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A FORCE FIELD MODEL FOR BORON ENOLATES

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Summary : Empirical boron enolate parameters for incorporation in Allinger's MM2 force field (*via* MacroModel) have been derived from *ab initio* studies of model enolborane systems.

Boron enolates are useful reagents for achieving high levels of both relative and absolute stereocontrol in aldol condensations[1]. Chiral boron enolates, where a chiral auxiliary or other group is attached to the carbonyl carbon or chiral ligands are attached to the boron, have emerged as powerful tools for the asymmetric synthesis of β-hydroxycarbonyl compounds. However, the fundamental factors influencing enolization stereoselectivity and enolate π-face stereodifferentiation in these systems are still not well understood. While theoretical studies[2] have provided some insights regarding simple *syn*/*anti* diastereoselectivity in the aldol step for prochiral enolates, more exploratory work is needed before reliable predictions of new reaction sequences can be made and the rational design of new chiral reagents attempted. Unfortunately, the size of typical enolate systems incorporating chiral groups precludes the use of non-empirical theoretical methods, and parameters for empirical force fields, e.g. Allinger's MM2[3], are altogether lacking.

With the goal of providing a useful model for investigating the structures and structural biases of enolate systems, reported herein (**Table**) are a preliminary set of empirical force field parameters (*i.e.* for MM2) for boron enolates, which have been derived from *ab initio* molecular orbital calculations[4]. Values for typical equilibrium bond lengths and angles in boron enolates were formulated from the structures illustrated in **Figures 1** and **2**, bond stretching and angle bending constants were calculated from the normal mode vibrational frequencies[7], and Mulliken population analysis was used to obtain values for bond dipole moments. Values for the van der Waals radius and "hardness" of boron were not modified from those already employed in MM2. The stretch-bend cross term, as well as the improper torsion term, significant for description of 3- and 4-membered rings, has been set to zero for the purposes of these initial investigations. The torsional parameters V_1, V_2, and V_3, were obtained from a least-squares fit to the truncated Fourier expansion[9],

$$E_{\mathrm{Torsion}} = \frac{V_1}{2}(1-\cos(\Theta)) + \frac{V_2}{2}(1-\cos(2\Theta)) + \frac{V_3}{2}(1-\cos(3\Theta))$$

where the energies were obtained from partial geometry optimizations of structures (**Figures 1** and **2**) in which the torsion angle was systematically varied[10]. Inspection of the resultant geometries and parameters for structures **1-4** reveals some interesting features of boron enolates.

In contrast to previous calculations[2a,b,11], forms in which the boron moiety is S-*cis* to the olefinic carbons (**Fig. 2**) are found as transition structures for rotation about the C-O σ bond (*i.e.* each has a single imaginary normal mode); whereas forms having an orientation S-*trans* (**Fig. 1**) are generally found to be ground-state minima on the potential surface. Minima have also been located where the boron moiety is tilted out of the plane by *ca* 35° to the olefinic carbons, but these are of higher energy than the S-*trans* forms for enolates **1-3**. In the case of the acetone

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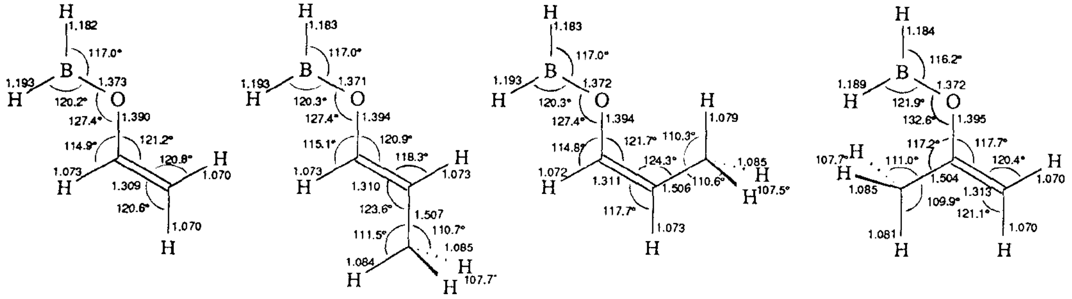
enolate, **4**, however, the S-*trans* form is distorted by the steric interference between the boron moiety and the C_1 methyl group. This results in a non-planar minimum energy structure[12,13], where the BH_2 group is 37.0° to the olefinic carbons (0.82 kcal•mol^{-1} lower in energy than **4a**). In the enolate of acetaldehyde, **1**, the barrier to rotation is 0.73 kcal•mol^{-1}, whereas substitution at C_2 with a **E** (**2**) or **Z** (**3**) methyl group increases the barrier to 1.06 and 5.38 kcal•mol^{-1}, respectively. These barriers are reflected in a V_3 term for $C_{sp^2}C_{sp^2}O_{sp^2}B$ of 1.0 kcal•mol^{-1}, with the large barrier for **3** resulting from the substantial geometric distortions of the enolate skeleton (see **Fig. 2**) imposed by the steric repulsion between the boron moiety and the allylic methyl group, rather than from any electronic consequences. The reduced barrier to rotation in the acetone enolate, **4**, is a result of the destabilization of the S-*trans* form, **4a**. It is interesting that in both **3b** and **4a**, all distortions result from angular modifications, as opposed to bond length variation, and that this would have been anticipated upon examination of the "average" normal modes of the ground-state structures presented in the **Table**.

Fig. 1: S-trans structures



E=-177.20935

1a

E=-216.03170

2a

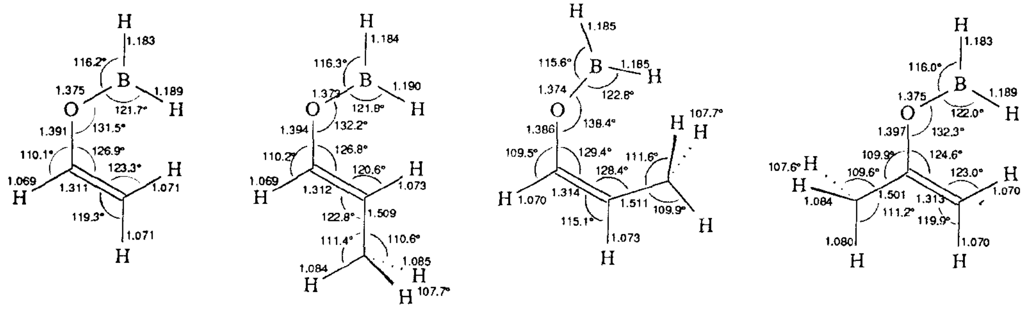
E=-216.03347

3a

E=-216.03395

4a

Fig. 2: S-cis structures



E=-177.20818

1b

E=-216.03001

2b

E=-216.02489

3b

E=-216.03480

4b

The strong preference for planar enolate structures[13] in **1**-**3** results from the conjugative delocalization of 4 π electrons over the olefinic carbons, the enol oxygen, and the coordinatively unsaturated trivalent boron, and is in accord with the large V_2 term (*cf.* ref. 9) obtained for boron enolates of 1.5 kcal•mol^{-1}. That this preference is largely independent of substitution on the olefin[12], as well as alkyl substitution on boron[14], is reflected in the invarience of the C=C, CO, and OB bond lengths, all of which should be good indicators of electronic differences in enolates. The shortened OB bond length[15] of 1.3728Å and the >110° COB bond angle are both indicative of donation of a lone pair on oxygen into the empty p-orbital on boron[16].

Table. MM2 parameters for model boron enolates derived from *ab initio* molecular orbital theory.

Quantity	Atom types		Frequency[a]	Parameter	
Bond length[b]				r_0	
	26-6	(B-O)		1.3728	
	26-5	(B-H)		1.1867	
Bond angle[c]				Θ_0	
	5-26-6	(H-B-O)		118.85	
	26-6-2	(B-O-C)		130.11	
	5-26-5	(H-B-H)		122.31	
Dipole moment[d]				μ	
	26-6	(B-O)		0.72	
	26-5	(B-H)		0.43	
Bond stretch[e]				K_S	
	26-6	(B-O)	1451 (1277)	6.2601	
	26-5	(B-H)	2774 (2441)	3.2396	
Angle bend[f]				K_B	
	5-26-6	(H-B-O)	1083 (953)	0.7290	
	26-6-2	(B-O-C)	273 (240)	0.3733	
	5-26-5	(H-B-H)	1367 (1203)	1.1572	
Torsional barrier[g]			V_1	V_2	V_3
	26-6-2-2	(B-O-C=C)	0.0	1.5	1.0
	26-6-2-1	(B-O-C-C)	-1.15	0.77	0.58
	5-26-6-2	(H-B-O-C)	0.0	10.0	0.0

(a) cm^{-1}, calculated (corrected); (b) Angstroms; (c) Degrees; (d) Debye; (e) mdyn•Å^{-1}; (f) mdyn•rad^{-2}; (g) kcal•mol^{-1}.

Finally, inclusion of the above parameter set in the MM2 force field implemented in Still's MacroModel program successfully allows boron enolates to be modeled. While the present data will permit the effects of chiral substitution on the carbon skeleton to be explored, chiral groups on boron require further parameters to be developed. An expanded parameter set which includes alkyl and alkoxy substituents on boron is being developed[14], and will be reported in due course.

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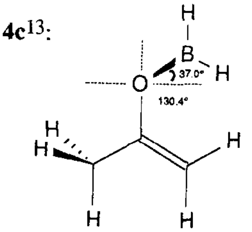
References and notes

1. For reviews, see: (a) Heathcock, C.H. in *Asymmetric Synthesis*, J.D. Morrison, ed., Academic Press, New York, Vol. 3, 1984; (b) Evans, D.A.; Nelson, J.V.; Taber, T.R. *Topics in Stereochemistry*, **1982**, *13*, 1. For chiral auxiliary methods, see: (c) Masamune, S.; Choy, W.; Kerdesky, F.A.J.; Imperiali, B. *J. Am. Chem. Soc.*, **1981**, *103*, 1566; (d) Evans, D.A.; Bartroli, J.; Shih, T.L. *ibid.*, **1981**, *103*, 2127. For methods using chiral ligands on boron, see: (e) Meyers, A.I.; Yamamoto, Y. *ibid.*, **1981**, *103*, 4278; (f) Paterson, I.; Lister, M.A.; McClure, C.K. *Tetrahedron Lett.*, **1986**, *27*, 4787; (g) Paterson, I.; McClure, C.K. *ibid.*, **1987**, *28*, 1229; (h) Masamune, S.; Sato, T.; Kim, B.M.; Wollmann, T.A. *J. Am.Chem. Soc.*, **1986**, *108*, 8279; (i) Reetz, M.T.; Kunisch, F.; Heitmann, P.*Tetrahedron Lett.*, **1986**, *27*, 4721.

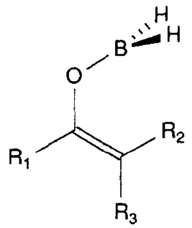
2. (a) Hoffmann, R.W.; Ditrich, K.; Froech, S.; Cremer, D. *Tetrahedron*, **1985**, *41*, 5517; (b) Gennari, C.; Todeschini, R.; Beretta, M.G.; Favina, G.; Scolastico, C. *J. Org. Chem.*, **1986**, *51*, 612. See, also: (c) Houk, K.N.; Paddon-Row, M.N. *J. Am. Chem. Soc.*, **1986**, *108*, 2659.
3. (a) Allinger, N.L. *J. Am. Chem. Soc.* **1977**, *99*, 8127; (b) Burkert, U.; Allinger, N.L. *Molecular Mechanics*, ACS Monograph 177, Washington, D.C. (1982). All molecular mechanics calculations employed the MacroModel program : Still, W.C., Columbia University, New York. We thank Professor Still for a copy of the MacroModel program.
4. All calculations were performed at the Hartree-Fock (SCF) level with the *Gaussian 82* program system[5], using the 3-21G split-valence basis set[6]. Geometries of all species were constrained to have C_s symmetry, but otherwise were fully optimized. The nature of all stationary points was characterized *via* normal mode analysis.
5. Binkley, J.S; Frisch, M.J.; DeFrees, D.J.; Raghavachari, K.; Whiteside, R.A.; Schlegel, H.B.; Fluder, E.M; Pople, J.A., Carnegie-Mellon University, Pittsburgh, PA 15213, USA.
6. Binkley, J.S.; Pople, J.A.; Hehre, W.J. *J. Am. Chem. Soc.*, **1980**, *102*, 939.
7. Calculation of force constants have utilized a harmonic force field approximation and have been scaled according to the method of Pople[8], to account for the over-estimation of vibrational frequencies by Hartree-Fock theory using a 3-21G basis set.
8. All force constants have been reduced by 12%, see: Pople, J.A.; Schlegel, H.B.; Krishnan, R.; DeFrees, D.J.; Binkley, J.S.; Frisch, M.J.; Whiteside, R.A.; Hout, R.F., Jr.; Hehre, W.J. *Int. J. Quantum Chem. : Quantum Chem. Symp.*, **1981**, *15*, 269. For an alternative scaling scheme, see: Pulay, P.; Meyer, W. *Mol. Phys.*, **1974**, *27*, 473.
9. For a description of the fitting procedure, and an interesting interpretation of the resultant terms, see: (a) Pople, J.A.; Radom, L. *Jerusalem Symp. Quantum Chem. BioChem.*, **1973**, *5*, 747; (b) Radom, L.; Hehre, W.J.; Pople, J.A. *J. Am. Chem. Soc.*, **1972**, *94*, 2371. All fits reported had a standard deviation (in energy) of 0.10 kcal•mol^{-1}. Inclusion of additional sine terms resulted in a small reduction in σ_E to 0.05 kcal•mol^{-1}.
10. The MM2 torsional parameters for $C_{sp^2}C_{sp^2}O_{sp^2}B$ and $C_{sp^3}C_{sp^2}O_{sp^2}B$ were generated by rotating the $-BH_2$ moiety around the C-O bond in thirty degree increments, allowing all bond angles which change significantly between the S-*cis* and S-*trans* forms to relax at each step. The $C_{sp^2}O_{sp^2}BH$ parameters are based on the energy differences between planar and non-planar structures, cognizant that the non-planar forms are not ground-state minima.
11. Previous work (ref. 2a,b) used MNDO calculations for geometry optimizations, however the nature of the stationary points was not reported.
12. The lowest energy structure detected for the acetone enolate is **4c**[13]:

4c

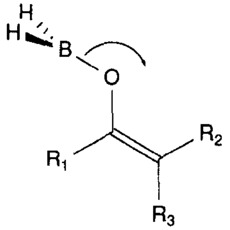


13. Non-planar forms other than **4c** were considered, but these normally relaxed without barrier to a planar form. The only exceptions involve forms such as **5a** and **5b**:

5a



5b



which are generally characterized higher-order stationary points (>1 imaginary normal mode), or transition structures of higher energy than those in **Figure 2**. A full study of boron enolates is underway[14].
14. Goodman, J.M.; Paterson, I.; Kahn, S.D., research in progress.
15. The OB bond length in salicylaldehydato-diphenylboron is 1.497Å. See : Rettig, S.J.; Trotter, J. *Can. J. Chem.*, **1976**, *54*, 1168.
16. Kahn, S.D.; Keck, G.E.; Hehre, W.J. *Tetrahedron Lett.*, **1987**, *28*, 279.

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