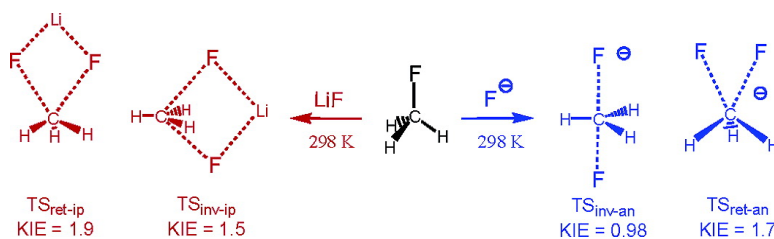


A Computational Study of the Effect of Bending on Secondary Kinetic Isotope Effects in S₂ Transition States

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A Computational Study of the Effect of Bending on Secondary Kinetic Isotope Effects in S_N2 Transition States

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Abstract: Using conventional transition state theory, the secondary deuterium kinetic isotope effect (KIE) in the inversion S_N2 reaction of CH₃F and F⁻ is calculated to be small, 0.98 (T = 298 K). This is shown to be the result of a balance among opposing entropy and enthalpy terms. By contrast, KIE in the retention S_N2 mechanism is calculated to be large (1.5). Accordingly, KIE is a potential observable for discriminating between the two mechanisms. Large KIE's are also found for the inversion and retention mechanisms of the ion pair reactions between CH₃F and LiF. All of the transition structures leading to large KIE's have a bent FCF angle and an imaginary frequency that is sensitive to deuterium labeling.

Introduction

The nucleophilic substitution reaction of methyl halides by anionic nucleophiles¹ has been found to have generally a small secondary kinetic isotope effect (KIE) that is comparable in the gas^{2,3} and condensed phases.⁴ This result has been the subject of numerous theoretical studies, all of which satisfactorily reproduce the observed KIE,^{5,6} and provide different levels of analysis of its origin. Some of the more recent of these studies have addressed the possible correlation between calculated KIE and transition state looseness,⁷ but the conclusions remain controversial.⁸ Although theory is most valuable for mechanistic purposes when it identifies observables that can rule out certain reaction pathways, most isotope effect studies of S_N2 reactions have considered only the transition state of the inversion mechanism (TS_{inv}). This is justifiable on the grounds that the other conceivable substitution pathway for a retention transition state (TS_{ret}, Scheme 1) should be high in energy for ionic systems. Nonetheless, it is still fundamental to know if TS_{ret} would or would not have the same KIE as TS_{inv}. In addition,

such knowledge becomes important for reactions involving ion-pairs, transition metal nucleophiles and enzymes, where changes in the mechanism might not be unlikely. Indeed, the only case of which we are aware in which alternative S_N2-related TSs were considered is a communication by Cook and Haynes of the CH₃/CD₃I oxidative addition to square planar d⁸-[M(CO)₂L₂]⁻ (M = Rh and Ir) for which concerted (related to TS_{ret}) and stepwise (inversion) mechanisms can be envisaged.⁹

We have long been interested in using experimental and theoretical methods to address reactivity issues in ion-pair reactions in comparison with their ionic counterparts.^{10–12} As part of these efforts, we had calculated the unsolvated identity substitution reaction of MeX by MX (M = Li and Na, X = F and Cl, Scheme 1).¹² The results revealed two modifications compared to anionic reactions. First, the geometry of the ion-pair TS_{inv-ip} has bent CX angles in contrast to the linear arrangement characteristic of TS_{inv-an}. The second modification pertained to the energy differences between TS_{inv} and TS_{ret} which are smaller in the ion-pair reactions (–15 to +10 kcal/mol) compared to the anionic ones (ca. 45 kcal/mol).¹³

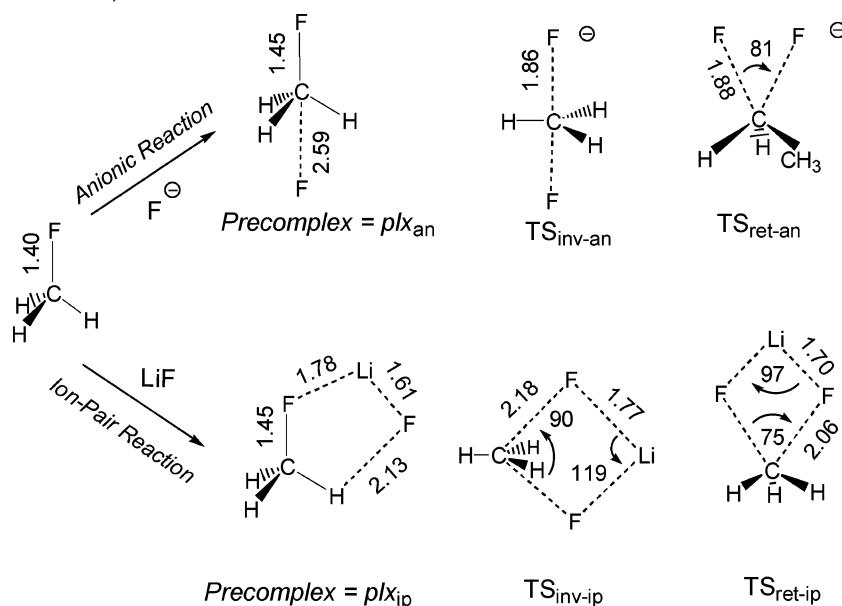
The TSs in Scheme 1 form a simple model set to study the extent to which several structural variations influence the KIE in S_N2 reactions. To this end we have calculated the d₃-KIE for the transformation from CH₃F to each of these TSs. Except in the case of the extensively studied TS_{inv-an} where KIE is essentially nil, all of the other TSs are calculated to have normal and substantial KIEs (1.5–1.9). One entity that stands out in discriminating between the two sets of KIEs is the reaction

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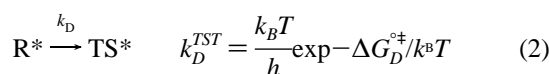
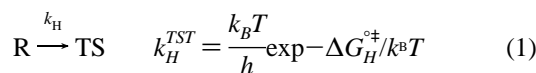
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Scheme 1. Geometry of the Precomplex, Inversion, and Retention Transition Structures in the Anionic and Ion-Pair S_N2 Reactions^a

^a The parameters shown are from the B3LYP/6-311++G** minimizations used in the present study (units in degrees and Å).

coordinate normal mode of vibration (ν^\ddagger). In TS_{inv-an} , ν^\ddagger is the pure asym FCF stretching mode (ν_{FCF}) and is insensitive to deuterium labeling. In all of the other TSSs, ν^\ddagger is a mixture of the asym FCF stretch and an asymmetric CH_3 bend (ν_{CH_3}). In the latter TSSs, ν^\ddagger is lowered upon d_3 -labeling. Such behavior is similar in nature to a primary KIE. Analysis of the results suggests that tilting of the entering and leaving groups is the structural feature that renders ν^\ddagger sensitive to deuterium labeling.

Background and Computational Methods. Within the quasi-thermodynamic formulation of conventional transition state theory (TST), which assumes a unity transmission coefficient in the calculated rate constants,¹⁴ a KIE may be expressed as the quasi-equilibrium constant in eq 3, where R and TS are the proteo reactants and TSs of interest, and R^* and TS^* are the deuterated analogues.¹⁵ In such formulations, ΔG_H^\ddagger and ΔG_D^\ddagger in eq 1 and 2 are the transition state approximations to the standard-state free energy of activation at a given T ,¹⁶ which can in turn be used to associate the quasi-thermodynamic quantities to KIE ($\Delta\Delta G_T^\ddagger = \Delta\Delta H_T^\ddagger - T\Delta\Delta S_T^\ddagger$ in eq 4). Normal and inverse KIE's at a given T would refer to cases in which K_{q-eq} is greater or smaller than unity, respectively.



The geometry and vibrational frequencies of the species in eq 4 can be computed by standard electronic structure methods.¹⁷ Using statistical mechanics, the calculated masses, moments of inertia, and vibrational frequencies of these species can then be used to evaluate KIE at a given temperature as a partition function ratio (eq 5) having translational (η_{tr}), rotational (η_{rot}), and vibrational (η_{vib}) components.^{15,14} The latter is often separated into two terms, one accounting for the effects of vibrational excitation (EXC) and one (EXP) accounting for the effects of the zero-point energy changes ($\Delta\Delta ZPE^\ddagger$) in eq 4. The molecular partition functions making eq 5 can also be transformed to express KIE in terms of quasi-thermodynamic quantities ($\Delta\Delta H_T^\ddagger$ and $\Delta\Delta S_T^\ddagger$; eq 4) arising from translational, rotational, and vibrational contributions.¹⁸

$$KIE = \frac{k_H^{TST}}{k_D^{TST}} = K_{q-eq} = \left(\frac{Q_{tr}^{R^*} Q_{tr}^{TS}}{Q_{tr}^R Q_{tr}^{TS^*}} \right) \left(\frac{Q_{rot}^{R^*} Q_{rot}^{TS}}{Q_{rot}^R Q_{rot}^{TS^*}} \right) \left(\frac{Q_{vib}^{R^*} Q_{vib}^{TS}}{Q_{vib}^R Q_{vib}^{TS^*}} \right) \exp\left(-\frac{\Delta\Delta ZPE^\ddagger}{RT}\right) \\ KIE = (\eta_{tr})(\eta_{rot})EXC \cdot EXP \quad (5)$$

where: $Q_{tr} = (2\pi M k_B T)^{3/2}/h^3$; $Q_{rot} = 8\pi^2(8\pi^3 I_A I_B I_C)^{1/2}(k_B T)^{1/2}/\sigma h^3$; $Q_{vib} = \prod_i (1 - e^{-(h\nu_i/k_B T)})^{-1}$ (index "i" scans only real vibrations). $\Delta\Delta ZPE^\ddagger = \Delta ZPE_{TS}^{TS^*} - \Delta ZPE_R^{R^*}$; $\Delta ZPE_{TS}^{TS^*} = ZPE_{TS} - ZPE_{TS^*}$; and $\Delta ZPE_R^{R^*} = ZPE_R - ZPE_{R^*}$. M is the molecular mass, h is Planck's constant, k_B is Boltzmann's constant, T is the absolute temperature, I is the moment of inertia, σ is the symmetry number, and ν_i is the vibrational frequency with the index i covering the modes with real frequencies.

In the present study we obtained the geometries of the species in Scheme 1 at the B3LYP/6-311++G** (5d) level of theory¹⁹

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using Gaussian 03.²⁰ Vibrational frequencies were computed using the harmonic approximation and were used without scaling. KIEs were then calculated according to eq 5 at $T = 298$ K, and $P = 1$ atm. The results are discussed using both the partition function ratios (eq 5) and the quasi-thermodynamic quantities (eq 4).

We note that the conventional TST adopted in our study assumes that for a given mechanism the geometry of the proto and deuterio TSs is the same and does not account for tunneling and recrossing effects. A more accurate theoretical treatment of KIEs would require calculation of dynamic trajectories²¹ and is beyond the scope of the present study. Over the past two decades, Truhlar and co-workers have led extensive research efforts to develop theories and computational protocols for accurate calculation of rate constants in which TS geometries are located variationally, and dynamic recrossing, tunneling, and nonequilibrium effects are accounted for in a generalized transmission coefficient term.^{22,23} The applications have addressed primary and secondary KIEs in a range of chemical reactions,²⁴ including the inversion S_N2 anionic mechanism.²⁵ Some results from these investigations were compared with results from conventional TST KIEs. These available comparisons will be used in a later section to evaluate how such effects might impact the conclusions of the present more limited study.

Results and Discussion

Reactions Energies. Gas-phase anionic S_N2 reactions proceed via an initial encounter complex followed by a TS.²⁶ Because the main objective of the present study is to compare how a change in the TS structure influences KIE, it should not matter whether the discussion is based on transformation starting from separate reactants or from the precomplex. For convenience, and to allow comparison with other theoretical studies, we base the discussion on the direct transformation from separate reactants to TS. For completeness we include the equilibrium IE for precomplex formation in the tables. The geometries of

Table 1. Calculated Energy and Entropy Parameters for the Reaction of CH_3F with F^- and LiF (in kcal mol^{-1} and $\text{cal mol}^{-1} \text{K}^{-1}$; $T = 298$ K, $P = 1$ atm)

precomplexes	ΔZPE_{298}°	ΔH_{298}°	ΔS_{298}°	ΔG_{298}°
$\text{CH}_3\text{F} + \text{F}^- \rightarrow \text{complex}_{\text{an}}$	0.08	-14.6	-20.0	-8.7
$\text{CH}_3\text{F} + \text{LiF} \rightarrow \text{complex}_{\text{ip}}$	1.4	-14.8	-27.0	-6.8
ionic TSs	ΔZPE^\ddagger	ΔH_{298}^\ddagger	ΔS_{298}^\ddagger	ΔG_{298}^\ddagger
$\text{CH}_3\text{F} + \text{F}^- \rightarrow \text{TS}_{\text{inv-an}}$	-0.33	-6.1	-27.1	2.0
$\text{CH}_3\text{F} + \text{F}^- \rightarrow \text{TS}_{\text{ret-an}}$	-1.02	38.4	-24.4	45.7
ion-pair TSs	ΔZPE^\ddagger	ΔH_{298}^\ddagger	ΔS_{298}^\ddagger	ΔG_{298}^\ddagger
$\text{CH}_3\text{F} + \text{LiF} \rightarrow \text{TS}_{\text{inv-ip}}$	-0.43	40.8	-34.3	51.0
$\text{CH}_3\text{F} + \text{LiF} \rightarrow \text{TS}_{\text{ret-ip}}$	-0.11	25.7	-31.6	35.1

the precomplexes and TSs are given in Scheme 1, and the reaction and quasi-thermodynamic activation parameters for their formation are collected in Table 1. The data show that in the anionic identity reaction of MeF, $\text{TS}_{\text{inv-an}}$ is much lower than $\text{TS}_{\text{ret-an}}$, while the reverse is true for the ion-pair reaction. This result was discussed in detail in previous studies.^{12,13}

Reaction Coordinate Normal Mode of Vibration (ν^\ddagger).

Figure 1 compares ν^\ddagger in $\text{TS}_{\text{inv-an}}$ and $\text{TS}_{\text{ret-an}}$ and includes also the three CH bending modes pertaining to CH_3 pyramidalization (ν_{out}). In $\text{TS}_{\text{inv-an}}$, ν^\ddagger is the pure asym FCF stretch and has a_2'' symmetry within D_{3h} . The only other vibration in $\text{TS}_{\text{ret-an}}$ with a_2'' symmetry is the symmetric out-of-plane CH_3 bend ($\nu_{\text{out}}^{a_2''}$; Figure 1). However, there is no indication of any mixing in the coordinates of these two modes, and the value of $\nu_{\text{inv-an}}^\ddagger$ does not change upon deuterium labeling. Even with tritium labeling, which brings $\nu_{\text{out}}^{a_2''}$ down to 734 cm^{-1} , $\nu_{\text{inv-an}}^\ddagger$ remains the same as in the protio TS.

In the retention anionic TS, the entering and leaving groups are related by a plane of symmetry and CH_3 is pyramidal. In the resulting C_s geometry, the bending CH_3 modes related to the e'' mode in $\text{TS}_{\text{inv-an}}$ are split into a' and a'' modes. Figure 1 shows that, in addition to the asym FCF motion expected for the S_N2 mechanism, the coordinates of $\nu_{\text{ret-an}}^\ddagger$ also include components from the a'' CH_3 bending mode. Consequently, when $\nu_{\text{out}}^{a''}$ is decreased by d_3 -substitution, $\nu_{\text{ret-an}}^\ddagger$ also decreases from $631i$ to $570i \text{ cm}^{-1}$. Tritium substitution lowers $\nu_{\text{ret-an}}^\ddagger$ further to $536i$.

The switch from $\text{TS}_{\text{inv-an}}$ to $\text{TS}_{\text{ret-an}}$ involves simultaneous change in the methyl moiety as well as in the FCF angle. In $\text{TS}_{\text{inv-ip}}$, on the other hand, the methyl moiety is planar but FCF is bent (Scheme 1). Figure 2 shows that in this case too the coordinates of $\nu_{\text{inv-ip}}^\ddagger$ include components from the asym- CH_3 bend and ν^\ddagger is isotope sensitive. This suggests that tilting of the entering and leaving groups rather than methyl pyramidalization is the structural parameter that makes ν^\ddagger sensitive to deuterium labeling. For $\text{TS}_{\text{inv-ip}}$, perdeuterio labeling lowers $\nu_{\text{inv-ip}}^\ddagger$ from $629i$ to $524i \text{ cm}^{-1}$. Finally, and not surprisingly, Figure 2 shows that $\nu_{\text{ret-ip}}^\ddagger$ has CH_3 components and is isotope sensitive. In summary, it appears that the D_{3h} geometry of $\text{TS}_{\text{inv-an}}$ is unique in having an isotope insensitive ν^\ddagger . As discussed below, whether ν^\ddagger changes upon isotope labeling or not appears to play an important role in determining the KIE.

Calculated KIEs. The KIE for the four TSs considered in this study are given in Table 2. As in previous studies, our calculations using harmonic frequencies at 298 K yield a small KIE for the direct transformation from F^- and MeF and to

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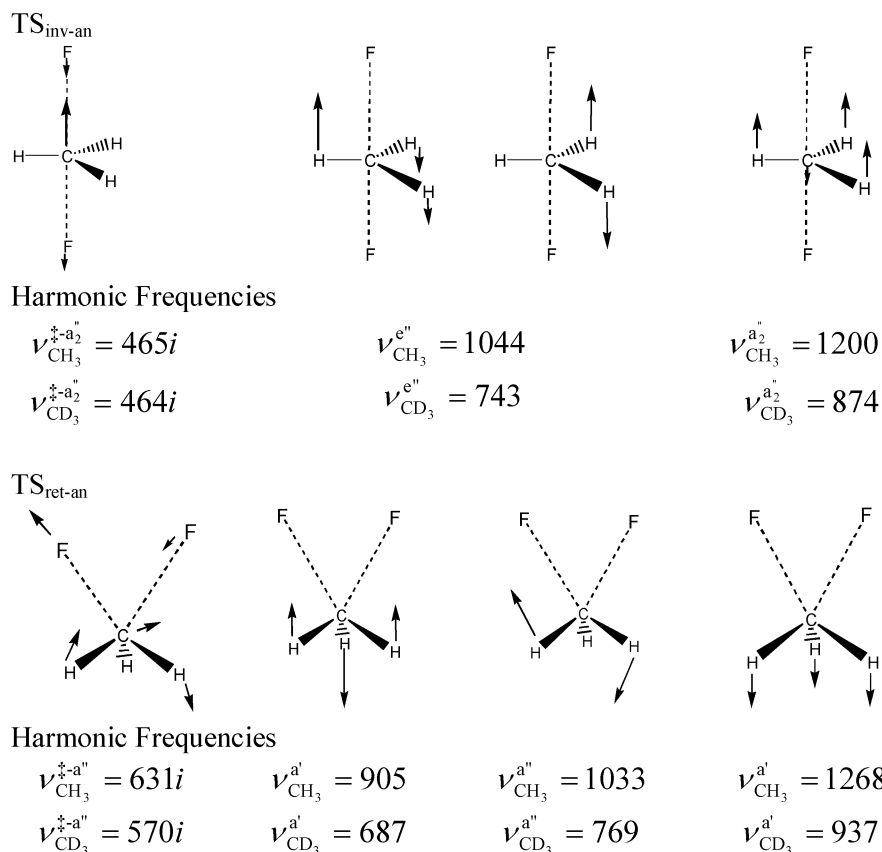


Figure 1. Coordinates of ν^\ddagger and the bending modes related to pyramidalization of CH_3 in $\text{TS}_{\text{inv-an}}$ and $\text{TS}_{\text{ret-an}}$ (in cm^{-1}).

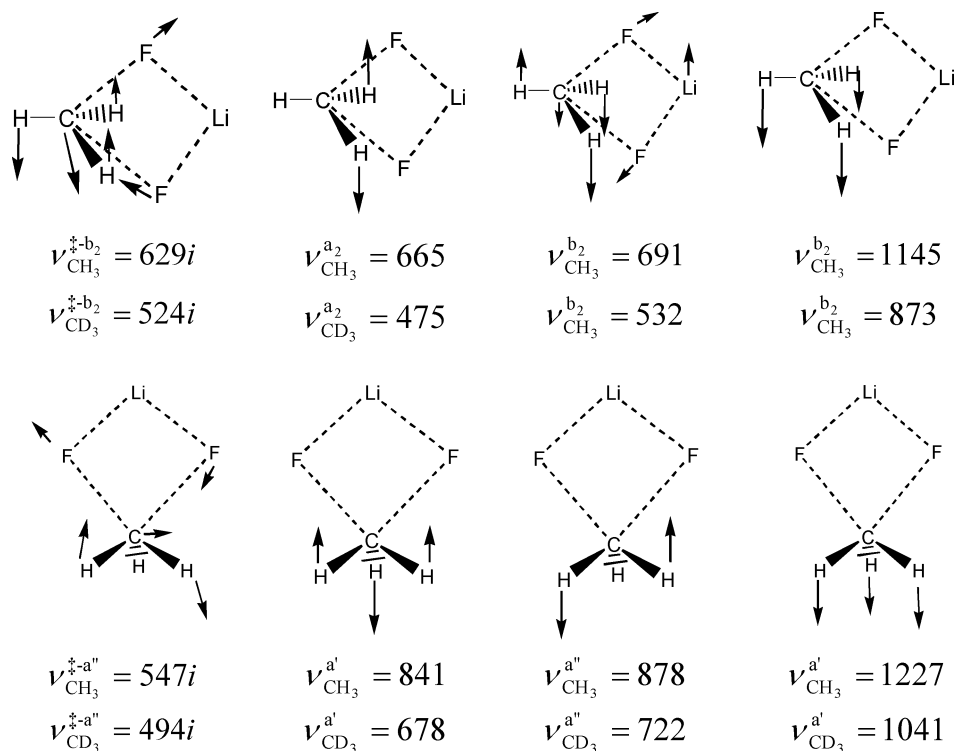


Figure 2. Coordinates of ν^\ddagger and the bending modes related to pyramidalization of CH_3 in $\text{TS}_{\text{inv-ip}}$ and $\text{TS}_{\text{ret-ip}}$ and their harmonic frequencies (in cm^{-1}).

$\text{TS}_{\text{inv-an}}$ (0.98), which is close to the experimental result.³ On the other hand, the KIE in the mechanism leading to $\text{TS}_{\text{ret-an}}$ is large at 1.68. This indicates that KIE is an observable that can discriminate between the two given mechanisms in the anionic reactions. For the reactions of LiF, both mechanisms are

predicted to yield normal KIE's with substantial but comparable magnitudes: 1.86 ($\text{KIE}_{\text{inv-ip}}$) and 1.46 ($\text{KIE}_{\text{ret-ip}}$). Thus, $\text{TS}_{\text{inv-an}}$ appears to be unique in yielding a small KIE. In the remaining part of the study, we attempt to understand the nature of the factors that lead to this result. To this end we utilize the partition

Table 2. Kinetic and Equilibrium Isotope Effects Calculated at 298 K Using the Partition Functions^a

	η_{tr}	η_{rot}	EXC	EXP	isotope effect
anionic TSs (F ⁻)					
$\text{CH}_3\text{F} + \text{TS}_{\text{inv-an}}^{\text{CD}_3} \rightleftharpoons \text{CD}_3\text{F} + \text{TS}_{\text{inv-an}}^{\text{CH}_3}$	1.05	1.23	0.91	0.84	$\text{KIE}_{\text{inv-an}} = 0.98$
$\text{CH}_3\text{F} + \text{TS}_{\text{ret-an}}^{\text{CD}_3} \rightleftharpoons \text{CD}_3\text{F} + \text{TS}_{\text{ret-an}}^{\text{CH}_3}$	1.05	1.47	0.80	1.25	$\text{KIE}_{\text{ret-an}} = 1.68$
ion pair TSs (LiF)					
$\text{CH}_3\text{F} + \text{TS}_{\text{inv-ip}}^{\text{CD}_3} \rightleftharpoons \text{CD}_3\text{F} + \text{TS}_{\text{inv-ip}}^{\text{CH}_3}$	1.06	1.55	0.82	1.21	$\text{KIE}_{\text{inv-ip}} = 1.86$
$68\text{CH}_3\text{F} + \text{TS}_{\text{ret-ip}}^{\text{CD}_3} \rightleftharpoons \text{CD}_3\text{F} + \text{TS}_{\text{ret-ip}}^{\text{CH}_3}$	1.06	1.53	0.73	1.20	$\text{KIE}_{\text{ret-ip}} = 1.49$
precomplex formation					
$\text{CH}_3\text{F} + \text{plx}_{\text{an}}^{\text{CD}_3} \rightleftharpoons \text{CD}_3\text{F} + \text{plx}_{\text{an}}^{\text{CH}_3}$	1.05	1.24	0.81	1.02	$\text{EIE}_{\text{an}} = 1.06$
$\text{CH}_3\text{F} + \text{plx}_{\text{ip}}^{\text{CD}_3} \rightleftharpoons \text{CD}_3\text{F} + \text{plx}_{\text{ip}}^{\text{CH}_3}$	1.06	1.52	0.72	0.79	$\text{EIE}_{\text{ip}} = 0.91$

^a Results calculated at $T = 298$ K and $P = 1$ atm using unscaled harmonic frequencies. ^b The $(\eta_{tr})(\eta_{rot})$ is often referred to as the mass moment of inertia (MMI) term to KIE.

Table 3. Calculated Energy and Entropy Components of the Isotope Effects^a

	individual components ($T = 298$ K)				sum			effect of ν^\ddagger		
	$\Delta\Delta\text{ZPE}^\ddagger$	$\Delta\Delta E_{\text{vib}}^{\text{Exc}}$	$\Delta\Delta S_{tr}^\ddagger$	$\Delta\Delta S_{rot}^\ddagger$	$\Delta\Delta S_{\text{vib}}^\ddagger$	$\Delta\Delta H_{298}^\ddagger$	$\Delta\Delta G_{298}^\ddagger$	$\Delta\Delta S_{298}^\ddagger$	$\Delta\Delta G_{298}^\ddagger$	
anionic TSs										
$\text{KIE}_{\text{inv-an}}$	0.11	-0.089	0.089	0.41	-0.49	0.017	0.014	0.013	0.00	1.00
$\text{KIE}_{\text{ret-an}}$	-0.13	-0.096	0.089	0.77	-0.76	-0.23	0.097	-0.26	-0.09	1.11
ion pair TSs										
$\text{KIE}_{\text{inv-ip}}$	-0.11	-0.16	0.11	0.87	-0.95	-0.28	0.030	-0.28	-0.15	1.19
$\text{KIE}_{\text{ret-ip}}$	-0.11	-0.11	0.11	0.84	-0.99	-0.22	-0.038	-0.21	-0.08	1.11
complexes										
EIE_{an}	-0.011	-0.049	0.089	0.42	-0.59	-0.59	-0.060	-0.081	-0.036	
EIE_{ip}	0.14	-0.072	0.11	0.83	-0.88	-0.88	0.069	0.053	0.054	

^a Results calculated at $T = 298$ K and $P = 1$ atm using unscaled harmonic frequencies. Entropy units in $\text{cal mol}^{-1} \text{K}^{-1}$, and energy units in kcal/mol. $\Delta\Delta E_{\text{vib}}^{\text{Exc}}$ relates to the energy difference due to vibrational excitation at 298 K. The translational and rotational motions do not contribute to $\Delta\Delta H_{\text{rot}}^\ddagger$ of an IE, and thus $\Delta\Delta H_{\text{rot}}^\ddagger = \Delta\Delta\text{ZPE}^\ddagger + \Delta\Delta E_{\text{vib}}^{\text{Exc}}$. $E_{\nu^\ddagger}^\ddagger = \text{ZPE}_{\nu^\ddagger}^{\text{CD}_3} - \text{ZPE}_{\nu^\ddagger}^{\text{CH}_3}$, and each $\text{ZPE}_{\nu^\ddagger}$ is $1/2(h|\nu^\ddagger|)$.

function ratios (Table 2) as well as the thermodynamic parameters (Table 3).

In all the TSs considered, η_{tr} and η_{rot} each makes a normal contribution to KIE. Variations in η_{tr} depend on the variations in the mass of the TS and are thus minor ($\eta_{tr} = 1.05$ and 1.06 in the ionic and ion-pair TSs, respectively). η_{rot} depends on the moment of inertia of the TSs, which is in turn determined by the mass as well as the geometry of the TSs. In $\text{TS}_{\text{ret-an}}$, η_{rot} is significantly greater than that in $\text{TS}_{\text{inv-an}}$ (1.47 and 1.23, respectively), and is therefore a discriminating factor between the two anionic mechanisms. In the ion pair reactions, η_{rot} is larger than that in the ionic TSs and is comparable in the two mechanisms ($\eta_{rot} \approx 1.54$, Table 2). In a comprehensive experimental and theoretical study of KIE in gas-phase anion and radical-anion $\text{S}_{\text{N}}2$ reactions, Bierbaum presented a thorough discussion of how η_{tr} and η_{rot} are determined.^{3b} We add here that the translational and rotational motions do not contribute to the enthalpy of KIE ($\Delta\Delta H_{298}^\ddagger$ of eq 4), and η_{tr} and η_{rot} correspond therefore to entropy terms having values of $\Delta\Delta S_{tr}^\ddagger \approx 0.1$ and $\Delta\Delta S_{rot}^\ddagger \approx 0.4\text{--}0.9 \text{ cal K}^{-1} \text{ mol}^{-1}$ (at 298 K, Table 3).

Table 2 shows that EXC is inverse in all the TSs considered. In the anion reactions, for example, EXC is 0.91 in $\text{TS}_{\text{inv-an}}$ and 0.80 in $\text{TS}_{\text{ret-an}}$. This term sums the entropy and energy effects resulting from variation in the degree of vibrational excitations in the species in eq 4 at a given temperature ($\Delta\Delta S_{\text{vib}}^\ddagger$ and $\Delta\Delta E_{\text{vib}}^{\text{Exc}}$, Table 3). In the reactant CH_3F and CD_3F molecules, all the vibrations are of too high energy to have any significant excited populations at 298 K. For example, the lowest

energy mode in CH_3F and CD_3F is calculated at 1030 and 981 cm^{-1} , respectively. Thus the contribution of the reactant molecules in eq 4 to EXC is minor (when all the vibrations are included, $Q_{\text{vib}}^{\text{R}^*}/Q_{\text{vib}}^{\text{R}}$ in eq 5 is 1.05). The addition of F⁻ or LiF to CH_3F or CD_3F to form a TS introduces additional low energy ISVs. $\text{TS}_{\text{inv-an}}$ for example has an e⁻-mode for FCF bending that has values of 314 and 292 cm^{-1} for the proteo and deuterio TSs, respectively. Such modes will have significant excited populations at room temperature, and more so in TS_{CD_3} . Because the latter is on the left-hand side of eq 4, it would yield a negative $\Delta\Delta S_{\text{vib}}^\ddagger$ and a negative $\Delta\Delta E_{\text{vib}}^{\text{Exc}}$ (Table 3). For the given TSs, the entropy effect dominates at room temperature and EXC is thus inverse.

Unlike the above parameters that contribute in the same direction in all of the TSs, at 298 K the EXP term is inverse in $\text{TS}_{\text{inv-an}}$ (0.84) but normal and comparable in all the other cases (≈ 1.2 ; Table 2). This follows from a positive $\Delta\Delta\text{ZPE}^\ddagger$ in $\text{TS}_{\text{ret-an}}$ (+0.11 kcal/mol) against a negative $\Delta\Delta\text{ZPE}^\ddagger$ in the other cases (ca. -0.12 kcal/mol, Table 3). The sum of $\Delta\Delta\text{ZPE}^\ddagger$ and $\Delta\Delta E_{\text{vib}}^{\text{Exc}}$ is equal to $\Delta\Delta H_{298}^\ddagger$ of eq 4.²⁷ Since these two terms have different signs in $\text{TS}_{\text{inv-an}}$, the final $\Delta\Delta H_{298}^\ddagger$ for this mechanism is negligible (0.018 kcal/mol). For $\text{TS}_{\text{inv-an}}$ $\Delta\Delta S_{298}^\ddagger$ is positive and small (0.015 $\text{cal K}^{-1} \text{ mol}^{-1}$), and the final $\Delta\Delta G_{298}^\ddagger$ comes close to zero. In the other mechanisms, both $\Delta\Delta E_{\text{vib}}^{\text{Exc}}$ and $\Delta\Delta\text{ZPE}^\ddagger$ are negative, and $\Delta\Delta H_{298}^\ddagger$ (-0.22 to

(27) Because the classical translational and rotational energies for each species in eq 3 is $3/2RT$, they cancel out and do not contribute to the enthalpy of a KIE.

-0.27 kcal/mol) dominates $\Delta\Delta G_{298}^{\ddagger\circ}$ (-0.21 to -0.28) which yield normal and substantial KIEs.

Clearly, $\Delta\Delta ZPE^{\ddagger}$ is the principal parameter that separates the calculated KIE in TS_{inv-an} from the other TSs. Since the given variations in $\Delta\Delta ZPE^{\ddagger}$ are rather small (± 0.1 kcal/mol), and in the absence of a one-to-one correspondence among the isotope sensitive vibrations in the reactants and the TSs, we do not attempt to evaluate the weights of the individual normal modes in yielding the variations in $\Delta\Delta ZPE^{\ddagger}$. Such attempts have been made in previous studies of TS_{inv-an} by grouping them into low, medium and high energy ranges.^{3b,5,7} We instead discuss qualitatively the potential role of the isotope sensitivity of ν^{\ddagger} in determining $\Delta\Delta ZPE^{\ddagger}$. ν^{\ddagger} may be thought of as a vibration that has been removed from the TS. The energy associated with this mode ($ZPE_{\nu^{\ddagger}}$) would have the effect of lowering the ZPE of the TS, and consequently the activation enthalpy. If $ZPE_{\nu^{\ddagger}}$ is simplistically quantified as $1/2(h|\nu^{\ddagger}|)$, where the imaginary component of ν^{\ddagger} has been dropped out, the effect of the isotope sensitivity of ν^{\ddagger} on KIE (eq 5) can be estimated using $\Delta ZPE_{\nu^{\ddagger}}$ defined as $ZPE_{\nu^{\ddagger}}^{CD_3} - ZPE_{\nu^{\ddagger}}^{CH_3}$. In TS_{inv-an} , ν^{\ddagger} is the same in the proteo and deuterio TSs, so $\Delta ZPE_{\nu^{\ddagger}}$ is zero. In the other TSs, $\Delta ZPE_{\nu^{\ddagger}}$ is negative because in these cases ZPE would be lowered more in the proteo species with the larger ν^{\ddagger} . The magnitude of $\Delta ZPE_{\nu^{\ddagger}}$ obtained this way (-0.08 to -0.15 kcal/mol) is comparable to the total $\Delta\Delta ZPE^{\ddagger}$ (-0.10 to -0.13 kcal/mol, Table 3). We stress the point that eq 5 does not cover ν^{\ddagger} in the calculation of $\Delta\Delta ZPE^{\ddagger}$, and we attempt only to infer the effect of this absent vibration. An alternative expression of KIE that demonstrates explicitly the importance of the isotope sensitivity of ν^{\ddagger} in determining KIE is the Biegeleisen equation,²⁸ eq 6, which includes ν^{\ddagger} in a ratio term (values included in Table 3). Evidently, the isotope sensitivity of ν^{\ddagger} is an important contributor to the normal KIE.

$$KIE = \left(\frac{\nu_H^{\ddagger}}{\nu_D^{\ddagger}} \right) \left(\frac{f_R^{\ddagger}}{f_{TS}^{\ddagger}} \right) \quad (6)$$

where

$$f_H^D = \prod \frac{u_i^D}{u_i^H} \frac{1 - \exp(-u_i^H)}{1 - \exp(-u_i^D)} \exp(u_i^H - u_i^D)/2, \quad u_i = (h\nu_i/k_B T)$$

with index “ i ” covering the real vibrations.

Possible Impact of Variational and Tunneling Effects. In conventional TST, a TS is located at the saddle point on a hypersurface orthogonal to the reaction coordinate. The force constants calculated at this point are then used to obtain the harmonic frequencies in the calculation of the reaction rate constants of both the proteo and deuterio species (k_H^{TST} and k_D^{TST} eqs 1 and 2). In variational transition state theory without tunneling (VTST), different dividing surfaces at different positions along the reaction path are considered.²² In canonical VTST the TS is located at a point on the dividing surface following free energy optimization and is sensitive to isotope labeling. Because such optimization can in principle give

different bond distances and force constants for the proteo and deuterio TSs, KIEs calculated by VTST can become different from those obtained by conventional TST. Truhlar and co-workers have used VTST to study a large number of KIEs and have also accounted for multidimensional tunneling corrections in the calculated KIEs. Several comparisons between VTST and conventional TST KIEs included in these studies of the Truhlar group can provide a basis to estimate the potential impact of VTST and tunneling on the conclusions of our study.

Few examples are known in which VTST and tunneling effects were found to decrease the KIEs calculated by conventional TST.^{29–32} Moreover, these examples are cases of primary KIEs and appear to be most pronounced in systems in which the proteo and deuterio TSs exhibit substantially different geometries at the site involving the H/D bond making and breaking.³¹ For secondary KIEs it is more common to find only minor differences between TST and VTST results, with the latter usually larger.^{31,33–35} In the anionic inversion S_N2 reaction in particular, VTST and tunneling effects on KIE have been shown to be essentially absent.²⁵ Thus, for the new TSs considered in the present study, variational and tunneling effects are unlikely to decrease the large secondary KIEs predicted for their reactions by TST. Any possible increase in the KIEs due to VTST or tunneling on the other hand should enforce the major finding of our study, namely that changing the geometry of the S_N2 reaction from one in which the entering and leaving groups are collinear to one in which they are bent should lead to a substantial increase in KIE.

Concluding Remarks

Kinetic isotope effects are among the few experimental parameters that can be used to infer transition state structures. The secondary KIE of S_N2 reactions of methyl halides and anionic groups has been studied extensively by experimental and theoretical means in the past and is established to be small. The present study adds a new contribution to understanding the origin of the observed small KIE, namely that it is the product of a delicate balance among several small entropy and enthalpy terms. The present study also explores how changing the geometry of the S_N2 TS from one in which the entering and leaving groups are collinear to one in which they are bent influences the KIE. Such modification in the TS structure is conceivable in reactions involving ion pairs, transition metals, and enzymes. The results strongly suggest that such changes would yield large KIEs in a normal range (1.5–1.9). Analysis of the new TSs reveals an interesting condition in which the imaginary frequency appears to play a role in determining the secondary KIE. Although some of the TSs we consider are of high energy and might not be chemically relevant in the simple models computed, the systematic comparison among different TSs and the determination of their entropy and enthalpy

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components provide new insights to understanding KIEs in S_N2 reactions in general.

Supporting Information Available: Cartesian coordinates, thermodynamic parameters, partition functions and vector coordinates of the vibrational modes of MeF and the four transition states, and their deuterated analogues (11 pages, PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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