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Kinetic isotope effects for gas phase S_N2 methyl transfer: a computational study of anionic and cationic identity reactions

Giuseppe D. Ruggiero and Ian H. Williams*

Department of Chemistry, University of Bath, Bath, UK BA2 7AY.
E-mail: i.h.williams@bath.ac.uk

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The relationship between energy barriers, transition-state looseness and 2° α-deuterium kinetic isotope effects (KIEs) has been re-evaluated for a range of identity S_N2 methyl transfer reactions that extends to "exploded" transition structures (TSs). *Ab initio* MP2/6-311+G* molecular orbital calculations have been performed for reactions involving the neutral nucleophiles X = *C*O, N_2, NH_3, $N(CH_3)_3$, OH_2, Kr, Ar, Ne and He, along with anionic nucleophiles X^- = F, Cl, Br, *C*N, *N*C, CCH, and OH. The behaviour previously noted by Wolfe and co-workers, from MP2/6-31+G* studies of identity and non-identity methyl transfers with anionic nucleophiles and neutral electrophiles only, does not apply to the broader range which also includes neutral nucleophiles and cationic electrophiles: a looser TS is not associated with a higher energy barrier and a more inverse 2° α-D KIE. Moreover, when the interaction of the nucleophile with the electrophile in the reactant complex (RC) is considered, no simple relationships between "looseness" or "tightness" and either energy barriers or KIEs are found. The variation in energy barriers may be understood by means of a simple model involving the distance travelled by the methyl group within the encounter complex from RC to the product complex (PC) and the force constant for stretching the bond to the leaving group in RC. There is a fair linear correlation between the 2° α-D KIE and the change in this same stretching force constant, from RC to TS. The methyl group in the S_N2 TS does not resemble an isolated methyl cation, even for systems showing "S_N1-like" properties, owing to the significant influence of the nucleophile and leaving group. Consideration of the unusual range of nucleophiles X = Kr, Ar, Ne and He in identity reactions with CH_3X^+ shows a mechanistic changeover from a double-well potential with a true S_N2 TS to a single-well potential with a symmetric intermediate corresponding to a solvated methyl cation.

Introduction

Methyl group transfer by an S_N2 mechanism is an archetypal reaction in organic chemistry and is still the subject of much experimental[1] and theoretical study.[2] Due to its relative simplicity, the S_N2 process with inversion of configuration is one of the most important organic reaction mechanisms, and has been the subject of extensive studies using kinetic isotope effects (KIEs).[3] Secondary α-deuterium (2° α-D) isotope effects have been widely used to elucidate the structure of transition states.

Computational studies of identity[4] (X = Y) and non-identity[5] (X ≠ Y) gas phase methyl transfer reactions $X^- + CH_3Y \longrightarrow XCH_3 + Y^-$, with anionic nucleophiles and neutral electrophiles, at levels up to MP2/6-31+G*, led Wolfe and co-workers to report that energy barriers were directly related to the looseness of the transition structures (TSs) but were inversely related to the 2° α-D KIEs. In other words, in contrast to the prevailing belief, the KIEs became stronger (further from unity) in the inverse direction ($k_H < k_D$) as the TS became looser. In contrast, Glad and Jensen[6] presented MP2/6-31++G(d,p) results for identity reactions with nucleophiles X^- (X = Y = F, Cl, Br), which indicated that the α-D KIE became weaker (closer to unity, although still inverse) as the TS became looser. These contradicting conclusions hinged upon how TS looseness was defined.[7]

Most previous computational studies[8,9] were restricted to reactions of anionic nucleophiles X^- with neutral electrophiles CH_3Y, for the good reason that gas-phase experimental data were generally available only for this type of reaction.[10] Gas-phase reactions of neutral nucleophiles X with cationic electrophiles CH_3Y^+ have been studied much less, both theoretically[11–13] and experimentally.[13,14] Our intention in the present study is to re-evaluate the relationship between energy barriers, TS looseness and 2° α-D KIEs, for a range of identity S_N2 methyl transfer reactions that extends to very loose, open, or "exploded" TSs. In particular, we present results of *ab initio* molecular orbital calculations for reactions involving the neutral nucleophiles X = CO, N_2, NH_3, $N(CH_3)_3$, OH_2, Kr, Ar, Ne and He, along with anionic nucleophiles X^- = F^-, Cl^-, Br^-, CN^-, NC^-, CCH^-, and OH^-.

Computational procedure

The Gaussian 98 program[15] was employed with the 6-311+G* basis for second-order Møller–Plesset (MP2) gas-phase geometry optimisations, using the Berny routine for reactant complexes (RC) and the EF algorithm for TSs. No symmetry constraints were imposed, and the nature of each stationary point was verified through frequency calculations. Charge distributions were obtained by natural population analysis (NPA).

KIEs k_{CH_3}/k_{CD_3} at 298 K were evaluated from the optimised geometries and Hessians using our CAMISO program.[16] Unwanted contamination by spurious translational and rotational contributions, which give rise to small non-zero frequencies, was eliminated by a projection method. The resultant pure vibrational frequencies for isotopomeric species satisfied the Teller–Redlich product rule, being entirely consistent with the masses and moments of inertia obtained from the molecular geometries. This provides a stern and unambiguous test for the correctness of the procedures employed in the isotope effect calculations. Partition functions were evaluated within the harmonic oscillator, rigid-rotor, ideal-gas approximations and were utilised within a standard semiclassical transition-state theoretical treatment of isotope effects.

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Table 1 MP2/6–311+G* total energy for RC (hartree),[a] relative energy barrier (kJ mol^{-1}) and transition frequency (cm^{-1}) for TS and selected bond lengths (Å) for identity S_N2 methyl transfer $(X_{nuc}\cdots CH_3X_{lg})^{RC} \longrightarrow (X\cdots CH_3\cdots X)^{TS}$

X	$(E_{total})^{RC}$	$\Delta E^{\ddagger}$	$\nu^{\ddagger}$	$(CX_{lg})^{RC}$	$(CX_{nuc})^{RC}$	$(CX)^{TS}$	$\langle CH\rangle^{RC}$	$\langle CH\rangle^{TS}$
Anionic nucleophiles								
F	−239.124857	63.78	595*i*	1.436	2.661	1.833	1.083	1.073
Cl	−959.125718	72.86	540*i*	1.811	3.218	2.305	1.083	1.071
Br	−5184.838719	59.66	474*i*	1.970	3.373	2.459	1.083	1.073
OH	−191.075930	193.23	666*i*	1.446	3.142	1.902	1.088	1.075
$\underline{C}N$	−255.045154	195.53	738*i*	1.463	3.302	2.070	1.089	1.073
$\underline{N}C$	−255.003662	133.29	685*i*	1.440	3.040	1.969	1.087	1.073
CCH	−192.790505	214.09	774*i*	1.463	3.334	2.074	1.092	1.072
Neutral nucleophiles								
$\underline{C}O$	−265.630282	152.31	583*i*	1.439	3.281	2.092	1.094	1.081
N_2	−258.018206	70.72	407*i*	1.467	3.030	2.081	1.090	1.082
NH_3	−152.310298	95.43	633*i*	1.516	2.960	2.004	1.084	1.077
$N(CH_3)_3$	−387.372667	87.94	587*i*	1.506	2.956	1.942	1.088	1.083
OH_2	−191.969238	48.57	512*i*	1.530	2.617	1.953	1.082	1.076
Ar	−1093.273635	6.07	175*i*	2.021	2.987	2.422	1.084	1.083
Kr	−5543.566855	9.30	202*i*	2.133	3.206	2.537	1.084	1.082
Ne	−296.821356			2.416	2.416		1.088	
He	−45.084778			2.315	2.315		1.088	

[a] 1 hartree = 2625.5 kJ mol^{-1}.

Hessians were transformed from Cartesian co-ordinates to non-redundant internal co-ordinates. The latter comprised generally of a subset of bond stretches, angle bends, and torsions, but local symmetry co-ordinates were constructed for bending of the methyl groups, as described previously, to eliminate local redundancies: five independent symmetry co-ordinates from the six valence co-ordinates of the distorted tetrahedral RCs and seven from the nine valence co-ordinates of the trigonal-bipyramidal TSs. Inversion of the nonsingular matrix of internal co-ordinates yielded the compliance constant matrix, the reciprocal of the diagonal elements of which are relaxed force constants. The relaxed force constants were obtained by back-transformation of the compliance matrix from non-redundant internal co-ordinates to redundant valence co-ordinates. It is possible to introduce scaling factors for the force constants for each of the diagonal valance force constants, either by the comparison of experimental with calculated frequencies for ground state reactants or by applying a method dependent scaling factor. Scaling was not employed because firstly, not all of the experimental frequencies are available for the reactions studied and secondly, the use of a uniform factor had little or no effect compared to the normal values.

Results and discussion

Table 1 contains MP2/6-311+G* total energies for the RCs, and relative potential energies and transition frequencies for the TSs, together with selected bond lengths for these optimised species. Table 2 gives the looseness and tightness parameters, and methyl-transfer distances, as defined below, and natural population (NPA) group charges are listed in Table 3. Secondary α-D_3 KIEs are shown in Table 4 for the identity S_N2 methyl transfer $(X_{nuc}\cdots CH_3X_{lg})^{RC} \longrightarrow (X\cdots CH_3\cdots X)^{TS}$, and in Table 5 for the fragmentation $(X\cdots CH_3\cdots X) \longrightarrow 2X + CH_3^+$. Selected force constants are presented in Table 6.

Tightness and looseness

The looseness parameter, $L^{\ddagger}$, as defined by Wolfe and co-workers,[17] is the percentage lengthening of the C–X and C–Y bonds given by eqn. (1), where d^{RC} and d^{TS} are the C–X (C–Y) bond lengths of CH_3X (CH_3Y) in RC and TS, respectively.

$$L^{\ddagger} = \%CX^{\ddagger} + \%CY^{\ddagger} \qquad (1)$$
$$\%CX^{\ddagger} = 100(d^{TS}{}_{CX} - d^{RC}{}_{CX})/d^{RC}{}_{CX}$$
$$\%CY^{\ddagger} = 100(d^{TS}{}_{CY} - d^{RC}{}_{CY})/d^{RC}{}_{CY}$$

For the identity reactions the expression simplifies to eqn. (2).

$$L^{\ddagger} = 200\,(d^{TS}{}_{CX} - d^{RC}{}_{CX})/d^{RC}{}_{CX} \qquad (2)$$

This definition of $L^{\ddagger}$ has been criticised by Poirier *et al.* who concluded[7b] that it was not a good measure, and suggested that the sum ($CX^{\ddagger}$ + $CY^{\ddagger}$) would be better. Glad and Jensen, however, pointed out[6] that this quantity fails to distinguish between different nucleophiles and nucleofuges, and that it would be better to take the size of the entering and leaving groups into account when discussing TS looseness. These authors argued instead that, for identity reactions, the simple bond length elongation $\Delta d^{\ddagger}{}_{CX}$ [eqn. (3)] was best, or equivalently the Pauling bond order n_{CX} [eqn. (4)], as indeed we have previously used ourselves in this context.[11f] In eqn. (4), $d_{CX}(n)$ represents the length of a C–X bond with Pauling bond order *n*.

$$\Delta d^{\ddagger}{}_{CX} = d^{TS}{}_{CX} - d^{RC}{}_{CX} \qquad (3)$$

$$n_{CX} = \exp\{[d_{CX}(1) - d_{CX}(n)]/c\} \qquad (4)$$

Another limitation of $L^{\ddagger}$, as a measure of TS looseness, is that it disregards any interaction between the nucleophile and the electrophile in the RC. Whilst this is not a problem for genuinely bimolecular processes, for which the activation parameters are evaluated with respect to an isolated reactant, it may obscure significant features of reactions occurring within encounter complexes, cages and active sites of catalysts. Albery and Kreevoy defined[18] a tightness parameter τ as the sum of the Pauling bond orders n_{CX} and n_{CY} involving the bonds to the entering group X and leaving group Y [eqns. (4) and (5)]. In this study, $d_{CX}(1) = d_{CY}(1)$ is defined as the C–X bond length in the isolated reactant, and $d_{CX}(0.5)$ as the bond length $(C\cdots X_{lg})^{TS} = (C\cdots X_{nuc})^{TS}$ in the S_N2 transition structure for methyl transfer with X = Br; accordingly $\tau^{TS} = 1$ by definition. The value of the coefficient *c* determined in this way is 0.75. The relative tightness or looseness of the TSs are then related to the case of X = Br. Since barrier heights and KIEs reflect differences between the RC and the TS, tightness parameters τ^{RC} and τ^{TS} and their differences may be evaluated in order to determine whether they are related to the classical barrier heights ($\Delta E^{\ddagger} = E^{TS} - E^{RC}$).

$$\tau = n_{CX} + n_{CY} \qquad (5)$$

Table 2 Looseness and tightness parameters, and methyl-transfer distance for identity S_N2 methyl transfer $(X_{nuc}\cdots CH_3X_{lg})^{RC} \longrightarrow (X\cdots CH_3\cdots X)^{TS}$

X	$L^‡$	$\Delta d^‡_{CX}$/Å	τ^{RC}	τ^{TS}	$\Delta\tau^‡$	D_{Me}/Å
Anionic nucleophiles						
F	55	0.397	1.09	0.95	−0.14	1.23
Cl	55	0.494	1.18	1.06	−0.11	1.41
Br	50	0.489	1.09	0.96	−0.13	1.40
OH	63	0.456	1.05	1.01	−0.04	1.70
$\underline{C}N$	83	0.607	1.08	0.89	−0.19	1.84
$\underline{N}C$	73	0.529	1.11	0.97	−0.13	1.60
CCH	84	0.611	1.08	0.88	−0.20	1.87
Neutral nucleophiles						
$\underline{C}O$	91	0.653	1.07	0.79	−0.28	1.84
N_2	84	0.614	1.10	0.83	−0.27	1.56
NH_3	64	0.488	1.11	0.99	−0.13	1.44
$N(CH_3)_3$	58	0.436	1.12	1.07	−0.05	1.45
OH_2	55	0.423	1.09	0.96	−0.13	1.09
Ar	40	0.401	1.19	1.07	−0.11	0.97
Kr	38	0.404	1.16	1.07	−0.09	1.07

Table 3 MP2/6-311+G* group charges from natural population analysis

X	$(CH_3)^{RC}$	$(CH_3)^{TS}$	$(X_{lg})^{RC}$	$(X_{nuc})^{RC}$	$(X)^{TS}$
Anionic nucleophiles					
F	0.50	0.58	−0.51	−0.99	−0.79
Cl	0.18	0.40	−0.19	−0.99	−0.70
Br	0.13	0.36	−0.14	−0.99	−0.68
OH	0.37	0.46	−0.39	−0.98	−0.73
$\underline{C}N$	0.10	0.28	−0.11	−0.99	−0.64
$\underline{N}C$	0.33	0.52	−0.34	−0.99	−0.76
CCH	0.08	0.28	−0.10	−0.98	−0.86
Neutral nucleophiles					
$\underline{C}O$	0.20	0.42	0.57	0.23	0.29
N_2	0.49	0.70	0.51	0.00	0.15
NH_3	0.39	0.50	0.61	0.01	0.25
$N(CH_3)_3$	0.36	0.40	0.61	0.03	0.30
OH_2	0.57	0.70	0.34	0.09	0.15
Ar	0.65	0.76	0.33	0.02	0.12
Kr	0.54	0.68	0.44	0.02	0.16
Ne	0.96		0.02	0.02	
He	0.98		0.01	0.01	

Table 4 Analysis of secondary α-D_3 kinetic isotope effects (298 K) for identity S_N2 methyl transfer $(X_{nuc}\cdots CH_3X_{lg})^{RC} \longrightarrow (X\cdots CH_3\cdots X)^{TS}$

X	k_{CH_3}/k_{CD_3}	MMI[a]	EXC[a]	ZPE[a]	ZPE(CH_{str})	ZPE(rest)
Anionic nucleophiles						
F	0.920	1.00	1.13	0.81	0.85	0.95
Cl	0.949	1.00	1.10	0.86	0.79	1.10
Br	0.968	1.00	1.06	0.91	0.71	1.28
OH	0.902	1.00	1.13	0.80	0.84	0.95
$\underline{C}N$	0.714	0.79	1.40	0.64	0.73	0.88
$\underline{N}C$	0.780	0.79	1.39	0.71	0.76	0.94
CCH	0.729	0.88	1.22	0.68	0.77	0.88
Neutral nucleophiles						
$\underline{C}O$	0.869	0.99	1.15	0.77	0.78	0.99
N_2	0.920	0.99	1.12	0.83	0.84	0.91
NH_3	0.879	0.99	1.13	0.79	0.87	0.91
$N(CH_3)_3$	0.931	1.00	1.06	0.88	0.87	1.02
OH_2	0.969	0.99	1.08	0.93	0.73	1.27
Ar	1.168	1.00	1.04	1.12	0.96	1.16
Kr	1.103	1.00	1.05	1.05	0.97	1.08

[a] Mass/moment-of-inertia (MMI), excitational (EXC) and zero-point energy (ZPE) factors as conventionally defined (refs. 23*a* and 23*c*).

The TSs show tightness parameters in the range $0.83 < \tau^{TS} < 1.07$, with the lowest value being for X = N_2 (the loosest) and the highest being for X = Ar, Kr, and $N(CH_3)_3$ (the tightest). However, the RCs all possess tightness parameters $\tau^{RC} > 1$, with the lowest value for X = OH and the highest for X = Ar. Thus according to this measure, for every reaction considered here, progress from RC to TS within an encounter complex is accompanied by a decrease in tightness; in other words, $\Delta\tau^‡$ is negative. The largest changes occur for X = CO and N_2, and the smallest for X = OH and $N(CH_3)_3$.

Table 5 Analysis of secondary α-D_3 kinetic isotope effects for the fragmentation $(X\cdots CH_3\cdots X) \longrightarrow 2X + CH_3^+$

X	EIE	MMI	EXC	ZPE	ZPE(CH_{str})	ZPE(rest)
Anionic nucleophiles						
F	2.86	0.42	1.10	6.20	0.86	7.21
Cl	2.49	0.40	1.17	5.31	0.91	5.84
Br	2.18	0.39	1.23	4.54	0.86	5.28
OH	2.62	0.41	1.14	5.60	0.88	6.39
$\underline{C}N$	2.64	0.41	1.15	5.61	0.94	5.97
$\underline{N}C$	2.92	0.44	1.11	5.99	0.95	6.31
CCH	2.50	0.37	1.29	5.34	0.94	5.68
Neutral nucleophiles						
$\underline{C}O$	2.75	0.40	1.14	5.95	0.92	6.47
N_2	3.60	0.41	1.51	5.85	0.91	6.43
NH_3	3.08	0.35	1.23	7.14	0.89	7.98
$N(CH_3)_3$	2.75	0.28	1.40	6.99	0.87	8.03
OH_2	3.15	0.37	1.21	6.99	0.85	8.23
Ar	2.04	0.40	1.22	4.15	0.92	4.52
Kr	2.05	0.41	1.30	3.85	0.92	2.23
Ne[a]	1.23	0.42	1.47	2.02	0.99	2.04
He[a]	1.09	0.48	1.40	1.73	0.98	1.77

[a] Equilibrium isotope effects.

Table 6 Selected force constants[a]

	C_α–H stretch		C_α–X stretch		H–C_α–H bend		H–C_α–X bend	
X	RC	TS	RC	TS	RC	TS	RC	TS
Anionic nucleophiles								
F	5.81	6.10	4.55	0.52	0.49 (0.67)	0.27 (0.61)	0.79 (0.83)	0.81 (0.91)
Cl	5.79	6.24	3.27	0.28	0.48 (0.63)	0.38 (0.61)	0.65 (0.77)	0.87 (0.65)
Br	5.79	6.14	2.68	0.18	0.46 (0.64)	0.51 (0.21)	0.54 (0.70)	0.83 (0.46)
OH	5.70	6.01	4.90	0.42	0.45 (0.68)	0.55 (0.62)	0.77 (0.85)	0.58 (0.92)
$\underline{C}N$	5.5	6.18	5.28	0.28	0.52 (0.62)	0.28 (0.60)	0.55 (0.66)	0.51 (0.10)
$\underline{N}C$	5.49	5.98	5.03	0.18	0.60 (0.69)	0.32 (0.21)	0.80 (0.60)	0.63 (0.10)
CCH	5.45	6.21	5.43	0.26	0.46 (0.06)	0.32 (0.27)	0.54 (0.67)	0.36 (0.17)
Neutral nucleophiles								
$\underline{C}O$	5.49	5.98	5.03	0.18	0.60 (0.69)	0.32 (0.21)	0.80 (0.60)	0.63 (0.10)
N_2	5.67	6.21	5.21	0.46	0.49 (0.65)	0.28 (0.05)	0.64 (0.83)	0.54 (0.09)
NH_3	5.79	6.04	4.26	0.50	0.49 (0.67)	0.26 (0.35)	0.73 (0.88)	0.70 (0.28)
$N(CH_3)_3$	5.68	5.71	4.51	0.70	1.35 (0.72)	0.73 (0.47)	0.81 (0.90)	0.84 (0.89)
OH_2	5.97	6.15	3.35	0.20	0.81 (0.63)	0.35 (0.32)	0.35 (0.89)	0.80 (0.26)
Ar	5.90	5.97	1.08	0.25	0.37 (0.63)	0.29 (0.64)	0.69 (0.64)	0.29 (0.51)
Kr	5.87	5.97	1.23	0.30	0.39 (0.63)	0.29 (0.64)	0.64 (0.64)	0.30 (0.52)
Ne	5.81		0.08		0.90 (0.66)			
He	5.83		0.04		0.89 (0.67)			
CH_3^+	5.79				0.89 (0.67)		0.39 (0.39)	

[a] Units are mdyn $Å^{-1}$ and mdyn Å rad^{-2} (1 dyn = 10^{-5} N) for the stretching and bending force constants, respectively. Relaxed force constants in parentheses.

Transition structures and barrier heights

It is now well established that the gas-phase S_N2 reaction proceeds *via* a double well potential. The ion–molecule complexes RC and PC considered in this work are the local energy-minimum species occurring immediately before and after the energy maximum along the reaction coordinate for S_N2 methyl transfer; they are not necessarily global minima on the energy surfaces. For example, we have not considered strongly hydrogen-bonded complexes such as $CH_3–NH_3^+\cdots NH_3$. The ion–molecule complexes with X = CN, NC and CCH do not contain a collinear XCX moiety: the HOMO of the nucleophile interacts with the LUMO of the methyl group to form a π-complex; nonetheless, these species are precursors to the S_N2 TS. Of course, for identity reactions, the ion–molecule complexes RC and PC corresponding to the reactant and product energy minima are identical; they are separated by a potential-energy barrier, whose maximum corresponds to a 5-coordinate TS. This is true for all of the systems studied here except for X = He and Ne, for which the 5-coordinate configuration is at an energy minimum and not a saddle point, as discussed below. With X = Ar and Kr, the 5-coordinate symmetrical species are TSs whose tightness parameters ($\Delta\tau^\ddagger$ = 0.11 and 0.09, respectively) and small barrier heights are in line with the rest of the series. The nature of noble gas bimolecular reactions has previously been demonstrated experimentally by means of photodissociation spectroscopy.[19]

There is no overall linear correlation of barrier height $\Delta E^\ddagger$ for anionic and cationic reactions with either looseness $L^\ddagger$ (Fig. 1) or elongation $\Delta d^\ddagger_{CX}$, for the reason that both parameters ignore the incoming nucleophile, which is just as important as the departing leaving group. However, neither is there any correlation between $\Delta E^\ddagger$ and $\Delta\tau^\ddagger$, which does involve both groups.

The principle of least nuclear motion (PLNM) states that those elementary reactions that involve the least change in atomic position and electronic configuration will be favoured.[20] The PLNM deals with reactivity in terms of the reactants and products of the reaction. The underlying assumption is that a reaction occurs in such a way as to involve a minimum expenditure of energy in changing the positions of the atoms in the

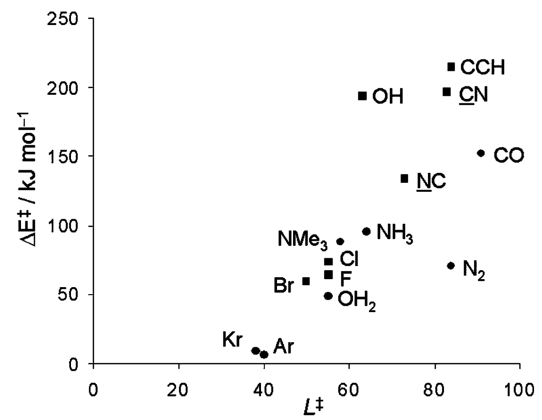

Fig. 1 Plot of the MP2/6-311+G* calculated energy barriers ($\Delta E^{\ddagger}$) against the looseness parameter ($L^{\ddagger}$). Solid squares denote anionic nucleophiles and solid circles denote neutral nucleophiles.

reactant to their corresponding positions in the product.[21,22] If the stretching and bending of the bonds essentially obey Hooke's Law, then the energy required to stretch or bend the bond is proportional to the square of the displacement; this simple-harmonic potential approach leads to eqn. (6), where

$$\Delta E_{\text{harm}}^{\ddagger} = \tfrac{1}{2}(F_{\text{CX}_{\text{lg}}})^{\text{RC}}[D_{\text{Me}}/2]^2 \times 75.3 \qquad (6)$$

the harmonic barrier $\Delta E_{\text{harm}}^{\ddagger}$ is related to the stretching force constant F of the C–X bond to the leaving group in the RC and the distance D_{Me} travelled by the methyl group from RC to its mirror-image PC [equal to $(\text{CX}_{\text{nuc}})^{\text{RC}} - (\text{CX}_{\text{lg}})^{\text{RC}}$]; the final factor converts from units of mdyn Å to kJ mol^{-1}.

This relationship is not meant to represent a means for calculation of barrier heights, as the harmonic potential is too gross an approximation; it serves only as a simple way to correlate the reaction barriers. Use of the force constant $F_{\text{CX}_{\text{lg}}}$ in the RC, and not the isolated species, takes care of any effect that the nucleophile has within the ion–molecule complex. There are satisfying linear correlations between $\Delta E_{\text{harm}}^{\ddagger}$ and $\Delta E^{\ddagger}$ for either the cationic (r = 0.932) or the anionic (r = 0.973) series considered separately or all taken together (r = 0.936). The same simple analysis was recently applied to a series of identity S_N2 methyl transfers between amine nucleophiles and leaving groups at the B3LYP/6-31G* level,[12] and yielded a correlation coefficient for linear regression of $r = 0.995$.

Charge distribution

The NPA charges show little charge transfer in the RC from the nucleophile to the electrophile: the charge on each anionic nucleophile is only slightly less negative than −1, and on each neutral nucleophile is only slightly more positive than 0. The one exception is for X = CO, where the HOMO of the nucleophile is strongly σ-donating towards the unoccupied methyl group orbital of A_1 symmetry, and the nucleophile bears a +0.23 charge in the RC and the methyl group is less positive than for the other overall cationic systems. The charge on the methyl group is always positive and, as expected, increases from RC to TS. The methyl moiety at the centre of the symmetrical energy minimum ("RC") for X = He or Ne possesses essentially a full positive charge of +1.

Secondary α-D isotope effect

Small inverse or normal KIEs ($0.85 < k_{\text{CH}_3}/k_{\text{CD}_3} < 1.12$) are generally observed for S_N2 reactions of primary alkyl substrates.[23] The KIE arises not only from steric interference of the bending vibrations[24] of the C_αH (or C_αD) in the trigonal-bipyramidal S_N2 TS, as compared with the reactants, but also from change in the stretching vibrations of these bonds.[3,5,7,11d,25] The MP2/6-311+G* calculated results (Table 3) confirm this view. Overall the α-D KIE is usually the resultant of a normal EXC factor and an inverse ZPE factor; the exception is for reactions involving Ar or Kr where ZPE is also normal. Vibrational analysis permits identification of the stretching modes for the CH and CD bonds in the RC and the TS and allows the contribution to the total ZPE factor from changes in their frequencies to be evaluated; this is denoted as ZPE(CH_{str}). The contribution of the all the rest of the stretching, bending and torsional modes is denoted as ZPE(rest). The analysis (Table 4) shows that, although the strongly inverse ZPE(CH_{str}) factor mainly responsible for the overall inverse α-D KIE, it does not dominate over the other factors in determining the actual value of the KIE. There is no useful correlation between ZPE(CH_{str}) and KIE; the coefficient of linear regression (~0.7) is as bad as for correlation of ZPE(rest) with KIE.

The range of KIEs is not split in two groups for anionic and cationic systems; the latter show both strongly inverse and normal values. The largest inverse KIEs are obtained with nucleophiles that contain a triple bond. The deviation from unity for the MMI term for the triply bonded species with X = CN, NC and CCH is due to the fact that in these cases RC does not contain a collinear XCX moiety: the HOMO of the nucleophile interacts with the LUMO of the methyl group to form a π-complex. The change from a reactant π-complex to a TS with a collinear XCX moiety is manifest in large inverse MMI and normal EXC factors. For X = CO, the RC is collinear because the HOMO of the nucleophile is σ-bonding. The different nature of the RC is not the major reason for strongly inverse KIEs, as calculations of the KIEs using isolated reactants still yield strongly inverse KIEs, *e.g.* $k_{\text{CH}_3}/k_{\text{CD}_3} = 0.767$ for X = CN. The large inverse KIE can be seen to arise from the large change in the CH stretching force constant in going from RC to TS.

The KIEs for systems involving the noble-gas atoms show values usually attributed to borderline S_N1–S_N2 mechanisms. There is a good deal of evidence that nucleophilic substitutions at centres with strongly electron-donating substituents are characterised by large α-deuterium KIEs, for S_N2 as well as for S_N1 mechanisms.[26] In these cases the "exploded" transition state for an S_N2 displacement can be considered as an unusually open species stabilised by weak interactions with the nucleophile and leaving group.[27] However, the TSs for X = Ar and Kr obviously do not contain strongly electron donating substituents but they do show large normal KIEs even though they are not particularly loose as compared to the other systems.

The C_α–H bonds are shorter in the TS than in the RC (Table 1), and also stiffer as evidenced by their stretching force constants (Table 6), but there is no simple relationship between α-D KIE and the changes from RC to TS in either the C_α–H bond length or the C_α–H stretching force constant. There is no obvious relationship between the KIE and any of the looseness or tightness parameters listed in Table 1 that would extend over the full range of nucleophiles and leaving groups X. However, there is a fair linear relationship (r = 0.91) between KIE and the change in C–X stretching force constant from RC to TS, but not from the isolated reactants to TS; this demonstrates the importance of the nucleophilic interaction in the RC.

The methyl group in the S_N2 TS

As the nucleophile and leaving group X for the identity methyl transfer is changed, so the symmetrical TS changes from tight to loose. One may imagine an "exploded" S_N2 TS in which the central methyl group might behave essentially like a methyl cation. Several properties may be considered. The CH bond length is consistently shorter in each TS than in CH_3^+, and the stretching force constant is usually larger. The methyl-group charge in the TS is smallest (+0.28) for X = CN and CCH, and largest (+0.76) for X = Ar, but these are not the tightest and loosest TSs, respectively, according to the measures listed in Table 2.

Another property of interest is the isotope effect for fragmentation of the S_N2 TS into 2X + CH_3^+ (Table 5). As the CH_3 moiety becomes more like a methyl cation, so the KIE is expected to approach unity in value, but the calculated values are greater than 2 for all the reactions considered. The strongly inverse MMI contribution is compensated by a large normal ZPE factor. The contribution from CH stretching is small and inverse; the overall effect is due mostly to the ZPE(rest) factor. In all the TSs the presence of the X groups influences the properties of the methyl moiety so that it does not resemble an isolated methyl cation.

S_N2 TS *vs.* solvated CH_3^+

The series of noble-gas nucleophiles and leaving groups, X = Kr, Ar, Ne, and He, displays an interesting variation in potential energy surface topography that spans the changeover from a double well to a single well (Fig. 2). There is a very low energy barrier (9 kJ mol^{-1}) for S_N2 methyl transfer with X = Kr and an even lower barrier (6 kJ mol^{-1}) for X = Ar. In both cases the methyl group in RC is significantly non-planar; the CX_{lg} bond is long (2.133 Å for X = Kr, 2.021 Å for X = Ar), but τ^{RC} is large owing to the influence of X_{nuc}. The TSs are not loose according to $L^‡$, $\Delta d^‡_{CX}$, or τ^{TS}. However the methyl-group charge in the TSs is large (+0.68 for X = Kr, +0.76 for X = Ar), and the α-D_3 KIEs are normal and large for S_N2 reactions (1.103 for X = Kr, 1.168 for X = Ar). One might interpret such values as indicating "S_N1 character" to the S_N2 TS.

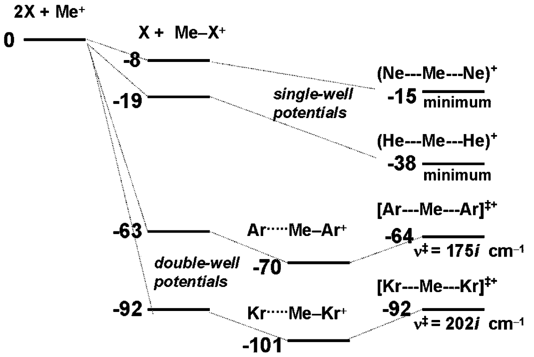

Fig. 2 S_N2 methyl transfer between noble-gas atoms: MP2/6-311+G* calculated relative energies (kJ mol^{-1}).

So what happens with the smaller noble-gas atoms, Ne and He? Now there is no barrier to approach of X towards CH_3X^+ and the only energy minimum along the reaction coordinate for methyl transfer is the symmetrical species which may be denoted as "RC". The methyl group has essentially a full positive charge (+0.96 for X = Ne, +0.98 for X = He); this central cation may be considered to be "solvated" by the two noble gas atoms. The well depth with respect to X + CH_3X^+ is −7 kJ mol^{-1} for X = Ne, and −19 kJ mol^{-1} for X = He. Fragmentation to 2X + CH_3^+ is now a true equilibrium, and the EIE for this dissociation does indeed approach a value of unity (1.23 for X = Ne, 1.09 for X = He) as the methyl group becomes more like a methyl cation.

Conclusions

The behaviour noted by Wolfe and co-workers[4,5] from MP2/6-31+G* studies of identity and non-identity methyl transfers with anionic nucleophiles and neutral electrophiles does not apply to a broader range of identity reactions including neutral nucleophiles and cationic electrophiles. We do not find that a looser TS is associated with a higher energy barrier and a more inverse 2° α-D KIE. Moreover, when the interaction of the nucleophile with the electrophile in the RC is considered, we do not find any simple relationships between "looseness" or "tightness" and either energy barriers or KIEs. The variation in energy barriers may be understood by means of a simple model involving the distance travelled by the methyl group within the encounter complex from RC to PC and the force constant for stretching the bond to the leaving group in RC. There is a fair linear correlation between the 2° α-D KIE and the change in this same stretching force constant, from RC to TS. The methyl group in the S_N2 TS does not resemble an isolated methyl cation, even for systems showing "S_N1-like" properties, owing to the significant influence of the nucleophile and leaving group. Consideration of the unusual range of nucleophiles X = Kr, Ar, Ne and He in identity reactions with CH_3X^+ shows a mechanistic changeover from a double-well potential with a true S_N2 TS to a single-well potential with a symmetric intermediate corresponding to a solvated methyl cation.

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