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Communications

Origins of the Enantioselectivity Observed in Oxazaborolidine-Catalyzed Reductions of Ketones

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Summary: An investigation into the origins of the enantioselectivity observed in oxazaborolidine-catalyzed reductions of ketones was carried out by examination of the reaction surfaces generated using the MNDO Hamiltonian.

The reports describing the enantioselective reduction of ketones using stoichiometric borane in the presence of catalytic amounts of chiral oxazaborolidines represent a significant advance in rational reagent design (Figure 1).[1] These reactions presumably occur by the following sequence: (a) complexation of borane to the ring nitrogen; (b) coordination of the ketone oxygen to the ring boron; (c) hydrogen transfer from the NBH_3^- unit to the carbonyl carbon via a six-membered cyclic transition state. The

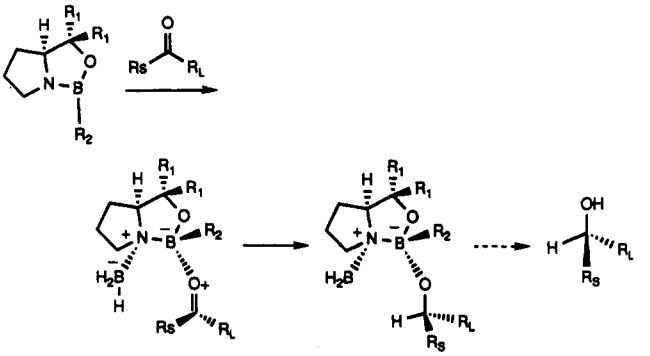

Figure 1. Proposed mechanism for the oxazaborolidine-catalyzed reduction of ketones.

enantioselectivity observed in these reactions is thought to be controlled by steric factors which apparently force the larger group (R_L) to occupy the less hindered exo face of the ring system (vide infra). Both Corey et al.[1c] and Evans[2] have suggested that these processes occur by way of a boat transition state.

Our approach to studying these reactions was to use molecular orbital methods (MOPAC)[3] to investigate the origins of the selectivity and the effects of substituent modifications (R_1 = Ph, β-Naph and R_2 = H, Me, n-Bu have been the most effective modifications, the remaining groups being ineffective). Such information should prove

(1) (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (c) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1989**, *30*, 6275. (d) Corey, E. J.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5207. (e) Corey, E. J.; Gavai, A. V. *Tetrahedron Lett.* **1988**, *29*, 3201. (f) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1990**, *31*, 601. (g) Corey, E. J.; Jardine, P.; Mohri, T. *Tetrahedron Lett.* **1988**, *29*, 6409. (h) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469. (i) Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Org. Chem.* **1984**, *49*, 555. (j) Itsuno, S.; Nakano, M.; Miyazaki, K.; Masuda, H.; Ito, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2039. (k) Itsuno, S.; Nakano, M.; Ito, K.; Hirao, A.; Owa, M.; Kanda, N.; Nakahama, S. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2615. (l) Itsuno, S.; Sakurai, Y.; Ito, K.; Hirao, A.; Nakahama, S. *Bull. Chem. Soc. Jpn.* **1987**, *60*, 395. (m) Rao, A. V. R.; Gurjar, M. K.; Sharma, P. A.; Kaiwar, V. *Tetrahedron Lett.* **1990**, *31*, 2341. (n) Jones, T. K.; Mohan, J. J.; Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T.; Turner; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763. (o) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906. (p) Corey, E. J.; Link, J. O. *Tetrahedron Lett.* **1992**, *33*, 3431.

(2) Evans, D. A. *Science* **1988**, *240*, 420.
(3) QCPE Program No. 455, Version 5.0.

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Table I. Comparison of Experimental and Calculated Results

	R_1	R_2	R_L	R_S	E_a[a] chair1	E_a boat1	E_a chair2	E_a boat2	calcd[b] % ee	exptl % ee
1	Ph	H	Ph	Me	15.78	16.78	19.32	17.06	98	97.0[c]
2	Ph	H	Ph	Et[h]	15.58	16.88	17.23	16.74	80	90.0[c]
3	Ph	H	t-Bu	Me	15.17	16.51	16.56	17.43	90	92.0[c]
4	Ph	Me	Ph	Me	14.58	16.07	16.63	16.89	93	96.5[c]
5	Ph	Me	Ph	Et[h]	12.48	13.64	14.48	14.46	94	97.6[c]
6	Ph	Me	t-Bu	Me	13.92	16.09	16.49	17.19	96	97.3[c]
7	Ph	Et	Ph	Et[h]	12.51	15.79	13.88	14.83	88[d]	95.6[e]
8	β-Naph	H	Ph	Me	17.22	18.14	18.28	19.21	94	97.8[f]
9	i-Pr	Me	Ph	Me	14.97	21.97	15.19	15.53	59[f]	poor
10	α-Naph	H	Ph	Me	17.07	17.55	17.23	17.47	58[f,g]	poor
11	o-MeOPh	H	Ph	Me	16.92	17.35	16.81	18.13	11[f,g]	poor
12	o-MeOPh	Me	Ph	Me	15.17	17.02	15.11	16.65	48[f]	poor
13	H	H	Ph	Me	16.52	17.06	16.54	17.05	2[f]	poor
14	H	Me	Ph	Me	14.21	14.68	14.39	14.79	42[f]	poor

[a] kcal/mol. [b] Half-chair E_a in all cases more than 5 kcal/mol higher in energy than lowest energy transition state. Its contribution to the final product distribution will be negligible. [c] See ref 1a and b. [d] Reaction temperature of 253 K. [e] Unpublished results. [f] Assumes a reaction temperature of 263 K. Exact experimental % ee values not given. See ref 1c. [g] The *R*-enantiomer is the major product in all examples except 10 and 11. [h] Since it is difficult to systematically search the conformational space of transition states which possess several remote rotatable bonds using semi-empirical techniques, the calculated % ee's for these entries should be considered somewhat less reliable.

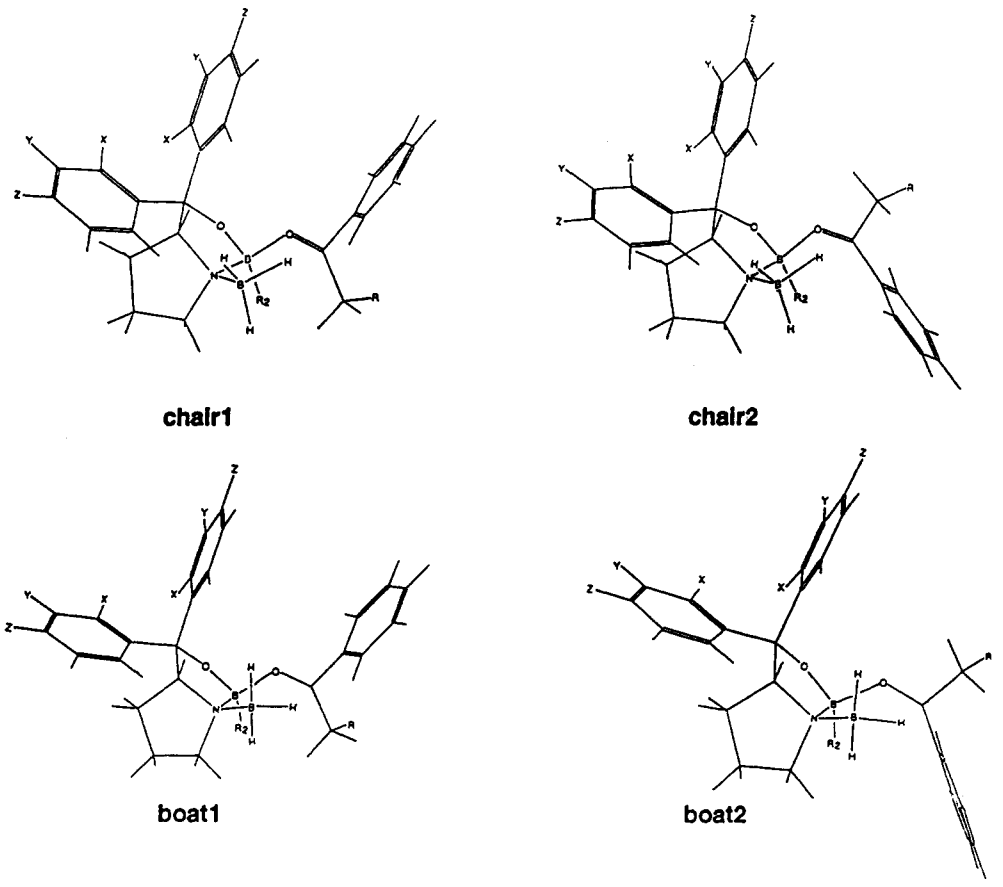

Figure 2. Diastereomeric chair and boat transition states.

valuable in the rational design of the next generation of oxazaborolidines.

Using the MNDO Hamiltonian,[4,5] the reaction surface for the hydrogen transfer was examined for a variety of oxazaborolidines (Table I). In each case the location of the transition state was verified by the presence of one negative force constant. For each set of reactants the diastereomeric chair, half-chair, and boat transition states were located and their energies compared with the starting oxazaborolidine/borane/ketone complex.

The rate constant for the reaction associated with each (located) transition state was determined by evaluating calculated partition functions in accord with transition state theory.[6] Theoretical ee's calculated using these rate constants agreed quite well with the experimental results

(4) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

(5) The excellent agreement observed between the crystal structure geometry of an oxazaborolidine/borane complex (see refs 5a and 5b) and its calculated geometry validates the use of MNDO for studying this problem. (a) Mathre, D. 203rd American Chemical Society National Meeting, San Francisco, CA, Abstract 85. (b) Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Lett.* **1992**, *33*, 3429.

(6) Rate constants calculated using $k = (RT/h)\mathrm{ex}^{(-V_o/RT)}$. (Q^*_{vib}/Q_{vib}) where R = gas constant (cal K^{-1} mol^{-1}); T = temperature (K); V_o = activation energy (cal mol^{-1}); Q^*_{vib} = transition-state vibrational partition function; Q_{vib} = ground-state vibrational partition function. Translational partition functions cancel. Since the differences in the moments of inertia among the alternative transition states were small, the contributions of rotational partition functions were assumed to be negligible compared to the vibrational partition functions.

(see Table I). In contrast to the boat transition state proposed by Corey et al.[1c] and Evans,[2] *the transition state with the lowest overall E_a in every case was a chair.*

In the lowest energy transition state for entry 1 (Table I; (chair 1, Figure 2), the phenyl group occupies the more energetically-favorable exo position (i.e., anti to R_2) because it can lie in a plane parallel to the diphenylprolinol ring at a distance of more than 5.5 Å from the angular phenyl group.[7] The next lowest energy transition state (boat 1, Figure 2) leads to the formation of the same enantiomer. Conversely, in the first diastereomeric transition state (chair 2, Figure 2), the *exo*-methyl group, due to its tetrahedral geometry, is approximately 1.5 Å closer to the phenyl group. Moreover, considerable interactions of the phenyl group with hydrogens on the endo face of the catalyst (i.e., syn to R_2) also disfavor this arrangement.

Selectivity is considerably more sensitive to the choice of the catalyst than to the nature of the ketone being reduced (e.g., entries 1 and 2, Table I). Variation of the boron substituent (entries 1 and 4; 2 and 5; and 7 and 3, Table I), has a "fine-tuning" effect on the oxazaborolidine performance. Changing from H to Me increases congestion on the endo face, amplifying interactions with one of the two ketone substituents and thereby giving greater impetus for R_L to occupy the exo face.

The nature of the prolinol substituents is the single, most important determinant of stereoselectivity. In the effective catalysts these groups are conformationally linked to provide a facial bias which greatly favors one set of diastereomeric transition states over the other. For example, the phenyl and β-naphthyl groups (Figure 2, YZ = benzo) are able to lie parallel to the R_L substituent at a distance of more than 5.5 Å. Conversely, the less effective groups (entries 9–12, Table I) all lie at approximately 1–2 Å closer with rotation causing greater interactions with R_L. While these interactions alone do not govern the observed selectivity, they nonetheless appear to parallel the total steric interactions for the various transition states. For ortho-substituted aryl derivatives, (e.g., Figure 2, X = OMe or XY = benzo) the groups suffer increased interactions with their geminal counterparts, resulting in the population of rotamers which decrease the difference in congestion between the exo and endo faces of the catalyst. For the cases when R_1 = H (entries 13 and 14, Table I), the inherent steric bias associated with the bicyclo[3.3.0] ring system is insufficient on its own to permit any significant facial differentiation. Thus, the only effective catalysts are those in which the substituents, as a consequence of a conformational synergy, amplify the facial bias which an approaching substrate encounters, thereby increasing the energy differences among the various alternative transition states.

In summary, it has been shown that the hydride transfer occurs via a chair transition state, with the oxazaborolidine and ketone substituents effects reinforcing each other, resulting in the selectivity observed.

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Supplementary Material Available: Sample calculations for evaluating the partition functions for entry 1 (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(7) All distances are measured from center to center for aryl groups, and the closest proton is the point of measurement for alkyl groups.