Tetrahedron: Asymmetry Vol. 2, No 8, pp. 827-842, 1991
Printed in Great Britain

0957-4166/91 \$3.00+.00
Pergamon Press plc

Quantum Chemical Modeling of Chiral Catalysis. Part 3. On the Role of a Lewis Basic Solvent in the Mechanism of Catalytic Enantioselective Reduction of Carbonyl Compounds by Chiral Oxazaborolidines

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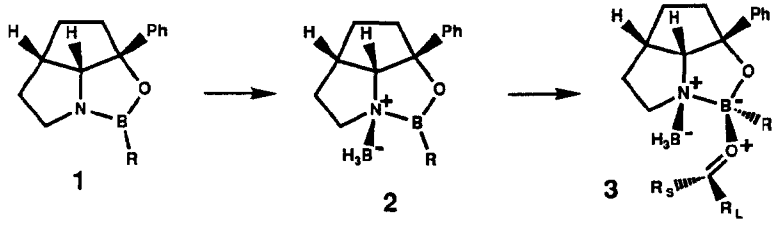
(*Received* 21 *June* 1991)

Summary: - Structures and energies of formation of complexes of Lewis basic solvents with borane - oxazaborolidine adducts functioning as chiral catalysts were investigated by using *ab initio* molecular orbital methods (6-31G*//6-31G*). Formation of complexes of water with a borane adduct of 1,3,2-oxazaborolidine and simpler analogs of it was examined as a model system. Coordination of water to the borane adduct of 1,3,2-oxazaborolidine stabilized the adduct by about 50 - 60 % of that of a free borane. Substitution of water bound to the borane adduct of the catalyst by formaldehyde required about 4 - 5 times more energy than coordination of formaldehyde to the corresponding solvent free borane adduct.

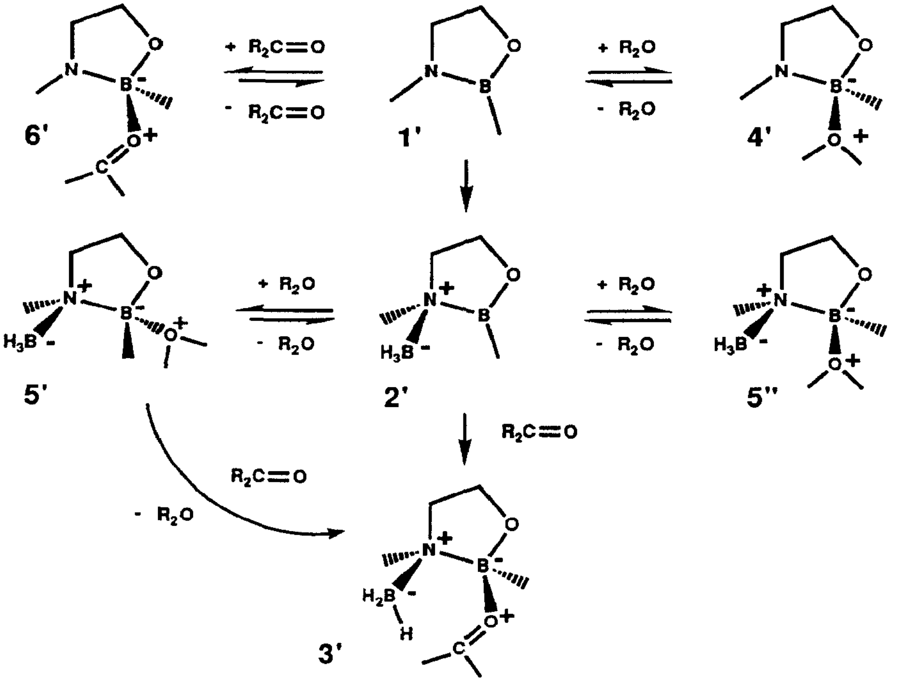
INTRODUCTION

The lately discovered chiral catalysts known also as "chemzymes" or "molecular robots"[1] have opened a new scope to the planning of asymmetric syntheses. Oxazaborolidines (e.g. **1**) used as catalysts for the enantioselective reduction of ketones (CBS reduction) form one of the most prominent class of these new tools for controlling absolute stereochemistry in the synthesis of organic compounds.[1,2] A reasonable reaction mechanism has been suggested for the oxazaborolidine catalysis.[1] The reduction utilizes a borane (e.g. THF•BH_3) as a source of hydrogen and on the basis of NMR studies the intermediate binding the ketone to be reduced has been proposed to be a borane adduct of the oxazaborolidine (e.g. **2**).[2a] Coordination of the ketone to the boron of the oxazaborolidine moiety of **2** would lead to the formation of the complex **3**. This part of the mechanism of the catalysis has been evaluated recently also by using computational methods.[3]



The oxazaborolidine system has been suggested to exist normally as a dimer [including solutions of oxazaborolidines in the case of nonpolar solvents (e.g. benzene)] but to decompose to the corresponding monomers in the presence of a Lewis basic solvent (e.g in THF).[2a] As a solvent clearly plays a role already in the behaviour of a free oxazaborolidine catalyst it could be even more important in the stabilization of reactive intermediates involved in the catalytic cycle.

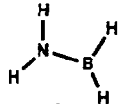
The aim of the work described in this paper was to study energetics of the coordination of a Lewis basic solvent (e.g. THF) to **1** and **2** and the role of solvent in the formation of the ketone complex **3** as depicted in Scheme 1 by using *ab initio* molecular orbital calculations.



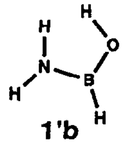
Scheme 1. A plausible role of a Lewis basic solvent (R_2O) in the formation of a borane - ketone complex of an oxazaborolidine catalysts illustrated by using models **1'**- **6'** and **5"**.

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.[4] Techniques similar to those applied in the case of previous studies of this series[3] were employed, i.e. simpler analogous models of the structures to be investigated were examined. The analogs of **1'**-**6'** and **5"** used as models were as follows: **1'a-c** of **1'**; **2'a-c** of **2'**; **3'a-c** of **3'**; **4'a-b** of **4'**; **5'a-c** of **5'**; **5"a-c** of **5"**; and **6'a-b** of **6'**.

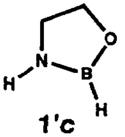
The model **4'** corresponds to a solvent adduct to the boron of an oxazaborolidine whereas the models **5'** and **5"** represent the coordination of a solvent to the boron of the oxazaborolidine ring of **2'** [*anti* (**5'**) and *syn* (**5"**) with respect to the borane moiety]. In principle the ketone adduct **3'** could arise either from the coordination of the ketone to the free borane adduct **2'** or from the substitution of the solvent of **5'** by the ketone. It has been shown earlier that the *anti* coordination of a carbonyl compound to a solvent free borane adduct of an oxazaborolidine would not be favored and that the B-$O_{C=O}$ "bond" of the *anti* complex would be longer than 3 Å.[3a] The possibility of formation of complexes of carbonyl compounds with free oxazaborolidines was studied by using models **6'a-b**.



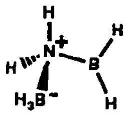
1'a



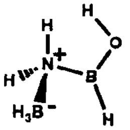
1'b



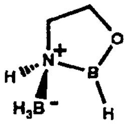
1'c



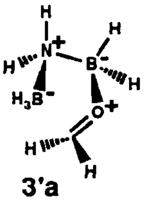
2'a



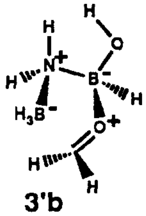
2'b



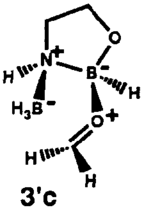
2'c



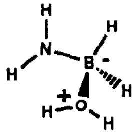
3'a



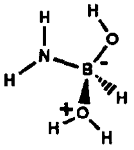
3'b



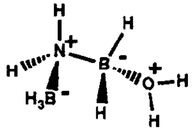
3'c



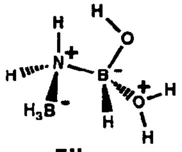
4'a



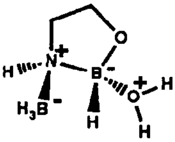
4'b



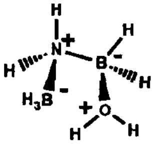
5'a



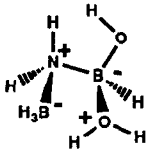
5'b



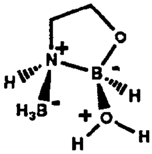
5'c



5"a

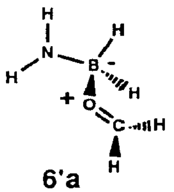


5"b

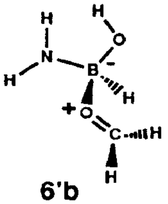


5"c

No other calculations on the structures **4'a-b**, **5'a-c**, **5"a-c**, **6'a-b** or $H_3B\bullet O(CH_3)_2$ (calculated for purposes of comparison) appeared to have been published. The models **1'a-c**, formation of **2'a-c** in the reactions of **1'a-c** with $H_3B\bullet OH_2$, and coordination of $H_2C{=}O$ to **2'a-c** and H_3B giving rise to **3'a-c** and $H_3B\bullet O{=}CH_2$ have been discussed in a more broad scope already.[3a-b] The $H_3C\text{-}O\text{-}CH_3$ and H_2O molecules were calculated for reference purposes. The results were similar to those reported in the literature.[5]



6'a



6'b

RESULTS AND DISCUSSION

Total energies and dipole moments calculated are summarized in Table 1.

Table 1. Total energies (E)[a] and dipole moments (D)[b] of models of **1'** - **5'**, **5"**, **6'** and other structures examined.

Structure	3-21G//3-21G		4-31G//4-31G		6-31G//6-31G		4-31G*//4-31G*		6-31G*//6-31G*	
	E[a]	D[b]	E	D	E	D	E	D	E	D
1'a	-81.04343	2.01	-81.37857	1.76	-81.46276	1.76	-81.40935	1.84	-81.48910	1.82
1'b	-155.55682	3.27	-156.19671	3.20	-156.35434	3.23	-156.25862	2.95	-156.40862	2.96
1'c	-232.01452	3.16	-232.95883	3.18	-233.19703	3.21	-233.07225	2.65	-233.29859	2.67
2'a	-107.29823	4.35	-107.73575	3.84	-107.84578	3.78	-107.78128	4.21	-107.88689	4.24
2'b	-181.82032	4.72	-182.55939	4 21	-182.74260	4.21	-182.63855	4.48	-182.81418	4.46
2'c	-258.28393	5.22	-259.32696	4.93	-259.59052	4.89	-259.45727	4.98	-259.70944	4.97
3'a	-220.54866	3.68	-221.44102	3.60	-221.66706	3.90	-221.55240	3.53	-221.76572	3.50
3'b	-295.05704	2.52	-296.25298	3.21	-296.55198	3.23	-296.39390	3.00	-296.67764	2.95
3'c	-371.52030	2.88	-373.02076	2.53	-373.39848	2.47	-	-	-	-
4'a	-156.63855	0.77	-157.28981	1.06	-157.45044	1.06	-157.35092	0.87	-157.50209	0.86
4'a' [c]	-156.63609	3.75	-157.28850	3.42	-157.44886	3.43	-157.34907	3.34	-157.50025	3.34
4'b	-231.15188	3.10	-232.11083	3.52	-232.34488	3.53	-232.20276	3.27	-232 42422	3.27
5'a	-182.91734	10.82	-183.65982	9.61	-183.84472	9.58	-183.73145	8.51	-183.90747	8.47
5'a' [d]	-182.91363	10.73	-183.65728	9.48	-183.84229	9.39	-183.72869	8.12	-183.90554	8.00
5"a	-182.93533	2.26	-183.67171	2.19	-183.85570	2.16	-183.74535	1.99	-183.92059	1.98
5'b	-257.43739	8.35	-258.48295	7.16	-258.74222	6.70	-258.59013	6.20	-258.83678	6.18
5"b	-257.44823	2.66	-258.48987	2.59	-258.74763	2.57	-258.59193	2.19	-258.83771	2.15
5"b' [e]	-	-	-	-	-	-	-258.58461	1.00	-258.83025	0.94
5'c	-333.89548	9.02	-335.24793	7.11	-335.58750	7.03	-335.40594	6.43	-335.72915	6.39
5"c	-333.91043	2.31	-335.25471	2.02	-335.59281	1.95	-335.40560	2.37	-335.72777	2.32
6'a	-194.26662	3.36	-195.07141	3.10	-195.27124	3.13	-195.16665	2.78	-195.35554	2.81
6'b	-267.78557	0.64	-269.89332	0.41	-270.16742	1.21	-270.01883	0.55	-	-
H_3B	-26.23730	0.00	-26.34927	0.00	-26.37679	0.00	-26.36322	0.00	-26.39000	0.00
$H_3B{\cdot}OH_2$	-101.86336	5.28	-102.28057	4.92	-102.38267	4.86	-102.31848	4.28	-102.41525	4.26
$H_3B{\cdot}O(CH_3)_2$	-179.49234	5.61	-180.21470	5.28	-180.39623	5.20	-180.29864	4.80	-180.47171	4.77
$H_3B{\cdot}O{=}CH_2$	-139.48641	5.78	-140.05755	5.48	-140.19900	5.46	-140.13337	5.38	-140.26800	5.37
H_2O	-75.58596	2.39	-75.90864	2.49	-75.98536	2.51	-75.93900	2.18	-76.01075	2.20
$H_3C\text{-}O\text{-}CH_3$	-153.21319	1.85	-153.83833	1.97	-153.99468	1.97	-153.91690	1.46	-154.06457	1.49
$H_2C{=}O$	-113.22182	2.66	-113.69261	3.02	-113.80836	3.04	-113.75706	2.64	-113.86633	2.67

[a] Total energies given in hartrees. [b] Dipole moments given in debye. [c] A structure in which the boron, nitrogen, oxygen and both the hydrogens of water were all forced to the same plane by symmetry. [d] A structure in which both the borons, nitrogen, oxygen and both the hydrogens of water were all forced to the same plane by symmetry. [e] A conformer of **5"b** in which both the borons, nitrogen and the oxygen of water were found to reside almost in the same plane.

Properties and Formation of the Water Complexes

Energies of the formation of the water complexes are shown in Table 2 whereas the most important bond angles of the complexes are summarized in Table 3. Stereo representations of the structures **5'a-c** optimized at the 6-31G* level are shown in Scheme 2 and those of **5"a-c** in Scheme 3.

Table 2. Energies (ΔE)[a] of the coordination of water to oxazaborolidine models (**1'a-c**) and to the borane complexes (**2'a-c**) of the oxazaborolidine models.

Reaction						3-21G	4-31G	6-31G	4-31G*	6-31G*
									ΔE[a]	
1'a	+	H_2O	->	**4'a**		-24	-7	-6	-7	-6
1'a	+	H_2O	->	**4'a'** [b]		-18	-3	-2	-2	-1
1'b	+	H_2O	->	**4'b**		-24	-14	-14	-14	-13
2'a	+	H_2O	->	**5'a**	(*anti*)	-87	-41	-36	-29	-26
2'a	+	H_2O	->	**5'a'**	(*anti*) [b]	-77	-34	-29	-22	-21
2'a	+	H_2O	->	**5"a**	(*syn*)	-134	-72	-65	-66	-60
2'b	+	H_2O	->	**5'b**	(*anti*)	-82	-39	-38	-33	-31
2'b	+	H_2O	->	**5"b**	(*syn*)	-110	-57	-52	-38	-34
2'b	+	H_2O	->	**5"b'**	(*syn*) [b]	-	-	-	-19	-14
2'c	+	H_2O	->	**5'c**	(*anti*)	-67	-32	-31	-25	-24
2'c	+	H_2O	->	**5"c**	(*syn*)	-107	-50	-45	-25	-20
H_3B	+	H_2O	->	$H_3B{\bullet}OH_2$		-105	-60	-54	-43	-38
H_3B	+	$H_3C\text{-}O\text{-}CH_3$	->	$H_3B{\bullet}O(CH_3)_2$		-110	-71	-65	-49	-45

[a] Energies given in kJ mol^{-1}. [b] See Table 1.

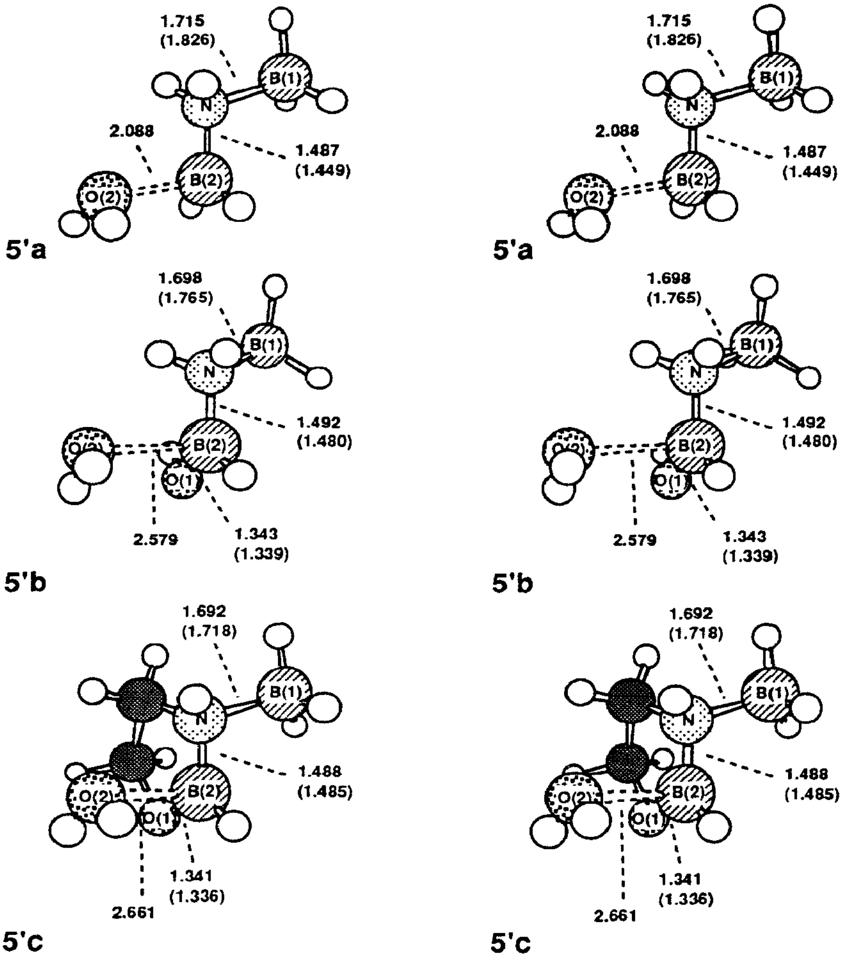
Table 3. The most important bond angles of the water complexes **5'a-c** and **5"a-c**.[a,b]

Angle [b]	5'a	5'b	5'c	5"a	5"b	5"b'	5"c
B-N-B	108.4	108.6	106.8	118.4	118.2	120.7	118.8
O-B-O	-	91.4	96.4	-	105.5	105.0	104.5
N-B-O(1)	-	120.3	110.5	-	115.5	115.7	106.7
N-B-O(2)	100.2	92.0	91.2	106.4	98.8	103.2	105.8
B-N-B-O(1)	-	-66.0	-107.3	-	-61.2	-110.4	-114.0
B-N-B-O(2)	180.0	-158.9	155.0	0.0	50.7	3.6	-3.2

[a] Based on 6-31G*//6-31G*, see Schemes 2 and 3. [b] Bond angles given in degrees.

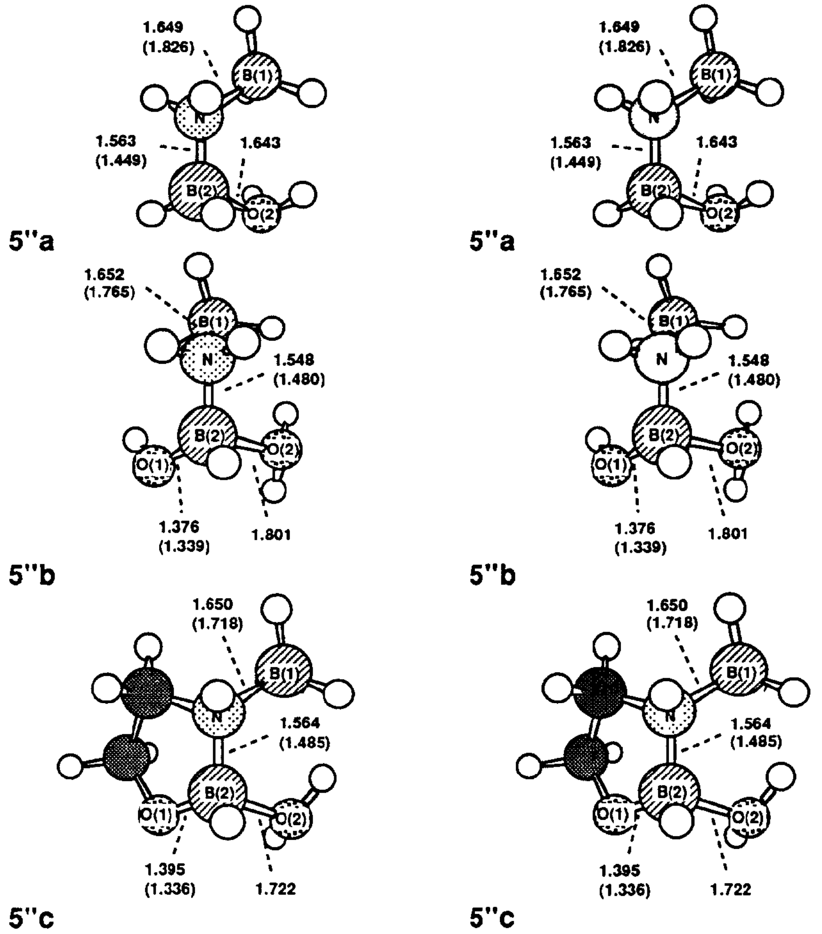
The formation of complexes **4'a-b** turned out to be only slightly energetically favored and the complexes were so loose that the water - boron distance was longer than 3 Å (6-31G*//6-31G*). Significant structural changes were observed neither in the oxazaborolidine models nor in the coordinating water moiety. In the case of **4'b** the hydrogens of water are oriented to point towards the oxazaborolidine model (**1'b**) which indicate clearly that not even that low energetic preference calculated for the coordination of water to **1'b** arises from the B - O_{H_2O} interaction but more likely from the hydrogen bond formation between the hydrogens of water and the oxygen and nitrogen of **1'b**. Thus it looks as if the experimentally observed[2a] propensity of a Lewis basic solvent to favor the monomeric state of an oxazaborolidine would not arise from the solvent - oxazaborolidine complex formation based on the coordination of the solvent to the boron of the oxazaborolidine ring (or at least that effect would not be the most important one of those involved).

The *anti* coordination of water to **2'a-c** (see Scheme 2) also gave rise to the formation of loose complexes (**5'a-c**) but the coordination energy was more advantageous than in the case of formation of water complexes of free oxazaborolidines (**4'a-b**). Nevertheless the B - O_{H_2O} distance in the *anti* complexes (**5'a-c**) remained longer than 2 Å [the most close B-O_{H_2O} contact (2.088 Å) was observed in the case of **5'a** (the 6-31G*//6-31G* level), see Scheme 2].



Scheme 2. Stereo representations of the optimized (6-31G*//6-31G*) structures of *anti* adducts (**5'a-c**) of water to the models of borane adducts of oxazaborolidines (**2'a-c**). Some of the most important bond lengths [in Å] are shown. The values in parenthesis are the corresponding bond lengths of the borane adducts **2'a-c**.

Although the B - O_{H_2O} distance is rather long in the case of **5'a-c** the water approaching the Lewis acidic boron of **2'a-c** from the *anti* site has clearly caused structural changes in the borane adduct moiety. It has been shown previously that the H_3B-N bond of a borane adduct of an oxazaborolidine would be sensitive to changes of the electron structure of the boron of oxazaborolidine moiety;[3b] i.e. if a Lewis base coordinates to the boron of oxazaborolidine moiety of **2'a-c** the H_3B-N interaction becomes more advantageous and the H_3B-N bond shortens. This was observed also in the case of the models **5'a-c**. On the basis of the bond lengths of **5'a-c** shown in Scheme 2 it looks as if the amount by which the H_3B-N bond shortens would depend on the $B - O_{H_2O}$ distance, i.e. the closer the Lewis base (water) comes to the boron of the oxazaborolidine moiety the shorter would be the H_3B-N bond.



Scheme 3. Stereo representations of the optimized (6-31G*//6-31G*) structures of the *syn* adducts (**5"a-c**) of water to the models of borane adducts of oxazaborolidines (**2'a-c**). Some of the most important bond lengths [in Å] are shown. The values in parenthesis are the corresponding bond lengths of the BH_3 adducts **2'a-c**.

In the case of *syn* coordination (i.e. the formation of **5"a-c**) the water is clearly in a more close contact with the boron of the oxazaborolidine moiety, e.g. the B-O_{H_2O} distance was shorter than 1.8 Å in the case of all **5"a-c** (see Scheme 3). Structural changes in the formation of **5"a-c** were similar to those observed in the case of *anti* coordination but the effects were larger [e.g. the H_3B-N bond shortened by 0.026 Å in the case of **5'c** (*anti* coordination) whereas the corresponding effect was 0.068 Å in the case of **5''c** (*syn* coordination)]. Nevertheless, the *syn* coordination energy in the case of **2'b-c** (the energy of formation of **5''b-c**) was less negative than the energy of the corresponding *anti* coordination (formation of **5'b-c**) which could be explained by higher repulsion between the borane and water moieties of **5''a-c**.

These differences observed between the *syn* and *anti* coordination of water to the Lewis acidic boron of **2'a-c** resemble the previously discussed behaviour of formaldehyde,[3a] e.g. the coordination of formaldehyde to **2'a-b** (*syn* with respect to the borane moiety) gave rise to the formation of complex (**3'a-b**) but the corresponding *anti* interaction appeared to be repulsive (i.e. the $B\text{-}O_{O=CH_2}$ "bond" was longer than 3 Å). Although the coordination of water to the borane adducts **2'a-c** is energetically more advantageous than the formation of the corresponding complexes of formaldehyde the $B\text{-}O_{H_2O}$ bonds of the *syn* adducts of water (**5''a-c**) appear to be longer that the corresponding (i.e.the $B\text{-}O_{O=CH_2}$ distance) bonds of **3'a-c**.[3a] Obviously the sp^3 hybridized oxygen of water (coordinating species tetrahedral) feels more repulsion than the sp^2 hybridized oxygen of formaldehyde (coordinating species planar).

The observed propensity of the borane adducts of oxazaborolidines to bind more tightly a ligand coordinated to the boron of the oxazaborolidine ring *syn* with respect to the borane moiety may be considered peculiar, e.g. because the *syn* site should be sterically more crowded. One of possible properties of the borane adducts related with the *syn* selectivity could be the dipole moment. Therefore, in addition to the dipole moment values given in Table 1 (where the values represent actually the "lengths" of the dipole moment vectors), orientations of the dipole moment vectors in the case of the borane adduct **2'c**, the *syn* complexes **5''c**, and *anti* complexes **5'c** were inspected as shown in Figure 1.

The orientational analysis of the dipole moments shown in Figure 1 appears interesting in that the orientation of the vector of the borane adduct (**2'c**) looks almost to invite a *syn* coordinating Lewis base in the case in which the free electron pair of the base being involved in the coordination would point to a direction opposite to that of the dipole moment vector of the Lewis base. In that case the total dipole moment of the system (which is the sum of the moments of the borane adduct and the coordinating Lewis base) would be in a minimum. In the case of corresponding *anti* coordination the effect of the dipole moment should be the opposite one because the dipole moment vector of the incoming solvent would point to the same direction as the dipole moment vector of the borane adduct. This concept would indeed be fully applicable to water (and THF) if their coordination to **2'a-c** would occur in the same way as they coordinate to a proton (i.e. giving rise to the formation of a planar oxonium ion). However, the configuration of the water moiety in the case of *syn* adducts **5''a-c** looks closely similar to that of a conventional tetrahedral arrangement; e.g. the H-O-B bond angles are 110.5° and 109.0° (see also Figure 1). In the case of the *anti* coordination the H-O-B bond angles deviate from those of the tetrahedral values; e.g. in the case of **5'c** the H-O-B bond angles are 105.0° and 94.2°. On this basis one could conclude that in the case of the *syn* approach the dipole moment of the borane adduct moiety would favor the coordination of a Lewis base but in the case in which the coordinating solvent would be water, THF or any other analogous system in which an sp^3 hybridized oxygen serves as the Lewis base the dipole moment of the coordinating species would cancel the moment of the borane adduct only partially and changes in the electron structure of the borane adduct moiety (**2'a-c**) arising from the *syn* coordination contribute significantly to the observed decrease of the dipole moment. Furthermore, in the case of the *syn* adducts the polarized bonds (e.g. B-O, B-N and B-H of the borane moiety) form a cyclic arrangement which is optimal with respect to the minimization of the dipole moment.

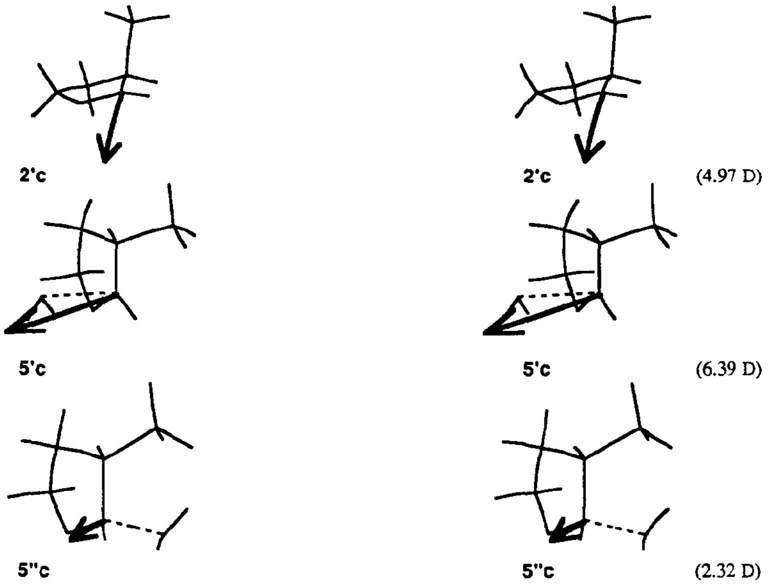


Figure 1. Stereo representations of orientations of the dipole moment vectors (6-31G*//6-31G*) of the borane adduct of 1,3,2-oxazaborolidine (2'c) and the *syn* (5"c) and *anti* (5'c) complexes of water with the borane adduct of 1,3,2-oxazaborolidine (2'c). The vectors were set to originate from the boron of the oxazaborolidine ring.

In the case of the *anti* coordination the water moiety cannot acquire a conformation in which it could decrease the dipole moment of the complex and simultaneously orient an electron pair towards the Lewis acidic boron of the borane adduct. On the other hand, if the *anti* coordination had taken place as far as the corresponding *syn* coordination does, it would have given rise to a further increase of the dipole moment of the system because in the *anti* adduct the polarized B-O and B-N bonds would be in a linear arrangement (in contrast to the cyclic arrangement of the *syn* adducts).

Conformational Analysis of the Water Complexes

In the case of different ethers (water is the most simple model of an ether) the ease of access of a Lewis acid to the Lewis basic oxygen of the ether may vary; e.g. due to spatial interactions. Therefore, as a solvent coordinated to a borane adduct of an oxazaborolidine catalyst may acquire different conformations even in the case of solvents in which the coordinating oxygens would have closely similar electronic properties related to Lewis basicity (appendages of the oxygen would be different), a conformational analysis of the water adducts **5'b**, **5"b** and **5"c** was undertaken. The B-O_{H_2O} bond of the optimized (6-31G*//6-31G*) adducts was rotated 360° by steps of 15° and the conformational energy and dipole moment of each configuration was calculated. In the case of the *anti* complex **5'b** the energy and dipole moment of the system was determined also as a function of a deviation from the optimum of the angle which the plane of water forms with the plane set on the atoms B(2), O(2) and the hydrogen of water which is *syn* to O(2) (see Scheme 2). That operation covers also configurations in which the free electron pairs of the water point away from the Lewis acidic boron of the oxazaborolidine moiety of **5'b**. Results of the conformational analysis of the *syn* complexes **5"b** and **5"c** are shown in Diagram 1 and those of the *anti* complexes in Diagram 2.

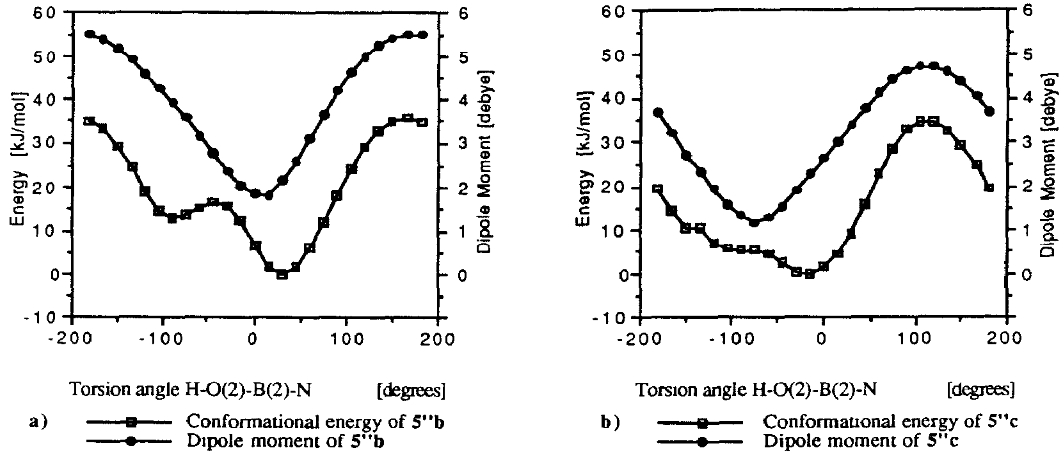


Diagram 1. Conformational energies and dipole moments of the *syn* complexes of water (**5"b** and **5"c**) as a function of the torsion angle H-O(2)-B(2)-N (corresponds to rotating the B-OH_2 bond) calculated at the 6-31G* level.

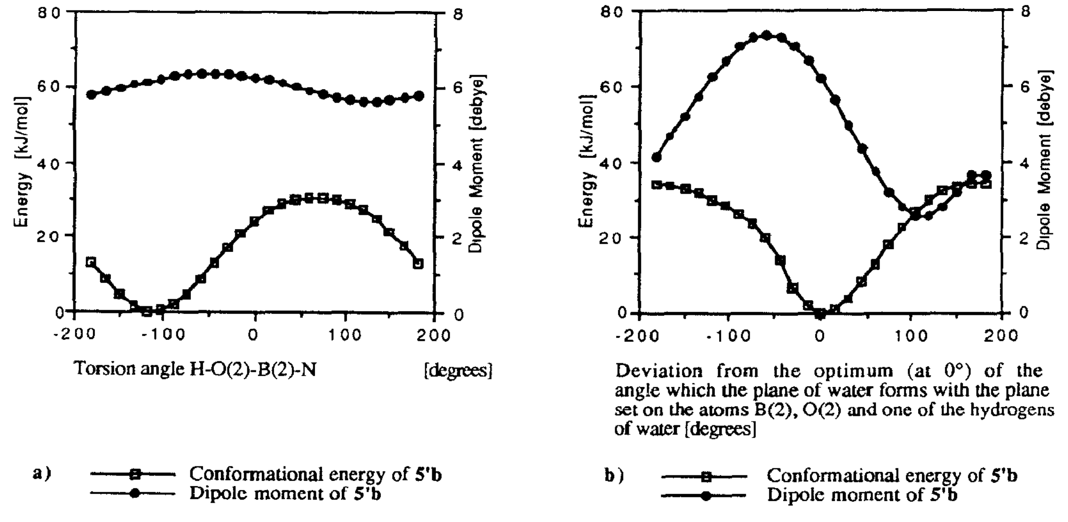


Diagram 2. Conformational energy and dipole moment (6-31G* level) of the *anti* complex of water (**5'b**): **a)** as a function of the torsion angle H-O(2)-B(2)-N (corresponds to rotating the B-OH_2 bond); **b)** as a function of a deviation from the optimum of the angle which the plane of water forms with the plane set on the atoms B(2), O(2) and the hydrogen of water which is *syn* to O(2) (see Scheme 2) of **5'b**.

The conformational analysis of the adduct **5"c** shown in Diagram 1 [part (b)] implies that the *syn* coordinated solvent may turn around the B-OR_2 axis almost freely in the sector from -150° to +30°. However, orientations in which the second free electron pair of the solvent points towards to the borane moiety appear to correspond to energies which are higher that the energy of the formation of the solvent complex [e.g. the energy released in the formation of the *syn* adduct 5"c is 20 kJ mol^{-1} (see Table 2) whereas the maximum energy observed in the conformational analysis of 5"c shown in of Diagram 1 [part (b)] resides about 35 kJ mol^{-1} above the optimum energy of 5"c]. In the case of those configurations the solvent may be either eliminated, turn around towards the more advantageous torsion angles, or however, an inversion of the solvent could take place. In order to study the relative importance of the inversion and elimination pathways the water moiety of the optimized (6-31G*//6-31G*) *syn* complex 5"a was rotated 180° around the B-O_{H_2O} axis and the resulting system was allowed to relax at the 6-31G* level. Both the borons, the nitrogen and the oxygen of water were forced to stay in the same plane by symmetry in order to prevent potential undesired movements. Results of the relaxation experiment are shown in Diagram 3.

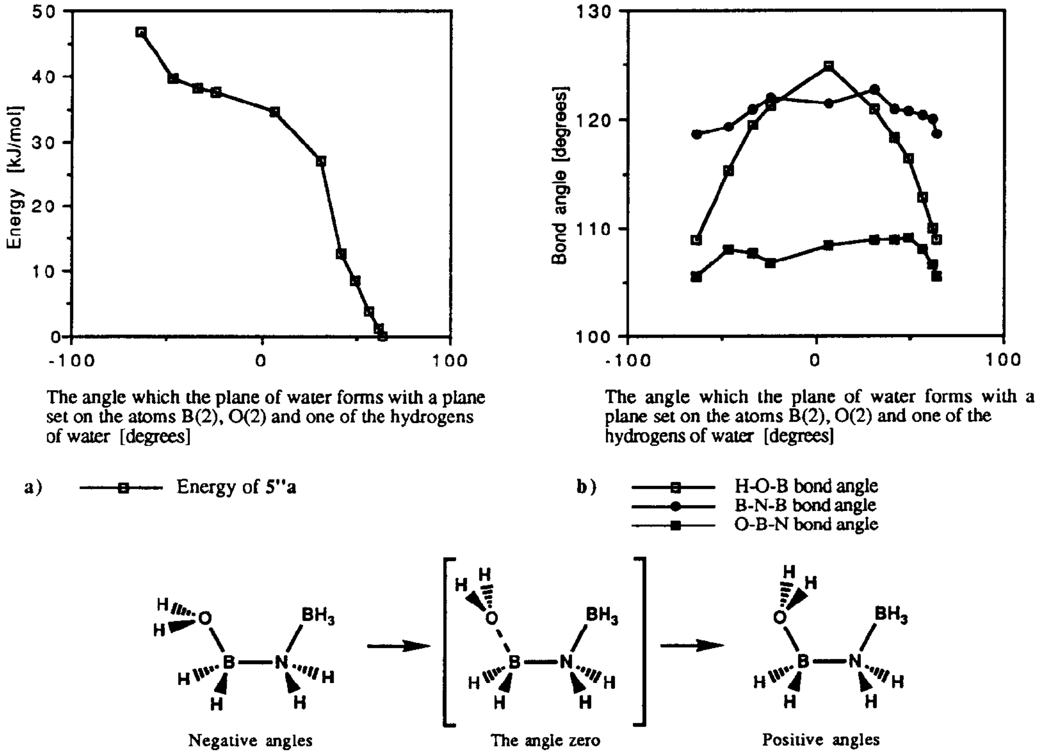


Diagram 3. Relaxation (6-31G* level) of the configuration of the water complexes 5"a provided by rotating the B-OH_2 bond 180° from the optimum value of 5"a. The relaxation is depicted as a function of the angle which the plane of water forms with a plane set on the atoms B(2), O(2) and one of the hydrogens of water of 5"a. Negative values were assigned (arbitrarily) for configurations in which the hydrogens of the water are *anti* to the borane moiety.

In the beginning of the relaxation experiment of the rotated configuration of 5"a (see Diagram 3) the oxygen and hydrogens of the water and the acidic boron [B(2)] started to move towards a configuration in which these atoms would be in the same plane. When the inversion had progressed so far that the acidic boron and the atoms of the water moiety resided all in the same plane (at 0° degrees, see Diagram 3) both of the lone electron pairs of the water pointed at the same angle towards the Lewis acidic boron of the catalysts, consequently the H-O-B bond angle increased to about 125° [see Diagram 3, part (b), at the optimum geometry the H-O-B bond angle is about 106°, i.e. close to a value typical to a tetrahedral geometry)]. However, at 0° the total energy of the system was still about 35 kJ mol^{-1} above the optimum energy of **5"a** [see Diagram 3, part (a)]. Further steps of the relaxation gave rise to a fast decrease of the energy of the system. On the basis of the energy profile of the relaxation it looks as if the inversion would be a spontaneous process, i.e. the energy of the system decreases continuously until the inversion is complete. The results also imply the total energy of a *syn* complex to be rather sensitive to the angle at which the lone pair of the Lewis basic solvent approaches the acidic boron of the borane complex.

The results provided in the case of **5"b** [see Diagram 2] deviate slightly from those of **5"c**, for instance in that the torsion angle corresponding to the optimum of the conformational energy of **5"b** appears to be about 45° - 60° higher than in the case of **5"c**, and there is another shallow minimum of the conformational energy in the case of **5"b**. Altogether these differences could be related to the higher B-N-B-O_{H_2O} torsion angle value of the optimized structure of **5"b** (the angle of **5"b** is 50.7° whereas the corresponding value of **5"c** is -3.2°, see Table 3). The structure **5"b'** (a conformer of **5"b** in which the B-N-B-O_{H_2O} torsion angle is 3.6°, see Table 3) is more closely superimposable with **5"c** and with **5"a** but the structure **5"b'** is about 20 kJ mol^{-1} higher in energy than **5"b** (see Tables 1 and 2).

The maxima of the dipole moments of these *syn* adducts (see Diagram 1) appear to reside at angle values close to those corresponding to the maxima of the conformational energies. Examination of orientations of the dipole moment vectors corresponding to the moments of **5"c** shown in Diagram 1 revealed that the dipole moment vector moves inside a flat cone when the B-O_{H_2O} bond is rotated. The cone resides almost in the plane of the oxazaborolidine ring, i.e. the direction of the moment is not significantly changed.

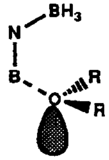
The conformational analysis of **5'b** shown in Diagram 2 [part (a)] implies that a solvent coordinated *anti* to the Lewis acidic boron of a borane adduct of an oxazaborolidine would have less rotational freedom that the corresponding *syn* coordinated solvent. It looks also as if the free lone electron pair of the oxygen of water, in contrast to that of the corresponding *syn* adduct, would prefer staying *syn* with respect to the B-N bond of the oxazaborolidine ring [i.e. the torsion angle "lone pair"-O(2)-B(2)-N prefers to be close to 0°]. On the other hand, rotating the water moiety of the adduct **5'b** around the B-O_{H_2O} bond affects significantly neither the strength nor the orientation of the dipole moment of the system.

In the conformational analysis of the *anti* adduct **5'b** shown in Diagram 2 [part (b)] the energy and dipole moment of the system was determined as a function of a deviation from the optimum of the angle which the plane of water forms with the plane set on the atoms B(2), O(2) and the hydrogen of water which is *syn* to O(2) (see Scheme 2). The results imply the energy of **5'b** to be rather sensitive also to moving of the oxygen of water either away from or closer to the Lewis acidic boron of the oxazaborolidine moiety.

The values close to the maximum of the conformational energy of **5'b** shown in Diagram 2 [part (b), the range 180°±30°] correspond to configurations in which the lone electron pairs of the oxygen of water point away from the Lewis acidic boron of the oxazaborolidine model. Also the minimum of the dipole moment appears to be close to the value corresponding to the maximum of the conformational energy of **5'b**. In the configuration corresponding to the minimum of the dipole moment [Diagram 2, part (b)] the dipole moment vector of the water and that of the borane adduct moiety are almost collinear but point to opposite directions.

On the other hand also the configurations in which the oxygen has been brought closer to the Lewis acidic boron are energetically unfavorable [energies corresponding to angles in the range from -120° to 0° where the B-O_{H_2O} distance changes from 2.579 Å at 0° to 2.363 Å at -120° (minimum 2.267 Å of the B-O_{H_2O} distance at -60° corresponds to an energy of about +20 kJ mol^{-1})]. The maximum of dipole moment [Diagram 2, part (b)] turned out to correspond to the configuration in which the dipole moment vectors of both the water and borane adduct moieties point to the same direction.

The results of the conformational analysis of the water adducts discussed above could be roughly summarized as shown below.



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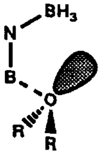

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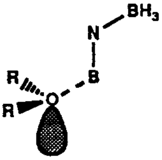

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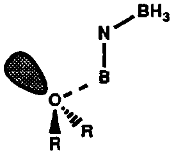

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Formation of the Formaldehyde Complexes

Properties of the *anti* and *syn* adducts of water (**5'a-c** and **5''a-c**) imply significant differences for the ease of substitution of the solvent by the ketone to be reduced. Namely as the *syn* coordinated solvent appeared to be in a more close contact with the borane adduct and the structure of the oxazaborolidine moiety changes more as the *syn* coordination occurs it would be more difficult to replace the *syn* coordinated solvent by the ketone that the corresponding *anti* coordinated solvent. Furthermore, in the *anti* adducts the *syn* site is still "open", the boron of the oxazaborolidine moiety is still sp^2 hybridized, the LUMO-2 orbital still consists mostly of the 2p function the boron of the oxazaborolidine moiety (the LUMO-1 orbital of both the *syn* and *anti* adducts consisted of functions centered to the water moiety), the dipole moment has both strengthened and kept almost the same advantageous direction which the dipole moment has in the solvent free borane adducts (see Figure 1). This indicates clearly that the boron of the oxazaborolidine moiety of the *anti* adduct would still be able to function as a Lewis acid. Thus the *anti* coordinated solvent could be likely replaced by the incoming ketone by a simple S_N2 process.

In the *syn* adduct the *syn* site is obviously blocked by the solvent, the boron of the oxazaborolidine ring is not sp^2 hybridized anymore, there are no LUMO orbitals in the *syn* adduct typical to structures showing properties of Lewis acids, the dipole moment of the system is low and the moment points to a wrong direction to attract a ketone to approach the boron of the oxazaborolidine ring (see Figure 1). Therefore in the case of the *syn* adduct an elimination of the solvent may be required before the coordination of a ketone to the boron of the oxazaborolidine moiety, i.e. conversion of a *syn* adduct of a solvent to the corresponding ketone adduct could be characterized as an S_N1 type of process.

Energies of the formation of formaldehyde complexes **3'a-c** are shown in Table 4. On the basis of these energies it looks as if the substitution of both the *syn* or *anti* coordinated solvents by a ketone could be almost equally favored. However, when these energies are compared one should remember that the mechanism of the substitution of an *anti* coordinated solvent would likely be different from that of the corresponding *syn* coordinated solvent. The energies of the coordination of formaldehyde to **1'a** and **1'b** (the proposed formation of adducts **6'a** and **6'b**) turned out to be low. The B-O_{H_2CO} distance was longer that 3 Å in the both adducts. These results imply that a free oxazaborolidine hardly interacts with the ketone to be reduced.

Although the solvent stabilizes the borane adduct of an oxazaborolidine catalyst it, however, simultaneously inhibits coordination of the ketone to be reduced, i.e. more energy would be needed for the reaction of a solvent stabilized borane adduct of an oxazaborolidine with a ketone than for the corresponding reaction with the solvent free adduct. The height of the energy barrier for the coordination of formaldehyde to a solvent free borane adduct of an oxazaborolidine is about 10 kJ mol^{-1} (e.g. 8 kJ mol^{-1} in the case of the conversion **2'b** -> **3'b**, see Table 4) whereas in the case of a solvent stabilized borane adduct the corresponding energy appears to be about 40 kJ mol^{-1} [e.g. the energy of the replacement of water is 39 kJ mol^{-1} (for **5'b**) or 42 kJ mol^{-1} (for **5"b**) at the 6-31G*//6-31G* level (practically the same conclusion could be drawn in the case of **5'c** and **5"c** but only on the basis of a comparison of results provided for **5'c**, **5"c**, **5'b** and **5"b** at the 6-31G level with those of **5'b** and **5"b** provided at the 6-31G* levels), see Table 4].

Table 4. Energies (ΔE)[a] of the coordination of formaldehyde to oxazaborolidines (**1'a-c**), to the borane complexes (**2'a-c**) and to the water of adducts **5'a-c** and **5"a-c**.

Reaction	3-21G	4-31G	6-31G	4-31G*	6-31G*
			ΔE[a]		
1'a + $H_2C{=}O$ -> **6'a**	-4	-1	0	-1	0
1'b + $H_2C{=}O$ -> **6'b**	-19	-11	-12	-8	-7
4'a + $H_2C{=}O$ -> **6'a** + H_2O	+20	+6	+6	+6	+6
4'b + $H_2C{=}O$ -> **6'b** + H_2O	+5	+3	+2	+6	+6
2'a + $H_2C{=}O$ -> **3'a**	-75	-33	-40	-37	-33
5'a + $H_2C{=}O$ -> **3'a** + H_2O	+12	+8	+4	-8	-7
5"a + $H_2C{=}O$ -> **3'a** + H_2O	+59	+39	+25	+29	+27
2'b + $H_2C{=}O$ -> **3'b**	-39	-3	-3	+4	+8
5'b + $H_2C{=}O$ -> **3'b** + H_2O	+43	+36	+35	+37	+39
5"b + $H_2C{=}O$ -> **3'b** + H_2O	+71	+54	+49	+42	+42
5"b' + $H_2C{=}O$ -> **3'b** + H_2O[b]	-	-	-	+23	+22
2'c + $H_2C{=}O$ -> **3'c**	-38	-3	+1	-	-
5'c + $H_2C{=}O$ -> **3'c** + H_2O	+29	+29	+32	-	-
5"c + $H_2C{=}O$ -> **3'c** + H_2O	+69	+47	+46	-	-
$H_3B{\bullet}OH_2$ + $H_2C{=}O$ -> $H_2C{=}O{\bullet}BH_3$ + H_2O	+34	+19	+18	+9	+7
$H_3B{\bullet}O(CH_3)_2$ + $H_2C{=}O$ -> $H_2C{=}O{\bullet}BH_3$ + $O(CH_3)_2$	+38	+30	+29	+14	+14

[a] Energies given in kJ mol^{-1}. [b] See Table 1.

Altogether, the relative stability of complexes of ethers with borane adducts of oxazaborolidines with respect to the corresponding complexes of ketones is clearly higher than could have been expected on the basis of the comparison of relative stabilities of water and formaldehyde complexes of a free borane [e.g. replacement of the water in the complex $H_3B{\bullet}OH_2$ by formaldehyde requires only an energy of 7 kJ mol^{-1}, whereas the related reactions in the case of water complexes of borane adducts of oxazaborolidines require about 4 - 6 times that (6-31G*//6-31G*), see Table 4]. This means also that the coordination of borane to the ketone to be reduced could occur and enhance the rate of undesired noncatalytic reductions (it has been experimentally observed[2a] that the enantioselection of oxazaborolidine catalyzed reductions decreases with the increasing concentration of THF•BH_3 above the level of 0.6 mol %).

On the basis of the results discussed in this paper and by making use of some energy values published earlier[3b] a diagram describing the energy profile of the formation of a ketone - borane complex of an oxazaborolidine catalyst was constructed as shown in Figure 2.

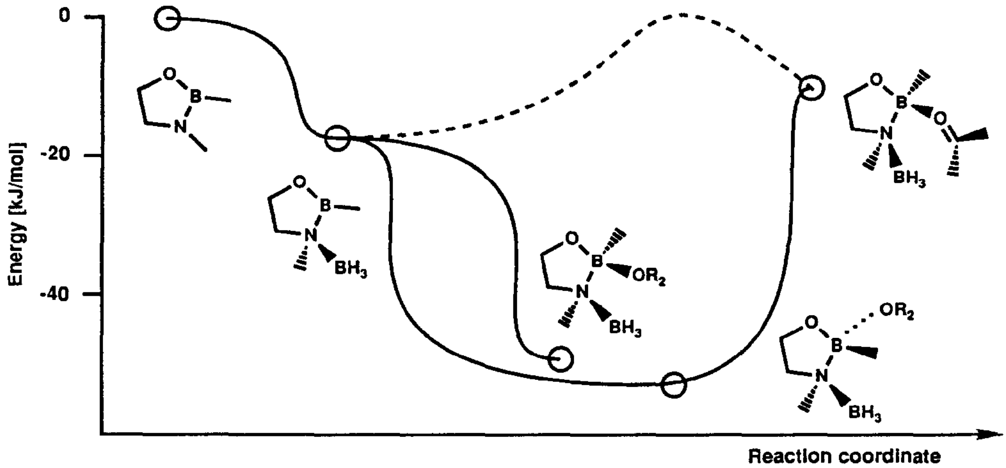
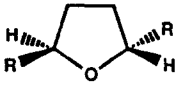


Figure 2. Energy diagram of the formation of a ketone - borane complex of an oxazaborolidine catalyst (OR_2 is a solvent).

In addition to the basic mechanistic knowledge acquired on the role of Lewis basic solvents in the function of the oxazaborolidine type of catalysts, the results of the present work imply that the use of a chiral solvent could have some potential in the optimization of the activity of the catalysts; e.g. the THF derivative **A** shown below should behave in a different way than **B** with respect to the coordination to the borane adduct **2** (note the absolute stereochemistry of **A**, **B** and **2**).



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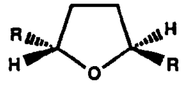

B

On the other hand, as the Lewis basic solvent, e.g. THF, used in the reductions catalyzed by oxazaborolidines would favor also noncatalytic reactions of the borane with the ketone to be reduced leading to racemic products it could be advantageous to optimize the amount of the Lewis basic solvent used (i.e. potentially a mixture of a Lewis basic and a nonpolar solvent could be used). As the best location of a Lewis basic solvent has been determined in the present work one could consider constructing a system in which an ether group would be covalently bound to the catalyst with an inert spacer. The spacer should be devised in such a way that it would allow the ether group to coordinate to the boron of the oxazaborolidine moiety when a stabilizing interaction is needed.

CONCLUSIONS

Coordination of an ether type of solvent to the Lewis acidic boron of the oxazaborolidine ring of the borane adduct of the catalyst may occur as likely in the *syn* or *anti* orientation with respect to the borane moiety of the adduct. The coordinating solvent stabilizes the borane adduct but because binding of the solvent would be energetically about 4 - 5 times more advantageous than the coordination of a carbonyl compound the solvent inhibits the coordination of the ketone to be reduced to the borane complex of the catalyst. On the other hand, in the absence of the stabilization arising from the coordination of a solvent other undesirable reactions (e.g. coordination of another oxazaborolidine to the Lewis acidic boron of the borane adduct and other effects related to aggregation) could take place. Computational studies on these exciting catalysts continue.

ACKNOWLEDGEMENTS

The University of Helsinki and the TEKES foundation are acknowledged for providing computational resources needed to carry out this study.

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