Ab initio Study of the Nucleophilic Ring Opening of Ethylene Oxide. Connection Between Secondary Kinetic Isotope Effects and Transition Structures

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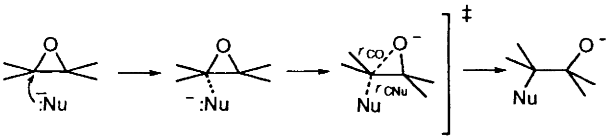
Deuterium α-secondary kinetic isotope effects for the ring opening of ethylene oxide with seven different nucleophiles are calculated at RHF/6-31G*, RHF/6-31+G*, MP2/6-31G*, MP2/6-31+G* and MP2/6-311+G(2d) levels of theory. The theoretical isotope effects are compared with optimized transition state geometries and the absolute value of the isotope effect is found to decrease as the transition state becomes more product-like, which for this system correlates with getting tighter. It appears that the isotope effect mainly is a measure of the loose/tight nature of the transition state, and less of the early/late feature. Within a limited class of nucleophiles there is an almost linear correlation between transition state geometry and isotope effect. This correlation is mainly due to bending vibrations, while the absolute value of the isotope effects is determined by stretching vibrations. Tunnelling calculations on two reactions show only minor corrections.

Kinetic isotope effects (KIEs), which are relative reaction rates between isotopically different molecules, are important tools in evaluating reaction mechanisms.[1-5] Transition state theory is usually the model of choice for interpreting KIEs. Within this model, reaction rates are evaluated from activation enthalpies and entropies, both of which can be calculated from properties of individual molecules by means of statistical mechanics. It is usually assumed that the total energy of a molecule can be written as a sum of contributions from electronic, vibrational, rotational and translational motion. The difference in electronic energy between the reactant and transition state (TS) is the major factor in determining absolute reaction rates, while KIEs mainly arise from the vibrational contributions. Harmonic frequencies can be calculated within the usual Born–Oppenheimer approximation from force constants and atomic masses. The vibrational contribution to the activation energy originates from all molecular vibrations. However, only those modes where the force constant is significantly different in the reactant and TS contribute to the KIE. Isotope effects therefore contain information on force constants at the TS, which again indirectly is related to the geometry. In principle, therefore, TS geometries can be inferred from KIEs, although a quantitative correlation may be difficult to establish.

As only force constants which change between the reactant and TS can give rise to KIEs, these are mainly observed for isotopic substitution close to the reaction centre. Primary kinetic isotope effects (PKIEs) are seen when the bond to the isotope is broken or formed during reaction, and stretching vibrations are of major importance. Secondary kinetic isotope effects (SKIEs) are seen when the isotopic substitution is at a spectator bond, in this case both stretching and bending vibrations may be important.

Different groups have tried to establish links between KIEs and TS-geometries. Streitwieser *et al.*[6] in 1958 presented theoretical considerations concerning SKIEs and hybridization. Based on model calculations, they concluded that the change in the C_α–H(D) out-of-plane bending frequency should cause a reaction going from sp^3 to sp^2 hybridization to have a normal KIE (> 1) while an inverse KIE (< 1) characterized the opposite direction. The interpretation of SKIEs has until recently focussed almost exclusively on the out-of-plane C_α–H(D) bending mode.[3,7-11] More recently it has been shown by factor analyses that not only bending but also stretching vibrations are important for the absolute value of SKIEs for S_N2 reactions.[12-16]

There has been a series of studies on the effect of substituents on isotope effects in S_N2 reactions.[8,16-23] Least work has been done on changes in the nucleophile, and in general there does not seem to be any consistent correlation between the results obtained. The main purpose of the present work is to investigate systematically if there exists a quantitative relation between SKIEs and TS-geometries, through a series of *ab initio* calculations on an appropriate model system. As a model we have chosen the ring opening of ethylene oxide by different nucleophiles, Scheme 1. This system is small enough to allow application of a reasonably sophisticated level of *ab initio* theory, and experiments on systems of this type should be possible. Gas phase S_N2 reactions proceed through an initial formation of an ion–molecule complex, which subsequently rearranges to the product. In solution the reaction goes directly from the individual reactants *via* the transition state to the product. The KIEs in this study have been calculated from properties of the individual reactants and the TS. Although we will make comparisons with other work on S_N2 reactions, it should be noted that the ring opening of an epoxide has a somewhat different TS geometry than a typical S_N2 reaction, since the nucleophile and leaving group are not at apical positions in an approximate trigonal bipyramid.



Scheme 1

Computational Details

All calculations have been made using the GAUSSIAN90[24] or GAUSSIAN92[25] program packages. Three different standard basis sets were employed: 6-31G*, 6-31+G* and 6-311+G(2d) with wavefunctions being determined either by Hartree–Fock (HF) or Møller–Plesset perturbation theory through second order (MP2).[26] All geometries have been fully optimized at each level of theory.

The KIEs were calculated from statistical mechanics

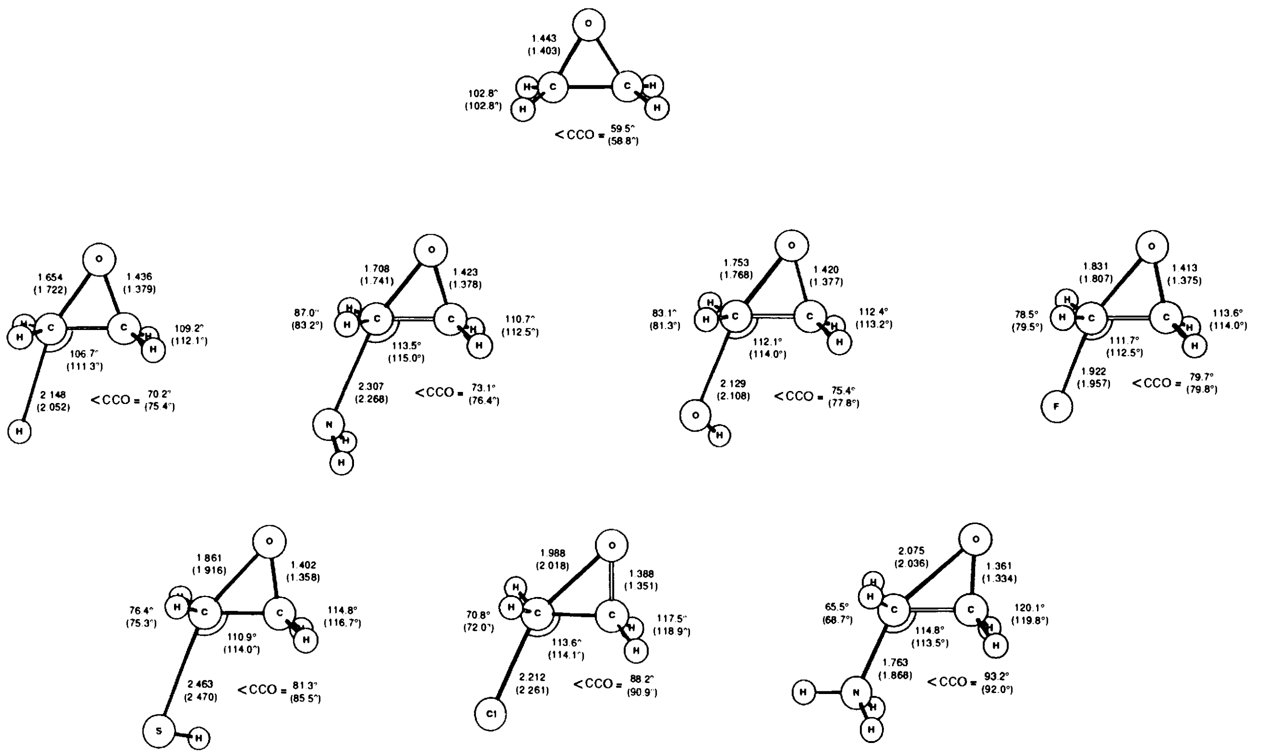


Fig. 1 MP2/6-31+G* transition state geometries, RHF/6-31+G* values in parentheses. Bond lengths are in Å, angles in degrees. The values at each end of the CC bond are HCCO torsional angles.

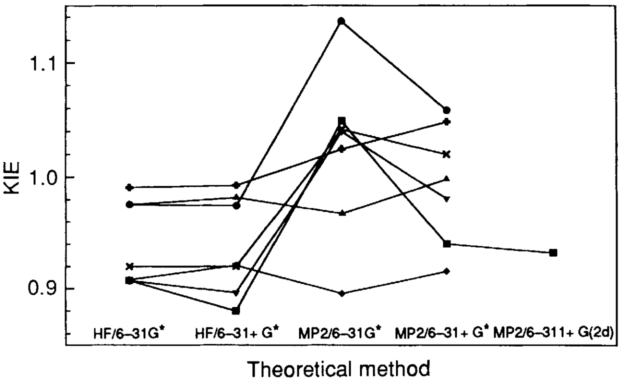


Fig. 2 SKIE as a function of theoretical method: ●, H^-; +, SH^-; ×, NH_2^-; ▲, Cl^-; ▼, OH^-; ■, F^-; ◆, NH_3

according to standard TS-theory.[1] Harmonic vibrational frequencies were calculated by diagonalizing the mass-weighted force constant matrix, calculated analytically at the optimized geometries. No frequency scaling has been employed. KIEs calculated at seven different temperatures in the range from 100 to 1000 K showed that the ordering of the nucleophiles is temperature independent. The results presented below are for a temperature of 298.15 K.

Tunnelling calculations have been accomplished using the POLYRATE program,[27] by computing rate constants from interpolation of MP2/6-31+G* data at selected points along the minimum energy path,[25,28] assuming the small-curvature approximation and canonical variational transition state theory (SCSAG/CVT).[29] The reaction path covered 31 points around the TS with a 0.1 au distance, using the ion–molecule complex as reactant.

Results

The seven nucleophiles used are NH_3, F^-, Cl^-, OH^-, SH^-, NH_2^- and H^-, written in the expected order of increasing nucleophilicity in solution.[30] Within each combination of basis sets and level of approximation we have calculated reactant and TS geometries, vibrational frequencies and corresponding SKIEs.

The obtained MP2/6-31+G* geometries are shown in Fig. 1, where numbers in parentheses refer to RHF/6-31+G* calculations. The C–C distance (not shown) is 1.44–1.46 Å for all systems, except when NH_3 is the nucleophile, where it is 1.49 Å. There are some systematic changes in the breaking and forming bond lengths when electron correlation is introduced by the MP2 procedure. For H^-, NH_2^- and OH^- the TS becomes slightly earlier (r_{CO} decreases and r_{CNu} increases), while the opposite is observed for F^- and NH_3. The TS for the reactions involving SH^- and Cl^- appear to be slightly tighter at the MP2 level, both r_{CO} and r_{CNu} decrease. The distant C–O bond is elongated by 0.03–0.06 Å by the MP2 procedure. Fig. 1 indicates an increasing degree of product-like character of the TSs for the series H^-, NH_2^-, OH^-, F^-, SH^-, Cl^- and NH_3. There is a high degree of correlation between the different geometrical parameters, the breaking C–O bond elongates, the distant C–O bond is shortened, and the CCO angle and the HCCO torsional angles varies smoothly along the series. The angle of attack, CCNu, is fairly constant and does not show any systematic variation.

In the calculation of the α-secondary hydrogen–deuterium kinetic isotope effects both hydrogen atoms on the central carbon atom were replaced with deuteriums. Fig. 2 shows the calculated KIEs for the seven nucleophiles as a function of the different theoretical levels. The MP2 numbers are significantly different from the HF results. In general the absolute values become larger and the order of the nucleophiles changes on inclusion of electron correlation. As the MP2 method should be the more accurate, the HF level does not seem to produce reliable results. The effect of increasing the basis set from 6-31G* to 6-31+G* at the MP2 level was investigated for all reactions. There is a significant change in both geometries and KIEs when diffuse orbitals are included in the basis set (*e.g.* for the fluoride reaction: r_{CO} changes from 1.67 to 1.83 Å, r_{CNu} from

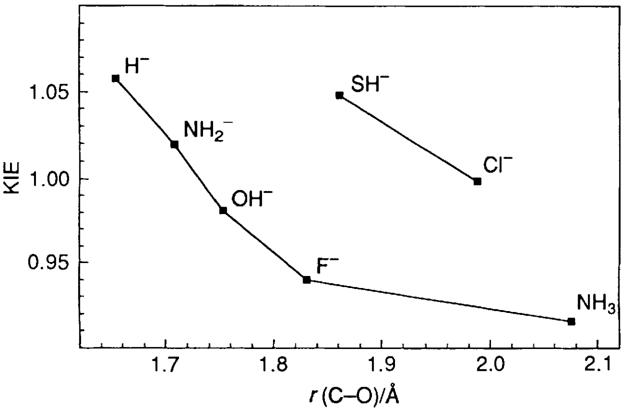


Fig. 3 SKIE as a function of C–O distance at the transition state, r_{CO} (Å)

Table 1 Contribution to the total kinetic isotope effect from translational, rotational and vibrational motion

Nuc.	KIE_{tot}	KIE_{trans}	KIE_{rot}	KIE_{vib}
NH_3	0.916	1.018	1.105	0.816
F^-	0.940	1.020	1.111	0.831
OH^-	0.981	1.018	1.119	0.862
NH_2^-	1.011	1.018	1.127	0.881
H^-	1.058	1.001	1.041	1.018
Cl^-	0.999	1.030	1.101	0.883
SH^-	1.049	1.030	1.115	0.916

Table 2 Contribution to the vibrational kinetic isotope effect from individual groups of frequencies

Nuc.	KIE_{vib}	KIE_{low}	KIE_{mid}	KIE_{high}
NH_3	0.816	0.708	1.212	0.950
F^-	0.831	0.936	1.017	0.871
OH^-	0.862	0.918	1.084	0.866
NH_2^-	0.881	0.911	1.111	0.870
H^-	1.018	0.904	1.307	0.860
Cl^-	0.883	0.945	1.057	0.883
SH^-	0.916	0.920	1.143	0.870

2.03 to 1.92 Å, θ_{HCCO} from 87.4° to 78.5°, SKIE from 1.049 to 0.940). This is as expected since there is substantial anionic character in the systems. The basis set increase from 6-31+G* to 6-311+G(2d) was investigated for the fluoride reaction. This basis set improvement produced only slight alterations (r_{CO} changes from 1.83 to 1.81 Å, r_{CNu} from 1.92 to 1.94 Å, θ_{HCCO} from 78.5° to 79.3°, SKIE from 0.940 to 0.932), and on this account the MP2/6-31+G* level is used in the analyses presented below.

The primary goal of the present investigation is to study a possible connection between TS geometry and KIE. Fig. 3 shows the KIE as a function of the breaking C–O bond distance. As mentioned above, there exists a high degree of correlation between all the geometrical parameters, thus very similar types of plots may be obtained by depicting the KIE against *e.g.* θ_{HCCO} or the distant C–O bond length. From Fig. 3 it is interesting to note that the nucleophiles group according to the periodic table, with H^- placed along with the nucleophiles of the second period. Within each of these groups there appear to be a smooth connection between the kinetic isotope effects and the TS parameters, where the most product-like transition structures show the largest inverse isotope effects (smallest absolute value).

Factor Analysis of Frequencies.—In order to get a more

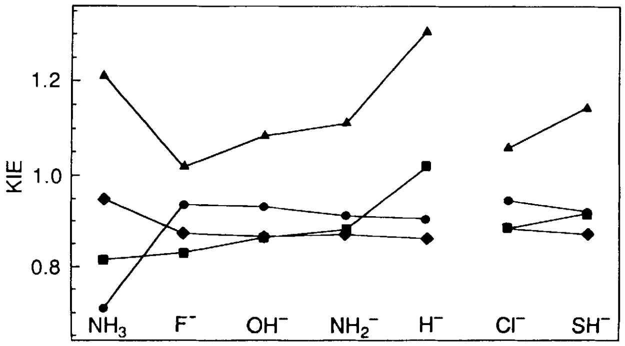


Fig. 4 SKIE based on all vibrations and on individual groups of frequencies: ■, KIE_{vib}; ●, KIE_{low}; ▲, KIE_{mid}; ◆, KIE_{high}

detailed picture of the origin of the KIEs a factor analysis was carried out. The H/D ratio of the rate constants may be written as eqn. (1), where $\Delta\Delta G_X$ is the free energy difference between

$$k_H/k_D = KIE_{vib} \times KIE_{trans} \times KIE_{rot}$$
$$KIE_X = \exp(\Delta\Delta G_X/RT) \qquad (1)$$

the deuteriated and the non-deuteriated reaction, calculated on the basis of the individual partition functions. Table 1 shows the results of the factor analysis at 298 K.† The translational and rotational contributions are normal, while the vibrational contributions are inverse. Excluding KIE_{rot} for H^-, both vibrational and rotational contributions show the same variation of KIE with nucleophiles as KIE_{total}. The translational contributions are almost constant, with a small dependence on total mass. Accordingly, since most of the total KIEs are inverse, the vibrations determine both the absolute value of the KIE and most of the variation.

In order to achieve a more detailed understanding, the vibrational contributions were further divided into individual frequency contributions. A unique correspondence between individual reactant and TS normal modes proved difficult as the nature of several of the bands change significantly during the reaction. An attempt of a more rigorous assignment would require a number of frequency calculations along the reaction path for each nucleophile. We have instead chosen to collect the contributions into three groups: low frequencies, mid frequencies and high frequencies. All modes unique to the TSs (*i.e.* those where there is no corresponding vibration in the reactant) and the symmetric component of the antisymmetric reaction coordinate are placed in the low frequency group, which approximately correlates to $\nu < 750$ cm^{-1}. The mid frequencies typically represent bending modes ($750 < \nu < 2000$ cm^{-1}), while the stretching modes all belong to the high frequency group ($\nu > 2000$ cm^{-1}). This analysis provides a picture of which vibrations are responsible for the absolute value of the SKIE and which are responsible for the variation. The results are shown in Table 2 and Fig. 4. From Fig. 4 it is clear that the mid frequencies show the largest variation, but all values are normal. Furthermore it can be seen that mainly the high frequencies are responsible for the total inverse values. NH_3 behaves differently from the other nucleophiles. This diverging picture depends entirely on one vibration placed in the low frequency group (primarily an NH_3 twist). If the groups instead were defined only with respect to absolute numbers (*e.g.* $\nu < 700$ cm^{-1}), this vibration would be placed in the mid

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† Due to roundoff errors, the KIE as a product of the last three columns in Tables 1 and 2 does not exactly match the KIE in the first column. The deviation is less than 0.003 and does not interfere with any of the conclusions reported.

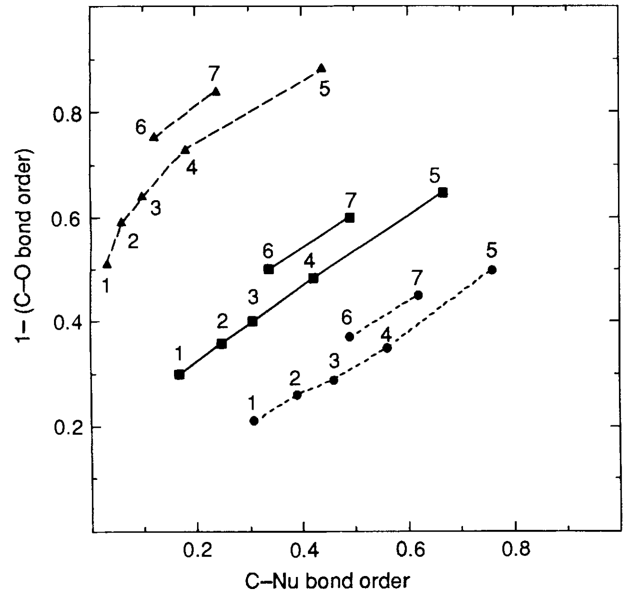

Fig. 5 More O'Ferrall–Jencks diagram for the ring opening of ethylene oxide. The points connected by the long dashed line are calculated using $a = 0.3$ in eqn. (2), the solid line is for $a = 0.6$ and the short dashed line is for $a = 0.9$: ▲, $a = 0.3$; ■, $a = 0.6$; ●, $a = 0.9$: 1, H^-, KIE = 1.058; 2, NH_2^-, KIE = 1.011; 3, OH^-, KIE = 0.981; 4, F^-, KIE = 0.940; 5, NH_3, KIE = 0.916; 6, SH^-, KIE = 1.049; 7, Cl^-, KIE = 0.999

frequency group and NH_3 would be in continuation of the other nucleophiles (KIE_{low} moves from 0.71 to 0.94 and KIE_{mid} from 1.21 to 0.91).

Tunnelling Calculations.—Quantum mechanical tunnelling has long been known to affect KIEs,[1,3,31] and several approximations have been developed in order to calculate this contribution.[29,32] While tunnelling often is very important in PKIEs,[33] it is generally assumed to be negligible in SKIEs. However, Lu *et al.* showed, for the reaction of CH_4/CD_3H with H, that the isotope effect changed from 1.07 to 1.22 when tunnelling was included.[13] Using the same type of calculation, the SKIE for the fluoride reaction increased by 0.037 when tunnelling was included, while the effect for the chloride reaction was less than 0.001. It is possible that tunnelling can have an effect on the presented SKIEs, but the influence appears to be small and should not change the general conclusions.

Discussion

The data presented in Fig. 2 show that the HF level of theory gives KIEs significantly different from those obtained with the MP2 method. The effect of increasing the basis set beyond 6-31+G* is small, as judged from the 6-311+G(2d) calculation for the fluoride system. The effect of electron correlation on the KIE is not directly a consequence of the change in geometry (Fig. 1), *e.g.* while the NH_3 TS geometry changes significantly upon going from the HF to the MP2 level, the KIE is largely unaffected (Fig. 2).

The TS geometry as a function of the nucleophiles H^-, NH_2^-, OH^-, F^-, SH^-, Cl^- and NH_3 indicates an increasing degree of product-like character. Except for the C–Nu bond length, which is heavily dependent on the nature of the nucleophile, all geometrical parameters indicate the same ordering for the TS position along the reaction coordinate. It is significant that the KIE does not directly follow this sequence. From Fig. 3 it is clear that the seven nucleophiles should be partitioned into groups according to rows in the periodic table. The division was not expected, although it has been noted before in connection with leaving group abilities.[34] Within each of these groups the KIE decreases as the TSs become more product like.

Usually H/D SKIEs larger than 1.07 are indicative of an S_N1 reaction while S_N2 reactions show very small or inverse effects.[8,35] The calculated SKIEs in this study all lie between 0.91 and 1.06 in absolute value, typical for an S_N2 reaction. Although the calculated variation is rather small, it is still significant enough that it should be possible to measure experimentally. A difference in SKIE of 0.02 (a typical experimental uncertainty) corresponds to geometry changes at the TS of ~0.03 Å in bond length (r_{CO}) and ~3° difference in torsional angle (θ_{HCCO}), *i.e.* isotope effects are quite sensitive to the TS geometry. There does not appear to be an overall correlation between nucleophilicity and SKIE.

To our knowledge, no experimental KIEs have been reported for these specific reactions, but Hanzlik and Westkaemper have published a value of 0.949 ± 0.029 for CH_3O^- attack on *p*-nitrostyrene oxide,[36] best compared with our value of 0.981 for OH^-.† A direct comparison of these two numbers cannot be made due to different nucleophiles, substrates and solvation effects, but they do not seem contradictory.

Beside the characterization of TS geometries as early (reactant-like) or late (product-like), the descriptions loose and tight are also frequently used. Interpretation of SKIEs has primarily focussed on force constants for the out-of-plane C_α–H(D) bending mode. It is usually assumed that a loose transition state will have a lower C–H out-of-plane bending frequency than a tight TS, leading to a larger SKIE for the former.[11,17,19–21,35,38–40] As mentioned in the introduction, recent work has shown that not only bending but also stretching vibrations are important for the absolute value of SKIEs.[12–16]

To discuss the early/late and loose/tight features of the TSs, it is customary to convert bond distances to bond orders and display these in a two-dimensional More O'Ferrall–Jencks (MOJ) diagram.[41–43] The bond lengths are converted to bond orders by a non-linear transformation according to eqn. (2). For

$$n^{\ddagger} = \exp\left(\frac{r^{\circ} - r^{\ddagger}}{a}\right) \qquad (2)$$

interpolation between bond orders in the range 1–3, the constant *a* is fairly independent on the nature of the bond and is usually set to 0.3.[43] This value is too small for extrapolating to bond orders less than 1, and Houk *et al.* have recently used a value of 0.6 for such cases in pericyclic reactions.[41] Shaik *et al.* have evaluated *a* values from HF/4-31G calculations for identity reactions of the type $X^- + CH_3X$ by defining the TS to have a bond order of 0.5.[44] These values depend on the nature of X and lie in the range 0.6–1.0.

We have calculated bond orders from TS bond lengths, with r^{0}_{CNu} being the CH_3–Nu bond length and r^{0}_{CO} the reactant r_{CO}, employing both $a = 0.3$, 0.6 and 0.9. The resulting MOJ diagram is shown in Fig. 5 with the bond-making axis equal to $n^{\ddagger}_{CNu}$ and the bond-breaking axis equal to $[1 - n^{\ddagger}_{CO}]$. The reactant is located in the lower left hand corner and the product in the upper right hand corner. The upper left hand corner corresponds to an S_N1 type reaction with the C–O bond breaking before attack of the nucleophile, while the lower right hand corner is a hypothetical species where the nucleophile adds before any C–O bond breaking occurs. The lower-left/upper-right diagonal thus indicates the early/late character

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† For the CH_3O^- attack on *p*-nitrostyrene oxide, Jacober and Hanzlik[37] have reported the heavy-atom isotope effects $k_{^{12}C}/k_{^{13}C}$ equal to 1.082 ± 0.012 and $k_{^{16}O}/k_{^{18}O}$ to 1.035 ± 0.013. The corresponding calculated values for OH^- attack on ethylene oxide are 1.051 and 1.027.

while the perpendicular direction is a measurement of the loose/tight feature.

From Fig. 5 the same division into groups according to the periodic table as inferred from the KIE (Fig. 3) is observed. This partition is independent of the specific value of *a*. An *a* value of 0.3 gives the conclusion that these reactions are very S_N1-like (the C–O bond nearly broken before any C–Nu bonding takes place), while the values of 0.6 or 0.9 lead to much more central S_N2 type mechanisms.* It appears that the reason for the larger KIE for the third period nucleophiles compared to those from the second row is due to more loose TSs. This contrasts the findings of Wolfe *et al.*[15] but agrees with other work.[11,17,19-21,35,38-40] Regardless of the specific proportionality constant used, the diagram also shows that the more product-like TSs correspond to being more tight. A movement of 0.5 along the reaction diagonal corresponds approximately to a movement of 0.1 in the perpendicular direction. The diagram indicates that the more product-like TSs have the smaller absolute value of the KIE, a conclusion which also can be obtained from Fig. 3. Although the number of data points is small, it appears that the main determining factor for the SKIE is the loose/tight feature of the TS rather than the early/late position, *i.e.* the lower KIE for the more product-like TSs is primarily due to the increased tightness. This is in agreement with model calculations reported by Yamataka *et al.*[39]

The main determining factor for the variation in the KIE arises from the vibrations, and Fig. 4 shows that this contribution can be decomposed into three groups of frequencies. The low and high frequencies give a more or less constant inverse contribution to the KIE for all nucleophiles. The group of mid frequencies, which contains all bending modes normally attributed to cause the SKIE, gives a normal contribution and is the main factor for determining the variation of the KIE.[12-16]

Finally, it should be stressed that the computational results refer to isolated molecules. Solvation may alter the structure of the TSs and change the magnitude of the KIEs.[20] Monte Carlo simulations suggest that the TS for the identity reaction of Cl^- with CH_3Cl is slightly looser in solution that in the gas phase,[45] while *ab initio* calculations suggest that micro solvation by one or two water molecules actually decreases the C–Cl bond at the TS slightly.[12,†] In both cases the effect is small, which agrees with the analysis by Westaway.[46] Experimental solution phase data is likely to give KIEs which differ in absolute magnitude from those reported here. It would be interesting, however, to see whether the calculated variation in the KIEs with respect to different nucleophiles can be confirmed by experiments.

Conclusions

We have presented a series of *ab initio* calculations on the variation of transition structures and α-secondary hydrogen–deuterium kinetic isotope effects in an S_N2 reaction by different nucleophiles. For this reaction the absolute value of the SKIE decreases as the transition state becomes more product-like, which is shown to correlate with geometries getting tighter. Based on the calculated data for the seven nucleophiles, it appears that the isotope effect mainly is determined by the loose/tight nature of the transition state.

Within a limited class of nucleophiles, like anions from the same row in the periodic table, there is a good correlation between transition state geometry and secondary kinetic isotope effect. A variation in the isotope effect of 0.02 corresponds to changes of ~0.03 Å in bond length and ~3° in torsional angle at the TS. The variation in the isotope effect is primarily due to bending vibrations, but the magnitude of the SKIEs is governed mainly by the stretching vibrations and cannot be explained by exclusively considering the C_α–H(D) out-of-plane bending vibration. Tunnelling calculations on the halide reactions show only minor corrections, and we do not believe that tunnelling affects the general conclusions drawn above.

Acknowledgements

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References

1 B. Carpenter, *Determination of Organic Reaction Mechanisms*, Wiley-Interscience, New York, 1984.

2 K. C. Westaway, in *Isotopes in Organic Chemistry*, eds. E. Buncel and C. C. Lee, 1987, **7**, ch. 5.

3 C. J. Collins and N. S. Bowman, *Isotope Effects in Chemical Reactions*, Van Nostrand-Reinhold, New York, 1970.

4 T. H. Lowry and K. S. Richardson, *Mechanism and Theory in Organic Chemistry*, Harper and Row, New York, 1981.

5 L. Melander and J. H. Saunders, Jr., *Reaction Rates of Isotopic Molecules*, Wiley, New York, 1980.

6 A. Streitwieser Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Am. Chem. Soc.*, 1958, **80**, 2326.

7 J. H. Saunders, Jr., *Investigation of Rates and Mechanisms of Reactions*, 4th edn., part 1, ed. C. F. Bernasconi, Wiley, New York, 1986.

8 S. E. Scheppele, *Chem. Rev.*, 1972, **72**, 511.

9 D. J. McLennan, in *Isotopes in Organic Chemistry*, eds. E. Buncel and C. C. Lee, 1987, **7**, ch. 6.

10 (*a*) J. Bron, *Can. J. Chem.*, 1974, **52**, 903; (*b*) K. T. Leffek, J. A. Llewellyn and R. E. Robertson, *Can. J. Chem.*, 1960, **38**, 1505.

11 K. C. Westaway and S. F. Ali, *Can. J. Chem.*, 1979, **57**, 1354.

12 (*a*) X. G. Zhao, S. C. Tucker and D. G. Truhlar, *J. Am. Chem. Soc.*, 1991, **113**, 826; (*b*) X. G. Zhao, D.-H. Lu, Y.-P. Liu, D. G. Lynch and D. G. Truhlar, *J. Chem. Phys.*, 1992, **97**, 6369.

13 D.-H. Lu, D. Maurice and D. G. Truhlar, *J. Am. Chem. Soc.*, 1990, **112**, 6206.

14 J. A. Barnes and I. H. Williams, *J. Chem. Soc., Chem. Commun.*, 1993, 1286.

15 (*a*) S. Wolfe and C.-K. Kim, *J. Am. Chem. Soc.*, 1991, **113**, 8056; (*b*) R. J. Boyd, C.-K. Kim, Z. Shi, N. Weinberg and S. Wolfe, *J. Am. Chem. Soc.*, 1993, **115**, 10147.

16 A. A. Viggiano, J. S. Paschkewitz, R. A. Morris, J. F. Paulson, A. Gonzales-Lafont and D. G. Truhlar, *J. Am. Chem. Soc.*, 1991, **113**, 9404.

17 J. Hayani, N. Hihara, N. Tanaka and A. Kaji, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 831.

18 (*a*) C. Y. Wu and R. E. Robertson, *Chem. Ind.*, 1964, 1803; (*b*) J. M. Harris, M. S. Paley and T. W. Prasthofer, *J. Am. Chem. Soc.*, 1981, **103**, 5915.

19 (*a*) V. P. Vitullo, J. Grabowski and S. Sridharan, *J. Am. Chem. Soc.*, 1980, **102**, 6463; (*b*) B. L. Knier and W. P. Jencks, *J. Am. Chem. Soc.*, 1980, **102**, 6789.

20 (*a*) K. C. Westaway and S. F. Ali, *Can. J. Chem.*, 1979, **57**, 1089; (*b*) K. C. Westaway and Z. Wazczylo, *Can. J. Chem.*, 1982, **60**, 2500; (*c*) K. C. Westaway and Z. Lai, *Can. J. Chem.*, 1988, **66**, 1263; (*d*) Z. Lai and K. C. Westaway, *Can. J. Chem.*, 1989, **67**, 21; (*e*) K. C. Westaway and Z. Lai, *Can. J. Chem.*, 1989, **67**, 345; (*f*) Y. Fang and K. C. Westaway, *Can. J. Chem.*, 1991, **69**, 1017.

21 (*a*) C. H. Gray, J. K. Coward, K. B. Schowen and R. L. Schowen, *J. Am. Chem. Soc.*, 1979, **101**, 4351; (*b*) M. F. Hegazi, R. T. Borchardt and R. L. Schowen, *J. Am. Chem. Soc.*, 1979, **101**, 4359.

22 S. Gronert, C. H. DePuy and V. M. Bierbaum, *J. Am. Chem. Soc.*, 1991, **113**, 4009.

23 I. Lee, H. J. Koh, B.-S. Lee, D. S. Sohn and B. C. Lee, *J. Chem. Soc., Perkin Trans. 2*, 1991, 1741.

24 GAUSSIAN90, M. J. Frisch, M. Head-Gordon, G. W. Trucks, J. B. Foresman, H. B. Schlegel, K. Raghavachari, M. A. Robb, J. S. Binkley, C. Gonzalez, D. J. Defrees, D. J. Fox, R. A. Whiteside, R. Seeger, C. F. Melius, J. Baker, R. L. Martin, L. R. Kahn, J. J. P. Stewart, S. Topiol and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1990.

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* Conservation of bond order (*i.e.* $n_{CO} + n_{CNu} = 1$) produces $a = 0.7$.

† The calculated KIE changes from 0.96 to 0.94–0.90 by solvation of one or two water molecules.

25 GAUSSIAN92, Revision A, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomberts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, S. Topiol and J. A. Pople, Gaussian, Inc., Pittsburgh, PA, 1992.

26 W. J. Hehre, L. Radom, P. v. R. Schleyer and J. A. Pople, *Ab Initio Molecular Orbital Theory*, Wiley-Interscience, New York, 1986.

27 D.-H. Lu, T. N. Truong, B. C. Garrett, R. Steckler, A. D. Isaacson, S. N. Rai, G. C. Hancock, J. G. Lauderdale, T. Joseph, V. S. Melissas and D. G. Truhlar POLYRATE; version 2.5, Quantum Chemistry Program Exchange program 601, Department of Chemistry, Indiana University, Bloomington, IN, 1990.

28 C. Gonzales and H. B. Schlegel, *J. Phys. Chem.*, 1989, **90**, 2154.

29 (*a*) D. G. Truhlar, A. D. Isaacson and B. C. Garrett, in *The Theory of Chemical Reaction Dynamics*, ed. M. Baer, CRC Press; Boca Raton, FL; 1985, **4**, ch. 2; (*b*) A. Gonzalez-Lafont, T. N. Truong and D. G. Truhlar, *J. Chem. Phys.*, 1991, **95**, 8875.

30 J. March, *Advanced Organic Chemistry*, Wiley, New York, 1985, ch. 10.

31 R. P. Bell, *The Tunnel Effect in Chemistry*, Chapman and Hall, London, 1980.

32 (*a*) D. G. Truhlar, R. Steckler and M. S. Gordon, *Chem. Rev.*, 1987, **87**, 217; (*b*) G. C. Schatz, *Chem. Rev.*, 1987, **87**, 81.

33 See *e.g.* (*a*) E. Bosch, M. Moreno and J. M. Lluch, *J. Am. Chem. Soc.*, 1992, **114**, 2072; (*b*) S. Wolfe, S. Hoz, C.-K. Kim and K. Yang, *J. Am. Chem. Soc.*, 1990, **112**, 4186; (*c*) B. C. Garrett and D. G. Truhlar, *J. Chem. Phys.*, 1980, **72**, 3460; (*d*) B. C. Garrett and D. G. Truhlar, *J. Am. Chem. Soc.*, 1980, **102**, 2559; (*e*) J. V. Michael, J. R. Fisher, J. M. Bowman and Q. Sun, *Science*, 1990, **249**, 269; (*f*) A. Thibblin and P. Ahlberg, *Chem. Soc. Rev.*, 1989, **18**, 209.

34 Z. Shi and R. J. Boyd, *J. Am. Chem. Soc.*, 1991, **113**, 2434.

35 P. J. Smith and K. C. Westaway, *Synthesis and Applications of Isotopically Labelled Compounds*, 1988, 213.

36 R. P. Hanzlik and R. B. Westkaemper, *J. Am. Chem. Soc.*, 1980, **102**, 2464.

37 S. P. Jacober and R. P. Hanzlik, *J. Am. Chem. Soc.*, 1986, **108**, 1594.

38 (*a*) E. R. Pohl and D. J. Hupe, *J. Am. Chem. Soc.*, 1980, **102**, 2763; (*b*) I. Mihel, J. O. Knipe, J. K. Coward and R. L. Schowen, *J. Am. Chem. Soc.*, 1979, **101**, 4349; (*c*) C. Guo, M. L. Brownawell and J. S. Filippo, Jr., *J. Am. Chem. Soc.*, 1985, **107**, 6028; (*d*) B. S. Axelsson, O. Matsson and B. Långström, *J. Am. Chem. Soc.*, 1990, **112**, 6661.

39 H. Yamataka, S. Tamura, T. Hanafusa and T. Ando, *J. Am. Chem. Soc.*, 1985, **107**, 5429.

40 I. H. Williams, *J. Am. Chem. Soc.*, 1984, **106**, 7206.

41 K. N. Houk, S. M. Gustafson and K. A. Black, *J. Am. Chem. Soc.*, 1992, **114**, 8565.

42 V. J. Shiner, Jr. and W. E. Buddenbaum, in *Isotope Effects in Enzyme-catalyzed Reactions*, eds., W. W. Cleland, M. H. O'Leary and D. B. Northrop, University Park Press, Baltimore, 1977.

43 (*a*) W. P. Jencks, *Chem. Rev.*, 1972, **72**, 705; (*b*) R. A. More O'Ferrall, *J. Chem. Soc. B*, 1970, 274; (*c*) L. Pauling, *J. Am. Chem. Soc.*, 1947, **69**, 542; (*d*) J. P. Paolini, *J. Comput. Chem.*, 1990, **11**, 1160; (*e*) J. Rodgers, D. A. Femec and R. L. Schowen, *J. Am. Chem. Soc.*, 1982, **104**, 3263.

44 S. S. Shaik, B. H. Schlegel and S. Wolfe, *Theoretical Aspects of Physical Organic Chemistry. The S_N2 Mechanism*, Wiley, New York, 1992.

45 W. L. Jorgensen and K. L. Buckner, *J. Phys. Chem.*, 1986, **90**, 4651.

46 K. C. Westaway, *Can. J. Chem.*, 1978, **56**, 2691.

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