Tetrahedron: Asymmetry Vol. 2, No. 11, pp. 1133-1155, 1991
Printed in Great Britain

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

Quantum Chemical Modeling of Chiral Catalysis. Part 4. On the Hydride Transfer in Ketone Complexes of Borane Adducts of Oxazaborolidines and Regeneration of the Catalyst

Vesa Nevalainen

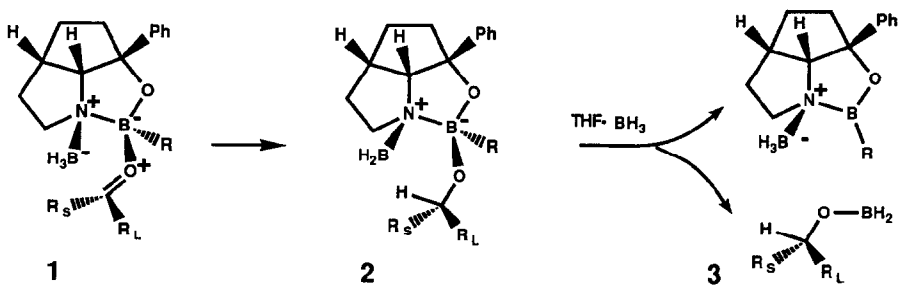
University of Helsinki, Department of Chemistry, Vuorikatu 20, SF-00100 Helsinki, Finland

(*Received* 20 *August* 1991)

Summary: - Hydride transfer and regeneration steps in ketone complexes of borane - oxazaborolidine adducts functioning as chiral catalysts were investigated by using *ab initio* molecular orbital methods. The hydride transfer was found to be highly exothermic. Formation of a novel 1,3-oxazadiboretane structure was found to precede the regeneration of the catalyst. The regeneration occurring *via* a cleavage of the 1,3-oxazadiboretane ring was found to require about 10% of the energy released in the hydride transfer. Reactions being potentially involved in the deactivation of oxazaborolidine catalysts were found.

INTRODUCTION

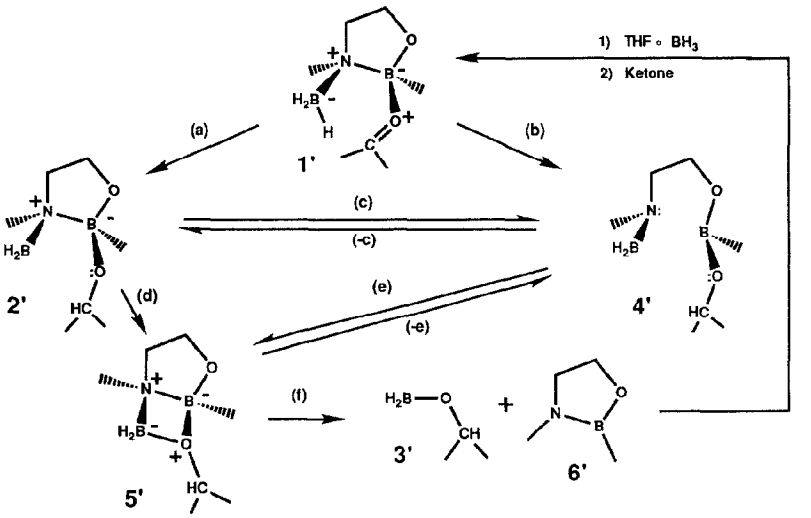
The chiral catalysts known as "chemzymes"[1] or "molecular robots"[1g] have provided us with a new challenging area of research and a promising source of practical applications. Borane adducts of oxazaborolidines, among the first examples of working catalysts, formed *in situ* in a mixture of an oxazaborolidine and H_3B•THF appeared to be highly effective for the enantioselective reduction of ketones (CBS reduction).[1] A reasonable reaction mechanism has been suggested for the catalysis,[1] which has been partially evaluated also by using computational methods[2] including the role of a Lewis basic solvent[2h] in the formation of the key intermediate **1**. Nevertheless, there are still "grey" areas in the catalytic cycle; e.g. what really happens after the hydride transfer from the BH_3 moiety to the carbon of the ketone coordinated to the boron of the oxazaborolidine moiety of **1** ?



The complex **2** has been assumed to be the first intermediate arising from the hydride transfer (**1** -> **2**). Even though the mechanism involving **2** is reasonable, there is a number of plausible reaction pathways not

evaluated yet by which the complex **2** could be converted to final products. It looks likely that the first cycle of the catalysis could produce the alkoxyborane **3**. However, in the case in which H_3B•THF has been used as a source of hydrogen the final product has been found to be the dialkoxyborane derivative of the newly formed chiral alcohol indicating that two hydrogens of BH_3 would eventually be consumed in the reduction (which does not mean that even the third hydrogen could not be consumed; namely, also catecholborane has been shown to function as a source of hydrogen in the CBS reduction).[1]

The aim of the work described in this paper was to study the energetics of the first hydride transfer and evaluate the stability and subsequent reactions of the complex **2** leading eventually to the regeneration of the catalyst. In addition to studies on the formation of **1**,[2a,2g-h] some potential products arising from further reactions of the complexes **1** and **2** have been previously briefly introduced.[2e-f] The reactions discussed are depicted in Scheme 1.



Scheme 1. Potential reactive intermediates arising from the hydride transfer occurring in the ketone - borane complex of an oxazaborolidine catalyst illustrated by using the models **1'- 6'**.

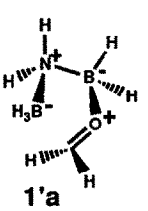
As previously mentioned, the first intermediate arising from the hydride transfer occurring in **1'** could be either **2'** [pathway (a)][1] or **4'** [pathway (b)].[2c-f] The intermediate **2'** could be converted to **4'** by a cleavage of the B-N bond of the oxazaborolidine moiety of **2'** [pathway (c)]. Both the intermediates **2'** and **4'** could react further to form an oxazadiboretane structure **5'** [pathway (d) in the case of **2'**, or pathway (e) in the case of **4'**]. The oxazadiboretane ring could be cleaved leading either back to **4'** [pathway (-e)] or to the regeneration of the catalyst [the formation of **3'** and **6'**, pathway (f)].

MODELING METHODS

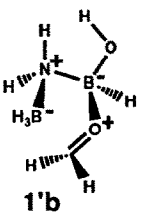
As the goal of this work was to elucidate the mechanism of the enantioselective reduction of ketones catalyzed by oxazaborolidines with respect to the relative stabilities of intermediates arising from the hydride

transfer occurring in the ketone - borane complex of an oxazaborolidine (in contrast to refining a few intermediates or a reaction to the utmost high level of inspection) standard methods of computational quantum chemistry were the obvious choice of research tools. On the other hand, as the study involved a close inspection of reactive intermediates the methods used needed to be the most reliable ones among those affordable at the level of the size of structures involved in the modeling. Consequently, *ab initio* calculations at various levels of sophistication were selected as the final tools. However, *ab initio* calculation, even when performed at the restricted Hartree-Fock level, may depending on the number of atoms of the target structure turn out to be extremely time consuming. Albeit the efficiency of commonly available computers has continuously increased planning of the computational work with respect to the relation between the size of the target structures and the amount of information affordable by the study of the targets would be still necessary in many cases. Considering a modeling project in this respect leads to a conclusion that the most essential parts of the structures of actual interest should be described best also in the models being eventually evaluated computationally. A series of models in which the compatibility of the models with the actual working catalysts gradually increases may then be examined. Inspection of different properties calculated for the members of the series represented for example as a function of the increasing structural complexity of the models (or any other useful variable), would allow one to provide further confirmation on the reliability of the conclusions drawn on the basis of the most small models (which, in contrast to the more advanced models, could be normally studied at the best level of accuracy).

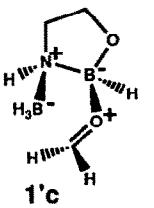
In the case of this work the most essential area of the structures of interest would be obviously found in the active center of the catalysts and in the close neighborhood of it. Actually the active center of oxazaborolidine catalysts could be simplified even to the level of adjacent boron and nitrogen atoms [i.e. the "parent model" of an oxazaborolidine catalyst would be aminoborane (H_2B-NH_2)]. The series of models in which the degree of similarity between the models and the real working catalysts gradually increases may not have to be long. For example such a series could consist of H_2B-NH_2, HO-BH-NH_2 and, already as the last member of the series, a system in which the second model is embedded into a five membered ring (i.e. 1,3,2-oxazaborolidine). This short series would take into account the effect of the oxygen of the oxazaborolidine system to the function of the catalyst and the effects arising from rigidity and ring strain of the oxazaborolidine ring. Although these models are indeed rather simple it has been shown in the previous parts of the series of these reports that selected properties of oxazaborolidine catalysts and reactive intermediates can be evaluated by studying even the most simple models of the catalysts by *ab initio* methods.[2] Consequently, these modeling principles were applied also in the case of this work. The analogs of **1'-6'** used as models were as follows: **1'a-c** of **1'**; **2'a-c** of **2'**; **3'a-d** of **3'**; **4'a-b**, **4'a'** and **4'b'** of **4'**; **5'a-f** of **5'**; and **6'a-c**, **6'b'** of **6'**.



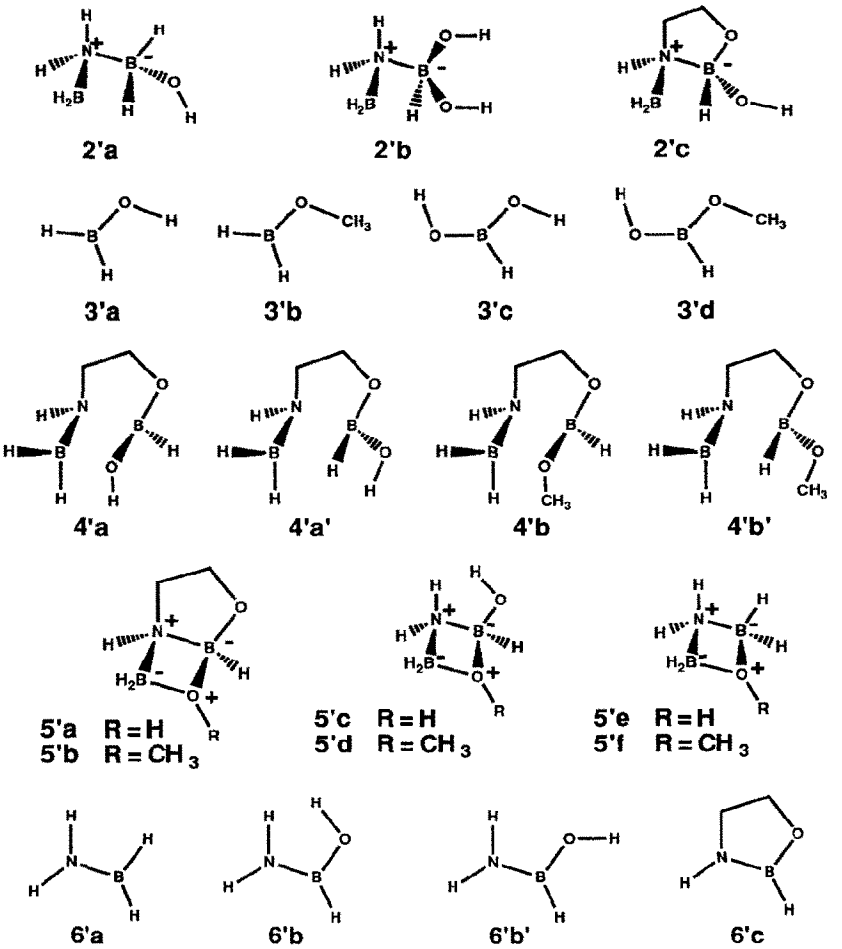
1'a



1'b



1'c



Standards *ab initio* calculations were performed by using the Gaussian 80 series of programs at the 3-21G, 4-31G, 6-31G, 4-31G* and 6-31G* levels.[3] Polarization functions were included only in the case of models containing seven or less atoms heavier than hydrogen whereas the split-valence basis sets (3-21G, 4-31G and 6-31G) were used to characterize all the structures studied. Totally five different basis sets were used to allow comparison of the results of this work with those of earlier reports of this series[2a-h] and with those of other studies of related boron containing structures; and of course, to allow the performance of different basis sets to be compared.

No other calculations on the structures **2'a-c**, **4'a-b**, **4'a'**, **4'b'** and **5'a-f** appeared to have been published except a few preliminary communications.[2e-f] The oxazadiboretane system turned out to be not mentioned in the literature before these communications.[2e-f] However, the corresponding cycloborazane [i.e.

$(H_2B\text{-}NH_2)_2$] has been a subject of a number of studies in which the propensity of aminoboranes to form cyclic dimeric structures analogous to **5'** has been proven [formation of the corresponding trimeric aminoboranes (cyclotriborazanes) appeared to be even more favored].[4] Also the adduct $(H_2B\text{-}OH)_2$ has been mentioned in the literature.[5] In the light of these observations and also by taking into account that even the oxazaborolidine catalysts (**6'**) are observed to exist as dimers,[1a] it is not particularly surprising that the oxazadiboretane system was finally recognized. In the case of the borane - ketone adducts (**1'a-c**) only the energetics of the formation of **1'c** has been reported before[2h] whereas the models **1'a-b** and **6'a-c** [including structures $H_2C{=}O{\bullet}BH_3$, $H_3B{\bullet}NH_3$, $H_3B{\bullet}OH_2$, $H_2C{=}O$ and the potential role of analogs of **6'b'** (an isomer of **6'b**) as catalysts] have been discussed in a more broad scope already.[2a,2g-h] Results calculated on hydroxy and alkoxy substituted boranes (**3'a-d**) were similar to those provided by Boggs and Cordell[6] who examined thoroughly the structures $H_2B\text{-}OH$ (i.e. **3'a**), $HB\text{-}(OH)_2$ (i.e. **3'c**) and other related boranes. The molecules $H_3C\text{-}OH$ and H_2 were calculated for reference purposes. The results were practically equal to those reported in the literature.[7]

The Gaussian 80 series of programs, in contrast to the more recent versions of the Gaussian system, do not make use of the Hessian matrix in the geometry optimization but the optimization would be finished when first derivatives of the energy with respect to the coordinates of the target structure would reach the threshold level (0.001 hartree $bohr^{-1}$).[3] Thus, as the second derivatives are not automatically calculated there is no confirmation on the minimum found; i.e. whether it would really represents a stationary point of the PE hypersurface. This may not be a serious problem in the case of structures which have been studied before or with those which are simple derivatives of previously studied systems. However, as the oxazadiboretane ring appeared to be a novel system eigenvalues of Hessian matrix and vibrational frequencies of the optimized (6-31G*//6-31G*) structures of **5'c** and **5'e** were determined separately. In the case of both **5'c** and **5'e** all the eigenvalues of the second derivative matrix were positive within the accuracy of the calculation; i.e. the minima found represent real stationary points of the PE hypersurfaces of **5'c** and **5'e**. Furthermore, the same structures (**5'c** and **5'e**) were optimized also by using the Gaussian 90 system (6-31G*//6-31G*, by employing the Berny method) and the vibrational frequencies of **5'e** were calculated.[8] The total energies deviated from those computed by using Gaussian 80 only by 0.5 kJ mol^{-1}, the bond lengths by 0.003 Å and the frequency values of **5'e** (compared in the range of 4131 - 614 cm^{-1}) by 16 cm^{-1} in maximum. On this basis it looks that the results provided by using the Gaussian 80 system do not differ significantly from those provided by using the Gaussian 90 package albeit Gaussian 90 is more accurately parametrized and works more efficiently. The calculations were carried out in two cluster systems composed of VAX 8800, VAX 6000-420 and MicroVAX 3300 computers and six VAXstation 3100 workstations running the VMS operating system.

RESULTS AND DISCUSSION

Total energies and dipole moments calculated are summarized in Table 1. Optimized (6-31G//6-31G) structures of **1'c, 4'b** and **5'b** are depicted in Scheme 2. Optimized structures of **4'a** and **5'a** (6-31G*//6-31G*) are shown in Scheme 3. Optimizations of **2'a-c** turned out to be difficult because these structures either decomposed to systems analogous to **4'** or collapsed to the corresponding oxazadiboretanes, except in the case of **2'a** which had one conformation "surviving" the optimization even at the 6-31G* level.

On the Formation of Borane - Ketone Complexes of Oxazaborolidines

The formation of **1'a** and **1'b** has been discussed earlier,[2a,2h] whereas only the energetics of **1'c** has been mentioned in the literature before.[2h] As the complex **1'c** is a better model of **1** it could be useful to compare also the structural properties of **1'c** with those of **1'a-b**. A comparison of the most important bond lengths and bond angles of **1'a-c** is shown in Table 2.

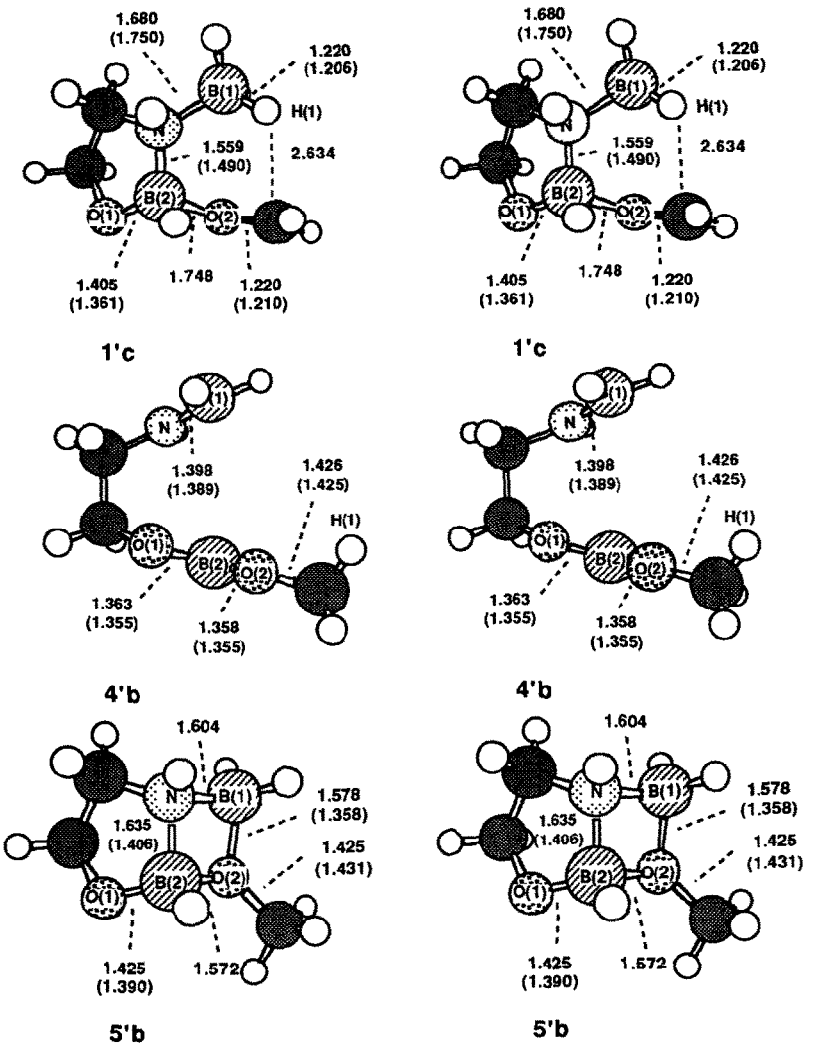
Table 1. Total energies (E)[a] and dipole moments (D)[b] of the models 1' - 6', $H_2C{=}O{\cdot}BH_3$, $H_3C{-}O(\cdot BH_3)H$ and some other small molecules involved in the study.

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	-220.54866	3.68	-221.44102	3.60	-221.66706	3.90	-221.55240	3.53	-221.76572	3.50
1'b	-295.05704	2.52	-296.25298	3.21	-296.55198	3.23	-296.39390	3.00	-296.67764	2.95
1'c	-371.52030	2.88	-373.02076	2.53	-373.39848	2.47	-	-	-	-
2'a[c]	-181.79567	2.40	-182.53885	1.68	-182.72366	1.89	-182.61243	2.18	-182.78896	2.15
2'b	-256.30918	1.76	-257.35554	2.39	-257.61387	2.42	-257.61387	-[d,e]	-	-
2'c	-332.77529	2.97	-334.12623	-[d,e]	-	-	-	-	-	-
3'a	-100.76196	1.91	-101.17676	1.87	-101.27793	1.89	-101.22430	1.68	-101.32139	1.68
3'b	-139.57090	2.16	-140.13955	2.08	-140.28052	2.06	-140.21037	1.71	-140.34556	1.71
3'c	-175.28746	1.92	-176.00798	1.95	-176.18225	1.97	-176.08616	1.68	-176.25336	1.69
3'd	-214.09647	2.25	-214.97015	2.36	-215.18420	2.39	-215.07167	1.99	-215.27694	2.01
4'a	-332.79772	3.52	-334.15809	3.62	-334.49656	3.63	-334.31677	3.06	-334.63933	3.11
4'a'	-332.79891	1.21	-334.15960	1.42	-334.49807	1.49	-334.31767	0.99	-334.64029	1.04
4'b	-371.60716	3.29	-373.12059	3.34	-373.49882	3.40	-	-	-	-
4'b'	-371.60909	1.32	-373.12236	1.47	-373.50064	1.54	-	-	-	-
5'a	-332.82019	1.57	-334.15586	1.85	-334.49239	1.90	-334.30493	1.65	-334.62681	1.75
5'b	-371.63266	1.31	-373.12185	1.58	-373.49818	1.67	-	-	-	-
5'c	-256.35880	1.71	-257.39068	1.62	-257.64734	1.62	-257.49078	2.06	-257.73638	2.06
5'd	-295.17021	1.94	-296.35536	2.03	-296.65164	2.04	-296.47763	1.84	-296.76124	1.87
5'e	-181.84477	0.82	-182.57271	1.01	-182.75550	1.07	-182.64372	1.45	-182.81873	1.48
5'f	-220.65768	0.60	-221.53912	0.67	-221.76155	0.73	-221.63330	0.80	-221.84643	0.81
6'a	-81.04343	2.01	-81.37857	1.76	-81.46276	1.76	-81.40935	1.84	-81.48910	1.82
6'b	-155.55682	3.27	-156.19671	3.20	-156.35434	3.23	-156.25862	2.95	-156.40862	2.96
6'b'	-155.55972	0.71	-156.20025	0.91	-156.35806	0.97	-156.26137	0.67	-156.41145	0.71
6'c	-232.01452	3.16	-232.95883	3.18	-233.19703	3.21	-233.07225	2.65	-233.29859	2.67
$H_2C{=}O{\cdot}BH_3$	-139.48641	5.78	-140.05755	5.48	-140.19900	5.46	-140.13337	5.38	-140.26800	5.37
$H_3C{-}O(\cdot BH_3)H$	-140.67696	5.65	-141.24677	5.33	-141.38863	5.26	-141.30766	4.78	-141.44256	4.73
$H_3B{\cdot}NH_3$	-82.16629	5.70	-82.49789	5.52	-82.58166	5.52	-82.53244	5.59	-82.61180	5.58
$H_3B{\cdot}OH_2$	-101.86336	5.28	-102.28057	4.92	-102.38267	4.86	-102.31848	4.28	-102.41525	4.26
$H_2C{=}O$	-113.22182	2.66	-113.69261	3.02	-113.80836	3.04	-113.75706	2.64	-113.86633	2.67
$H_3C{-}OH$	-114.39802	2.12	-114.87151	2.29	-114.98815	2.29	-114.92563	1.85	-115.03537	1.87
H_2	-1.12296	-	-1.12683	-	-1.12683	-	-	-	-	-

[a] Total energies given in hartrees. [b] Dipole moments given in debye. [c] The only stable conformation of **2'a** [d] The initial structure decomposed (bonds longer than 2Å were formed). [e] The energy of the complex before it started to decompose

On the basis of the bond lengths and bond angles shown in Table 2 all the structures **1'a**, **1'b** and **1'c** look closely similar. The only clearly recognizable difference appears in the torsion angles B-N-B-O(1) and B-N-B-O(2) from which the former is larger in **1'a** than in **1'c** whereas in the latter case the order of the values obviously is the opposite one. Although differences of the H(1)-$C_{c=o}$ distances in **1'a-c** are small the carbonyl moiety of **1'c** is closer to the hydride [i.e. H(1)] than that of **1'a-b**. Consequently, additional

confirmation of the validity of properties of the intermediates arising from the further reactions of **1'c** inspected here only in the light of calculations performed without polarization functions could be achieved by comparing the properties to those of corresponding more simple models treated also by using polarization functions.

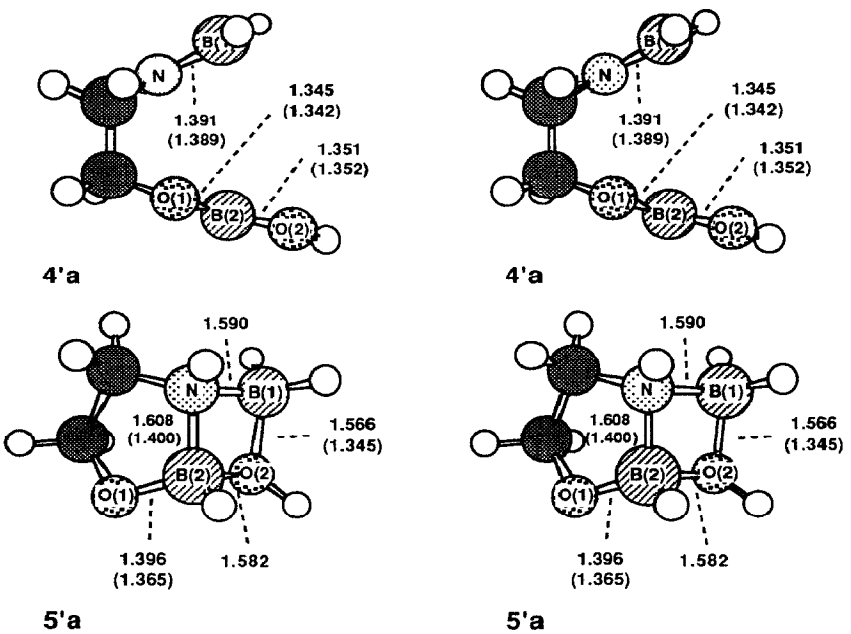


Scheme 2. Stereo representations of the optimized (6-31G//6-31G) structures of **1'c**, **4'b** and **5'b**. Some of the most important bond lengths are shown. The values in parentheses are the corresponding bond lengths of the BH_3 adduct of **6'c** and free $H_2C{=}O$ (in the case of **1'c**), or bond lengths of **3'd** and **6'a** (in the case of **4'b**), or bond lengths of **3'b** and **6'c** (in the case of **5'b**).

Table 2. Bond lengths and bond angles of the borane - ketone complexes **1'a-c** calculated at the 6-31G//6-31G level.[a]

Parameter[b]	1'a	1'b	1'c	Parameter[b]	1'a	1'b	1'c
B(1)-N	1.676	1.687	1.680	B-N-B	117.9	118.2	119.7
B(2)-N	1.558	1.551	1.559	N-B-O(1)	-	117.4	106.3
B(2)-O(1)	-	1.404	1.405	N-B-O(2)	102.9	100.4	104.8
B(2)-O(2)	1.675	1.754	1.748	B-O=C	125.4	124.3	126.2
C=O	1.226	1.223	1.220	B-N-B-O(1)	-	-159.5	-132.3
B(1)-H(1)	1.214	1.214	1.220	B-N-B-O(2)	-49.9	-46.3	-22.0
C--H(1)	2.764	2.761	2.634	N-B-O=C	83.8	90.2	87.2

[a] Bond lengths given in ångströms and bond angles in degrees. [b] See Scheme 2.



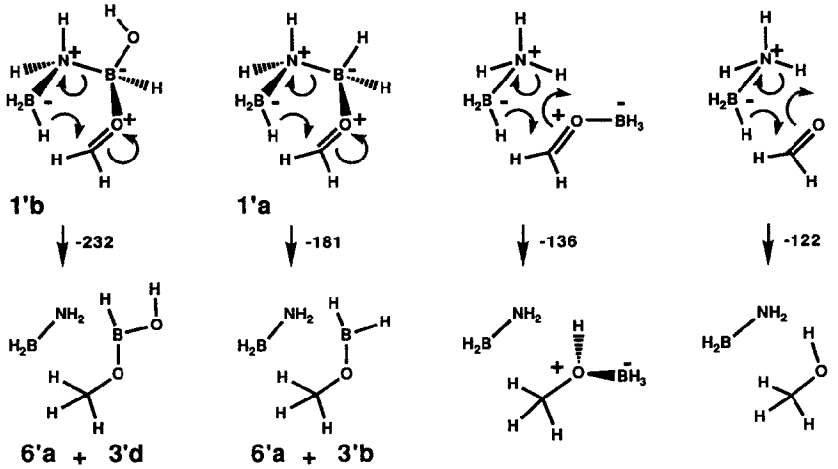
Scheme 3. Stereo representations of the optimized (6-31G*//6-31G*) structures of **4'a** and **5'a**. Some of the most important bond lengths are shown. The values in parentheses are the corresponding bond lengths of **3'd** and **6'a** (in the case of **4'a**) or **3'a** and **6'c** (in the case of **5'a**).

Products and Energies of the Hydride Transfer

As shown in Scheme 1, there are two plausible intermediates (**2'** and **4'**) arising from the intramolecular hydride transfer occurring in **1'**. When the models of **2'** were optimized, depending on the initial geometry and the basis set used, they either collapsed to the corresponding oxazadiboretanes or decomposed giving rise to the formation of analogs of **4'**. Although an optimum geometry was found in the case of all the structures **2'a-c** at the 3-21G level (which strongly overestimates attractive forces in the case of these Lewis acid - base interactions), only **2'a** (and only one conformer of **2'a**; a conformation in which the torsion angle N-B-O-H

was forced to 180° by symmetry) turned out to be stable at the 6-31G*//6-31G* level. Consequently, on the basis of these calculations processes involving **2'** would be described less reliably than those involving **4'**.

Energies of the intramolecular hydride transfer occurring formally *via* the pathway [(**b**), see Scheme 1] and energies of a number of related intermolecular reactions are shown in Table 3. The formal analogy of these reactions ($H\text{-}B^{+}\text{-}X^{-}\text{-}H + C{=}O \rightarrow B\text{-}X + H\text{-}C\text{-}O\text{-}H$; X = N or O) is illustrated in Scheme 4. On the basis of those energies one concludes that the most energy releasing hydride transfer occurs in **1'b**. The effect of the oxygen of the oxazaborolidine moiety to the energetic advantageousness of the hydride transfer is rather large, e.g. the hydride transfer energy of **1'b** is about 51 kJ mol^{-1} (≈ 22%) more negative than that of **1'a** (on the basis of 6-31G*//6-31G*, see Table 3). This difference could be rationalized by taking into account that the energy of formation of **1'a** (-33 kJ mol^{-1}; 6-31G*//6-31G*) is more favorable than that of **1'b** (+8 kJ mol^{-1}).[2a] Rest of the difference arises from the different stability of **3'd** and **3'b**.



Scheme 4. Energies [kJ mol^{-1}, (6-31G*//6-31G*)] and the formal analogy of intramolecular hydride transfer (**1** -> **4**) and intermolecular reactions summarized in Table 3.

Deviations of the hydride transfer energies calculated on the basis of results provided by using different basis sets are considerably large. Nevertheless, the relative order of the 6-31G energies is the same (with one exception) as that of the 6-31G* energies, results provided with the 4-31G basis are closely similar to those of 6-31G (the same applies to the basis sets 4-31G* and 6-31G*) whereas the relative order of hydride transfer energies provided at the 3-21G and 6-31G levels appears to be almost random (i.e. in some cases the 3-21G energies are larger than the corresponding 6-31G energies and *vice versa*). In addition to that, in the case of closely similar systems some useful conclusions on the properties of the "heavier" systems calculated at the 6-31G level could be drawn by comparing the results to those of corresponding smaller systems calculated at both the 6-31G and 6-31G* levels. For example, as the energies of the formation of **1'b** and **1'c**,[2a,2h] also the hydride transfer energies of **1'b** and **1'c** deviate only little although the value of **1'c** is clearly lower than that of **1'b**. Consequently, one could predict the hydride transfer energy of **1'c**, if calculated at the 6-31G* level, to be about -220 ± 10 kJ mol^{-1}, i.e. close below the corresponding value of **1'b** (-232 kJ mol^{-1}).

Table 3. Energies of the hydride transfer reactions 1' -> 4' (ΔE)[a] [the pathway (b)],[b] the conversion of $H_2C{=}O{\bullet}BH_3$ to $H_3C\text{-}O\text{-}BH_2$, and the hydrogenation of $H_2C{=}O$ and $H_2C{=}O{\bullet}BH_3$ by H_2, $H_3B{\bullet}NH_3$ and $H_3B{\bullet}OH_2$.

				3-21G	4-31G	6-31G	4-31G*	6-31G*
Reaction				ΔE[a]				
1'b	->	**3'd**	+ $H_2B\text{-}NH_2$ (**6'a**)	-218	-252	-250	-229	-232
1'c	->	**4'b**		-204	-238	-240	-	-
$H_2C{=}O{\bullet}BH_3$ + $H_3B{\bullet}OH_2$	->	$H_3C\text{-}O({\bullet}BH_3)H$	+ $H_2B\text{-}OH$ (**3'a**)	-234	-225	-223	-211	-212
$H_2C{=}O{\bullet}BH_3$	->	$H_3C\text{-}O\text{-}BH_2$ (**3'b**)		-222	-216	-214	-202	-204
$H_2C{=}O$ + $H_3B{\bullet}OH_2$	->	$H_3C\text{-}OH$	+ $H_2B\text{-}OH$ (**3'a**)	-197	-197	-197	-196	-198
1'a	->	$H_3C\text{-}O\text{-}BH_2$ (**3'b**)	+ $H_2B\text{-}NH_2$ (**6'a**)	-183	-203	-200	-177	-181
$H_2C{=}O{\bullet}BH_3$ + $H_3B{\bullet}NH_3$	->	$H_3C\text{-}O({\bullet}BH_3)H$	+ $H_2B\text{-}NH_2$ (**6'a**)	-178	-184	-186	-135	-136
$H_2C{=}O{\bullet}BH_3$ + H_2	->	$H_3C\text{-}O({\bullet}BH_3)H$		-178	-164	-165	-125	-125
$H_2C{=}O$ + $H_3B{\bullet}NH_3$	->	$H_3C\text{-}OH$	+ $H_2B\text{-}NH_2$ (**6'a**)	-140	-157	-160	-120	-122
$H_2C{=}O$ + H_2	->	$H_3C\text{-}OH$		-140	-137	-139	-110	-111

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

On the basis of these results it looks as if, in addition to the advantage arising from the intramolecular nature of the hydride transfer favored by entropy, the hydride transfer in the case of oxazaborolidine type of catalysts had also more favorable enthalpy related features than the corresponding intermolecular reductions. The energy of isomerization of $H_2C{=}O{\bullet}BH_3$ to $H_3C\text{-}O\text{-}BH_2$ and all the intermolecular reactions of formaldehyde and borane complexes of $H_2C{=}O{\bullet}BH_3$ with $H_3B{\bullet}OH_2$ (a model for $H_3B{\bullet}THF$) are energetically clearly less advantageous than the intramolecular hydride transfer occurring in the formaldehyde complex **1'b**; albeit the energy of the reaction of $H_2C{=}O{\bullet}BH_3$ with $H_3B{\bullet}OH_2$ is only 30 kJ mol^{-1} below the value of **1'b** (see Table 3) which implies that if the borane used as a source of hydrogen has a chance to coordinate to the ketone to be reduced it could lead to a non-enantioselective reduction of the ketone. The same problem might arise in the presence of compounds bearing protic groups (moisture or functional groups of the ketone to be reduced). On the other hand, the strength of the solvent as a Lewis base would also affect the feasibility of both the formation of the H_3B adduct of the oxazaborolidine and the formation of the H_3B adduct of the ketone.[2h]

Because of lability of derivatives of **2'** (e.g. spontaneous decomposition of **2'c** to **4'a** took place during the geometry optimization of **2'c** at the 4-31G level) estimation of the energetic advantageousness of the hydride transfer occurring *via* the pathway [(a), see Scheme 1] was not possible at the desired level. Nevertheless, one could estimate how much higher in energy the system **2'** is with respect to **4'**, by calculating the energies of decomposition of **2'a-c** in those cases in which a local "minimum" was found. The results are summarized in Table 4.

The energies shown in Table 4 must be considered with caution. In spite of that, they imply the stability of **2'** to decrease with the increasing quality of the basis set used in the calculations. Furthermore, it looks as if about 50 - 85 % of the total energy release of the hydride transfer occurring *via* the pathway **1'** -> **2'** -> **4'** (see Scheme 1) would be liberated during the step **1'** -> **2'**.

In order to prevent the collapse of **2'a** and **2'c** to the corresponding oxazadiboretanes (**5'e** and **5'a**) the OH group of **2'a** was forced to an arrangement *anti* to the BH_2 moiety and in the case of **2'c** the OH group was *trans* to the BH_2 group. However, even though the structure **2'b** was also forced by symmetry during the geometry optimization, the OH groups of **2'b** were kept *syn* to the Lewis acidic BH_2 group. Symmetry

was used only to keep both the OH groups at the same distance from the BH_2 group so that falling of either of the oxygens of the OH groups leading to the formation of the corresponding oxazadiboretane (**5'c**) was prevented. Therefore one may consider **2'b** as the best model of **2'** among the systems **2'a-c**.

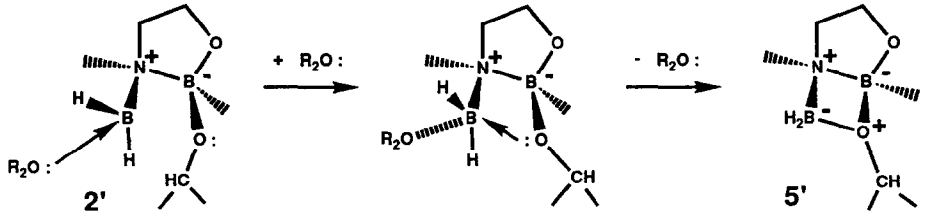
Table 4. Energies of the reactions **2'** -> **4'** (ΔE)[a,b] estimated on the basis of limited results provided in the case of models **2'a-c**.

Reaction	3-21G	4-31G	6-31G	4-31G*	6-31G*
			ΔE^a		
2'a [c] -> **3'a** + H_2B-NH_2	-25	-43	-45	-56	-57
2'b [c] -> **3'c** + H_2B-NH_2	-57	-82	-82	-109 [d]	-
2'c -> **4'a**	59	-88 [e]	-	-	-

[a] Energies given in kJ mol^{-1}. [b] See Scheme 1. [c] The structure was forced by symmetry.
[d] Based on the energy value observed before the complex started to decompose [the energy gradient at that point was 1.47 kJ mol^{-1} $Å^{-1}$ when the threshold of geometry optimization was 1.39 kJ mol^{-1} $Å^{-1}$ (0.001 hartree / bohr)]. [e] Based on the energy value observed before the complex started to decompose [the energy gradient at that point was 6.26 kJ mol^{-1} $Å^{-1}$].

The energy (-109 kJ mol^{-1}) estimated on the basis of the 4-31G* calculation (see Table 4) for the decomposition of **2'b** is almost 50 % of the total energy release (-229 kJ mol^{-1}, see Table 3) of the hydride transfer of **1'b**. Thus, in the case of **1'b** the energy of the step corresponding to **1'** -> **2'** diminishes down to the level of about -120 kJ mol^{-1} which is, however, surprisingly close to the energies of related formal hydrogenation reactions $H_2C{=}O + H_3B{\bullet}NH_3$ -> H_3C-OH + H_2B-NH_2 and $H_2C{=}O{\bullet}BH_3 + H_3B{\bullet}NH_3$ -> H_3C-$O{\bullet}BH_3(H)$ + H_2B-NH_2 (-120 and -135 kJ mol^{-1}, 4-31G*//4-31G*, see Table 3).

As the complex **2'** appeared to be so labile it is likely that systems analogous to **2'** would not be very long living intermediates but they would be indeed converted to their derivatives corresponding to **4'** or **5'**. However, the intermediate **2'** being structurally analogous to an adduct of dialkoxyborane to an aminoborane could naturally be stabilized also by a Lewis basic solvent coordinating to the Lewis acidic BH_2 group of **2'** as illustrated below; i.e. in the same way as other related borane adducts studied before.[2h]



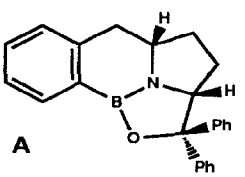
On the basis of the previously calculated energies of coordination of water to borane adducts of aminoborane and other models of oxazaborolidines one could predict the coordination of a Lewis basic solvent to the Lewis acidic BH_2 group of **2'** to be a process releasing about 20 - 60 kJ mol^{-1} energy.[2h] As that process would decrease the demand of B(1) to draw the free electron pair of the nitrogen [coordination of the free electron pair of the nitrogen to the boron of the oxazaborolidine moiety [i.e. to B(2)] is the only force in the complex **2'** which could prevent the ring from opening; i.e. the covalent B-N bonding of the parent oxazaborolidine (**6'**) is lost] it would actually inhibit the cleavage **2'** -> **4'**. That would be good only, because

the intermediate **4'** could be considered almost as an unnecessary complication in the mechanism of the catalysis.

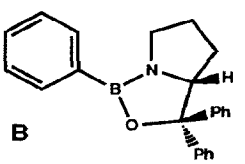
An association between the proposed role of a Lewis basic solvent in the stabilization of the intermediate **2'** and experimental observations could be found too. Namely, the propensity of the complex **2'** to decompose to **4'** would likely decrease with the decreasing Lewis acidity of the boron B(1) of **2'** [the boron B(1) delivering the hydride becomes Lewis acidic after the hydride transfer]. This imply further that the importance of the Lewis basicity of the solvent to the stability of **2'** should decrease with the decreasing Lewis acidity of the borane used as the source of hydrogen. However, on the basis of the literature[1] it looks as if successful reductions in which H_3B was used as the source of hydrogen have been done in Lewis basic solvents (.e.g. THF) whereas reductions in which a less acidic borane (e.g. catecholborane) was used have been successful even in toluene;[1f] i.e. implications of the experimental observations are not in conflict with the proposed role of the solvent.

Further implications of problems being potentially associated with the open system **4'** could be found by examining the dipole moments and relative energies of the conformer pairs **4'a/4'a'** and **4'b/4'b'** (see Table 1 and Schemes 2 and 3). As the dipole moments of the systems **4'a'** and **4'b'** in which the B(2)-O(2)R (R = H or CH_3) group points away from the N-BH_2 group appear to be about 2 D lower than those of **4'a** and **4'b** and the energies of **4'a'** and **4'b'** are also about 3 - 5 kJ mol^{-1} lower with respect to those of **4'a'** and **4'b'** conformers of **4'** corresponding to **4'a'** or **4'b'** could be likely the dominating ones. However, those more advantageous conformers would not cyclize directly to form the corresponding oxazadiboretane structure (the distance of the reacting groups would be long and the direct cyclization would anyway lead to a highly strained *trans*-fused 4,5-ring system). This imply further that if the conversion **2'** -> **4'** takes place the open system (**4'**) may not be completely converted to the corresponding oxazadiboretane system (**5'**); i.e. the catalyst may be deactivated *via* the pathways leading to the formation of **4'**. More research on the properties of **4'** in this respect is clearly called for.

An experimental approach for probing the role of **4'** could be based on the synthesis of the structure **A** shown below and subsequent studies of **A** as a catalyst.



A



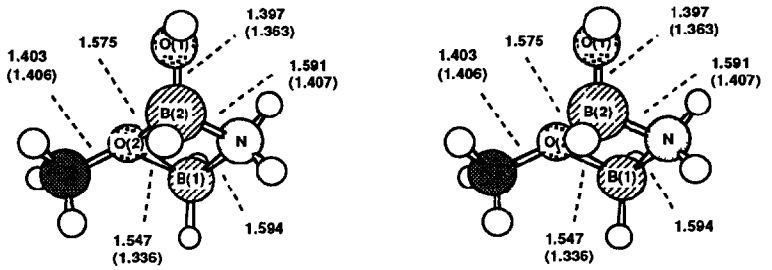
B

The cyclic arrangement of this catalyst should be rigid enough for preventing the B(2)-O(2)R moiety from getting too far from the N-BH_2 group even if the oxazaborolidine system should open. Because the potentially harmful consequences related to the pathway **2'** -> **4'** should be likely eliminated in the case of **A** the number of cycles the catalyst works should increase with respect to the activities of catalysts described in the literature (the amount of the catalyst needed for a decent enantioselective reduction of a ketone should go much below the level of 5 mol %; except if it should turn out that the rather large amount of the catalyst needed would be fully attributable to the competing nonenantioselective reductions).[1] As the catalyst **B** has been reported to work in the same manner as the *B*-alkyl systems[9] it could be used as a reference in the study of the performance of **A** (albeit **A** is more strained than **B**).

Structures and Energies of Formation of 1,3-Oxazadiboretanes

As shown in Scheme 1, the oxazadiboretane structure (**5'**) may arise either from further reactions of **2'** [pathway (d)] or those of **4'** [pathway (e)]. Although systems analogous to **2'** were observed to collapse to the corresponding analogs of **5'** or decompose to their analogs of **4'** (a related reaction, i.e. the dimerization of H_2B-NH_2 to give $(H_2B\text{-}NH_2)_2$, has been observed experimentally),[4] one cannot say on the basis of the results of this work whether the oxazadiboretane (**5'**) could be formed directly from **4'** or only *via* **2'**. Nevertheless, it is clear that the first step of the route **4'** -> **2'** -> **5'** would require a considerable amount of energy anyway.

Since the conclusions drawn on the basis of this work are based on the inspection of small models which should have been structurally analogous to the actual working catalysts it is important to assess also the performance of the models; i.e. how the models eventually reflect properties of the original structures of interest. Significant deviations of structural parameters were observed only in the case of torsion angles of **5'a-f**. For example, when geometries of the nonfused oxazadiboretanes (**5'c-d**) were optimized the torsion angle H-O(1)-B(2)-N appeared to acquire a too large value (e.g. in the case of **5'd** the optimum was at about -158°) so that it may not be decent to accept the optimized structures of **5'c-d** as good models of the fused oxazadiboretane - oxazaborolidine system **5'** [the corresponding torsion angle was 25° in **5'a** (see Scheme 3)]. The optimized geometry of **5'd** (6-31G*//6-31G*) is shown in Scheme 5.



Scheme 5. A Stereo representation of the optimized (6-31G*//6-31G*) structure of the oxazadiboretane **5'd**. Some of the most important bond lengths [Å] are shown. The values in parentheses are the corresponding bond lengths of **3'b** and **6'b**.

In order to determine energies of those conformers of **5'c-d** which would be best superimposable with **5'a-b** the bond B(2)-O(1) [corresponding to the torsion angle H-O(1)-B(2)-N of **5'd**] was rotated 360° by steps of 15° and the total energy of each configuration was calculated (6-31G*). The energies, dipole moments and Mulliken overlap populations of the atoms of the oxazadiboretane ring of **5'd** as a function of the H-O(1)-B(2)-N torsion angle are shown in Diagram 1.

The analysis shown in the part (a) of Diagram 1 clearly reveals that the torsion angle H-O(1)-B(2)-N of **5'd** has another optimum corresponding to the value of about 67° of the angle. The optimum resides about 8 kJ mol^{-1} above the first minimum (corresponding to -158°) found in the geometry optimization of **5'd**. Although this second minimum is somewhat more closely superimposable with the fused oxazadiboretane structure of **5'a** [in which the torsion angle C-O(1)-B(2)-N is 25°], a difference of 42° remains. On the other hand, the energy of **5'd** corresponding to the angle 25° is about 18 kJ mol^{-1} above the first minimum.

Therefore, in order to compare energies of the formation of oxazadiboretanes, the energies of **5'c-d** could be corrected up by about 18 kJ mol^{-1}. Energies of the formal cyclization reactions **4'** -> **5'** are summarized in Table 5. As we see, the corrected energy of the formation of oxazadiboretane **5'd** (+31 kJ mol^{-1}) became close to the corresponding energy of **5'a** (+33 kJ mol^{-1}, 6-31G*//6-31G*).

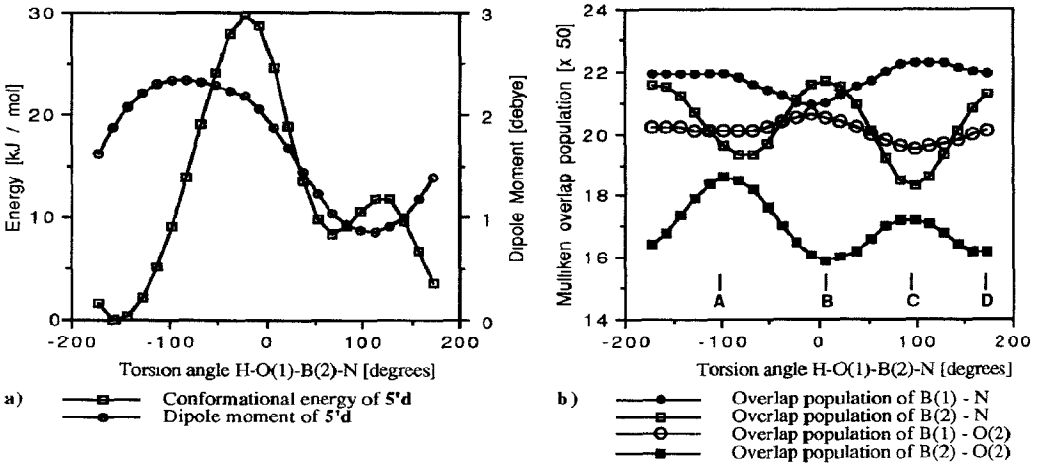


Diagram 1. Conformational energies, dipole moments and Mulliken overlap populations for the atoms of the four membered ring of the oxazadiboretane **5'd** as a function of the torsion angle H-O(1)-B(2)-N calculated at the 6-31G* level.

Table 5. Energies[a] of the formation of oxazadiboretanes.

Reaction					3-21G	4-31G	6-31G	4-31G*	6-31G*
							ΔE^a		
4'a			->	**5'a**	-59	+6	+11	+31	+33
4'a'			->	**5'a**	-56	+10	+15	+33	+35
4'b			->	**5'b**	-91	-28	-22	-	-
4'b'			->	**5'b**	-83	-17	-11	-	-
3'c	+	H_2B-NH_2	->	**5'c**	-73	-8	-6	+12	+16
3'c	+	H_2B-NH_2	->	**5'c'**	-	-	-	-	+27
3'd	+	H_2B-NH_2	->	**5'd**	-80	-17	-12	+9	+13
3'd	+	H_2B-NH_2	->	**5'd'**	-	-	-	-	+31 [b]
3'a	+	H_2B-NH_2	->	**5'e**	-104	-46	-39	-26	-22
3'b	+	H_2B-NH_2	->	**5'f**	-112	-53	-46	-16	-10

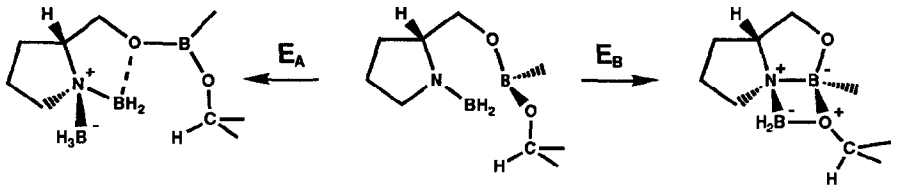
[a] Energies given in kJ mol^{-1}. [b] The energy corrected to correspond to the torsion angle H-O(1)-B(2)-N value 25° on the basis of the conformational analysis of the oxazadiboretane **5'd** shown in Diagram 1

In order to confirm that the second minimum found was a real one, the geometry of **5'c** was modified to correspond as closely as possible to that of the second minimum of **5'd**. That structure (**5'c'**) was then reoptimized at the 6-31G* level, and indeed, a minimum was found where the energy of **5'c'** appeared to be

about 11 kJ mol^{-1} higher than that of **5'c** [i.e. very close to the value (8 kJ mol^{-1}) provided by the conformational analysis of **5'd**, see Diagram 1].

As the energies of the conversions corresponding to **4'** -> **5'** shown in Table 5 (except those of **5'e** and **5'f**) are positive one could predict energies of the formation of oxazadiboretane - oxazaborolidine systems to be clearly endothermic also in the case of actual working catalysts. On the other hand, **4'** may not be formed if the intermediate **2'** reacts directly to **5'**. Although the system **4'** is clearly more stable (on the basis of the energies shown in Table 5) than the oxazadiboretane form of it (**5'**) it is not possible to say on the basis of the results of this work whether the further reactions of **2'** would lead to **4'** or **5'**. Nevertheless, one may note again that both the pathways **2'** -> **4'** [(c), see Scheme 1] and **2'** -> **5'** [(d), see Scheme 1] are clearly exothermic.

The energies of formation of bicyclic oxazadiboretanes (e.g. **5'a**) are, as one could expect, more positive that those of nonfused systems; even though the difference is surprisingly small, only about 10 - 20 kJ mol^{-1}. Nevertheless the status of **4'** in the mechanism of the catalysis would not be improved in the light of these energies. Furthermore, even the coordination of the borane (used as a source of hydrogen) to the nitrogen of **4'** would be energetically more advantageous than the conversion **4'** -> **5'** as illustrated below [$E_B > E_A$ estimated on the basis of previous studies[2a,2h] on the reactions of aminoborane analogs with $H_3B{\bullet}OH_2$]. The oxygen of the dialkoxyborane moiety or a Lewis basic solvent could also coordinate to the BH_2 group stabilizing the borane adduct further by about 20 - 60 kJ mol^{-1} with respect to the oxazadiboretane system.[2h]



More conclusions on the relative stability of different oxazadiboretanes could be drawn on the basis the energies shown in Table 5. Energies of the formation of **5'e** and **5'f** in which there are no substituents on the borons of the oxazadiboretane ring are clearly negative [e.g. -22 kJ mol^{-1} in the case of the most simple oxazadiboretane system **5'e** (6-31G*//6-31G*)] whereas those of oxazadiboretanes in which one of the borons of the ring has an alkoxy or hydroxy substituent are clearly positive [e.g. +13 kJ mol^{-1} in the case of **5'd** is (6-31G*//6-31G*)]. This imply the relative stability of the oxazadiboretane ring to decrease with the increasing number of π-electron donating oxygen and nitrogen atoms adjacent to the borons of the oxazadiboretane ring. The higher stability of less substituted systems (e.g. **5'e** and **5'f**) could be likely attributable to the higher Lewis acidity of the parent amino- and hydroxyboranes.

In addition to the structural features of oxazadiboretanes shown in Schemes 2, 3 and 5 a comparison of bond lengths and overlap populations of the atoms of oxazadiboretane rings of **5'a-f** and **5'c** is summarized in Table 6. Selected bond angles of oxazadiboretanes optimized at the 6-31G* level are collected in Table 7. A comparison of these structural data with those of related systems studied before reveals that the structural parameters of **5'e** resemble those of $(H_2B\text{-}NH_2)_2$ in that also the B-N-B bond angle of $(H_2B\text{-}NH_2)_2$ has been calculated to be smaller than 90° and the B-N bond length to be about 1.63 Å.[4c]

Table 6. Lengths of the ring bonds of oxazadiboretanes **5'a** and **5'c-f**.[a]

Structure	Bond lengths [Å]				Overlap populations			
	N-B(2)	N-B(1)	O-B(2)	O-B(1)	N-B(2)	N-B(1)	O-B(2)	O-B(1)
5'a	1.608	1.590	1.582	1.566	0.498	0.434	0.294	0.380
5'c	1.602	1.596	1.575	1.567	0.396	0.434	0.388	0.390
5'c'	1.620	1.588	1.577	1.572	0.346	0.444	0.354	0.370
5'd	1.591	1.594	1.575	1.547	0.430	0.438	0.336	0.404
5'e	1.600	1.600	1.541	1.541	0.434	0.434	0.384	0.384
5'f	1.598	1.598	1.550	1.550	0.440	0.440	0.398	0.398

[a] Only parameters of structures optimized at the 6-31G* level are shown.

As the lone electron pairs of the oxygen of the substructure O-B-N could in principle be either *cis* or *trans* to the B-N bond (about the B-O bond; although in the case of an oxazaborolidine system the *cis* arrangement would be impossible) there should exist also two stable conformers of the nonfused oxazadiboretanes in which the free electron pairs of the oxygen O(2) point either away from the centre of the oxazadiboretane ring or towards it. However, a comparison of the optimized structures of oxazadiboretanes **5'd** (see Scheme 5), **5'c** and **5'c'** reveals that the more stable conformers (i.e. **5'd** and **5'c**) actually correspond to H_2B-OR adducts of **6'b'** whereas the less stable conformers [i.e. **5'c'** and the configuration of **5'd** in which the torsion angle H-O(1)-B(2)-N is 25° (**5'd'**), see Table 5] correspond to H_2B-OR adducts of **6'b**. This supports the previous suggestion that analogs of **6'b'** could function as catalysts in the same manner as oxazaborolidines (analogs of **6'b**).[2a]

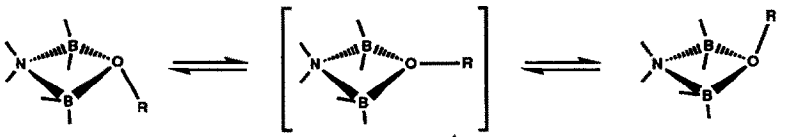
Table 7. Selected bond and torsion angles of the oxazadiboretanes **5'a**, **5'c**, **5'c'**, **5'd**, **5'e** and **5'f** [a]

Angle [b]	5'a	5'c	5'c'	5'd	5'e	5'f
B-N-B	88.7	88.8	89.3	89.6	88.0	87.9
B-O-B	90.6	90.8	91.5	91.9	90.0	91.4
N-B(2)-O(2)	88.8	89.8	88.5	88.4	90.0	89.4
N-B(1)-O(2)	90.0	90.3	89.9	89.3	90.0	89.4
C-O(2)-B(2)[c]	116.7	111.8	117.3	124.9	115.6	123.5
C-O(2)-B(1)[c]	117.3	114.2	117.9	123.6	115.6	123.5
N-B(2)-O(1)	104.9	111.2	115.7	111.1	-	-
O(2)-B(2)-O(1)	112.5	109.5	111.8	112.9	-	-
B(1)-N-B(2)-O(2)	-10.3	4.3	-6.8	-6.8	10.0	-10.2
C-O(2)-B(2)-N[c]	131.7	-120.9	129.5	141.3	129.0	143.2
B(1)-N-B(2)-O(1)	-123.2	-106.7	-120.4	-120.8	-	-
N-B(2)-O(1)-C[d]	25.1	-138.7	67.7	-157.7	-	-

[a] Only parameters of structures optimized at the 6-31G* level are shown. For the numbering of atoms see Schemes 3 and 5 [b] Angles given in degrees. [c] In the case of oxazadiboretanes **5'a**, **5'c**, **5'c'** and **5'e** a value based on the hydrogen residing in place of the carbon corresponding to $C_{C=O}$ is given. [d] In the case of oxazadiboretanes **5'c**, **5'c'**, **5'd**, **5'e** and **5'f** a value based on the hydrogen residing in place of the carbon adjacent to the oxygen of the oxazaborolidine [i.e. O(1)] is given.

One of the results emanating from the inspection of the bond lengths and torsion angles of the oxazadiboretanes shown in Table 7 is the fact that the oxazadiboretane ring is not planar [e.g. see the values of the torsion angle B(1)-N-B(2)-O(2)]; neither is the substituent of the oxygen of the ring in the plane of the atoms O(2)-B-N [e.g. see the values of the torsion angle C-O(2)-B(2)-N]. However, such a planar system

turned out to be not much higher in energy. Namely, when the model **5'e** was forced to a planar arrangement by using symmetry constraints and the system was reoptimized the energy of the system increased only by about 10 kJ mol^{-1} [6-31G*//6-31G*; the increase appeared to be also very sensitive to the nature of the basis set used in the calculation (i.e. the barrier almost disappeared at the 3-21G, 4-31G and 6-31G levels)]. This low energy barrier for the inversion of the configuration of O(2) illustrated below imply the B-O bond of an oxazadiboretane ring to be loose and that the alkyl substituent of the oxygen of the ring [i.e. O(2)] could easily flip from one side of the ring to the other.



$\Delta E \approx +10$ kJ mol^{-1}

More information on the nature of bonding in oxazadiboretane systems, e.g. the relative strengths of the B(1)-O and B(2)-O bonds, could be provided by inspecting the Mulliken population analyses shown in Table 6. The results imply that in the case of fused oxazadiboretane - oxazaborolidine systems (e.g. **5'a** or **5'b**) the B(2)-N bond would be stronger than the B(1)-N bond and the B(1)-O(2) bond markedly stronger that the B(2)-O(2) bond, and that the most weak bond of the oxazadiboretane ring of **5'** would be the B(2)-O(2) bond (e.g. see the overlap populations of **5'a**, Table 6). Implications of the overlap populations in the case of **5'c**, **5'c'** and **5'd** are less clear but also there the B(2)-O(2) interaction appears to be weaker than the B(1)-O(2) ones. These results are interesting also in that purely on the basis of the bond lengths of the oxazadiboretanes (**5'a-d**) one could have predicted both of the B-N bonds to be almost equally strong and the same in the case of the B-O bonds.

In spite of the discrepancy found between the conclusions drawn on the basis of the comparison of bond lengths and those drawn on the basis of the comparison of overlap populations it could be useful due to the novel nature of the oxazadiboretane system to try to locate it in the family of boron containing structures in general; e.g. by comparing bond lengths. In the case of fused oxazadiboretane - oxazaborolidine systems B-O bonds of the oxazadiboretane rings are lengthy in comparison to the B-O bonds of the oxazaborolidine moieties [e.g. in the case of **5'a** the B(2)-O(2) bond is 1.582 Å long and the B(2)-O(1) bond 1.396 Å long (6-31G*//6-31G*, see Scheme 3); and even in the case of **5'd** the B(2)-O(2) bond is 1.575 Å long whereas the length of the B(2)-O(1) bond is 1.397 Å (6-31G*//6-31G*, see Scheme 5)]. A comparison of the bond lengths of alkoxyborane and oxazaborolidine models with those of their oxazadiboretane adducts reveals that the B-N bond of the oxazaborolidine moiety is about 0.200 Å longer and the B-O bond of the alkoxyborane moiety more than 0.300 Å longer in the oxazadiboretane system than in the corresponding free oxazaborolidine and alkoxyborane [e.g. in the case of **5'a** (6-31G*//6-31G*) the B(2)-N and B(1)-O(2) bonds are 1.608 Å and 1.566 Å long whereas lengths of the corresponding bonds of the free oxazaborolidine (**6'c**) and H_2B-OH (**3'a**) are 1.400 Å and 1.345 Å, see Scheme 3]. Similar results arise from the comparison of bond lengths of **4'a** and **5'a**; the lengths of the B(1)-N and B(2)-O(2) bonds of **4'a** are 1.391 Å and 1.351 Å whereas the lengths of the corresponding bonds of **5'a** are 1.590 Å and 1.582 Å (6-31G*//6-31G*, see Scheme 3). On the other hand, bonds of the oxazadiboretane ring are short in comparison to the corresponding bonds of other related structures containing tetrahedral boron centers; e.g. lengths of the H_3B-N bonds of the borane adducts of **6'a-c** are 1.826, 1.765 and 1.718 Å (6-31G*//6-31G*),[2a] and even in the

adducts $H_3B{\bullet}NH_3$ and $H_3B{\bullet}OH_2$ the B-N bond is 1.683 Å and the B-O bond 1.814 Å long (6-31G*//6-31G*). Thus it looks as if in the oxazadiboretane system the donor - acceptor relations would allow stronger binding than could be expected on the basis of treating the ring as an adduct of isolated bidentate Lewis acids and bases, i.e. the acid - base interactions have strengthened due to the adjacency of the donor acceptor centers (each acid binds two bases and *vice versa*).

A feature potentially favoring the formation of oxazadiboretanes could be the relatively low dipole moment of the oxazadiboretane system (see Table 1). Dipoles of the B-N and B-O bonds appear almost to cancel one another as the oxazadiboretane system is formed [e.g. the dipole moment of the planar configuration of **5'd** was only 0.36 D (6-31G*//6-31G*) and even the moment of the nonplanar **5'd** was only 0.81 D]. The same observation can be made in the case of fused oxazadiboretanes; e.g. the dipole moment of **5'a** is only 1.75 D whereas the moment of **4'a** is 3.11 D (6-31G*//6-31G*, see Table 1 and Scheme 3). However, on this basis one could predict the oxazadiboretane system to be more easily soluble to nonpolar solvents than any other among the intermediates proposed so far to be involved in the mechanism of the catalysis. This association drawn between the dipole moment and solubility is not in conflict with implications of experimental observations on the behaviour of oxazaborolidines [assuming that the oxazaborolidine dimer is composed of two molecules arranged to form a four membered ring analogous to the dimer of aminoborane $(H_2B\text{-}NH_2)_2$]; namely the dimeric form of an oxazaborolidine catalyst has been found to dominate over the monomeric one in nonpolar solvents.[1]

Regeneration of the Catalyst

The regeneration energies are shown in Table 8. As a regeneration energy is considered an energy of a cleavage of an oxazadiboretane ring which corresponds to that of the pathway (f) shown in Scheme 1. An analogous reaction has been observed in the case of the dimer of aminoborane [pyrolysis of $(H_2B\text{-}NH_2)_2$ at the temperature of 135° C; or in a solution the dimer reacts already at 40° - 50° C].[4d]

Table 8. Regeneration energies.[a]

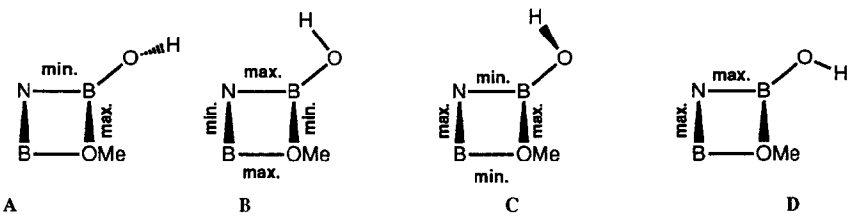
Reaction					3-21G	4-31G	6-31G	4-31G*	6-31G*
							ΔE[a]		
5'a	->	**6'c**	+	H_2B-O-H (**3'a**)	+115	+53	+46	+22	+18
5'b	->	**6'c**	+	H_2B-O-CH_3 (**3'b**)	+124	+62	+54	-	-
5'c	->	**6'b'**	+	H_2B-O-H	+98	+36	+30	+13	+9
5'c'	->	**6'b**	+	H_2B-O-H	+99	+36	+30	+10	+6
5'd	->	**6'b**	+	H_2B-O-CH_3	+112	+50	+44	+23	+19
5'd	->	**6'b'**	+	H_2B-O-CH_3	+104	+41	+34	+15	+11
5'e	->	**6'a**	+	H_2B-O-H	+104	+46	+39	+26	+22
5'f	->	**6'a**	+	H_2B-O-CH_3	+114	+54	+47	+26	+21

[a] Regeneration energies given in kJ mol^{-1}

On the basis of energies of the formation of oxazadiboretane ring systems (see Table 5) and the regeneration energies (see Table 8) it is easy to draw a conclusion that, even though the regeneration energies are low, opening of the oxazadiboretane ring of **5'** leading back to the corresponding derivative of **4'** would be energetically advantageous whereas the desired regeneration step would require energy. As the amount of

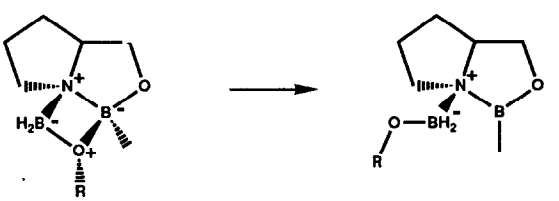
energy liberated in the hydride transfer is much higher with respect to the energies of the formation of **5'** and the regeneration steps (**5'** -> **3'** + **6'**) one could predict (although it is not possible to draw any conclusion on the nature of kinetic effects in the regeneration of the catalyst on the basis of these calculations) the energy released in the hydride transfer (more than 200 kJ mol^{-1}) to be enough for the regeneration process (provided that cooling of the reaction mixture is not too efficient).

The Mulliken overlap populations [see part (b), Diagram 1] of atoms of the oxazadiboretane ring of **5'd** as a function of the torsion angle H-O(1)-B(2)-N reflect interesting properties of the oxazadiboretane system **5'** in general. There are four values [marked with **A** - **D** in part (b) in Diagram 1] of the torsion angle indicating maxima and minima of the overlaps. The configurations correspondint to **A** - **D** are illustrated in Scheme 6. However, as the regeneration mechanism involves one of the two possible cleavages of the oxazadiboretane ring it could be useful to find conformers in which the overlaps of the atoms of the oxazadiboretane ring would favor the desired cleavage; i.e. the B(2)-N bond of the oxazaborolidine moiety and the B(1)-O(2) bond of the alkoxyborane moiety should have maximum overlaps and the B(2)-O(2) and B(1)-N bonds minimum overlaps. Conformations of **5'd** satisfying these requirements best are those corresponding to the configurations **B** and **D** (see Scheme 6). Values of the torsion angle H-O(1)-B(2)-N corresponding to **B** are in the range of -8° - +30° and those of **D** in the range of 155° - 175°. The configuration **B** corresponds best to an adduct of H_2B-OR to **6'b** whereas **D** is more likely recognized as an adduct of H_2B-OR to **6'b'**. This result could be considered as an additional evidence for the proposed similar type of catalytic function of the analogs of **6'b** and **6'b'**.[2a] Furthermore, it clearly looks as if the active center of actually working oxazaborolidine catalysts would be optimal for the regeneration to occur *via* the pathway (f) shown in Scheme 1.



Scheme 6. Minima and maxima of overlap populations of the members of the oxazadiboretane ring of **5'd** found in the conformational analysis of the bond B(2)-O(1) i.e. the B-OH bond of **5'd** [see part (b) in Diagram 1 and Scheme 5].

The discovery of the most weak bond of the oxazadiboretane ring system (see Scheme 6 and Table 6) together with the conformational analysis of the oxazadiboretane (**5'd**) (see Diagram 1) and the population analyses of the oxazadiboretane ring of **5'a** (6-31G*//6-31G*, see Table 6) imply that the oxazadiboretane ring of a fused oxazadiboretane - oxazaborolidine system could be cleaved also by a rupture of the B(2)-O(2) bond, i.e. as illustrated below.



This cleavage would lead to the formation of an alkoxyborane adduct of the oxazaborolidine (the alkoxy substituent of the borane originates from the ketone having been reduced). The cleavage actually corresponds to a process in which the alkoxyborane **3'** having been eliminated in the reaction **5'** -> **3'** + **6'** had coordinated back to the oxazaborolidine but this time in the same manner in which the parent borane used as the source of hydrogen is proposed to do.[1,2] This could allows one to explain why a dialkoxyborane would be the final product of the oxazaborolidine catalyzed enantioselective reduction of ketones[1] in the case in which THF•BH_3 has been used as a source of hydrogen. Namely, as this alkoxyborane system shown above would presumably function as a catalyst in the same way as the corresponding adduct of the parent borane it would be converted to the corresponding dialkoxyborane during the second catalytic cycle. However, when the Lewis acidity of the boron of the alkoxyborane moiety decreases with the increasing level of substitution of the hydrogens of the borane by π-electron donating alkoxy substituents binding of the borane to the catalyst would become weaker as the degree of alkoxy substitution of the borane increases and apparently already at the dialkoxy level binding of the borane to the catalyst would be so loose bound that the elimination of the dialkoxyborane would be favored over the cleavage of the B(2)-O(2) bond and because the dialkoxyborane would be weaker than BH_3 as a Lewis acid it would not be able to compete with BH_3, and consequently, the third hydrogen of the borane would not be used in the catalytic reduction [nevertheless, this does not mean that the third hydrogen of the borane could not be consumed in competing noncatalytic reductions leading to racemic products; in order to test importance if this possibility one could compare the performance of H_3B•THF and (CH_3-BH_2)•THF under identical reaction conditions].

This cleavage of the B(2)-O(2) bond has been briefly mentioned to be potentially involved in the regeneration mechanism of oxazaborolidine catalysts.[2e-f] In those introductory studies it was found to require somewhat more energy than the regeneration step (about 74 kJ mol^{-1} at the 4-31G level in the case of **5'b**[2e-f] whereas the elimination of the entire CH_3-O-BH_2 system from **5'b** inspected at the same level required 62 kJ mol^{-1} energy, see Table 8). In the light of the recent studies on the role of a Lewis basic solvent in the stabilization of borane adducts of oxazaborolidines[2h] one could predict this cleavage to be even more favored than could be expected purely on the basis of energetics of these cleavages. Recent studies have revealed also that the stability of alkoxyborane adducts of oxazaborolidines depends drastically on orientations of the alkoxy groups.[10] More research is clearly needed on relative effects in the behaviour of BH_3, RO-BH_2 and $(RO)_2BH$ type of systems with oxazaborolidine catalysts.

Evaluation of Energetics of the Catalytic Cycle

A representation summarizing energetics and the evaluated mechanism of the enantioselective reduction of ketones catalyzed by oxazaborolidines determined on the basis of the present and previously reported[2] *ab initio* molecular orbital calculations is shown in Figure 1.

Each energy level (marked with a short bold line) corresponds to a local minimum except that of **2**. As the transition structures have not been determined yet the energy barriers presumably separating the local minima have been ignored in Figure 1 and the proposed order of the intermediates is marked by dashed lines connecting the local minima. As the vectors corresponding to the negative eigenvalue of the Hessian matrix of the transition states have not been determined either it is not strictly possible at this stage to order the species

sequentially along a reaction coordinate. Thus, the arrangement of the structures along the reaction coordinate shown in Figure 1 should be considered as proposal only.

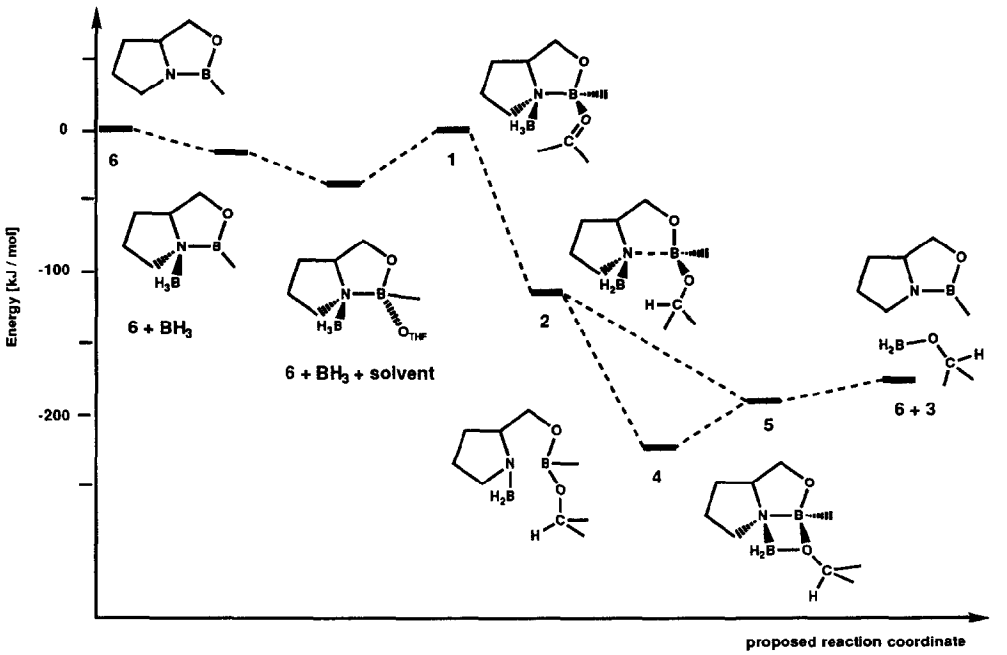


Figure 1. Energy diagram of the enantioselective reduction of ketones by oxazaborolidine catalysts.

As the total energy change of a reaction does not depend on the way by which the starting materials are converted to the products, one could check the energetics being calculated for the catalytic cycle by using the results discussed above and those of earlier works.[2a,2h] For example, in the case of the catalyst model **6'b** the following energies were calculated (6-31G*//6-31G*): formation of the BH_3 adduct: -3 kJ mol^{-1} [in the reaction of $H_3B{\bullet}OH_2$ with **6'b** ($H_3B{\bullet}OH_2$ used as a model of $H_3B{\bullet}THF$)];[2a] coordination of a Lewis basic solvent (H_2O as a model of the solvent) to the borane adduct: -31 kJ mol^{-1};[2h] substitution of the solvent by formaldehyde leading to the formation of **1'b**: +39 kJ mol^{-1};[2h] the hydride transfer: -232 kJ mol^{-1} (see Table 3); formation of oxazadiboretane (**5'd**): +13 kJ mol^{-1} (see Table 5); and the regeneration: +19 kJ mol^{-1} (see Table 8). These energies summarize to -195 kJ mol^{-1}. Energies of the noncatalytic pathway; i.e. $H_3B{\bullet}OH_2$ + $H_2C{=}O$ -> H_2O + $H_2C{=}O{\bullet}BH_3$ (+7 kJ mol^{-1})[2a] followed by the rearrangement $H_2C{=}O{\bullet}BH_3$ -> H_3C-O-BH_2 (-204 kJ mol^{-1}, see Table 3), summarize to -197 kJ mol^{-1}. Thus the total energy changes of the noncatalytic and catalytic pathways are the same within the accuracy of the calculation (energies of the reactions used to calculate the total energy change had been rounded to the nearest integer value).

CONCLUSIONS

This work has provided additional confirmation on the previously proposed mechanism of the transfer

of hydride from the borane group to the ketone moiety of the ketone - borane complex of an oxazaborolidine catalyst (corresponding to the reaction **1'** -> **2'**) and led to further rationalization of mechanisms by which the first intermediate (**2'**) arising from the hydride transfer could be converted to experimentally observed products. On the other hand, the role of the first intermediate (**2'**) remains unclear in that it appeared not to represent a minimum of the potential energy hypersurface but it was found to undergo a cleavage of the oxazaborolidine ring (corresponding to the reaction **2'** - > **4'**) or to collapse to form a fused oxazadiboretane - oxazaborolidine system (corresponding to the reaction **2'** -> **5'**).

The oxazadiboretane system (**5'**) could be cleaved in three ways: by the rupture of the B-N bond of the oxazaborolidine moiety and the bond between the oxygen of the newly formed alkoxy group and the boron of the borane which delivered the hydride (corresponding to the reaction **5'** -> **4'**); by the elimination of the alkoxyborane moiety giving rise to the regeneration of the catalyst (corresponding to the reaction **5'** -> **3'** + **6'**), or potentially also the by rupture of the bond between the oxygen of the alkoxy group and the boron of the oxazaborolidine moiety leading to the formation of an alkoxyborane adduct of the oxazaborolidine. The first cleavage appeared to be energetically advantageous, whereas the second requires energy about 50% of the amount the first one liberates. The third cleavage, albeit only an introductory characterization of it was afforded at this stage, appeared to require somewhat more energy that the second one.

The work has revealed also pathways which could be involved in the deactivation of oxazaborolidine catalysts. Reactions of this type could be the cleavage of the oxazaborolidine ring (i.e. **2'** -> **4'**) of the first intermediate (**2'**) arising from the hydride transfer and also the cleavage of **5'** leading back to **4'**. Experimental studies on oxazaborolidine catalysts in which the potentially harmful cleavage of the oxazaborolidine ring (leading to the formation of **4'**) would not be possible are clearly called for. 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. The author thanks Drs. T. Hase and G. Brunow for helpful discussions.

REFERENCES AND NOTES

1. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; (c) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861; (d) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Lett.* **1989**, *30*, 5547; (e) Corey, E. J.; Proceedings of the 31th National Organic Symposium, ACS **1989**, 1; (f) Corey, E. J.; Bakshi, K.; Reichard, G. A. *Tetrahedron Lett.* **1990**, *31*, 611; (g) Corey, E. J. *Pure & Appl. Chem.* **1990**, *62*, 1209.

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

3. (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.

4. (a) Wang, J. S.; Geanangel, R. A. *Inorg. Chim. Acta* **1988**, *148*, 185; (b) Dewar, M. J. S.; McKee, M. L. *J. Mol. Struct.* **1980**, *68*, 105; (c) Armstrong, D. R.; Perkins, P. G. *J. Chem. Soc. (A)* **1970**, 2748; (d) Böddeker, K. W.; Shore, S. G.; Bunting, R. K. *J. Am. Chem. Soc.* **1966**, *88*, 4396; (e) Gunderloy, F. C.; Erickson, C. E. *Inorg. Chem.* **1962**, *1*, 349.

5. Flood, E.; Gropen, O. *J. Organomet. Chem.* **1976**, *110*, 7.

6. Boggs, J. E.; Cordell, F. R. *J. Mol. Structure (THEOCHEM)* **1981**, *76*, 329.

7. Pulay, P.; Fogarasi, G.; Pang, F.; Boggs, J. E. *J. Am. Chem. Soc.* **1979**, *101*, 2550.

8. Gaussian 90, Revision I, Frisch, M. J.; Head-Gordon, M.; Trucks, G. W.; Foresman, J. B.; Schlegel, H. B.; Raghavachari, K.; Robb, M.; Binkley, J. S.; Gonzalez, C.; Defrees, D. J.; Fox, D. J.; Whiteside, R. A.; Seeger, R.; Melius, C. F.; Baker, J.; Martin, R. L.; Kahn, L. R.; Stewart, J. J. P.; Topiol, S.; Pople, J. A., Gaussian, Inc., Pittsburgh PA, 1990.

9. DeNinno, M. P.; Perner, R. J.; Lijewski, L. *Tetrahedron Lett.* **1990**, *31*, 7415.

10. Nevalainen, V., to be published.