# Theoretical Investigation of the Origin of Secondary α-Deuterium Kinetic Isotope Effects

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Although the secondary α-deuterium kinetic isotope effect upon the degenerate S_N2 reaction of chloromethane with chloride anion arises from changes in α-CH stretching force constants, α-substitution by methyl and/or methoxy groups shows this inverse inductive contribution to be approximately constant and reveals that the trend in the isotope effect (calculated by semiempirical molecular orbital theory) is determined by changes in bending force constants, in accord with the conventional view.

Recent theoretical studies[1,2] of S_N2 methyl transfer reactions have questioned the conventional view[3] of the origin of secondary α-deuterium kinetic isotope effects (2° α-D KIEs) as arising from changes in bending-force constants HCX {(where X is the nucleofuge and/or nucleophile) in a degenerate process [eqn. (1)]} between reactant and transition state.

$$X^- + MeX \rightarrow XMe + X^- \qquad (1)$$
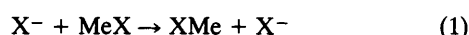
Instead, it has been pointed out that the inverse α-D KIEs for eqn. (1) (X = Cl, F, OF, NC, OMe, CN and CCH) calculated by means of *ab initio* molecular orbital theory arise from an increase in the α-CH bond stretching force constant accompanying the change from tetrahedral to trigonal geometry about C_α along the reaction coordinate. We now report preliminary results of semiempirical molecular orbital theory calculations of 2° α-D KIEs for degenerate S_N2 reactions involving α-substitution by methyl and/or methoxy groups [eqn. (2), R', R'' = H, Me, OMe]: these confirm the recent

$$Cl^- + CHR'R''Cl \rightarrow ClCHR'R'' + Cl^- \qquad (2)$$

findings for methyl transfer (R' = R'' = H) but suggest that the overall trend in the α-D KIEs may be understood within the framework of the conventional view.

The trend in the AM1[4] semiclassical[5] 2° α-D KIEs calculated at 298 K (Table 1; results are for replacement of a single H by D) for the range of degenerate S_N2 reactions [eqn. (2)] is clearly dominated by the zero-point energy factor (ZPE), the

magnitude of which is offset by the product (MMI × EXC) of the mass/moment-of-inertia and excitational factors; there is an excellent linear correlation between $(k_H/k_D)_s$ and ZPE. Further factorization of the overall ZPE term reveals an almost constant inverse contribution from the CH stretching modes but a contribution from all the other modes ('the rest'), which varies proportionally with $(k_H/k_D)_s$. The inverse CH-stretching contribution agrees with the findings of both Wolfe[1] and Truhlar[2] and indeed with our own previously reported *ab initio* calculated α-D KIEs for methyl transfer.[6] The range of values from 0.952 to 0.960 are consistent with this contribution being regarded as inductive: a typical value[5,7] for an inductive β-D KIE is 0.985 from which, if an attenuation factor of about three per C–C bond is applied,[5,8] a value of *ca.* 0.955 may be estimated for an inductive α-D KIE.

The contribution to the α-D KIE from all the rest of the vibrational modes, but especially including α-CH bending modes, tends to be normal. Increasing the number of electron-donating methyl or methoxy substituents attached to C_α causes more carbocation character to develop in the transition state 1 and the $C_\alpha\cdots$Cl partial bonds to increase in length (Table 1). This opening up of the transition-state structure does indeed involve a trend towards loosening of the α-CH bending motions, in turn giving rise to a normal ZPE contribution to the α-D KIE. The value of this factor ('the rest') is just slightly greater than unity with a single α-methyl substituent (R' = H, R'' = Me), but is just slightly less than unity for the unsubstituted system (R' = R'' = H); in these cases the product of the ZPE factors appears to be dominated by the α-CH stretching contribution. Analysis of the molecular vibrational force fields is complicated by the presence of redundancies involving the bending modes about C_α in both the tetrahedral reactant structures and the trigonal bipyramidal transition-state structures, with the consequence that a valence force constant for HCCl angle bending is not

Table 1 AM1 calculated semiclassical 2° α-D KIEs at 298 K for degenerate S_N2 reaction of Cl⁻ with CLR'R''Cl (L = H, D), together with zero-point energy factors and transition-state partial-bond lengths

R'	R''	$(k_H/k_D)_s$	ZPE	ZPE factors CH stretches	The rest	C···Cl/Å
H	H	0.982	0.935	0.959	0.975	2.154
H	Me	1.015	0.977	0.954	1.024	2.202
H	MeO	1.048	1.027	0.954	1.077	2.252
Me	Me	1.090	1.114	0.952	1.170	2.270
Me	MeO	1.156	1.196	0.960	1.246	2.335

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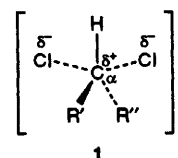
Table 2 AM1 calculated force constants [mdyn Å rad⁻² (1 dyn = 10⁻⁵ N)] for α-CH bending in reactants and transition states

		Method A			Method B		
		F_{HCCl}		ΔF_{HCCl}	F_{umbr}	F_{wag}	$\Delta F_{wag\text{-}umbr}$
R'	R''	Reactant	Transition state		Reactant	Transition state	
H	H	0.551	0.375	−0.176	0.632	0.769	0.137
H	Me	0.583	0.402	−0.181	0.780	0.627	−0.153
H	MeO	0.589	0.424	−0.165	0.860	0.606	−0.254
Me	Me	0.621	0.410	−0.211	0.996	0.626	−0.370
Me	MeO	0.648	0.415	−0.233	1.061	0.493	−0.568

unambiguously defined. However, Table 2 contains two different representations of the AM1 calculated force constants, each of which suggests a trend towards looser α-CH bending with increasing electron-donating α-substitution. In method A the redundancies are eliminated as previously reported for distorted tetrahedra[9] and trigonal bipyramids[6,10] and HCCl force constants are obtained from sets of six or nine redundant valence coordinates for bending about C_α in reactants and transition states, respectively. In method B the force constant for the 'umbrella' symmetry coordinate for bending about C_α in the reactants is compared with the force constant for wagging of the α-CH bond out of the plane of the trigonal C_α moiety of the transition states. Linear regression of the changes ΔF in these force constants from reactant to transition state against the ZPE factor (Table 1, 'the rest') gives correlation coefficients of 0.952 and 0.961 for methods A and B, respectively.

In a recent experimental study[11] of deuterium isotope effects in gas-phase reactions of alkyl halides, inverse values of k_H/k_D were interpreted as characterizing the S_N2 mechanism and all significantly normal values were taken to indicate reactions proceeding mainly by the E2 mechanism. Our present results suggest, however, that it is quite reasonable for S_N2 reactions of α-substituted alkyl chlorides to manifest significantly normal α-D KIEs, in accord with conventional views. Reactions of N-(methoxymethyl)-N,N-dimethylanilinium[12] or 1-(methoxymethyl)-2,4-dinitrobenzene[13] in solution show 2° α-D KIEs (per D) in the ranges 0.99–1.18 and 1.05–1.16, respectively, depending upon the choice of nucleophile, for bimolecular substitutions proceeding by means of very loose transition states.

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