Direct Measurements of Deuterium Kinetic Isotope Effects in Anionic, Gas-Phase Substitution and Elimination Reactions

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Kinetic isotope effects (KIE's) have proven to be powerful tools for investigating the nature of transition states, particularly, in complex reaction processes that involve two or more concerted bonding changes.[1] A good example is the E2 elimination, where proton transfer, double-bond formation, and leaving group expulsion occur with varying degrees of synchronicity.[2] Numerous studies have explored this issue in solution, but gas-phase studies have been greatly limited because typical approaches are unable to distinguish between S_N2 and E2 products. Here we employ our ionic platform approach to directly measure kinetic isotope effects in gas-phase E2 reactions. The results span a remarkable range and highlight factors unique to measuring isotope effects in ion/molecule reactions.

Because the ionic products often are the same for both processes (i.e., leaving group), direct measures of KIE's by mass spectrometry generally have been limited to systems that give exclusively S_N2 reactions (e.g., methyl) or E2 reactions (e.g., *tert*-butyl). Data for E2 reactions in *tert*-butyl systems indicate KIE's (k_H/k_D) on the order of 2−3.[3,4] Data are also available for the eliminations of some ethers, and those values generally vary from about 2−7 at room temperature.[5-8]

In 1999, we proposed an ionic platform approach to address systems with this problem.[9,10] In short, a dianion with an inert and a reactive ionic site is used as the nucleophile. The partially neutralized dianion product retains a charge and identifies the reaction process (Scheme 1). In this case, alkylation versus protonation distinguishes between the S_N2 and E2 reaction. Because the approach also can distinguish between proton and deuteron transfer, it is ideally suited for probing isotope effects.

One drawback of gas-phase studies is that technical issues limit measurements to a narrow kinetic window, and only reactions with efficiencies that range from about 0.0001 to 1.0 (observed rate divided by collision rate) can be characterized. The systems in Scheme 2 exhibit favorable kinetic parameters.

Experiments were completed on the systems in Scheme 2 using a modified Finnigan LCQ quadrupole ion trap that has been described in the past.[11] Although it is possible to measure absolute kinetics, relative rate measurements offer smaller experimental uncertainties. Mixtures of the substrate and its perdeutero analogue were prepared, introduced into the helium buffer gas of the ion trap, and allowed to react with the mass-selected dianion nucleophiles. In addition to the leaving group, the reactions typically led to four other ionic products, the S_N2 and E2 products from the labeled and unlabeled substrates (Figure 1). An analysis based on the branching ratios and mixing ratios provides the data in Table 1.[12] Computational estimates are also included.[13] They are based on differences in zero-point energies and partition functions at 298 K.[14] The calculations predict k_H/k_D values near unity for S_N2 reactions[15] and around 7 for E2 reactions. The values are in accord

Scheme 1. Ionic Platform Approach
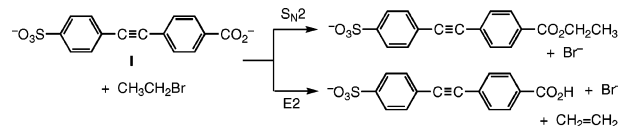
Scheme 2. Reaction Systems
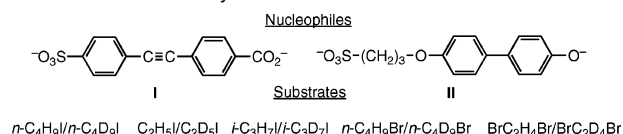
Table 1. Efficiencies and Kinetic Isotope Effects[a]

reaction	S_N2		E2	
	eff.[b]	k_H/k_D[c]	eff.[b]	k_H/k_D[c]
EtI + **II**	0.060(−30.6)	0.97(0.98)	N/A(−14.8)	N/A
i-PrI + **II**	0.015(−31.7)	1.02(1.07)	0.081(−15.1)	6.8(6.1)
n-BuI + **II**	0.146(−30.6)	0.78(0.98)	0.082(−17.5)	7.2(6.7)
n-BuBr + **II**[d]	0.002(−22.9)	0.98(0.95)	0.001(−9.9)	22(7.1)
BrEtBr + **II**[e]	N/A(−23.0)	N/A	0.72(−5.4)	1.3(6.0)
i-PrI + **I**	0.02(−17.6)	1.07(1.05)	0.008(−5.1)	8.7(7.0)

[a] N/A indicates insignificant reaction channel. BrEtBr refers to 1,2-dibromoethane. [b] Partial reaction efficiency (observed S_N2 or E2 rate divided by collision rate) for unlabeled substrate. Reaction with chlorotrimethylsilane used as estimate of collision rate. Expected uncertainties ±20%. Estimated reaction enthalpy for singly charged analogue (phenolate or benzoate) given parenthetically (kcal/mol). Dianion reactions will be more exothermic by ~20 kcal/mol. [c] Partial rate ratio for all H versus all D substrate. Estimated uncertainties are ±10% for S_N2 and ±20% for E2 reactions. Calculated isotope effect given parenthetically for singly charged analogue (benzoate or phenolate). In calculations, *n*-Pr used to model *n*-Bu. [d] The computed barriers are −3.7 (−3.8 d7) kcal/mol for the S_N2 reaction and −0.5 (+0.6 d7) kcal/mol for the E2 reaction. [e] The computed barriers are −8.1 (−8.2 d4) kcal/mol for the S_N2 reaction and −10.7 (−9.7 d4) kcal/mol for the E2 reaction. Barriers for alkyl iodides are not reliable at this level of theory and were not computed.
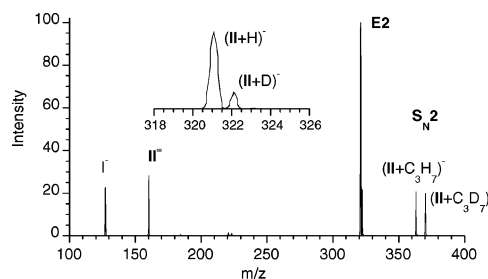
Figure 1. Reaction of **II** with a 1:1 mixture of *i*-C_3H_7I and *i*-C_3D_7I. Inset shows E2 products. Low signal for I^- is an artifact of instrument settings.

with previous computational estimates.[14,16,17] It needs to be stressed that these values are for semi-classical, barrier-controlled reactions and do not take into account any reaction dynamics effects.[18] The k_H/k_D values for the E2 reactions contain a significant contribution

from secondary deuterium isotope effects. For example, the primary deuterium isotope effect calculated for **II** + *n*-PrI is 5.48 and the net secondary isotope effect is 1.24.

Generally, the experimental KIE's match expectations, but there are striking exceptions. The E2 reaction of **II** with *n*-butyl bromide gives a k_H/k_D value well outside the semi-classical limit, whereas its reaction with 1,2-dibromoethane has a very small E2 isotope effect. As expected, the secondary deuterium isotope effects in the S_N2 reactions are modest, but an anomalously large inverse isotope effect is observed for the S_N2 reaction of **II** with *n*-butyl iodide. The unusual results are a consequence of special features of ion/molecule kinetics.

The reaction with 1,2-dibromoethane is highly efficient and approaches the collision-controlled limit. Calculations also indicate a low barrier for the HBr and DBr eliminations (both ~10 kcal/mol below the entrance channel). It is well-known that, under these circumstances, k_H and k_D approach the collision-controlled limit and the observed isotope effect is much lower than that predicted for a barrier-controlled process.

The E2 reaction of *n*-butyl bromide leads to the opposite situation. The barrier is calculated to be near the entrance channel energy and the efficiency is about 10^{-3}. The observed isotope effect is very large and well beyond the computed estimate, 7.1. An adventitious impurity (i.e., proton source) is always a concern with a slow reaction, but multiple control experiments were completed.[19] Aside from an experimental artifact, two explanations are likely. Tunneling is possible, but two factors argue against it. First, E2 eliminations couple proton transfer to heavy atom motion and reduce the tunneling probability. Second, a crude Wigner prediction indicates tunneling is insufficient to explain the difference at 300 K.[20] The other explanation involves the reaction dynamics. With a significant barrier, the lifetime of the collision complex plays a role in the reaction efficiency because not all of the complexes may have time to explore the reaction surface and funnel energy into the reaction coordinate motion. This is particularly critical when the barrier is above the entrance channel.[21] Deuterium labeling pushes the barrier up by about 1 kcal/mol and exacerbates lifetime issues. As a result, k_D can drop more sharply than expectations based on relative reaction barriers.[22] This effect is not observed in the faster reactions with the alkyl iodides, but there is a slightly elevated KIE in the moderately slow reaction of **I** with *i*-PrI.[23]

The S_N2 reactions uniformly give k_H/k_D values near unity, with the exception of **II** + *n*-BuI, which has a significant inverse isotope effect that is not predicted by the calculations. Substitution and elimination are relatively efficient here, so the S_N2 and E2 channels are competing fairly evenly with dissociation in the collision complex. Deuterium labeling sharply suppresses the E2 channel, increasing the pool of complexes available for partitioning into the S_N2 and back-dissociation channels. The net effect is an enhancement of the S_N2 channel for the deuterated system. Hu and Truhlar previously have pointed out the effects of competition on KIE's.[18] Finally, our data with the ethyl halide provide support for Bierbaum's recent conclusion that the reaction of OCl$^-$ with ethyl chloride has a small overall isotope effect because the S_N2 path dominates.[4]

These results point to several important factors that affect gas-phase kinetic deuterium isotope effects. As expected, the isotope effects are attenuated in highly efficient reactions because k_H and k_D approach the collision-controlled limit. In reactions with very low efficiencies, it appears that the lifetime of the collision complex plays a role, and the higher barriers of the deuterated systems can lead to marked drops in elimination rates. Consequently, only a portion of the range of measurable gas-phase rates provides a useful measure of isotope effects. Finally, in systems where the S_N2 and E2 reactions are both efficient, an isotope effect in the elimination can push the deuterated system toward the S_N2 path. Each of these scenarios represents a way in which the gas-phase kinetics become controlled, to some extent, by a factor other than simply the difference in reaction barriers.

Supporting Information Available: Complete citation for ref 13 as well as tables including the geometries, energies, and details of the computational work. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) All frequency calculations were completed with Gaussian03 at the HF/6-31+G(d) level for bromides and HF/6-311+G(d) level for iodides (Radom's all-electron iodide basis set was used). Energies at MP2 level. Details in Supporting Information. Frisch, M. J.; et al. *Gaussian 03*, revision B04; Gaussian, Inc.: Pittsburgh, PA, 2003.
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(19) Substrates were of the highest commercial quality, and mass spectra indicated >99.7% deuterium incorporation in the perdeutero substrates; this level of isotopic impurity has a trivial effect on k_H/k_D. Substrates were extracted with aqueous base immediately before use. Extractions with H$_2$O and D$_2$O produced similar results. Some samples were co-injected with CH$_3$OD (ESI and substrate) with no significant effect on the HX to DX elimination ratio.
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(22) A truncated Boltzmann distribution would have the same effect.
(23) Intramolecular competitive experiments with CH$_3$CH$_2$CHICD$_2$CD$_3$ also suggest an E2 isotope effect of about 7 with these nucleophiles.

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