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Carbon and secondary deuterium kinetic isotope effects on S_N2 methyl transfer reactions

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ABSTRACT: Carbon and secondary deuterium kinetic isotope effect (KIE) for three types of S_N2 methyl transfer reactions have been predicted theoretically at a DFT level in gas phase and in aqueous solution modelled by the PCM continuum solvent model. No correlation between these isotope effects and geometrical features of the corresponding transition states (TSs), force constants of the imaginary frequency or Gibbs free energies of the studied reactions has been found. These findings suggest that comparative analysis of the magnitudes of the studied KIEs should be constrained to interpretation of the TS localization on the reaction coordinate only in a series of very closely related reactions. Copyright © 2007 John Wiley & Sons, Ltd.

KEYWORDS: isotope effects; deuterium; nucleophilic substitution; DFT

INTRODUCTION

Kinetic isotope effects (KIEs) of atoms at different positions within a molecule can provide details of the transition state (TS) structure.[1] Secondary α-deuterium KIEs in particular should provide a very insightful and convenient tool for studies of reaction mechanisms because they are large and relatively easy to measure.[2] A majority of the studies were devoted to the influence of either a substituent, or the solvent on the magnitude of these KIEs. Present interpretation of these KIEs correlates their magnitude with bond distances[3] or looseness/tightness of the corresponding TS.[4] Despite the extensive studies, there is no generally accepted way of relating magnitudes of secondary α-deuterium KIEs to the TS structure.[5] Furthermore, our recent studies[6] identified problems with interpretation of KIEs on a model S_N2 reaction. Therefore, the present studies were aimed at determining if any generalization can be made about the correlation between a TS property and the secondary α-deuterium KIE, not within a series of closely related reactants that differ in a substituent or within a series of solvents, but for different classes of S_N2 reactions.

Methyl transfer reactions play the key role in many biological processes[7] and their mechanisms are still the subject of much experimental and theoretical study.[8] Enzymatic methylation of hydroxyl and carboxyl moieties is catalyzed by *O*-methyltransferases;[9] catechol *O*-methyltransferase (COMT) is a ubiquitous enzyme that catalyzes the transfer of the activated methyl group of *S*-adenosyl-L-methionine to an oxygen atom of catechol through a tight S_N2-like TS.[10,11] S-methylmethionine (SMM), also called vitamin U, synthesized by Met *S*-methyltransferase is a dimethyl sulphide precursor.[12,13]

Because of the importance of methyl transfer reactions and evident voids in understanding of its biological role we have decided to carry out our studies on chemical models of these reactions. In particular, we have based our calculations on the reactions that can serve as models for the methyl transfer to SMM by considering the different oxidation states of sulphur.

COMPUTATIONAL DETAILS

All calculations were carried out using the modified Perdew–Wang single parameter method modified for kinetics (MPW1K)[14] which is a hybrid of Hartree–Fock and DFT methods. The basis set employed was the 6-31+*G*(*d*,*p*) basis set[15,16] where the 6-31*G* [16–24] basis set was supplemented by single set of diffuse functions,[25] a set of *d* functions on heavy atoms, and a set of *p* functions on hydrogen atoms.[26]

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Molecular geometries were fully optimized in the gas phase and in aqueous solution, which was modelled using the polarizable conductor continuum model[27–29] (C-PCM). Partial atomic charges were obtained using the CHelpG scheme.[30] Bond orders were calculated using the formalism introduced by Wiberg.[31] Vibrational analysis has been carried out to confirm identity of the stationary points ($3n-6$ real vibrations in case of reactants and one imaginary frequency corresponding to the desired reaction coordinate in case of TS structures).

All quantum-mechanical calculations were done using Gaussian03.[32] Calculations of KIEs were performed using our ISOEFF98 program.[33] KIEs were obtained from the complete Bigeleisen equation[1] at 300 K for the transition from proximity complexes of both reactants to the corresponding TS. Deuterium isotope effects were calculated assuming full deuteration of a single group. Carbon isotope effects were calculated for the ^{13}C isotope.

RESULTS AND DISCUSSION

Selected model reactions (1–3) comprise all possible combinations of the charge flow from reactants to product. The net charge on the reactants is +1, 0 and −1, for reactions 1, 2 and 3, respectively. Both directions were studied. The reactions that are exothermic in the gas phase are arbitrarily called forward reactions and labelled with ‘f’.

$$Me_3S^+ + NMe_3 \rightarrow Me_2S + MeN^+Me_3 \tag{1-f}$$

$$Me_2S + MeN^+Me_3 \rightarrow Me_3S^+ + NMe_3 \tag{1-r}$$

$$Me_3S^+ + Cl^- \rightarrow Me_2S + MeCl \tag{2-f}$$

$$Me_2S + MeCl \rightarrow Me_3S^+ + Cl^- \tag{2-r}$$

$$MeS^- + MeCl \rightarrow Me_2S + Cl^- \tag{3-f}$$

$$Me_2S + Cl^- \rightarrow MeS^- + MeCl \tag{3-r}$$

Optimized geometries of all stationary points for reactions 1–3 were obtained at the MPW1K/6-31+$G(d,p)$ level of theory in the gas phase and in aqueous solution were modelled using the PCM continuum solvent model with the electrostatic part represented by the COSMO formalism.[34] The main geometric parameters are collected in Table 1. They include bond lengths to the central carbon atom $r(C_\alpha—X)$ from the nucleophile (X=Nu) and the leaving group (X=LG), bond lengths of the carbon—hydrogen bonds (C—H), the valence angles describing linearity of the nucleophilic attack ∠(Nu—C_α—LG), and the location of hydrogen atoms attached to the α-carbon atom in the TS ∠(LG—C_α—H). It should be noted that two rows of Table 1 fully describe a reaction in the typical chemical sense; the role of reactants (substrates) and products reverses from the first row to the

Table 1. Main properties of the studied reactions, their substrates and transition states

	Substrate			TS							Reaction				
	δCH_3[a] [a.u.]	$r(C_\alpha–X)$ [Å]	$r(C–H)$[a] [Å]	δLG [a.u.]	$\delta C_\alpha H_3$ [a.u.]	$r(LG–C_\alpha)$ [Å]	$n(LG–C_\alpha)$	$r(C_\alpha–H)$[a] [Å]	∠Nu–C_α–LG [°]	∠LG–C_α–H[a] [°]	$\nu^{\neq}$ [$i$cm^{-1}]	$\Delta G^{\neq}$ [kcal/mol]	ΔG_r [kcal/mol]	D_3-KIE[a]	^{13}C-KIE
1f-g	0.598	1.791	1.086	0.366	0.218	2.224	0.593	1.075	179.7	87.2	526.9	18.8	−17.6	0.806	1.064
1r-g	0.471	1.487	1.084	0.416		2.092	0.321			92.8		36.4	17.6	1.059	1.086
1f-s	0.635	1.788	1.087	0.342	0.268	2.22	0.591	1.077	179.8	87.4	599.2	13.8	−22.0	0.779	1.062
1r-s	0.442	1.485	1.085	0.390		2.084	0.318			92.6		35.8	22.0	1.027	1.082
2f-g	0.718	1.791	1.086	0.382	0.374	2.073	0.666	1.076	176.6	100.0	409.1	−80.9	−129.0	0.978	1.064
2r-g	0.374	1.772	1.083	−0.756		2.487	0.317			80.0		47.7	129.0	1.108	1.069
2f-s	0.826	1.788	1.087	−0.716	0.463	2.370	0.449	1.074	179.5	89.5	563.8	24.5	6.3	0.851	1.065
2r-s	0.463	1.782	1.083	0.253		2.272	0.472			90.5		18.2	−6.3	0.982	1.070
3f-g	0.436	1.797	1.087	−0.652	0.436	2.147	0.581	1.071	178.3	83.5	431.9	3.8	−20.1	1.051	1.067
3r-g	0.517	1.777	1.083	−0.784		2.574	0.380			96.5		23.8	20.1	0.867	1.069
3f-s	0.492	1.799	1.087	−0.669	0.492	2.145	0.581	1.072	178.3	83.9	580.5	10.7	−38.3	1.027	1.064
3r-s	0.663	1.782	1.083	−0.823		2.565	0.357			96.1		48.9	38.3	0.853	1.067

[a] Values given are averaged over all indistinguishable positions.

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Table 2. Analysis of vibrational contributions to KIEs

Reaction	KIE	$\nu_L^{\neq}/\nu_H^{\neq}$	$\nu < 515\,\mathrm{cm}^{-1}$	$515 < \nu < 1900\,\mathrm{cm}^{-1}$	$\nu > 1900\,\mathrm{cm}^{-1}$	All real ν	KIE
1f-s	D_3	1.0002	0.9883	0.9166	0.9953	0.7793	0.779
2r-g	D_3	1.0038	0.9678	1.4045	0.8122	1.1040	1.108
1f-s	^{13}C	1.0343	0.9908	1.0424	0.9952	1.0278	1.062
1r-g	^{13}C	1.0348	0.9967	1.0571	0.9956	1.0490	1.085

second of a particular reactant as the nucleophile becomes the leaving group and vice versa, while the TS is the same for both directions.

The $\angle$(LG—C$_\alpha$—H) angle allows one to classify a TS as an early TS ($\angle$(LG—C$_\alpha$—H) larger than 90°), symmetrical TS ($\angle$(LG—C$_\alpha$—H) equal to 90°) and late TS ($\angle$(LG—C$_\alpha$—H) smaller than 90°). Wiberg bond orders are listed for the breaking and forming C$_\alpha$—X bonds. Again, they can be used for the classification of the TS. With the exception of reaction 2 in water, the same information regarding the TS location on the reaction coordinate is embedded in both the $\angle$(LG—C$_\alpha$—H) angles and the C$_\alpha$—X bond orders, that is, the TSs are early ($\angle$(LG—C$_\alpha$—H) is smaller than 90° and the C$_\alpha$—LG bond orders larger than 0.5). Reaction 2 in aqueous solution is the closest to thermo-neutrality and therefore the TS structure is the most symmetrical one with the $\angle$(LG—C$_\alpha$—H) closest to 90° and the C$_\alpha$—LG bond order closest to Nu—C$_\alpha$ bond order. It should be noted that this reaction in the gas phase is so exothermic that the TS is calculated to be more stable than the substrates. Furthermore, in all TSs the sum of C$_\alpha$—LG and Nu—C$_\alpha$ bond orders is less than unity.

Table 1 lists also the energetic results; the Gibbs free energies of activation and the reaction Gibbs free energies together with the secondary α-deuterium and α-carbon KIEs for all the reactions studied. All secondary deuterium KIEs in the exothermic direction are inverse, that is, smaller than unity, indicating that the heavy isotopomer reacts faster. For closely related reactions that differ in solvent or a substituent, these isotope effects usually correlate with geometric and energetic changes upon going from reactants to the TS. However, it is not known if such a correlation exists also for a series of reactions as different as considered. It is frequently assumed that inverse secondary deuterium KIEs originate in bending vibrations since hydrogen atoms attached to the central carbon atom are forced into the plane perpendicular to the reaction coordinate although there has been evidence to the contrary, what implicates that KIEs often do not provide clear guidance regarding TS structure.[35] Until recently,[6b] it has been thought that primary carbon isotope effects are due mainly to the changes in stretching vibrations on the transition from the reactants to the TS. In order to verify these assumptions we have dissected contributions from different vibrational modes to the isotope effects for the reactions. For this purpose, we grouped the vibrations following Truhlar's division into low, middle and high frequencies.[36] In all reactions studied contributions from these three groups were qualitatively the same. In Table 2 the results for largest and smallest deuterium and carbon KIEs are collected.

The results collected in Table 2 indicate that the KIEs of the studied reactions are dominated by vibrational frequencies of the middle region. They correspond to bond stretching modes that involve heavy-atom movements and bending modes of C—H bonds. In case of carbon KIEs inverse contributions originating in bending vibrations (frequencies in the low group) and in stretching vibrations that involve hydrogen atoms (frequencies in the high group) are comparable and indicate that stiffening of stretching modes is equally important as forcing hydrogen atoms into the plane perpendicular to the reaction coordinate. Deuterium KIEs are dominated by changes in C—H bending modes.

In the literature, the magnitudes of KIEs in a series of related reactions are usually correlated with such geometric parameters as bond lengths of breaking and/or forming bonds, their elongation in the TSs compared to reactants, the corresponding bond orders or energetic parameters. All these quantities are thought to correspond to the position of the TS on the reaction coordinate. We aimed our studies at finding out if such correlation holds for different S$_N$2 reactions. Figure 1 shows the relations between the calculated deuterium and carbon (shown side by side) KIEs and a number of such quantities. First three rows show relationships between KIEs and energetic parameters; the Gibbs free energy of activation, $\Delta G^{\neq}$ (A), the Gibbs free energy of reaction, ΔG_r (B) and their ratio $\Delta G^{\neq}/\Delta G_r$ (C). Subsequently, corresponding relationships between KIEs and the partial atomic charge on the leaving group, δLG (D) (note that leaving group in the forward direction is the nucleophile in the reverse direction) and force constant of the imaginary frequency, F (E) are given. Finally, the relationship between KIEs and bond orders, n(LG—C$_\alpha$) (F), and the LG—C$_\alpha$—H angles $\angle$LG—C$_\alpha$—H (G) are listed. Since the C$_\alpha$—H bond lengths, r(C$_\alpha$—H), the bond lengths of the breaking/forming bonds, r(LG—C$_\alpha$), their elongation, % δr(LG—C$_\alpha$) and bond orders, n(LG—C$_\alpha$), are closely related quantities and corresponding dependencies were identical only the results for the latter are shown. Normally one does not look for the relationship between

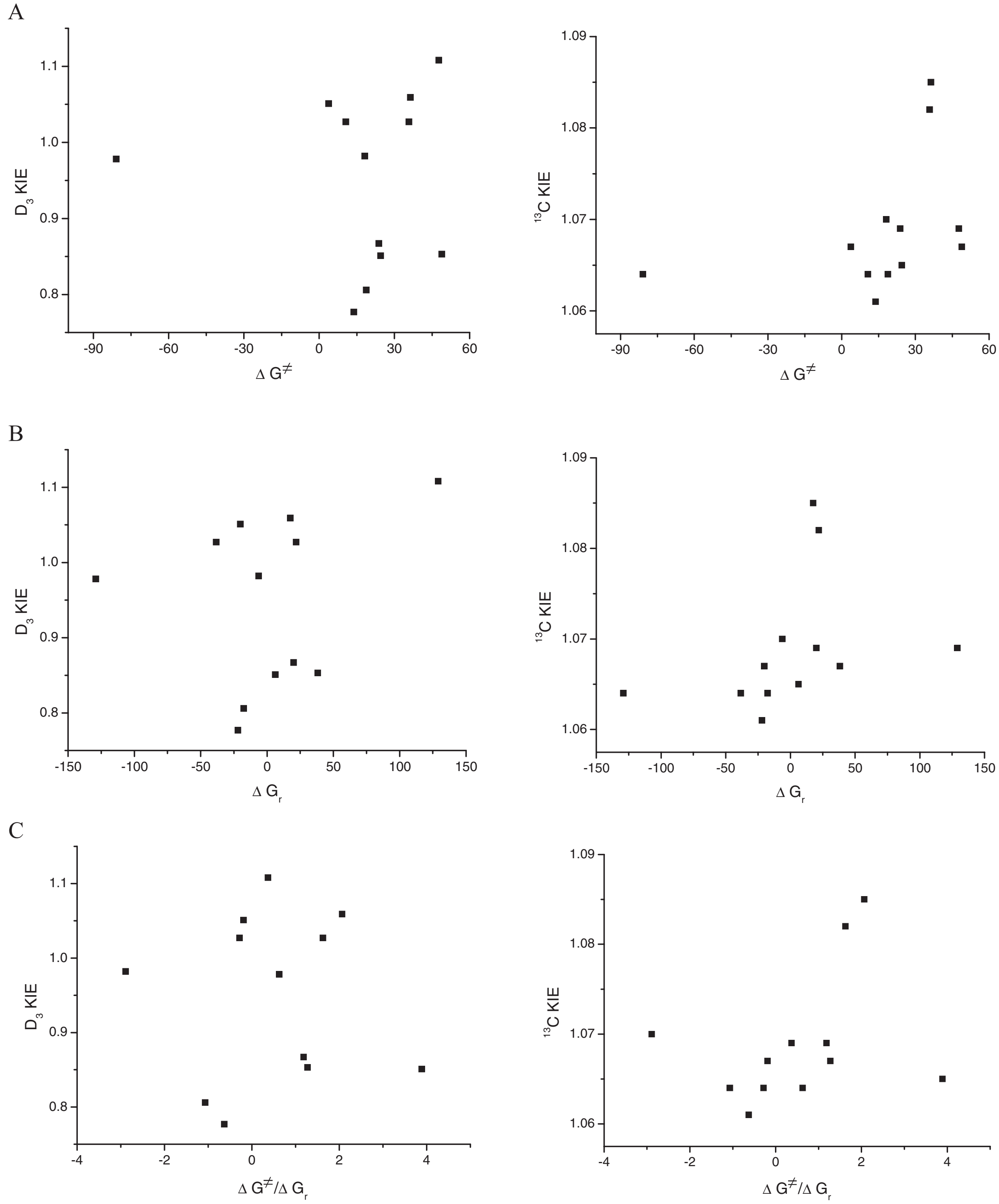

Figure 1. Relations between calculated KIEs and geometrical and energetic parameters (see text for discussion)

the magnitude of a KIEs and the angle that is form by α-hydrogen, central carbon and the first atom of the leaving group or the nucleophile. This angle should, however, be indicative of the position of the TS on the reaction coordinate, reaching 90° in an idealized, totally symmetric case (e.g. an identity reaction). Therefore, we have included the relationship of the KIEs on this angle.

As can be seen, none of the relationships indicate any systematic dependence across the reactions. Additionally, Fig. 2 illustrates that there is no apparent correlation between isotope effects of deuterium and carbon.

In each graph containing data on the carbon KIEs, there are two outliners. These two points correspond to reactions 1r in both gas phase (1r-g) and in aqueous solution (1r-s). Large values of these isotope effects result

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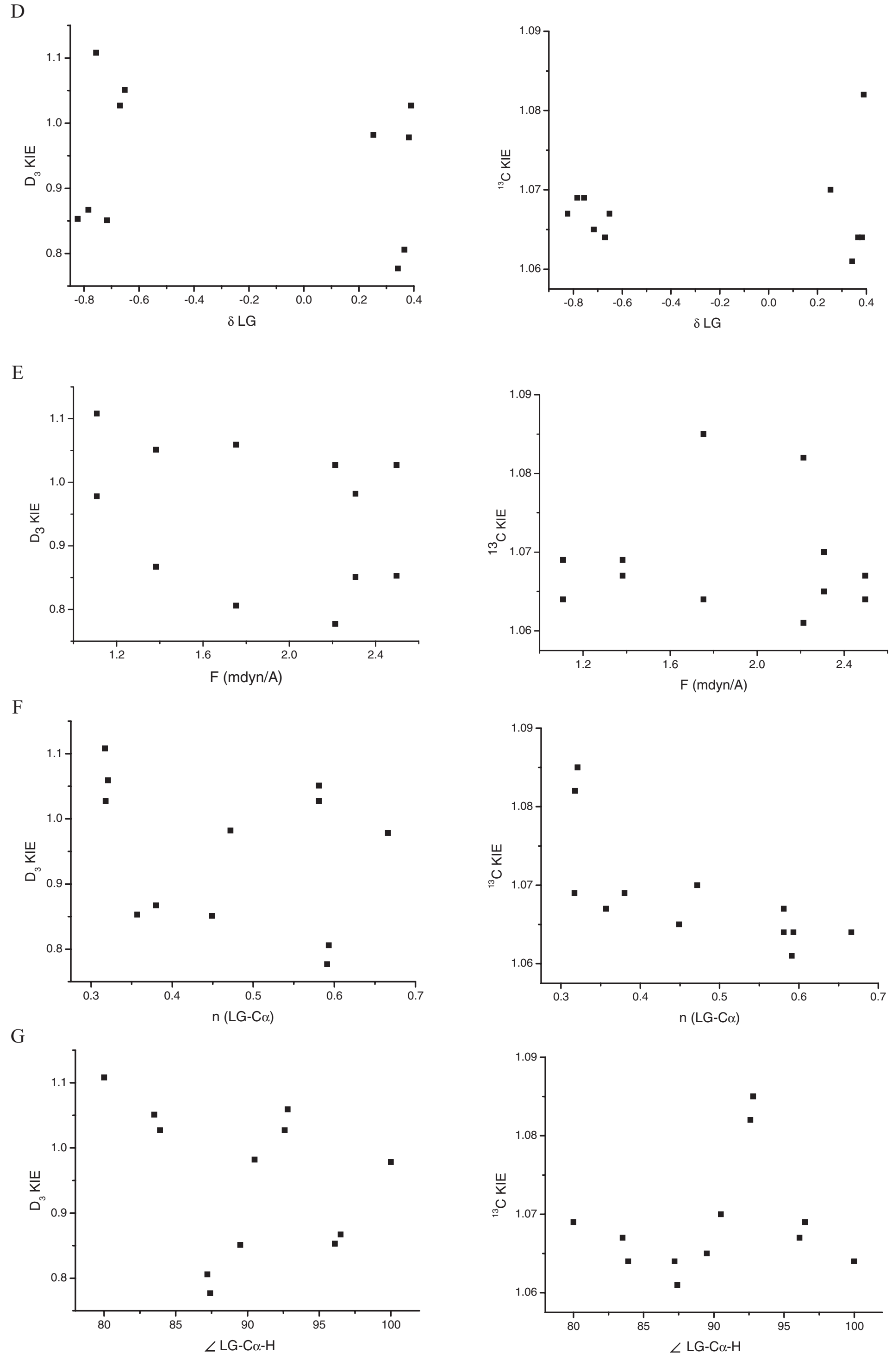

Figure 1. *Continued*

from the very short C—C bond length in the reactant. In both cases, this bond length is slightly shorter than 1.49 Å while in all other reactants this bond length is about 1.79 Å. The variation of this isotope effect is, however, not large, and, as we have shown earlier,[6b] cannot be solely indicative of the type of the reaction and details of its mechanism.

CONCLUSIONS

The lack of any correlation between deuterium and carbon KIEs calculated for a series of S_N2 reactions that differ in nature suggests that these isotope effects cannot be taken as an indication of TS structure. Thus, their application seems to be constrained to interpretation of

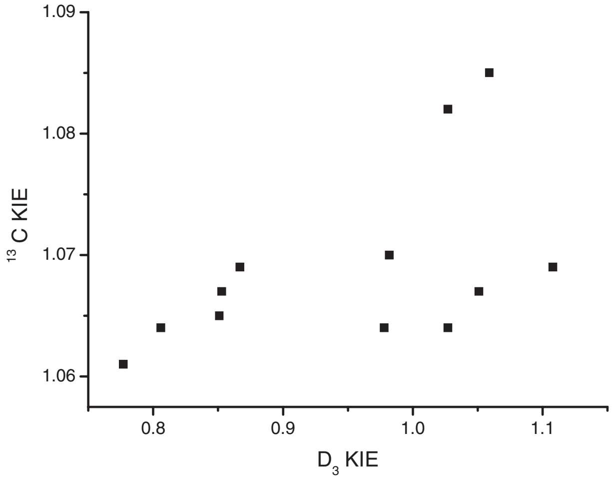

Figure 2. Relationship between D_3-KIE and ^{13}C-KIE for studied reactions

the TS localization on the reaction coordinate in series of closely related reactions.

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