Experimental transition state for the *B*-chlorodiisopinocampheylborane (DIP-Cl) reduction

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ABSTRACT

Asymmetric reductions of prochiral ketones are important transformations in the syntheses of natural products, pharmaceuticals, and fine chemicals. *B*-Chlorodiisopinocampheylborane (DIP-Cl), a stoichiometric reagent that is capable of reducing prochiral aralkyl ketones with high selectivity. Here, we utilize a recently developed ^{13}C kinetic isotope effect (KIE) methodology to probe the symmetry breaking process inherent to this asymmetric reduction. Experimental KIEs and computed transition structures indicate significant roles for non-bonding interaction, specific directed orbital interactions, and hydrogen tunneling in this reaction.

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Stereoselective reductions of prochiral ketones are of prime importance in the syntheses of natural products, pharmaceuticals, and fine chemicals. However, it is often difficult to choose an appropriate reduction system, a priori. The *B*-chlorodiisopinocampheylborane (DIP-Cl) reagent is an exemplary case, where subtle changes in substrate can have profound effects upon selectivity and reactivity.[1] While isobutyrophenone is reduced in high yield with good selectivity (90% ee), 4′-methylphenyl isopropyl ketone is reduced in high yield with very high selectivity (>99% ee).[2] More surprisingly, in our hands, 2′,5′-dimethylphenyl isopropyl ketone is inert to reduction by DIP-Cl at 25 °C.

Numerous processes can erode selectivity in asymmetric reactions: (1) racemization occurring after the selective step, (2) competition from non-selective pathways, and (3) close competition between diastereomeric transition states. Much like the chiral reductant, *B*-3-Pinanyl-9-borabicyclo[3.3.1]nonane (Alpine-Borane), DIP-Cl utilizes α-pinene as a chiral auxiliary. While low selectivity in the Alpine–Borane reduction of prochiral ketones has been shown to arise from a competing formation of the dehydroboration product,[3,4] 9-BBN, it is likely that poorly selective DIP-Cl reductions are the result of close competition between diastereomeric transition states.[5] This can be surmised by the negligible reaction progress observed over a 24-h period when attempts at reducing 2′,5′-dimethylphenyl isopropyl ketone were made. To our knowledge, no reports of side reactions have been made by other research groups investigating DIP-Cl reductions. As a means of understanding the interplay of structure and energetics in the competition between diastereomeric transition states, we have computed transition structures for both the favored and unfavored

reaction pathways. Qualitative differences for the two modes of attack are evident in Figure 1.

Primary among the factors that determine stereoselection are non-bonding interactions. Early seminal work illustrated a significant role for steric interactions in directing stereoselection.[6] From this work came numerous qualitative models in which steric interactions play key roles in determining transition structures. In spite of the obvious importance of non-bonding interactions to stereoselection, few efforts have been made to develop quantitative models of how these interactions influence the outcomes of stereoselective reactions. While notable work on kinetic isotope effects (KIEs) that derive from steric interactions has been performed,[7] the systems in which substantial and unequivocal steric KIEs have been reliably measured are constrained to inversions involving aromatic compounds.[8–10] In fact, after a dearth of activity in this area, a recent, elegant contribution has re-asserted the importance of non-bonding interactions in chemical reactions.[11]
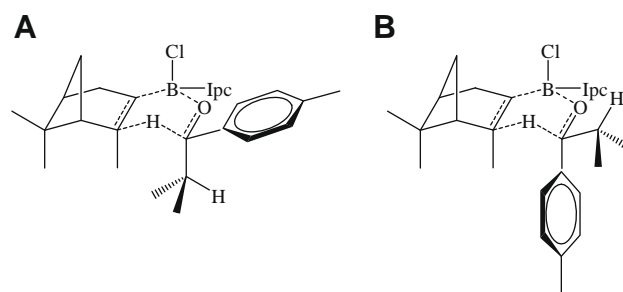
**Figure 1.** Qualitative models for (A) favored (Re) and (B) unfavored (Si) approach in the DIP-Cl reduction.

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The purpose of this Letter is to explore the factors that lead to a significant preference for the favored diastereomeric transition structure (Fig. 1A) over the unfavored diastereomer shown in Figure 1B. The simplest explanation is that steric occlusion between the proximal methyl group on the reactive isopinocampheyl group and the aromatic ring preclude Re attack. In large part, this simple view is borne out in recent ^{2}H KIE experiments designed to probe the role of non-bonding interactions in stereoselection.[12] Here, we attempt to understand the combined roles of orbital interaction and non-bonding interactions as directing forces in the transition state for the DIP-Cl reduction.

Following the same guiding principle as in earlier work, we have endeavored to utilize ^{13}C KIEs to gain insight into the origins of both selectivity and reactivity in the DIP-Cl reduction.[13] The method employed here is capable of resolving individual KIEs upon both of the enantiotopic methyl groups on the isopropyl substituent (Fig. 2). This approach is designed to gain information regarding the fundamental symmetry breaking process that occurs when a reactant possessing one or more symmetry elements is exposed to an asymmetric reactant, catalyst, or reactant–catalyst complex. As a means of interpreting these experimental measurements, we have computed transition structures for both the favored (Re attack) and disfavored (Si attack) reaction channels (Fig. 3).

The KIE results shown in Figure 2 were acquired in a method similar to that utilized in a recent study of the Corey–Bakshi–Shibata (CBS) reaction.[13] Fractionation of naturally occurring ^{13}C in 4′-methylphenyl isopropyl ketone is measured by comparing quantitative ^{13}C NMR spectra of remaining reactant taken from a high conversion (∼85–95%) reaction and stock ketone reactant. Before quantitative ^{13}C NMR analysis, however, we desymmetrize the re-isolated reactant and stock ketone using a highly stereoselective reduction. This process converts the enantiotopic methyl groups to diastereotopic groups, each having a distinct ^{13}C resonance. In the experiments performed here, four (−)-DIP-Cl reductions of 4′-methylphenyl isopropyl ketone were taken to 82.5%, 90.8%, 91.9%, and 93.2% conversion. The reactions were quenched using NaOH/H$_2$O$_2$ to ensure conversion of all products to the free alcohol form. The unreacted ketone was re-isolated using flash chromatography and desymmetrized using the CBS reduction, which pro-
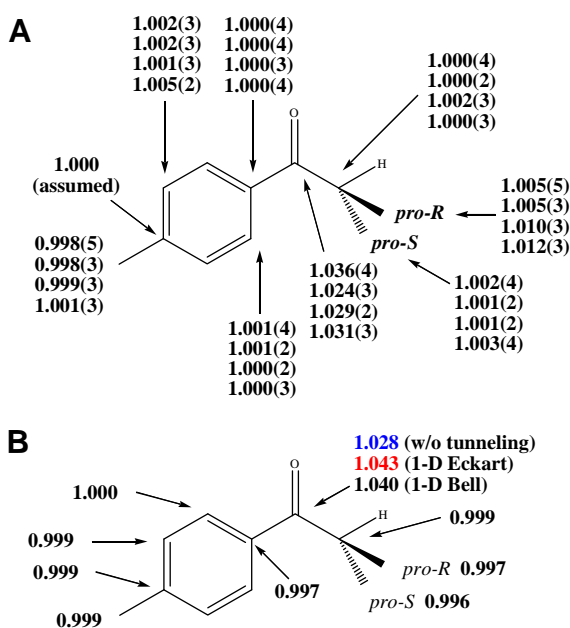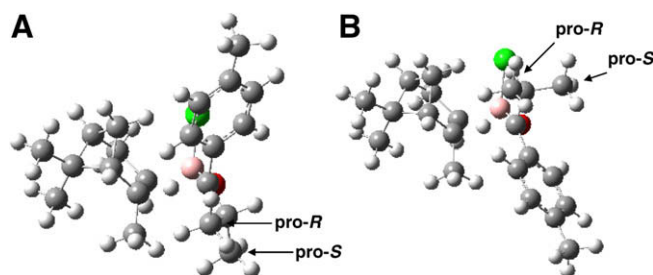
Figure 3. Computed transition structures [B3LYP/6-31G(d)] for the (A) favored Re attack and (B) disfavored Si attack of (−)-DIP-Cl. One isopinocampheyl group has been eliminated for clarity.

ceeds cleanly and with very high selectivity (>99% ee). Likewise, stock ketone was also desymmetrized using the CBS reduction. Reduction using (S)-Me–CBS and BH$_3$–THF was used for desymmetrization in preference to the DIP-Cl reduction because it is more easily worked up and resulting products are more easily purified. The resonances of the pro-R and pro-S methyl groups were assigned using NMR predictions using the CSGT[14] methodology and the IGAIM[15] variation upon a fully optimized B3LYP/6-31G(d) model of the anticipated R enantiomer of the benzylic alcohol product.

Among the results shown in Figure 2, the KIEs at the carbonyl and prochiral methyl groups lend insight into the determinants of reactivity and selectivity in the DIP-Cl reduction. First, the KIE upon the carbonyl carbon will be discussed. The experimentally determined KIE measurements at the carbonyl have an average value of 1.030. This measurement is in accordance with what might be expected in a reaction where the carbonyl carbon experiences a net reduction in bond order. The net reduction of bond order at the transition state is reflective of an early transition state where the bond order of the nascent C–H bond does not compensate for the reduction of bond order in the carbonyl.

We utilized two commonly used barrier shapes to compute a one-dimensional tunnel correction: the truncated parabolic barrier[16] and the Eckart barrier.[17] Estimations of the free energy of reaction were accomplished using empirical estimates of the rate constant for this reaction (see Supplementary data). This value was used to compute the barrier heights for the truncated parabola and Eckart barriers. The concave downward curvature of the barriers was computed using the reduced mass and frequency for the imaginary frequency associated with the unstable mode in the computed transition structure. Typically, inclusion of the effects of tunneling upon the computed KIE results in greater agreement between measured and computed values. Here, the opposite is observed.[18] While tunneling can reasonably be expected to contribute to the KIE in this reaction, given the substantial imaginary frequency of 776i cm^{-1}, the overestimation of tunneling suggests two possible reasons for disagreements between experimental and computed estimates of the KIE at the carbonyl position. One possibility is that the basis set employed does not provide enough coverage upon and near the transferred hydride, which could artificially inflate the imaginary frequency. Artificial inflation of the imaginary frequency would result in spurious overestimations of the effect of tunneling upon the KIE. Another possibility is that the first order saddle point upon the potential energy surface is not an appropriate representation of the transition state. The inherently quantum nature of hydride transfer may distort the position and orientation of the dividing surface that separates the reactant and product portions of the potential energy surface.[19] This effect has been noted recently in various gas phase reactions that involve simultaneous and substantial hydrogenic and heavy atom motion.[20]

Figure 2. (A) Experimental ^{13}C KIEs (k_{12C}/k_{13C}) for the (−)-DIP-Cl reduction of 4′-methylphenyl isopropyl ketone. (B) Computed KIEs based on the [B3LYP/6-31G(d)] transition structure for Re attack.

Measurements of the KIEs at the prochiral methyl groups that reside upon the reactant ketone suggest that non-bonding interactions in the transition states of asymmetric reactions are more complex than simple steric repulsion. The pro-*R* methyl group on the isopropyl moiety displays an isotope effect that is greater than unity. It is puzzling that a KIE that might reasonably be expected to arise from steric interaction would be greater than unity. In fact, non-bonding interactions, in general, are more complicated. Both attractive and repulsive forces are present in non-bonding interactions. It is somewhat reassuring that the ^{13}C KIEs measured here correspond with ^{2}H KIEs measured upon the enantiotopic methyl groups. In an earlier report, we measured an average ^{2}H KIE upon the pro-*S* group as 0.972. The average of ^{2}H KIE values measured for the pro-*R* group was 0.990.[12] As in the ^{2}H KIEs, the smaller ^{13}C KIE is observed at the pro-*S* position. This similar trend suggests that repulsive forces are stronger for the pro-*S* position. However, it appears from the measured ^{13}C KIEs presented here, that more than conventional steric repulsion is operative.

Secondary KIEs, especially those which are essentially decoupled from the reaction coordinate, are largely indicators in frequency shifts in going from the reactant to the transition state. Several studies have been performed upon the IR[21,22] and Raman[23,24] frequency shifts that occur with applied pressure in ground state molecules. Nearly universally, C–H bonds become red-shifted as pressure is applied until sufficient pressure develops such that repulsive forces override attractive intermolecular forces. Although examples of frequency shifts in C–C single bond stretches are fewer in number, the associated frequency is blue-shifted upon the application of pressure.[23,24] Contrarily, heavy atom bonds with significant dipoles, such as the C–F bond in $CFCl_3$, the C=C bond in CH_2CCl_2, and the C≡N bond in CH_3CN are red-shifted over a significant portion of the pressure range explored.[21,22] Furthermore, some triple- and double-bonded C–C stretches experience red-shifts upon the application of pressure.[21,22] Infrared and Raman spectra of ground state molecules under pressure are perhaps not perfectly suited to comparisons with transition states experiencing steric occlusion. However, the same inter- and intramolecular forces are present and can be expected to play a role in determining changes in vibrational frequencies. The data mentioned above suggest that dipolar and polarizable bonds can experience reductions in frequency upon close contact with a polarizable solvent. Perhaps a similar situation prevails at the transition state. An increase in polarizability is expected to be a general feature of transition states. In reactions like the DIP-Cl reduction of ketones, the creation of partial charges and resulting dipoles can be expected. The difficulty arises in explaining the simultaneous inverse ^{2}H KIEs that occur at both prochiral methyl groups and the normal ^{13}C KIE that occurs at the pro-*R* methyl group. At least three scenarios are possible: First, dispersion forces attenuate as the inverse sixth power of the separation distance, while repulsive forces are well modeled by inverse twelfth power interactions. It is possible that dispersion forces act upon the entire methyl group but the repulsive interactions only extend to the hydrogen atoms on the methyl. However, repulsive forces upon the hydrogen atoms should translate into inverse ^{13}C KIEs, if the predominant effect of steric interaction is upon the C–H(D) stretch. A second possibility is that steric interactions affect the vibrational manifolds of methyl groups largely via blue shifts in asymmetric bending and stretching motions that include little motion of the carbon atom. Finally, it may be that the C–CH_3 bond is red-shifted as the result of inductive effects arising from charge and dipolar localization at the reaction center. This scenario might be likely to affect the carbon atom more due to the relative proximity of the methyl carbon to the carbonyl undergoing reduction.

In computing transition structures for both the favored Re attack and disfavored Si attack of (−)-DIP-Cl upon 4′-methylphenyl

Table 1
Key lengths and angles in the TS for Re and Si attack

Structural element	Re attack (preferred)	Si attack (disfavored)
C(=O)···H	1.3412 Å	1.2979 Å
C=O	1.3245 Å	1.3375 Å
C_{Ipc}···H	1.3663 Å	1.3969 Å
B–O	1.4782 Å	1.4672 Å
C_{Ipc}···B	1.7719 Å	1.7736 Å
∠R_S–C(=O)–R_L	111.89°	116.92°
$v^{\neq}$	776i	659i

isopropyl ketone, key structural elements (Table 1) suggest the origins of stereoselection in this system. These quantitative estimates agree in essence with the qualitative transition structures shown in Figure 1. Not surprisingly, the transition structure for Si attack is later, with greater transfer of the hydride to the carbonyl. A surprising structural characteristic is the advanced distortion of the bond angle at the formerly sp^2 carbonyl carbon. The transition structure for favored Re attack shows significant distortion of this angle toward what might be expected in the product alcohol. The modest disagreement between computed and measured KIE values at the carbonyl may be, in part, due to the exaggerated deformation of the carbonyl. Another interesting, although expected observation is the attenuated magnitude of the imaginary frequency for disfavored Si attack. The closer approach between the acceptor (C=O) and donor (C_{Ipc}) carbons implies a more adiabatic transfer, leading to an attenuated negative force constant. In fact, the computed transition structures show an attenuated negative force constant for Si attack relative to that computed for favored Re attack. Ultimately, the simplest explanation for this difference in transition structures can be attributed to the greater steric repulsion between the aromatic group on the ketone and the proximal methyl upon the isopinocampheyl group from which the hydride transfers. A greater degree of bond formation is necessary to compensate for the increased steric repulsion.

In conclusion, we have measured ^{13}C KIEs for the (−)-DIP-Cl reduction of 4′-methylphenyl isopropyl ketone and computed a model transition structure that yields insights into the process of stereoselection in this reaction. We have also presented an isotope effect methodology by which ^{13}C KIEs may be measured for each individual enantiotopic group in reactions where symmetry breaking makes the groups inequivalent. Finally, the results of our experimental and computational work have suggested that, in addition to steric repulsion, other non-bonding interactions such as dispersion forces and inductive interactions may be important in mediating stereoselection.

Acknowledgments

Supplementary data

Supplementary data (experimental procedures, NMR integration results, computational procedures, and energies and geometries of all calculated structures) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.03.216.

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