Kinetic Isotope Effects and Transition State Geometries. A Theoretical Investigation of E2 Model Systems

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Ab initio calculations at the MP2/6-31+G* level have been performed on E2 model systems to investigate whether differences in kinetic isotope effects correlate with changes in transition state geometries. By combining various nucleophiles (NH_2^-, OH^-, F^-, PH_2^-, SH^-, Cl^-) and leaving groups (NH_3, Br^-, Cl^-, F^-, SH^-) for reactions of the type $Nu^- + CH_3CH_2X$, a large diversity of transition structures from reactant-like to product-like are generated. For each reaction one primary and two different α-secondary kinetic isotope effects are calculated. The primary kinetic isotope effects depend strongly on the nucleophilic placement in the periodic system, which mainly is due to differences in equilibrium isotope effects. When this effect is subtracted, the primary kinetic isotope effects display the expected maximum for symmetric transition structures, although the maximum is broad. The secondary kinetic isotope effects associated with the leaving group provide a qualitative correlation with the hybridization at the carbon, but the corresponding effects at the carbon where the hydrogen abstraction takes place is uncorrelated with the transition state geometry.

Introduction

Determination of reaction mechanisms is an issue of major concern in chemistry, and the assessment of transition structures is therefore important. Kinetic isotope effects (KIEs) provide information on changes in vibrational frequencies between the reactant and transition state (TS), which in turn are connected to force constant changes. For related reactions, the variation in reactant frequencies is usually much smaller than the corresponding TS changes, and KIEs have consequently been used to provide experimental estimates of TS geometries.[1,2] The connection between transition structures and kinetic isotope effects is derived from theoretical considerations of model systems. The interpretation of primary kinetic isotope effects (PKIEs) is normally based on the results from a three-body transition state model, first discussed in detail by Melander, Westheimer, and More O'Ferrall.[1b,3,4] The isotope effect for a linear hydrogen transfer was shown to have a maximum when the transition structure is symmetric, defined as equal force constants for the breaking/forming bonds. Furthermore, the isotope effect decreases when the hydrogen transfer becomes bent. Changes in measured PKIEs are consequently taken to imply changes in transition structures, i.e. a smaller isotope effect indicates a less symmetric geometry.

Secondary kinetic isotope effects (SKIEs) are often taken to reflect changes in the hybridization of the

isotopic substituted center, first analyzed by Streitwieser et al.[5] On the basis of changes in the out-of-plane $C_\alpha-$H(D) bending frequency, it was shown that a reaction going from sp^3 to sp^2 hybridization should have a normal (>1) SKIE. The out-of-plane bending modes can also be influenced by changes in the loose/tight character around the bonding, and SKIEs are often interpreted in these terms as well.[6,7] An increase in SKIE is therefore taken to reflect a change in the TS toward more sp^2-like character or an increasing looseness. Interpretation of SKIEs has primarily focused on the bending vibrations, but it has been shown that stretching vibrations are also important.[8−11]

The primary purpose of this study is to investigate whether the correlations between kinetic isotope effects and transition state geometries established by model calculations hold for more complicated systems. By theoretical procedures it is possible to locate transition structures, calculate the frequencies and thereby the isotope effects, and to assess any correlation directly. In a previous study we calculated three different isotope effects in the E2 reaction of 11 nucleophiles with ethyl chloride.[8] The results appeared to cast doubt on the validity of the common interpretations connecting TS geometries with KIEs. In the present work we extend the scope to a larger array of systems by combining five substituted ethanes with six nucleophiles, Scheme 1. The resulting 30 TSs span a very wide range of geometries and allow an investigation of any large-scale correlation between TS geometries and KIEs. A complimentary

⊗ Abstract published in *Advance ACS Abstracts*, December 15, 1996.
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Scheme 1

X: SH, F, Cl, Br, NH₃
Nu: NH₂, OH, F, PH₂, SH, Cl
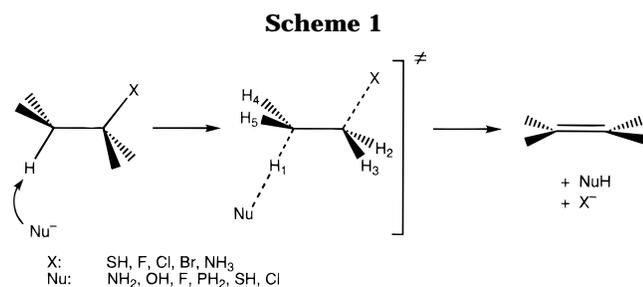
study of closely related systems for probing small-scale correlations is published separately.[12]

Computational Details

All calculations have been performed at the MP2/6-31+G* level, which has been shown to provide results in good agreement with more elaborate methods.[13] All calculations were performed using the GAUSSIAN 92 or GAUSSIAN 94 program packages.[14]

Reactant and TS geometries have been fully optimized for all combinations of five leaving groups and six nucleophiles in the E2 reaction, Scheme 1. One primary and two α-secondary kinetic isotope effects have been obtained from MP2/6-31+G* harmonic frequencies.

Kinetic isotope effects were calculated from statistical mechanics according to standard transition state theory

$$k_H/k_D = \exp((\Delta G_D - \Delta G_H)/RT)$$

$$\Delta G = G^{\ddagger} - G^{r}$$

Equilibrium isotope effects were calculated from the same formula using G^p instead of $G^{\ddagger}$. All results refer to a temperature of 298.15 K.

No scaling has been applied to the vibrational frequencies. A uniform scaling of 0.982 has been recommended for calculating equilibrium isotope effects at the MP2/6-31G* level of theory and a scaling of 0.983 with the 6-311+G** basis set.[15] For the series with SH⁻ as the leaving group, a scale factor of 0.982 results in KIE changes from 0.2% to 3.2%, increasing with increasing kinetic isotope effect. Frequency scaling thus changes absolute values by a few percent, but does not alter the variation of KIEs.[13] Since the major contribution to the kinetic isotope effect is from zero-point energies, the results based on scaled frequencies can to a very good approximation be estimated by the given unscaled isotope effects raised to the power of 0.98.

Bond orders are calculated as[16,17]

$$n = \exp\left(\frac{R_0 - R^{\ddagger}}{0.6}\right)$$

where R_0 refers to either reactant or product.

Results and Discussion

In the gas phase, E2 reactions are characterized by a double-well potential where the minima correspond to ion−dipole complexes. In solution, the reaction proceeds directly from individual reactants through the transition state to products. In experiments there will, in addition, be competition between the E2 reaction pathway and the S_N2 mechanism, an aspect considered in several theoretical investigations.[18,19] In the present work we consider only E2 reactions in an anti-coplanar configuration. The kinetic isotope effects have been calculated with reference to the individual reactants and not the ion−dipole complexes. As such they cannot be directly compared to experimental (solution or gas phase) data, but the calculated trends may mirror the behavior in solution. Nevertheless, we have included experimental data for systems which are relevant for the present models. Hu and Truhlar have recently made a thorough study of the gas phase reaction of ClO⁻ and CH_3CH_2Cl and concluded that a quantitative prediction of the kinetic isotope effect is a difficult theoretical problem.[19]

Inclusion of quantum mechanical tunnelling is known to affect both primary and secondary kinetic isotope effects.[20−22] Owing to difficulties in calculating tunneling contributions by multidimensional procedures, either the Wigner or the Bell formula for one-dimensional tunneling is often applied.[6,23,24] For the series with Br⁻ as leaving group, Bell's tunneling correction changes the primary kinetic isotope effects by factors up to 3, producing isotope effects up to 18, while Wigner's transmission coefficients

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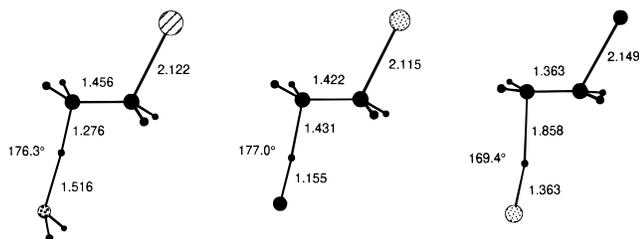
Figure 1. Three examples of transition state geometries: Br^-/NH_2^- as very reactant-like, Cl^-/F^- as a prototypic E2, and F^-/Cl^- as very product-like. Distances are in Å, angles in degrees.

vary from 1 to 1.3. It is difficult to evaluate whether either of these values are realistic, and we have not included tunneling in any of the presented isotope effects.

In our previous paper we analyzed in detail the translational, rotational, and vibrational contributions to the KIE.[8] These is no reason to expect the present systems to behave differently, and we merely state the previous findings. The major determining factor is the vibrations, with the rotational contribution being significantly smaller and the translational effect essentially constant. For the PKIE the absolute value is determined by the stretching frequency of the breaking bond in the reactant, but the variation is due to the bending modes. For the SKIE, both the absolute value and the variation is determined primarily by the bending frequencies.

We stress that the present investigation concentrates on trends rather than absolute values. We wish to evaluate whether the rules established for simple model systems also hold for more complex reactions within the same set of fundamental approximations, i.e. neglecting tunneling, solvent, and dynamical effects, etc. Inclusion of such effects is likely to decrease any correlation between TS geometries and KIEs, and a detailed understanding of possible connections is desired before embarking on more elaborate treatments.

Transition State Geometries. Figure 1 shows examples of three transition states: Br^-/NH_2^- as very reactant-like, Cl^-/F^- as prototypic E2, and F^-/Cl^- as very product-like. The vast majority of the structures can be characterized according to the Bunnet−Cram E2H spectrum involving linear proton transfer.[2] Only the two most reactant-like transition structures with NH_3 as the leaving group involve bent proton transfer with a certain degree of base/C_1 covalent interaction and are, according to the Winstein−Parker E2H−E2C spectrum, more E2C-like.[2] The progress along the reaction coordinate is characterized by increasing R_{CH} and R_{CX} bond lengths, decreasing R_{CC} and R_{NuH} bond lengths, and increased flattening (increased dihedral angles for the hydrogens). The three structures shown indicate central reactions where both the C−H bond and the C−X bond are breaking, in contrast to an E1$_{cb}$-like mechanism where C−H bond breaking precedes bond rupture to the leaving group.

Table 1 shows the breaking (R_{CH}) and forming (R_{NuH}) bonds around the transferred hydrogen, which are the most relevant parameters for correlation with the primary kinetic isotope effects. In addition, the ΔR_{NuH} values obtained by subtraction of the Nu−H bond lengths in the products are given in parentheses. The reactant R_{CH} is almost independent of the leaving group, but different nucleophiles introduce a dependency on the leaving group at the transition state. This is consistent
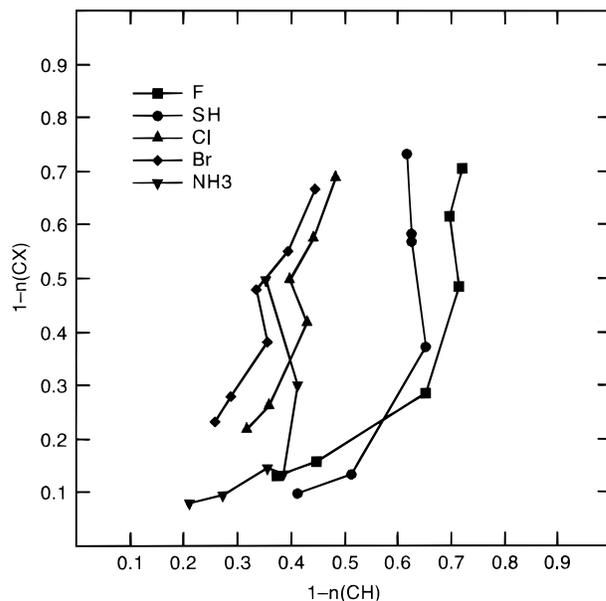
Figure 2. More O'Ferrall−Jencks diagram depicting CX bond order versus CH bond order, with labels refering to the leaving group. The order of nucleophiles from bottom to top is for the series Cl^-, Br^-, and NH_3: NH_2^-, OH^-, F^-, PH_2^-, SH^-, and Cl^-; for F^-: NH_2^-, OH^-, PH_2^-, SH^-, F^-, and Cl^-; and for SH^-: NH_2^-, OH^-, PH_2^-, F^-, SH^-, and Cl^-.

with normal expectations; changes in the reactant by substituents are much smaller than those in the TS.

Table 2 gives the forming double bond length (R_{CC}) and the length of the bond to the leaving group (R_{CX}); the ΔR_{CX} values are given in parentheses. It should be noted that there is not a correlation between the C−H and C−C bond lengths, i.e. an early/late ordering of the TSs will be different depending on the variable that is selected. The transition state SH^-/NH_2^-, for example, is the most reactant-like from the R_{CC} value, while the R_{CH} value places it near the middle of the 30 TSs. Furthermore, while there is a reasonable correlation between R_{CC} and ΔR_{CX}, this is not the case for R_{CH} and ΔR_{NuH}.

Table 3 lists the torsional angles for the two sets of hydrogens which are of relevance for the secondary kinetic isotope effects. Traditionally, such torsional angles are defined with respect to a specific atom on the opposite side of the C−C bond (e.g. θ_{C2} could be defined as the angle between the four atoms H_4/H_5, C_2, C_1, and X), where an sp³-hybridized angle corresponds to 60° and an sp² to 90°. If C_2 is rotated with respect to the plane of the two carbons and the leaving group, this definition implies that the two C_2 hydrogens will have different torsional angles although the hybridization is constant. To avoid this, we define the θ_{C1} torsional angle as $H_2C_1C_2H_3$ and θ_{C2} as $H_4C_2C_1H_5$, and consequently an sp²-hybridized atom has a torsional angle of 180° and an sp³-hybridized one of 120°. Table 3 shows that the torsional angles for the reactants are rather insensitive to the nature of the leaving group, varying only between 120° and 124°. There is a reasonable correlation between θ_{C1} and θ_{C2} for the whole series, and the early/late ordering of TSs is similar, but not identical, to the ordering obtained from the C−C distances.

Dividing the 30 transition states into five series with a constant leaving group provides correlations between the geometry parameters describing the CH_2CH_2X moiety (R_{CC}, ΔR_{CX}, θ_{C1}, and θ_{C2}), but not between parameters describing the C_2−H−Nu moiety (R_{CH} and ΔR_{NuH}), and

Table 1. MP2/6-31+G* Distances for the Breaking and the Forming Bonds around the Transferred Hydrogen (Å)[a]

	NH$_3$		Br$^-$		Cl$^-$		F$^-$		SH$^-$	
Nu$^-$	R_{CH}	R_{NuH}[b]	R_{CH}	R_{NuH}[b]	R_{CH}	R_{NuH}[b]	R_{CH}	R_{NuH}[b]	R_{CH}	R_{NuH}[b]
reactant	1.093		1.096		1.095		1.095		1.094	
NH$_2^-$	1.235	1.561 (0.544)	1.276	1.516 (0.499)	1.325	1.444 (0.427)	1.375	1.389 (0.372)	1.412	1.343 (0.326)
OH$^-$	1.285	1.363 (0.392)	1.299	1.373 (0.402)	1.363	1.298 (0.327)	1.451	1.221 (0.250)	1.524	1.166 (0.195)
F$^-$	1.356	1.197 (0.256)	1.360	1.218 (0.277)	1.431	1.155 (0.214)	1.811	0.998 (0.057)	1.684	1.029 (0.088)
PH$_2^-$	1.387	1.807 (0.393)	1.342	1.859 (0.445)	1.400	1.796 (0.382)	1.729	1.591 (0.177)	1.728	1.583 (0.169)
SH$^-$	1.413	1.658 (0.318)	1.397	1.676 (0.336)	1.445	1.635 (0.295)	1.850	1.441 (0.101)	1.683	1.492 (0.152)
Cl$^-$	1.353	1.620 (0.339)	1.449	1.546 (0.265)	1.494	1.514 (0.233)	1.858	1.363 (0.082)	1.670	1.419 (0.138)

[a] Distances in parentheses are $\Delta R_{NuH} = R_{NuH}^{\ddagger} - R_{NuH}^{p}$. [b] The product R_{NuH} bond lengths are NH$_3$, 1.017; H$_2$O, 0.971; HF, 0.941; PH$_3$, 1.414; H$_2$S, 1.340; HCl, 1.281.

Table 2. MP2/6-31+G* Distances for the Forming Double Bond and the Breaking Leaving Group Bond (Å)[a]

	NH$_3$		Br$^-$		Cl$^-$		F$^-$		SH$^-$	
Nu$^-$	R_{CC}	R_{CX}	R_{CC}	R_{CX}	R_{CC}	R_{CX}	R_{CC}	R_{CX}	R_{CC}	R_{CX}
reactant	1.515	1.521	1.516	1.964	1.516	1.792	1.509	1.417	1.524	1.825
NH$_2^-$	1.482	1.571 (0.050)	1.456	2.122 (0.158)	1.460	1.939 (0.147)	1.464	1.502 (0.085)	1.491	1.886 (0.061)
OH$^-$	1.475	1.580 (0.059)	1.449	2.162 (0.198)	1.453	1.975 (0.183)	1.460	1.520 (0.103)	1.485	1.911 (0.086)
F$^-$	1.459	1.615 (0.094)	1.428	2.250 (0.286)	1.422	2.115 (0.323)	1.374	1.991 (0.574)	1.402	2.330 (0.505)
PH$_2^-$	1.450	1.607 (0.086)	1.415	2.355 (0.391)	1.411	2.204 (0.412)	1.425	1.618 (0.201)	1.431	2.105 (0.280)
SH$^-$	1.427	1.737 (0.216)	1.399	2.446 (0.482)	1.396	2.306 (0.514)	1.391	1.814 (0.397)	1.399	2.348 (0.523)
Cl$^-$	1.403	1.935 (0.414)	1.381	2.620 (0.656)	1.378	2.488 (0.696)	1.363	2.149 (0.732)	1.376	2.616 (0.791)

[a] Distances in parentheses are $\Delta R_{CX} = R_{CX}^{\ddagger} - R_{CX}^{r}$.

Table 3. MP2/6-31+G* Torsional Angles[a]

	NH$_3$		Br$^-$		Cl$^-$		F$^-$		SH$^-$	
Nu$^-$	θ_{C1}	θ_{C2}	θ_{C1}	θ_{C2}	θ_{C1}	θ_{C2}	θ_{C1}	θ_{C2}	θ_{C1}	θ_{C2}
reactant	123.8	122.9	123.5	120.9	121.8	120.6	124.1	120.5	119.6	120.6
NH$_2^-$	122.7	129.1	128.6	127.3	126.0	126.2	125.0	125.1	120.3	123.0
OH$^-$	123.5	130.1	130.9	128.0	128.0	126.8	126.2	124.9	121.5	122.9
F$^-$	126.3	131.9	135.8	132.2	135.6	133.7	154.3	153.6	141.1	142.4
PH$_2^-$	125.5	138.2	140.4	134.3	139.3	135.8	131.4	137.3	129.4	137.4
SH$^-$	131.4	140.9	145.7	139.5	145.2	140.6	143.1	146.9	141.1	143.3
Cl$^-$	140.9	144.8	155.1	147.1	155.5	147.9	163.2	158.9	155.7	151.1

[a] θ_{C1} refers to the torsional angle between the two hydrogens on C$_1$ with respect to the CC axis and θ_{C2} to the torsional angle between the two nonreacting hydrogens at C$_2$ with respect to the CC axis (degrees). Both angles in the product are 180.0°.

Table 4. MP2/6-31+G Reaction Energies (kcal/mol)

Nu$^-$	NH$_3$	Br$^-$	Cl$^-$	F$^-$	SH$^-$
NH$_2^-$	−164.0	−62.4	−53.4	−25.1	−37.0
OH$^-$	−143.5	−41.8	−32.9	−4.6	−16.4
F$^-$	−118.4	−16.8	−7.8	20.4	8.6
PH$_2^-$	−126.6	−25.0	−16.0	12.2	0.4
SH$^-$	−100.0	1.6	10.6	38.9	27.0
Cl$^-$	−83.4	18.2	27.2	55.4	43.6

there is no correlation between the two parts of the molecule. Only by a further division according to the placement of the nucleophile in the periodic table can a consistent ordering be obtained. Bond breaking and bond making is therefore concerted but uncorrelated in the E2 system.

The reaction energies in Table 4 show that the combination of the nucleophiles and the four anionic leaving groups cover both exothermic and endothermic reactions, while the transition states with NH$_3$ as the leaving group are strongly exothermic. There is no strict correlation between the reaction energy and TS geometry parameters, although an exothermic (endothermic) reaction in general has an early (late) TS, in agreement with the Hammond postulate.[25] Table 4 allows a calculation of relative basicities (kcal/mol) which can be compared to experimental values (given in parentheses):[26] NH$_2^-$/OH$^-$ 20 (13), OH$^-$/PH$_2^-$ 17 (20), PH$_2^-$/F$^-$ 8 (0), F$^-$/SH$^-$ 18 (19), and SH$^-$/Cl$^-$ 17 (18). The errors are slightly larger than

those expected, but since our main purpose is to compare transition structures and isotope effects and not to reproduce experimental results, this is inconsequential.

The diversity of the reactions can be displayed by a More O'Ferrall−Jencks diagram[16] depicting CX bond order against CH bond order, shown as Figure 2. The diagonal from the lower left corner to the upper right corner connects reactant-like (early) transition states and product-like (late) TSs, respectively. The perpendicular diagonal describes the transition structures as E1-like (upper left corner) to E1$_{cb}$-like (lower right corner). The figure shows that the reactions cover a large variation of early to late transition states going from NH$_3$/NH$_2^-$ to F$^-$/Cl$^-$, as is also indicated by the reaction energies. The series with Cl$^-$ and Br$^-$ as leaving groups are mostly central reactions, whereas the other three display varying degrees of central to E1$_{cb}$-like reactions. In addition, there is a tendency that a change from early to late transition states is connected with a shift along the perpendicular direction to more central transition structures. For a constant leaving group, a better nucleophile should preferentially stabilize the two right hand corners, resulting in a parallel shift toward reactants and a perpendicular shift toward the E1$_{cb}$-like TS geometry. The figure shows that the most important effect is the parallel effect. The same kind of analysis can be applied to series of constant nucleophiles, where a better leaving

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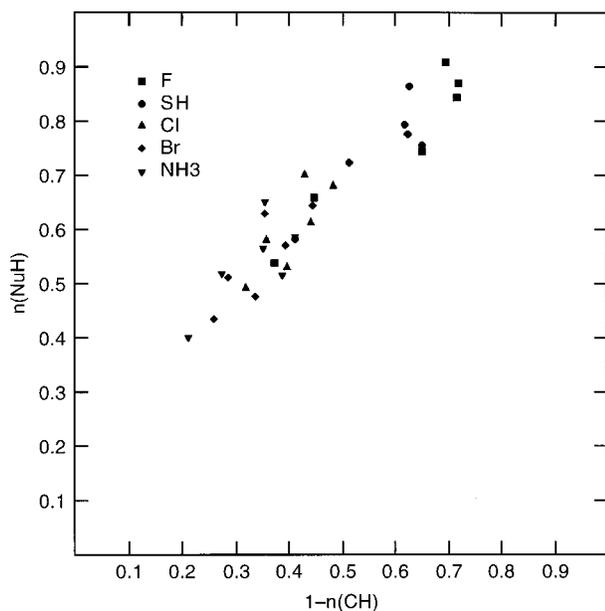
Figure 3. More O'Ferrall−Jencks diagram depicting symmetry around the transferred hydrogen/deuterium by NuH versus CH bond order. The labels refer to the leaving group.

group should stabilize the two top corners, resulting in a parallel shift toward reactants but a perpendicular effect toward the E1-like TS. These series are found in Figure 2 by comparing points representing the same nucleophile from the different series of constant leaving groups. Only with fluoride as the nucleophile does the change of leaving group cause a parallel shift in TS geometry, while for all other nucleophiles the perpendicular effect is by far the most important.

Figure 3 shows a More O'Ferrall−Jencks diagram depicting the symmetry around the transferred hydrogen in terms of NuH and CH bond orders. The lower left/upper right diagonal again reflects the early/late character of the transition structures, whereas the perpendicular diagonal represents variation from a tight (upper left corner) to a loose TS geometry (lower right corner). The figure shows all transition structures to have an almost equal degree of looseness around the transferred hydrogen, i.e. the sum of the two bond orders is approximately constant (∼1.2 for the present choice of a) for all the TSs.

The present systems cover a difference in reaction energies of over 200 kcal/mol. Changes in the transition structures are also quite significant; the breaking C−H bond, for example, varies by 0.62 Å (1.24−1.86 Å) and the hybridization angles by 43° (120°−163°). This is clearly a much larger variation than can be realized experimentally; however, we believe it is important to probe connections over a wide range to investigate large-scale trends. We have shown elsewhere that closely related systems do not provide a quantitative correlation between kinetic isotope effects and TS geometries.[12]

Primary Kinetic Isotope Effects. Exchange of the transferred hydrogen (H_1) with deuterium results in a primary kinetic isotope effect as well as an equilibrium isotope effect (EIE), given in Table 5. The PKIE is expected to depend on the symmetry and the linearity of the C_2−H−Nu moiety. All except two TSs in this study have angles around the transferred hydrogen close to 180° (>168°); only the NH_3/NH_2^- (152.5°) and NH_3/OH^- (153.1°) reactions have bent angles. The reaction sym-

metry is therefore expected to be the main determining factor for the PKIE. When the hydrogen transfer is not between two identical atoms (or groups of atoms), "symmetric" is not an unambiguous definition. The original definition was based on identical force constants;[3] however, this is of little use for probing geometries. Since force constants usually are assumed to be inversely correlated with bond lengths, the symmetry consideration also holds for the geometry. A symmetry parameter can be defined as either equal bond lengths, equal (absolute or relative) elongations over the reactant/product value, or equal deformation energies for stretching the bond. Absolute bond lengths do not take different reactants into account. The elongation can be defined either as an absolute value, $\Delta R = R^{\ddagger} - R_0$, or as a relative change, $\Delta R_{rel} = (R^{\ddagger} - R_0)/R_0$, or bond orders can be used, $n = e^{-\Delta R/a}$.[27] There are only minor differences between these representations for the present systems, and we have chosen $n_{NuH} - n_{CH}$ as a measure of reaction symmetry. The primary kinetic isotope effect as a function of this parameter is shown in Figure 4. The correlation for a series with a constant leaving group has been analyzed previously,[8] and Figure 4 shows that a series with a constant nucleophile tends to show a maximum for a symmetric TS. As the leaving group is furthest away from the transferred hydrogen, it is expected to be the smallest perturbation and consequently yield the best correlation. The first-row nucleophiles have a broad maximum around 0.0, while that for the second row is slightly later, around 0.1. For all the reactions taken together, however, there is no connection between the PKIE and the reaction symmetry, although it is clear that the second-row nucleophiles consistently give higher values than those from the first row.

By definition, an extremely reactant-like TS should have an isotope effect of 1 and an extremely product-like TS an effect equal to the EIE. It is therefore expected that there is a contribution from the EIE to the kinetic isotope effect.[28] As different leaving groups and nucleophiles are employed in order to create a variety of transition state geometries, different scales are also introduced. Differences in the EIE mean that two transition states will display different KIEs only because the reactants/products are not identical and not because their position along the reaction coordinate is different. In theoretical investigations it is possible to correct for this effect, but it requires two choices to be made: (i) selecting a suitable reaction coordinate and (ii) deciding how the contribution from the EIE depends on this. We have chosen to use $1 - n_{CH}$ as the reaction coordinate, which has the advantage of involving the same geometrical parameter for all the systems. The simplest model for (ii) is a linear free-energy relationship, i.e. the isotopic energy difference between reactant and product progresses linearly along the reaction coordinate, leading to the following formula

$$\ln(PKIE_0) = \ln(PKIE) - (1 - n_{CH}) \ln(EIE)$$

The "intrinsic" $PKIE_0$ values are depicted in Figure 5, and it is seen that essentially all of the differences between the first- and second-row nucleophiles are due to differences in EIE. The resulting scatter plot displays

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Table 5.　MP2/6-31+G* Primary Kinetic Isotope Effects[a]

Nu⁻	NH₃	Br⁻	Cl⁻	F⁻	SH⁻
NH_2^-	3.787 (0.926)	4.420 (0.900)	4.695 (0.904)	4.718 (0.894)	4.735 (0.916)
OH^-	4.562 (1.052)	4.762 (1.022)	4.964 (1.026)	4.944 (1.014)	4.873 (1.039)
F^-	5.008 (1.383)	5.273 (1.344)	5.041 (1.349)	1.471 (1.334)	1.961 (1.366)
PH_2^-	6.159 (2.206)	5.858 (2.144)	6.213 (2.153)	6.295 (2.127)	6.270 (2.178)
SH^-	6.283 (2.179)	6.579 (2.118)	6.769 (2.127)	2.617 (2.102)	5.750 (2.152)
Cl^-	6.512 (2.408)	7.663 (2.341)	7.738 (2.350)	3.373 (2.323)	5.491 (2.378)

[a] Equilibrium isotope effects are given in parentheses.
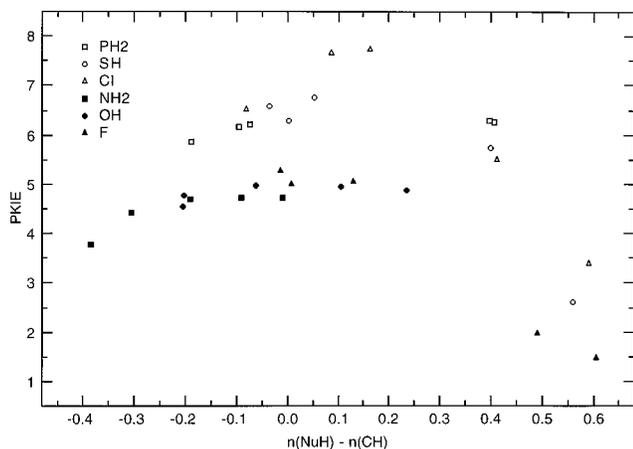
Figure 4. Primary kinetic isotope effect shown as function of symmetry around the transferred hydrogen/deuterium. The labels refer to the nucleophile.
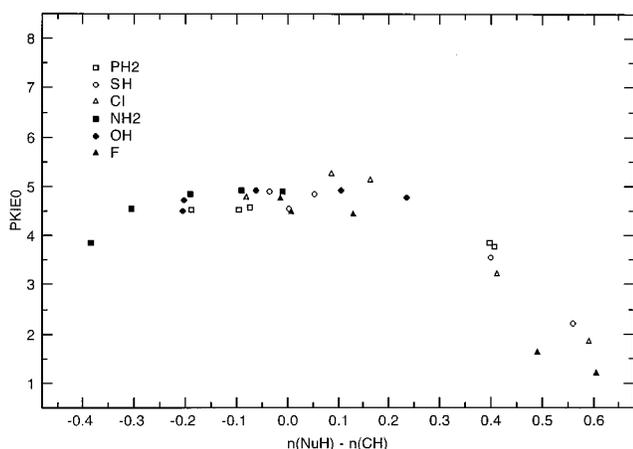
Figure 5. Primary kinetic isotope effects corrected for differences in equilibrium isotope effects shown as function of symmetry around the transferred hydrogen/deuterium. The labels refer to the nucleophile.

a broad maximum for the whole group of reactions around 0.0. The two TSs (NH_3/NH_2^- and NH_3/OH^-) which have transfer angles deviating by almost 30° from linearity are the two left-most points for the NH_2^- and OH^- series in Figure 5. Model calculations suggest that such a bending should lower the PKIE by 1.5,[4b] but there is no indication that these two points are significantly lower than those for the linear hydrogen transfers with the same asymmetry in terms of bond orders. It should be noted that the maximum is rather broad; there is very little variation of the $PKIE_0$ (or PKIE, Figure 4) for values of the symmetry parameter between −0.2 and +0.2. This corresponds to a variation of ~0.2 Å in the C−H distance, a significant change in the TS without a corresponding $PKIE_0$ effect.

The usual interpretation of PKIEs as displaying a maximum for the most symmetric transition state is

based on model calculations where the equilibrium isotope effects do not constitute problems. The present results partly reproduce this maximum, but only for $PKIE_0$. It is important to realize that the EIE correction may only be performed if the location of the TS is known. Furthermore, it depends on the chosen reaction coordinate and the interpolating function. It will, in general, not be possible to arrive at such corrected PKIEs from experimental data only. Without any corrections, the primary kinetic isotope effect is not a simple function of the reaction coordinate symmetry, as demonstrated in Figure 4.[29]

Most solution experiments consider either cyclic or aromatic systems, and variations of isotope effects are primarily generated by varying the para substituent of the aromatic moiety.[1,2,30] Furthermore, absolute values depend on the base concentration and on the solvent and have contributions from tunneling. For these reasons, a direct comparison with the calculated values is not possible. The systems studied in the gas phase are more similar to the ones employed here, but only a few KIEs have been determined.[31] To our knowledge the only matching system is SH^- + ethyl bromide where the PKIE is reported to be as small as 1.02 ± 0.07, a result taken as an indication of an S_N2 reaction and not an E2 reaction.[31c] In the E2 reaction of diethyl ether, the PKIE with NH_2^- as the nucleophile is 5.60 ± 0.03 and with OH^- 2.20 ± 0.03,[31a] which is the trend opposite of the one we calculate.

Secondary Kinetic Isotope Effects. There are two different α-secondary kinetic isotope effects, one for substitution of H_2 and H_3 with deuterium and one for exchange of H_4 and H_5; both are given in Table 6 (C_1 and C_2, respectively) along with the corresponding EIEs. All SKIEs are normal (>1), as expected for a reaction going from sp^3 to sp^2 hybridization.[5] The C_2-SKIEs are, in general, larger than the C_1-SKIEs, but more importantly, nearly all the calculated C_2-SKIEs are larger than the corresponding equilibrium isotope effects.

Analogous to the PKIE, the variation of leaving groups introduces differences in the EIE associated with the SKIEs. There is a further complication for the SKIEs since the length of the reaction path is slightly different. The ethene product is independent of the nucleophile and

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(30) See for example: (a) Cook, D.; Hutchinson, R. E. J.; MacLeod, J. K.; Parker, A. J. *J. Org. Chem.* **1974**, *39*, 534−539. (b) More O'Ferrall, R. A.; Warren, P. J. *J. Chem. Soc., Chem. Commun.* **1975**, 483−484. (c) Baciocchi, E. *Acc. Chem. Res.* **1979**, *12*, 430−436. (d) Thibblin, A. *J. Am. Chem. Soc.* **1988**, *110*, 4582−4586. (e) Thibblin, A. *J. Am. Chem. Soc.* **1989**, *111*, 5412−5416.

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

Nu[-]	NH$_3$		Br^{-}		Cl^{-}		F[-]		SH[-]	
	C$_1$	C$_2$	C$_1$	C$_2$	C$_1$	C$_2$	C$_1$	C$_2$	C$_1$	C$_2$
NH$_2$[-]	1.099	1.327	1.076	1.289	1.072	1.330	1.108	1.417	1.101	1.493
OH^{-}	1.087	1.331	1.071	1.278	1.086	1.347	1.111	1.451	1.087	1.527
F[-]	1.087	1.352	1.096	1.279	1.130	1.321	1.381	1.369	1.172	1.390
PH$_2$[-]	1.117	1.300	1.198	1.168	1.224	1.196	1.207	1.497	1.155	1.499
SH[-]	1.135	1.261	1.213	1.190	1.253	1.206	1.317	1.427	1.213	1.356
Cl^{-}	1.182	1.153	1.260	1.181	1.320	1.191	1.495	1.326	1.292	1.266
EIE	1.731	1.271	1.490	1.279	1.581	1.271	1.686	1.246	1.455	1.250

[a] C$_1$ refers to the C$_1$-SKIE of substitution of two hydrogens at C$_1$ with deuterium and C$_2$ to the C$_2$-SKIE of substitution of two hydrogens at C$_2$ with deuterium.

leaving group, but the reactants differ in their torsional angles. The total hybridization change for going from reactant to product is therefore slightly different for each leaving group. A normalized measure of the hybridization change may be defined as

$$\Delta\theta^{\ddagger} = (\theta^{\ddagger} - \theta_0)/(180° - \theta_0)$$

Assuming a linear free energy relationship, the expected connection is given as[17,32,33]

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

The ln(SKIE)/ln(EIE) ratio has been used to provide experimental estimates of the reaction coordinate, although the correction for differences in reactant hybridization is normally not done.[32–34] The present data allow a direct evaluation of the validity of the above formula. The correlation between ln(C$_1$-SKIE)/ln(EIE) and $\Delta\theta^{\ddagger}_{C1}$ (Figure 6) shows a general increase in SKIE with increasing sp^2 hybridization, although there is some scattering of the points relative to the ideal straight line. As the reactant geometries depend little on the nature of the leaving group and the EIE values are also relatively constant for the present systems, there is also a reasonable correlation directly between C$_1$-SKIE and $\theta^{\ddagger}_{C1}$. The reaction coordinate defined by the isotope effects is consistently larger than the value from the actual geometry, with the isotope value leveling off at ~0.2 for the early TSs. As the C$_1$-SKIE is associated with the carbon bearing the leaving group, it may be expected that the correlation for a series with a constant leaving group (and varying nucleophiles) should be better than that for the whole reaction series. This is indeed borne

Figure 6. Correlation between the reaction coordinate calculated from the ln(SKIE)/ln(EIE) ratio and that given by the change in dihedral angle of the hydrogens at C$_1$. The labels refer to the leaving group.

Figure 7. Correlation between the reaction coordinate calculated from the ln(SKIE)/ln(EIE) ratio and that given by the change in dihedral angle of the hydrogens at C$_2$. The labels refer to the leaving group.

out by the data in Figure 6, although the trend for the early TSs is inconsistent. For a large-scale variation, the C$_1$-SKIEs thus give a reasonable estimate of the TS position, but is should be noted that a prediction of relative positions for similar systems may well be incorrect.

The corresponding plot for the C$_2$-SKIE is displayed in Figure 7. It is immediately clear that the C$_2$-SKIEs do not conform to the expectation, since most of the SKIEs are larger than the corresponding equilibrium effects, which have also been observed in solution experiments.[35] Although there is a vague tendency of *decreas-*

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ing SKIE with increasing hybridization, the dominating picture is random scatter. The SKIEs associated with the carbon bearing the hydrogen being abstracted thus predict qualitative incorrect changes in the TS geometry according to the commonly used models.

There are numerous examples of experimentally determined secondary kinetic isotope effects, but the vast majority deal with S_N2 reactions,[36] and the substituent effects indicated are not consistent.[37] Only a few studies of E2 reactions consider SKIEs, where aromatic or cyclic substrates, solvents, and tunneling make comparison to the theoretical values difficult. The E2 reactions of 2-phenylethyl halides have been reported to be markedly dependent on the concentration of base,[38] with SKIEs ranging from 0.808 ± 0.004 (at 0.09 M BuOH) to 1.165 ± 0.010 (at 0.35 M BuOH) for Cl^- as leaving group. The inverse effects were suggested to be indications of syn eliminations. Secondary kinetic isotope effects of base-induced dehydrotosylations and dehydrobrominations of cyclohexyl derivatives were reported to lie between 1.13 and 1.15 for deuterium substitution corresponding to C_1-SKIE and between 1.15 and 1.25 for substitution corresponding to C_2-SKIE.[39] Thus, the C_2-SKIE is measured to be larger than C_1-SKIE, but not to the extent indicated by the present theoretical results. In better agreement with our results are the gas phase results of diethyl ether with OH^- where a C_2-SKIE of 1.55 ± 0.03 and a C_1-SKIE of 1.00 ± 0.02 were obtained.[31b]

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Conclusions

From the present results it is clear that there is no obvious answer to the question of whether transition state geometries can be inferred from kinetic isotope effects. For the E2 reaction the primary kinetic isotope effect displays little correlation with transition structure unless corrected for differences in equilibrium values. The secondary kinetic isotope effect associated with the leaving group provides a qualitative estimate of the TS hybridization, but this is not the case for the secondary kinetic isotope effect closest to the C–H bond rupture. The accuracy of the TS geometries estimated from the $PKIE_0$ and C_1-SKIE is not high; variations of up to 0.2 Å in the breaking C–H bond and differences in the hybridization angle of ~10° can occur with little or no observable change in the KIE. Although it may be expected that a better correlation should exist for more closely related systems, we have shown elsewhere that this is not the case for E2 reactions.[12] The C_1-SKIE thus shows the expected correlation with TS geometry, but only on a large-scale variation.

The fundamental basis for correlating TS properties with reactant/product values is the assumption that the TS somehow is "intermediate" between the two end points. The finding of SKIEs which are larger than the corresponding EIEs for the C_2 carbon implies that the TS has properties that are not an interpolation between the reactant and product, and consequently there is no simple connection between C_2-SKIE and the TS geometry.

JO9618379