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Quantum Chemical Modeling of Chiral Catalysis. Part 19. Strain and Stability - Oxazadiboretanes Potentially Involved in the Enantioselective Reduction of Ketones Promoted by Chiral Oxazaborolidines

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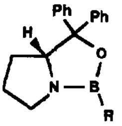
Abstract: - The relative stabilities of 2,7-dioxa-5-aza-1,6-diborabicyclo[3.2.$0^{1,5}$]heptane (e.g. **4'a**) and 2,10-dioxa-8-aza-1,9-diboratricyclo[6.2.$0^{1,8}$.$0^{4,8}$]decane derivatives (e.g. **4'b**) were studied by means of *ab initio* MO (RHF) methods. The stabilities were assessed in the light of energies of reactions leading to the opening of the oxazadiboretane ring system of the derivatives. Opening reactions of the tricyclo derivatives giving rise to the regeneration of the catalyst were found to require ≈ 20 kJ mol^{-1} (MP2/6-31G//6-31G) more energy than those of the corresponding bicyclo derivatives. Cleavages of the tricyclo systems leading to the rupture of both the oxazaborolidine and oxazadiboretane rings were found to require ≈ 30 kJ mol^{-1} (MP2/6-31G//6-31G) more energy than those of the bicyclo ones. The stability of oxazadiboretane adducts increases with the increasing angle strain related to the partial B=N π-bond of the parent oxazaborolidines. The role of electron correlation in the description of the stability of oxazadiboretanes (relative to the parent amino- and alkoxyboranes) was found to be more significant than that of polarization functions.

INTRODUCTION

Chiral oxazaborolidines **1** are known to induce a highly enantioselective catalytic reduction of ketones when borane is used as a source of hydrogen (the CBS reduction). Two review articles summarize the present status of oxazaborolidines in the field of enantioselective synthesis.[1] The formation of the borane - ketone adduct **2** of oxazaborolidines and the subsequent hydride transfer (**2** -> **3**) have been proposed to be among the key steps of the mechanism of CBS reduction.[1,2]



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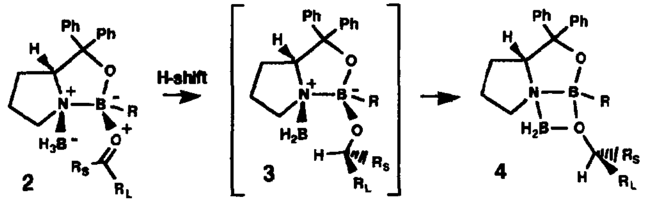
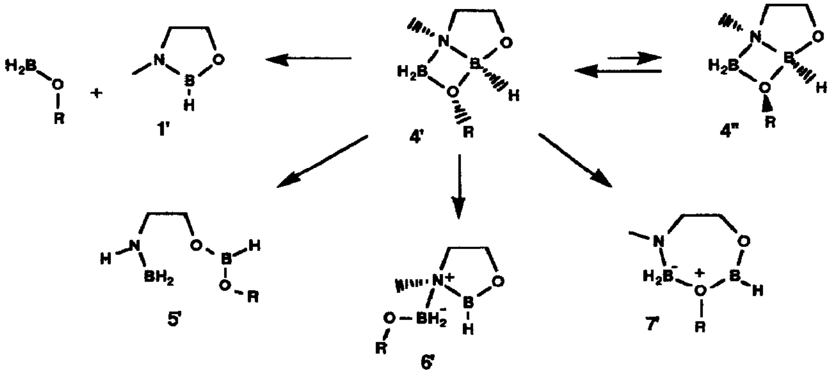


2 3 4

The formation of **2** and **3** has been studied by means of *ab initio* MO (RHF) methods.[3-5] Those studies indicated that **3** (unstable) could react further to form an oxazadiboretane system **4**.[3] An elimination of the alkoxyborane derivative (H_2B-O-CHR_SR_L) of the newly formed chiral alcohol from **4** would regenerate the catalyst (**1**).[3] These and other plausible reactions of analogs of **4** are illustrated in Scheme I.

All the earlier studies of this series on the properties and reactions of **4** are based on 2,7-dioxa-5-aza-1,6-diborabicyclo[3.2.$0^{1,5}$]heptanes (e.g. **4'a**) or on even more simplified models. Earlier studies[4c] on the Itsuno (based on the cyclic framework of **1'a**) and CBS (based on the cyclic framework of **1'b**) type of catalysts indicate that the origin of enantioselectivity of these two types of catalysts could be different.[4c] Analogs of **4** (e.g. **4'b**) which represent better the CBS type of systems have not yet been studied. Therefore, the main goal of the present work was to compare properties of the intermediates (**4**) related to the Itsuno and CBS type of catalysts and estimate energetics of the reactions **4'** -> **1'** plus alkoxyborane (regeneration of the catalyst), **4'** -> **5'**, **4'** -> **7'** and **4''** -> **4'** (Scheme I). Strain effects related to the conversion **4'** -> **6'** can be predicted on the basis of earlier studies on the borane, hydroxy- and methoxyborane adducts[3a,4a] of **1'a** and borane adducts of oxazaborolidine derivative (**1'b**)[4c] of prolinol.

Scheme I



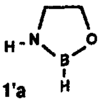
MODELS AND METHODS

Standard *ab initio* MO calculations (RHF) were carried out using the Gaussian 80 series of programs at the 3-21G, 4-31G and 6-31G levels.[6] Single-point Moller-Plesset calculations were performed on the structures optimized at the 6-31G and 6-31G* levels (denoted as MP2/6-31G//6-31G and MP2/6-31G*//6-31G*) using the Gaussian 90 system.[6c] Modeling techniques similar to those applied in the case of previous reports of this series[3d] were employed. Oxazaborolidines **1'a**, **1'b** and aminoborane (**1'c**) were used as models of oxazaborolidine catalysts (**1**); **4'a**, **4'a'**, **4''a**, **4'b**, **4'b'**, **4''b**, **4'c** and **4'c'** as models of the intermediates analogous to **4**; **5'a**, **5'a'**, **5'b** and **5'b'** as models of the intermediates analogous to **5**; **7'a** and **7'b** as models of the intermediates analogous to **7** and hydroxy- and methoxyborane as models of alkoxyboranes. The models **1'a**, **1'b**, **4'a**, **4'a'**, **4'c**, **4'c'**, **5'a**, **5'a'** and hydroxy- and methoxyborane have been described in the literature[3-5] whereas no other calculations on the models **4'b**, **4'b'**, **4''b**, **5'b** and **5'b'** appear to have been published.

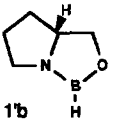
RESULTS AND DISCUSSION

The model **7'b'** was stable only at the 3-21G level whereas **7'a** appeared to be unstable also at the 3-21G level.[7] Total energies and dipole moments of the optimized structures of models of **1'**, **4'**, **5'** and **7'** are presented in Table 1.

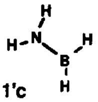
Energy changes (ΔE) related to the reactions 4' -> 1' plus alkoxyborane; 4' -> 5'; 4' -> 7' and the equilibrium 4' -> 4'' are shown in Table 2. The optimized (6-31G//6-31G) structures of 4'b and 5'b are presented in the Figure.



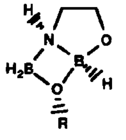
1'a



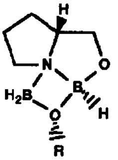
1'b



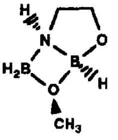
1'c



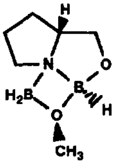
4'a R = CH_3
4'a' R = H



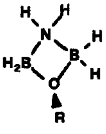
4'b R = CH_3
4'b' R = H



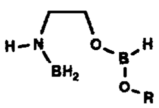
4''a



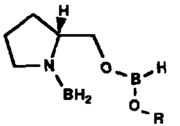
4''b



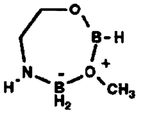
4'c R = CH_3
4'c' R = H



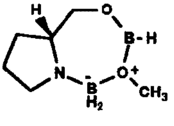
5'a R = CH_3
5'a' R = H



5'b R = CH_3
5'b' R = H



7'a



7'b

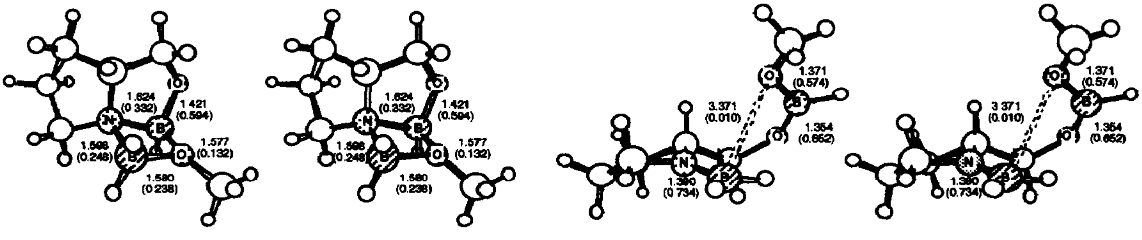
Table 1. Total energies and dipole moments of the optimized structures of models of 1', 4', 5' and 7'.[a]

Model	3-21G//3-21G		6-31G//6-31G		MP2/6-31G//6-31G	6-31G*//6-31G*		MP2/6-31G*//6-31G*
	E[a]	D[a]	E	D	E	E	D	E
1'a	-232.01452	3.16	-233.19703	3.21	-233.65062	-233.29859	2.67	-233.96562
1'b	-347.30477	3.36	-349.07697	3.49	-349.79918	-	-	-
1'c	-81.04343	2.01	-81.46276	1.76	-81.62774	-81.48910	1.82	-81.73077
4'a	-371.63266	1.31	-373.49818	1.67	-374.22901	-	-	-
4''a	-371.63255	1.76	-373.49767	1.89	-374.22832	-	-	-
4'a'	-332.82019	1.57	-334.49239	1.90	-335.13374	-334.62681	1.75	-335.57350
4'b	-486.93039	1.48	-489.38442	1.81	-490.38626	-	-	-
4''b	-486.92973	1.71	-489.38274	2.14	-490.38357	-	-	-
4'b'	-448.11752	1.89	-450.37831	2.22	-451.29017	-	-	-
4'c	-220.65768	0.60	-221.76155	0.73	-222.20189	-221.84643	0.81	-222.49174
4'c'	-181.84477	0.82	-182.75554	1.04	-183.10651	-182.81891	1.78	-183.33637
5'a	-371.60716	3.29	-373.49882	3.40	-374.22215	-	-	-
5'a'	-332.79772	3.52	-334.49656	3.63	-335.13089	-334.63933	3.11	-335.56668
5'b	-486.89536	2.68	-489.37514	2.46	-490.36731	-	-	-
5'b'	-448.08563	2.51	-450.37287	2.25	-451.27543	-	-	-
7'b	-486.88561	2.10	-	-[b]	-	-	-	-
H_2B-O-H	-100.76196	1.91	-101.27793	1.89	-101.45582	-101.32139	1.68	-101.57685
H_2B-O-CH_3	-139.57090	2.16	-140.28052	2.06	-140.54684	-140.34556	1.71	-140.72740

[a] Total energies (E) given in hartrees and dipole moments (D) in debyes. [b] The complex was found to be unstable.

Structure and bonding

Bond lengths and Mulliken overlap populations of **4'b**/**4'b'** are closely similar to those of **4'a**/**4'a'**. Apart form the B-N bond of the oxazaborolidine moiety [0.011 Å shorter (overlap 0.016 lower) in **4'b** (the Figure) than in **4'a**,[3d] 6-31G//6-31G] lengths of the B-N and B-O bonds of **4'b** deviate only by 0.006 Å (overlap populations by 0.006) or less from those of **4'a**. Bond angles of the 4-membered oxazadiboretane ring of the models of **4'** are also closely similar. For example, bond angles of **4'a-b**, **4'a'-b'** and **4''a-b** are within the following ranges (6-31G//6-31G; the alkoxyborane moiety denoted as "alk." and the catalyst moiety as "cat."): 87.0°±0.5° ($N\text{-}B_{cat.}\text{-}O_{alk.}$); 87.8°±0.6° ($N\text{-}B_{alk.}\text{-}O_{alk.}$); 93.2°±1.1° ($B_{cat.}\text{-}O_{alk.}\text{-}B_{alk.}$); 90.5°±0.7° ($B_{cat.}\text{-}N\text{-}B_{alk.}$); 104.0°±0.8° ($N\text{-}B_{cat.}\text{-}O_{cat.}$). The torsion angles of these models vary more than the bond angles (e.g. values of the torsion angle $B_{alk.}\text{-}N\text{-}B_{cat.}\text{-}O_{alk.}$ are within the range of -123.3°±3.4°; 6-31G//6-31G). Earlier studies[3d] have shown that the *O*-alkyl substituent of an oxazadiboretane would not be in the plane of the 4-ring. In the case of **4'a**, **4'b** (R=Me) and **4'b'** (R=H) the torsion angle $N\text{-}B_{cat.}\text{-}O\text{-}R_{alk.}$ is 157.6°±0.6° (R *trans* to the oxazaborolidine moiety) whereas the corresponding values of the conformers (**4''a** and **4''b**; R=Me) are in the range of -162.7°±1.0° (R *cis* to the oxazaborolidine moiety). The angle of **4'a'** (165.5°; R=H; R *trans* to the oxazaborolidine moiety) does not fall into these two ranges.



4'b **4'b** **5'b** **5'b**

Figure. Stereo representations of the optimized (6-31G//6-31G) structures of **4'b** and **5'b**. Some of the most important bond lengths [in Å] and the corresponding Mulliken overlap populations (values in parentheses below the bond lengths) are shown.

Another noticeable difference between the torsion angles of the models of **4'** is related to the $X\text{-}N\text{-}B_{cat.}\text{-}O_{cat.}$ (X an atom adjacent to the ring nitrogen; X-N *exo* to the oxazaborolidine ring) angle which is either within 111.6°±0.4° (X = C; tricyclic systems **4'b**, **4'b'** and **4''b**) or 122.9°±0.3° (X = H; bicyclic systems **4'a**, **4'a'** and **4''a**). A similar difference, although a smaller one, was observed as borane *N*-adducts of **1'a** and **1'b** were studied.[4c] In the borane *N*-adduct of **1'a** the angle $H\text{-}N\text{-}B_{cat.}\text{-}O_{cat.}$ was 141.9° whereas the corresponding value of the borane adduct of **1'b** (carbon in place of the hydrogen) was 121.0°.[4c] The smaller values of the $X\text{-}N\text{-}B_{cat.}\text{-}O_{cat.}$ angle of **4'b** and **4'b'** indicate that the angle strain related to the partial B=N π-bond[2a,4c] is higher in **1'b** than in **1'a**.

Structural parameters of the models of **5'** are similar to those of other related analogs studied before.[3d] Lengths of the B-N and B-O bonds of **5'a**, **5'a'**, **5'b** (the Figure) and **5'b'** are similar to those of alkoxy- and aminoboranes.[3d]

Energetics of cleavage reactions of oxazadiboretanes

Energies of the ring opening reactions **4'b** / **4'b'** -> **5'b** / **5'b'** are 32 kJ mol^{-1} (MP2/6-31G//6-31G, Table 2) more positive that those of **4'a** / **4'a'** -> **5'a** / **5'a'**. The regeneration energies in the former group (**4'b** / **4'b'** -> **1'b** plus $MeO\text{-}BH_2$ / $HO\text{-}BH_2$) are about 20 kJ mol^{-1} (MP2/6-31G//6-31G, Table 2) more positive than those in the latter group. Therefore, it looks as if fusing another ring (e.g. the formal conversion **1'a** -> **1'b**) to the N-C bond of the parent oxazaborolidine giving rise to an increase of the angle strain of the partial B=N π-bond of the oxazaborolidine could decrease the possibility of the unwanted cleavage (i.e. **4'** -> **5'**) to occur [energies of the unwanted reactions increase more than those of the wanted ones]. These results indicate that oxazaborolidines of which the angle strain of the partial B=N π-bond is high (e.g. CBS type of catalysts analogous to **1'b**) could retain their activity for longer times under the conditions of oxazaborolidine catalyzed reduction of ketones than the corresponding less strained analogs (e.g. Itsuno type of catalysts analogous to **1'a**).

Table 2. Energies of the reactions (ΔE)[a,b] of analogs of **4**.

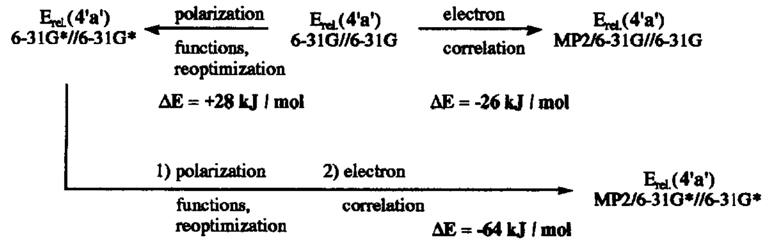
Reaction	ΔE(3-21G)	ΔE(6-31G)	ΔE(MP2/6-31G)	ΔE(6-31G*)	ΔE(MP2/6-31G*)
4'a -> 4''a	0	1	2	-	-
4'b -> 4''b	2	4	7	-	-
4'a -> 1'a + H_2B-O-CH_3	124	54	83	-	-
4'b -> 1'b + H_2B-O-CH_3	144	71	106	-	-
4'a' -> 1'a + H_2B-O-H	115	46	72	18	82
4'b' -> 1'b + H_2B-O-H	134	62	92	-	-
4'c -> 1'c + H_2B-O-CH_3	112	46	72	10	88
4'c' -> 1'c + H_2B-O-H	104	39	60	22	76
4'a -> 5'a	91	22	18	-	-
4'b -> 5'b	90	24	50	-	-
4'a' -> 5'a'	59	-11	7	-33	18
4'b' -> 5'b'	84	14	39	-	-
4'b -> 7'b	118	-[c]	-	-	-

[a] Energies (ΔE) given in kJ mol^{-1}. [b] These energies should not be considered as absolute reaction enthalpies. These energies should be used only for comparisons between closely related analogs or series of analogs. [c] See Table 1.

A comparison of energies of the elimination of hydroxy- and methoxyborane from **1'a-c** reveals that all the energies related to the methoxyborane derivatives are about 7 - 14 kJ mol^{-1} higher than those of the corresponding hydroxy ones (i.e. methoxyborane adducts are more stable than the corresponding hydroxyborane analogs). Furthermore, the same difference can be found at all the levels of inspection (i.e. the differences observed at the 3-21G//3-21G level are closely similar to those of MP2/6-31G*//6-31G*) indicating that neither polarization functions nor electron correlation would have been needed for the determination of these *relative* values.

The importance of the quality of basis sets, inclusion of polarization functions and involvement of electron correlation could be assessed in the light of the energies of elimination of H_2B-OH from **4'a'** calculated at different levels (Scheme II). However, it can be seen (Scheme II), that the influence of inclusion of polarization functions is opposite to that of involvement of electron correlation. Furthermore, the stability of **4'a'** (relative to **1'a** and hydroxyborane) determined at the MP2/6-31G//6-31G level is almost as good as that provided at the MP2/6-31G*//6-31G* level. In this light it looks as if one could predict relative stabilities of oxazadiboretanes rather reliably already on the basis of calculations carried out at the MP2/6-31G//6-31G level (inclusion of polarization functions would not be necessary).

Scheme II



Conclusions similar to those drawn on the basis of the inspection of **4'a'** (Scheme II) could have been drawn also in the case of other oxazadiboretanes (**4'c** and **4'c'**) studied with inclusion of polarization functions. For example, the stability (towards the cleavage of the 4-ring) of **4'c'** decreases in consequence of inclusion of polarization functions (at the 6-31G level) and reoptimization whereas the involvement of electron correlation at the 6-31G level stabilizes **4'c'** almost as much as the full geometry optimization with inclusion of polarization functions followed by involvement of electron correlation (the stability of **4'c'** at the MP2/6-31G*//6-31G* level is only 16 kJ mol^{-1} higher than that obtained at the MP2/6-31G//6-31G level, Table 2). Computational studies on chiral catalytically active oxazaborolidines continue.

CONCLUSIONS

The results of this work indicate that fusing another ring to the N-C bond of the parent oxazaborolidine system could decrease the possibility of the unwanted cleavage (leading to the rupture of the oxazaborolidine ring) in alkoxyborane - oxazaborolidine adducts [energies of the unwanted reactions increase more than those of the wanted ones]. Therefore, oxazaborolidines of which the angle strain of the partial B=N π-bond is high (e.g. CBS type of catalysts analogous to **1'b**) could retain their activity for longer times under the conditions of oxazaborolidine catalyzed reduction of ketones than the corresponding less strained analogs (e.g. Itsuno type of catalysts analogous to **1'a**).

Stabilities of oxazadiboretanes (relative to the parent amino- and alkoxyboranes) can be predicted rather reliably on the basis of calculations carried out at the MP2/6-31G//6-31G level. It looks as if inclusion of polarization functions would not be necessary until highly accurate absolute energies are needed.

ACKNOWLEDGEMENTS

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7. All attempts to optimize structures **7'a / 7'b** (except that performed at the 3-21G level) led to the corresponding analogs of **5'**. Reasons behind this behaviour would require a study on the transition state structures. That was not undertaken as conclusions satisfactory for the purposes of understanding the most important properties of oxazadiboretanes can be drawn on the basis of the present work already.

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