Deuterium Isotope Effects

DOI: 10.1002/anie.201007322

On the Origin of Conformational Kinetic Isotope Effects**

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The only means by which the size of a substituent can be altered without changing the potential energy surface for a chemical process of interest is isotopic labeling. Several recent studies have demonstrated the effectiveness of this approach.[1–5] It is widely accepted that deuterated alkyl or aryl substituents are effectively "smaller" than the corresponding perprotiated isotopologs, as a consequence of a shorter C–D bond.[6] This simple and conceptually satisfying model was recently challenged by Dunitz and Ibberson, who showed that the unit cell of solid C_6H_6 is smaller than C_6D_6 above 170 K.[7] The authors explained this observation in terms of thermal excitation of low frequency motions in the deuterated compound and raised the question that such effects might be relevant to the origin of certain conformational kinetic isotope effects (KIEs) where deuterium appears to present a larger effective size than protium.

To investigate this possibility, we initiated a computational study of the KIE in Mislow's doubly bridged diketone **1**, the compound mentioned by Dunitz and Ibberson as having an anomalous conformational KIE. To better calibrate our methodology, we also performed calculations on 9,10-dihydro-4,5-dimethylphenanthrene **2**. The effect of deuteration upon the rate of stereoinversion in these systems is opposite, lowering the rate of racemization of $[D_8]$-**1** (k_H/k_D 1.06, 368 K)[8] and accelerating the process in $[D_6]$-**2** (k_H/k_D 0.880, 315 K).[9] Using the standard convention based upon reaction kinetics, the KIE in $[D_8]$-**1** is regarded as "normal" ($k_H/k_D > 1$) and that in $[D_6]$-**2** as "inverse" ($k_H/k_D < 1$). Apart from the suggestions made by Dunitz and Ibberson, the origin of the normal KIE in $[D_8]$-**1** has remained unexplored. On the other hand, the singly bridged biphenyl $[D_6]$-**2** is often used to illustrate a steric conformational KIE in which the CD_3 groups enhance the rate by presenting a smaller effective size.

While zero-point vibrational energy (enthalpic) differences are often proposed to be the controlling factor in KIEs and equilibrium isotope effects (EIEs),[10] thermal excitation of low vibrational frequencies—which contributes to vibrational entropy—has been shown to be important for a select number of kinetic and equilibrium isotope effects. These include KIEs in amide bond rotation,[11] EIE/KIEs in metal–H_2 and metal–CH interactions,[12] and EIEs in intramolecular OH/OD hydrogen bonds.[13] Of particular relevance to the results presented here, Mislow and co-workers also found antagonistic enthalpic and entropic KIE contributions in $[D_6]$-**2**.[9] The aim of the present study is to investigate the potential energy surfaces corresponding to the stereoinversions of biphenyls **1** and **2** and to compute and compare the relative contributions of enthalpy and entropy to the KIEs in these systems.

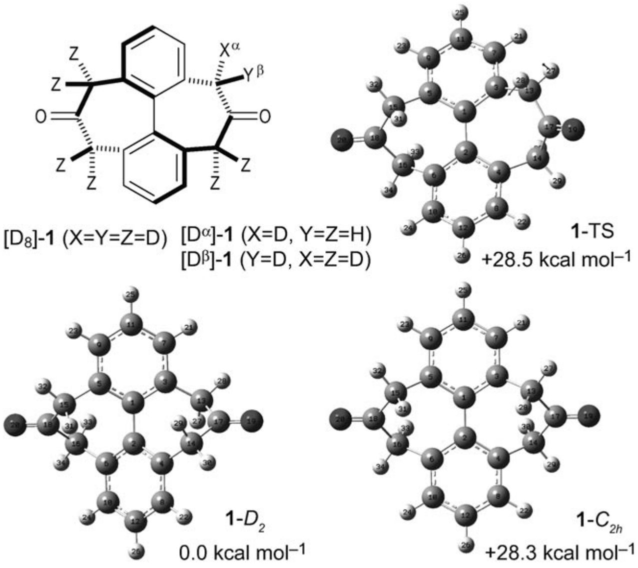

Figure 1. A B3LYP/6-31G(d,p) transition structure (**1**-TS-C_1) was located by scanning the central torsion angle of ground state structure **1**-D_2. TS displacement vectors are shown in the upper right CH_2 group of **1**-TS-C_1. An intrinsic reaction coordinate (IRC) calculation starting with **1**-TS-C_1 correlated the transition state with chiral **1**-D_2 and an achiral higher-energy structure, **1**-C_{2h}.

The potential energy surface of diketone **1** was characterized by computing chiral ground state conformer **1**-D_2 (Figure 1) and a central bond torsional scan revealed a chiral C_1 transition structure **1**-TS ($\Delta H^{\ddagger} = 28.5\ \text{kcal mol}^{-1}$, $\tilde{\nu}^{\ddagger} = -43.98\ \text{cm}^{-1}$, experiment: $\Delta H^{\ddagger} = 30.4\ \text{kcal mol}^{-1}$[8]). An intrinsic reaction coordinate (IRC) calculation[14] was used to produce intermediate structures on either side of the potential energy maximum; one structure minimized to **1**-D_2 while the other optimized to an achiral stationary point just 0.2 kcal mol^{-1} lower in energy than **1**-TS (**1**-C_{2h}, $\Delta H = 28.3\ \text{kcal mol}^{-1}$). KIEs for **1** were calculated[14] (Table 1) using scaled B3LYP/6-31G(d,p) harmonic frequencies for

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[**] D.J.O. thanks Pomona College for supporting this research. M.P.M. acknowledges NIGMS (GM87706-01).

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201007322.

Table 1: KIEs for deuterated **1** at 368 K using scaled harmonic frequencies via the Bigeleisen–Mayer or $\Delta H\Delta S$ approaches.

k_H/k_D[a]	[D_8]-**1**	[D^α]-**1**	[D^β]-**1**
experimental[b]	1.06		
Bigeleisen–Mayer	1.075	1.006	1.126
ZPE	1.026	0.998	1.121
EXC	1.050	1.022	1.002
MMI	0.998	0.996	1.002
$\Delta\Delta G^{\ddagger}$	1.075	1.006	1.126
$\Delta\Delta H^{\ddagger}$	0.973	0.960	1.108
$-T\Delta\Delta S^{\ddagger}$	1.105	1.046	1.017

[a] ZPE: zero-point vibrational energy term, EXC: excitation term, MMI: mass and moment of inertia term. [b] Ref. [8].

structures **1**-D_2 and **1**-TS according to two protocols: 1) the Bigeleisen–Mayer[15] equation or its QUIVER[16] implementation, which computes the reduced partition function in the form of $k_H/k_D = \text{ZPE} \times \text{EXC} \times \text{MMI}$, where ZPE is an enthalpic zero-point vibrational energy term, and EXC and MMI are entropic thermal excitation and mass-moment of inertia terms, and 2) the rigid-rotor harmonic oscillator approach ($\Delta H\Delta S$) to computing $\Delta\Delta H^{\ddagger}$, $\Delta\Delta S^{\ddagger}$, and $\Delta\Delta G^{\ddagger}$.[17] Either approach gives the same overall KIE for [D_8]-**1** (1.075 368 K) and is reproducible using other computational approaches (HF/6-31G(d,p): 1.064), MP2/6-31G(d,p): 1.068). These values are in good agreement with the experimental KIE (1.06).[8]

Using the Bigeleisen–Mayer analysis, the normal KIE in [D_8]-**1** is calculated to consist primarily of normal ZPE (1.026) and EXC (1.050) terms, with the latter dominant. Interestingly, the $\Delta H\Delta S$ approach provides a different dissection in that the KIE consists of an inverse enthalpic (0.973) and a normal and large entropic contribution (1.105). The $\Delta\Delta H^{\ddagger}$ contribution might at first seem at odds with the Bigeleisen–Mayer ZPE term, which is generally thought to dominate enthalpy differences involved in the isotope effect. This is not the case for [D_8]-**1**, as the zero-point vibrational energy differences ($\Delta\Delta H^{\ddagger}_{\text{ZPE}}$) are small and the overall enthalpy term becomes negative due to an unusually large $\Delta\Delta H^{\ddagger}_{\text{vib}}$ term of opposite sign.[18] While ZPE differences often tend to dominate the enthalpic contribution to isotope effects (e.g., [D^β]-**1** and [D_6]-**2**, Table 2), exceptions such as [D_8]-**1** exist. Although the enthalpy terms for this molecule are unique, the dominance of the entropic contribution lends credence to the explanation suggested by Dunitz and Ibberson for the KIE in [D_8]-**1**.

Table 2: Frequency-dependent enthalpic KIE contributions for select isotopologs of diketone **1** (368 K) and dihydrophenanthrene **2** (315 K).[a]

Term[a]	[D_8]-**1**	[D^β]-**1**	[D_6]-**2**
$\Delta\Delta H^{\ddagger}_{\text{vib}}$	−0.038	−0.009	−0.009
$\Delta\Delta H^{\ddagger}_{\text{ZPE}}$	0.018	0.083	−0.176
$\Delta\Delta H^{\ddagger}_{\text{thermal}}$	−0.020	0.074	−0.185
k_H/k_D ($\Delta\Delta H^{\ddagger}_{\text{thermal}}$)	0.973	1.108	0.743

[a] Enthalpic terms are given in kcal mol^{-1}.

We next calculated KIEs for more lightly deuterated analogs of **1** in order to study the effect of deuteration at the site of greatest motion in the transition structure (Figure 1, Table 1). These calculations suggest that one of the diastereotopic methylene positions is particularly sensitive to isotopic replacement. In theory, such a compound ([D^β]-**1**) would exhibit a large normal KIE (1.126) that is primarily enthalpic in origin. However, the $\Delta H\Delta S$ dissection reveals that deuterium at the other position ([D^α]-**1**) gives an inverse enthalpic contribution (0.960) to the overall KIE, which is nearly unity because the enthalpic contribution is masked by a nearly equal $T\Delta\Delta S^{\ddagger}$ term of opposite sign. This analysis reveals the KIE in [D_8]-**1** is strongly influenced by deuteration at sites remote from the location of large amplitude motions in the transition structure. The results also suggest that vibrational entropy makes the largest contribution in the most heavily deuterated isotopolog.

Our computational study of dihydrophenanthrene **2** proceeded along similar lines but in this case the computed KIEs could be compared with experimental data for three isotopologs as well as a set of temperature-dependent KIEs (Figure 2, Table 3). A transition structure (R)-**2**-TS ($\Delta H^{\ddagger} =$ 23.6 kcal mol^{-1}, $\tilde{\nu}^{\ddagger} = -100.43$ cm^{-1}, experiment: $\Delta H^{\ddagger} =$ 21.9 kcal mol^{-1}[9]) with C_2 symmetry was used in an IRC calculation linking enantiomeric C_2-symmetric ground state conformations. As shown in Figure 2, the (R)-**2** ground state conformation arises from an optimization of the IRC intermediate structure involving relief of Me/Me steric interactions, while optimization to the (S)-**2** conformation involves methyl motion *and* ring inversion. Two enantiomeric racemization pathways must exist, but they have the same energies and isotope effects, so there is no need to consider them separately.

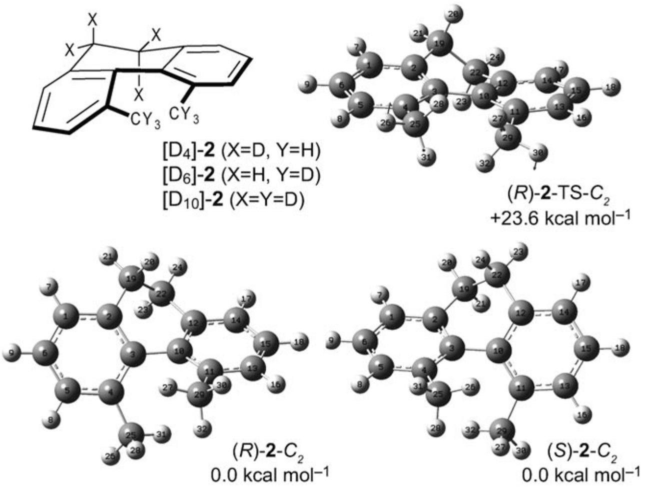

Figure 2. A B3LYP/6-31G(d,p) transition structure (**2**-TS-C_2) was located by scanning the central torsion angle of ground state structure (R)-**2**-C_2. TS displacement vectors are shown in each methyl group of **2**-TS-C_2. An intrinsic reaction coordinate (IRC) calculation starting with **2**-TS-C_2 correlated the transition state with enantiomeric (R)-**2**-C_2 and (S)-**2**-C_2 structures.

Table 3: KIEs for deuterated **2** at 315 K using scaled harmonic frequencies via the Bigeleisen–Mayer and $\Delta H \Delta S$ approaches.

k_H/k_D[a]	[D_6]-**2**	[D_4]-**2**	[D_{10}]-**2**
experimental[b]	0.880	0.952	0.847
Bigeleisen–Mayer	0.888	0.953	0.846
ZPE	0.755	0.943	0.712
EXC	1.182	1.009	1.193
MMI	0.995	1.001	0.997
$\Delta\Delta G^{\ddagger}$	0.888	0.953	0.846
$\Delta\Delta H^{\ddagger}$	0.743	0.927	0.689
$-T\Delta\Delta S^{\ddagger}$	1.193	1.028	1.227

[a] ZPE: zero-point vibrational energy term, EXC: excitation term, MMI: mass and moment of inertia term. [b] Ref. [9].

Mislow and co-workers measured KIEs at 315 K for dihydrophenanthrene derivatives labeled with deuterium at the methyl groups ([D_6]-**2**), the bridging methylene positions ([D_4]-**2**), or both ([D_{10}]-**2**).[9] The B3LYP 6-31G(d,p) KIEs align very nicely with these values (Table 3) and the predictions are again relatively invariant to theoretical approach (for [D_6]-**2**), HF/6-31G(d,p): 0.846; MP2/6-31G(d,p): 0.884). For dihydrophenanthrene [D_6]-**2**, either the Bigeleisen–Mayer or $\Delta H \Delta S$ approaches predict sizable yet oppositely signed enthalpic and entropic contributions. The ZPE (0.755) and $\Delta\Delta H^{\ddagger}$ (0.743) KIE components are both inverse and combine with normal EXC (1.182) or $-T\Delta\Delta S^{\ddagger}$ (1.193) terms to yield the calculated inverse KIE. The computed inverse KIE (0.953) in dihydrophenanthrene [D_4]-**2** appears to arise from similarly antagonistic, yet smaller, inverse enthalpic and normal entropic components. In this isotopolog the heavy atoms are remote from the sterically compressed methyl groups and are not involved in any significantly perturbed (e.g., eclipsed) bonds in the transition structure (Figure 2). The details of this KIE are outside the scope of this report and will be discussed elsewhere. The normal KIE in [D_{10}]-**2** arises in an additive manner and, as such, does not offer any new insights beyond serving as an additional check on the agreement between theory and experiment.

The $\Delta H \Delta$S decomposition for [D_6]-**2** compares quite well with the experimental $\Delta\Delta H^{\ddagger}$ (190 cal mol^{-1}, theory: 186 cal mol^{-1}), $-T\Delta\Delta S^{\ddagger}$ (-113 cal mol^{-1}, theory: -111 cal mol^{-1}), and $\Delta\Delta G^{\ddagger}_{315}$ (77 cal mol^{-1}, theory: 75 cal mol^{-1}) values, which were obtained by studying the KIE temperature dependence in heptane from 295 to 325 K.[9b] This level of agreement between experiment and theory reveals that it is possible to accurately calculate enthalpic and entropic KIE contributions in stereoinversions of medium-sized organic molecules. Our studies therefore have defined a viable potential energy surface for the racemization process in dihydrophenanthrene **2**, and our computationally derived KIEs and their enthalpic and entropic contributions have been validated by comparison with experimental data.

Our study of diketone [D_8]-**1** likewise revealed a potential energy surface compatible with the racemization process characterized by Mislow and co-workers. The normal KIE in this system is found to be composed of an inverse enthalpic component working against a normal and dominant entropic effect. This antagonistic interplay between enthalpy and entropy is missed by the Bigeleisen–Mayer equation, underscoring the utility of computing enthalpy and entropy terms directly. Both approaches do indicate the KIE in [D_8]-**1** has a dominant normal entropic contribution, which is consistent with Dunitz and Ibberson's suggestion that low-frequency vibrational modes are important for this unusual isotope effect.

Our calculations have shown that the degree to which a conformational KIE in deuterated forms of **1** or **2** is normal or inverse is a consequence of the sign and relative magnitudes of the enthalpic and entropic contributions to the isotope effect. Vibrational entropy governs the conformational KIE in [D_8]-**1**, but does this imply that deuterium is acting larger than protium? The conceptual model for steric isotope effects relates isotopic identity to size in a way that considers only ZPE contributions to the KIE. The KIE associated with the stereoinversion of [D_8]-**1** and the study by Ibberson and Dunitz illustrates that entropic contributions can obfuscate the interpretation of KIEs arising from non-bonding interactions. Other systems illustrate the difficulty in correlating deuterium substitution with a reduction in size. In deuterated cyclohexane, for example, deuterium favors the equatorial bond by some 6–8 cal mol^{-1}.[19] Although it might be tempting to conclude that this means D is larger than H, this preference is mainly a consequence of the equatorial bond having a larger force constant than the axial bond. Likewise, we attribute KIE differences between **1** and **2** to site-specific differences, complicated as they are, in the vibrational characteristics of these two molecules.

It is clear from the work presented here that conformational KIEs for certain systems need to be viewed with a much wider aperture than simply accounting for zero-point vibrational differences between ground and transition states. As our understanding of conformational KIEs develops, we are better able to interpret KIE and EIE measurements in systems where apparent substituent size can have profound effects upon both reactivity and selectivity. Future applications of the method of partitioning steric ^{2}H KIEs into their enthalpic and entropic contributions may prove useful in related conformational processes, host–guest systems, and more precisely examining recent measurements of steric ^{2}H KIEs in asymmetric reactions.[3,4]

Methods

The calculations reported here utilized Gaussian 09.[20] To ensure accurate calculation of low frequencies, MP2 and HF geometries were optimized using the opt = vtight keyword. B3LYP geometries were optimized with the opt = vtight, scf = (conver = 10), integral = (grid = ultrafine) keywords. Intrinsic reaction coordinate (IRC) calculations utilized the default implementation. $\Delta H \Delta S$ KIEs were calculated using the default Gaussian 09 thermochemistry output which accompanies harmonic frequency calculations, as adjusted for temperature and positions of isotopes. The Bigeleisen–Mayer terms were calculated with a spreadsheet and the harmonic vibrational frequencies according to existing protocols.[15,16]

Received: November 22, 2010

Keywords: ab initio calculations · biaryls · chirality · conformation analysis · isotope effects

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