

## Quantum Chemical Modeling of Chiral Catalysis. Part 2. On the Origin of Enantioselection in the Coordination of Carbonyl Compounds to Borane Adducts of Chiral Oxazaborolidines

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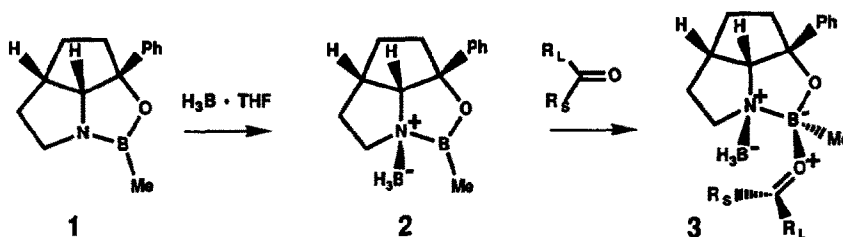
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**Abstract:** - Energies of formation and structural parameters of formaldehyde and acetaldehyde complexes of a model system of borane adducts of oxazaborolidine type of chiral reduction catalysts (CBS reduction) were calculated by using ab initio molecular orbital methods (6-31G\*//6-31G\*). The energetic preference was determined for the formation of complexes in which the Lewis acidic boron of the borane adduct of an oxazaborolidine would coordinate either *syn* or *anti* to the methyl group of acetaldehyde. The formation of *anti* complex was favored by 15.2 kJ mol<sup>-1</sup> which corresponds to a relative *anti* : *syn* abundance ratio of 461:1 and an enantiomeric excess of 99.8 %.

### INTRODUCTION

Oxazaborolidine type of chiral catalysts, e.g. 1, (also called "chemzymes") have been shown to be highly effective for the enantioselective reduction of ketones (CBS reduction).<sup>1</sup> Oxazaborolidines react with BH<sub>3</sub>·THF to form Lewis acid - base adducts, e.g. 2. These adducts are assumed to form complexes with ketones, e.g. 3, in which an intramolecular hydride transfer from the N-BH<sub>3</sub> moiety to the carbonyl occurs.<sup>1</sup> Lately reported ab initio molecular orbital studies on models of the catalysts (1) and reactive intermediates (2 and 3) have provided further support for this mechanism.<sup>2</sup>

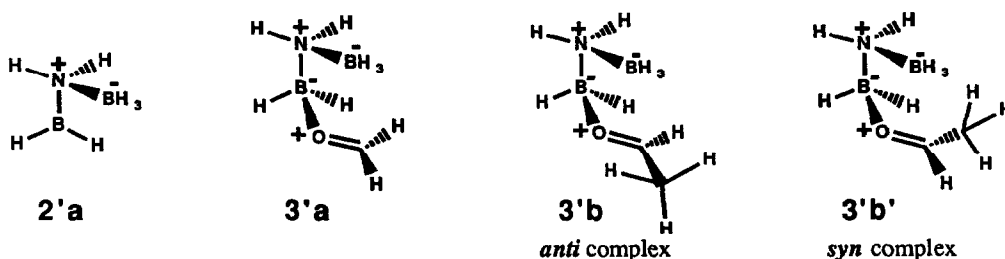


Although it has been shown that a carbonyl compound may indeed coordinate to the boron of the oxazaborolidine moiety of 2 effects of substituents (R<sub>S</sub> and R<sub>L</sub>) of the ketone moiety have not been studied yet. A considerable amount of light on the formation of Lewis acid complexes of carbonyl compounds has

been provided by LePage and Wiberg<sup>3</sup> who calculated the coordination of  $\text{BH}_3$  *anti* to the methyl group of acetaldehyde to be about  $9 \text{ kJ mol}^{-1}$  more favored than the *syn* coordination (6-31G\*\*/3-21G). Even though in the coordination of acetaldehyde to the borane adduct (**2**) the confrontation of the Lewis acid - base pair is basically the same as in the coordination of  $\text{BH}_3$  to acetaldehyde there are more energetically important factors to be taken into account in the case of **2**.

The aim of the work summarized in this report was to study structural properties and energies of formation of **3** by using using **2'a** as a model of **2** and **3'a**, **3'b** and **3'b'** as models of **3**. The analog **2'a** may be considered as the most simple model system for a borane adduct of an oxazaborolidine (**2**). Nevertheless, it contains all the atoms essential in the modeling of formation of the ketone complex (**3**). It has been shown previously that **2'a** behaves in the same way as more closely related analogs of **2** do, although most energetic and structural effects appear to be larger in the case of **2'a**.<sup>2a</sup> In the complex **3'b** the Lewis acid is coordinated *anti* to the methyl group of acetaldehyde whereas in the case of **3'b'** the coordination has taken place in the *syn* orientation.

All calculations were done by using the Gaussian 80 series of programs at the 3-21G, 4-31G, 6-31G, 4-31G\* and 6-31G\* levels.<sup>4</sup> Standard optimization procedures were utilized. The formaldehyde and acetaldehyde molecules were calculated for reference purposes. The results were practically equal to those reported in the literature.<sup>5</sup>



## RESULTS AND DISCUSSION

Stereo representations of the 6-31G\* optimized structures and the most important bond lengths of **3'b** and **3'b'** are shown in Scheme 1. The calculated net atomic charges, HOMO/LUMO energies, total energies and dipole moments are summarized in Table 1. Selected bond and torsion angles are shown in Table 2 and the most important Mulliken overlap populations in Table 3.

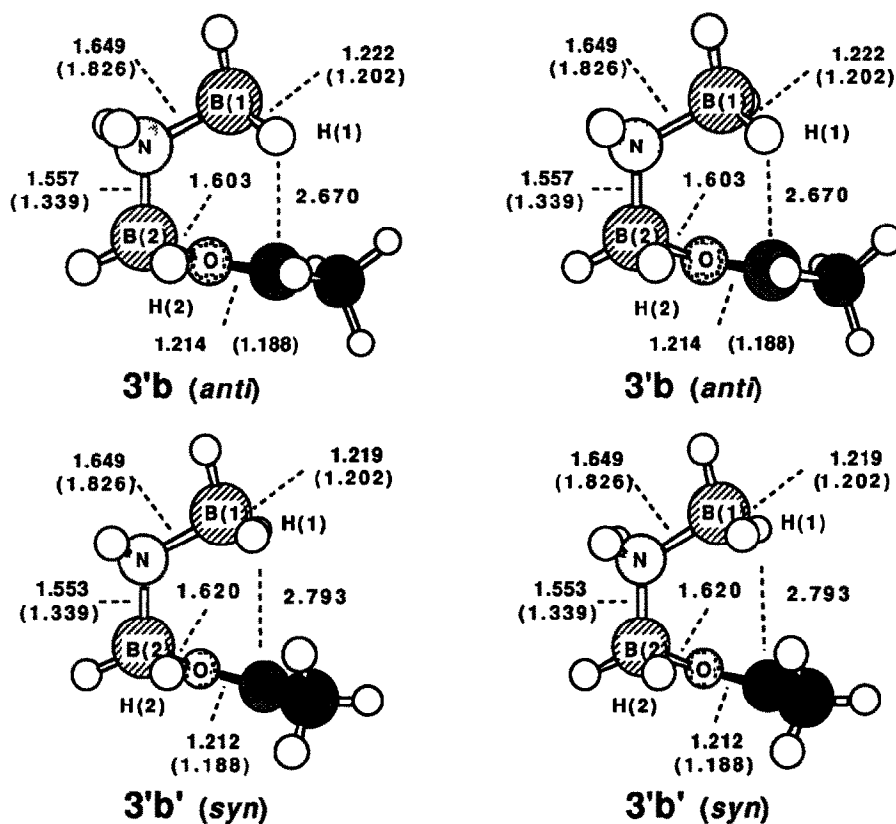
By comparing the total energies of **3'b** and **3'b'** (see Table 1) we observe that the formation of the *anti* adduct (**3'b**) is energetically more advantageous by  $15.2 \text{ kJ mol}^{-1}$  which corresponds to an *anti*:*syn* ratio of 461:1 and an enantiomeric excess of 99.8 %. The calculated energetic preference for the formation of *anti* adduct is higher than the energetic difference of  $9 \text{ kJ mol}^{-1}$  found in the case of *anti*/*syn* coordination of  $\text{BH}_3$  to acetaldehyde.<sup>3</sup>

Table 1. Net atomic charges of B(1), H(1), B(2), N, O and C<sub>C=O</sub>, HOMO and LUMO energies, total energies, dipole moments (D) and coordination energies ( $\Delta E$ ) of 2'a, 3'a-b and 3'b'.<sup>a</sup>

Structure	B(1)	H(1)	B(2)	N	O <sub>C=O</sub>	C <sub>C=O</sub>	HOMO <sup>b</sup>	LUMO <sup>b</sup>	Total Energies <sup>c</sup>	D <sup>d</sup>	$\Delta E^e$
2'a	+0.077	-0.094 <sup>f</sup>	+0.346	-0.906	-	-	11.76	2.94	-107.88689	4.21	-
3'a	+0.148	-0.208	+0.452	-0.919	-0.437	+0.175	10.94	2.14	-221.76572	3.50	-33
3'b ( <i>anti</i> )	+0.133	-0.184	+0.452	-0.899	-0.480	+0.395	10.65	2.54	-260.82215	4.59	-55
3'b' ( <i>syn</i> )	+0.140	-0.192	+0.465	-0.912	-0.461	+0.373	10.56	2.23	-260.81635	5.17	-40
H <sub>2</sub> CO	-	-	-	-	-0.416	+0.134	11.80	3.95	-113.86633	2.67	-
H <sub>3</sub> C-CHO	-	-	-	-	-0.464	+0.307	11.39	4.17	-152.91435	2.91	-

<sup>a</sup> All values give are based on 6-31G\*/6-31G\*. <sup>b</sup> Orbital energies are given in electron volts. <sup>c</sup> Total energies given in hartrees.

<sup>d</sup> Dipole moments given in debye. <sup>e</sup> Coordination energy given in kJ mol<sup>-1</sup>. <sup>f</sup> An average value of the hydrogens of BH<sub>3</sub> moiety.



Scheme 1. Stereo representations of the optimized geometries of 3'b and 3'b' (6-31G\*/6-31G\*). Some of the most important bond lengths [in Å] are included. The values in parenthesis are the corresponding bond lengths of the 6-31G\* optimized structures of 2'a and the free aldehyde.

Direction of changes of bond lengths, net atomic charges, and other structural features in the catalyst moiety turned out to be closely similar in the case of **3'b** and **3'b'**, e.g. the variation of bond lengths appears to be  $\leq 0.004$  Å. An exception is the B-O<sub>C=O</sub> bond which is 0.017 Å longer in the *syn* adduct (**3'b'**). The torsion angle B(1)-N-B(2)-O values of **3'a**, **3'b** and **3'b'** imply that the configuration of the BH<sub>3</sub> and C=O moieties corresponds as good to a configuration of vicinal substituents of a six membered ring (where the angle  $\approx -50^\circ - 60^\circ$ ) than to that of a five membered ring (the angle  $\approx -20^\circ - 40^\circ$ ). Thus it could be possible that a catalyst, in which the O-B-N substructure would be embedded in a six membered ring, could work as well as an oxazaborolidine where the O-B-N substructure is a part of a five membered ring. This assumption is supported also by one of our preliminary results, namely it was observed that there is practically no energy barrier for the rotation of B(1)-N-B(2)-O of **3'a** from  $-10^\circ$  to  $-60^\circ$  (6-31G\*\*//6-31G\*).

As the only significant difference of the bond lengths of **3'b** and **3'b'** was in the B(2)-O bond and the difference was rather small, it could be useful to consider also other properties of these adducts in order to find the origin of the difference of the energies of **3'b** and **3'b'**. Inspection of the bond angles (see Table 2) reveals that the *syn* complex **3'b'** is more "open" than **3'a** or **3'b**. The angle B(2)-O=C of **3'b** is  $121.4^\circ$ , whereas that of **3'b'** is  $129.4^\circ$  (i.e. the difference is  $8^\circ$ ) and the carbonyl of **3'b'** resides further away from the hydride which could be attributed to the larger value of the torsion angle N-B(2)-O=C of **3'b'** (*syn*). Other recognizable differences turn out to reside in the acetaldehyde moiety of the complexes (**3'b** and **3'b'**). The H-C=O angle of **3'b** is almost  $4^\circ$  larger than that of **3'b'** and the C-C=O angle of **3'b** is about  $5^\circ$  larger than that of **3'b'**.

Table 2. Selected bond and torsion angles.<sup>a,b</sup>

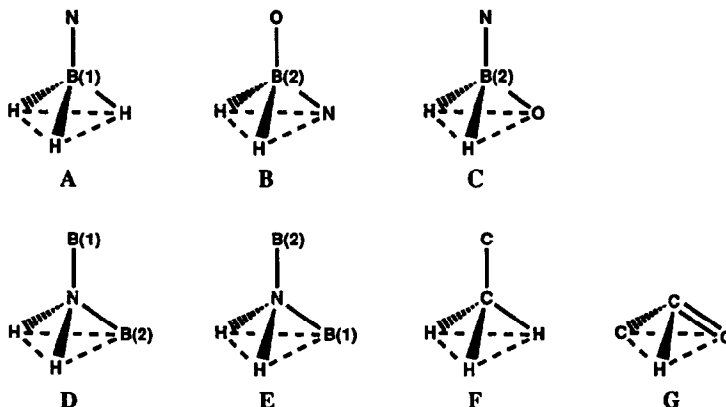
Structure	<b>2'a</b>	<b>3'a</b>	<b>3'b</b> ( <i>anti</i> )	<b>3'b'</b> ( <i>syn</i> )	CH <sub>3</sub> CHO	H <sub>2</sub> CO
B(2)-O=C	-	119.3	121.4	129.4	-	-
O-B(2)-N	-	103.9	104.1	103.8	-	-
B(2)-N-B(1)	102.7	120.8	118.3	119.8	-	-
N-B(1)-H(1)	103.6	107.5	106.6	106.5	-	-
O-B(2)-H(2)	-	105.5	106.1	108.0	-	-
H-B(2)-H	122.8	116.4	115.7	115.7	-	-
H-N-H	110.3	105.2	105.3	105.2	-	-
C-C=O	-	118.9 ( <i>anti</i> -H)	121.9	126.8	123.3	-
H-C=O	-	121.6 ( <i>syn</i> -H)	119.2	115.3	120.2	122.1
H-C-C	-	-	118.9	117.2	116.4	-
H-C-H	-	119.4	-	-	-	115.8
B(1)-N-B(2)-O	-	-18.1	-40.4	-53.6	-	-
N-B(2)-O=C	-	76.9	89.8	96.9	-	-
B-O=C-C	-	-163.6 ( <i>anti</i> -H)	-171.4	6.7	-	-
B-O=C-H	-	19.8 ( <i>syn</i> -H)	10.3	-175.6	-	-

<sup>a</sup> Based on 6-31G\*\*//6-31G\*. <sup>b</sup> Angles given in degrees.

A comparison of Mulliken overlap population values (see Table 3) of **3'b** and **3'b'** implies that in the *anti* complex **3'b** the B(2)-O bond would be somewhat stronger than in the *syn* complex (**3'b'**) which is consistent with the observed shorter B(2)-O bond length of **3'b** (see Scheme 1). The CH<sub>3</sub> group of the acetaldehyde appears to stabilize the carbonyl carbon (which became more positive as the coordination to **2'a** took place) more in the *anti* complex than in the *syn* complex (the C-C overlap is larger in the *anti* complex

than in the *syn* complex). One more recognizable difference in the properties of 3'b and 3'b' related with overlap populations can be seen in the B(2)-N interaction. The B(2)-N overlap is higher in the case of the *syn* configuration (3'b') (the value is closer to that of 2'a).

As the coordination of C=O to the catalyst model (2'a) occurs the trigonal configuration of B(2) turns to a tetrahedral one. Thus it could be useful to compare properties of 3'b and 3'b' related to hybridization. In the present work the hybridization of 3'b and 3'b' is inspected by determining the degree of tetrahedral nature of the complexes 2'a, 3'a, 3'b and 3'b' as shown in Scheme 2.



Structure	Hights of the tetrahedrons [Å]						
	A	B	C	D	E	F	G
2'a	0.261	0.001	-	0.259	0.447	-	-
3'a	0.357	0.335	0.438	0.414	0.446	-	0.019
3'b	0.351	0.337	0.441	0.411	0.434	0.361	0.010
3'b'	0.349	0.333	0.442	0.416	0.439	0.364	0.014
H <sub>3</sub> CCHO				-	-	0.374	0.001

**Scheme 2.** Estimation of the degree of tetrahedral nature of complexes 2'a, 3'a, 3'b and 3'b' on the basis of the hight [ångströms] of tetrahedrons (6-31G\*\*/6-31G\*). The values of acetaldehyde were provided by optimizing acetaldehyde without symmetry to see how much the carbonyl moiety would deviate from the planar geometry [the hight of the carbonyl carbon of acetaldehyde from the plane of atoms adjacent to C<sub>C=O</sub> appeared to be 0.001 Å (should be 0.000) which could be considered as a measure of the accuracy of calculations of the hights of tetrahedrons].

Differences of hybridization between the complexes 3'b and 3'b' appear to be small (see Scheme 2). Nevertheless, the results shown in Scheme 2 are interesting in that the coordination of a carbonyl compound to B(2) of the model 2'a affects markedly, not only the Lewis acidic boron B(2) [which has a planar configuration in the model 2'a], but also the hybridization of the nitrogen and B(1) (boron of the BH<sub>3</sub> moiety). The carbonyl carbon of formaldehyde and acetaldehyde moieties of 3'a-b and 3'b' are also slightly

drawn out of the planar arrangement (towards the BH<sub>3</sub> moiety). Deformation of the carbonyl groups is small but clearly a real effect [the calculation of acetaldehyde without symmetry (6-31G\*\*//6-31G\*\*) suggest that the height of the carbonyl carbon from the plane of the atoms adjacent to it would be 0.001 Å which may be considered as a measure of the accuracy of the calculations shown in Scheme 2).

**Table 3.** Mulliken overlap populations of 2'a, 3'a, 3'b, 3'b' and the aldehydes.<sup>a,b</sup>

Structure	2'a	3'a	3'b ( <i>anti</i> )	3'b' ( <i>syn</i> )	CH <sub>3</sub> CHO	H <sub>2</sub> CO
B(1)-N	0.081	0.171	0.169	0.175	-	-
B(2)-N	0.339	0.245	0.261	0.271	-	-
B(2)-O	-	0.147	0.143	0.133	-	-
B(1)-H(1)	0.423	0.375	0.402	0.409	-	-
C=O	-	0.439	0.454	0.458	0.553	0.543
C-C	-	-	0.346	0.337	0.318	-
C-H ( <i>anti</i> )	-	0.386	-	0.397	0.391	0.376
C-H ( <i>syn</i> )	-	0.382	0.384	-	0.391	0.376
B(1)-B(2)	0.008	-0.009	-0.010	-0.012	-	-
N-O	-	-0.027	-0.030	-0.030	-	-
O-H(2)	-	-0.032	-0.030	-0.026	-	-
H <sub>C=O</sub> -C <sub>CH<sub>3</sub></sub>	-	-	-0.052	-0.059	-0.094	-
H <sub>C=O</sub> -H <sub>C=O</sub>	-	-0.039	-	-	-	-0.074
O-C <sub>CH<sub>3</sub></sub>	-	-	-0.057	-0.048	-0.077	-
O-H <sub>C=O</sub> ( <i>anti</i> )	-	-0.040	-	-	-0.051	-0.055
O-H <sub>C=O</sub> ( <i>syn</i> )	-	-0.040	-	-	-0.051	-0.055

<sup>a</sup> Based on 6-31G\*\*//6-31G\*. The values shown are directly the off-diagonal elements of the symmetric overlap matrix; i.e. the values contain one half of the actual overlap.

<sup>b</sup> Positive values imply bonding and negative values repulsive interactions.

On the basis of the results discussed above it looks as if the considerably high difference of the energies of formation of complexes 3'b and 3'b' could not be clearly attributed to any particular structural change or a change of the electronic structure of the complexes but many small differences appear instead. Therefore it might be useful to try to explain why all these changes coincide.

When the complex 2'a is formed the lone electron pair of the nitrogen of 2'a would become shared between the both borons B(1) and B(2) so that the formation of the N-BH<sub>3</sub> bond cannot complete. Thus there remains potential energy pending in the complex (2'a) [i.e. the N-BH<sub>3</sub> bonding could strengthen considerably (releasing energy) if the nitrogen could offer more electron density for the N-BH<sub>3</sub> interaction]. As the coordination of C=O to B(2) of 2'a occurs the hybridization of B(2) changes so that B(2) cannot compete with B(1) in the interaction with the lone pair of the adjacent nitrogen anymore. Consequently the N-BH<sub>3</sub> interaction strengthens and the potential energy pending is released. This is indeed what we see to happen. As the coordination of C=O to B(2) to 2'a occurs the N-B(2) bond lengthens (e.g. in the case of 3'b by 0.229 Å), the N-B(1) shortens (e.g. in the case of 3'b by 0.172 Å), and the effect of the coordination is felt even in the hydrogens of the BH<sub>3</sub> group; i.e. the B(1)-H(1) bond lengthens (in the case of 3'b by 0.030 Å), (see Scheme 1). Thus, consequences of the coordination of a Lewis base to the Lewis acidic boron [B(2)] of a borane adduct of an oxazaborolidine type of catalyst appear to delocalize to the entire active center. The active center of the catalyst looks to function as an amplifier reflecting changes of the electronic structure of B(2). The energy for amplification would be taken from strengthening of the N-BH<sub>3</sub> bond. Therefore, small differences in the binding of carbonyl compounds to the Lewis acidic boron B(2) would give rise to a large

difference in the energy of the complexes being formed (e.g. the formation of 3'b and 3'b'). However, this attempt to rationalize the coordination phenomenon leads to a logical conclusion that the stronger Lewis acid the borane used a source of hydrogen would be the higher would be the difference of energies of formation of the *syn/anti* complexes [i.e. the more acidic borane the higher degree of amplification]. Unfortunately there are no experimental data available which could be used to confirm this conclusion.

## CONCLUSIONS

Because effects of the coordination of a Lewis base to the Lewis acidic boron [B(2)] of a borane adduct of an oxazaborolidine type of catalyst appear to delocalize to the entire active center it turned out to be difficult to point out any particular effect which could explain why the energy of formation of the *anti* complex (3'b) is so much more advantageous than the energy of formation of the *syn* complex (3'b'). Nevertheless, it has been shown in the present work that the size difference of substituents of a carbonyl compound, coordinating to a borane adduct of an oxazaborolidine, affects the bond angle at which the carbonyl would be bound to the catalyst and that the energy difference between *syn* and *anti* complexes is large enough to explain the high enantioselectivity observed<sup>1</sup> in the catalytic reduction of ketones by chiral oxazaborolidines. Our computational studies on these exciting catalysts continue.

## ACKNOWLEDGEMENTS

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