ORGANIC LETTERS

2009
Vol. 11, No. 19
4338−4341

Nonbonding Interactions and Stereoselection in the Corey−Bakshi−Shibata Reduction

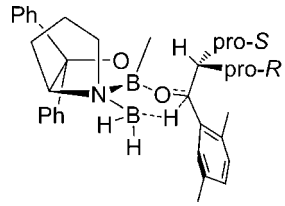
Matthew P. Meyer*

University of California, Merced, School of Natural Sciences, P.O. Box 2039, Merced, California 95344

mmeyer@ucmerced.edu

Received July 24, 2009

ABSTRACT



k_1/k_2 = 0.939(2)
$k_{S\text{-}D3}/k_{R\text{-}D3}$ = 0.991(4)
$k_1/k_{R\text{-}D3}$ = 0.965(3)
$k_1/k_{S\text{-}D3}$ = 0.974(3)

Deuterium kinetic isotope effect measurements upon enantiotopic methyl groups for the Corey−Bakshi−Shibata reduction of 2′,5′-dimethylphenyl isopropyl ketone suggest a complex role for nonbonding interactions in the mediation of stereoselection.

Asymmetric catalysis has established a firm foothold in natural product synthesis[1] and is of growing importance in industrial processes.[2] Qualitative transition-structure models are capable of explaining product distributions in a number of stereoselective reactions and reaction classes. Comparative estimates of steric repulsion play a key role in these models. Unfortunately, it is often difficult to quantitatively measure nonbonding interactions that arise in the transition state. Methods relying upon linear free energy relationships have been somewhat successful in elucidating the role of steric interactions in determining reactivity;[3] however, it is often difficult to extricate the role of steric interactions in these studies from spurious orbital interaction and solvation effects.[4,5]

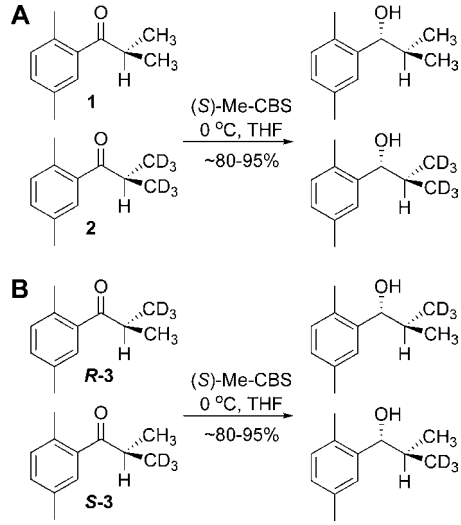
Pioneered by Carter and Melander, steric kinetic isotope effects (KIEs) offer a less perturbative probe of steric repulsion that develops at the transition state.[6] Similarly, other research groups have performed elegant steric equilibrium isotope effect measurements that illustrate the influence of isotopic perturbation upon processes ranging from conformational equilibria to enzyme−substrate binding. Until recently, however, a general approach to measuring steric interactions that develop in the transition states of asymmetric reactions was lacking. The new methodology uses two isotopic competition experiments to arrive at an estimate of the ^{2}H KIEs upon chemically innocuous prochiral groups (Scheme 1). In asymmetric reactions, the symmetry element that makes these prochiral groups chemically equivalent is broken in a deterministic way in the transition state. If these enantiotopic probe groups are close to the reaction center, then they can be used to interrogate nonbonding forces that contribute to symmetry breaking at the transition state.

The CBS reduction is of interest in its own right and as a point of comparison with results obtained recently for the *B*-chlorodiisopinocampheylborane (DIP-Cl) reduction of 4′-methylisobutyrophenone.[7] The DIP-Cl reduction is somewhat limited in its substrate range, being primarily used for the

(1) Taylor, M. S.; Jacobsen, E. N. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5368–5373.
(2) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev.* **2006**, *106*, 2734–2793.
(3) (a) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 2729–2732. (b) Taft, R. W., Jr. *J. Am. Chem. Soc.* **1952**, *74*, 3120–3128. (c) Pavelich, W. A; Taft, R. W., Jr. *J. Am. Chem. Soc.* **1957**, *79*, 4935–4940.
(4) McClelland, R. A.; Steenken, S. *J. Am. Chem. Soc.* **1988**, *110*, 5860–5866.
(5) Unger, S. H.; Hansch, C. *Prog. Phys. Org. Chem.* **2007**, *12*, 91–118.
(6) Carter, R. E.; Melander, L. *Adv. Phys. Org. Chem.* **1973**, *10*, 1–23.
(7) West, J. D.; Stafford, S. E.; Meyer, M. P. *J. Am. Chem. Soc.* **2008**, *130*, 7816–7817.

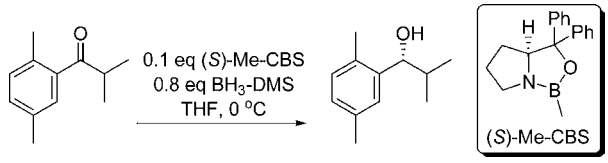
10.1021/ol901707h CCC: $40.75
Published on Web 09/04/2009

Scheme 1. Two Competition Reactions by which ^{2}H KIEs at Enantiotopic Methyl Groups Are Determined



reduction of aralkyl ketones.[8] By contrast, the most commonly used CBS catalyst, employing a *B*-methyl substituent (Scheme 2), has an unusually broad substrate range.[9,10]

Scheme 2. CBS Reduction Studied Here



Qualitative[11] and precise[12] transition-structure models illustrate a clear and distinct role for steric repulsion in the DIP-Cl reduction. The determinants of stereoselection in (*S*)-Me-CBS-catalyzed reductions and other analogues are not immediately obvious from qualitative transition structures. In this paper, we interpret the ^{2}H KIEs measured at prochiral groups (Scheme 2) in the context of similar experiments upon the DIP-Cl reduction[7] and ^{13}C KIEs recently measured for the CBS reduction of 2′,5′-dimethylisobutyrophenone.[13]

The methodology employed in the current studies (Scheme 1) utilizes two competition reactions. Both competition reactions use the fractionation in unreacted starting material and the fractional conversion of the reaction to arrive at rate constant ratios. The first competition reaction (Scheme 1A) is used to measure the product of isotope effects resulting from ^{2}H-substitution upon the enantiotopic groups (eq 1). Inherent in this assumption is the rule of the geometric mean.[14] This assumption is likely to be exceptionally good in the current context because the enantiotopic methyl groups under consideration do not appear to participate significantly in the reaction coordinate mode at the transition state.[13] The second competition reaction is used to measure the ratio of isotope effects resulting from ^{2}H-substitution upon each enantiotopic group (eq 2). Together, these measurements can be used to compute the isotope effects resulting from ^{2}H-substitution upon both the pro-*S* and pro-*R* methyl groups (eqs 3a and 3b).

$$\frac{k_1}{k_2} = \frac{k_1}{k_{R\text{-}3}} \times \frac{k_1}{k_{S\text{-}3}} \tag{1}$$

$$\frac{k_{S\text{-}3}}{k_{R\text{-}3}} = \frac{k_1}{k_{R\text{-}3}} \times \frac{k_{S\text{-}3}}{k_1} \tag{2}$$

$$\frac{k_1}{k_{R\text{-}3}} = \sqrt{\frac{k_1}{k_2} \times \frac{k_{S\text{-}3}}{k_{R\text{-}3}}} \tag{3a}$$

$$\frac{k_1}{k_{S\text{-}3}} = \sqrt{\frac{k_1}{k_2} / \frac{k_{S\text{-}3}}{k_{R\text{-}3}}} \tag{3b}$$

The rate ratios in eqs 1 and 2 are computed from fractionation observed in reisolated reactant in reactions taken to high (~80−95%) conversion. Measurements of the relative amounts of ***R*-3** and ***S*-3** reisolated in the second competition experiment are performed following a desymmetrization step that converts the enantiotopic methyl groups into diastereotopic groups. The measurements presented here utilize the CBS reduction as the desymmetrization method. Reduction of 2′,5′-dimethylphenyl isopropyl ketone by BH_3·DMS catalyzed by (*S*)-Me-CBS proceeds with essentially quantitative conversion and greater than 98% ee. Quantitative conversion ensures that the desymmetrization step does not introduce spurious isotopic fractionation. High stereoselectivity ensures that isotopic fractionation in the prochiral methyl groups (Scheme 1B) results almost exclusively from the *Si*-facial reduction channel.

All measurements of isotopolog (**1** vs **2**) or isotopomer (***R*-3** vs ***S*-3**) ratios utilize quantitative ^{1}H NMR employing calibrated 90° pulses separated by delays of greater than $5T_1$ for the methyl doublets of interest. The relative NMR assignments of the diastereotopic methyl groups in the product were accomplished using the CSGT[15] methodology and the IGAIM[16] variation upon a fully optimized B3LYP/6-31+G(d,p) model of the anticipated *R* enantiomer of the benzylic alcohol product.

(8) Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16–24.
(9) Corey, E. j.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925–7926.
(10) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986–2012.
(11) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539–1546.
(12) Stafford, S. E.; Meyer, M. P. *Tetrahedron Lett.* **2009**, *50*, 3027–3030.
(13) Saavedra, J.; Stafford, S. E.; Meyer, M. P. *Tetrahedron Lett.* **2009**, *50*, 1324–1327.
(14) Decius, J. C.; Wilson, E. B., Jr. *J. Chem. Phys.* **1951**, *19*, 1409–1412.

Each type of competition experiment shown in Scheme 1 was performed in triplicate. The rate constant ratios from the competition experiments in Scheme 1 (k_1/k_2 and $k_{S\text{-}D3}/k_{R\text{-}D3}$) were computed using equations reported recently.[7] The ^{2}H KIE upon each enantiotopic group was computed using the weighted average values of the two rate constant ratios measured in triplicate (Figure 1). The relative amounts of **1** and **2** in the stock ketone mixture and reisolated samples were computed in the following way: The methyl doublet integration was used as a measure of the amount of **1** present, while the total amount of **1** and **2** could be estimated from the integration of the septet corresponding to the aliphatic methyne proton. The errors on the isotope effects at each position are propagated from the error estimates taken from the single value estimates computed from the competition experiments.[17]

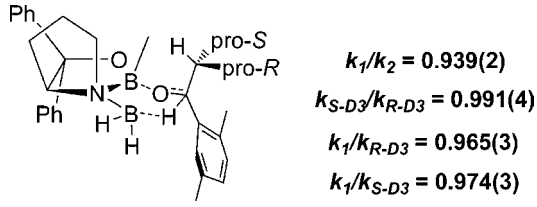


Figure 1. Relative rate constants computed from fractionation in reisolated reactant and resulting KIEs upon the prochiral methyl groups in the substrate. Errors in the last digit are in parentheses.

The computed transition structure in Figure 2 reproduces ^{13}C KIEs measured for the BH_3-DMS reduction of 2′,5′-dimethylphenyl isopropyl ketone catalyzed by (*S*)-Me-CBS.[13] In light of this transition structure and the ^{13}C KIE measurements reported in the previous study, the ^{2}H KIEs shown in Figure 1 have a simple and satisfying explanation. In the transition state, significant steric repulsion develops at each prochiral methyl group, with more steric repulsion occurring at the pro-*R* group. These values agree qualitatively with the comparatively more inverse ^{13}C KIE measured at the pro-*R* group for this reaction.[13]

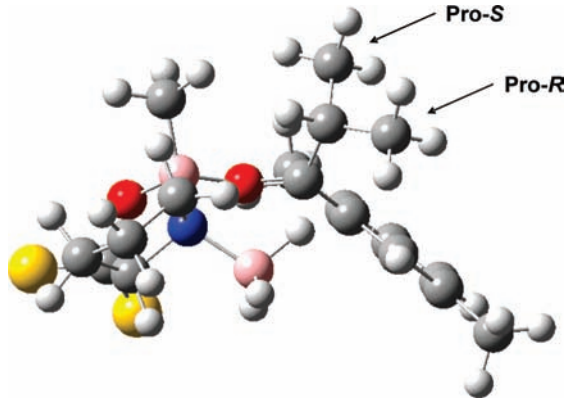


Figure 2. Computed transition structure [B3LYP/6-31+G(d,p)]for *Re* attack of hydride upon 2′,5′-dimethylphenyl isopropyl ketone. The two phenyl groups on the CBS catalyst are denoted by gold spheres.

To date, quantitative measurements of steric interactions arising in asymmetric reactions have been limited to a recent report from our laboratory.[7] Other examples of unequivocal steric ^{2}H KIEs have been limited to systems in which the sterically impacted atoms participate substantially in the reaction coordinate at the transition state. These reactions, none of which involve bond breaking or bond forming, can be characterized as inversions[18] or internal rotations[19] within molecules with rigid aromatic frameworks. Another notable example is the deslipping reaction of rotaxanes.[20] As might be expected, these reactions, in which the free energy of reaction *results from* steric interaction, yield steric ^{2}H KIEs (k_H/k_D = 0.85−0.82) well in excess of those measured in the current study.

The relative magnitudes of the inverse ^{2}H KIEs can be understood in terms of individual pairwise interactions between neighboring groups. Figure 3 shows that the immediate environment of the pro-*R* methyl group residing on the isopropyl moiety experiences closer nonbonding contacts than the pro-*S* methyl group. What is perhaps surprising is that each of the prochiral methyl groups has nonbonding interactions with the aryl group on the substrate. Judging from the high stereoselectivity observed in (*S*)-Me-CBS/BH_3 reductions of acetophenone, self-interaction is not requisite for high selectivity but is rather simply an artifact of having a tertiary α-carbon on the alkyl substituent of the aralkyl ketone.[9,10]

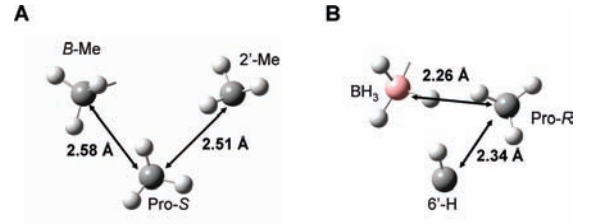


Figure 3. Nearest neighbor nonbonding interactions in the computed transition structure for the (A) pro-*S* and (B) pro-*R* methyl groups. Distances are nearest H−H contact distances between the groups indicated.

In contrast to earlier semiempirical computational studies,[21,22] we find that the cyclic arrangement of the reactive

(15) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1992**, *194*, 1–8.
(16) Keith, T. A.; Bader, R. F. W. *Chem. Phys. Lett.* **1993**, *210*, 223–231.
(17) Mandel, J. *The Statistical Analysis of Experimental Data*; Dover Press: New York, 1984.
(18) (a) Mislow, K.; Graeve, R.; Gordon, A. J.; Wahl, G. H. *J. Am. Chem. Soc.* **1964**, *86*, 1733–1741. (b) Hayama, T.; Baldridge, K. K.; Wu, Y.-T.; Linden, A.; Siegel, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 1583–1591.
(19) (a) Melander, L.; Carter, R. E. *J. Am. Chem. Soc.* **1964**, *86*, 295–296. (b) Carter, R. E.; Dahlgren, L. *Acta Chem. Scand.* **1969**, *23*, 504–514. (c) Sherrod, S. A.; da Costa, R. L.; Barnes, R. A.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1565–1577.
(20) Felder, T.; Schalley, C. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 2258–2260.

portion of the transition structure, including the borane reductant and the carbonyl of the ketone, is arrayed in a boat conformation as predicted by Evans.[23] This difference may be due to the presence of α-branching present on the isopropyl group of 2′,5′-dimethylisobutyrophenone. In contrast, the earlier semiempirical studies utilized acetone and acetophenone as model substrates.

As can be seen in Figure 3, the only neighboring group *on the CBS catalyst* to come into close proximity with the prochiral methyl groups is the *B*-Me group. This may infer that stereoselection is primarily determined by the *B*-alkyl group when the boat conformer of the transition state predominates. This finding is in contrast to what is observed in reductions of acetophenone with a series of oxazaborolidine catalysts bearing different *B*-alkyl groups. Analogues of the CBS catalyst bearing boron substituents of H, Me, Et, and *n*-Bu catalyze the borane reduction of acetophenone in nearly quantitative yields and with selectivities greater than or equal to 96% ee.[10,24,25] This indicates that the steric presence of the *B*-alkyl group on the CBS catalyst has little impact upon stereoselection in the reduction of acetophenone. This may simply reflect a preference for the chair conformer of the transition state for acetophenone reduction.

While previously measured ^{13}C KIEs correspond exceedingly well with those computed from the boat-like structure in Figure 2, the ^{2}H KIEs computed (B3LYP/6-31+G**) at the pro-*S* and pro-*R* groups are 0.964 and 0.934, respectively. This represents a substantial overestimation of the inverse steric isotope effect. Computed estimates of the ^{2}H KIEs on the prochiral methyl groups in the DIP-Cl reduction of 4′-methylisobutyrophenone also significantly overestimate the inverse isotope effect. It is doubtful that conformational uncertainty is the cause of the discrepancy in the DIP-Cl reduction, as the boat conformation for the transition structure is mandated by severe 1,3-interactions that would develop in a chair conformer.[8,12] We are currently developing a computational methodology that incorporates anharmonicity into estimations of steric ^{2}H KIEs in order to reconcile experiment and theory.

We have presented ^{2}H KIE measurements at the prochiral methyl groups in the (*S*)-Me-CBS-catalyzed reduction of 2′,5′-dimethylisobutyrophenone. These measurements indicate that significant steric interactions develop at each prochiral group in the transition structure. Computed transition structures identify internal interactions within the ketone substrate as the origin of some of the steric occlusion that is indicated by the inverse ^{2}H KIEs measured. The primary steric interaction between the substrate and catalyst appears to be repulsion that develops between the *B*-Me substituent and the pro-*S* methyl group. Minimization of the interaction between the *B*-Me group residing on the (*S*)-Me-CBS catalyst and the isopropyl group residing upon the substrate seems a likely origin of at least some stereoselectivity in the (*S*)-Me-CBS catalyzed reduction of 2′,5′-dimethylisobutyrophenone. This finding contrasts with previous studies that explored the effect of *B*-alkyl group identity upon stereoselection in the reduction of acetophenone.[10,24,25] However, computed transition structures for acetophenone reduction using the (*S*)-Me-CBS catalyst exhibit a chairlike conformation of the reacting atoms in the transition state as compared to the boatlike transition state computed here.

In light of the exceedingly broad substrate range of (*S*)-Me-CBS, these findings suggest that there may be two avenues for stereoselection. In prochiral ketones having small substituents that are sterically unobtrusive, it may be that the chair conformer predominates, in which case the prolinol substituents enforce stereoselection. Conversely, in prochiral ketones bearing small substituents with greater steric presence, it may be that the boat conformer predominates, resulting in stereoselection mediated by the *B*-alkyl substituent. It is also possible that the transition state is best represented by an admixture of the chair and boat conformers. We are currently exploring this possibility by measuring ^{2}H KIEs upon the 2′- and 5′-methyl substituents of 2′,5′-dimethyisobutyrophenone.

Acknowledgment. M.P.M. thanks the ACS Petroleum Research Fund (No. 48064-G4) for support of this research and Prof. Michael Colvin (UCM) for the use of his Linux cluster.

Supporting Information Available: Detailed experimental procedures, derivation of equations for computing kinetic isotope effects from NMR measurements, and tables of integrations from quantitative NMR measurements.This material is available free of charge via the Internet at http://pubs.acs.org.

OL901707H

(21) Linney, L. P.; Self, C. R.; Williams, I. H. *J. Chem. Soc., Chem. Commun.* **1994**, 1651–1652.
(22) Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799–801.
(23) Evans, D. A. *Science* **1988**, *240*, 420–426.
(24) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
(25) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 4141–4144.