Tetrahedron. Asymmetry Vol. 3, No. 12, pp. 1563-1572, 1992
Printed in Great Britain

0957-4166/92 $5.00+.00
Pergamon Press Ltd

Quantum Chemical Modeling of Chiral Catalysis. Part 8. On the Conformational Freedom of the Ketone of Ketone-Borane Complexes of Oxazaborolidines Used as Catalysts in the Enantioselective Reduction of Ketones

Vesa Nevalainen

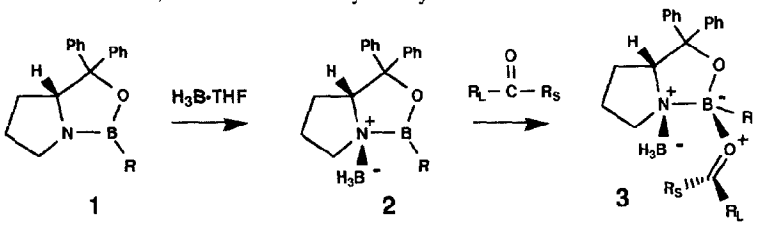
University of Helsinki, Department of Chemistry, Vuorikatu 20, SF-00100 Helsinki, Finland

(*Received in UK* 22 *September* 1992)

Abstract: - Standard *ab initio* molecular orbital methods were employed to study conformational freedom of the ketone of ketone-borane complexes of chiral oxazaborolidines used as catalysts for the enantioselective reduction of ketones (CBS reduction). A formaldehyde-borane complex of 1,3,2-oxazaborolidine was used as a model system. A new conformation was found which was energetically more advantageous than the original one predicted by Corey *et al* The new conformation was predicted to be destabilized by bulky substituents at the C-5 of the ring. A new class of potential oxazaborolidine catalysts for the enantioselective reduction of ketones was invented.

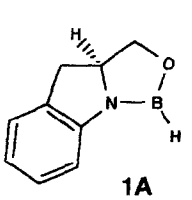
INTRODUCTION

Chiral oxazaborolidines **1** are efficient catalysts for the enantioselective reduction of ketones (the CBS reduction).[1] Since the discovery of the mechanism of action[1] of these catalysts a number of structural and methodological modifications[2] of the original CBS-method[1] and intermediates involved in the preparation of the catalysts[2f] have been developed in order to improve the performance of the catalysts. The mechanism, of which the first two steps are shown below, has been studied lately also by means of *ab initio* molecular orbital methods.[3]

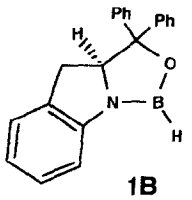


The mechanism of the catalysis suggested by Corey *et al.*[1] involves: formation of the borane adduct **2**; coordination of the ketone to be reduced to the adduct **2** leading to the formation of **3**; a hydride transfer from the BH_3 moiety to the carbonyl in **3** followed by a number of regenerative steps. The final product of the reaction would be the chiral alcohol $R_LR_SC(OH)H$ as a dialkoxyborane derivative obtained in high enantiomeric excess.[1] Even though the mechanism is reasonable and explains the observed enantioselectivity of the reduction, the role of the phenyl substituents of the oxazaborolidine rings of all known working catalysts appears to be incompletely understood as yet. However, recent studies of Martens *et al.*[2b] imply that oxazaborolidines which are not 5,5-diphenyl substituted would be very poor catalysts for the enantioselective reduction of ketones. For example, H_3B•THF + 2 mol% of **1A** was found to give an enantiomeric excess of only 3 % in the reduction of

acetophenone whereas the corresponding reaction with **1B** in place of **1A** gave 93 % e.e.[2b] Therefore, it looks as if bulky substituents at the C-5 of the oxazaborolidine ring could prevent the formation of the other enantiomer and therefore play a crucial role in the asymmetric induction of the catalysis.



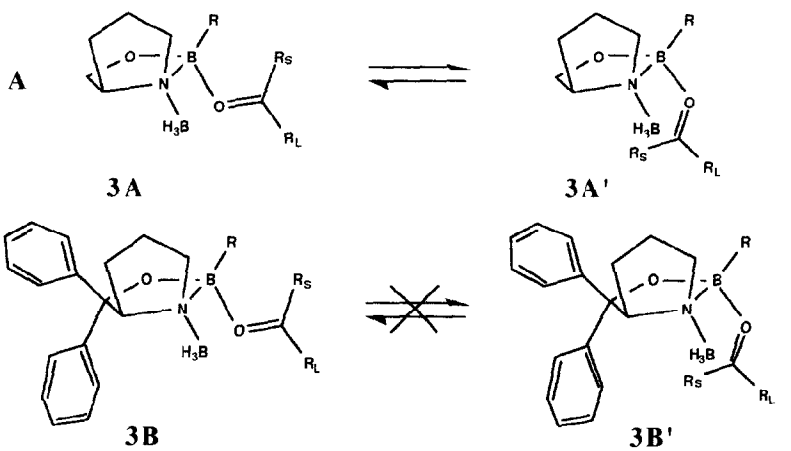
1A



1B

The conformational analysis of a simple model [formaldehyde coordinated to a borane adduct of aminohydroxyborane][3a] structurally analogous to the complex **3A** (Scheme I) has been described in part I of previous reports of this series.[3a] This analysis implied that a ketone-borane complex of an oxazaborolidine structurally analogous to **3A** could possess another favourable conformation (**3A'**) in which the ketone moiety would reside closer to the oxazaborolidine ring [Scheme I, part A].

Scheme I



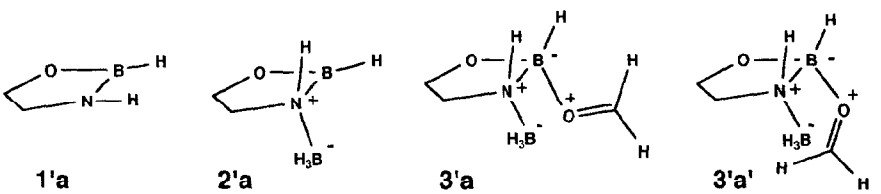
The equilibrium **3A** - **3A'** (Scheme I, part A) was not studied further[3a] because the conclusion was drawn that in the case of 5,5-diphenyl derivatives of oxazaborolidines (e.g. **3B** and **3B'**, in Scheme I, part B) a similar equilibrium would be hardly possible as the conformer **3B'** would be destabilized by repulsive interactions between the ketone and one of the phenyl substituents (they would be brought so close to one another that the R_S group would almost overlap with the phenyl). Altogether, if both the conformers **3B** and **3B'** would be involved in the reduction of ketones and if the hydride transfer in **3B** and **3B'** would take place with about equal ease, enantioselectivity of the reduction would be poor. On the other hand, it could be possible to control the reduction to go selectively through complexes in which the orientation of the ketone would be similar to that of **3B'** or **3A'**. That could be done by changing the place of the bulky 5,5-substituents of the oxazaborolidine ring.

As practically nothing appears to be known about ketone-borane complexes in conformations such as **3A'**

even a comparison of a simple model of **3A'** with the corresponding model of **3A** could be helpful in the evaluation of the value of **3A'** in the oxazaborolidine catalyzed enantioselective reduction of ketones. The aim of this work was to study structures and relative energies of formation of complexes analogous to **3A** , **3A'**, **3B** and **3B'** by means of *ab initio* molecular orbital methods, using a better model than that in the previous conformational study.[3d] Another goal was to evaluate the above proposed role of bulky 5,5-substituents as guides of the coordination of the ketone to the borane adduct of the oxazaborolidine catalyst.

MODELS AND COMPUTATIONAL METHODS

Standard *ab initio* molecular orbital calculations were carried out by using the Gaussian 80 series of programs at the 3-21G, 4-31G and 6-31G levels.[4] Modeling techniques similar to those applied in the case of previous reports of this series[3] were employed, i.e. simple models analogous to the actual catalytically active systems were examined. The structure **1'a** was used as a model of an oxazaborolidine catalyst (**1**), **2'a** as a model of the borane adduct (**2**), and **3'a** and **3'a'** as models of the borane - ketone complexes **3A/3B** and **3A'/3B'**.

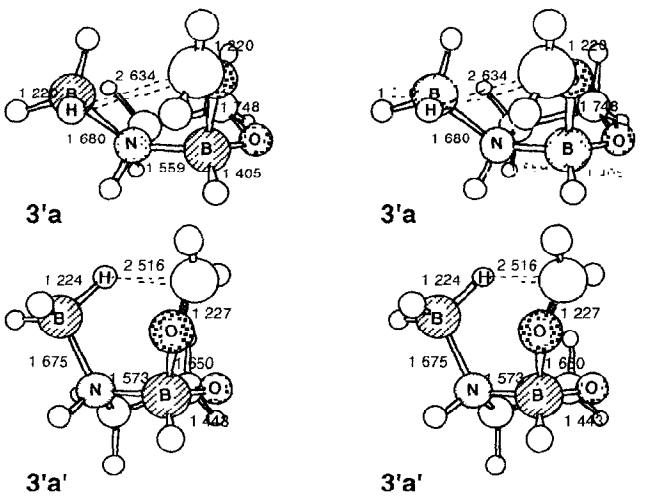


As both the models **3'a** and **3'a'** consist of eight atoms heavier than hydrogen they were best studied at the 6-31G level (polarization functions were not used because inclusion of *d*-functions would have given rise to very time demanding calculations). Properties and structures of **1'a**, **2'a** and **3'a** (as those of related less complicated models calculated at the 6-31G* level at best) have been discussed in previous reports of this series.[3] No other calculations on **3'a'** appear to have been published.

Effects related to steric crowding caused by the 5,5-diphenyl substituents were studied also by constructing derivative models of **3'a** and **3'a'**. Those models were built by replacing the hydrogens at the C-5 of the ring of optimized structures (6-31G//6-31G) of **3'a** and **3'a'** by phenyls. As the derivative structures consisting of twenty atoms heavier than hydrogen were too large to be reoptimized only a rough estimation of steric crowding effects was possible.

RESULTS AND DISCUSSION

The total energies and dipole moments calculated are summarized in Table 1. Optimized (6-31G//6-31G) structures of **3'a** and **3'a'** are shown in Figure 1 and the corresponding 5,5-diphenyl derivatives (partially optimized) in Figure 2. Selected Mulliken overlaps calculated at the 6-31G level are summarized in Table 2. Energies of the formation of **2'a**, **3'a** and **3'a'** are shown in Table 3 and group charges (charge transfer between the BH_3, $H_2C{=}O$ and oxazaborolidine systems) are summarized in Table 4.



Bond angles	3'a	3'a'	2'a
B-N-B	119 7°	117 3°	103 7°
N-B-O_{nng}	106.3°	103 5°	108 4°
N-B-O_{CO}	104.8°	106.8°	
O-B-O	104 4°	105.9°	
B-O-C_{CO}	126 2°	123 9°	
H-C_{CO}-H	119 0°	120 5°	
B-H_{BH3}-C_{CO}	105 4°	106 8°	
H_{BH3}-C_{CO}-O_{CO}	85 7°	88 3°	

Torsion angles	3'a	3'a'	2'a
B_{BH3}-N-B-O_{CO}	-22.0°	18.4°	
B_{BH3}-N-B-O_{nng}	132 3°	93.0°	104 9°
C_{CO}-O_{CO}-B-O	-161 3°	24 8°	
C_{CO}-O_{CO}-B-N	87 0°	-85 0°	
N-C-C-O	25.5°	31 3°	-24 7°
N-B-O-C_{nng}	20 9°	-10 0°	-3.4°
B-O_{nng}-C-C	-29 4°	-12 8°	18 0°
H_{BH3}-B-N-B	-47 2°	49.0°	-46 4°
C-N-B-O_{nng}	-3 6°	29 0°	-13 0°

Figure 1. Stereo representations of the optimized (6-31G//6-31G) structures of formaldehyde-borane complexes (**3'a** and **3'a'**) of 1,3,2-oxazaborolidine (**2'a**). The most important bond lengths [Å], bond angles and torsion angles are shown. The corresponding values of **2'a**[3d] are given for purposes of comparison.

In the case of the models **3'a** and **3'a'** the 6-membered transition state analogous to that predicted to be involved in the hydride transfer taking place in **3**[1a] consists of the atoms C_{CO}, O_{CO}, B_{nng}, N, B_{BH_3} and H_{BH_3} (Figure 1). Although the shape of those six atoms in **3'a** and **3'a'** appears to correspond to a twist conformation, the shape of **3'a'** is closer to that of a boat. The hydride (H_{BH_3}) - carbonyl carbon (C_{CO}) distance is also shorter in **3'a'** as is the B-O_{CO} bond (Figure 1). This already implies that the hydride transfer from the borane moiety to the carbonyl carbon could take place even more easily in complexes structurally analogous to **3'a'** than in those analogous to **3'a**. Also the energies of formation of **3'a'** are more advantageous than those of **3'a** [e.g. coordination of formaldehyde to **2'a** leading to the formation of **3'a'** releases about 5 kJ mol^{-1} energy whereas the corresponding reaction leading to **3'a** requires about 1 kJ mol^{-1} energy, (6-31G//6-31G) Table 3]. The difference of the energies corresponds to a relative **3'a** / **3'a'** abundance ratio of about 1:10.

Table 1. Total energies and dipole moments of models **1'a**, **2'a**, **3'a**, **3'a'** and formaldehyde.[a]

Structure	3-21G//3-21G		4-31G//4-31G		6-31G//6-31G	
	E[a]	D[a]	E	D	E	D
1'a	-232 01452	3 16	-232 95883	3 18	-233 19703	3.21
2'a	-258 28393	5.22	-259 32696	4 93	-259 59052	4 89
3'a	-371 52030	2 88	-373 02076	2 53	-373 39848	2 47
3'a'	-371 52516	2 81	-373 02352	2 67	-373 40084	2.59
H_2C=O	-113 22182	2.66	-113 69261	3 02	-113 80836	3 04

[a] Total energies (E) given in hartrees and dipole moments (D) in debye

Further evidence for the advantageousness of the formation of complexes analogous to **3'a'** can be found if

the structures of **3'a** and **3'a'** are compared with respect to the degree they resemble the transition state structure (and the primary product) of the hydride transfer. Although the exact geometry of the transition state of the hydride transfer appears to be unknown certain properties of the transition state could be deduced on the basis of Hammond's postulate[5] and previous computational studies on the energetics of the hydride transfer and structure and stability of the primary product of the reaction.[3d] Structural changes predicted to take place in the hydride transfer are illustrated in Scheme II.

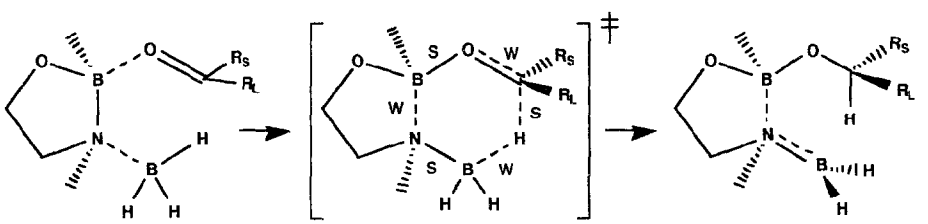
Table 2. Selected Mulliken populations of the borane adduct **2'a** and complexes **3'a** and **3'a'**.[a]

Structure	3'a	3'a'	2'a	H2C=O
$N\text{-}B_{ring}$	0.338	0 324	0.436	-
$N\text{-}B_{BH3}$	0 078	0 118	0 030	-
$B\text{-}O_{ring}$	0 660	0 566	0 690	-
$B\text{-}O_{CO}$	0 070	0 144	-	-
$B\text{-}H_{BH3}$	0.784	0 774	0 839	-
C=O	0.694	0.646	-	0.862
$H_{BH3}\text{-}C_{CO}$	0 004	0 014	-	-

[a] On the basis of calculations carried out at the 6-31G level

It has been shown in part IV of previous reports of this series[3d] that the hydride transfer occurring in analogs of **3** is a highly exothermic reaction and that the energy change involved in the formation of **3** (from **2**) is much smaller than that involved in the hydride transfer. Consequently, according to Hammond's postulate,[5] the geometry of the transition state structure of the hydride transfer should resemble that of **3A** and the activation energy of the reaction should be low with respect to the hydride transfer energy. On the other hand, even though **3A** and **3A'** would structurally resemble the transition state, it could be reasonable to predict that the hydride transfer would occur at the highest rate in that complex which most closely resembles the primary product of the hydride transfer. Because some bonds of **3A** (and **3A'**) will weaken (even finally breaking in the reaction) in the transition state and some others strengthen (even formed in the reaction), the transition state structure of the hydride transfer was inspected in the light of bonds predicted either to be weakened or strengthened (Scheme II).

Scheme II



The bonds predicted to weaken in the transition state shown in Scheme II are those which either would not exist in the primary product of the hydride transfer or those which had clearly been found to weaken in previous computational studies[3d] of the hydride transfer (e.g. the C=O and $B\text{-}H_{BH_3}$ bonds would not exist in the product, and it has been shown[3d] that the $N\text{-}B_{ring}$ bond weakens already in the reaction **2** -> **3** (the $N\text{-}B_{ring}$ bond lengthens

0.069 Å[3c-d] in the reaction **2'a** -> **3'a**) and would weaken further as the hydride transfer occurs: in the primary product of the hydride transfer the N-B_{ring} bond is so weak that it can even break down depending on the orientations of the H_2B-N and $R_LR_SC(H)O$ groups of the primary product[3d]). When bonds of ketone-borane complexes analogous to **3A** and **3A'** are inspected, it could be rational to think that the more closely the structure of the complex resembles that of the actual transition state the more the bonds being weakened in the transition state (and in the product) had lengthened already in the complex. Some of those bonds could be hardly recognizable, e.g. the "bond" between the hydride and the carbonyl carbon in the complex **3** in which the B-H_{BH_3} bond is still much stronger than the H_{BH_3}-C_{CO} "bond" [e.g. the H_{BH_3}-C_{CO} "bonds" of **3'a** and **3'a'** are more than 2.5 Å long (Figure 1); nevertheless, inspection of the corresponding Mulliken overlaps (Table 2) reveals that binding interactions, although weak ones, exist between the atoms H_{BH_3} and C_{CO}].

Table 3. Energies[a] of the coordination of formaldehyde to the borane adduct **2'a**.[b]

Reaction	3-21G	4-31G	6-31G
		ΔE^a	
2'a + $H_2C{=}O$ -> **3'a**	-38	-3	+1
2'a + $H_2C{=}O$ -> **3'a'**	-51	-10	-5

[a] Energies (ΔE) given in kJ mol^{-1} [b] See Figure 1

On the same basis the bonds predicted to strengthen in the transition state shown in Scheme II are those which either would be formed in the reaction or had been found to clearly strengthen in previous computational studies[3d] of the reaction (e.g. the C_{CO}-H_{BH_3} bond would be formed in the hydride transfer; the N-B_{BH_2} bond in the primary product of the hydride transfer would strengthen and draw the free electron pair of the adjacent nitrogen so much that the adjacent N-B_{ring} bond can break,[3d] and also the B-O_{CO} bond would strengthen substantially as the weak Lewis acid-base interactions B^-_{ring} - O^+_{CO} would be transformed to a normal sigma B-O bond).

Table 4. Charge transfer in the borane, formaldehyde and oxazaborolidine (**1'a**) systems of **2'a**, **3'a** and **3'a'**.[a]

Group	3'a	3'a'	2'a
		Charges	
H_3B	-0 232	-0 230	-0.178
$H_2C{=}O$	+0 122	+0 156	-
C_2H_6BNO (1'a)	+0 110	+0 074	+0 178

[a] On the basis of calculations carried out at the 6-31G level

Comparison of the bond lengths of **3'a** and **3'a'** (Figure 1) reveals that the C=O, B-H_{BH_3} and N-B_{ring} bonds of **3'a'** predicted to weaken in the transition state (and in the product, see Scheme II) are longer than the corresponding bonds of **3'a** [e.g. the C=O, B-H_{BH_3} and N-B_{ring} bonds of **3'a'** are 0.007, 0.004 and 0.014 Å longer than those of **3'a**]. Expected differences were found also when lengths of the bonds predicted to strengthen were compared; the N-B_{BH_3} bond of **3'a'** is 0.005 Å shorter than that of **3'a** and the C_{CO}-H_{BH_3} and B-O_{CO} distances in **3'a'** are about 0.118 and 0.098 Å shorter than those in **3'a**. Therefore, not only the energy of formation of **3'a'** is more advantageous than that of **3'a** (about 6 kJ mol^{-1} at the 6-31G level), but it looks also as if the structure of the complex **3'a'** could be closer to the predicted transition state of the hydride transfer (and the

primary product of the hydride transfer) than the complex **3'a**. This implies again that the hydride transfer could occur more easily in analogs of **3'a'** than in those of **3'a**.

The above deduction based on the bond lengths could have been carried out as well by reference to the Mulliken overlap populations shown in Table 2. The bonds predicted to weaken should possess lower overlaps in **3'a'** than in **3'a** whereas, obviously, the bonds predicted to strengthen should possess larger overlaps in **3'a'** than in **3'a**. This was indeed what was observed when overlaps of **3'a'** and **3'a** were compared. The C=O, B-H_{BH_3} and B_{ring}-N overlaps (weakening interactions) of **3'a'** were 93.1, 98.7 and 85.8 % of those of **3'a** and the N-B_{BH_3}, C_{CO}-H_{BH_3} and B-O_{CO} overlaps (strengthening interactions) of **3'a** were 66.1, 28.6, and 48.6 % of those of **3'a'**, respectively.

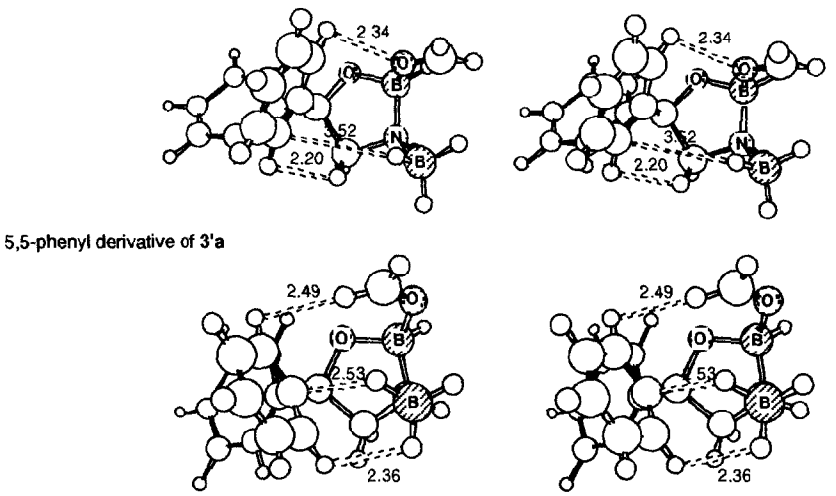


Figure 2. Stereo representations of the models derived from the optimized (6-31G//6-31G) structures of formaldehyde-borane complexes (**3'a** and **3'a'**, see Figure 1) by replacing the hydrogens at the ring position-5 by phenyls (standard bond lengths and angles were used to construct the phenyls). Some distances [Å] between the phenyl groups, borane and formaldehyde are shown.

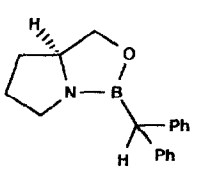
Perhaps one of the most unexpected structural differences between the complexes **3'a** and **3'a'** was in the length of the B-O_{CO} bond. As the B-O_{CO} bond of **3'a'** is 0.098 Å shorter than that of **3'a** and the B-O_{CO} overlap of **3'a'** is more than twice that of **3'a** it looks as if the formaldehyde of **3'a'** would be bound to the oxazaborolidine ring much more tightly than that of **3'a**. Some consequences of the strengthened coordination of the formaldehyde of **3'a'** can be observed if the charge transfer values shown in Table 4 are compared. When an electron poor Lewis acid such as borane coordinates to the nitrogen of the oxazaborolidine the latter donates electron density to the borane (e.g. in the case of **2'a** the negative charge transferred to the borane was -0.178). As a Lewis base such as formaldehyde coordinates to the acidic ring boron of the borane adduct of the oxazaborolidine the latter in turn receives electron density from the Lewis base. Therefore, a portion of the electron density the oxazaborolidine donates to the borane would be compensated by the density the oxazaborolidine receives from the coordinating carbonyl compound (e.g. in the case of **3'a** the charge lost by the formaldehyde was 0.122). When the complexes **3'a** and **3'a'** were compared in the light of the charge transfer values shown in Table 4 it was observed that the negative charges of the borane moieties of **3'a** and **3'a'** were almost equal but the

formaldehyde of **3'a'** had lost considerably more electrons to the oxazaborolidine ring than that of **3'a**. Therefore, not only the formaldehyde of **3'a'** is more tightly bound to the oxazaborolidine boron, but it is also more polarized than that of **3'a**; i.e. the propensity of the carbonyl of **3'a'** to accept a hydride would be higher than that of **3'a**.

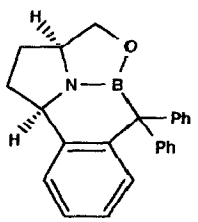
As it looks, on the basis the above comparison of properties of **3'a** and **3'a'**, that the hydride transfer from the borane to the carbonyl group could occur as easily in analogs of **3'a'** as in those of **3'a** (or even more easily in the analogs of **3'a'**) it would be crucial to know what are the features that control the formation of these adducts. Actually for the enantioselective reduction of ketones by borane and an oxazaborolidine catalyst it would be enough that the ketone-borane complex in which the hydride transfer occurs would be structurally analogous to either one of **3A** (**3'a**) or **3A'** (**3'a'**); the only limitation is that both of them must not be involved in the same reduction or enantioselectivity of the reduction would be poor. As the formation of conformers **3B** and **3B'** was predicted to be controlled by steric crowding related to the bulky 5-substituents of the oxazaborolidine ring the optimized structures (6-31G//6-31G) of models **3'a** and **3'a'** modified by replacing the hydrogens at the ring position-5 by phenyls (phenyls constructed by using standard bonds lengths and angles) shown in Figure 2 were examined.

Comparison of the structures of 5,5-diphenyl derivatives of **3'a** and **3'a'** shown in Figure 2 reveals that the gap between one the phenyls and the formaldehyde and borane is more open in the case of **3'a**; i.e. there is less steric crowding between these groups in the derivative of **3'a**; neither the hydrogens of the formaldehyde group of **3'a** are directed towards to the phenyl groups. This indicates that there would be no steric crowding either between the ketone oxygen and the phenyl or between the substituents of the ketone and the phenyl in the case of ketone-borane complexes structurally analogous to **3'a** (or **3A** or **3B**). However, in the diphenyl derivative of **3'a'** one of the hydrogens of the formaldehyde resides at a distance of 2.49 Å from one of the phenyls (Figure 2). For a hydrogen atom this could be possible but already in a methyl ketone the methyl group would come too close to the phenyl. It looks as if one could conclude also on the basis of this rather rough inspection that ketones cannot coordinate to borane adducts of 5,5-diphenyl substituted oxazaborolidines in a way analogous to that of the formation of **3'a'**.

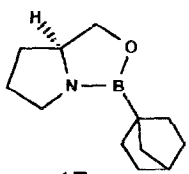
It was concluded above that the enantioselective reduction of a ketone could go either through the ketone-borane complex structurally analogous to **3A** or through another analogous to **3A'**. However, all known examples of enantioselective reduction of ketones catalyzed by oxazaborolidines appeared to be based on the controlled formation of complexes analogous to **3A**. As no reactions in which the enantioselectivity would be based on the formation of ketone-borane complexes analogous to **3A'** appeared to be known, a few catalysts potentially working on this basis were invented. For example, the oxazaborolidines **1C**, **1D** and **1E** or their derivatives might function as chiral catalysts for the enantioselective reduction of ketones. A model corresponding to **1C** (derived from **3'a'**, Figure 3) was built in the same way as those of the 5,5-diphenyl derivatives (Figure 2). The B-C bond length (1.566 Å) was taken from 2-methyl-1,3,2-oxazaborolidine optimized at the 6-31G level.



1C

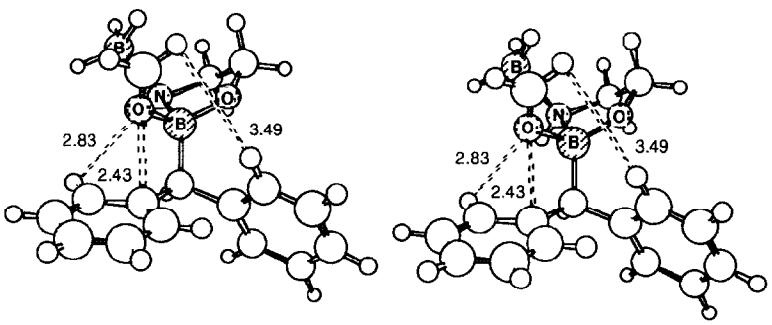


1D



1E

On the basis of a comparison of the distances between the formaldehyde and phenyls of the diphenylmethyl derivative of **3'a'** shown in Figure 3 it looks as if replacing the hydrogen of the ring boron by a diphenylmethyl group could allow the ketone to coordinate only in the orientation analogous to that of **3A'**. Actually, if the distances between the formaldehyde and phenyls of the diphenylmethyl derivative of **3'a'** shown in Figure 3 are compared with those of the 5,5-diphenyl derivative of **3'a** shown in Figure 2 the models appear to be rather equal with respect to steric crowding [e.g. the shortest distance between the carbonyl oxygen and the phenyls is 2.43 Å in the diphenylmethyl derivative of **3'a'** (Figure 3) and the corresponding distance in the 5,5-diphenyl derivative of **3'a** is 2.34 Å (Figure 2)].



3-diphenylmethyl derivative of 3'a'

Figure 3. A stereo representation of the model derived from the optimized (6-31G//6-31G) structure of formaldehyde-borane complexes (**3'a'**, see Figure 1) by replacing the hydrogen of the ring boron by a diphenylmethyl group (standard bond lengths and angles were used). Some distances [Å] between the phenyls and formaldehyde are shown.

Provided that one of these compounds is active as a catalysts, one would then have access from L-proline to two oxazaborolidine catalysts complementing each other in the enantioselectivity of the reduction of a ketone. One of these would be the CBS type of reduction catalyst[1,2] carrying bulky substituents at the C-5 of the oxazaborolidine ring, and the other catalyst would have the bulky groups on the carbon atom adjacent to the ring boron, derived from the R group of the dialkoxyborane $(R'O)_2B$-R used to construct the catalyst model. The latter catalyst would furnish the enantiomeric alcohol by way of the ketone-borane complex **3A'**. Computational studies on these exciting catalysts continue.

CONCLUSIONS

All the results of this study imply that, in addition to the original mode of coordination of a carbonyl compound to an adduct of borane to oxazaborolidine as represented by Corey *et al.*,[1] another advantageous way by which the coordination could occur may exist. The new coordination mode suggested a new type of oxazaborolidine catalyst which would produce the chiral alcohol as the enantiomer of that obtainable by using the conventional CBS reduction.

ACKNOWLEDGEMENTS

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

REFERENCES AND NOTES

1. (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.

2. (a) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1992**, *33*, 4141; (b) Martens, J.; Dauelsberg, Ch.; Behnen, W.; Wallbaum, S. *Tetrahedron Asymmetry* **1992**, *3*, 347; (c) Rao, A. V. R.; Gurjan, M. K.; Kaiwar, V. *Tetrahedron Asymmetry* **1992**, *3*, 859; (d) Jones, T. K., Mohan, J. J., Xavier, L. C.; Blacklock, T. J.; Mathre, D. J.; Sohar, P.; Jones, E. T. T.; Reamer, R. A.; Roberts, F. E.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 763; (e) Parmee, E. R.; Tempkin, O.; Masamune, S. *J. Am. Chem. Soc.* **1991**, *113*, 9365; (f) Mathre, D. J.; Jones, T. K.; Xavier, L. C.; Blacklock, T. J.; Reamer, R. A.; Mohan, J. J.; Jones, E. T. T.; Hoogsteen, K.; Baum, M. W.; Grabowski, E. J. J. *J. Org. Chem.* **1991**, *56*, 751; (g) DeNinno, M. P.; Permer, R. J.; Lijewski, L. *Tetrahedron Letters* **1990**, *31*, 7415; (h) Rao, A. V. R.; Gurjan, M. K.; Sharma, P. A.; Kaiwar, V. *Tetrahedron Letters* **1990**, *31*, 2341; (i) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1989**, *30*, 6275; (j) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Letters* **1989**, *30*, 5547; (k) Youn, I. K.; Lee, S. W.; Pak, C. S. *Tetrahedron Letters* **1988**, *29*, 4453.

3. (a) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 63; (b) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 429; (c) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 827; (d) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 1133; (e) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 921; (f) Nevalainen, V. *Tetrahedron Asymmetry* **1992**, *3*, 933; (g) Nevalainen, V. Abstracts of 8th Int. Conf. on Organic Synthesis, Helsinki, IUPAC, **1990**, 317; (h) ibid. 319; (i) ibid. 320; (j) ibid. 316; (k) Nevalainen, V. Proceedings of the 9th Annual Meeting of the Molecular Graphics Society, Uppsala, MGS **1990**.

4. (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.

5. Hammond, G. S. *J. Am. Chem. Soc.* **1955**, *77*, 334.