Tetrahedron: Asymmetry Vol. 4, No. 7, pp. 1569-1572, 1993
Printed in Great Britain.

0957-4166/93 $6.00+.00
Pergamon Press Ltd

Quantum Chemical Modeling of Chiral Catalysis. Part 11. Isomerism in Borane Adducts of Chiral Oxazaborolidines Used as Catalysts in the Enantioselective Reduction of Ketones ?

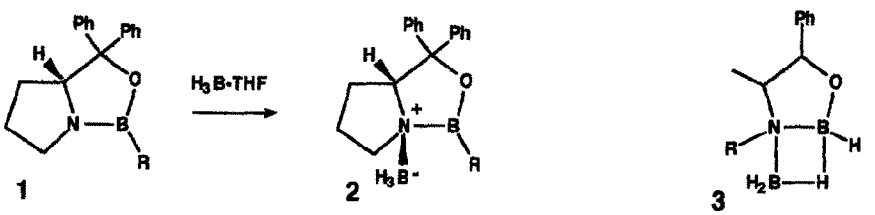
Vesa Nevalainen

Division of Organic Chemistry, P.O. Box 6, SF-00014 University of Helsinki, Finland

(*Received in UK* 19 *March* 1993; *accepted* 5 *May* 1993)

Abstract: - The relative stability of isomers of borane adducts of 1,3,2-oxazaborolidines was investigated by means of *ab initio* molecular orbital methods. One open-chain isomer was found to be more stable than the borane *N*-adduct proposed to be one of the key-intermediates of the catalytic enantioselective reduction of ketones. Borane *N*-adduct of 1,3,2-oxazaborolidine was found to be 19 kJ mol^{-1} (6-31G*//6-31G*) more stable than the corresponding *O*-adduct. Geometry of the ring oxygen of the *O*-adduct appeared out to be practically planar.

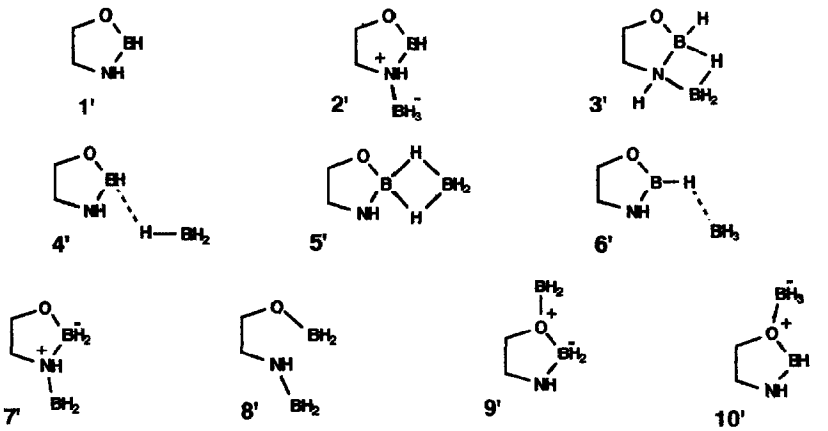
Chiral oxazaborolidines **1** are known to induce a highly enantioselective reduction of ketones when a Lewis acidic borane is used as a source of hydrogen.[1] The borane adduct **2** has been suggested to play a key-role in the mechanism of the catalysis.[1,2] The formation of **2** has been recently confirmed by Corey *et al.* by determining the three dimensional structure of the enantiomer of **2** (R=CH_3) by means of X-ray crystallography.[3] Mechanistic details of the catalysis have been lately investigated also by using *ab initio* molecular orbital methods.[4-5]



Although the adducts **2** are already rather well characterized plausible isomerization reactions of **2**, some of which may deactivate / destroy the catalyst, have not yet been considered. Furthermore, it is not known how much more stable are borane *N*-adducts than the corresponding *O*-adducts; or whether hydride bridging occurs in the adducts. Also hydrogens bound to boron(s) could "scramble" in these adducts. This is what takes place as catalysts are prepared from borane and the corresponding aminoalcohols. However, it has been observed that treatment of oxazaborolidines, of which the ring boron is not substituted, with B_2D_6 will give rise to a hydrogen-deuterium exchange at the ring boron.[6] It has been suggested also that, as borane coordinates to an oxazaborolidine, one of the hydrogens of the borane moiety would coordinate to the ring boron leading to the formation of a hydrogen bridged diborane system (e.g. **3**).[6] Formation of diborane structures has been reliably observed in the case of highly reactive electron poor borane derivatives (e.g. in the case of μ-amino-diborane, on the basis of microwave[7] and *ab initio*[4a] studies of borane adducts of aminoborane). On the other hand, results of an *ab initio* treatment of an unsubstituted simple analog of **3** imply hydride bridged 4-membered ring systems to be unstable and also other mechanisms explaining the hydrogen-deuterium exchange have been found.[8]

Although mechanisms explaining the hydrogen-deuterium exchange have been proposed[8] it still appears to be difficult to assess what role the isomers of borane adducts could play under conditions used in oxazaborolidine

catalyzed reductions. Therefore the aim of this work was to determine the relative stability of the most important isomers by using computational methods. Standard *ab initio* molecular orbital calculations (RHF) were carried out by using the Gaussian 80 series of programs at the 3-21G, 4-31G, 6-31G, 4-31G* and 6-31G* levels.[9] Modeling techniques similar to those applied in the case of previous reports of this series[4d] were employed. The structure **1'** was used as a model of oxazaborolidine catalysts (**1**) and **2'** - **10'** as a model of the isomers. No other calculations on the structures **3'** - **10'** appeared to have been published. Properties of the models **1'** and **2'** have been discussed in the previous parts of this series.[4,5]



No optima corresponding the structures **3'**, **5'**, **7'** and **9'** were found.[10] Optimized (6-31G*//6-31G*) structures of **4'**, **6'**, **8'**, **10'** are shown in the Figure. Total energies and dipole moments of stable systems **1'**, **2'**, **4'**, **6'**, **8'** and **10'** are shown in Table 1. Energies of the formation of adducts **2'**, **4'**, **6'**, **8'**, **10'** are shown in Table 2.

Inspection of the optimized structures of adducts **4'**, **6'** and **10'** shown in the Figure reveals clearly that borane can interact favorably with both the oxygen and nitrogen atoms of **1'** [e.g. the length of the N-BH_3 bond of **2'** (1.718 Å; 6-31G*//6-31G*)[4a] is rather close to that of the O-BH_3 bond of **10'** (1.738 Å; 6-31G*//6-31G*; the Figure)] but not particularly well with the hydrogen of the ring boron. Even though structural features of **2'**[4a] and **10'** (the Figure) imply the formation of both the *N*- and *O*-adducts to be possible formation of the *N*-adducts could be predicted to be much favoured over that of the corresponding *O*-adducts. This can be seen as energies of the formation of **2'** and **10'** are compared (e.g. **2'** is 18.9 kJ mol^{-1} more stable than **10'**; 6-31G*//6-31G*; Table 2). Moreover, even if *O*-adducts would be formed in a mixture of borane and an oxazaborolidine catalyst and if the ketone to be reduced would coordinate to the ring boron of the *O*-adduct orientation of the borane moiety would be wrong for the hydride transfer to occur (to the carbonyl carbon). The borane also would reside too far from the ketone and hydrides of the *O*-bound borane would not point towards the ketone. Therefore, if borane *O*-adducts to chiral oxazaborolidines used as catalysts in the enantioselective reduction of ketones would form the adducts would not play a role of a catalyst.

Although the B-H distance between the hydrogen of ring boron and boron of the BH_3 moiety in **6'** is considerably shorter than that between the ring boron and one of the hydrogens of the BH_3 moiety in **4'** the B-H "bridges" are too long in both **4'** and **6'** to represent any significant binding.[11] Therefore, also these results imply the formation of hydrogen bridged 4-membered diborane ring systems to be less advantageous than that of the corresponding *O*- or *N*-adducts.[11]

Inspection of **8'** and **8''** reveals that intramolecular Lewis acid - base interactions are not strong between the O-BH_2 and N-BH_2 end of these "degradation products" of **2'**. Nevertheless, on the basis of the relative energies

shown in Table 2 isomers analogous to 8'' could be more stable than those analogous to 2' [e.g. 8'' is 7.5 kJ mol^{-1} more stable than 2'; (6-31G*//6-31G*); and the dipole moment of 8'' is lower than that of any other of the isomers studied (Table 1)]. Although there is a thermodynamic driving force for the degradative conversion 2' -> 8'' the stability difference between 2' and 8'' is not high which implies this reaction not to cause problems in the case of fast reductions (most oxazaborolidine catalyzed reductions are very fast).[1,2] Computational studies of these exciting catalysts continue.

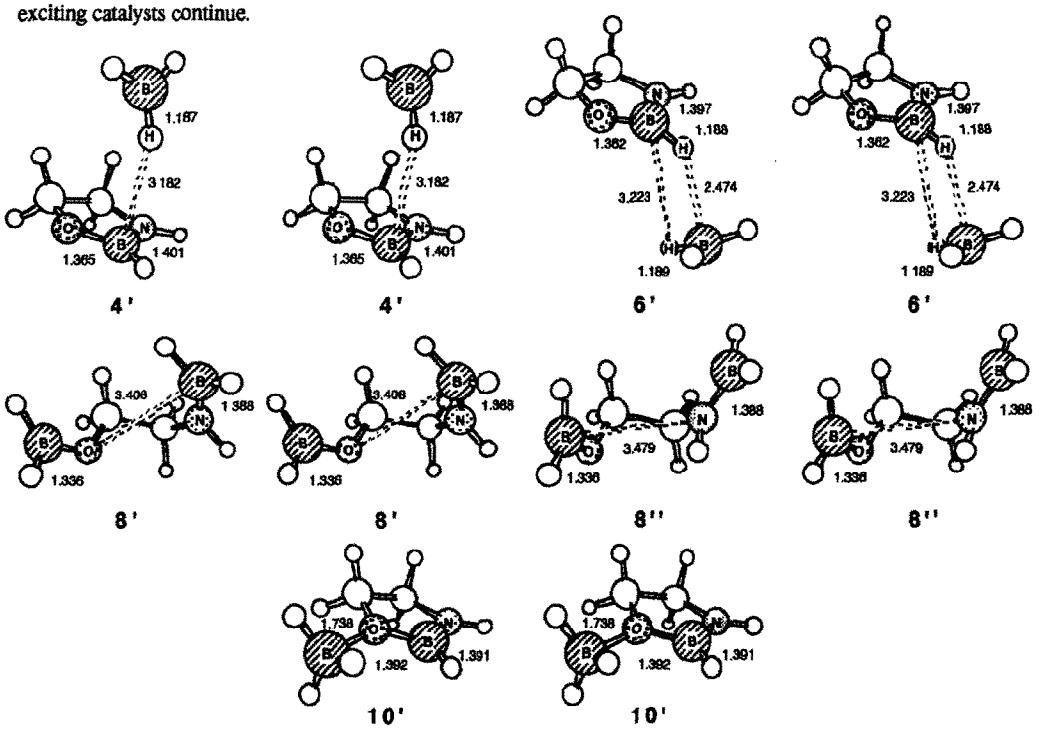


Figure. Stereo representations of the optimized (6-31G*//6-31G*) structures of isomers 4', 6', 8', 8'' and 10'. Some of the most important bond lengths and distances [Å] are shown (see ref 11).

Table 1. Total energies and dipole moments of 1', 2', 2'', 4', 6', 8', 8'' and 10'.[a]

Structure	3-21G//3-21G		4-31G//4-31G		6-31G//6-31G		4-31G*//4-31G*		6-31G*//6-31G*	
	E[a]	D[a]	E	D	E	D	E	D	E	D
1'	-232.01452	3.16	-232.95883	3.18	-233.19703	3.21	-233.07225	2.65	-233.29859	2.67
2' [b]	-258.28393	5.22	-259.32696	4.93	-259.59052	4.89	-259.45727	4.98	-259.70944	4.97
2'' [c]	-258.28200	5.14	-259.32550	4.85	-259.58919	4.82	-259.45588	4.86	-259.70807	4.85
4' [d]	-258.25152	3.09	-259.30782	3.11	-259.57350	3.14	-259.43520	2.59	-259.68829	2.61
6' [d]	-258.25337	3.39	-259.30830	3.38	-259.57388	3.39	-259.43591	2.86	-259.68897	2.89
8' [e]	-258.27107	2.85	-259.32704	2.57	-259.59301	2.45	-259.45341	2.35	-259.70609	2.34
8'' [f]	-258.27797	1.86	-259.33463	1.43	-259.60002	1.40	-259.45977	1.41	-259.71231	1.39
10'	-258.28934	7.17	-259.33435	6.74	-259.59810	6.67	-259.45063	6.22	-259.70225	6.13
H_3B	-26.23730	0	-26.34927	0	-26.37679	0	-26.36322	0	-26.39000	0

[a] Total energies (E) given in hartrees and dipole moments (D) in debyes. [b] The N-BH_3 group in a staggered conformation. [c] A conformer of 2', the N-BH_3 group in an eclipsed conformation. [d] See ref. 11. [e] A conformer in which the B_N - O distance in minimum. [f] A conformer in which the B_O - N distance in minimum.

Table 2. Relative energies[a] of 2', 2'', 4', 6', 8', 8'' and 10'.[b]

Structure	3-21G	4-31G	6-31G	4-31G*	6-31G*
2' (staggered)[c]	0	0	0	0	0
2'' (eclipsed)[c]	+5.1	+3.8	+3.5	+3.7	+3.6
4' [d]	+85.2	+50.3	+44.7	+58.0	+55.6
6' [d]	+80.3	+49.1	+43.7	+56.2	+53.8
8' [c]	+33.8	-0.2	-6.5	+10.1	+8.8
8'' [c]	+15.7	-20.2	-25.0	-6.6	-7.5
10'	-14.2	-19.4	-19.9	+17.45	+18.9

[a] Energies (ΔE) given in kJ mol^{-1}; energies normalized with respect to the value of 2' (set zero). [b] See the Figure. [c] See Table 1. [d] See ref. 11.

ACKNOWLEDGEMENTS

The University of Helsinki and the TEKES foundation are acknowledged for providing computational resources needed to carry out this study. The author thanks Dr. G. Brunow for valuable comments.

REFERENCES AND NOTES

1. Wallbaum, S.; Martens, J. *Tetrahedron Asymmetry* **1992**, *3*, 1475.

2. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J.; Proceedings of the 31th National Organic Symposium, ACS **1989**, 1; (c) Corey, E. J. *Pure & Appl. Chem.* **1990**, *62*, 1209.

3. Corey, E. J.; Azimioara, M.; Sarshar, S. *Tetrahedron Letters* **1992**, *33*, 3429.

4. (a) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 63; (b) ibid. 429; (c) ibid. 827; (d) ibid. 1133; (e) Nevalainen, V. Abstracts of 8th Int. Conf. on Organic Synthesis, Helsinki, IUPAC, **1990**, 317; (f) ibid. 319; (g) ibid. 320; (h) ibid. 316; (i) Nevalainen, V. Proceedings of the 9th Annual Meeting of the Molecular Graphics Society, Uppsala, MGS **1990**.

5. (a) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 921; (b) ibid. 933; (c) ibid. 1441; (d) ibid. 1563.

6. Tlahuext, H.; Contreras, R. *Tetrahedron Asymmetry* **1992**, *3*, 1145.

7. Lau, K. K.; Burg, A. B.; Beaudet, R. A. *Inorg. Chem.* **1974**, *13*, 2787.

8. (a) Nevalainen, V. *Tetrahedron Asymmetry*, in press; (b) Very recent results of an *ab initio* study on the coordination of two borane molecules to one oxazaborolidine have revealed the formation of hydrogen bridged diborane type of adducts analogous to 3 to be possible. Further studies on these adducts are in progress.

9. (a) 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, Pennsylvania 15213. (b) Singh, U. Chandra; Kollman, P. A. School of Pharmacy, Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143.

10. All attempts to optimize the structures 3', 5', 7' and 9' led to the isomers 4', 6', 8', 10'. Reasons behind this behaviour would require a study on the transition state structures and involvement of electron correlation. That was not undertaken as one can conclude on the basis of results of this work that 4', 6', 8', 10' are more stable than the isomers 3', 5', 7' and 9'. This conclusion is also satisfactory for purposes of understanding the most important phenomena responsible for the catalytic activity of chiral oxazaborolidines.

11. As electron correlation has not been taken into account in this work energies of all complexes which have long B-H bonds must be treated with caution.