE}[1 + (f/2)(\text{XIE} - 1)] \quad (4)$$

developed by Dr. Sigma R. Alpha,<sup>10</sup> in which CIE is the corrected isotope effect, XIE is the experimentally measured isotope effect, and  $f$  is the fractional conversion of reactant chlorine to product chlorine. The experimentally determined isotope effects, % reaction, and the individual corrected isotope effects from which all averages in this paper were determined are available elsewhere.<sup>46</sup>

The standard deviations reported in this paper are standard deviations of the corrected isotope effects (not standard deviations of the mean of these values). An "experiment" means a completely independent reaction, sample preparation, and isotopic ratio measurement. In many cases a sample of  $\text{CH}_3\text{Cl}$  was measured more than once and the average value reported, but this average value was considered to be a single experiment.

**Acknowledgment.** This research was supported in part by a research grant from the National Science Foundation.

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