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Influence of Substituents on Kinetic Isotope Effects

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Abstract: The E2 reactions of methyl- and fluoro-substituted ethyl chlorides with CH_3^-, NH_2^-, OH^-, F^-, SH^-, and Cl^- have been investigated at the MP2/6-31+G(d) level of theory for probing whether kinetic isotope effects are related to the geometry of the transition stucture. The primary kinetic isotope effects only display the expected maximum for the most symmetric transition structure when corrections for equilibrium isotope effects are taken into account. Such corrections are in general not possible from experimental data alone. Secondary kinetic isotope effects at the CH_2Cl end of ethyl chloride correlate qualitatively with the carbon hybridization, although a quantitative relationship is lacking, even for closely related systems. The corresponding isotope effects at the carbon where a hydrogen is abstracted show little correlation with the geometry of the transition state.

Introduction

Within the usual Born−Oppenheimer approximation the potential energy surface for a reaction is independent of the nuclear masses. Reactivity differences of isotopically different molecules are mainly due to differences in the vibrational zero point energies, although corrections due to finite temperature may in some cases be significant. The most common form of Kinetic Isotope Effects (KIEs) is relative reaction rates for a protio/deuterio system. If the reaction involves breaking/forming a bond to hydrogen, the corresponding effect is denoted primary, while H/D substitution elsewhere gives raise to a secondary effect.

The reaction rate in transition state theory is determined by the difference in free energy between the reactant and transition structure (TS). This value can be calculated from the reactant and TS geometries and the corresponding vibrational frequencies. Kinetic isotope effects therefore contain information regarding the TS, a geometrical configuration which otherwise is difficult to probe experimentally. The information, however, is rather indirect, as the KIE is given in terms of a double energy difference between H/D substituted reactants and transition structures. Furthermore, the connection between the geometrical arrangement of the nuclei and the corresponding vibrational frequencies may be complicated.

Calculations on simple model systems have shown that the qualitative, and in some cases also the quantitative, change in the TS can be directly related to the KIE. The interpretation of primary kinetic isotope effects is usually done based on a three-center model, first examined in detail by Melander, Westheimer, and More O'Ferrall.[1−4] The PKIE calculated from this model was shown to have a maximum for a symmetric hydrogen transfer, and consequently, a variation in experimental PKIEs is usually taken to imply a change in the symmetry of the TS.

Secondary kinetic isotope effects (SKIEs) are normally only significantly different from unity when the H/D exchange is near the breaking/forming bond (α or β effects). Again based on calculations for model systems, the α-effects are interpretated as reflecting changes in the out-of-plane bending motion, i.e. hybridization changes or differences in the loose/tight character of the TS.[5−8] These models for interpretating KIEs are widely used; some recent examples are given in ref 9.

More recently, ab initio methods have been used for directly probing the connection between KIEs and transition structures.[10−12] For a series of E2 reactions of the type $X^- + CH_3CH_2Y$, we have found that equilibrium isotope effects may give a significant contribution to the PKIE, and the maximum as a function of the symmetry of the hydrogen transfer is very broad.[10] The SKIEs of the CH_2Y moiety reflect the corresponding hybridization fairly accurate, but the values for the

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CH_3 part are essentially unrelated to the geometry. These findings cast some doubt on the validity of interpreting differences in KIEs as changes in the TS. Nevertheless, it is expected that the KIE is a measure of the TS change for a series of sufficiently similar systems, the question being exactly how closely the systems should be related in order for a quantitative relation to hold. Our previous studies used several combinations of nucleophile/leaving groups, and the findings that the TS and KIE variations are not necessarily related may be because the systems are too dissimilar to allow a quantitative correlation. In the present work we examine E2 reactions for systems of the type $X^- + HCR_2CR_2Cl$, with R being either H, CH_3, or F. The substitution of a methyl group for a hydrogen is normally considered a minor perturbation, and should consequently represent a near optimum case for a quantitative correlation.

As in our previous work we are not attempting to reproduce or predict absolute KIE values for comparison with experimental results. The E2 reaction profile is significantly different in solution and the gas phase, and an accurate prediction of absolute values is a complicated problem, as discussed in detail by Hu and Truhlar.[13] We consider only the E2 reaction in an *anti* configuration, and concentrate on trends, i.e. whether variations in KIEs are related to changes in transition state geometries. For a more detailed survey of the literature related to E2 reactions, and the possibility of competing S_N2 reactions, we refer to previous papers.[10]

Quantum mechanical tunneling is likely to influence the magnitude of the isotope effects, especially the primary effect.[4,14−17] Corrections based on a one-dimensional reaction coordinate are not expected to provide a reliable estimate of these effects,[10b,18] and a multidimensional treatment is very demanding.[14] Consequently we have not included tunneling in any of the presented isotope effects. The usual interpretation of KIEs is based on model calculations which also neglect tunneling, and the current work is aimed at investigating the validity of these models. In some cases where the tunnel effect has been considered in model calculations, it is found to increase the PKIE values, but leave the qualitative interpretation unchanged (i.e. a maximum effect for a symmetric TS).[3b,16a]

Computational Methods

All calculations have been performed at the MP2/6-31+G(d) level with the Gaussian-92 and Gaussian-94 program packages.[19] This level of theory has been found to provide results in close agreement with calculations at the MP2/6-311++G(2df,2p) and QCISD/6-31++G(d,p) levels for E2 reactions of the present type.[20] Kinetic isotope effects have been calculated relative to the isolated reactants at a temperature of 298.15 K from statistical mechanics according to standard transition state theory. Harmonic frequencies have been employed without any scaling. A uniform scaling of all frequencies will change the absolute values of the isotope effects by a few percent, but the variation as a function of substituents is unaffected.[20]

For the systems involving CH_3^-, NH_2^-, OH^-, and SH^- as the nucleophile, one of the vibrational modes at the TS corresponds to a rotation around the breaking/forming C−H−Nu bond. This frequency is rather low (typical 40−50 cm^{-1}) since the rotational barrier is small. Consequently a description in terms of a harmonic oscillator is poor. The frequency, however, is virtually unaffected by the considered isotopic substitutions (changes less than 0.1 cm^{-1}), and it therefore makes no contribution to the isotope effects.

Bond orders are calculated as[11a]

$$n = \exp\left(\frac{R_0 - R_{TS}}{0.6}\right)$$

where R_0 refers to either the reactant or product geometry.

Results and Discussion

In the present work we have calculated transition structures and corresponding kinetic isotope effects for the E2 reactions of substituted ethyl chlorides HCR_2CR_2Cl with the nucleophiles CH_3^-, NH_2^-, OH^-, F^-, SH^-, and Cl^-. The reactions of ethyl chloride itself are found to be prototypical E2 reactions.[10] A variation of the TSs has been generated by replacing one or two of the nonreacting hydrogens by either methyl or fluoro groups. There are apparently no TSs corresponding to E2 reactions for the 1,1- and 2,2-difluoro-substituted systems with F^- as the nucleophile. Attempts of optimization lead to a collapse to transition structures for S_N2 reactions. Substitution of H by CH_3 is normally considered a minor perturbation, while a F group often changes the properties significantly. The use of for example NH_2 or OH groups would correspond to smaller electronic perturbations than F; however, the possibilities of intramolecular hydrogen bonding, and the additional conformational degrees of freedom, may give complications in terms of interpreting the results. The general features of the reactions, variation of the geometry as a function of nucleophile, analysis of the KIEs in terms of different contributions (translational, rotational, and vibrational), and charge distributions have been discussed in previous work,[10a] and will not be repeated here.

The labeling used is shown in Chart 1. Replacement of the migrating hydrogen by deuterium results in a primary KIE, while replacement of R groups (when not CH_3 or F) gives rise to a secondary KIE. All KIEs reported in this work refer to a single H/D substitution.

The calculated isotope effects are given in Tables 1−6. Geometrical data for all reactants, products, and TSs are provided as Supporting Information. The TS geometries for the methyl-substituted systems are in general close to the parent compounds, which may be found in ref 10a. For a constant

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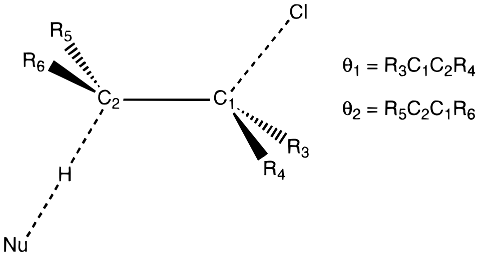
Chart 1



nucleophile belonging to the first row (CH_3^-, NH_2^-, OH^-, and F^-), the variation in R_{CH} and R_{NuH} for different substitution patterns is 0.05 Å, while the spread in the C−Cl distance is 0.10 Å. The dihedral angles θ_1 and θ_2 typically differ by a maximum of 2° and 5°, respectively, within these groups. The proton transfer angles are in all cases close to linear, always being above 175°. The difference between the methyl-substituted TSs for the SH^- and Cl^- nucleophiles is somewhat larger, and the hydrogen transfer angle deviates in certain cases by 15° from linearity. The spread in TS geometries caused by fluoro substitution is larger than for the corresponding methyl cases; typical variations within a group having a constant nucleophile are $\Delta R_{CH} = 0.08{-}0.23$ Å, $\Delta R_{NuH} = 0.02{-}0.18$ Å, $\Delta R_{CCl} = 0.07{-}0.16$ Å, $\Delta\theta_1 = 5{-}8°$, and $\Delta\theta_2 = 8{-}14°$. The proton transfer angle is in all cases above 170°.

The TS geometries may be classified as E2/E1/E1$_{cb}$-like, depending on their location in a More O'Ferrall−Jencks diagram with $1 - n_{CH}$ and $1 - n_{CCl}$ as the axes. The parent systems are discussed in ref 10a, where it is shown that all TSs have dominantly E2 character. For the first-row nucleophiles, the introduction of methyl substituents tends to form a cluster of TSs spread along the reaction diagonal, while the effect for the second-row nucleophiles primarily is in the perpendicular direction. These differences, however, do not appear to be correlated with the KIEs.

The activation energies for the first-row nucleophiles are in general slightly negative (−5 to −10 kcal/mol), but significantly positive for SH^- and Cl^- (20−25 kcal/mol). The reaction energy varies systematically from about −70 kcal/mol with F^- as the nucleophile to +30 kcal/mol for Cl^-. The calculated values are provided as Supporting Information.

The classical work of Melander, Westheimer, and More O'Ferrall[1−4] showed that the maximum PKIE is expected for a linear symmetric TS. The symmetry in these model calculations was defined in terms of the force constants for the two breaking/forming bonds to the migrating hydrogen. Since it is generally assumed that there is a correlation between bond distances and force constants, the symmetry consideration carries over to the TS geometries. When the two groups between which the hydrogen transfer occurs are not identical, the definition of geometrical symmetry becomes somewhat arbitrary. It would seem clear that some form of correction for the equilibrium distance in the corresponding reactant/product molecules must be made; however, several different choices are possible. While the uncorrected TS distances R_{CH} and R_{NuH} may be used when the nucleophile is CH_3^-, since the reactant and product C−H bonds are nearly identical, this does not seem appropriate when the nucleophile is for example OH^-. The O−H bond length in H_2O is shorter (and the force constant larger) than the C−H bond in CH_3CH_2Cl, which somehow must be taken into account when discussing the symmetry of the TS. One possibility is to subtract the equilibrium length, $\Delta R = R_{TS} - R_0$, or equivalently use bond orders, $n = e^{-\Delta R/a}$. This does not take into account that a longer bond in general also is a weaker bond, i.e. the energy cost for stretching a long bond by 0.3 Å is less than that for stretching a short bond by the same amount. This effect could be modeled by using a relative elongation, such as $\Delta R/R_0$, or by using bond orders where the a constant depends on the nature of the specific bond.[21] It should be noted that all such measures provide the same correlation when only the substituent pattern is varied, but will give slightly different representations when comparing reactions with different nucleophiles. For the present systems there is little difference between either of these measures, and we have chosen to use bond orders with a constant a value of 0.6.

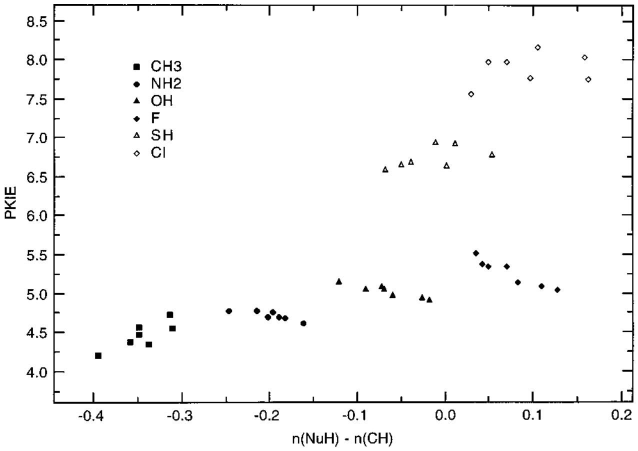


Figure 1. Primary kinetic isotope effect as a function of reaction symmetry for methyl-substituted ethyl chlorides.

Since the hydrogen transfer angles in all cases are very close to linear, only differences in the breaking/forming bond strengths are expected to influence the PKIE. The PKIEs as a function of the reaction symmetry ($n_{NuH} - n_{CH}$) for the methyl-substituted systems are shown in Figure 1, where the bond order axis corresponds to a variation of 0.23 Å in terms of the breaking C−H distance. The data for the first-row nucleophiles (CH_3^-, NH_2^-, OH^-, F^-) fall into separated groups in terms of $n_{NuH} - n_{CH}$, with a small gab between these groups. While the results for a constant nucleophile form a rather smooth variation of the PKIE as a function of reaction symmetry, there is a discontinuity between the end point in one group and the starting point of the next. Furthermore, the variation within these groups is opposite for CH_3^- than for the other three nucleophiles. The data for CH_3^- and NH_2^- alone might suggest a maximum around $n_{NuH} - n_{CH} \approx -0.25$; however, the OH^- and F^- values are all higher than this maximum. The results for the second-row elements (SH^- and Cl^-) are more scattered, and the absolute values are significantly larger.

The corresponding results for the fluoro-substituted systems are shown in Figure 2. The scatter within a group having a constant nucleophile is somewhat larger than for the methyl substitution, and the groups now overlap significantly. There is again a discontinuity of the PKIE variation between different nucleophiles.

As discussed previously,[10] the direct use of PKIEs is not completely appropriate since different systems in general will also have different equilibrum isotope effects (EIEs). A reaction with a very early TS will have a KIE of 1 (by definition), while one with a very late TS will have a KIE equal to the EIE. When comparing different systems, the PKIE scales are therefore different, and part of the difference in KIE will be due to differences in EIE. The calculated EIEs associated with the PKIEs are given in Tables 1 and 2, and it is immediately clear that part of the high PKIE values for the SH^- and Cl^- nucleophiles are due to the much larger EIEs.

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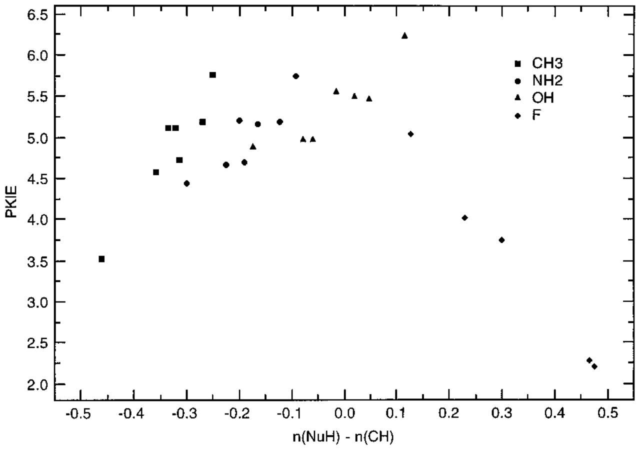

Figure 2. Primary kinetic isotope effect as a function of reaction symmetry for fluoro-substituted ethyl chlorides.

Table 1. Calculated Primary Kinetic Isotope Effects (Equilibrium Isotope Effects in Parentheses) for Methyl-Substituted Ethyl Chlorides as a Function of Nucleophile

R_3	R_4	R_5	R_6	CH_3^-	NH_2^-	OH^-	F^-	SH^-	Cl^-
H	H	H	H	4.718	4.693	4.965	5.039	6.768	7.743
				(1.065)	(0.905)	(1.027)	(1.350)	(2.127)	(2.351)
H	H	CH_3	H	4.559	4.776	5.044	5.339	6.911	8.034
				(1.145)	(0.973)	(1.104)	(1.452)	(2.287)	(2.528)
CH_3	H	H	H	4.557	4.671	4.933	5.094	6.624	7.760
				(1.069)	(0.909)	(1.031)	(1.353)	(2.135)	(2.360)
H	H	CH_3	CH_3	4.208	4.771	5.136	5.511	6.922	8.165
				(1.214)	(1.032)	(1.171)	(1.539)	(2.424)	(2.680)
CH_3	H	CH_3	H	4.370	4.685	5.069	5.368	6.641	7.976
				(1.143)	(0.972)	(1.025)	(1.449)	(2.283)	(2.524)
H	CH_3	CH_3	H	4.471	4.750	5.037	5.343	6.672	7.968
				(1.151)	(0.978)	(1.110)	(1.459)	(2.298)	(2.540)
CH_3	CH_3	H	H	4.345	4.613	4.905	5.135	6.577	7.566
				(1.068)	(0.908)	(1.030)	(1.354)	(2.132)	(2.357)

Table 2. Calculated Primary Kinetic Isotope Effects (Equilibrium Isotope Effects in Parentheses) for Fluoro-Substituted Ethyl Chlorides as a Function of Nucleophile

R_3	R_4	R_5	R_6	CH_3^-	NH_2^-	OH^-	F^-
H	H	H	H	4.718	4.693	4.965	5.039
				(1.065)	(0.905)	(1.027)	(1.350)
H	H	F	H	5.192	5.183	5.462	3.755
				(1.251)	(1.064)	(1.207)	(1.586)
F	H	H	H	4.581	4.663	4.960	4.015
				(1.091)	(0.928)	(1.052)	(1.383)
H	H	F	F	5.761	5.742	6.229	
				(1.439)	(1.224)	(1.388)	
F	H	F	H	5.113	5.199	5.557	2.198
				(1.261)	(1.072)	(1.216)	(1.599)
H	F	F	H	5.108	5.154	5.496	2.277
				(1.271)	(1.081)	(1.226)	(1.612)
F	F	H	H	3.524	4.445	4.868	
				(1.099)	(0.934)	(1.060)	

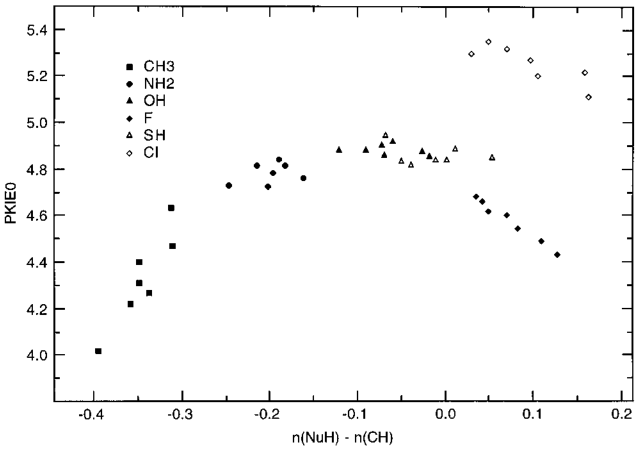

Figure 3. Primary kinetic isotope effect corrected for differences in equilibrium isotope effects as a function of reaction symmetry for methyl-substituted ethyl chlorides.

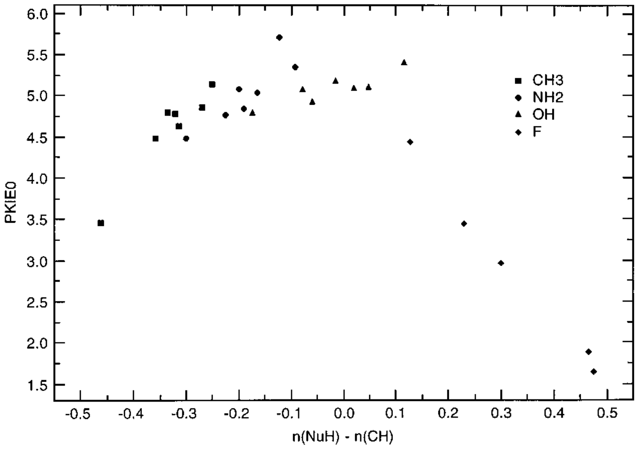

Figure 4. Primary kinetic isotope effect corrected for differences in equilibrium isotope effects as a function of reaction symmetry for fluoro-substituted ethyl chlorides.

In order to correct for this effect, two choices have to be made: (i) selection of a suitable reaction coordinate, and (ii) assignment of how the EIE contribution depends on this coordinate. In the present case we have chosen the reaction coordinate as $(1 - n_{CH})$, which has the advantage that it involves the same geometrical variable for all the systems, independent of the nucleophile. The simplest assumption for describing the EIE contribution is that the isotopic energy difference between the reactant and product is linear in the reaction coordinate, resulting in the following correction formula.

$$\ln(\mathrm{PKIE}_0) = \ln(\mathrm{PKIE}) - (1 - n_{CH}) \ln(\mathrm{EIE})$$

The "intrinsic" isotope effects are plotted as a function of the reaction symmetry in Figures 3 and 4. Note that the KIE axis in Figure 3 has been expanded by a factor of 3 relative to Figure 1. All the data for the methyl-substituted systems with first-row nucleophiles now display a rather smooth parabolic dependence on the TS symmetry. Furthermore, the scatter in the SH^- and Cl^- results is considerably reduced. The SH^- data now conform closely to those of the first-row nucleophiles, while the Cl^- results still are somewhat high.[22] The same trend is observed for the fluoro-substituted systems (Figure 4), although the improvement is not quite as impressive. Both curves appear to have a maximum corresponding to $n_{NuH} - n_{CH} \approx -0.1$ instead of 0.0; however, given the ambiguity in defining the symmetry discussed above, we do not consider this significant.

These results suggest that raw PKIEs do not necessarily agree with the common expectation of a parabolic dependence on the reaction symmetry, this requires a correction for differences in EIEs. Even for systems which differ only in the replacement of hydrogen by a methyl group is this correction necessary for obtaining consistent results. For the SH^- or Cl^- systems the main reason for the scatter is seen to be EIE differences. It should be noted that while both PKIEs and EIEs are experimentally accessible, the corrected PKIE_0 are not, as they require a knowledge of the value of the reaction coordinate at the TS.

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(22) The overlap of the SH^- and OH^- data is partly due to the choice of bond orders as a measure of the reaction symmetry. If the $\Delta R/R_0$ variables discussed in the text were used instead, the SH^- and Cl^- results would be displaced slightly toward the right in Figure 3.

Table 3. Calculated C_1 Secondary Kinetic Isotope Effects (Equilibrium Isotope Effects in Parentheses) for Methyl-Substituted Ethyl Chlorides as a Function of Nucleophile

				CH_3^-		NH_2^-		OH^-		F^-		SH^-		Cl^-	
R_3	R_4	R_5	R_6	d_3	d_4	d_3	d_4	d_3	d_4	d_3	d_4	d_3	d_4	d_3	d_4
H	H	H	H	1.045 (1.255)	1.045 (1.255)	1.040	1.040	1.042	1.042	1.063	1.063	1.119	1.116	1.148	1.148
H	H	CH_3	H	1.044 (1.257)	1.047 (1.247)	1.041	1.042	1.044	1.045	1.063	1.064	1.120	1.122	1.150	1.150
CH_3	H	H	H		1.050 (1.271)		1.053		1.051		1.078		1.138		1.168
H	H	CH_3	CH_3	1.042 (1.251)	1.042 (1.251)	1.038	1.038	1.042	1.041	1.060	1.059	1.116	1.120	1.147	1.147
CH_3	H	CH_3	H		1.053 (1.262)		1.041		1.055		1.080		1.144		1.170
H	CH_3	CH_3	H	1.049 (1.274)		1.048		1.054		1.079		1.130		1.169	

Table 4. Calculated C_1 Secondary Kinetic Isotope Effects (Equilibrium Isotope Effects in Parentheses) for Fluoro-Substituted Ethyl Chlorides as a Function of Nucleophile

				CH_3^-		NH_2^-		OH^-		F^-	
R_3	R_4	R_5	R_6	d_3	d_4	d_3	d_4	d_3	d_4	d_3	d_4
H	H	H	H	1.045 (1.255)	1.045 (1.255)	1.040	1.040	1.042	1.042	1.063	1.063
H	H	F	H	1.033 (1.285)	1.030 (1.229)	1.035	1.028	1.032	1.030	1.075	1.053
F	H	H	H		1.042 (1.301)		1.039		1.037		1.069
H	H	F	F	1.021 (1.270)	1.020 (1.270)	1.021	1.020	1.020	1.023		
F	H	F	H		1.024 (1.283)		1.020		1.024		1.082
H	F	F	H	1.027 (1.323)		1.025		1.023		1.095	

Even when the PKIEs are corrected for EIE differences, the inherent scatter for a series of substituted compounds near the maximum is larger than the change due to differences in reaction symmetry. For the methyl-substituted systems with NH_2^- and OH^- as the nucleophile, the $PKIE_0$ shows little connection with the symmetry of the H transfer. Similarly, the OH^- results for the fluoro systems have an increasing $PKIE_0$ as a function of $n_{NuH} - n_{CH}$, although the overall picture indicates that these data should be essentially on the maximum on the curve.

The interpretation of secondary kinetic isotope effects is usually taken as reflecting differences in the out-of-plane bending vibrations at the TS.[5,6] For a reaction going from sp^3 to sp^2 hybridization (as in the present case), the force constant should decrease, and a normal (>1) isotope effect is expected. For S_N2 reactions the SKIE is usually taken to reflect the loose/tight character of the TS, i.e. the C−H bending frequency is expected to increase if the nucleophile/leaving groups are geometrically close to the reacting center.[7,8,17]

We have chosen to describe the hybridization by the angles θ_1 and θ_2 defined in Chart 1. These definitions are preferred over the usual torsional angles (e.g. $R_5C_2C_1Cl$) since they avoid ambiguities associated with rotation around the C−C bond. In terms of the θ angles an idealized sp^3-hybridized center has an angle of 120°, and an sp^2 atom has an angle of 180°. For the 1- and 2-monosubstituted systems, the same hybridization (torsional angle) will be associated with two different SKIEs. The difference is small for the methyl-substituted C_1-SKIEs, less than 0.003, but the C_2-SKIEs differ by up to 0.018. The corresponding differences for the fluoro systems are 0.022 and 0.019. In the figures only the average values have been plotted.

A comparison of SKIEs between systems is again complicated by differences in EIEs (Tables 3−6), and in this case also differences in the reaction coordinate. The products are in all cases planar, but the torsional angles in the reactants differ. For the methyl-substituted ethyl chlorides, the reactant θ_1 angle varies from 121.0° to 124.8°, and θ_2 from 120.6° to 126.8°, which are of the same magnitude or larger than the variations in the TSs. In the fluoro-substituted reactants the θ_1 angle varies from 117.1° to 120.3°, and θ_2 from 119.0° to 120.7°.

The secondary kinetic isotope effect is normally taken to directly reflect the position of the TS, i.e. varying smoothly between 1 and the EIE for reactions having progressively later TS. Since the product in each case has a torsional angle of 180°, a normalized measure of the hybridization change may be defined as $\Delta\theta^\ddagger = (\theta_{TS} - \theta_0)/(180 - \theta_0)$. Assuming a linear free energy relationship, the connection between the SKIE and TS position is given as[5,11,23]

$$\ln(\text{SKIE}) = \Delta\theta^\ddagger \ln(\text{EIE})$$

By plotting ln(SKIE)/ln(EIE) against the calculated $\Delta\theta$, we probe whether the TS hybridization derived from the SKIE agrees with the actual TS geometry. These results are shown in Figures 5−8. It should be noted that if the above formula holds, it allows a determination of the TS angle from the corresponding reactant and product angles and the ln(SKIE)/ln(EIE) ratio, which all can be determined experimentally. In practice, however, the reactant/product geometries are rarely available, and the ln(SKIE)/ln(EIE) ratio is taken to directly reflect the TS hybridization.[23]

The C_1-SKIEs for the methyl-substituted systems (Figure 5) give a semiquantitative measure of the TS geometries. The straight line represents a perfect correlation, and it is seen that the TS hybridization calculated from the SKIE in general is more sp^2-like than is actually the case, or equivalently, the SKIE predicts a TS which is too late. Especially it appears that early TSs are problematic, since the reaction coordinate calculated from the SKIE levels off at a value ≈0.2. For the systems with CH_3^-, NH_2^-, and OH^- as the nucleophile, the ln(SKIE)/ln(EIE) ratio is essentially independent on the reaction coordinate. For

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Table 5. Calculated C_2 Secondary Kinetic Isotope Effects (Equilibrium Isotope Effects in Parentheses) for Methyl-Substituted Ethyl Chlorides as a Function of Nucleophile

				CH_3^-		NH_2^-		OH^-		F^-		SH^-		Cl^-	
R_3	R_4	R_5	R_6	d_5	d_6	d_5	d_6	d_5	d_6	d_5	d_6	d_5	d_6	d_5	d_6
H	H	H	H	1.149 (1.124)	1.149 (1.124)	1.160	1.160	1.165	1.155	1.147	1.147	1.089	1.103	1.088	1.088
H	H	CH_3	H		1.145 (1.146)		1.161		1.154		1.149		1.106		1.099
CH_3	H	H	H	1.138 (1.129)	1.137 (1.122)	1.165	1.153	1.161	1.167	1.120	1.138	1.084	1.084	1.078	1.068
CH_3	H	CH_3	H		1.133 (1.144)		1.143		1.158		1.135		1.087		1.083
H	CH_3	CH_3	H		1.146 (1.152)		1.164		1.158		1.147		1.090		1.091
CH_3	CH_3	H	H	1.131 (1.131)	1.131 (1.131)	1.162	1.162	1.161	1.161	1.132	1.132	1.116	1.116	1.059	1.059

Table 6. Calculated C_2 Secondary Kinetic Isotope Effects (Equilibrium Isotope Effects in Parentheses) for Fluoro-Substituted Ethyl Chlorides as a Function of Nucleophile

				CH_3^-		NH_2^-		OH^-		F^-	
R_3	R_4	R_5	R_6	d_5	d_6	d_5	d_6	d_5	d_6	d_5	d_6
H	H	H	H	1.149 (1.124)	1.149 (1.124)	1.160	1.160	1.165	1.155	1.147	1.147
H	H	F	H		1.189 (1.175)		1.205		1.200		1.228
F	H	H	H	1.163 (1.160)	1.144 (1.124)	1.165	1.166	1.168	1.164	1.184	1.173
F	H	F	H		1.157 (1.185)		1.178		1.190		1.228
H	F	F	H		1.187 (1.208)		1.184		1.190		1.255
F	F	H	H	1.121 (1.161)	1.121 (1.161)	1.135	1.135	1.144	1.144		

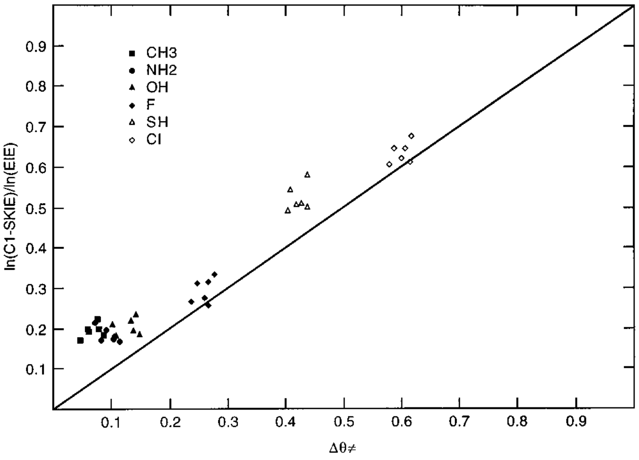

Figure 5. Transition structure position calculated from the C_1 secondary kinetic isotope effect as a function of the actual geometry for methyl-substituted ethyl chlorides. The line represents a perfect correlation.

reaction coordinates larger than 0.1, the overall trend of TS changes is correctly predicted by changes in the SKIE. It should be noted, however, that the correlation between systems differing only in terms of methyl substitution (constant nucleophile) is not quantitative, there is considerable scatter relative to a straight line. This is significant, as it implies that relative TS positions (early/late) may be predicted incorrectly by SKIE changes for such closely related reactions.

The corresponding plot (Figure 6) for the fluoro-substituted systems is similar to the methyl case, although there is no clear indication that the ln(SKIE)/ln(EIE) ratio levels off for small values. Most of the fluoro systems have very early TSs in terms of hybridization. Introduction of either methyl or fluoro groups produces both positive and negative changes in the R_{CH} and R_{NuH} distances relative to the unsubstituted cases. For the dihedral angles, however, exchange of a hydrogen by a methyl group consistently makes the TS angles larger than the parent system, while exchange by a fluoro atom consistently makes the angles smaller. In Figure 5 the substituted ethyl chlorides thus spread upwards by 2−4° from the parent values, while the fluoro compounds (Figure 6) spread downwards by 4−8°.

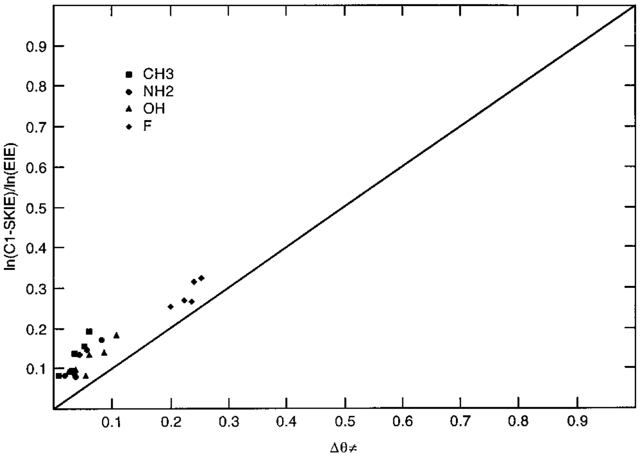

Figure 6. Transition structure position calculated from the C_1 secondary kinetic isotope effect as a function of actual geometry for fluoro-substituted ethyl chorides. The line represents a perfect correlation.

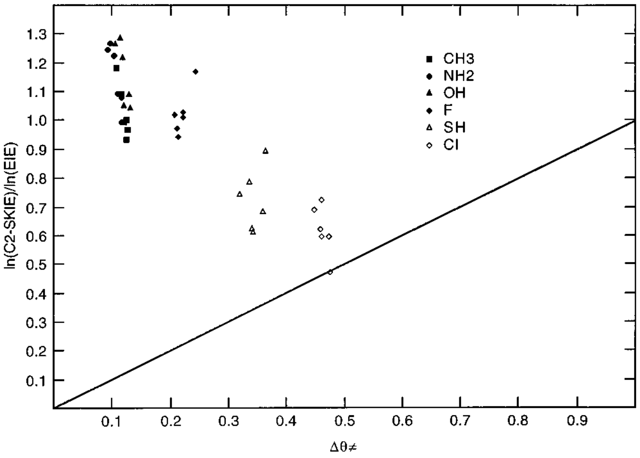

Figure 7. Transition structure position calculated from the C_2 secondary kinetic isotope effect as a function of actual geometry for methyl-substituted ethyl chlorides. The line represents a perfect correlation.

The C_2-SKIEs for the first-row nucleophiles are in general larger than the corresponding EIE, which in terms of the usual interpretation would imply that the TSs are more product-like than the products themselves. For the fluoro systems there are

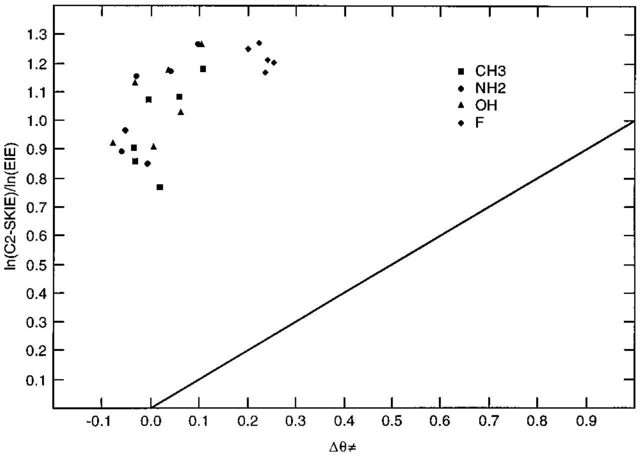

Figure 8. Transition structure position calculated from the C_2 secondary kinetic isotope effect as a function of actual geometry for fluoro-substituted ethyl chlorides. The line represents a perfect correlation.

furthermore several cases where the TS hybridization angle decreases upon going to the TS, i.e. the TS is more sp^3-hybridized than the reactant. Figures 7 and 8 (CH_3 and F substitution) clearly show that both absolute and relative TS positions along the reaction coordinate as inferred from the ln(SKIE)/ln(EIE) ratios will be qualitatively wrong. The variation in the C_2-SKIE for the methyl-substituted systems (Figure 7) is a decrease as the TS becomes more sp^2-hybridized, i.e. opposite to the expected correlation. The scatter in the fluoro-substituted systems is again somewhat larger than for the methyl systems, and the inherent variation obscures any trends. For the fluoro-substituted systems, essentially all the TSs fall outside the reaction coordinate range of 0−1 for either the *x*- or *y*-coordinate (or both). The experimental observation of a SKIE which is larger than the EIE would clearly indicate that the results cannot be interpretated by the usual models. However, as seen for the SH^- and Cl^- data in Figure 7, even SKIEs which are smaller than the EIEs may lead to qualitative incorrect interpretations regarding the change in the TS geometry. The reason for the lack of correlation between the C_2-SKIEs and TS geometries has been discussed previously,[10a] and it appears to be due to a TS "imbalance",[24] i.e. the charge transfer along the reaction coordinate behaves differently from the change in bonding.

Conclusion

The present investigation of E2 reactions shows that kinetic isotope effects cannot be relied on to correlate with the geometry of the TS, even for a series of compounds which are structurally very similar. The expected parabolic dependence of the primary KIE on the symmetry of the TS is only recovered when corrections are made for differences in equilibrium isotope effects. Even then, only limited subsets of reactions, like first-row nucleophiles and methyl substitution, give a reasonable correlation. Such EIE corrections are in general not possible from experimental data alone. Secondary KIEs for hydrogens associated with the carbon bearing the leaving group qualitatively reflect the hybridization, although the behavior for early TSs is inconsistent. A quantitative correlation, however, is lacking, even for systems which differ only in terms of methyl substitution. This is significant, since it implies that SKIEs not necessarily reflect TS changes, even for closely related systems. Secondary KIEs for hydrogens on the carbon where the abstraction takes place are unrelated to the corresponding hybridization. The KIEs are in many cases larger than the corresponding equilibrium values, or the hybridization angles decrease along the reaction coordinate, implying that the properties of the TS are not intermediate between the reactant and product. Even when the KIE is smaller than the EIE the qualitative change in the TS geometry is incorrectly predicted.

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Supporting Information Available: Tables containing geometrical data for all reactants, products, and transition structures and activation and reaction energies (15 pages). See any current masthead page for ordering and Internet access instructions.

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