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Distinguishing the S_N2 and the S_N2' Mechanisms in the Gas Phase

Gustavo E. Davico[†]

Departamento de Química Orgánica, Facultad de Ciencias Químicas, Universidad Nacional de Córdoba, Agencia Postal 4, C.C. 61, 5000 Córdoba, Argentina

davico@jilau1.colorado.edu

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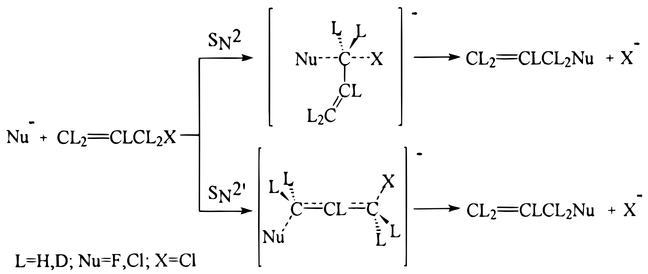
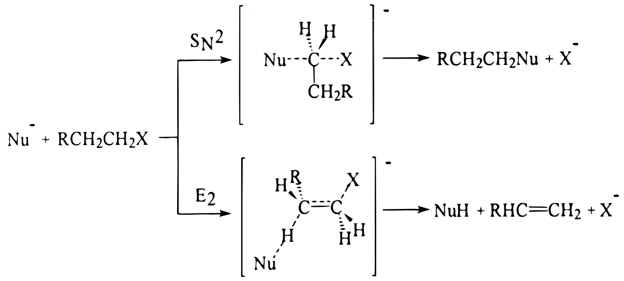
ABSTRACT



The secondary deuterium kinetic isotope effects (KIE) for both mechanisms were calculated by using ab initio results and transition state theory. The S_N2' mechanism shows very inverse ($k_H/k_D < 1$) KIEs, smaller than those for the S_N2 pathway. The difference is primarily originated in the vibrational contribution to the KIE, and more specifically the mid-frequency factor. These results suggest that the reaction mechanism can be determined by measuring the KIE.

Determining an ionic reaction mechanism in the gas phase can be very difficult because most of the techniques used to study those reactions detect only the ionic species.[1,2] Consider for example the S_N2 versus the E_2 mechanisms[3] (Scheme 1). Since both reactions produce the same ionic product, the mechanism for a particular reaction cannot be discerned.[4]

Scheme 1



However, both mechanisms can be distinguished by measuring the deuterium kinetic isotope effects (KIE).[5] While the E_2 mechanism exhibits primary, normal ($k_H/k_D > 1$) KIE; the S_N2 mechanism shows secondary, usually inverse ($k_H/k_D < 1$) KIE.[5,6] This remarkable difference in the KIEs has been exploited successfully to distinguish these mechanisms in the gas phase. Theoretical calculations have been very successful in predicting the KIEs in the S_N2 mechanism,[7−9] including reactions involving microsolvated nucleophiles.[10] In all cases, transition state theory was used even when the reactions showed large negative activation barriers, as in the

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[†] Present address: JILA, University of Colorado and National Institute of Standards and Technology, and Department of Chemistry and Biochemistry, University of Colorado, Boulder, CO 80309-0440.

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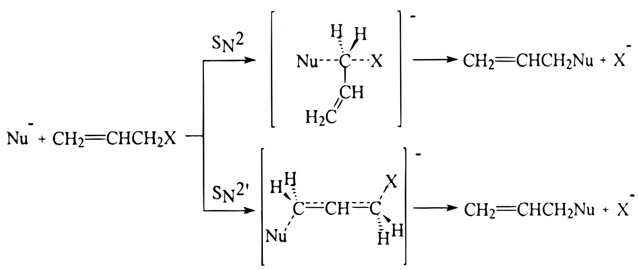
case of the reactions of F^- and HO^- with methyl chloride. The agreement with experiments was excellent.[6,8,10]

A similar situation occurs between the S_N2 and the S_N2' mechanisms (see Scheme 2). As in the previous case, both reaction mechanisms generate the same ion product and thus cannot be discernible by mass spectrometric methods. In this case, they also give rise to the same neutral product. In addition, both reactions exhibit secondary deuterium KIEs and it is not straightforward to establish a priori if the S_N2' mechanism will show a different KIE than that from the S_N2. In contrast to the S_N2 mechanism, very little is known about the S_N2' pathway in the gas phase: if it can compete with the S_N2 mechanism, what kind of values the KIE is expected to show, and what factors determine those values. This paper presents theoretical results on the energetics and KIEs for the reactions of F^- and Cl^- with 3-chloropropene (**1**) for both the S_N2 and S_N2' mechanisms. These results represent the first theoretical data available for nonidentity S_N2' reactions as well as conclusive results that suggest that the KIEs are very different for both mechanisms and therefore can be distinguished in the gas phase.

Scheme 2



The calculations were carried out by using the Gaussian 94 suite of programs.[11] Geometry optimizations and frequency calculations were performed at the MP2/6-31++G** level. These frequencies (not scaled) were used to calculate the zero point vibrational energies (ZPVE) and the KIEs by using conventional transition state theory.[12] The use of variational transition state theory or the inclusion of tunneling effects has been proven to have a minimal effect on the KIEs in these types of reactions.[10,13] MP4(SDTQ)/6-31++G** single point energy calculations were carried out (MP4/6-31++G**//MP2/6-31++G**) on reactants, products, and transition states.

The results of the calculations for both pathways are shown in Table 1. These reactions exhibit the normal double-well potential energy surface, typical for most gas-phase ionic reactions.[14,15] For the reaction of Cl^-, both mechanisms show a transition state (TS) lying above the reactants, with the S_N2 mechanism 4.6 kcal/mol more energetically favored (5.8 kcal/mol including the zero point vibrational energy correction). The activation barrier for the S_N2 pathway is consistent with previous results for similar S_N2 reactions.[8,16−23] Very recently, an activation energy of 8.1 kcal/mol has been reported for the S_N2 reaction of Cl^- with **1** at the MP2/6-31++G**//MP2/6-31++G** level.[24]

Table 1. Heats of Reaction (ΔE_R) and Heats of Activation ($\Delta E^\ddagger$) with Respect to Reactants for the S_N2 and S_N2' Mechanisms (MP4(SDTQ)/6-31++G**//MP2/6-31++G**), in kcal/mol[a]

	$\Delta E^\ddagger$		
nucleophile	S_N2	S_N2'	ΔE_R
Cl^-	4.8 (3.7)	9.4 (9.5)	0
F^-	−12.1 (−12.4)	−7.8 (−7.6)	−28.3 (−27.4)

[a] Values in parentheses are corrected for vibrational zero point energies.

In contrast to the Cl^- reaction, both mechanisms show negative activation barriers in the reaction of F^- with **1**. This means that the energies of the TSs are located below those of the reactants and that, in principle, both mechanisms could be observed experimentally at thermal energies. However, as in the case of Cl^-, the S_N2 is favored over the S_N2' mechanism by about 4−5 kcal/mol. The S_N2 process is not always the preferred mechanism; for instance, in the reaction of F^- with 3-fluoropropene, calculations show evidence that the S_N2' mechanism is favored.[24] Gronert also calculated that the two mechanisms can compete in the reaction of F^- with halocyclohexenes.[25] It has also been suggested, based on experimental evidence, that the reaction of Cl^- with 3-bromopropene in the gas phase may proceed by the S_N2' mechanism.[26] The reaction energy (ΔE_R) was also calculated for the reaction of F^- with **1**. A value of −28.3 kcal/mol was obtained (−27.4 kcal/mol including ZPVE correction), which could not be compared to the experimental value due

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to the unknown heat of formation of 3-fluoropropene. However, this value is consistent with the −31.8 kcal/mol value estimated by using the heat of formation of the halopropanes, the halogen atoms, and F^- and Cl^-;[27,28] it also agrees with a lower level calculation.[29]

The TSs for both S_N2 reactions show a 2-fold degenerate structure of C_s and C_1 symmetry for Cl^- and F^-, respectively. Only the TS with the anti configuration was calculated for the S_N2' mechanism since it had been established that this structure is preferred in the gas phase with respect to the syn.[24,30] The TS has the expected structure of C_2 symmetry for Cl^-, and C_1 symmetry for F^-, as nucleophiles.

The KIEs for both mechanisms, S_N2 and S_N2', for the reactions of F^- and Cl^- with **1** are shown in Table 2. The total KIEs (η_{total}) are very different for both mechanisms. On one hand, the S_N2 mechanism shows normal KIEs. In general, S_N2 reactions of methyl halides show inverse KIEs,[5,6,8,9] but in some instances, as in the case of the reaction of HS^- with methyl chloride, both the calculated and the experimental KIEs show normal values.[8] On the other hand, the KIEs are inverse for the S_N2' mechanism. To further understand the origin of these KIEs values, I partitioned the contributions from the translational, rotational, and vibrational components of the partition functions.[7,8,16] In addition, the vibrational factor was divided into the low (η_{low}), middle (η_{mid}), and high (η_{high}) frequency modes[10,16] (Table 2). No frequency was allowed to switch groups upon deuteration, and all the groups have the same number of frequencies in reactants and TSs. The only exception was η_{low}, which in the TSs incorporates the new frequencies that originate from translational degrees of freedom in the reactants (except the imaginary one).

Table 2. Factor Analysis of the KIEs for the S_N2 and S_N2' Mechanisms

nucleophile/	mechanism	η_{vib}						
		$\eta_{low}{}^a$	$\eta_{mid}{}^b$	$\eta_{high}{}^c$	$\eta_{vib}{}^d$	η_{rot}	η_{trans}	η_{total}
Cl^-	S_N2	1.19	1.04	0.78	0.96	1.16	1.03	1.15
	S_N2'	1.20	0.70	0.89	0.75	1.11	1.03	0.86
F^-	S_N2	1.18	0.92	0.80	0.87	1.14	1.02	1.01
	S_N2'	1.16	0.68	0.99	0.78	1.09	1.02	0.87

[a] Contribution from modes with $\nu_i < 600$ cm^{-1} in perprotio case. [b] Contribution from modes with 600 cm$^{-1} \le \nu_i \le 2000$ cm^{-1}. [c] Contribution from modes with $\nu_i > 2000$ cm^{-1}. [d] Total vibrational contribution, $\eta_{low} \times \eta_{mid} \times \eta_{high}$.

The translational contributions to the KIEs are constant and normal for both nucleophiles and reaction mechanisms. This is a consequence of the reactions being bimolecular. For the same reason, the rotational contributions should also be larger than 1, as can be seen in Table 2, but display some variability between the different reactions, depending on the changes of the moment of inertia upon deuteration in the TSs.[8] Thus, for each mechanism, the higher mass nucleophile (Cl^-) shows a larger contribution than the lower mass one (F^-). However, when comparing both mechanisms for the same reactants (and therefore same masses), the S_N2 pathway shows larger values, which agrees with the fact that in this mechanism the isotopic substitution occurs at positions further away from the moment of inertia axis. Therefore, the translational and rotational factors have a significant normal contribution to the KIEs and thus the total KIEs cannot be viewed only as a relative change in the zero point energies (ZPE). In other words, even when the ZPE difference between the hydrogen- and deuterium-substituted compounds is larger in the TS than in reactants, the total KIE could be normal due to the rotation and translation contributions. This is the case in both S_N2 reactions included in Table 2.

As in previous reports on the S_N2 mechanism, the vibrational contribution shows the largest dispersion of values for different reactions.[7,8,31−33] As shown in Table 2, this also seems to be the case for the S_N2' mechanism. This vibrational factor results from isotopically sensitive vibrational modes that change in frequency when proceeding from the reactants to the TS. The further factorization of the vibrational contributions allows for a better understanding of which frequencies are the most important. It is clear from the values reported in Table 2 that while the low frequencies group displays no dependence, with normal contributions, the high and middle frequencies groups (and particularly the latter) show large changes ranging from normal to very inverse values.

The high frequencies factor is inverse for each of the reactions studied in this report, in agreement with results obtained for other S_N2 reactions.[7,8,13,16,31−33] This factor involves contributions from C−H stretch modes. In the S_N2 mechanism, this inverse effect has been rationalized in terms of the C−H bonds from the α-carbon atom that change from sp^3 to sp^2 hybridization when proceeding from the reactants to the TS.[8,16,31−33] The concomitant increase of the associated C−H stretching frequencies results in the inverse contribution from this factor. In contrast, in the S_N2' mechanism, this hybridization effect occurring at the α-carbon atom is partially compensated with the reverse process that is taking place at the γ-carbon atom. Thus, this factor should be larger for this mechanism than for the S_N2, in agreement with the values shown in Table 2.

The mid-frequencies factor involves a variety of modes and is the group that includes the largest number of frequencies. This factor has been shown to depend greatly on the out-of-plane bending modes of the α-hydrogen atoms,[8,33] and thus on the "crowdedness" of the S_N2 TS.[8] Therefore, the S_N2 reactions are expected to show a smaller

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value for the most crowded TS; i.e., for the reaction of F^- as a nucleophile, in agreement with the values shown in Table 2. In the S_N2' mechanism, both α- and γ-hydrogen atoms are involved, doubling the number of hydrogen atoms and frequencies sensitive to the KIE. This effect produces the more inverse values observed in Table 2 for this factor when compared to those of the S_N2 mechanism. In the case of the S_N2' mechanism, the TS "crowdedness" is not determined by the compression of the α-hydrogen atoms produced by the nucleophile and the leaving group as in the S_N2 mechanism, but rather by the leaving group in the α-carbon atom (and the nucleophile in the γ-carbon atom) and the force to keep these hydrogen atoms in plane induced by the breaking (and forming) carbon−carbon double bond. This explanation also agrees with the lack of change in this factor by changing the nucleophile from Cl^- to F^- in this mechanism (Table 2), in contrast to the S_N2 pathway.

In summary, for the reactions of F^- and Cl^- with **1** the S_N2' mechanism shows very inverse KIEs. The values obtained indicate that for this mechanism the KIEs are smaller than those for the S_N2 pathway. The difference basically originates in the vibrational contribution to the isotope effect, and more specifically the mid-frequency factor, which is partially compensated by the high-frequency one. These results suggest that for a particular reaction where both mechanisms (S_N2 and S_N2') are possible, the reaction mechanism can be easily determined by measuring the KIE. In those adverse cases where the differences between the activation barriers between the two mechanisms are smaller than 1−2 kcal/mol, both mechanisms can compete and the measured KIE will be intermediate to the calculated values. In these cases, it would only be possible to determine the dominant reaction mechanism.

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