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Conformational Analysis and the Transition State in Asymmetric Reductions with Boranes Based on (+)-α-Pinene. 1. Benzaldehyde Reduction with Alpine Borane and Other *B*-Alkyl-9-borabicyclo[3.3.1]nonanes. A Semiempirical Study

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The results from this study show that, contrary to the accepted mechanism, *the reaction of benzaldehyde-1-d with B-Ipc-9-BBN involves a different conformation of the reagent and it does not proceed, as previously assumed, through a boat-like transition state.* The overall reactivity of the *B*-alkyl-9-BBN reagents is determined by the ability of the boron center to undergo efficient coordination expansion during the formation of the charge-dipole complex with benzaldehyde. The exclusive preference toward the (S)-benzyl-*1-d* alcohol in the reduction of benzaldehyde-*1-d* with *B*-Ipc-9-BBN is governed, also at the charge-complex stage, by preferential orientation of the benzaldehyde's C−D rather than C−Ph bond against one of the prostereogenic B−CH bonds of the 9-BBN moiety that is "gauche" to the C_1−C_2 bond of the Ipc ring.

Mikhailov originally reported that various trialkylboranes can reduce aldehydes by transferring β-hydrogen to the carbonyl carbon,[1] and Midland and co-workers subsequently demonstrated that *B*-3-pinanyl-9-borabicyclo-[3.3.1]nonane (*B*-Ipc-9-BBN)—Alpine Borane—is a highly effective asymmetric reducing agent for aldehydes[2] RCHO and alkynyl ketones.[3] They proposed[2b−d,3b] that the exceptionally high enantioselectivities in aldehyde reductions with this reagent were determined in a cyclic, boat-like six-membered transition state, by the preferential syn-1,3-steric interactions between the C_2-Me group of the Ipc ring and the aldehyde's C−H rather than C−R bond (Figure 1).

Transition-state models with this model's principal features have been evoked to explain asymmetric reductions of other carbonyl compounds[3b−d] with Alpine Borane as well as with different chiral boranes.[3d,4] However, there are some exceptions to the basic model.[4d,5]

Here, we report the results of reinvestigation of the asymmetric reduction of benzaldehyde-*1-d* with *B*-Ipc-9-BBN using readily available semiempirical methods[6a−h] and introduce a different explanation for the observed high enantioselectivity. In the subsequent papers of this series we will present similar studies of other asymmetric reductions with Alpine Borane and chloroborane reagents *B*-R-IpcBCl, including DIP-Chloride, and we will address those experiments inconsistent with the original transition-state model.

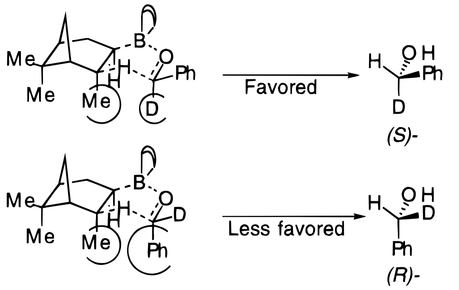

Figure 1. Proposed transition-state model for the asymmetric reduction of benzaldehyde-*1-d* with Alpine Borane. High enantioselectivity is determined by preferential 1,3-syn axial interactions in a *boat transition state* between the C_2-Me groups and substituents attached to the carbonyl carbon.

Computational Details

Semiempirical studies were carried out using the AM1[6] method as implemented by CAChe[7a] release 94 of MOPAC,[7b] version 6, on the CAChe worksystem.[7a]

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(1) Mikhailov, B. M.; Bubnov, Yu. N.; Kiselev, V. G. *J. Gen. Chem. USSR (Engl. Trans.)* **1966**, *36*, 65.

(2) (a) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1977**, *99*, 5211. (b) Midland, M. M.; Greer, S.; Tramontano, A.; Zderic, S. A. *J. Am. Chem. Soc.* **1979**, *101*, 2352. (c) Midland, M. M.; Zderic, S. A. *J. Am. Chem. Soc.* **1982**, *104*, 525. (d) Midland, M. M.; Tramontano, A.; Zderic, S. A. *J. Organomet. Chem.* **1978**, *156*, 203.

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(4) (a) For a recent review, see: Brown, H. C.; Ramachandran, P. V. *Acc. Chem. Res.* **1992**, *25*, 16 and references therein. (b) Brown, H. C.; Chandrasekharan, J.; Ramachandran, P. V. *J. Am. Chem. Soc.* **1988**, *110*, 1539. (c) Brown, H. C.; Srebnik, M.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 1577. (d) Brown, H. C.; Ramachandran, P. V. *J. Org. Chem.* **1989**, *54*, 4504. (e) Brown, H. C.; Ramachandran, P. V.; Teodorovic, A. V.; Swaminatham, S. *Tetrahedron Lett.* **1991**, *32*, 6691.

(5) (a) Ramachandran, P. V.; Teodorovic, A. V.; Rangaishenvi, M. V.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 2379. (b) Ramachandran, P. V.; Teodorovic, A. V.; Brown, H. C. *Tetrahedron* **1993**, *49*, 1725.

(6) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902. Liotta[6a] used the MNDO method to similarly evaluate enantioselectivity in oxazaborolidine-catalyzed reductions of ketones, and Houk et al. in their earlier work investigated stereoselectivities of various hydroborating reagents[6b−e] and in a more recent one[6f−h] investigated stereoselectivities of the reductions of ketones and conformational analysis of chiral alkenes and oxonium ions using ab initio calculations; they developed an improved MM2 force field which qualitatively reproduces observed stereoselectivities: (a) Jones, D. K.; Liotta, D. C.; Shinkai, I.; Mathre, D. J. *J. Org. Chem.* **1993**, *58*, 799. (b) Houk, K. N.; Rondan, N. G.; Wu, Y. D.; Metz, J. T.; Paddon-Row, M. N. *Tetrahedron* **1984**, *40*, 2257. (c) Houk, K. N.; Paddon-Row, M. N.; Rondan, N. G.; Wu, Y. D.; Brown, F. K.; Spellmeyer, D. C.; Metz, J. T.; Li, Y.; Loncharich, R. J. *Science* **1986**, *231*, 1108. (d) Masamune, S.; Kennedy, R. M.; Petersen, J. S.; Houk, K. N.; Wu, Y. D. *J. Am. Chem. Soc.* **1986**, *108*, 1986. (e) Eksterowez, J. E.; Houk, K. N. *Chem. Rev.* **1993**, *93*, 2439. (f) Wu, Y.-D.; Houk, K. N.; Florez, J.; Trost, B. M. *J. Org. Chem.* **1991**, *56*, 3656. (g) Wu, Y.-D.; Tucker, J. A.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5018. (h) Broeker, J. L.; Hoffmann, R. W.; Houk, K. N. *J. Am. Chem. Soc.* **1991**, *113*, 5006.

0022-3263/96/1961-1341$12.00/0

The molecular geometries of the reactants were generated using CAChe Molecular Editor[7a] and then fully optimized in MOPAC using eigenvector following.[8] The two-dimensional map of the rotational barriers about the B−Ipc bond was generated by optimizing individual geometries resulting from the two-degree dihedral angle changes.[9] Thermodynamic quantities for the reactions were obtained from the calculated heats of formation of the corresponding reactants and products.

Transition-state geometries and the energies of activation were obtained using the SADDLE calculation.[10] The reactants and products geometries, which are on the opposite sides of the transition states along the reaction coordinate, were first optimized. Initial transition-state geometry candidates were then generated by manually "docking" the reducing agent and benzaldehyde molecules in CAChe Visualizer until their frontier orbitals just begin to overlap without steric interactions. After visual inspection of the calculated transition-state geometry, the structure was further refined by minimizing gradient using eigenvector following. For each transition state, a vibrational spectrum calculation was carried out to verify that it had only one large negative frequency level and that this frequency was associated with the expected reaction coordinate.[11] Subsequent MOPAC Intrinsic Reaction Coordinate calculations[12] provided reaction coordinate maps connecting transition state with the precursor structures (reaction intermediates), as well as with the reaction products. Individual structures along the reaction coordinates and the corresponding potential energies were visualized and inspected using CAChe Visualizer module.

Results and Discussion

Stereochemical and Mechanistic Considerations. The *B*-Ipc-9-BBN is a chiral molecule with a prostereogenic boron center. By analogy to bicyclo[3.3.1]nonane,[13] the 9-BBN part of the molecule exists as a double chair structure, and the freely rotating chiral *B*-Ipc group can assume six unique conformations relative to the C−B−C moiety of the 9-BBN. Figure 2 shows schematically three of these six conformations together with their calculated heats of formation as a function of the R−B−C_1−H dihedral angle of the B−Ipc bond.[9] Since in the reaction with aldehydes the hydrogen required for the reduction —*β*-hydrogen—comes exclusively from the C_2-carbon of the Ipc ring,[14] the aldehyde must approach the boron center of the reagent with its carbonyl carbon syn to the C_2-carbon. Only conformations **A** and **B** (see Figure 2) satisfy this requirement and need to be considered.[15,16] Their calculated structures are displayed together with the calculated structures of the reaction intermediates and transition states in Figures 3 and 4.[17]

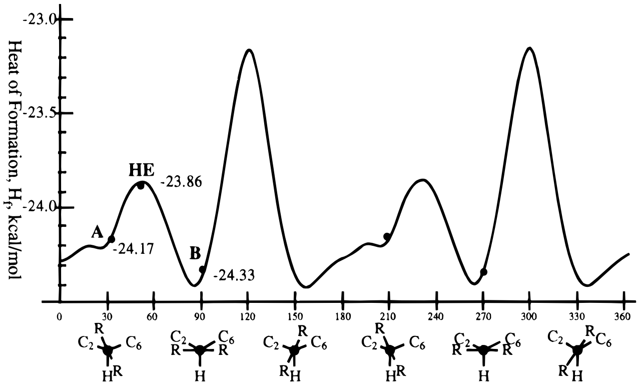

Figure 2. Calculated barriers for the rotation of the Ipc group about the B−Ipc bond in the *B*-Ipc-9-BBN molecule. The individual points **A** and **B** on the curve identify two reacting conformations (see text) and their heats of formation. The **HE** is the highest energy conformation (barrier for the rotation) on the lowest energy pathway between conformations **A** and **B**.

Scheme 1 shows four possible pathways for the reaction of benzaldehyde-*1-d* with these two conformations.[18a] To react with **A**, the benzaldehyde-*1-d* must approach the boron face from the C_2-side of the Ipc ring, opposite to the C_1−C_6 bond (e, for "equatorial approach"). To react with **B**, benzaldehyde-*1-d* must approach from the top side of the Ipc ring, opposite to the C_1−H bond (a, for "axial approach"). Note that in the both cases, benzaldehyde-*1-d* must orient either the C−D or C−Ph bond against the prostereogenic B−CH bonds of the 9-BBN moiety that is "gauche" to the C_2-carbon of the Ipc ring, shown as the B−R bonds[18a] in the Scheme 1. This is equivalent to the formation of the *E*- and *Z*-complexes in the reaction of the aldehyde with a Lewis acid. During

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[7] (a) CAChe Scientific, Inc., Beaverton, OR. (b) Clark, T. *A Handbook of Computational Chemistry*; J. Wiley & Sons: New York, 1985.

[8] Baker, J. *J. Comput. Chem.* **1986**, *7*, 385.

[9] The two-dimensional energy maps generated by MNDO or by MM2 force field differ somewhat from the one generated by the AM1 method. However, the relative differences in energies of the calculated **A** and **B** conformers remain small.

[10] Dewar, M. J. S.; Healy, E. F.; Stewart, J. J. P. *J. Chem. Soc., Faraday Trans. 2* **1984**, *3*, 227.

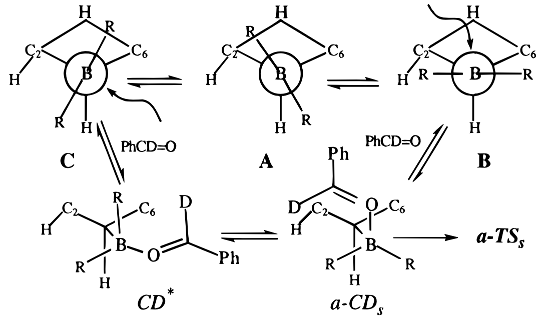
[11] McIver, J.; Komornicki, A. *J. Am. Chem. Soc.* **1972**, *94*, 2625.

[12] Dewar, M. J. S.; Kirschner, S. *J. Am. Chem. Soc.* **1971**, *93*, 4290.

[13] (a) Laszlo, I. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 251. (b) Brown, W. A. C.; Martin, J.; Sim, G. A. *J. Chem. Soc.* **1965**, 1844.

[14] Midland and co-workers documented exclusive involvement of the C_2-hydrogen from the Ipc ring in this reaction.[2b]

[15] Barriers for rotation about bonds where the sp^3 carbon is attached to an sp^2-hybridized center are generally lower then the barriers of the bonds between two sp^3-hybridized centers.[16] In other words, even if the conformation **C** is thermodynamically as favorable as **B**, the activation energy for the formation of the CD* complex would be even higher than the energy of the e-CD complex from **A** because the axial *B*-Ipc group with the sterically more demanding C_1−C_2 rather than the less demanding C_1−C_6 bond would be pointing into the 9-BBN ring. Moreover, in the CD* complex the carbonyl carbon would be away from the C_2-H; to react further, this intermediate would have to undergo a costlier rotation to the a-CD_s conformer, the same complex that is formed more efficiently directly from **B**.



[16] (a) Eliel, E. L. *Stereochemistry of Carbon Compounds*; McGraw-Hill: New York, 1962; p 149. (b) For a more recent discussion, examples, and references, see: Eliel, E. L.; Wilen, S. H. *Stereochemistry of Organic Compounds*; John Wiley & Sons; New York, 1994; Chapters 10.2 and 14.4.

[17] It is known[4b] that the solvent affects the reaction rates of the reductions with boranes and chloroboranes but has little effect on the enantioselectivity. It is therefore assumed[9] that the *relative* calculated energies in the gas phase would reasonably approximate those in solution or under neat conditions. Also, while the AM1's and MNDO's activation energies for the formation of the e-TS_r and a-TS_s were quite different, the relative energy differences within each method are similar.

[18] (a) In Scheme 1, the two prostereogeneic B−R substituents in the *B*-Ipc-9-BBN molecule are smaller in size than the Ipc substituent. The subscripts s and r describe the respective configurations of the developing chiral carbon in the CD complex and in the transition state TS. (b) Each CD complex is simply the lowest energy *bimolecular B-sp^3 structure* appearing on the reaction path between the two reactants and the transition state that follows.

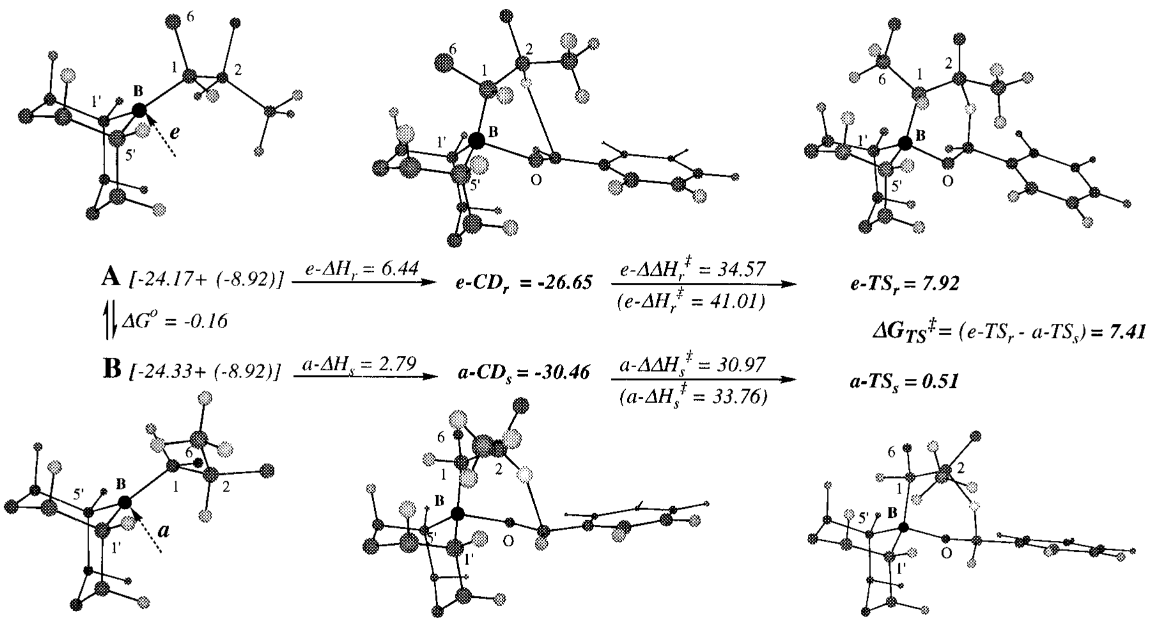
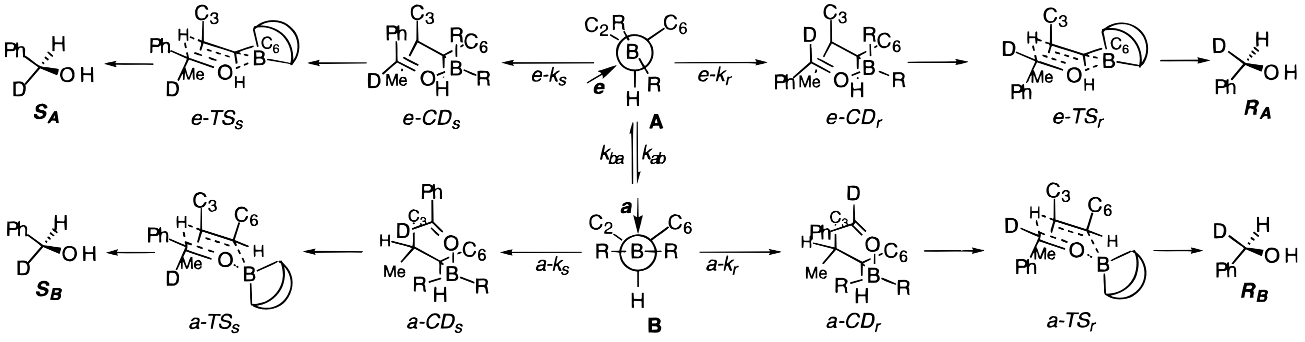


Figure 3. Stereochemical and energy changes during the charge-dipole complex formation (due to the coordination expansion at the boron center), and subsequent conversions of the e-CD_r and a-CD_s complexes to the corresponding transition states e-TS_r and a-TS_s. Calculated heats of formation of the reactants in parentheses. Only a part of the Ipc ring is shown. The other atoms are removed for clarity and only the more favorable (of the two possible) benzaldehyde-*1-d* orientation is illustrated. In the less favorable one the positions of the C−D and C−Ph bonds relative to the B−$C_{1'}$ bond would be exchanged. Note the differences in conformation of the axial B−Ipc bond in the complexes and in the transition states. Also note the "flattening" of the 9-BBN ring in the e-CD_r complex and in the e-TS_r transition state at the $C_{2'}$ and $C_{4'}$ and dihedral angles change in Table 2.

Scheme 1



the reaction, the boron center changes from B-sp^2 in the reagent into B-sp^3 in the charge-dipole complex intermediate, CD, and in the transition state, TS, that follows,[18b] and then back to the B-sp^2 in the generated borate ester. Since the boron in the *B*-Ipc-9-BBN molecule is prostereogenic but not prochiral, the generated tetragonal boron centers are not chiral.

Scheme 1 suggests that the (*S*)-benzyl-*1-d* alcohol could originate either from conformation **A** *via* cyclic transition state e-TS_s or from **B** *via* diastereomeric transition state a-TS_s. The main difference between the two geometries is that in the e-TS_s transition state the B−O bond is trans to the C_1−C_6 bond of the Ipc ring, while in the a-TS_s it is trans to the C_1−H bond of the Ipc ring.

Our results will show that the (*S*)-alcohol originates exclusively from conformation **B** *via* transition state a-TS_s.

Calculated Geometries and Energies of the Diastereomeric Pathways. The geometries of the four calculated diastereomeric transition states from Scheme 1, e-TS_r, e-TS_s and a-TS_s, a-TS_r together with their charge-dipole complex precursors e-CD_r, e-CD_s and a-CD_s, a-CD_r are shown later in Figure 4. The cyclic transition states are rather "flat" and resemble more the twisted geometries of the idealized representations of the *boat* and *chair* forms associated with the cyclohexane rings. The heats of formation and the enthalpy changes for the all four reaction paths, together with the rate constant equivalents of the calculated activation energies, are summarized in Table 1.

Scheme 2 is a simplified kinetic variant[19] of the reaction system shown in Scheme 1 and one of many related to the Curtin−Hammett principle[20a,b] and to kinetic analyses due to Winstein−Holnes[20c] and Eliel and Ro.[20d] As long as the rates of equilibration between the reacting conformers, k_{ab} and k_{ba}, are much faster than the specific rates e-k_r, e-k_s, a-k_r, and a-k_s leading to the diastereomeric transition states, the product ratio $[S]/[R]_\infty$ at the end of the reaction—where $[S] = [S_A] + [S_B]$ and $[R] = [R_A] + [R_B]$—can be determined from the familiar expressions $[S]/[R]_\infty$ = a-k_sK/e-k_r, or in terms of the

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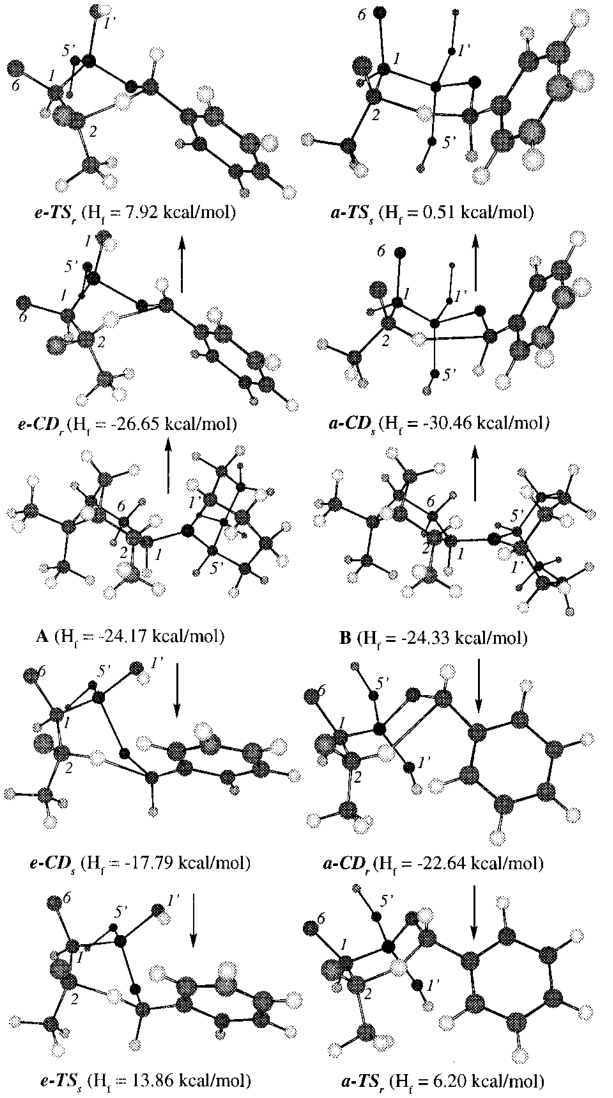
[19] (a) Zefirov, N. S.; Palyulin, V. A. *Zh. Org. Chem.* **1979**, *15*, 1098. (b) Zefirov, N. S. *Tetrahedron* **1977**, *33*, 2719.

[20] (a) Curtin, D. Y. *Rec. Chem. Prog.* **1954**, *15*, 111. (b) For extensive discussion of the conformation/reactivity relationships, the Curtin−Hammett principle, and kinetic analyses, see: Seeman, J. I. *Chem. Rev.* **1983**, *83*, 83. (c) Winstein, S.; Holness, N. J. *J. Am. Chem. Soc.* **1955**, *77*, 5562. (d) Eliel, E. L.; Ro, R. S. *Chem. Ind. (London)* **1956**, 251.

Table 1. Heats of Formation for Relevant Stationary Points and Enthalpies of Activation from Intrinsic Reaction Coordinates for Diastereomeric Reaction Pathways in the Reduction of Benzaldehyde-*1-d* with Alpine Borane in the Gas Phase at Room Temperature[a]

			heats of formation, H_f[b]				enthalpies of activation			
conformations (H_f[b])	$[B]_0/[A]_0$[d]	$x-i$[e]	reactants[f]	x-CD$_i$[g]	x-TS$_i$[h]	products[i]	x-$\Delta H_i^{\ddagger}$[j]	$(x - k_i)$[k]	x-$\Delta\Delta H_i^{\ddagger}$[l]	x-ΔH_i[m]
A (−24.17)	1.31	e-s	−33.09	−17.79	13.86	−70.49	46.95	(2.27×10^{-22})	31.65	15.30
A (−24.17)		e-r	−33.09	−26.65	7.92		41.01	(5.16×10^{-18})	34.57	6.44
B (−24.33)		a-s	−33.25	−30.46	0.51		33.76	(1.07×10^{-12})	30.97	2.79
B (−24.33)		a-r	−33.25	−22.64	6.20		39.45	(7.20×10^{-17})	28.84	10.61

[a] See text for the discussion and explanation. [b] Heats of formation are calculated values from the corresponding optimized geometries; heat of formation of benzaldehyde was −8.92 kcal/mol. [c] Enthalpies of activation for the formation of the charge-dipole complexes and transition states based on the heats of formation of the reactants (see f below). [d] The equilibrium constant between the two conformations at zero time, calculated from H_B-H_A. [e] Indices describing either the equatorial (e) or axial (a) direction of the benzaldehyde-*1-d* approach to the boron center relative to the Ipc ring; the s or r index identifies configuration of the carbonyl carbon in the CD complex and in the subsequent transition state TS. [f] Combined heats of formation of the reacting conformation and benzaldehyde. [g] Charge-dipole complex, e.g., e-CD$_r$, identifies the complex resulting from the equatorial approach and leading to the transition state for the formation of the (*R*)-deuterated benzyl alcohol. [h] A transition state, e.g., e-TS$_r$ formed from the e-CD$_r$ complex and leading to the (*R*)-alcohol. [i] Combined heats of formation of the products generated in the reaction, in this case the H_f of *B*-PhCH$_2$O-9-BBN and α-pinene. [j] The difference in enthalpies of formation of the reactants and the transition state in kcal/mol. [k] Rate constants in s^{-1} based on the enthalpy of activation (e.g., a-k) = $\kappa(kT/h)e^{-(\alpha-\Delta H_s^{\ddagger}/RT)}$ where κ is the transmission coefficient, assumed to be 1, and *k* and *h* are the Boltzman and Planck's constants. [l] Activation enthalpies for the formation of transition state from the CD complex. [m] Activation enthalpies for the formation of the CD complexes from the reacting conformation and benzaldehyde, assumed to be at least as high as the corresponding enthalpy of formation.



e-TS$_r$ (H_f = 7.92 kcal/mol) *a-TS$_s$* (H_f = 0.51 kcal/mol)

e-CD$_r$ (H_f = -26.65 kcal/mol) *a-CD$_s$* (H_f = -30.46 kcal/mol)

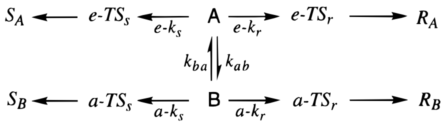
A (H_f = -24.17 kcal/mol) **B** (H_f = -24.33 kcal/mol)

e-CD$_s$ (H_f = -17.79 kcal/mol) *a-CD$_r$* (H_f = -22.64 kcal/mol)

e-TS$_s$ (H_f = 13.86 kcal/mol) *a-TS$_r$* (H_f = 6.20 kcal/mol)

Figure 4. Calculated geometries and heats of formation, H_f, of the conformations **A** and **B** and the respective charge-dipole complexes, CD, and transition states, TS, in the reaction of *B*-Ipc-9-BBN with benzaldehyde-*1-d*. Only C_1 and C_2 of the Ipc ring (with attached substituents) and $C_{1'}$ and $C_{5'}$ of the 9-BBN ring (with their hydrogen substituents) are shown. The remaining atoms have been removed to make the critical details more comprehensible.

Scheme 2



activation energies, $[S]/[R]_\infty = e^{-\Delta G_{TS}^{\ddagger}/RT}$. Here, $\Delta G_{TS}^{\ddagger}$ is the difference between the activation energies for the formation of the more stable transition states, a-TS$_s$ and e-TS$_r$, from the two reacting conformations.[19,21]

From Table 1 and Figure 2, the conformations **A** and **B** of *B*-Ipc-9-BBN molecule are separated from each other at room temperature by about 0.16 kcal/mol, corresponding to the equilibrium constant $K = 1.31$ in favor of the **B** conformer, or to the equilibrating rate constants k_{ab} and k_{ba} of 3.67×10^{12} and 2.81×10^{12}, respectively.

Since the rates of equilibration k_{ab}, k_{ba} were by many orders of magnitude greater than any of the four individual rate constants for formation of transition states[20b] (Table 1), it follows that more than 99.99% of the (*S*)-benzyl-*1-d* alcohol in this reduction comes from a-TS$_s$ and therefore from the **B** conformation, rather than from the boat-like transition state e-TS$_s$ and the conformation **A**, as the earlier transition state model predicts (see Figure 1 and Scheme 1).

Why Is Conformation B So Much More Reactive Than Conformation A? It can be easily seen that coordination expansion at the boron center in the *B*-Ipc-9-BBN molecule is equivalent to the introduction of two new axial groups in the two chair rings (Figure 3; for the extent of pyramidalization at the boron center in the CD complexes and TS transition states, see Table 2).

When benzaldehyde-*1-d* reacts with the **A** conformation (only the more preferred of the two possible aldehyde's orientation relative to **A** is shown), the newly created B−O bond will be in the *axial position* relative to the one chair and in the *equatorial*, relative to the other chair. Concurrently, the *B*-Ipc group is forced to the *axial position* relative to the one chair and *equatorial*, relative to the other. The unfavorable conformational energy resulting from the introduction of the two new axial groups should be close to the combined conforma-

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(21) Hutchins, R. O. *J. Org. Chem.* **1977**, *42*, 920.

Table 2. Selected Dihedral Angles, Bond Angles, and Atom Distances for the CD Complexes and Transition States TS from Conformations A and B[a]

	structure[b]					
	A	e-CD_r	e-TS_r	**B**	a-CD_s	a-TS_s
C_6-C_1-C_2-C_3[c]	4	1	−13	9	8	−2
H-C_2-C_1-B[c]	12	15	17	24	25	25
$C_{1'}$-B-C_1-X(Y)[c,d]	96(X)	67(X)	36(X)	−90(Y)	−61(Y)	−46(Y)
$C_{5'}$-B-C_1-C_6[c]	−83	−75	−89	−30	−38	−37
C_2-C_1-B-O[c]		49	25		−65	−54
C_1-B-O[e]		97	102		99	102
(θ_{B-C})[f]	0	27	43	0	34	48
(θ_{B-O})[f]		70	59		65	54
$C_{2'}$-*H*:Z(W)[g]	2.67(Z)	1.93(Z)	1.81(Z)	3.20(W)	2.36(W)	2.29(W)
$C_{4'}$-*H*:Z(W)[g]	2.50(Z)	2.11(Z)	2.41(Z)	3.14(W)	2.21(W)	2.02(W)

[a] Dihedral angles and bond angles in degrees, atom distances in angstroms. [b] From calculated structures, see Figure 4 for atom numbering. [c] Dihedral angles. [d] X stands for C_6 and **Y** for C_1-H. [e] Bond angle. [f] Extent of pyramidalization at the boron center defined as the angles of the $B-C_1$ and B−O bonds relative to the original B-sp^2 plane, (θ_{B-C}) and (θ_{B-O}), respectively. [g] Atom distances between underlined atoms; the Z stands for C_6-*H* and **W** for C_1-*H*.

tional energies[22] of an axial *tert*-alkyl group (*t*-Bu, ~4.9 kcal/mol)[23a] and an axial alkyl ether group (OMe, 0.55−0.75 kcal/mol),[23b] or approximately 5.45−5.65 kcal/mol. In addition, the portion of the activation energy for placing the C−D bond against the $B-C_{1'}-H$ bond could amount to ~0.8 kcal/mol.[24] On this basis, the activation energy e-ΔH_r for formation of the e-CD_r complex (or for the B-sp^2 to B-sp^3 coordination expansion)[25] from the conformation **A** should be about 6.25−6.45 kcal/mol, and the calculated activation energy e-ΔH_r agrees almost exactly (see Figure 3).

Consider now the reaction with the **B** conformation. In this case, the unfavorable conformational energy resulting from the introduction of the two new axial groups should be close to the combined conformational energies of an axial secondary alkyl group ($CHMe_2$), ~1.52 kcal/mol)[23c] and an axial alkyl ether group (OMe, 0.55 kcal/mol),[23b] or approximately 2.0−2.1 kcal/mol. The portion of the activation energy for placing the C−D bond against $B-C_{1'}-H$ bond should be approximately the same as in the e-CD_r case or ~0.8 kcal/mol.[24] Thus, the activation energy a-ΔH_s for formation of the a-CD_s complex from the conformation **B** should be about 2.8−2.9 kcal/mol, and the calculated activation energy a-ΔH_s agrees almost exactly with this value (see Figure 3).

Clearly, as far as the coordination expansion is concerned, the reaction of benzaldehyde with conformation **B** of the *B*-Ipc-9-BBN is at least 3.6 kcal/mol more favorable than with the conformation **A**.

Transition-State Geometry. The higher reactivity of the **B** conformation is even more evident when the overall activation energies e-$\Delta H_r^‡$ and a-$\Delta H_s^‡$ are compared: after initial formation of the e-CD_r complex, and the contributions due to the bond-making and bond-breaking processes,[26] the activation energy e-$\Delta\Delta H_r^‡$, 34.57 kcal/mol, is still be about 3.6 kcal/mol higher than the activation energy a-$\Delta\Delta H_s^‡$, 30.97 kcal/mol. The reason becomes clear when one inspects diastereomeric structures of the two CD/TS pairs in Figure 3 and the tabulated dihedral angles in Table 2. In order for the β-hydrogen on the C_2-carbon of the e-CD_r complex to come close to the carbonyl carbon, the entire Ipc ring has to rotate clockwise about the Ipc−B bond. This can happen only at the expense of the steric interactions between the C_6-H and the $C_{2'}-H$ bond of the 9-BBN ring (see e-TS_r structure in Figure 3 and corresponding dihedral angles and atom distances in Table 2). It can be argued that while the clockwise rotation increases steric interaction between C_1 and B by decreasing the $C_{1'}-B-C_1-C_6$ dihedral angle, it also relieves steric interactions between the C_1-C_6 and $B-C_{5'}$ bonds by increasing the $C_{5'}-B-C_1-C_6$ dihedral angle (from 75° to 89°, see Table 2). However, since these bonds in the e-CD_r complex are already sufficiently separated from each other, further separation should have no effect on the steric interactions between them. The "flattening" of the chair at the $C_{2'}$-carbon illustrates by how much one of the chairs had to be deformed so that the right geometry for the hydrogen transfer could be achieved.

In the a-CD_s complex, on the other hand, the Ipc ring must rotate counterclockwise about the Ipc−B bond so that the β-hydrogen can get close to the carbonyl carbon. Evidently, the geometry in the a-CD_s complex is such that only a minor $C_{5'}-B-C_1-C_6$ dihedral angle decrease in the counterclockwise direction would push the a-CD_s complex to the a-TS_s transition state. More importantly, the steric interactions between the C_1-H and the $C_{2'}$-H opposing this rotation are not as severe as interactions between C_6-H and the $C_{2'}$-H in the e-CD_r complex (compare distances between these hydrogens in Table 2).

Limitations of space prevent us from discussing the less stable pairs of the CD complexes and TS transition states. Their main features, however, show (see Figure 4) that in each pair the phenyl group had to rotate out of the sp^2 plane with the carbonyl group to avoid severe steric interactions of one of the *ortho* hydrogens with the $C_{1'}$-H of the 9-BBN ring during formation of the CD complex. The original transition-state model predicts the e-TS_s to be the most stable transition state. *Although in the e-TS_s the smaller C−D rather than the larger C−Ph bond occupies the 1,3-syn-axial position relative to the C_2-Me group, this was, contrary to the prediction, the least stable transition state.* The changes in the $C_6-C_1-C_2-C_3$ dihedral angles in the e-CD_r, e-TS_r and a-CD_s, a-TS_s pairs (Table 2), confirms that the ease of the reaction correlates well with the ability of the Ipc group to assume

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(22) For the discussion of additivity of conformational energies, see ref 16b, Chapter 11.4.

(23) Reference 16b: (a) p 697; (b) p 696. (c) p 699. The enthalpy rather than the free energy of the *i*-Pr group is used here.

(24) The conformational relationship of the aldehyde's C−D bond and the $B-C_{1'}-H$ bond in the CD complex resemble the relationship of the two primary C−H bonds in the "gauche" conformation of butane: ref 16b, p 600.

(25) Mikhailov reported that the "reorganization energy" for the conversion of boron from trigonal to tetragonal configuration is 6−10 kcal/mol: Mikhailov, B. M.; Baryshnikova, T. K.; Shashov, A. S. *J. Organomet. Chem.* **1981**, *219*, 301.

(26) The bond-making and bond-breaking contributions to the overall activation energy should be the same in both reaction pathways.

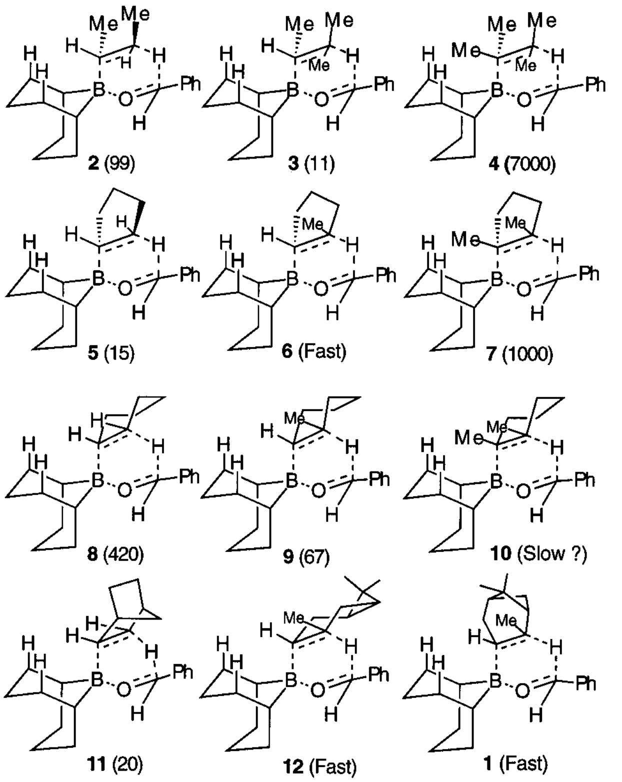
2 (99)
3 (11)
4 (7000)
5 (15)
6 (Fast)
7 (1000)
8 (420)
9 (67)
10 (Slow ?)
11 (20)
12 (Fast)
1 (Fast)

Figure 5. Schematic representation of the transition states for the reduction of benzaldehyde with *B*-alkyl-9-BBN reagents **1**−**12**. The rates of reductions are from the kinetic studies reported in ref 2c and 2d and are given in parentheses as required time, in min, for the 50% reaction completion.

an optimized geometry for the hydrogen transfer in which the $C_6-C_1-C_2-C_3$ dihedral angle approaches an eclipsed arrangement (see below).

Reductions with Other B-Alkyl-9-BBN Reagents. The kinetic study of the benzaldehyde reduction with a series of B-alkyl-9-BBN reagents (Figure 5, **2**−**12**) led to the conclusion that the reactivity of the borane is determined by the ability of the B−C−C−H group to form a syn coplanar arrangement.[2c,d] For example, *B*-cyclopentyl-, **5**, and *B*-*trans*-2-methylcyclopentyl-9-BBN, **6**, react very readily with benzaldehyde, while on the other hand, *B*-cyclohexyl-, **8**, and *B*-*trans*-2-methylcyclohexyl-9-BBN, **9**, react very slowly.[2c] It was concluded that the cyclohexyl reagents **8** and **9** were slower since to achieve the syn coplanar B-C-C-H arrangement the *B*-cyclohexyl group had to assume a boat cyclohexane conformation. When the boat conformation is more favorable, as in the case of *B*-4-isocaranyl-, **12**, and *B*-*exo*-norbornyl-9-BBN, **11**, the reductions were very rapid. The syn coplanar B−C−C−H arrangement is believed to be important because it presumably allows a maximum overlap of the developing π-system of the displaced olefin.[2c,d]

The above results with *B*-Ipc-9-BBN, however, clearly show higher reactivity of the **B** conformer and suggest that in other *B*-alkyl-9-BBN derivatives **2**−**12** the analogous conformations will also be more reactive (Figure 5). All transition-state geometries **2**−**12** correspond to the a-TS_s transition state from *B*-Ipc-9-BBN (shown in Figure 5 as **1**). This means that all reagents **1**−**12** react preferentially with their **B** conformations and that benzaldehyde approached the boron center from the *a-direction*, opposite to the C_1−H bond of the corresponding alkyl group, except in **4**, **7**, and **10**, where the approach was from the side opposite to the C_1-Me group. The low reactivities of **4**, **7**, and presumably **10**, relative to the less substituted analogues from the same group, are clearly the consequence of the higher activation energies required to push the *B*−*tert*-C bond to the axial position relative to the 9-BBN chair during the formation of the respective CD complexes. The facts that **5** is faster than **8** and **6** and **12** were faster than **9** illustrate again the importance of the ability of the *B*-alkyl group to assume an optimized geometry in which the dihedral angle of the four carbon atoms that will provide the π-system in the displaced olefin is approaching an eclipsed arrangement. When the conformation of the ring opposes this requirement (e.g., **8** *vs* **5** and **9** *vs* **6** and **12**), the reaction is slower.

Conclusions

The results from this study show that, contrary to the accepted mechanism, the reaction of benzaldehyde-*1-d* with *B*-Ipc-9-BBN *involves a different conformation of the reagent and it does not proceed, as previously assumed, through a boat-like transition state.* The overall reactivity of the *B*-alkyl-9-BBN reagents is determined by the ability of the boron center to undergo efficient coordination expansion during the formation of the charge-dipole complex with benzaldhyde. The exclusive preference toward the (*S*)-benzyl-*1-d* alcohol is determined, also at this stage of reaction, by preferential orientation of the benzaldehyde's C−D rather than C−Ph bond against one of the prostereogenic B−CH bonds of the 9-BBN moiety that is "gauche" to the C_1-C_2 bond of the Ipc ring.

Evidently, in the reaction with **B** conformation of the *B*-Ipc-9-BBN molecule, the Ipc group in the resulting a-CD_s complex could easily rotate about the B−Ipc bond to provide the required geometry for the subsequent transfer of the β-hydrogen to the carbonyl carbon. With **A**, for steric reasons, formation of the e-CD_r complex requires higher activation energy, and moreover, the needed rotation of the Ipc group in the complex is severely restricted by the rigid geometry of the 9-BBN rings. The combined activation energies for these two early processes favor the **B** (see Figures 3 and 4) and are responsible for the observed exclusive formation of the (*S*)-benzyl-*1-d* alcohol.

The previous transition-state model for this reaction also predicted the formation of the (*S*)-alcohol. Consequently, the significance of the new model must be viewed from a broader perspective: the new model provides a rational explanation for different reactivities of the two reacting conformations of the *B*-Ipc-9-BBN reagent and further refines interpretation of the kinetic results with various *B*-alkyl-9-BBN. More importantly, as subsequent articles from this series will show, the model provides a general, unifying, framework for understanding other puzzling results from asymmetric reductions with DIP-Chloride and with different *B*-alkyl-IpcBCl reagents based on α-pinene.

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