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A Mechanistic Probe for Asymmetric Reactions: Deuterium Isotope Effects at Enantiotopic Groups

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The rational development of stereoselective reagents and catalysts remains an elusive goal. While significant progress has been made using largely empirical approaches, quantitative measurements are necessary to develop predictive transition structure models. Two primary directing forces are often credited for stereoselectivity: (1) orbital geometry and (2) steric occlusion. The underlying physical phenomena responsible for these "forces" are well-understood. However, experiments capable of quantitatively assessing symmetry-breaking interactions at the transition state have yet to be developed as generally applicable tools. This paper describes a methodology that uses ^{2}H kinetic isotope effect (KIE) measurements upon "chemically innocuous" enantiotopic groups as a probe for symmetry breaking in the transition structure. In asymmetric reactions, enantiotopic groups become diastereotopic in the transition state, resulting in distinct average environments for each group. KIEs result from changes in structure and bonding that occur as the molecule of interest progresses along the reaction coordinate from the reactant to the transition state of the rate-limiting step. The effects of steric occlusion[1] and dispersion interactions[2] upon vibrational force constants are well-known. As a result, the measurements described here are the first steps in understanding the forces responsible for symmetry breaking in the transition state.

Stereoselective reductions of asymmetric ketones are of immense importance, especially in pharmaceutical synthesis.[3–8] While all commonly used reduction systems exhibit exemplary reactivity and selectivity with select substrates, all reduction systems have a class or classes of ketones that prove intractable.[9,10] Reductions using *B*-chlorodiisopinocampheyl-borane (DIP-Cl) have shown outstanding selectivity, especially in the reductions of aralkyl ketones and α-tertiary dialkyl ketones. However, subtle changes in substrate structure can seriously impact the effectiveness of DIP-Cl as a reductant. In fact, 2′,5′-dimethylisobutyrophenone is inert to DIP-Cl at room temperature; whereas, 4′-methylisobutyrophenone (**1**) is cleanly reduced to the *S*-enantiomer of the reduction product with >99% ee by (–)-DIP-Cl under the same conditions. These results are in contrast to the (–)-DIP-Cl reduction of isobutyrophenone, which predominately yields the *S*-enantiomer with lower selectivity (90% ee).[11]

Kinetic isotope effect (KIE) studies are exquisitely sensitive probes of the transition structure.[12,13] Empirical determinations of KIEs offer a means of evaluating computational or heuristic models of the transition structure. Enantiotopic groups are equivalent by symmetry in the reactant. Asymmetric reactions convert these positions into diastereotopic groups in the product-determining step. As a consequence, the measurement of KIEs at enantiotopic groups in asymmetric reactions is a natural choice for investigating the critical symmetry breaking event that occurs during the product-determining step. The enantiotopic groups utilized in our ongoing investigations of stereoselective reductions are chemically innocuous—meaning that changes in isotopic substitution at these positions have little effect upon the imaginary frequency associated with the reaction coordinate at the transition state. While this aspect of experimental design could be relaxed to investigate neighboring group phenomena such as hydrogen bond formation or Lewis acid/Lewis base interactions, the primary motivation of the current research is to ascertain the structural and energetic importance of steric occlusion and dispersion forces. Furthermore, ensuring that the isotopic substitution on the enantiotopic groups does not affect the imaginary frequency, makes the assumption of the rule of the geometric mean more credible (see eq. 2).[14]

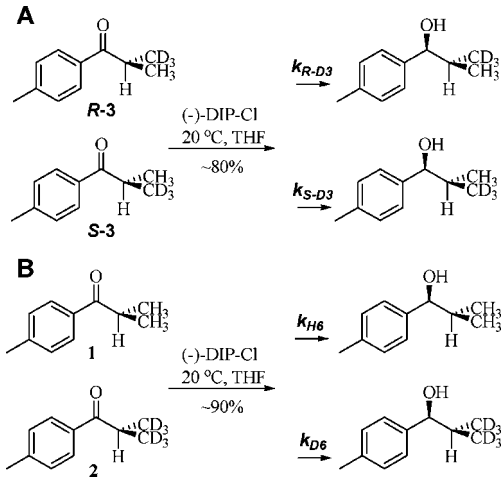

Figure 1. The two competition reactions by which ^{2}H KIEs upon enantiotopic methyl groups are determined.

The method for determining ^{2}H KIEs on the enantiotopic methyl groups in 4′-methylisobutyrophenone relies on determining the relative rates in two distinct competition reactions. The two competition reactions performed in these experiments are shown in Figure 1 panels A and B. Figure 1A illustrates a competition between isotopomers in the racemically d3-labeled substrates, where *R* is the ratio of ***S*-3** to ***R*-3** in reisolated ketone. While this competition reaction yields the relative isotope effects at each enantiotopic methyl group (eq 1), the competition reaction shown in Figure 1B yields the product of the isotope effects at the enantiotopic methyl groups, assuming the rule of the geometric mean[15] (eq 2). In eq 2, *R* is the ratio of **2** to **1** in ketone reisolated from high conversion reactions, and R_0 is the ratio of **2** to **1** in the stock ketone used as starting material in the high conversion reactions. In eqs 1 and 2, *F* is the overall fractional conversion. Using eqs 3 and 4, the absolute KIEs at both the *pro-R* and *pro-S* methyl group can be computed from the numerical values of the relative rates computed from the competition experiments in Figure 1A,B.

$$\frac{k_{S-D3}}{k_{R-D3}} = \frac{k_{H6}}{k_{R-D3}}\frac{k_{H6}}{k_{S-D3}} = \frac{\ln[2(1-F)/(1+1/R)]}{\ln[2(1-F)/(1+R)]} \qquad (1)$$

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$$\frac{k_{H6}}{k_{D6}} = \frac{k_{H6}}{k_{S-D3}} \times \frac{k_{H6}}{k_{R-D3}} = \frac{\ln[(1+1/R_0)(1-F)/(1+1/R)]}{\ln[(1+R_0)(1-F)/(1+R)]} \quad (2)$$

$$\frac{k_{H6}}{k_{R-D3}} = \sqrt{\frac{k_{S-D3}}{k_{R-D3}} \times \frac{k_{H6}}{k_{D6}}} \quad (3)$$

$$\frac{k_{H6}}{k_{S-D3}} = \sqrt{\left(\frac{k_{H6}}{k_{D6}}\right)\left(\frac{k_{S-D3}}{k_{R-D3}}\right)} \quad (4)$$

The competition reactions between enantiomeric isotopomers shown in Figure 1A were taken to 78.1, 84.8, and 80.3% conversion. The unreacted ketone was reisolated using flash chromatography and desymmetrized using the CBS reduction, which proceeds cleanly and with very high selectivity (>99% ee).[10] This desymmetrization was chosen in lieu of using DIP-Cl itself because the CBS reaction is more easily worked up. The desymmetrization allows for quantification of the relative amounts of ***S*-3** and ***R*-3** in the reisolated starting material by ^{1}H NMR. The doublets of each methyl group are easily resolved in the resulting spectrum performed in CD_2Cl_2. While these groups relax quickly, a T_1 calibration is performed to ensure that the resonances are fully relaxed between transients. The assignment of the resonance to each individual methyl group is performed using chemical shifts computed by the CSGT[16] methodology and the IGAIM[17] variation upon a fully optimized B3LYP/6-31+G(d,p) model of the anticipated[11] *R* enantiomer of the benzylic alcohol product. NMR chemical shift predictions showed that the *pro-S* position is downfield of the *pro-R* position in the ^{1}H NMR spectrum, while it is upfield of the *pro-R* position in the ^{13}C NMR spectrum. We acquired a HMQC spectrum upon the product to determine that the diastereotopic positions did, in fact, switch relative positions in the ^{1}H and ^{13}C spectra as a partial check on the accuracy of the NMR predictions.

The competition reactions between **1** and **2** shown in Figure 1B were taken to 87.9, 88.0, and 90.6% conversion. The unreacted ketone was reisolated as above. Reisolated reactant from these reactions was analyzed using ^{1}H NMR to determine the relative amounts of **1** and **2**. The methine resonance was used to account for total ketone present, since its resonance at 3.50 ppm is well-resolved and unlikely to overlap with any contaminants. The methyl resonance at 1.18 ppm was used to account for **1**. These measurements allowed for an accurate estimate of the ratio of **1** to **2** in the reisolated ketone, thus yielding *R*. The same measurement in stock ketone yields R_0.

The results from the competition reactions are shown in Figure 2. The competition reactions directly yield $k_{S\text{-}D3}/k_{R\text{-}D3}$ and k_{H6}/k_{D6}. The KIEs upon individual prochiral groups are obtained using eqs 3 and 4. Repulsive steric interactions cause an increase in force constant, thus further splitting the zero-point energy differences between C−D and C−H in the transition state, ultimately leading to an inverse (<1) KIE.[1] This appears to explain the inverse nature of the overall KIE (k_{H6}/k_{D6} < 1). Similar reasoning suggests that the *pro-S* group experiences greater repulsive steric interaction than the *pro-R* group in the transition state. In the context of the qualitative transition structure adapted from Brown,[11] it is possible that antiperiplanar donation of the methine C−H bond into the nascent C−H bond formed by the attacking hydride orients the prochiral groups such that the *pro-S* methyl group comes into strong incidence with the nearby methyl on the isopinocampheyl group. While such an explanation is satisfying in the context of the familiar principles of molecular orbital theory and the semiclassical origins of steric isotope effects, dispersion forces could contribute compensatory normal contributions to the KIE. While this effect is probably small and may seem counterintuitive in the context of a condensed phase transition structure, alkanes under moderate pressure exhibit red-shifts in C−H bond stretches.[18] Likewise, the transfer of cyclohexane from the gas phase to neat liquid lowers the frequency of both the axial and equatorial C−H stretches by more than 10 cm^{-1}.[19] In fact, isotope-dependent dispersion forces are thought to be responsible for reverse-phase HPLC separations of the perdeuterated and perprotiated isotopologues of several molecules.[20] Obviously, dispersion forces can affect force constants and result in a normal (>1) contribution to observed KIEs. What remains to be quantitatively determined is the relative importance of steric interactions and dispersion forces.

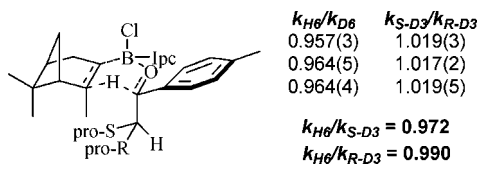

Figure 2. Relative rate constants computed from competition reactions and resulting KIEs on enantiotopic methyl groups.

We have illustrated a simple and powerful new method for probing symmetry breaking in the transition states of stereoselective reactions. Computational work is underway to explain the origins of the isotope effects observed here and in other systems. A new method is also under development to estimate the relative importance of dispersion forces and steric occlusion in these measurements.

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Supporting Information Available: Detailed experimental procedures, derivation of eqs 1 and 2, and tables of integrations from quantitative NMR measurements.This material is available free of charge via the Internet at http://pubs.acs.org.

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