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(26) Charge delocalization in the rearranged cation is not required by our data; cf. footnote 5, ref 2b.
(27) Does not include deltacyclene (**7**), the provenance of which is uncertain.
(28) Depicted as charge-delocalized by analogy to the 2-brexyl cation **20**.[2c]
(29) Just as symmetric double bond participation in **19**-OBs produces the bishomocyclopropenyl cation (**20**),[2c] simultaneous, symmetric $2^0 + 2^0$ laticyclic participation of both double bonds in **2**-OBs would lead to the "unsymmetric" $[2^0 + 2^0 + 1^+]$ laticyclic cation **3**.[14] A dissymmetric participation of both double bonds which results in the formation of the cyclopropylcarbinyl-type cation **4** would not be classified as laticyclic participation under the Goldstein–Hoffmann definition.[14]
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Entering Chloride Kinetic Isotope Effects in Protic and Aprotic Solvents

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Abstract: Chlorine kinetic isotope effects for the reaction of ethylene oxide and chloride ion are normal ($^{35}Cl/^{37}Cl$ greater than unity) in protic solvents and in acetone and dimethylformamide (DMF) in the presence of 1 equiv of 2,6-lutidinium ion. In the presence of 0.1 equiv of this cation (and 0.9 of Li^+) the isotope effect in DMF is inverse (0.9922). This is the first observation of an inverse entering-group heavy-atom isotope effect. The reaction of chloride ion with dimethyl sulfate is normal in water but inverse in DMF. The "normal" isotope effects are shown to be due in large measure to the dominance of changes in hydrogen bonding to chlorine over changes in carbon–chlorine bonding.

As noted in a previous paper,[2] kinetic chlorine isotope effects of organic reactions do not show as wide a variation in magnitude with changes in transition state structure as might have been expected.[3-6] One explanation that has been advanced is a leveling effect on the isotope effect by the hydroxylic solvents in which the reactions were studied.[7] As the chlorine at the transition state becomes more like a chloride ion, the isotope effect due to loss of carbon–chlorine bonding increases. The hydrogen bonding to this chloride ion may also increase, however, and this increase of bonding might lower the observed isotope effect. The simultaneous operation of these two opposing effects could lead to an insensitivity of the chlorine isotope effect to transition state structure. In support of this proposal, it has been noted that kinetic chlorine isotope effects measured in hydroxylic solvents are smaller than isotope effects for identical reactions in dipolar aprotic solvents.[8,9] Because the structural changes in the transition state for these reactions on transfer from hydroxylic solvents to dipolar aprotic solvents are not known, however, these observations do not prove that hydrogen bonding to chlorine at the transition state is responsible for the smaller isotope effects in protic solvents.

We recently reported kinetic and equilibrium chlorine isotope effects for the interconversion of ethylene oxide and 2-chloroethanol in the solvents H_2O, D_2O, ethanol, and *tert*-butyl alcohol.[2] One of the conclusions of that study was that, at least for equilibrium chlorine isotope effects, differences in solvation of chloride ion in those protic solvents are required to account for the experimental observations. We have now extended that study to entering group chlorine kinetic isotope effects in aprotic solvents and have found a striking dependence of such isotope effects on hydrogen bonding to chloride ion.

Results and Discussion

Heavy atom kinetic isotope effects are the product of two

Table I. Kinetic Chlorine Isotope Effects for Reaction of 1.0 M Ethylene Oxide with Chloride Ion in Aprotic Solvents at 25.0°

Solvent	(Cl^-), M	Ratio (H^+/Cl^-)[a]	% reaction[b]	No. of expts	Isotope effect[c]
Acetone	0.066	1.0	15-20	4	1.00252 ± 0.00015
DMF	0.061-0.0066	1.0	9-12	4	1.00214 ± 0.00020
DMF	0.074-0.12	0.06-0.10[d]	6-10	5	0.99218 ± 0.00022

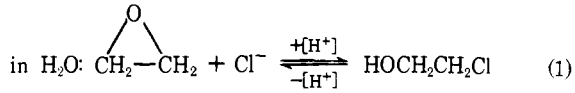
[a] Ratio of 2,6-litidinium ion chloride ion. [b] Range of percent conversion of chloride ion to 2-chloroethanol. [c] Corrected for percent reaction. Error is standard deviation. [d] 0.07-0.11 M LiCl used.

terms: (i) a temperature independent factor (TIF), which is due to an isotopic mass effect on the imaginary vibration that represents motion along the reaction coordinate, and (ii) a temperature dependent factor (TDF), which is determined by changes in bonding to the isotopic atom. For entering group heavy atom isotope effects, the TDF decreases as the bonding to the entering isotopic atom increases (transition state occurs later). The TIF also decreases as the transition state becomes later, but it always remains greater than unity.[10] For entering group isotope effects on reactions in which little bonding of the entering group has developed, the TIF will dominate the TDF and lead to normal ($^{35}Cl/^{37}Cl$ greater than unity) isotope effects. Such a situation was observed in the previous study of chlorine kinetic isotope effects for the reaction of chloride ion with ethylene oxide in H_2O, D_2O, ethanol, and *tert*-butyl alcohol, where the isotope effects were in the range 1.0022-1.0030.[2] As the transition state becomes later, the isotope effect should become smaller in magnitude and eventually less than one. It has been suggested that the opposition of the TIF (>1) and the TDF (<1) for entering group isotope effects restricts the utility of such effects, but this opposition can also be turned to advantage, as below.

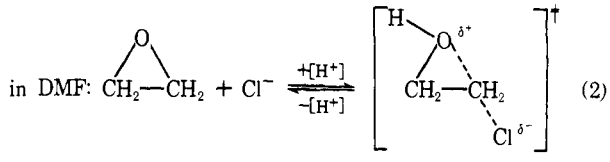
When isotope effects for the reaction of ethylene oxide with 1 equiv of 2,6-dimethylpyridinium (2,6-lutidinium) chloride were determined in acetone and in dimethylformamide (DMF), values of 1.0025 and 1.0021 were obtained (Table I). Not only are these isotope effects normal but they are not very different from the previous isotope effect found for this reaction in water.[2] The similarity of isotope effects for this reaction in protic and aprotic solvents implies a similarity of transition state insofar as the chlorine is concerned, and, therefore, no dependence of the chlorine isotope effect on the hydrogen bonding ability of the solvent, in contrast to our previous conclusion. However, it seemed possible that the 2,6-lutidinium ion present in the reaction in acetone and in DMF might have provided sufficient hydrogen bonding to chloride to provide the apparent similarity in isotope effects between the protic and aprotic solvents. The reaction of ethylene oxide and chloride ion does not occur in these aprotic solvents in the absence of a proton donor, but because isotope effect studies require the reaction to proceed only to 10-20% consumption of chloride ion to accumulate sufficient material for mass spectroscopic analysis, this problem can be partially circumvented. If 10% of the chloride ion in a reaction with ethylene oxide in DMF is provided as 2,6-lutidinium chloride and 90% as lithium chloride, the reaction can proceed until all of the 2,6-lutidinium ion (and 10% of the chloride ion) has reacted to give 2-chloroethanol and will then stop. It was determined that 2-chloroethanol and 2,6-lutidine under these conditions gave no measurable release of chloride ion in a period 50 times greater than the time required for completion of the ethylene oxide experiments. Thus a kinetic rather than an equilibrium isotope effect is being measured. Since it has been demonstrated that anionic nucleophiles are much more reactive in the absence of equivalent hydrogen bonding,[11] the reaction will then involve mainly non-hydrogen-bonded chloride ion. The chloride isotope effect for the reaction of ethylene oxide and chloride ion under these conditions has the remarkably large inverse value of 0.9922. This is the first example of an inverse heavy atom isotope effect for an entering group.

This change of isotope effect from 1.0021 in the presence of 1 equiv of 2,6-lutidinium ion to 0.9922 in the presence of 0.1 equiv of this cation might be due to one or both of two factors: change of transition state structure or change in hydrogen bonding to chloride ion. Preliminary kinetic studies on this reaction showed that it was first order in ethylene oxide and second order in 2,6-lutidinium hydrochloride. The leaving group in this reaction is probably ROH rather than RO^-, even at low concentrations of 2,6-lutidinium ion. The expected effect of an increase in nucleophilicity of chloride ion due to removal of the hydrogen bonding to 2,6-lutidinium ion would be to shift to a transition state with less bonding between chlorine and carbon and result in a smaller entering group isotope effect (larger absolute value). This is contrary to the experimental observation and therefore suggests that hydrogen bonding to chloride ion is the determining factor.

The importance of the effect of solvation on chlorine isotope effects can be seen by comparison of the equilibrium isotope effect (EIE) for the reaction of chloride ion with ethylene oxide in water[2] with the kinetic isotope effect (KIE) for the same reaction in DMF. Equilibrium isotope effects are determined

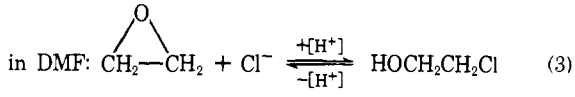


EIE = 0.9947 ± 0.0002



KIE = 0.9922 ± 0.0002

by only a TDF term (changes in bonding between reactant and product) whereas kinetic isotope effects are the product of a TDF term (changes in bonding between reactant and transition state) and a TIF term. Because the TIF term must be greater than unity,[10] the observed KIE for (2) must have a contribution from a TDF which is *at least* as large an inverse value as 0.9922, i.e., the TDF for (2) must be ≤0.9922. In addition, the TDF for an entering group EIE should be greater than the TDF for an entering group KIE in the same system, since a complete new bond to the entering group has been formed in the former case but only partially formed in the latter case. Therefore the equilibrium isotope effect for equilibrium 3 must be equal to or less than 0.9922. Comparison of the EIE for equilibria 1 and 3 demonstrates the effect of a change from a



EIE ≤ 0.9922

protic to an aprotic solvent on a chlorine isotope effect. It has been shown that the effect of solvent on an isotope effect should

Table II. Kinetic Chlorine Isotope Effects for Reaction of Dimethyl Sulfate with Chloride Ion at 25.0°

Solvent	$((CH_3O)_2SO_2)$, M	(Cl^-), M	% reaction	No. of expts	Isotope effect
H_2O	0.037–0.067[a]	0.20	3.3–4.2	5	1.00139 ± 0.00031
DMF	0.014–0.026	0.15	6.9–14.8	4	0.99511 ± 0.00021

[a] 0.01 M $NaHCO_3$ added.

Table III. Kinetic Chlorine Isotope Effects for Reaction of Chloride Ion with 1.0 M Ethylene Oxide with Different Acids in Water at 25.0°

Acid	(Cl^-), M	% reaction	No. of expts	Isotope effect
2,6-Lutidinium chloride	0.020–0.088	8–12	7	1.00280 ± 0.00017[a]
HCl	0.055–0.069	7–15	6	1.00245 ± 0.00015

[a] Reference 2.

Table IV. Kinetic Data for Reaction of 1.0 M Ethylene Oxide with Chloride Ion in DMF at 25.0°

(2,6-Lutidinium ion), M	(Cl^-), M	k_3, $M^{-2}\ s^{-1}$
0.027	0.027	6.49
0.054	0.054	4.40
0.068	0.068	3.08
0.081[a]	0.041	0.69[a]

[a] 0.040 M 2,6-lutidinium perchlorate.

be small in the absence of direct coupling of solvation bonds to a coordinate of the isotopic atom that is responsible for the isotope effect.[12,13] The effect of solvent in equilibria 1 and 3 will be exerted almost entirely on the chloride ion, for which the solvation bonds are all the bonds to the isotopic atom. From the two equilibrium isotope effects a *minimum* EIE for the transfer of a chloride ion from water to DMF of 1.0025 can be calculated. Therefore it is clear that hydrogen bonding to chloride ion can play a significant role in determining the magnitudes of chlorine isotope effects. This in turn makes it more certain that hydrogen bonding to chlorine in transition states is one cause of the lack of variation of chlorine kinetic isotope effects with structural changes in protic solvents.[7]

Since the reaction of chloride ion with ethylene oxide in DMF is a complicated reaction kinetically, a demonstration of this remarkable effect of a change from a protic to an aprotic solvent in a simpler system was sought. Because chloride ion is a poor nucleophile in water, a substrate with a good leaving group is required, if a simple SN2 reaction is to be studied. Dimethyl sulfate was chosen for experimental convenience. The isotope effect for the reaction in water is normal (Table II). The same reaction studied in DMF gives an inverse isotope effect of 0.9951. Without independent evidence on the structures of the transition states for the two reactions, the magnitude of the effect of solvation on this reaction cannot be determined, but the previous discussion suggests that solvation is again a dominant factor.

The difference in isotope effect between H_2O and DMF for the dimethyl sulfate reaction is remarkably large considering that the reaction is energetically favorable and that the transition state is therefore probably reactant-like in both solvents. More solvation of chloride seems to have been lost at the transition state that might have been expected for a reactant-like transition state. This suggests that the effect of solvent on the chlorine isotope effect is a nonlinear function of C–Cl bond order, i.e., that solvent effects are more important at low C–Cl bond orders (reactant-like entering-chloride isotope effects or product-like leaving-chloride isotope effects).

Consideration of the role of solvation in entering chloride isotope effects supplies a rationalization for a heretofore puzzling result. In Table III are recorded chlorine isotope effects for the reaction of ethylene oxide and chloride ion in water under weak- and strong-acid conditions. Whereas the first reaction is second-order overall and involves attack of chloride ion on unprotonated ethylene oxide, the HCl-catalyzed reaction is kinetically third-order overall and is considered to occur by attack of chloride ion on protonated ethylene oxide.[14,15] Since protonated ethylene oxide has a better leaving group, the transition state for the HCl-catalyzed reaction should be earlier (less C–Cl bonding), and an isotope effect of larger absolute magnitude might be expected for the HCl-catalyzed reaction. However, the reverse is experimentally found. These results can be rationalized by considering the effect of solvation on the chlorine isotope effects for these reactions. Since the isotope effects are small, early transition states for both reactions are likely.[2] Although the HCl-catalyzed reaction will have less C–Cl bonding (less decrease in the isotope effect) at the transition state, it will retain more of the original hydrogen bonding to water (less increase in the isotope effect). If the changes in bonding to solvent are more important than the changes in bonding to carbon for these early transition states in which very little C–Cl bonding has developed, the HCl-catalyzed reaction (earlier transition state) will have a smaller value for the entering-group isotope effect, even though the transition state is earlier than for the first reaction.

Experimental Section

The mass spectrometer used has been described, as have the materials, kinetic procedures, and preparation of samples for isotopic ratio measurements concerned with ethylene oxide and chloride ion.[2]

Acetone was purified as described by Wiberg.[16] DMF was dried over Linde 4A molecular sieves and distilled at reduced pressure (130 mm). Dimethyl sulfate was washed with cold water, dried over $CaCl_2$, and distilled, bp 36–37° at 2 mm (lit.[17] 76° at 15 mm).

A complete kinetic study of the reaction of ethylene oxide and 2,6-lutidinium hydrochloride in acetone was not made. It was determined that about 15% of the chloride in a 0.02 M solution of 2,6-lutidinium chloride reacted with 1.0 M ethylene oxide in acetone in 20 h at 25°. The actual percent reaction for the first two entries in Table I (required for calculation of the isotope effect) was determined from the amount of chloride reacted to give 2-chloroethanol by chloride ion titration.[2] Preliminary kinetic work on the reaction of 2,6-lutidinium chloride with 1.0 M ethylene oxide in DMF indicated that the reaction is first order in ethylene oxide and second order in 2,6-lutidinium chloride (Table IV). The kinetics was accurately second order in 2,6-lutidinium chloride within each experiment, and k_3 was calculated by dividing k_2 by the concentration of ethylene oxide. However, the third-order rate constant varied as a function of the initial concentration of salt in the reaction, probably due to ion-pairing effects.[2] The percent reaction for the third entry in Table I was determined from the ratio of 2,6-lutidinium ion to Cl^-. The reaction was allowed to proceed until no further Cl^- reacted (confirmed by titration to be equivalent to the initial concentration of 2,6-lutidinium ion). In the absence of a proton source no reaction between ethylene oxide and LiCl was observed after 5 days at 25°.

When 0.02 M $(CH_3)_2SO_4$ reacts with 0.1 M NaCl and 0.01 M $NaHCO_3$ in water, 0.015 M CH_3Cl and 0.005 M CH_3OH are pro-

duced within 8 h. The reaction of $(CH_3)_2SO_4$ with water to give methanol does not interfere with the reaction with chloride ion under study. The reaction was conducted in a round-bottom flask sealed with a vacuum stopcock. After the reaction was complete the CH_3Cl was distilled from the flask into a dry ice-acetone bath under vacuum at room temperature, and from the dry ice-acetone bath onto solid KOH at liquid N_2 temperature. The CH_3Cl was then purified as previously described.[2] The reaction was assumed to occur exclusively with $(CH_3)_2SO_4$ with no contribution from reaction of CH_3OSO_3H.[18]

$(CH_3)_2SO_4$ sulfate is known to react with DMF to give an adduct,[19] a reaction that can be conveniently followed by NMR. However, in the presence of 0.15 M LiCl no indication of the formation of this salt could be observed by NMR, and it was therefore assumed that this complication did not arise. Samples of CH_3Cl for mass spectroscopic analysis were collected by trap-to-trap distillation as described above from reaction of 0.1 g of $(CH_3)_2SO_4$ in 50 ml of 0.15 M LiCl for 12 h. The percent reaction of Cl^- was determined from titration of the initial and final concentrations of Cl^-.

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Comparison of the Mechanisms of Solvolysis and Rearrangement of K-Region vs. Non-K-Region Arene Oxides of Phenanthrene. Comparative Solvolytic Rate Constants of K-Region and Non-K-Region Arene Oxides

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Abstract: The non-K-region arene oxides, phenanthrene 1,2- and 3,4-oxide, rearrange in water to produce only phenanthrols. These unsymmetrical arene oxides open preferentially to the vinylogous benzylic carbonium ion; thus 1-phenanthrol and 4-phenanthrol are the major products obtained from the 1,2-oxide and 3,4-oxide, respectively. Opening of the epoxide ring is rate limiting, is subject to both specific acid and general acid catalysis, and in the absence of buffer follows the rate law $k_{obsd} = k_H a_H + k_{H_2O}$. Phenanthrene 9,10-oxide, the K-region arene oxide, rearranges to ~75% 9-phenanthrol, 18% trans 9,10-dihydro diol, and 7% cis 9,10-dihydro diol below pH 7 and ≥98% trans dihydro diol above pH 9. The rate-limiting opening of the epoxide ring is catalyzed by hydronium ion and general acids. Below pH 7, dihydro diol formation is the result of carbonium ion trapping by water. This reaction effectively competes with the NIH shift. From ~pH 9 to 11, dihydro diol formation results from nucleophilic attack of water on the arene oxide, while at pH's greater than 11 its formation is the result of nucleophilic attack by hydroxide ion. Thus the K-region arene oxide behaves like an ordinary aliphatic epoxide in basic solution. Deuterated analogues of phenanthrene 9,10-oxide were employed to verify carbonium ion formation as the rate-limiting step below pH 7 and the occurrence of the NIH-shift pathway for a K-region arene oxide.

Introduction

The metabolism of aromatic hydrocarbons involves the conversion of the hydrocarbon to an arene oxide by hepatic microsomal oxidation. Arene oxides have been implicated as the agents responsible for the carcinogenic and mutagenic activity displayed by certain polycyclic aromatic hydrocarbons.[2] Those hydrocarbons that exhibit carcinogenic activity have a common structural feature called a K-region[3] which is easily recognized since its excision from the aromatic hydrocarbon leaves only cyclic conjugated aromatic rings; thus, the 9,10 bond of phenanthrene is a K-region. Because of the association of carcinogenic activity with the presence of a K-region, we have undertaken an investigation of I and II (where the oxide is at a non-K-region position) and III (where the oxide is at the K-region position) in order to determine the