Inference of Transition State Geometries from Kinetic Isotope Effects: An ab Initio Study of an E2 Model System

Sanne Schrøder Glad and Frank Jensen*

Contribution from the Department of Chemistry, University of Odense, DK-5230 Odense M, Denmark

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Abstract: Transition states for the E2 reaction of ethyl chloride with 11 different nucleophiles have been calculated at the MP2/6-31+G* level. The geometries comply with the rules of Thornton and the postulate of Hammond, and More O'Ferrall–Jencks diagrams show that the reactions are central and do not indicate $E1_{cb}$-like mechanisms. Three different kinetic isotope effects have been calculated for each nucleophile, and the variation with respect to different nucleophiles is shown to be due to hydrogen bending vibrations. Contrary to commonly accepted theories of kinetic isotope effects, the primary isotope effect does not pass through a maximum for the most symmetric transition structures. Furthermore, there is no simple overall correlation between secondary kinetic isotope effects and the geometry of the transition states. It is shown that the charge distribution at the transition state is not directly correlated with the geometry and that the common assumption that bond distances and force constants are proportional may not be valid. This casts some doubt on the validity of drawing conclusions about the transition state geometry from kinetic isotope effects.

Introduction

Kinetic isotope effects (KIEs), which are the ratio of rate constants for a pair of isotopically different molecules, are considered important tools for the elucidation of reaction mechanisms.[1,2] These effects are divided into primary and secondary isotope effects (PKIEs and SKIEs, respectively). The former are observed in reactions where a bond to the labeled atom is broken or formed in the rate-determining step, while the latter are observed in cases where the isotopic substitution is at a spectator bond. KIEs are usually interpreted as reflecting changes in the force constants from the reactants to the transition state (TS) and, as such, contain information on TS geometries.

There have been several attempts to explain theoretically the origin and variation of the KIEs.[3–7] The simplest realistic model for primary isotope effects involves a three-body transition state. The implications of such a model were first discussed in detail by Westheimer and by Melander, where the isotope effect for a linear hydrogen transfer was shown to have a maximum when the transition state is symmetrically located between reactant and product, i.e., when the force constants are identical.[3] More O'Ferrall showed that the PKIE decreases when the transition state for the hydrogen transfer becomes nonlinear. Thus, a linear symmetric transition state should have the largest PKIE.[4b] The basic rules concerning secondary kinetic isotope effects and transition state geometries were formulated by Streitwieser et al.[6] On the basis of model calculations, it was concluded that a reaction going from sp^3 to sp^2 hybridization should have a normal SKIE (>1) while the opposite reaction shows an inverse SKIE (<1).

E2 reactions are fundamental processes in organic chemistry and have been studied extensively, mostly in solution,[1a,2,8] but more recently also in the gas phase.[9–11] A number of generalizations regarding the nature of the transition state has evolved through these studies.[1a,1b,1d,2,8] The hydrogen being abstracted and the leaving group are periplanar in the transition state, and an *anti* orientation is usually favored. The E2 mechanism involves concerted, but not necessarily synchronous, making and breaking of the four bonds in the transition state. TSs where the bond to the leaving group is only slightly elongated relative to the reactant are classified as $E1_{cb}$-like, whereas in E1-like transition states, the deprotonation has hardly started. A spectrum of transition states from $E1_{cb}$-like through prototypic E2-type (central) to E1-like is possible, although most studies indicate that bimolecular eliminations have transition states in the $E1_{cb}$-like to E2 limits of the spectrum.[1a]

Most experimental solution phase studies of the E2 reaction have used compounds of the $ArCH_2CH_2X$ type as substrate and concentrate on the effect of different *para* substituents on TS geometries.[2,12,13] Primarily on the basis of kinetic isotope effects and Hammett ρ values, it has been concluded that the TSs become more reactant-like and more $E1_{cb}$-like for increasing electron-withdrawing ability of the substituent. Only a few investigations have considered the effect of different nucleophiles;[1a,b] these data

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generally support Thornton's rules[14] that transition structures become more reactant-like as the base strength is increased.

Relatively little theoretical work on E2 reactions has been reported.[15-19] Minato and Yamabe[16] reported transition structures for the reactions of F^- and Cl^- with CH_3CH_2F and CH_3CH_2Cl, using relatively small basis sets. Recently, Dewar and Yuan[18] used the AM1 method to investigate a variety of E2 eliminations employing methoxide and ammonia as nucleophiles. They reported $E1_{cb}$-like transition state geometries and showed *anti* orientations to be favored. In addition, one primary and two different secondary deuterium kinetic isotope effects were reported for methoxide as the nucleophile. Recently, Gronert[15] published theoretical studies on systems related to the reaction of F^- with CH_3CH_2Cl, concentrating on the competition between the S_N2 and E2 mechanisms. Geometries were optimized at the HF level while reaction energies were calculated at correlated levels. Very recently, Bickelhaupt et al.[17] presented DFT calculations on the gas phase reaction of F^- with CH_3CH_2F, also focusing on the competition between the E2 and S_N2 mechanisms. In all cases, the base-induced E2 reaction is found to dominate over S_N2 reactions in the gas phase, in agreement with gas phase experiments[1a,11c] but in contrast to the situation in solution.

We report here ab initio calculations on the E2 reaction of ethyl chloride with 11 different bases. This system is small enough that a reasonably sophisticated level of ab initio theory can be employed, and investigation of three different hydrogen/deuterium isotope effects (one primary and two different α-secondary) is possible.

Computational Details

All calculations have been done using the GAUSSIAN 92 program package.[20] The 6-31+G* standard basis set has been employed within second-order Møller–Plesset perturbation theory (MP2), MP2/6-31+G*//MP2/6-31+G* in the Pople notation.

The kinetic isotope effects were calculated from statistical mechanics according to standard TS theory

$$\Delta G_X^{\ddagger} = \Delta H_X^{\ddagger} - T\Delta S_X^{\ddagger}; \quad X \equiv \text{H or D}$$

$$\Delta\Delta G^{\ddagger} = \Delta G_D^{\ddagger} - \Delta G_H^{\ddagger}$$

$$k_H/k_D = \exp(\Delta\Delta G^{\ddagger}/RT) \qquad (1)$$

Harmonic vibrational frequencies were calculated by diagonalizing the mass-weighted force constant matrix. No frequency scaling has been employed. The force constants for individual bond lengths used in Figures 9 and 10 have been obtained by transforming the Cartesian force constant matrix to a set of internal coordinates. All reported isotope effects were calculated at 298.15 K. The order of KIE with respect to different nucleophiles is found to be temperature-independent in the range 100–600 K.

The isotope effects can be decomposed into contributions from translations, rotations, and vibrations, and the vibrational part further into contributions from the individual normal modes. The latter requires that a correspondence between the reactant normal modes and those of the TS, and between the protio and deuterio systems, is established. This was attempted by calculating overlaps between normal modes, using the central CH_2CH_2 fragment to align the systems. This approach was not sufficient for establishing a unique one-to-one correspondence between all the reactant and TS frequencies; especially, the nature of the hydrogen bending modes often changes significantly between reactant and TS and between the different TSs. A more rigorous assignment would require a number of frequency calculations along the reaction path for each nucleophile, which represents a significant increase in computational effort. We have therefore chosen to collect the frequencies into three groups of low, middle, and high frequencies. The correlation within these groups of frequencies is unproblematic, except for the NH_3 and PH_3 TSs. The frequency patterns for these species are substantially different from the other TSs, and only a separation of the contribution from the high frequencies is possible.

Table 1. MP2/6-31+G* Geometry Parameters[a]

Nuc	R_{CCl}	R_{CC}	R_{CH}	R_{NuH}	θ_{HCCH}	θ_{HCCCl}
reactant	1.792	1.516	1.095		60.9	60.9
CH_3^-	1.929	1.462	1.300	1.642	62.6	63.5
NH_2^-	1.939	1.460	1.325	1.444	63.0	63.1
OH^-	1.975	1.453	1.363	1.298	64.0	63.4
H^-	1.990	1.445	1.290	1.232	64.3	64.8
F^-	2.115	1.422	1.431	1.155	67.8	66.8
SiH_3^-	2.194	1.413	1.399	1.903	69.4	67.8
PH_2^-	2.204	1.411	1.400	1.796	69.7	67.9
SH^-	2.306	1.396	1.445	1.635	72.6	70.3
Cl^-	2.488	1.378	1.494	1.514	77.8	74.0
NH_3	2.701	1.361	1.929	1.093	87.3	81.7
PH_3	2.747	1.359	1.938	1.505	87.9	83.4
product		1.340			90.0	90.0

[a] Bond lengths are in angstroms, angles in degrees.

Results

The 11 nucleophiles used are H^-, CH_3^-, NH_2^-, OH^-, F^-, SiH_3^-, PH_2^-, SH^-, Cl^-, NH_3, and PH_3. Transition state geometries and kinetic isotope effects calculated at the HF/6-31+G* level[21] were found to be significantly different from those obtained at the MP2/6-31+G* level, in agreement with a previous study.[22] For this reason we will discuss only the MP2 results in detail. Although the TS geometries involve bonds stretched significantly beyond their equilibrium values, the MP2 method has in general been found to provide quite accurate results, and for systems of the present size, it is currently prohibitively expensive to carry out calculations at more advanced levels. For all nucleophiles, we have calculated reactant and TS geometries, vibrational frequencies, and three kinetic isotope effects: one primary KIE and two α-secondary KIEs.

Transition State Geometries and Charge Distributions. The MP2/6-31+G* optimized transition state geometries and the reactant and product geometries are shown in Figure 1. Only *anti* orientations have been considered since these have been shown to dominate in several investigations.[8,15a,15c,17,18b] The MP2 geometries are significantly different from those obtained at the HF level.[15a,21] For example, with the same basis set and with F^- as nucleophile, R_{CH} increases from 1.36 to 1.43 Å, R_{NuH} decreases from 1.20 to 1.16 Å, and R_{CCl} is shortened from 2.18 to 2.12 Å upon going from the HF to the MP2 level. The corresponding changes for PH_2^- are as follows: R_{CH} increases from 1.35 to 1.40 Å, R_{NuH} decreases from 1.91 to 1.80 Å, and R_{CCl} is shortened from 2.45 to 2.20 Å.[21]

All TS parameters changing significantly during the reaction are given in Table 1, where θ_{HCCH} is the dihedral angle for the C_1 hydrogens with respect to the hydrogen being abstracted, and θ_{HCCCl} is the dihedral angle for the two nondeparting hydrogens at C_2 relative to Cl. These angles describe the hybridization of the carbon atoms, while R_{CC}, R_{CCl}, R_{CH}, and R_{NuH} indicate the four active bonds. Taking the C–C bond distances as our reference, the TSs corresponding to CH_3^-, NH_2^-, OH^-, and H^- may be classified as reactant-like (31%, 32%, 36%, 40%), the TS of F^- as central (53%), and all TSs from the third-period

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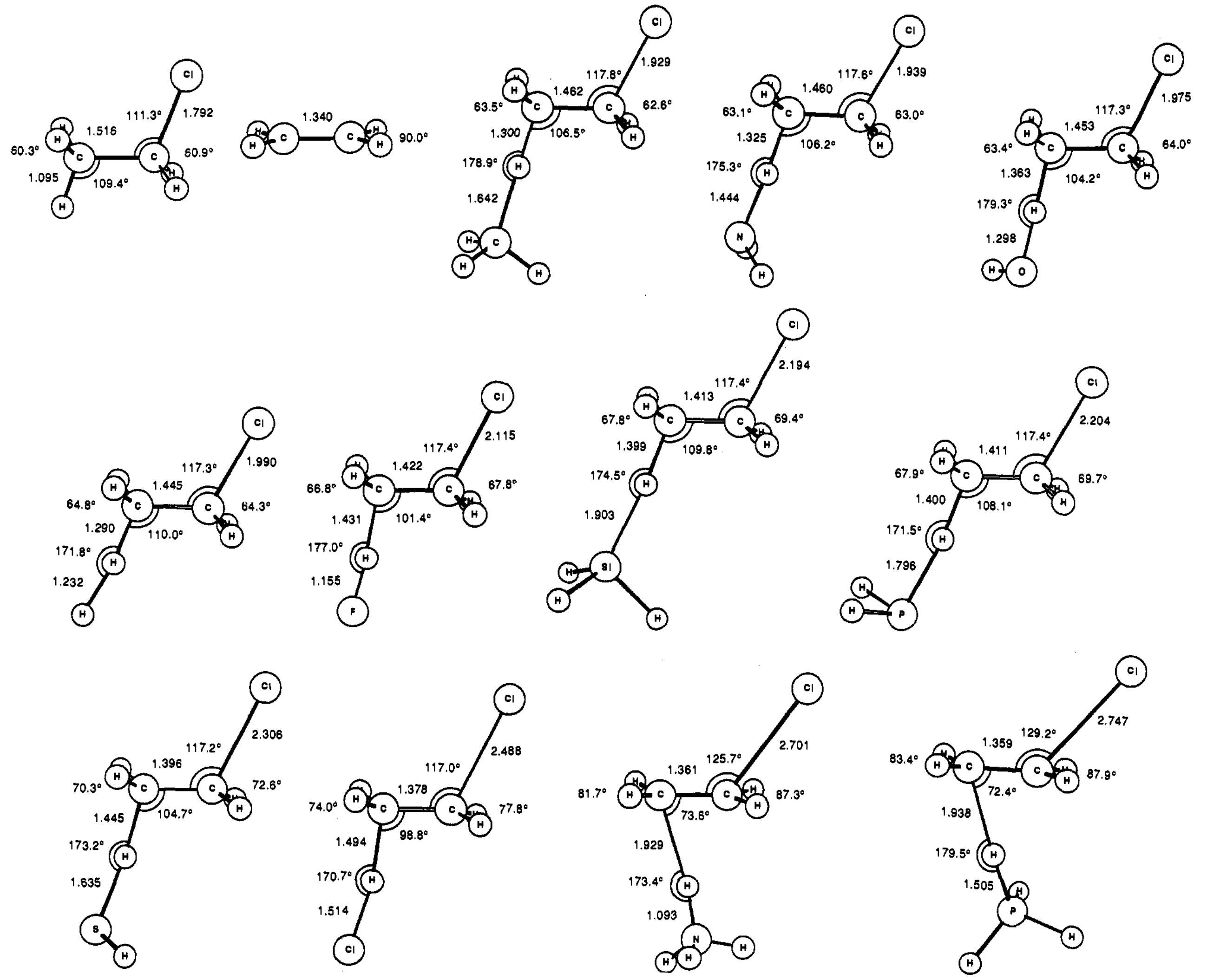

Figure 1. MP2/6-31+G* reactant, product, and transition state geometries. Bond lengths are in angstroms, and angles are in degrees.

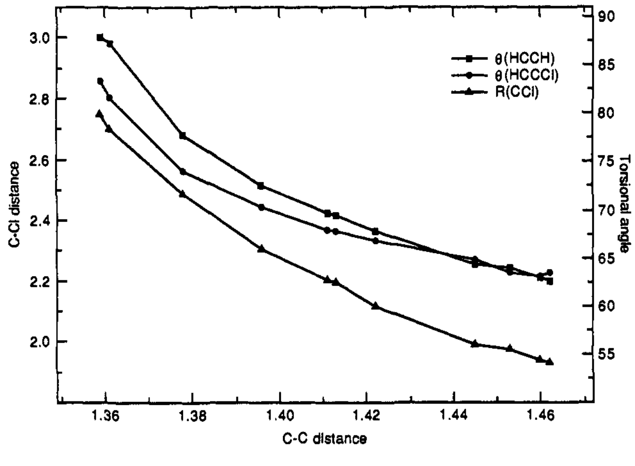

Figure 2. Correlation between geometrical parameters describing the ethyl chloride moiety. Bond lengths are in angstroms, and torsional angles are in degrees.

nucleophiles SiH_3^-, PH_2^-, SH^-, and Cl^- and the neutral nucleophiles NH_3 and PH_3 as productlike (59%, 59%, 68%, 79%, 88%, 89%). Thus, the order of nucleophiles, CH_3^-, NH_2^-, OH^-, H^-, F^-, SiH_3^-, PH_2^-, SH^-, Cl^-, NH_3, and PH_3, describes transition states of increasing productlike character. Figure 2 shows that there are strong correlations between the geometrical parameters R_{CC}, R_{CCl}, θ_{HCCH}, and θ_{HCCCl}; i.e., there is correlation inside the ethyl chloride moiety. In addition, there is an almost linear correlation between the Mulliken charge on Cl and these parameters (Tables 1 and 2). The C_2–H–Nu moiety, however, does not follow this trend (Table 1). Figure 3 shows that the breaking C–H distance mainly is determined by the reaction energy, behaving according to the Hammond postulate.[23] The R_{NuH} bond lengths depend on the nature of the nucleophile. We have made an approximate correction for this by converting the TS bond distance to a percent elongation from the corresponding distance in NuH ($\%\Delta R_{NuH} = 100\%(R_{TS} - R^{\circ}_{NuH})/R^{\circ}_{NuH}$). Figure 3 shows that $\%\Delta R_{NuH}$ also correlates with the reaction energy and R_{CH}. Except for the neutral NH_3 and PH_3 nucleophiles, the TSs have an almost constant CCCl angle, while the CCH angle displays some variation which correlates with R_{CC} within the series CH_3^-, NH_2^-, OH^-, F^- and SiH_3^-, PH_2^-, SH^-, Cl^-. Finally

Table 2. Mulliken Population Charge Distributions (HF/6-31+G*) at the Transition State Geometries and Reaction Energies (in kcal/mol) (MP2/6-31+G*)

Nuc	Cl	C_1H_2	C_2H_2	H	Nuc	ΔE
reactant	–0.06	0.04	–0.17	0.20		
CH_3^-	–0.24	–0.03	–0.22	0.33	–0.84	–71.0
NH_2^-	–0.29	–0.02	–0.33	0.43	–0.79	–53.4
OH^-	–0.34	0.11	–0.49	0.46	–0.75	–32.9
H^-	–0.43	0.27	–0.69	0.29	–0.45	–93.3
F^-	–0.49	0.14	–0.41	0.48	–0.73	–7.8
SiH_3^-	–0.52	0.05	–0.07	0.08	–0.55	–24.5
PH_2^-	–0.53	0.09	–0.13	0.12	–0.56	–16.0
SH^-	–0.64	0.14	–0.13	0.15	–0.51	10.6
Cl^-	–0.78	0.23	–0.15	0.21	–0.51	27.2
NH_3	–0.85	0.12	–0.07	0.43	0.37	143.5
PH_3	–0.86	0.07	0.04	0.08	0.67	162.0
product	–1.00	0.00	0.00			

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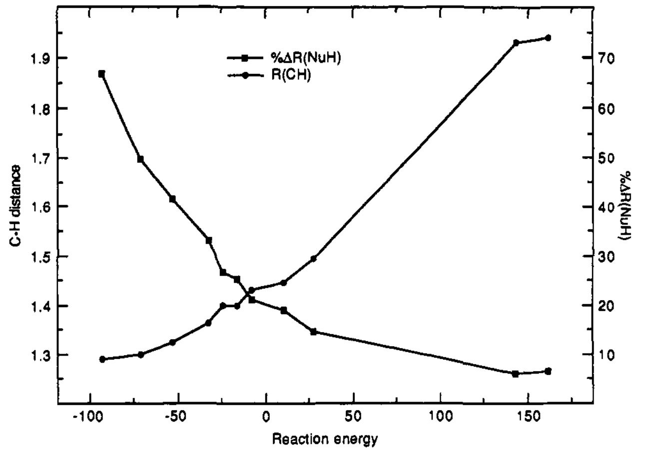

Figure 3. Correlation between geometrical parameters describing the C_2–H–Nu moiety and the reaction energy. Bond lengths are in angstroms, and energies are in kilocalories per mole.

it should be noted that the angle around the transferred hydrogen is close to linear for all TSs (171°–179°), and there does not appear to be any systematic correlation with other geometrical parameters.

The two neutral nucleophiles have very productlike transition structures. The dihedral angles indicate almost sp^2 hybridization, the two breaking bonds are very long, and the production of NH_4^+ and PH_4^+ is nearly complete. In addition, these TSs are characterized by CCH angles substantially smaller than for the anionic nucleophiles, and the distance between the nucleophile and C_1 is actually smaller than the distance to C_2. As such they resemble E2C-like TSs, although the angle around the abstracted hydrogen is still close to linear. The difference in geometry of the neutral and ionic nucleophiles can be explained by the charge distribution shown in Table 2. During the reaction, the neutral nucleophiles develop large positive charges in contrast to the anionic nucleophiles, which remain negatively charged. The departing chloride atom develops a full negative charge and the attraction or repulsion between the nucleophile and the chloride rationalizes the observed variation in TS geometry.

There are no correlations for the whole series of nucleophiles between the Mulliken charges and geometrical parameters besides the already mentioned correlation between $q(\mathrm{Cl})$ and R_{CC} (and thereby also with R_{CCl}). Nevertheless, it is evident from the data in Table 2 that there are correlations between charges and geometries within the above-mentioned two series of nucleophiles. In these series, C_1 and the transferred hydrogen become more positive while C_2 becomes more negative (F^- diverges slightly) as the TS gets more productlike. Furthermore, the C_2–H–Nu moieties for the nucleophiles belonging to the first and second periods in the periodic table (H^-, CH_3^-, NH_2^-, OH^-, F^-, NH_3) are much more polarized than for those belonging to the third period (SiH_3^-, PH_2^-, SH^-, Cl^-, PH_3). Gronert has also noted this effect in the study of the reaction of F^- and PH_2^- with CH_3CH_2Cl and attributed it to the fact that the transferred hydrogen is positively charged in the reactant and in the HF product but (slightly) negatively charged in PH_3.[15a,c] This, however, cannot explain the present observed variation in the whole series.[24] The charges on the hydrogen atoms in HCl and CH_4 are similar (+0.23 and +0.19), but differ significantly at the TS (+0.21 and +0.33). For the first- and second-period nucleophiles, the hydrogen is thus transferred with proton-like character, while it resembles a neutral atom transfer for the third-period nucleophiles.

In summary, for the whole series of nucleophiles, there is correlation between geometry parameters describing the ethyl chloride moiety and the chloride charge, and there is correlation between different geometry parameters describing the C_2–H–Nu moiety and the reaction energy. Within the two series consisting of anionic nucleophiles belonging to the same period in the periodic table, there is correlation between all six geometry parameters and the total charge distribution.

Table 3. Calculated MP2/6-31+G* Kinetic Isotope Effects[a]

Nuc	C_1-SKIE	C_2-SKIE	PKIE
CH_3^-	1.094	1.323	4.719
NH_2^-	1.072	1.330	4.695
OH^-	1.086	1.347	4.964
H^-	1.126	1.302	4.512
F^-	1.130	1.321	5.041
SiH_3^-	1.226	1.211	6.298
PH_2^-	1.224	1.196	6.213
SH^-	1.253	1.206	6.769
Cl^-	1.320	1.191	7.738
NH_3	1.517	1.334	1.245
PH_3	1.550	1.307	3.768

[a] C_1-SKIE refers to the secondary effect when two hydrogens at C_1 are substituted with deuterium, C_2-SKIE is the secondary effect for exchanging two C_2 hydrogens with deuterium, and PKIE is the primary effect for substituting the transferred hydrogen by deuterium.

Kinetic Isotope Effects. A main purpose of the present study is to investigate whether there exists a correlation between TS geometries and kinetic isotope effects. Table 3 shows three different deuterium isotope effects calculated for these systems. Replacement of the abstracted hydrogen by deuterium gives a primary effect (PKIE), while C_1-SKIE refers to the α-secondary effect resulting from replacement of two hydrogen atoms on the chloride carbon atom with deuterium, and C_2-SKIE is the value when the two nonreacting hydrogen atoms on the CH_3 carbon atom are replaced. In the gas phase, the E2 reaction is characterized by forming ion–molecule complexes between the reactants and TS and between the TS and products. In solution, the reactants proceed directly through the transition state to form products. The KIEs reported here have been calculated from the individual reactants. The general results are that the absolute values of the two SKIEs are normal (KIE > 1), as expected, and that the PKIEs are much larger than unity, except for the neutral nucleophiles, where the NH_3 value especially is substantially smaller than expected. For the anionic nucleophiles belonging to the first and second periods, the C_2-SKIE is larger than the C_1-SKIE while the opposite holds for the third period and the neutral nucleophiles.

The PKIE is expected to be dependent on the symmetry and linearity of the C–H–Nu moiety. All TSs in this study have angles around the transferred hydrogen close to 180°; thus the reaction symmetry is expected to be the main determining factor. The R_{CH} and R_{NuH} distances cannot be used directly as the latter is nucleophile dependent; we have taken instead the difference $\%\Delta R_{\mathrm{CH}} - \%\Delta R_{\mathrm{NuH}}$ as a measure of the symmetry of the TS. Figure 4 shows the PKIE as a function of this parameter. The percent difference indicates that SiH_3^- has the most symmetric TS, while the reaction energy places the midpoint between F^- and SH^- (Table 2). The PKIE for the third-period anionic nucleophiles (SiH_3^-, PH_2^-, SH^-, Cl^-) raises strongly as the TSs become more productlike, while the variation for the other charged nucleophiles is much smaller. There is no evidence from Figure 4 that the PKIE has a maximum for the most symmetric TS.

The usual interpretation of α-secondary isotope effects is in terms of hybridization changes of the isotopic center. The dihedral angles give a measure of this hybridization, and Figure 5 displays the C_1-SKIE and C_2-SKIE as a function of θ_{HCCH} and θ_{HCCCl}, respectively. While there is a tendency for the C_1-SKIE to increase with increasing angle (increasing productlike character of the TS), there is no correlation for the C_2-SKIE at all. The calculated equilibrium isotope effects (EIEs) are 1.581 and 1.271 for C_1 and C_2, respectively. Accordingly, the C_1-SKIEs lie between 1 and the EIE, which is the expected behavior, but several of the C_2-SKIEs are actually larger than the corresponding EIE.

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[24] The calculated Mulliken charges for the hydrogen: CH_4 (0.19), NH_3 (0.38), H_2O (0.49), HF (0.57), SiH_4 (–0.14), PH_3 (–0.02), H_2S (0.11), HCl (0.23), NH_4^+ (0.52), and PH_4^+ (0.12).

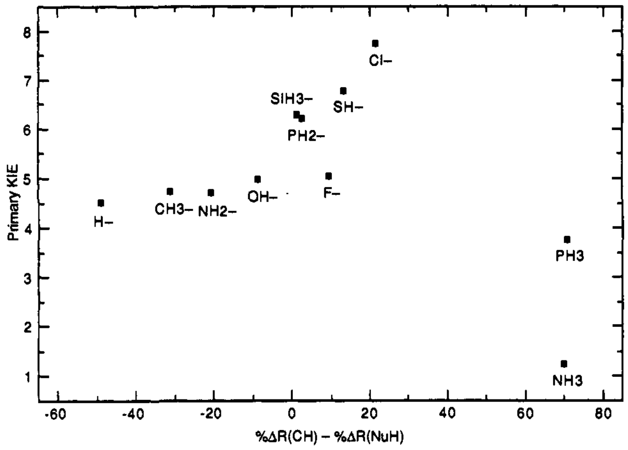

Figure 4. Primary kinetic isotope effect as a function of transition state symmetry around the transferred hydrogen.

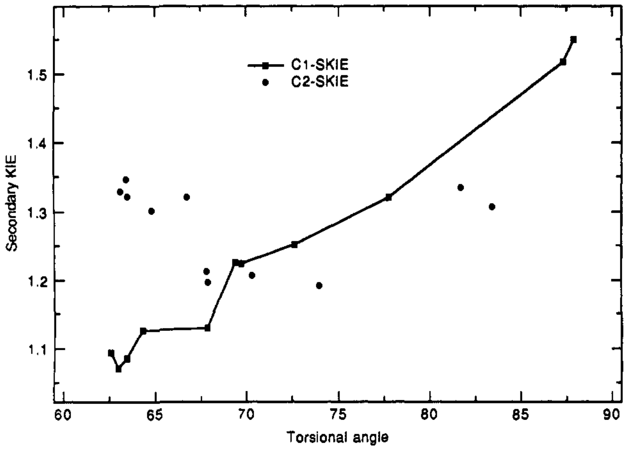

Figure 5. Secondary kinetic isotope effects (C_1-SKIE and C_2-SKIE) as functions of torsional angles at the deuterated centers (θ_{HCCH} and θ_{HCCCl}, respectively). Angles are in degrees.

Table 4. Contribution to the Total Secondary Kinetic Isotope Effect (C_1-SKIE) from Translational, Rotational, and Vibrational Motion[a]

Nuc	$SKIE_{tot}$	KIE_{trans}	KIE_{rot}	KIE_{vib}
NH_2^-	1.072	1.009	1.082	0.982
OH^-	1.086	1.010	1.080	0.996
CH_3^-	1.094	1.009	1.090	0.996
H^-	1.126	1.001	1.013	1.111
F^-	1.130	1.011	1.079	1.035
PH_2^-	1.224	1.016	1.080	1.115
SiH_3^-	1.226	1.015	1.090	1.108
SH^-	1.253	1.016	1.085	1.137
Cl^-	1.320	1.016	1.089	1.193
NH_3	1.517	1.010	1.150	1.307
PH_3	1.550	1.016	1.159	1.316

[a] Nucleophiles are arranged in order of increasing $SKIE_{tot}$.

Factor Analyses of Frequencies. In order to get a more detailed picture of the variation of the KIEs, these may be decomposed into contributions from translations, rotations, and vibrations. The H/D ratio of the rate constant may be written as

$$k_H/k_D = KIE_{vib}KIE_{trans}KIE_{rot}$$

$$KIE_x = \exp(\Delta\Delta G_x/RT) \quad (2)$$

where $\Delta\Delta G_x$ is the free energy difference between the deuterated and the nondeuterated reaction, calculated on the basis of the individual partition functions. Tables 4–6 show the results of such an analysis at 298.15 K for the C_1-SKIE, C_2-SKIE, and PKIE, respectively. The vibrational effects are the most important contribution to the absolute value of the KIEs, although for the C_1-SKIE for CH_3^-, NH_2^-, and OH^- it is actually the translational and rotational contributions which determine that the KIE is normal and not inverse. The variation in the C_1-SKIE is determined mainly by the vibrational contributions, although the rotational contributions for H^-, NH_3, and PH_3 differ slightly from those for the other nucleophiles. While the total variation in the C_1-SKIE is 0.42 across the series, the corresponding variation in the C_2-SKIE is only 0.16, and Table 5 shows that the rotational contribution is a significant factor in this variation. The vibrational KIEs for the SiH_3^-, PH_2^-, SH^-, and Cl^- nucleophiles are very similar, as are the contributions from those belonging to the second period, CH_3^-, NH_2^-, OH^-, F^-, and NH_3. The magnitude of the C_2-SKIE is thus a rather complex composite of vibrational and rotational factors, with these effects, to a certain extent, working in opposite phases. The variation in the PKIE, on the other hand, is entirely due to vibrational effects as seen in Table 6.

Table 5. Contribution to the Total Secondary Kinetic Isotope Effect (C_2-SKIE) from Translational, Rotational, and Vibrational Motion[a]

Nuc	$SKIE_{tot}$	KIE_{trans}	KIE_{rot}	KIE_{vib}
Cl^-	1.191	1.016	1.039	1.129
PH_2^-	1.196	1.016	1.060	1.110
SH^-	1.206	1.016	1.048	1.133
SiH_3^-	1.211	1.015	1.067	1.118
H^-	1.302	1.001	1.000	1.301
PH_3	1.307	1.016	1.090	1.180
F^-	1.321	1.011	1.035	1.263
CH_3^-	1.323	1.009	1.052	1.248
NH_2^-	1.330	1.009	1.046	1.260
NH_3	1.334	1.010	1.072	1.233
OH^-	1.347	1.010	1.038	1.284

[a] Nucleophiles are arranged in order of increasing $SKIE_{tot}$.

Table 6. Contribution to the Total Primary Kinetic Isotope Effect (PKIE) from Translational, Rotational, and Vibrational Motion[a]

Nuc	$PKIE_{tot}$	KIE_{trans}	KIE_{rot}	KIE_{vib}
NH_3	1.245	1.005	1.060	1.170
PH_3	3.768	1.008	1.067	3.503
H^-	4.512	1.000	1.010	4.468
NH_2^-	4.695	1.005	1.060	4.409
CH_3^-	4.719	1.004	1.060	4.432
OH^-	4.964	1.005	1.060	4.662
F^-	5.041	1.005	1.061	4.726
PH_2^-	6.213	1.008	1.070	5.760
SiH_3^-	6.298	1.008	1.069	5.848
SH^-	6.768	1.008	1.069	6.286
Cl^-	7.738	1.008	1.069	7.180

[a] Nucleophiles are arranged in order of increasing $PKIE_{tot}$.

In order to achieve a more detailed understanding of the variation of the C_1-SKIE and PKIE with transition state geometry, the vibrational contributions were further divided into individual frequency contributions. The variation in the C_2-SKIE is not dominated by the vibrational contribution; thus, a further partitioning is not relevant. As a unique one-to-one correspondence between the reactant and TS vibrations proved difficult to establish, we have instead chosen to collect the contributions into three groups: low, middle, and high frequencies. The low-frequency group encompasses the three vibrations of lowest frequency for the protio reactant (275, 343, 718 cm^{-1}), which corresponds to an internal rotation, a C–C–Cl bend, and a C–Cl stretch, respectively. Additional vibrations belonging to this group are the modes which are unique to the TS, such as the symmetric component of the reaction coordinate and internal rotations and bending vibrations around the transferred hydrogen. This translates approximately into frequencies below 750 cm^{-1}. The midfrequency group consists of all other vibrations below 2000 cm^{-1} which primarily corresponds to hydrogen bending modes. Finally, the group of high frequencies contains all stretching vibrations, i.e., modes with $\nu > 2000$ cm^{-1}. The frequency patterns for H^-, NH_3, and PH_3 are different from the other nucleophiles. The low mass of H^- causes this nucleophile to be part of almost all TS vibrations, which is not the case for

Table 7. Contribution to the Vibrational Secondary Kinetic Isotope Effect (C_1-SKIE) from Three Groups of Frequencies[a]

<table>
<tr><th>Nuc</th><th>$SKIE_{vib}$</th><th>KIE_{low}</th><th>KIE_{mid}</th><th>KIE_{high}</th></tr>
<tr><td>NH_2^-</td><td>0.982</td><td>0.856</td><td>1.139</td><td>1.006</td></tr>
<tr><td>CH_3^-</td><td>0.995</td><td>0.874</td><td>1.128</td><td>1.010</td></tr>
<tr><td>OH^-</td><td>0.996</td><td>0.860</td><td>1.175</td><td>0.985</td></tr>
<tr><td>F^-</td><td>1.035</td><td>0.848</td><td>1.278</td><td>0.955</td></tr>
<tr><td>SiH_3^-</td><td>1.108</td><td>0.806</td><td>1.435</td><td>0.957</td></tr>
<tr><td>H^-</td><td>1.111</td><td>0.914</td><td>1.217</td><td>1.000</td></tr>
<tr><td>PH_2^-</td><td>1.115</td><td>0.779</td><td>1.503</td><td>0.953</td></tr>
<tr><td>SH^-</td><td>1.137</td><td>0.728</td><td>1.680</td><td>0.928</td></tr>
<tr><td>Cl^-</td><td>1.193</td><td>0.715</td><td>1.854</td><td>0.901</td></tr>
<tr><td>NH_3</td><td>1.307</td><td colspan="2">1.429</td><td>0.915</td></tr>
<tr><td>PH_3</td><td>1.316</td><td colspan="2">1.422</td><td>0.926</td></tr>
</table>

[a] Nucleophiles are arranged in order of increasing $SKIE_{vib}$.

Table 8. Contribution to the Vibrational Primary Kinetic Isotope Effect from Three Groups of Frequencies[a]

<table>
<tr><th>Nuc</th><th>$PKIE_{vib}$</th><th>KIE_{low}</th><th>KIE_{mid}</th><th>KIE_{high}</th></tr>
<tr><td>NH_3</td><td>1.170</td><td colspan="2">0.155</td><td>7.559</td></tr>
<tr><td>PH_3</td><td>3.503</td><td colspan="2">0.464</td><td>7.549</td></tr>
<tr><td>NH_2^-</td><td>4.409</td><td>1.157</td><td>0.505</td><td>7.551</td></tr>
<tr><td>CH_3^-</td><td>4.432</td><td>1.123</td><td>0.522</td><td>7.556</td></tr>
<tr><td>H^-</td><td>4.468</td><td>1.024</td><td>0.577</td><td>7.557</td></tr>
<tr><td>OH^-</td><td>4.662</td><td>1.132</td><td>0.545</td><td>7.556</td></tr>
<tr><td>F^-</td><td>4.726</td><td>1.092</td><td>0.573</td><td>7.560</td></tr>
<tr><td>PH_2^-</td><td>5.760</td><td>1.104</td><td>0.691</td><td>7.555</td></tr>
<tr><td>SiH_3^-</td><td>5.848</td><td>1.109</td><td>0.701</td><td>7.532</td></tr>
<tr><td>SH^-</td><td>6.286</td><td>1.084</td><td>0.767</td><td>7.558</td></tr>
<tr><td>Cl^-</td><td>7.180</td><td>1.158</td><td>0.820</td><td>7.561</td></tr>
</table>

[a] Nucleophiles are arranged in order of increasing $PKIE_{vib}$.

the other nucleophiles. In the very productlike NH_3 and PH_3 transition states, the abstracted hydrogen is part of the XH_4 vibrations while for the other systems it typically is part of the ethyl chloride modes. This latter feature made a separation into low and middle frequencies impossible for NH_3 and PH_3, if the normal mode correlation should be consistent with the other nucleophiles.

The results for the factor analysis are given in Tables 7 and 8. Concentrating on the second and third period anionic nucleophiles, it is seen that the variation mainly is due to the midfrequencies. For the C_1-SKIE, the contributions from low and high frequencies are inverse and slightly decreasing as the KIE_{vib} increases, while the contribution from the midfrequency modes increases strongly. The bending modes thus determine the variation and are the main factor for the magnitude of the absolute value. Table 8 show that the low frequencies result in a contribution of approximately 1.1 to the PKIE, whereas the stretching vibrations give an essentially constant contribution of 7.6. The PKIE is primarily determined by the loss of zero-point energy due to the conversion of one stretching vibration in the reactant into the reaction coordinate. The KIE from the high frequency group is totally dominated by the change in this mode, and since this vibration is the same for all reactants, the high-frequency contribution is essentially independent of the nature of nucleophile. The variation in the PKIE is thus entirely due to the midfrequencies. These bending vibrations, however, are not the ones associated with the transferred hydrogen, as suggested by More O'Ferrall,[4b] but rather the bending modes primarily involving the hydrogen atoms of the ethyl chloride moiety.

Within our current partitioning of the frequencies, the low primary isotope effects for PH_3 and NH_3 are due to a large inverse contribution from the low/middle frequencies. The TSs for these nucleophiles are so productlike that the symmetric component of the reaction coordinate, which in our partitioning belongs to the low-frequency group, is almost completely converted to an X–H stretch in XH_4^+. The loss in zero-point energy for the CH stretch in the reactant is thus almost canceled by a corresponding term in the productlike TS.

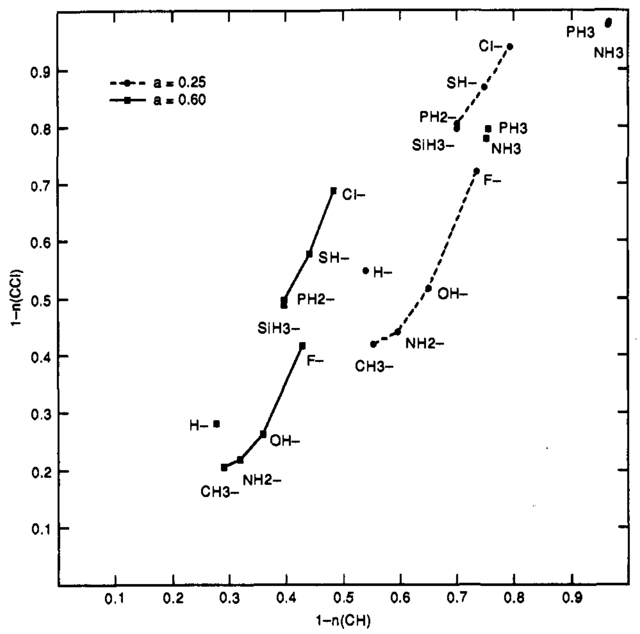

Figure 6. More O'Ferrall–Jencks diagram depicting CCl bond order against CH bond order using two different proportionality constants ($a = 0.25$; $a = 0.6$).

Discussion

Transition State Geometries and Atomic Charges. As mentioned in the Introduction, it has been inferred from experimental KIEs that the central E2 mechanism shifts toward $E1_{cb}$-like as the TS becomes more reactant-like. These assignments rely on a correspondence between the geometry and the KIE. On the contrary, Thornton's rules imply that the more productlike TSs have more carbanion than carbonium ion character, i.e., are more $E1_{cb}$-like.[1b]

The results presented here show that the 11 nucleophiles cover the whole range of reactant-like to very productlike transition structures. The early/late character of the TSs is determined by the R_{CH} and R_{CCl} bond lengths, which are not correlated across the total series, while the $E2/E1/E1_{cb}$ characterization arises from the synchronization of the breaking of these two bonds. Both variables can be illustrated by More O'Ferrall–Jencks (MOJ) diagrams,[25] which employ bond orders instead of bond lengths. The bond orders are calculated according to

$$n = \exp\left(\frac{R^\circ - R^\ddagger}{a}\right) \tag{3}$$

For interpolation between bond orders in the range 1–3, the constant a is usually set to 0.3.[1a,1b,1d] However, recently it has been suggested that a value of 0.6 is more appropriate for extrapolation to bond orders less than 1.[26] The CC bond length is well-defined both in the reactant and in the product, and by defining n_{CC} for the reactant and product to be equal to 1 and 2, respectively, an a value of 0.253 is obtained. As the exact value of a for the other bonds is debatable, we have chosen to depict the results for both $a = 0.25$ and $a = 0.6$. All bond orders are calculated using eq 3, with R°_{CH} and R°_{CCl} being the reactant values.

Figure 6 shows $1 - n_{CCl}$ as a function of $1 - n_{CH}$, which is the usual way of depicting E2 reactions. The reactants are located in the lower left corner and the products in the upper right corner. An $E1_{cb}$-like TS lies in the lower right corner whereas an E1-like TS belongs to the upper left corner. Transition states on the

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[25] (a) Pauling, L. *J. Am. Chem. Soc.* **1947**, *69*, 542–553. (b) More O'Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274–277. (c) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705–718. (d) Paolini, J. P. *J. Comput. Chem.* **1990**, *11*, 1160–1163.

[26] Houk, K. N.; Gustafson, S. M.; Black, K. A. *J. Am. Chem. Soc.* **1992**, *114*, 8565–8572.

diagonal from reactants to products classify the reaction as central. The figure indicates that all nucleophiles have more or less central (E2) TSs, regardless of the *a* value used, and the diagram does not support the idea that late TSs tend to display E1$_{cb}$-like mechanisms. The smaller of the two *a* values depicts the transition states as going from central to very productlike, while the larger indicates reactant-like to productlike TSs. On the basis of the reaction energies and the percent CC-bond values we believe the latter is the more appropriate.

Primary Kinetic Isotope Effects. The theoretical model calculations of hydrogen/deuterium primary kinetic isotope effects showed a reduction in the observed k_H/k_D as the transition state for the hydrogen transfer becomes nonlinear or unsymmetric.[3,4b] More O'Ferrall also considered proton tunneling[4a] by means of Bell's tunneling correction,[5a,5d,27] which is a one-dimensional correction depending only on the magnitude of the imaginary frequency. Inclusion of tunneling at this level does not fundamentally alter the conclusion that the isotope effect should pass through a maximum for a symmetric linear TS. Since these initial results, the subject of tunneling and PKIEs in E2 processes has been treated both experimentally[28] and theoretically.[29] The general conclusions are that the tunneling contribution is large when the PKIE is large; i.e., the variation with respect to different reactant parameters is not significantly altered. As accurate calculations of the tunneling contributions are rather time-consuming, and since we are primarily concerned with variation of isotope effects with geometries, we have chosen not to include tunneling calculations in this investigation. The absolute values of the calculated PKIEs are therefore most probably too low.

The theoretical model calculations of Westheimer and Melander focus on a single aspect of the TS geometry, the symmetry of the hydrogen transfer.[3] The results shown in Figure 4 indicate that this single aspect fails to explain the calculated behavior; there is no indication that the PKIE has a maximum for the most symmetric TS. The PKIEs may also be plotted in a MOJ-type diagram with the axes being $1 - n_{CH}$ and n_{NuH} as shown in Figure 7 ($R°_{NuH}$ is taken as the optimized bond length in NuH). The lower-left upper-right diagonal represents the symmetry of the hydrogen transfer, while the perpendicular diagonal describes the TSs as tight or loose. From the MOJ diagram it is seen that there is an increasing tightness for increasing productlike character. The loose/tight feature of the TS influences the KIE indirectly by changing the force constants for the bending vibrations, which were shown by the factor analysis to be responsible for the observed variation in the PKIE. Based exclusively on the C–H(D) out-of-plane bending vibration, it is believed that a loose TS will have a larger KIE,[1d,30] which is also indicated by the figure. This effect is not considered by model calculations.[3-5]

By definition, the isotope effect for a transition state located in the lower left corner is 1, while it is equal to the equilibrium isotope effect between reactant and product for a very productlike TS located in the top right corner. The EIEs, however, are not constant for this series of nucleophiles. The calculated values are as follows: H^- (3.57), SiH_3^- (2.47), Cl^- (2.35), PH_2^- (2.15), SH^- (2.13), PH_3 (1.79), F^- (1.35), CH_3^- (1.07), OH^- (1.03), NH_2^- (0.90), and NH_3 (0.76), ordered after decreasing values. Note that the ordering is not the one expected based on whether the stretching frequency for the XH bond is higher or lower than in CH_3CH_2Cl; the bending vibrations are also quite important. Strictly, the nucleophiles ought to have identical, or at least similar, EIEs to be analyzed in the same MOJ diagram. The different EIEs mean that the PKIE for very late TSs is different for each nucleophile, which to a certain extent also will influence the value for more central TSs. Any correction for the effect of different EIEs will have to rely on (i) selecting a suitable reaction coordinate and (ii) deciding how the contribution from the EIE depends on the chosen reaction coordinate. The simplest model may be taken as a linear free-energy relationship, i.e., the isotopic energy difference between reactant and product progresses linearly with the reaction coordinate. Taking the reaction coordinate as $1 - n_{CH}$ one obtains

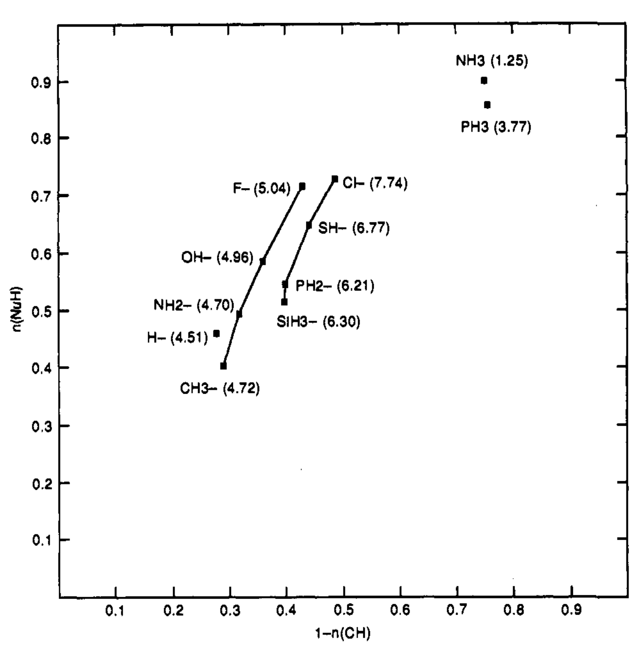

Figure 7. More O'Ferrall–Jencks diagram depicting NuH bond order against CH bond order ($a = 0.6$). Numbers in parentheses are the primary kinetic isotope effects.

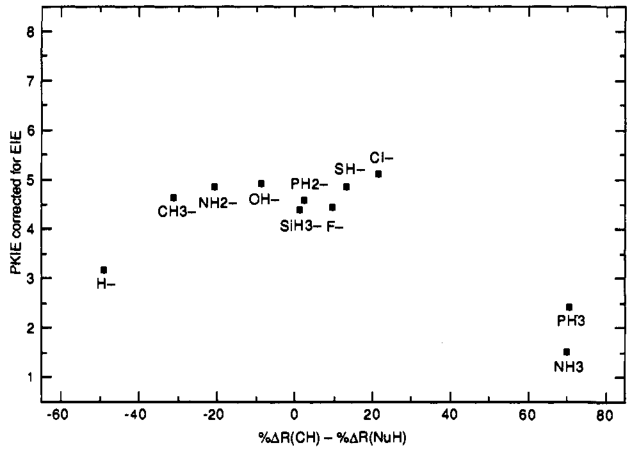

Figure 8. Primary kinetic isotope effects corrected for different equilibrium isotope effects as functions of the transition state symmetry around the transferred hydrogen.

$$\ln(\mathrm{PKIE}_0) = \ln(\mathrm{PKIE}) - (1 - n_{CH}) \ln(\mathrm{EIE}) \qquad (4)$$

In Figure 8, the PKIE$_0$, which is the hypothetical PKIE that would be observed if all EIEs were equal to 1.0, is plotted against the symmetry parameter $\%\Delta R_{CH} - \%\Delta R_{NuH}$. There are now some indications that the PKIE$_0$ may have a maximum for the most symmetric TS, although the maximum appears very broad. The second-period nucleophiles together with H^- appear to have a maximum close to OH^-, while the trend for the third-period

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(27) Bell, R. B. *The tunnel effect in chemistry*; Chapman and Hall: London, 1980.

(28) (a) Koch, H. F.; Dahlberg, D. B.; McEntee, M. F.; Klecha, C. J. *J. Am. Chem. Soc.* **1976**, *98*, 1060–1061. (b) Fouad, F. M.; Farrell, P. G. *Tetr. Lett.* **1978**, *47*, 4735–4738. (c) Miller, D. J.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 6749–6750. (d) Kaldor, S. B.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 7594–7599. (e) Thibblin, A.; Ahlberg, P. *Chem. Soc. Rev.* **1989**, *18*, 209–224. (f) Amin, M.; Price, R. C.; Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 4467–4471.

(29) (a) Saunders, W. H. *Chem. Scr.* **1976**, *10*, 82–89. (b) Burton, G. W.; Sims, L. B.; McLennan, D. J. *J. Chem. Soc., Perkin 2* **1977**, 1763–1770. (c) Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1984**, *106*, 2223–2224. (d) Saunders, W. H., Jr. *J. Am. Chem. Soc.* **1985**, *107*, 164–169.

(30) Smith, P. J.; Westaway, K. C. *Synthesis and Applications of Isotopically Labeled Compounds*, **1988**, 213–218.

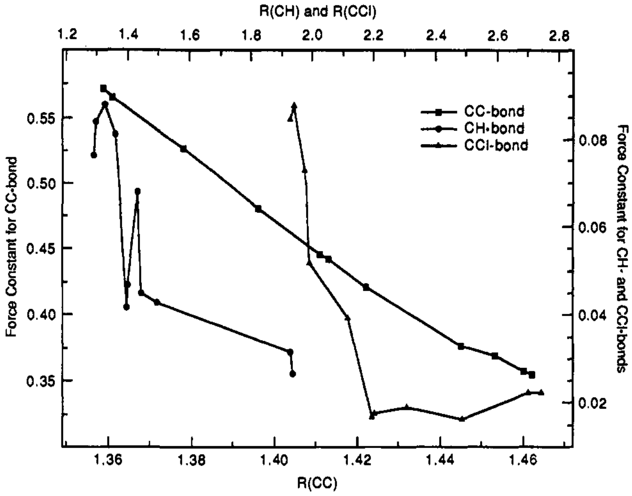

Figure 9. Correlation between bond lengths and force constants for the CC, CH, and CCl bonds. Force constants are in atomic units, and bond lengths are in angstroms.

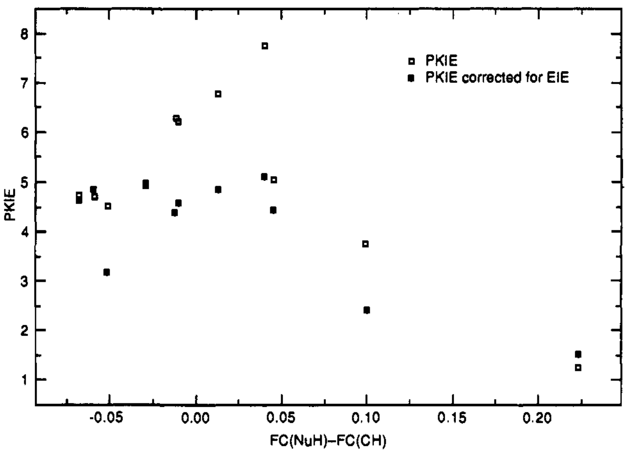

Figure 10. Primary kinetic isotope effects as functions of the transition state symmetry around the transferred hydrogen based on force constants (au).

nucleophiles still is an increase for increasing productlike character. Furthermore, the corrected PKIEs for the third-period nucleophiles are now very similar in absolute value to those for the second period; thus, the otherwise marked difference between the two sets appears to be due mainly to differences in EIEs.

The model calculations assess the symmetry of the TS on the basis of the force constants of the two bonds; however, it is generally assumed that bond distances and force constants are closely correlated.[3,4b] The present data allow an evaluation of this assumption. Figure 9 shows the calculated force constants as functions of the bond distances for the CC, CH, and CCl bonds at the TS. For the CC bond there is indeed an almost linear correlation, but the variation for the CH and CCl bonds is much more erratic. An analysis for the NuH bond is less relevant as it is nucleophile-dependent. Thus, instead of depicting the isotope effects as functions of bond lengths or bond orders, the PKIE and the EIE-corrected PKIE may be plotted against a symmetry parameter based on the force constants, $FC_{NuH} - FC_{CH}$; this is shown as Figure 10. As for Figures 4 and 8, there is little or no indication of a maximum for the PKIEs, and there is only a very qualitative correlation between the EIE-corrected PKIE and TS symmetry. It is important to realize that the EIE correction may only be performed if the location of the TS is known, and it furthermore depends on the chosen reaction coordinate and the interpolating function. It will therefore in general not be possible to arrive at such corrected PKIEs from experimental data only. Without the EIE correction, there is little or no correlation between PKIE and TS symmetry. The limitations of describing real systems by the simple three-center model have been recognized previously, and other systems also exhibit broad maxima of the KIE as a function of reaction symmetry.[31] Summarizing, it appears that previous model calculations are too limited in scope to explain the observed variation in PKIE. Both the reaction symmetry, the loose/tight feature of the TS, and the equilibrium isotope effect appear to influence the magnitude of the PKIE.

There are a number of experimental data for PKIEs for E2 reactions.[32] The ethyl chloride reagent used in this theoretical investigation may not be a good model for the experimental systems, which often involve aromatic rings as substituents. Furthermore, the experimental data have contributions from solvent and tunneling, which are not included in the calculated values. The available experimental data show large variation in the PKIE, even for quite similar systems. With Cl^- as the leaving group in a fluorene derivative, Thibblin has observed a PKIE of 8.1 when OH^- was the nucleophile and 6.6 when CH_3O^- was used.[32e] The latter is in good agreement with an earlier value of 6.4 obtained by More O'Ferrall and Warren.[32b] The reaction of 2-chloro-2-methyl-1-phenylpropane with CH_3O^- gave a lower value of 4.9.[32f] Elimination of Br^- by phenoxide from 2-phenylbromoethane has a reported PKIE of 7.6,[32d] while the corresponding reaction with cyclohexane bromide gives a value of only 4.0.[32a] These examples, which are the ones that resemble the present ethyl chloride system the most, clearly illustrate the sensitivity of the PKIE to variations in experimental conditions, and a direct comparison with the present theoretical data is of little use.

Secondary Kinetic Isotope Effects. An analysis of the changes in the force constants for the bending vibrations lead Streitwieser et al. to conclude that a reaction going from sp^3 to sp^2 hybridization should have a normal SKIE (>1).[6] The dihedral angles at C_1 and C_2 in the ethyl chloride system measure the carbon atom hybridizations; thus, the reactant is almost purely sp^3 hybridized (61°) and the product sp^2 (90°). All TSs have intermediate angles covering the range from 63° (CH_3^-) to 88° (PH_3) and thus represent $sp^{2.x}$ hybridizations. It is therefore expected that all reactions should have normal SKIEs, as indeed is found. Note, however, that the vibrational contributions to the C_1-SKIE for CH_3^-, NH_2^-, and OH^- actually are inverse (Table 4) and that it is the contribution from mainly the rotations which makes the KIEs normal. The factor analysis (Table 7) reveals that the midfrequencies, which cover bending vibrations, give a normal KIE, but this is to a certain extent offset by the inverse contribution from the low frequencies. The analysis by Streitwieser et al. focused exclusively on the bending vibrations, and our results confirm that these give a normal KIE; however, they show also that the other vibrations cannot be neglected. Furthermore, the C_2-SKIE for several of the nucleophiles is actually larger than the EIE, which in the Streitwieser analysis would indicate that these TSs are more sp^2 hybridized than the product.

The rules of Streitwieser suggest that the more sp^2-hybridized TSs should have the larger isotope effect. Figure 5 shows that this holds reasonably well for the C_1-SKIE, but clearly not for the C_2-SKIE. It has been questioned whether the magnitude of the secondary deuterium isotope effect contains any information concerning the geometry of the transition state for an E2 process.[12] The present study indicates that a change in C_1-SKIE of 0.02 (a typical experimental uncertainty) corresponds to changes in the TS geometry of approximately 0.05 Å in bond lengths and 2° in hybridization angle. Thus, one of the SKIEs does seem to contain information on geometry, but the results for the C_2-SKIEs show that this is not a fundamental property and that the TS geometry

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is not the only determining factor for the isotope effect. The θ_{HCCH} and θ_{HCCCl} dihedral angles are within a few degrees of each other for each nucleophile (Table 1), but the C_2-SKIEs for H^-, CH_3^-, NH_2^-, OH^-, and F^- are much larger than the C_1-SKIEs from this group. The reverse is true for NH_3 and PH_3, which have C_2-SKIEs close to those for NH_2^- and H^- despite having very different TSs.

The calculated SKIEs are directly related to the magnitude of the force constants for the CH bonds, which reflect the electron distribution in the vicinity of the bonds. As shown by the present data, there is not necessarily a correlation between the geometry and electron distribution, as indicated by the atomic charges. Given that both the Mulliken charges and the force constants are properties of the wave function, it thus follows that geometry and force constants may not correlate either. The C_2-SKIE values for all second-period nucleophiles are significantly larger than those for the third period. This correlates with the difference in charge polarization of the C_2–H–Nu moiety; i.e., the charge distribution appears quite important for the C_2-SKIE. However, a correlation between geometry and Mulliken charges does not necessarily imply that a correlation between geometry and force constants exists. This is seen in the two series of anionic nucleophiles where the C_2-SKIEs do not follow the geometries, despite correlations between the geometries and charges within these series. Atomic charges are only crude indicators of the wave function while force constants reflect more subtle changes.

There are only a few experimental reports on SKIEs for E2 reactions. The absolute value depends on the concentration of base[33,34] and is generally between 1 and 1.4.[2,9e,13,28b,34,35] Smith et al. have measured a C_1-SKIE value of 1.17 for the reaction of *tert*-butoxide with 1-chloro-2-phenylethane.[34] Cook et al. have measured both types of SKIE for cyclohexane derivatives. With Br^- or TsO^- as the leaving group and either PhO^- or AcO^- as the nucleophile, they obtained values in the range 1.13–1.15 and 1.15–1.25 for C_1-SKIE and C_2-SKIE, respectively.[35] The C_1-SKIE values are slightly higher than the present calculated value for OH^- (1.09), while the C_2-SKIE values are significantly lower than the calculated (1.35). As for the PKIE, the differences in substrate and leaving groups, and the influence of solvent, make a quantitative comparison between the theoretical and experimental data difficult.

Conclusion

The generally accepted view of kinetic isotope effects is that primary KIEs reflect the symmetry and linearity of the atom transfer, while secondary KIEs mainly reflect the hybridization and/or loose/tight feature of the TS. As such, KIEs have been used for inferring variations in TS geometries upon changes in substrate or solvent. These rationalizations are almost exclusively based on model calculations. In all of these calculations it is assumed a priori that there is a smooth variation of the force constants with geometry, e.g., a linear correlation between force constants and bond order. The present results show that this may not always be true, at least not for a relatively large series of TSs. The results also show that some of the fundamental assumptions of previous model calculations may not be generally valid. The dependence of the PKIE on the TS symmetry does not take into account contributions from differences in the looseness of the TS; i.e., for the E2 reaction the carbon–nucleophile distance should be "constant". This will very rarely be true. Even for a given nucleophile it is very unlikely that the CNu distance will be the same for, for example, different leaving groups. Furthermore, for a series of nucleophiles it is difficult to give a unique definition of a "constant" CNu distance as it will be very dependent on the nature of the nucleophile. Outside the model calculations, the symmetry of the atom transfer will thus always be coupled to the loose/tight feature of the TS. Comparisons between PKIEs for different nucleophiles are furthermore hampered by differences in equilibrium isotope effects. A correction for this effect requires knowledge of the TS position and selection of a suitable model for the progression of the EIE along the reaction coordinate. The first requirement is very difficult to determine experimentally, and the latter criteria will always be open to different opinions.

As mentioned above, there may be a fundamental problem that the correspondence between geometry and force constants is not generally valid for a series of TSs. Force constants are measures of bond strengths, i.e., the electron distribution in the vicinity of the atoms defining the bond. Only if the electron distribution varies smoothly with the geometry can a general correspondence between geometry and force constants be expected. The atomic charges may be taken as an indication of the electron distribution. As shown by the present data, there is only a correlation between charges and geometry within certain subsets of nucleophiles. Shaik et al. have recently shown that TS geometries are primarily determined by the reactant and product VB wave functions, while the charge distribution at the TS is controlled by electron configurations which are relatively unimportant for describing the reactant and product.[36] The fact that several of the C_2-SKIEs are larger than the corresponding EIEs indicates that the wave function at the TS is not simply an interpolation between those of the reactant and product, although the TS geometry is intermediate. Isotope effects are thus determined by the electron distribution at the TS, which may or not be correlated with the geometry.[36,37] The number of reaction series which have been investigated at suitable theoretical levels is currently too small to be able to draw any conclusions whether such a correlation in general is the rule or the exception.

The present series of calculations show that there is no reason to expect a priori that KIEs in a simple way reflect changes in TS geometries, as is clearly illustrated by the C_2-SKIE results. On the other hand, the results also show that some KIEs may contain valid information on TS geometries. If only anionic nucleophiles from the same period in the periodic table are considered, there is correlation between all different geometry parameters, the charge distribution, the reaction energy, and two kinetic isotope effects. Inside these groups, both the C_1-SKIE and the PKIE show a general increase as the TSs become more productlike. As such, the C_1-SKIE supports Streitwieser's rule of correlation between hybridization and secondary isotope effects, whereas the variation of the PKIE is not the expected according to the analysis by Westheimer and Melander.

The main point arising from the present work is that model calculations may indicate that KIEs mainly are determined by, for example, the symmetry of the TS, *all other things being equal*. However, in the real world all other things are in general *not* equal. Electric charge is quantized, and thus, only certain combinations of nuclei and electrons can be realized. This makes it impossible to vary only one parameter at a time, as assumed by model calculations. This would appear to cast doubts on the validity of such model calculations of kinetic isotope effects and, thereby, also on interpretations regarding variations in TS geometries based on KIEs.

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