Quantum Chemical Modeling of Chiral Catalysis. Part 9. On the Aggregation Reactions of Borane and Chiral Oxazaborolidines Used as Catalysts in the Enantioselective Reduction of Ketones

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Abstract: - Aggregation reactions of borane and oxazaborolidine type of chiral catalysts were investigated by means of *ab initio* molecular orbital methods. Aggregates consisting of borane and two catalyst molecules were studied by using 1,3,2-oxazaborolidine as a model of the catalyst and those of two boranes and two catalyst molecules by using H_2N-B(H)-OH. The behaviour of oxazaborolidines, as they react with intermediates of the CBS reduction, was found to resemble that of ketones or Lewis basic solvents (the polar $B^-=N^+$ bond of oxazaborolidine behaves as the C=O bond of ketone; nitrogen of oxazaborolidine behaves as a Lewis base).

INTRODUCTION

Chiral catalysts such as oxazaborolidines **1**, of which the mechanism of action was discovered by Corey *et al.*,[1] are known to induce a highly enantioselective reduction of ketones when a Lewis acidic borane is used as a source of hydrogen (the CBS reduction).[1-4] The borane adduct **2** has been suggested to play a key-role in the mechanism of the catalysis.[1] The formation of **2** has been recently confirmed by Corey *et al* by determining the three dimensional structure of the enantiomer of **2** (R=CH₃) by means of X-ray crystallography.[5] Mechanistic details of the catalysis have been lately investigated also by using *ab initio* molecular orbital methods.[6,7]

1   **2**
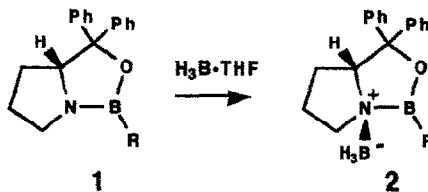
Although the adducts **2** are already rather well characterized they may still have some unrevealed properties which could be important to take into account when the best performance of these catalysts is sought. Moreover, to fully understand what are the limitations of the catalysts one should also be able to predict what properties they would not have. For example, Tlahuext and Contreras[8] report that when an oxazaborolidine derivative of ephedrine is treated with B_2D_6 the hydrogen of the ring boron will be replaced by deuterium. Furthermore, they also suggest[8] that, when borane coordinates to oxazaborolidine, a hydrogen bridged "diborane" (**3**, Scheme I) would be formed instead of the conventional adduct (e.g. **2**). Adducts **3** were predicted to dimerize to give aggregates **4**.

Scheme I
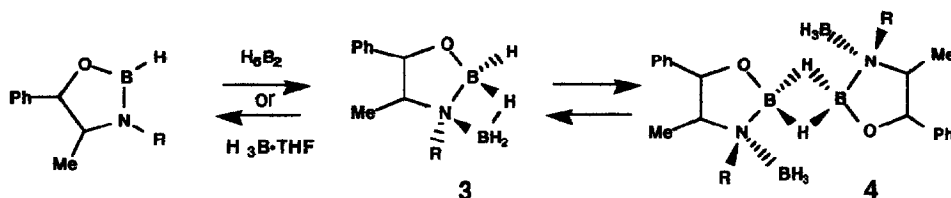
As the hydrogen-deuterium exchange has been observed there must exist a mechanism by which hydrogens of the borane interact with the boron of the catalyst. In this light the formation of 3 would explain the exchange. On the other hand, the formation of systems analogous to 3 has been observed reliably only in the case of highly reactive electron poor borane derivatives (e.g. on the basis of a microwave[9] study of a borane adduct of aminoborane). When considering these observations on a more advanced level it could be rational to assume that the propensity of these polar molecules to form aggregates would be attributable to the Lewis acid-base properties of the interacting moieties. In reference to the previous parts of these studies[6a] one could point out that the Lewis acidic and basic sites of oxazaborolidines (1) and their borane adducts (2) are known (on the basis of analysis of HOMO-1 and LUMO-1 of 1,3,2-oxazaborolidine and its borane adduct). The most acidic site of oxazaborolidines and their borane adducts is on the boron of the oxazaborolidine ring (though acidities of oxazaborolidines are clearly lower than those of their borane adducts).[6a] Basic properties of oxazaborolidines locate mostly to the ring nitrogen (and somewhat to the ring oxygen) whereas those of their borane adducts appear in the borane moiety (particularly in the hydrogens).[6a] On this basis one could perceive 3 as a system in which an intramolecular neutralization of the acidic and basic sites had taken place. Therefore, although the formation of 3 has not been confirmed so reliably as that of 2 (e.g. by means of X-ray crystallography) the assumption of the formation of 3 is not formally wrong. The same conclusion cannot be drawn in the case of the formation of 4 as the hydrogen of the ring boron of borane adducts of oxazaborolidines would not be involved in the most Lewis basic site of the borane adducts.

As not much is known about the aggregation of borane and oxazaborolidines and two different structures (2 and 3) have been suggested for the adducts the primary aim of this work was chosen to be the estimation of properties and relative stabilities of 2, 3 and aggregates 4. Formation of aggregates consisting of two catalyst molecules and one borane (5' - 8' and 7" - 8", Scheme II) was also investigated.

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, 6-31G, 4-31G* and 6-31G* levels.[10] Modeling techniques similar to those described in the previous reports of this series[6d] were employed. Reactions of borane with two catalyst molecules (i.e. reactions of one borane-catalyst adduct with another catalyst molecule, see Scheme II) were studied at the 3-21G, 4-31G and 6-31G levels by using 1'a (1', R=H; Scheme II) as a model of the catalyst and 2'a (2', R=H; Scheme II) as a model of its borane adduct. The formation of 4 was investigated by using the models 4'a, 4"a and 2'b. As models of 5' - 8' and 7" - 8" were used the analogs 5'a - 8'a, 7"a and 8"a (5' - 8' and 7" - 8"; R=H; Scheme II). Stability of the hydrogen bridged adducts 3 of Tlahuext and Contreras[8] was determined by using the model 3'a. No other calculations on the structures 3'a - 8'a, 4"a or 7"a - 8"a appeared to have been published. Properties of 1'a, 2'a and 2'b have been discussed in the previous parts of this series.[6,7]

Scheme II
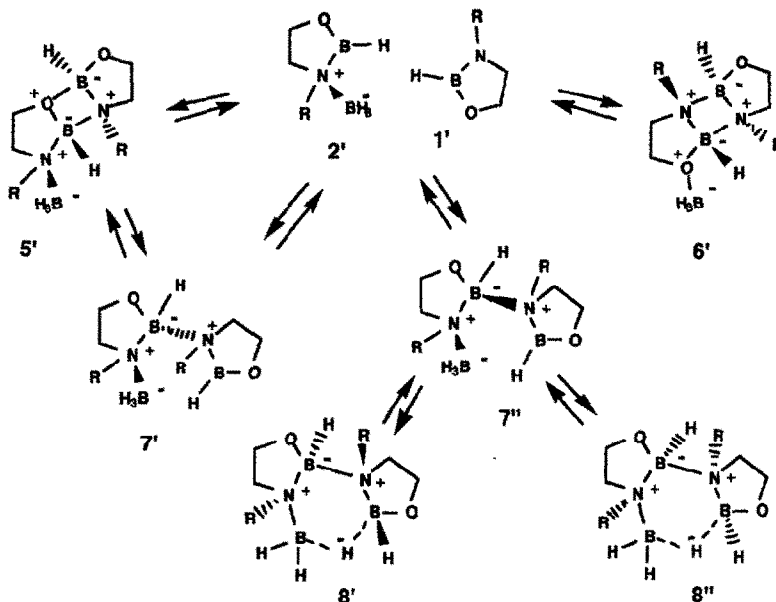
RESULTS AND DISCUSSION

Total energies and dipole moments calculated are summarized in Table 1. Optimized structures of the aggregates 4'a and 4''a (6-31G//6-31G) are shown in Figure 1. Mulliken overlap populations of 5'a - 8'a, 7''a and 8''a (6-31G//6-31G) are shown in Figure 2. The optimized structures (6-31G//6-31G) of 5'a and 6'a are depicted in Figure 3, those of 7'a and 7''a in Figure 4 and the structures of the hydrogen bridged systems (8'a and 8''a) in Figure 5. Energies of the formation of these aggregates are shown in Table 2.
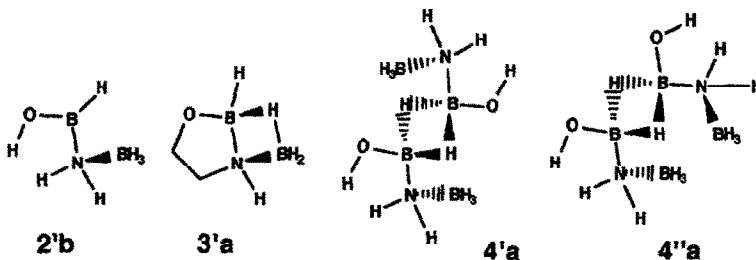
When geometries of 3'a, 4'a and 4''a were optimized their diborane ring systems were cleaved. Structural parameters of the monomeric moieties of optimized 4'a and 4''a appeared to resemble those of the free monomer 2'b.[6a] All attempts to optimize the bicyclic borane adduct (3'a) led to a conformer of 2'a of which one of the hydrogens of the BH₃ group resided above the B-N bond of the ring (the N-BH₃ in an eclipsed conformation).

This conformer was less stable than the other (the staggered one) reported in the literature (3.5 kJ mol^{-1} at the 6-31G level and 3.6 kJ mol^{-1} at the 6-31G* level).[6,7] On the basis of these results it looks, in contrast to the suggestions of Tlahuext and Contreras,[8] as if diboranes structurally analogous **3** or **4**, if formed under some conditions, would be unstable. They would be spontaneously converted to the corresponding borane adducts **2**.

Table 1. Total energies and dipole moments of the models **1'a** - **8'a** and **4''a** and **7''a** - **8''a**.[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'a	-232.01452	3.16	-232.95883	3.18	-233.19703	3.21	-233.07225	2.65	-233.29859	2.67
1'b	-155.55682	3.27	-156.19671	3.20	-156.35434	3.23	-156.25862	2.95	-156.40862	2.96
2'a	-258.28393	5.22	-259.32696	4.93	-259.59052	4.89	-259.45727	4.98	-259.70944	4.97
2'b	-181.82032	4.72	-182.59939	4.21	-182.74260	4.21	-182.63855	4.48	-182.81418	4.46
4'a	-363.64577	8.25	-365.12305	7.79	-365.48931	7.77	-	-	-	-
4''a	-363.65481	0.97	-365.13228	1.72	-365.49849	1.85	-	-	-	-
5'a	-490.33351	5.28	-492.29551	5.10	-492.79460	5.08	-	-	-	-
6'a	-490.34711	4.40	-492.30935	4.01	-492.80888	3.93	-	-	-	-
7'a	-490.30250	10.10	-492.27579	9.43	-492.77580	9.36	-	-	-	-
7''a	490.31476	5.66	-492.28765	5.27	-492.78796	5.18	-	-	-	-
8'a	-490.31136	3.29	-492.28283	3.21	-492.78388	3.19	-	-	-	-
8''a	-490.31348	4.11	-492.28378	3.91	-492.78472	3.83	-	-	-	-
H₃B	-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 debye.

Table 2. Energies (ΔE)[a] of the formation of aggregates **4'a** - **8'a**, **4''a**, **7''a** and **8''a** accompanied with those of the formation of formaldehyde[b] and water adducts[b] of **2'a** and **2'b** and the corresponding energies corrected[c] with respect to the most important solvent effects (ΔE$_{SC}$).

Reaction				3-21G		4-31G		6-31G	
				ΔE[a]	ΔE$_{SC}$[a,b]	ΔE[a]	ΔE$_{SC}$	ΔE[a]	ΔE$_{SC}$
2'b	+	**2'b**	-> **4'a**	-13	+207	-11	+103	-11	+93
2'b	+	**2'b**	-> **4''a**	-37	+183	-36	+67	-35	+69
1'a	+	**2'a**	-> **5'a**	-92	+15	-26	+24	-19	+26
1'a	+	**2'a**	-> **6'a**	-128	-21	-62	-12	-56	-11
1'a	+	**2'a**	-> **7'a**	-11	+96	+26	+76	+31	+76
1'a	+	**2'a**	-> **7''a**	-43	+64	-5	+45	-1	+44
1'a	+	**2'a**	-> **8'a**	-34	+73	+8	+58	+10	+55
1'a	+	**2'a**	-> **8''a**	-40	+67	+5	+55	+7	+52
2'a	+	H₂C=O	-> **2'a·O=CH₂**	-38	+69	-3	+47	+1	+46
2'b	+	H₂C=O	-> **2'b·O=CH₂**	-39	+71	-3	+54	-3	+49
2'a	+	H₂O	-> **2'a·OH₂**	-107	0	-50	0	-45	0
2'b	+	H₂O	-> **2'b·OH₂**	-110	0	-57	0	-52	0

[a] Energies given in kJ mol^{-1}. [b] From ref. 6c. [c] Solvent corrected aggregation energies (ΔE$_{SC}$) calculated by taking into account the energy needed to remove water from the most stable borane-water adduct of the corresponding oxazaborolidine model (ref. 6c).

Aggregation of Borane Adducts of Oxazaborolidines

Bonding interactions typical to hydrogen bridged diboranes (e.g. those suggested by Tlahuext and Contreras)[8] were not found when the optimized structures (6-31G//6-31G) of **4'a** and **4''a** (Fig. 1) were inspected. This implies aggregates structurally analogous to **4** to be loose and they could be more likely represented as two borane-oxazaborolidine adducts bound by electrostatic interactions. The looseness does not,

however, mean that the formation of this type of aggregates would not be advantageous. Namely, energies of the formation of **4'a** and **4''a** were clearly negative (ΔE, Table 2). Furthermore, the energy of formation of **4''a** was much more negative than that of **4'a** (e.g. at the 6-31G level ΔE of **4''a** was -35 kJ mol^{-1} whereas that of **4'a** was only -11 kJ mol^{-1}, Table 2). Also the dipole moment of **4''a** was lower, less than one third of that of **4'a** (e.g. at the 6-31G level the moments of **4'a** and **4''a** were 7.77 D and 1.85 D, Table 1).
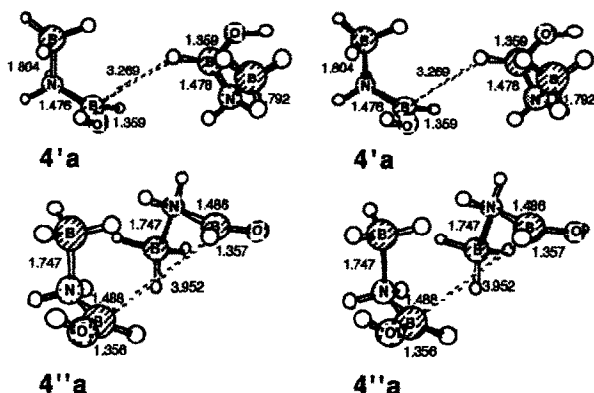

Figure 1. Stereo representations of the optimized (6-31G//6-31G) structures of the models of dimeric aggregates (**4'a** and **4''a**) of borane adducts **2'b**. Some of the most important bond lengths and distances [Å] are shown.

It has been shown in part three of this series[6c] that the orientation of dipole moment of a borane adduct of oxazaborolidine may have a great influence on the nature of the further reactions of the adduct. The dipole moment vector of these adducts has been found to be approximately perpendicular to the plane of the oxazaborolidine ring (Scheme III).[6c]

Scheme III
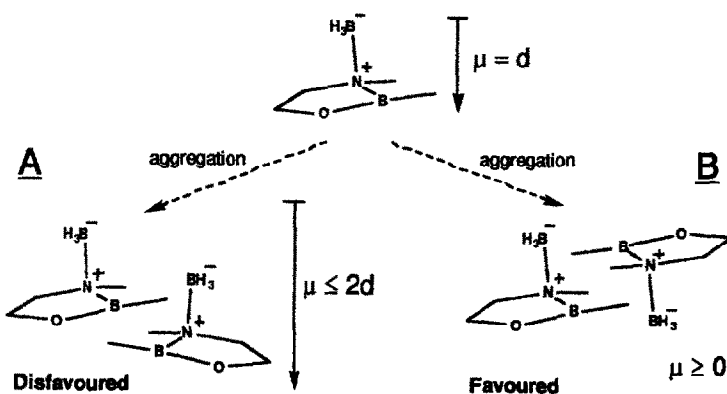
A great part of the total dipole moment of the system consisting of two borane adducts (**2**) may cancel if the adducts are oriented so that the moment of one moiety points to a direction opposite to that of the other. In that case the total dipole moment of the dimeric aggregate may become zero at best (e.g. **B**, Scheme III). On the other hand,

if the adducts are oriented in such a way that their moments points to the same direction the total dipole moment will increase (e.g. $\underline{A}$, Scheme III). If the relative orientations of monomeric moieties of 4'a and 4''a (Fig. 1) are compared with those shown in Scheme III it turns out that 4'a resembles the system of higher dipole moment ($\underline{A}$, Scheme III) and 4''a that of the lower dipole moment ($\underline{B}$, Scheme III).

Also other consequences of the formation of these dimeric aggregates can be found if structural parameters of 4'a and 4''a are compared with those of 2'b. The most significant difference appears in the lengths of $N\text{-}BH_3$ bonds. The $N\text{-}BH_3$ bonds of 4'a are 1.792 and 1.804 Å long; i.e. clearly shorter than the corresponding bond of 2'b (1.833 Å). Moreover, both the $N\text{-}BH_3$ bonds of 4''a are even shorter, they are only 1.747 Å (Fig. 1) long. This implies the binding of borane to the nitrogen of oxazaborolidine to tighten as borane adducts of oxazaborolidines form loose aggregates like 4'a or 4''a. That is indeed what could have been predicted to occur on the basis of the previous studies of this series.[6,7] Furthermore, the B-N bond of oxazaborolidine ring could be predicted to lengthen and the B-O bond to shorten, the positive charge of the ring boron should increase and the LUMO-1 energy decrease. Indeed, the formation of 4'a and 4''a was found to be accompanied also by these changes [e.g. in the case of 4''a (6-31G//6-31G): the B-N bond of the catalyst moiety is 0.012 - 0.014 Å longer and the B-O bond 0.003 - 0.004 Å shorter than the corresponding bond of the monomeric borane adduct 2'b, the positive charge of the boron of the catalyst moiety is 0.010 - 0.011 higher and the LUMO-1 energy 0.48 eV lower than the corresponding values of 2'b]. All these changes imply the formation of this type of loose aggregates to enhance the Lewis acidity of the boron of the catalyst moiety from the level at which it is in the corresponding monomeric borane adducts 2.

As the CBS reduction is normally done in the presence of a Lewis basic solvent (e.g. THF) and the borane is used as a borane-solvent complex (e.g. THF•BH_3) it could be useful to compare energies of the formation of aggregates structurally analogous to 4'a or 4''a with those of solvent complexes[6c] of the corresponding borane adducts. For example, at the 6-31G level energies of the formation of solvent complexes of 2'b (H_2O used as a model of the Lewis basic solvent) have been calculated[6c] to be, depending on the orientation of the solvent, -52 kJ mol^{-1} (BH_3 and H_2O *cis* about the oxazaborolidine ring, Table 2) and -38 kJ mol^{-1} (BH_3 and H_2O *trans* about the oxazaborolidine ring[6c]). As two molecules of the solvent must be removed in order to form one molecule of the dimeric aggregate the solvent corrected energies of 4'a and 4''a (ΔE_{SC}, Table 2) are considerably positive [e.g. as 2 x 52 kJ mol^{-1} = 104 kJ mol^{-1} (at the 6-31G level) will be required for removing solvents from two H_2O complexes of 2'b[6c] and the reaction 2'b + 2'b -> 4''a releases only -35 kJ mol^{-1} the solvent corrected energy (ΔE_{SC}) of the formation of 4''a will be +69 kJ mol^{-1}, Table 2]. Therefore, one could predict that in the presence of a Lewis basic solvent (e.g. THF) dimeric aggregates structurally analogous to 4'a or 4''a would hardly exist. They would be converted to the corresponding monomeric borane adducts which would be stabilized by the solvent.[6c]

If the energies of formation of dimeric aggregates (4'a and 4''a, Table 2) are inspected in the light of the study of the formation of dimeric aggregates of oxazaborolidines[7b] one could draw a conclusion that the aggregation energies of borane adducts of oxazaborolidines would be more negative than those the corresponding oxazaborolidines. Therefore, one could predict that adding borane to a solution of dimeric oxazaborolidine in a non-Lewis basic solvent would strengthen the forces which keep the oxazaborolidine moieties together. On the other hand, in the case of borane derivatives (e.g. catecholborane) which are substantially weaker Lewis acids than BH_3 no significant changes in the degree of aggregation should be seen as the borane and oxazaborolidine are mixed. Implications of this suggestion are not contrary to those of experimental observations of the behaviour of borane and catecholborane in that the catecholborane-oxazaborolidine system has been found to work well in toluene at -78°C[3g,4b,4e] (i.e. no aggregation even under these extreme conditions) whereas the corresponding borane-oxazaborolidine system is known to work smoothly in THF at +23°C [i.e. the Lewis basic solvent and

"high" temperature (in this case enantioselectivity decreases with decreasing temperature) guarantee that the amount of aggregates would be in minimum].[1-4]
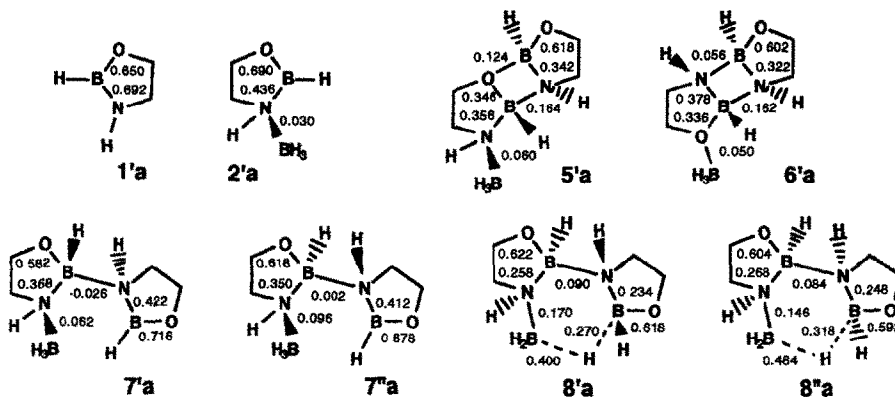

Figure 2. Mulliken overlap populations (6-31G//6-31G) of the most important B-N, B-O and B-H bonds in 1'a, 2'a, 5'a - 8'a, 7"a and 8"a. Formal charges and stereochemistry (Scheme II) are not shown for reasons of clarity.

Table 3. Charge transfer[a,b] in oxazaborolidine coordinating to 2'a.

Structure	Charge transfer[a,b]	Structure	Charge transfer[a,b]
2'a	+0.178 [c]	7"a	+0.150
5'a	+0.049	8'a	-0.041
6'a	+0.028	8"a	-0.052
7'a	+0.112		

[a] On the basis of calculations carried out at the 6-31G level. [b] Positive values indicate that the coordinating oxazaborolidine has lost charge (electrons) and negative ones that it has received charge (electrons). [c] The charge the oxazaborolidine moiety donates to BH_3 as the borane adduct 2'a is formed, ref. 7d.

Aggregates Consisting of one Borane and Two Oxazaborolidines

Borane Adducts of Dimeric Oxazaborolidines (aggregates 5' and 6')

Structures of 5'a and 6'a optimized at the 6-31G level are shown in Figure 3. Among all this type of isomeric aggregates (5'a - 8'a and 7"a - 8"a) studied were 5'a and 6'a the most stable ones (Table 2). Also the relative order of stabilities of 5'a and 6'a is interesting for two reasons. Namely, as the energy of coordination of borane to a Lewis basic nitrogen can be much higher than that of the corresponding oxygen analog[7a] one could predict that 5'a would be more stable than 6'a (the BH_3 group of 6'a is bound to an oxygen and that of 5'a to a nitrogen of one of the oxazaborolidine moieties). On the other hand, dimeric diazadiboretane derivatives of oxazaborolidines (e.g. 6'a without BH_3) have been found to be more stable than the corresponding oxazadiboretane ones (e.g. 5'a without BH_3).[7b] Consequently, one could also assume that the relative stability order of the borane adducts of the dimers could be the same as that of the dimers. This study reveals the energy of formation of 6'a to be 37 kJ mol^{-1} lower than that of 5'a (6-31G//6-31G, Table 2). Therefore, the relative order of stabilities of borane adducts of dimeric oxazaborolidines[7b] indeed appears to be the same as that of the corresponding dimeric oxazaborolidines.

Reasons behind the high stability of 5'a and 6'a could be inspected also by comparing their charge transfer values (Table 3), bond lengths (Fig. 3) and Mulliken overlap populations (Fig. 2) with the corresponding values of dimeric oxazaborolidines[7b] (5'a and 6'a without BH$_3$). As the aggregates 5'a and 6'a are formed the Lewis acidic oxazaborolidine (2'a) would receive electron density from its Lewis basic counterpart (1'a). Consequently, a positive charge will develop in the oxazaborolidine moiety coordinating to 2'a (Table 3). This type of conclusion is not without precedence, as described in the case of the formation of formaldehyde complexes of 2'a (formaldehyde donates electron density to 2'a).[7d] As the positive charge of the Lewis basic oxazaborolidine moiety of 6'a is considerably lower than that of 5'a (and much lower than those of 7'a or 7''a) the higher stability of 6'a could be related to its lower level of polarization (less charge separation).
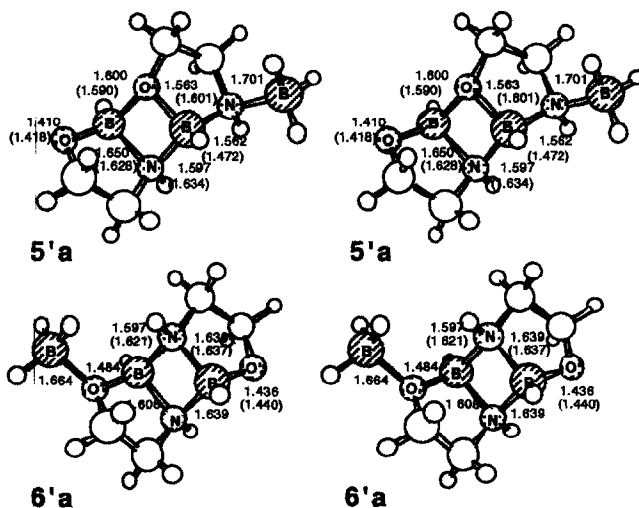

Figure 3. Stereo representations of the optimized (6-31G//6-31G) structures of the models of diazadiboretane and oxazadiboretane type of aggregates (5'a, 6'a) consisting of one borane and two catalyst molecules. Some of the most important bond lengths [Å] are shown. The corresponding bond lengths of systems without BH$_3$ (ref. 7b) are shown in parentheses.

Comparison of bond lengths of 5'a and 6'a (Fig. 3) with those of the corresponding dimeric oxazaborolidines (Fig. 3, values in parentheses) reveals that the relative changes the coordinating borane gives rise to in the heterocyclic skeletons of 5'a and 6'a occur to the same direction (i.e. both heterocyclic skeletons react in the same way as borane approaches their most Lewis basic sites). This is illustrated in Scheme IV (part A). If the corresponding changes of Mulliken overlap populations of 5'a (Fig. 2, ref. 6d) are compared only significant changes of populations locate to the B-N bonds of the ring boron of the Lewis acidic oxazaborolidine moiety (Scheme IV, part B, the bold bonds). In the case of 6'a, in addition to the same changes one more B-N bond and the B-O bond of the Lewis acidic oxazaborolidine moiety are affected (Scheme IV, part B, the bold bonds). Therefore, the high stability of 6'a could be attributed also to the better ability of the skeleton of 6'a to delocalize perturbations of its electron structure caused by the coordinating borane.
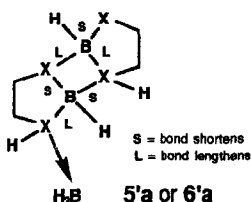
Although one could predict on the basis of the results discussed above that aggregates analogous to 5'a and 6'a could form when oxazaborolidines or dimers of oxazaborolidines are treated with borane, substituents and topology of the oxazaborolidine catalyst would eventually determine whether the aggregates would be formed or not. For example, in the case of conventional bicyclic CBS catalysts derived from diphenylprolinol formation of the cis-fused borane adducts would be highly favoured over the trans-fused ones.[7c] Furthermore, the concave
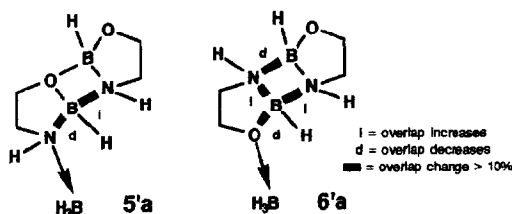
side of the adduct would be more-hindered than the convex one to the other oxazaborolidine to coordinate.

Scheme IV

A) Changes of bond lengths

S = bond shortens
L = bond lengthens

5'a or 6'a

B) Changes of Mulliken overlap populations

i = overlap increases
d = overlap decreases
■■ = overlap change > 10%

5'a   **6'a**

If two CBS catalysts are fit to the aggregate **5'a** so that the above mentioned limitations are taken into account it inevitably turns out that the two catalysts must be enantiomers; i.e. aggregates structurally analogous to **5'a** would not be formed in mixtures of borane and the catalyst **1** present as a single enantiomer. The same conclusion can be drawn in the case of the aggregate **6'a**. Therefore, aggregation analogous to that of the formation of **5'a** or **6'a** can be observed only in the mixtures of borane and enantiomers of the bicyclic CBS catalysts **1**. One the other hand, as the formation of **5'a** and **6'a** would be energetically advantageous and there are some molecules among the known working oxazaborolidine catalysts of which neither the topology nor ring substituents would clearly prevent this type of aggregation (e.g. 4-isopropyl-5,5-diphenyl-1,3,2-oxazaborolidine,[4g-k] 4-methyl-5-phenyl-1,3,2-oxazaborolidine,[2k] and related derivatives) it looks as if this type of aggregation would not seriously affect the performance of enantioselective reduction of ketones catalyzed by **1**.
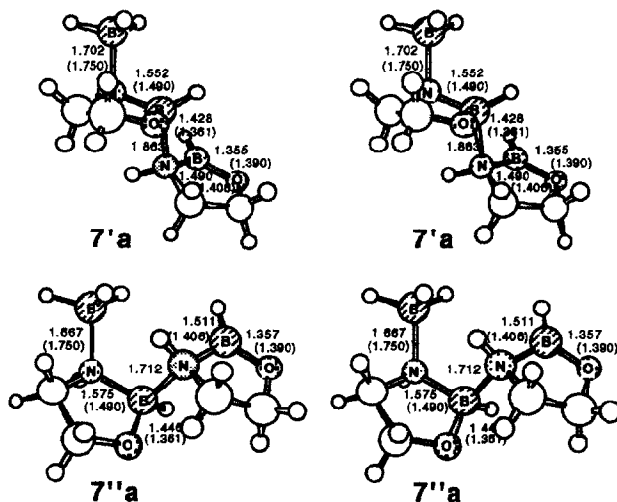

7'a   **7'a**

7''a   **7''a**

Figure 4. Stereo representations of the optimized (6-31G//6-31G) structures of the aggregates 7'a and 7''a consisting of one borane and two oxazaborolidines. Some of the most important bond lengths [Å] are shown. The corresponding values of 2'a and 1'a are shown in parentheses.

Linear "head-to-tail" aggregates (7' and 7")

Structures of the most simple linear aggregates (7'a and 7"a) optimized at the 6-31G level are shown in Figure 4. Energies of the formation of 7'a and 7"a (Table 2) are considerably higher (more positive) than those of 5'a or 6'a. Actually the energy of formation of the *trans*-adduct 7'a appears to be the most positive value (+31 kJ mol^{-1}, Table 2) among those of the isomers studied. The aggregates 7'a and 7"a are interesting in that they represent one of the most simple model of a linear chain polymer one could construct by connecting the Lewis acidic "head" of an activated (by coordination of borane) oxazaborolidine to the most Lewis basic "tail" of another oxazaborolidine. Consequently, the Lewis acidic head of the coordinated oxazaborolidine would in turn be activated to bind a third oxazaborolidine, and so on. In other words, as an oxazaborolidine coordinates to an activated oxazaborolidine the acidity of the activated oxazaborolidine would be transferred to the coordinating one. A few evidences of this type of acidity transfer can be found. For instance, the LUMO-1 orbitals of 7'a and 7"a consist mostly of the $2p_z$ functions of the boron of the oxazaborolidine which had the role of the Lewis basic counterpart (the tail) in the formation of 7'a and 7"a (i.e. the basic oxazaborolidine became acidic). Furthermore, the structural changes in the oxazaborolidine moiety are similar to those observed as BH$_3$ coordinates to the nitrogen of it[6a,7c] (the ring B-N bond lengthens by 0.095 ± 0.010 Å and the ring B-O bond shortens by 0.032 ± 0.002 Å). Altogether, this type aggregation/polymerization of oxazaborolidines as well as potential utility of the aggregates appear to be, except this brief note, not studied yet.

The aggregates 7'a and 7"a are structurally analogous to complexes of Lewis basic solvents and ketones with the borane adduct 2'a studied before (water as a model of the Lewis basic solvent and formaldehyde as a model of the ketone).[6c-d,7d] In consequence of the coordination of the Lewis basic nitrogen of 1'a to the acidic ring boron of 2'a structural parameters of the oxazaborolidine moiety of 2'a change. However, not only the structures but also the structural changes taking place as 7'a and 7"a form are similar to those observed in the case of corresponding reactions of water and formaldehyde.[6c-d,7d] The N-BH$_3$ bond shortens [e.g. 0.083 Å in the case of formation of 7"a (Fig. 4) and 0.085 Å in the case of the water adduct[6c]], the adjacent ring B-N bond lengthens [e.g. 0.086 Å in the case of the formation of 7"a (Fig. 4) and 0.083 Å in the case of the formation water adduct[6c]]. Also the distance between the Lewis base and the acidic ring boron is shorter in the complex in which the Lewis base and BH$_3$ are *cis* about the oxazaborolidine ring than in the corresponding *trans* arrangement [e.g. the B-N bond connecting the oxazaborolidine moieties of 7'a is 0.151 Å longer than that of 7"a (Fig. 4); in the case of the water adduct[6c] the corresponding difference is 0.761 Å].

The similarity of structural changes occurring as water, formaldehyde or oxazaborolidine complexes of 2'a form is not limited to the above described relative changes. Among the *cis*-coordinated complexes also bond lengths were found to be closely similar. The most important bond lengths and the corresponding Mulliken overlap populations of 1:1 complexes of borane - formaldehyde,[6d,7d] borane - water[6c] and borane - oxazaborolidine with oxazaborolidine are shown in Table 4.

Table 4. The most significant bond lengths[a] and Mulliken overlap populations[b] of 1:1 complexes of borane - formaldehyde,[c] borane - water[d] and borane - oxazaborolidine with oxazaborolidine (6-31G//6-31G).

		X = O$_{formaldehyde}$	X = O$_{water}$	X = N$_{oxazaborolidine}$
N-B	BH3	1.680 (0.078)	1.665 (0.082)	1.667 (0.096)
N-B	ring	1.559 (0.338)	1.573 (0.336)	1.575 (0.350)
B-O	ring	1.405 (0.660)	1.425 (0.630)	1.446 (0.618)
B-X		1.748 (0.070)	1.689 (0.028)	1.712 (0.002)

[a] In Ångströms. [b] Values in parentheses. [c] ref 6d and 7d. [d] ref 6c.

In the case of 7''a and the water adduct[6c] of 2'a most surprising are perhaps the N-BH$_3$ bond and its adjacent N-B$_{ring}$ bond. Lengths of these bonds differ only by ±0.002 Å (Table 4). So high level of similarity cannot be seen in the lengths of other bonds. On the other hand, even though water and oxazaborolidine (the nitrogen of 1'a) are different type of Lewis bases, the B-O$_{H_2O}$ bond of the water adduct[6c] is only 0.023 Å shorter than the corresponding (B-N) bond of 7''a (Table 4). Altogether, except the B-O$_{ring}$ bond which lengthens in the series X=O$_{H_2CO}$, O$_{H_2O}$, N$_{oxazaborolidine}$, the bond lengths shown in Table 4 do not show any significant structural correlations. However, implications of the Mulliken overlap populations are contrary to those of the corresponding bond lengths (Table 4). Namely, the overlap populations, except that of the N-B$_{ring}$ bond, correlate with the structure. Inspection of the populations shown in Table 4 in the series X=O$_{H_2CO}$, O$_{H_2O}$, N$_{oxazaborolidine}$, reveals that the values of N-B$_{BH_3}$ increase, those of B-O$_{ring}$ decrease and the B-X values decrease. In other words, as the attractive nature of the N-B$_{BH_3}$ interactions increases the repulsive one of the B-O$_{ring}$ and B-X interactions decreases. This behaviour looks rational in the light of the sizes of formaldehyde, water and 1'a in that the highest B-X population corresponds to the least-hindered complex (i.e. the formaldehyde complex of 2'a) and the lowest B-X population to the most-hindered one (i.e. 7''a).
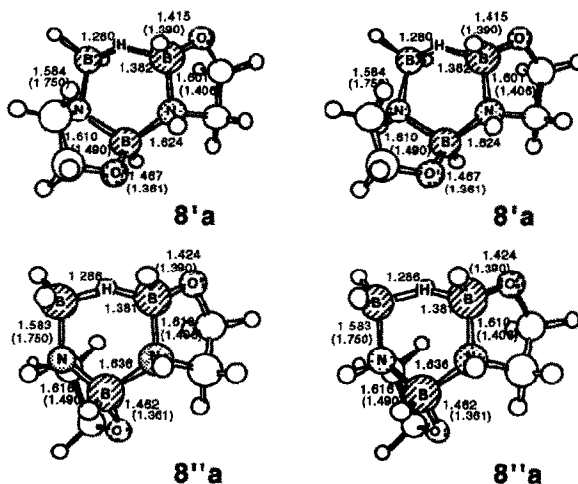

Figure 5.   Stereo representations of the optimized (6-31G//6-31G) structures of aggregates 8'a and 8''a consisting of the borane adduct 2'a and oxazaborolidine 1'a. The corresponding values of 2'a and 1'a are shown in parentheses.

Although the conclusion drawn above may look rational its beauty is disturbed by the discrepancy between the implication of bond lengths and overlap populations. How can the ligand causing more repulsion (oxazaborolidine, B-X bond shorter and overlap lower, Table 4) reside closer to the coordination center than that causing less repulsion (formaldehyde, B-X bond longer and overlap higher, Table 4)? Obviously, in the case of the formaldehyde complex of 2'a the formaldehyde moiety is bound to the catalyst mostly by the attractive interactions between the ring boron and the oxygen of formaldehyde and other interactions are less important. In the case of 7''a, however, the Lewis basic oxazaborolidine moiety is bound to the catalyst by other interactions (e.g. electrostatic ones) of which the importance is so high that they draw the Lewis basic oxazaborolidine so close to the acidic one that repulsive counterparts in the B-X interaction may take over the attractive ones. Indeed, the B-X interaction may become repulsive and still the oxazaborolidine moieties stay close together. That has happened in the case of 7'a; although the B-X overlap population in 7'a is -0.026 (Fig. 2) the B-X distance is still 1.863 Å

(Fig. 4). Furthermore, if this hypothesis is true formaldehyde should not be bound to 2'a if it approaches the ring boron from the side *trans* with respect to the BH$_3$ group. However, this is exactly what has been observed, the B-O$_{H_2CO}$ distance in the formaldehyde-borane *trans*-complex of 1'a has been found to be longer than 3 Å.[6c]

Inspection of the charge transfer values (Table 3) and dipole moments (Table 1) of 7'a (*trans* config.) and 7''a (*cis* config.) in the light of properties of water complexes of 2'a studied before[6c] reveals that the dipole moments of *trans* complexes are in general much higher than those of the corresponding *cis* complexes [e.g. at the 6-31G level the moment of 7'a is 4.18 higher than that of 7''a, (Table 1); in the case of the water complexes[6c] the corresponding difference of is 4.66 D]. If the charge transfer values of 7'a and 7''a are compared with the dipole moments the high charge transfer value appears to correspond to the low dipole moment and *vice versa*. Therefore, as proposed before,[6c] in the case of the formation of complexes of Lewis bases with borane adducts of oxazaborolidines, not only the amount of charge transferred from the Lewis basic moiety to the Lewis acidic one is responsible for the change of the dipole moment and the stability of the complex being formed but also the relative locations taken by the charged groups as the complex forms.[6c]

If a bicyclic oxazaborolidine catalyst derived from diphenylprolinol would be used instead of 1'a to construct aggregates structurally analogous to 7'a or 7''a the latter aggregate would consist of borane and two enantiomeric oxazaborolidines. The former aggregate would consist of borane and two identical enantiomers of the oxazaborolidine but, however, the Lewis basic oxazaborolidine moiety would be bound to the more-hindered concave face of the acidic oxazaborolidine. Therefore, it would be reasonable to predict that neither aggregates analogous to 7'a nor those analogous to 7''a would be formed in mixtures of borane and single enantiomers of CBS catalysts derived from diphenylprolinol or other related aminoalcohols. Nevertheless, it is not clear whether these type of aggregates could be formed from borane and less-hindered oxazaborolidines (e.g. 4-isopropyl-5,5-diphenyl-1,3,2-oxazaborolidine,[4g-k] 4-methyl-5-phenyl-1,3,2-oxazaborolidine,[2k] and related derivatives). Anyway, these aggregates form a new class of chiral Lewis acids of which the potential utility remains to be revealed.

<u>Hydrogen bridged aggregates (8' and 8'')</u>

Energies of the formation of aggregates 8'a and 8''a are only slightly more positive than the corresponding value of 7''a. Aggregates 8'a and 8''a (Fig. 5) are interesting in that they resemble the structure of the transition state of hydride transfer taking place in borane - ketone complexes of oxazaborolidines.[7d] In the reaction 7''a -> 8''a only 8 kJ mol^{-1} (6-31G//6-31G, Table 2) would be required as the BH$_3$ group of 7''a donates a hydride to the boron of the neighboring oxazaborolidine (Scheme V, part A). Because the hydride affinity of the boron of BH$_3$ group of 8''a is not significantly higher (the boron has three adjacent hydrogens and one nitrogen) than that of the ring boron (the boron has two adjacent hydrogens, one nitrogen and one oxygen) the hydride forms a bridge between the borons [Scheme V (part A) and Fig. 5]. That process resembles the formation of the transition state of the hydride transfer (Scheme V, part B). However, in the case of the hydride transfer the bridging hydrogen would be drawn very strongly by the carbonyl-end of the bridge (the hydride affinity of the carbonyl end is much higher than that of the borane one); eventually so strongly that the borane-end of the hydride bridge "crashes". Therefore, in the case of ketone-borane complexes of oxazaborolidines the hydride transfer would be a highly advantageous reaction and the reverse reaction (i.e. transfer of the hydride back to the borane end) would be hardly possible (Scheme V, part B). The same conclusion cannot be drawn in the case of 8''a.

Even though the formation of the hydride bridge was predicted by these calculations the hydride would not be necessarily bound equally tightly to the both ends of the bridge. The bond lengths and Mulliken overlap populations of the B-H bridge (Figures 5 and 2) imply the hydride to be more tightly bound to the boron of the

BH_3 group because the B_{BH_3}-H_{bridge} bond is shorter than the B_{ring}-H_{bridge} bond (e.g. 0.095 Å shorter in 8''a, Fig. 5) and the Mulliken overlap population of B_{BH_3}-H_{bridge} is considerably higher than that of the B_{ring}-H_{bridge} bond (e.g. 52 % higher in the case of 8''a, Fig. 2).

Scheme V
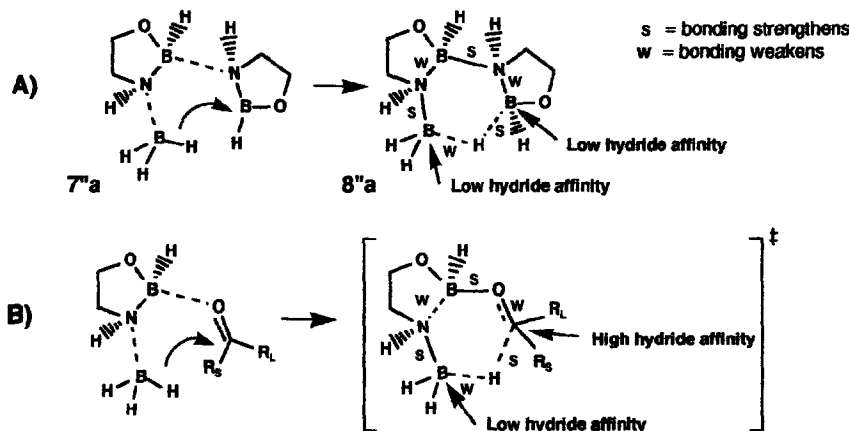
Additional support to the similarity of the logics of the formation of 8''a and the transition state of the hydride transfer can be found if the relative changes of bond lengths and Mulliken overlap populations of the reactions are inspected. In Scheme V these changes are indicates by letters "s" (bonding strengthens) and "w" (bonding weakens). Comparison of these changes reveals that the same bonds change to the same direction in the both reactions. In the light of these observations it looks as if borane adducts of oxazaborolidines would have a general propensity to form complexes with molecules which contain polar Lewis acidic and basic centers connected by one bond. Due to the structure of these system they could be called as "Lewis dipoles" (one end of the dipole behaves as a Lewis acid and the other as a base). The life time and further reactions of the complexes consisting of Lewis dipoles would obviously depend on the type of the stationary point of the hypersurface the complex represents and chemical propensities of the dipoles. In this light, the CBS reduction may actually represent only a single case of a larger group of analogous reactions occurring in stacks of Lewis dipoles which form a 6-membered cyclic arrangement illustrated in Scheme VI. Under this terminology the CBS reduction would be classified as a base exchange reaction between two acidic terminals of a stack consisting of three Lewis dipoles (Scheme VI). Theoretically also the analogous acid exchange reaction between basic terminals should exist but their utility for the chiral catalysis appears to be unknown yet. Nevertheless, some reactions of these groups, not yet discovered, could be of value to the development of technology of organic synthetic chemistry.

Scheme VI

A, A' and A" = Lewis acidic center   ;   B, B' and B" = Lewis basic center
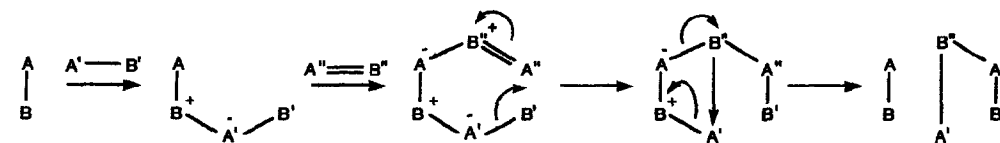
If the formation of aggregates analogous to 8'a and 8''a is considered in the case of catalysts derived from diphenylprolinol it turns out that for the formation of analogs of 8'a would be borane and two enantiomeric oxazaborolidines required whereas the formation of analogs of 8''a would be possible from two molecules of a single enantiomer of the catalyst. However, it is difficult to predict whether the aggregates analogous to 8''a would form or not as the aggregation process would require bringing the C-5 diphenyl substituents close together. Nevertheless, if one takes into account the conformational properties of oxazaborolidine ring (depending on the case the ring can be either in a planar or an envelope type of conformation) the optimized geometry of the model 8''a and standard bond lengths could be used to construct a rough model shown below (not optimized) to illustrate the shape of the aggregate. On the basis of a study of this rough model one could predict that this type of aggregates could form also form borane and two molecules of CBS catalysts derived from diphenyl prolinol or related aminoalcohols.
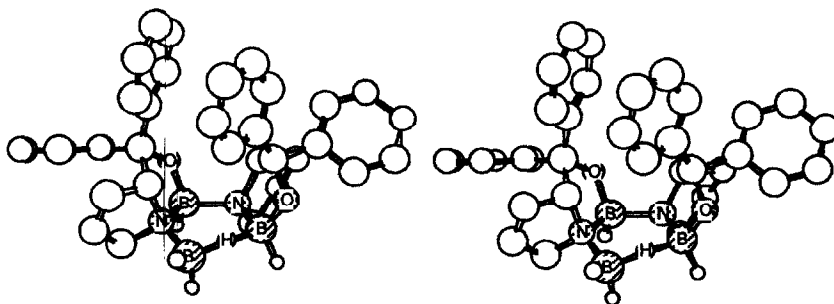
The mechanism of the hydrogen - deuterium exchange reported by Tlahuext and Contreras[8] could be as follows: the B-N ring bond of the Lewis basic oxazaborolidine moiety (right one in the model above) and the B_{BH_3}-D_{bridge} could both break (in the case of BD_3 adducts there would be a deuteride bridge instead of the hydride one). In the resulting intermediate the DHB-O group could turn around the B-O axis and as the boron of the DHB-O group coordinates back to the adjacent nitrogen to restore the oxazaborolidine moiety cleaved in the first step, a hydride bridge could be formed instead of the original deuteride one. Effectively only the two hydrogens (hydrogen and deuterium in the case of BD_3 adducts) adjacent to the Lewis basic oxazaborolidine moiety of the aggregate have changed their places. As the aggregate decomposes a B-deutero oxazaborolidine and a D_2BH adduct of the catalysts will be freed. Indeed, the hydrogen-deuterium exchange has taken place. Computational studies of these exciting catalysts continue.

CONCLUSIONS

Formation of aggregates consisting of two boranes and two oxazaborolidines was predicted to be energetically favorable in the absence of Lewis basic solvents. In the presence of Lewis basic solvents (e.g. THF) the aggregates were predicted to react with the solvent and decompose leading to the formation of solvent complexes of the corresponding monomeric borane adducts. Although energies of the formation of these aggregates were favorable even the most stable one of the aggregates was found to consist of two borane-oxazaborolidine adducts held only loosely together by electrostatic forces. The most stable aggregates were predicted to be those of which the relative positions of the counterparts allow the total dipole moment of the aggregate to cancel as completely as possible.

Formation of the aggregates consisting of one borane and two oxazaborolidines was predicted to be

energetically favorable. The most stable isomer of the aggregates appeared to be a borane O-adduct of dimeric oxazaborolidine containing a diazadiboretane ring of which the formation was predicted to be advantageous even in the presence of Lewis basic solvents (water as a model of the solvent). Formation of all these isomeric aggregates, except those analogous to 8''a, was predicted to be difficult in the case of catalysts derived from diphenylprolinol (the original CBS catalysts[1]) and related aminoalcohols. The formation of these aggregates required either both of the enantiomeric forms of the catalysts to be available (in the CBS reduction the catalyst is used as a single enantiomer) or coordination of one catalyst to the more-hindered concave side of the other.

One potential mechanism explaining why borane and oxazaborolidine can exchange hydrogens was introduced. The key step of the mechanism was the formation of a hydrogen/deuterium bridged aggregate structurally analogous to 8''a. Effects of diphenyl substituents on the C-5 of the oxazaborolidine ring were assessed by constructing a rough model of the key intermediate. On the basis of this model the hydrogen-deuterium exchange was predicted to be possible also in the case of conventional CBS catalysts constructed from diphenylprolinol and related aminoalcohols.

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