Quantum Chemical Modeling of Chiral Catalysis. Part 5. On the Role of Alkoxyboranes in the Catalytic Enantioselective Reduction of Carbonyl Compounds by the CBS Method

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Abstract: - Energies of the formation, relative stabilities and structural parameters of alkoxyborane *N*-adducts of oxazaborolidine type of chiral reduction catalysts were evaluated by means of *ab initio* molecular orbital calculations. Three models of the oxazaborolidine system were used. Stability of the alkoxyborane adducts and the nature of borane - catalyst interactions was found to depend strongly on the conformation of the alkoxy group. Two different mechanisms for the formation of the alkoxyborane adducts, a direct coordination of an alkoxyborane to the nitrogen of an oxazaborolidine ring and an intramolecular rearrangement of an oxazadiboretane intermediate, are discussed. Properties of borane and alkoxyborane adducts are compared.

INTRODUCTION

Oxazaborolidine type of chiral catalysts (e.g. **1**), of which the mechanism of action was discovered by Corey *et al.*,[1] have been shown to be highly effective for the enantioselective reduction of ketones (CBS reduction).[1,2] The catalytically active species is believed to be the borane adduct of **1** (e.g. **2**), which would be formed *in situ* in a reaction of **1** with $H_3B \cdot THF$.[1]
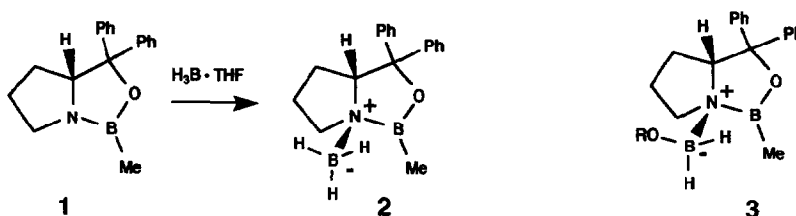
However, the ability of **2** to serve as a reducing agent almost disappears at the level where two hydrogens of BH_3 are substituted by alkoxy groups arising from the newly formed chiral alcohol [e.g. complete reduction is achieved when about 60 mol % of borane is used; and furthermore, the dialkoxyborane derivative of the newly formed chiral alcohol has been found to be the final product of the reduction].[1] This observation allows one to envision that not only the BH_3 adduct (**2**) but also the corresponding alkoxyborane adduct (**3**) could play a role in the catalysis in which BH_3 is used as a source of hydrogen.

The mechanism of chiral catalysis induced by oxazaborolidines has been lately studied also by means of *ab initio* molecular orbital calculations.[3] Although only simple models of intermediates were inspected[3] the results clearly provided further support for the previously proposed mechanism of the catalysis.[1] The studies also revealed that an 1,3-oxazadiboretane system **4** could be involved in the regeneration of an oxazaborolidine

catalyst[3d] as shown in Scheme 1. In that context the reaction (a) was evaluated whereas the potential importance of other reactions (b and c) was briefly mentioned only.[3d]
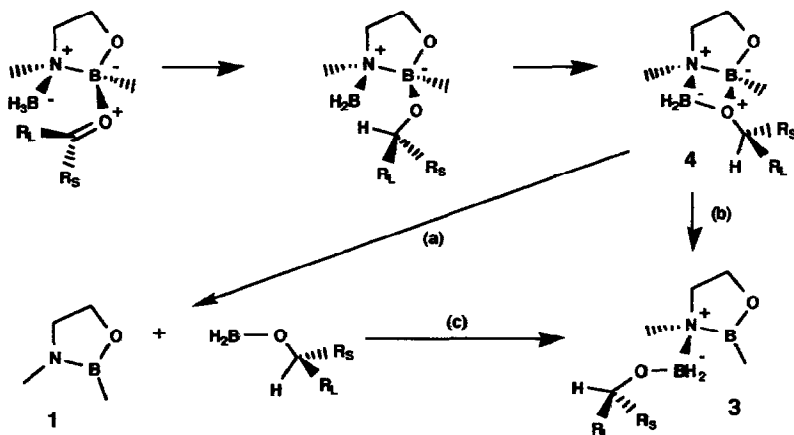

Scheme 1. A plausible mechanism for the regeneration of the catalyst (1) and the formation of the alkoxyborane adduct (3).

The oxazadiboretane system (4) formed after the intramolecular hydride transfer depicted in Scheme 1 (the first reaction) could react further either by eliminating the alkoxyborane moiety [reaction (a)] or 4 could rearrange to 3 [reaction (b)]. On the other hand, the alkoxyborane could, after the elimination (4 -> 1), coordinate back to the nitrogen of 1 also giving rise to the formation of 3 [reaction (c)]. The alkoxyborane adduct (3) could then function as a catalyst in the same way as 2 does.

The aim of this work was to study structural and electronic properties of 3, compare energetics of the coordination of borane and alkoxyboranes to 1 (i.e. the reactions 1 -> 2 and 1-> 3), and to assess the relative energetic advantage of the reactions (a, b and c) shown in Scheme 1. The study was carried out by using *ab initio* molecular orbital methods. In all calculations the Gaussian 80 series of programs were employed at the 3-21G, 4-31G, 6-31G, 4-31G* and 6-31G* levels.[4] Standard optimization procedures were used. In a few cases models were calculated by using both the Gaussian 80[4] and Gaussian 90[5] series of programs. Results provided by using both of these programs were closely similar, as has been observed earlier.[3d]
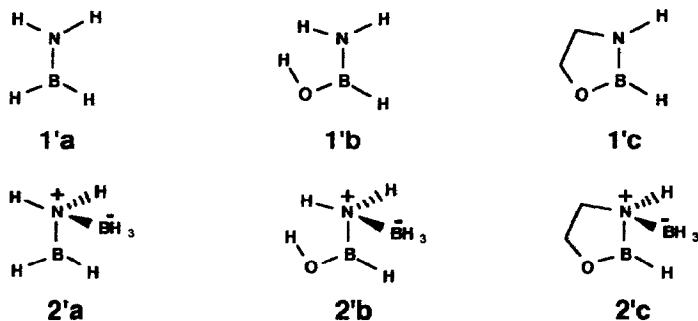
As in the case of the previous works of this series[3] smaller models analogous to 1 - 4 were used instead of the entire structures. The principles applied to select the models have been discussed before.[3d] The models used were as follows: 1'a, 1'b and 1'c for 1; 2'a, 2'b and 2'c for 2; 3'a, 3'a', 3'b, 3'b', 3'c and 3'c' for 3; and, 4'a, 4'b, 4'c for 4. The model pairs 3'a - 3'a', 3'b - 3'b', and 3'c - 3'c' are rotamers. In the group of 3'a-c the H-O-B-N torsion angle is ≈ 180° whereas in the case of 3'a'-c' the angle is ≈ 90°. Properties of the models 1'a-c, 2'a-c and 4'a-c, including $H_2O \cdot BH_3$, $Me_2O \cdot BH_3$, $H_3N \cdot BH_3$, $HO\text{-}BH_2$ and $MeO\text{-}BH_2$, have been discussed before,[3a-d] whereas, except our brief preliminary reports,[3e,3f] the structures 3'a, 3'a', 3'b, 3'b', 3'c, 3'c', as also adducts of H_2O, Me_2O and NH_3 to $MeO\text{-}BH_2$ appeared to have been not investigated before. Adducts of several oxygen, nitrogen and phosphorus containing nucleophiles to $HO\text{-}BH_2$ have been discussed in the literature[6] but no computational studies related to this work appeared to have been published.
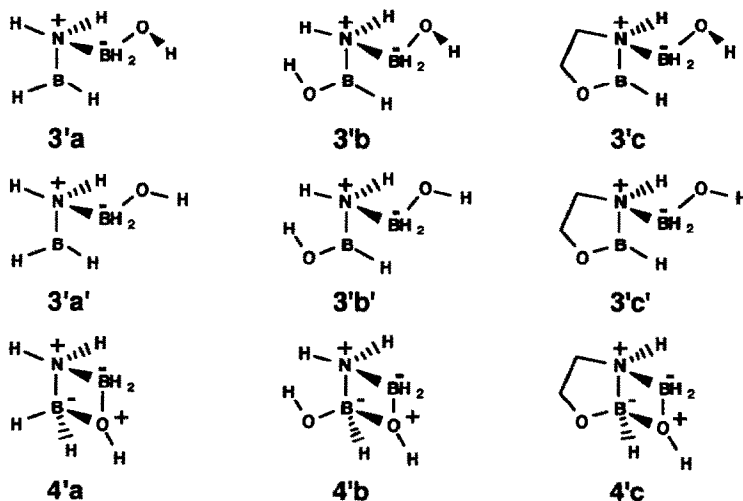
RESULTS AND DISCUSSION

Total energies and dipole moments calculated are summarized in Table 1. As the adducts 2'a-c studied before,[3a] the adducts 3'a-c appeared to be stable. However, when the torsion angles H-O-B-N of 3'a-c were modified to correspond to those of 3'a'-c' the oxazaborolidine moieties of the models started to repel the alkoxyborane ones and the adducts decomposed giving rise to the formation of loose complexes of 1'a-c and HO-BH_2 (in which the boron of the HO-BH_2 moiety appeared at a distance longer than 2.8 Å from the nitrogen of all 3'a', 3'b' and 3'c'). Nevertheless, the complexes 3'a', 3'b' and 3'c' were slightly more stable than separate HO-BH_2 and 1'a-c. Stereo representations of the 6-31G* optimized structures and the most important bond lengths of 3'a-c are shown in Scheme 2 and those of 3'a', 3'b' and 3'c' in Scheme 3.

Net atomic charges, Mulliken overlap populations and distances between acidic (A) and basic (B) centers of Lewis acid - base pairs $(A^-\text{-}B^+)$, and HOMO/LUMO energies are shown in Table 2. Energies of the formation of adducts 3'a-c, 3'a'-c'[reaction (c), see Scheme 1] and 2'a-c, are shown in Table 3. Regeneration energies of the catalyst models 1'a-c [reaction (a), see Scheme 1] and energies of opening of the four membered ring of 4'a-c to give 3'a-c [reaction (b), see Scheme 1] are shown in Table 4.

Table 1. Total energies (E)[a] and dipole moments (D)[b] of the models 1'a-c, 2'a-c, 3'a-c, 3'a'-c', 4'a-c, HO-BH₂, MeO-BH₂, the adducts of H₂O to HO-BH₂ and MeO-BH₂, the adducts of Me₂O to MeO-BH₂, and the adducts of NH₃ to HO-BH₂ and MeO-BH₂.

| Structure	3-21G//3-21G		4-31G//4-31G		6-31G//6-31G		4-31G*//4-31G*		6-31G*//6-31G*	
	E[a]	D[b]	E	D	E	D	E	D	E	D
1'a	-81.04343	2.01	-81.37857	1.76	-81.46276	1.76	-81.40935	1.84	-81.48910	1.82
1'b	-155.55682	3.27	-156.19671	3.20	-156.35434	3.23	-156.25862	2.95	-156.40862	2.96
1'c	-232.01452	3.16	-232.95883	3.18	-233.19703	3.21	-233.07225	2.65	-233.29859	2.67
2'a	-107.29823	4.35	-107.73575	3.84	-107.84578	3.78	-107.78128	4.21	-107.88689	4.24
2'b	-181.82032	4.72	-182.55939	4.21	-182.74260	4.21	-182.63855	4.48	-182.81418	4.46
2'c	-258.28393	5.22	-259.32696	4.93	-259.59052	4.89	-259.45727	4.98	-259.70944	4.97
3'a	-181.79567	2.40	-182.53885	1.68	-182.72366	1.89	-182.61243	2.18	-182.78896	2.15
3'b	-256.32022	2.91	-257.36494	2.47	-257.62294	2.43	-257.47262	2.57	-257.71933	2.53
3'c	-332.78427	3.42	-334.13228	0.00	-334.47058	3.07	-334.28942	3.36	-334.61258	3.35
3'a'	-181.80904	2.85 [c]	-182.55689	2.51 [c]	-182.74180	2.49 [c]	-182.63515	2.61 [c]	-182.81164	2.59 [c]
3'b'	-256.32510	3.99 [c]	-257.37707	4.09 [c]	-257.63545	4.12 [c]	-257.48530	3.76 [c]	-257.73198	3.77 [c]
3'c'	-332.78562	4.70	-334.13378	4.33	-334.47169	4.33	-334.29900	3.58 [c]	-334.62188	3.59 [c]
4'a	-181.84477	0.82	-182.57271	1.01	-182.75550	1.07	-182.64372	1.45	-182.81873	1.48
4'b	-256.35880	1.71	-257.39068	1.62	-257.64734	1.62	-257.49078	2.06	-257.73638	2.06
4'c	-332.82019	1.57	-334.15586	1.85	-334.49239	1.90	-334.30493	1.65	-334.62681	1.75
HO-BH₂[d]	-100.76196	1.91	-101.17676	1.87	-101.27793	1.89	-101.22430	1.68	-101.32139	1.68
HO-BH₂[e]	-100.74288	1.96	-101.15908	1.78	-101.26049	1.76	-101.20130	1.70	-101.29856	1.70
MeO-BH₂[f]	-139.57090	2.16	-140.13955	2.08	-140.28052	2.06	-140.21037	1.71	-140.34556	1.71
MeO-BH₂[g]	-139.55445	2.22	-140.12258	2.06	-140.26356	2.03	-140.18974	1.68	-140.32498	1.66
HO-BH₂·OH₂	-176.36841	5.02	-177.09373	4.27	-177.27050	4.27	-177.16796	3.37 [c]	-177.33608	3.38 [c]
HO-BH₂·OH₂[h]	-176.36634	3.20	-177.08769	2.84	-177.26423	2.79	-177.15523	2.64	-177.32285	2.60
MeO-BH₂·OH₂	-215.17854	4.03	-216.05689	2.87	-216.27352	2.86	-216.15553	1.29 [c]	-216.36174	1.28 [c]
MeO-BH₂·OH₂[i]	-215.17623	3.47	-216.05015	3.06	-216.26633	3.02	-216.14303	3.00	-216.34864	2.97
MeO-BH₂·OMe₂	-292.80528	5.01	-293.98615	4.55	-294.28193	4.49	-294.13072	2.58 [c]	-294.41316	2.57 [c]
MeO-BH₂·OMe₂[j]	-292.80613	4.03	-293.98556	3.77	-294.28112	3.72	-294.12223	3.72	-294.40406	3.68
HO-BH₂·NH₃	-156.66400 [k]	5.25	-157.30297 [k]	5.13	-157.46151 [k]	5.16	-157.36626	5.06	-157.51667	5.05
HO-BH₂·NH₃[l]	-156.66497	3.91	-157.30375	3.77	-157.46261	3.78	-157.36509	3.99	-157.51569	3.98
MeO-BH₂·NH₃	-195.44960	2.25	-196.26419	5.20	-196.46228	5.22	-196.35257	5.10	-196.54086	5.11
MeO-BH₂·NH₃[m]	-195.47490	4.27	-196.26653	4.04	-196.46503	4.07	-196.35325	4.42	-196.54180	4.42

[a] Total energies given in hartrees. [b] Dipole moments given in debye [c] The initial structure decomposed (the distance between the acidic and basic centers of the Lewis acid-base pair was longer than 2.5 Å) [d] Planar geometry [e] Symmetry used to keep the plane of H-O-B perpendicular to the plane of H-B-H. [f] Planar C-O-BH₂. [g] Symmetry used to keep the plane of C-O-B perpendicular to the plane of H-B-H. [h] The torsion angle H-O-B-OH₂ forced to 180° by symmetry. [i] The torsion angle C-O-B-OH₂ forced to 180° by symmetry. [j] The torsion angle C-O-B-OMe₂ forced to 180° by symmetry. [k] The torsion angle H-O-B-N was likely to fall to 180° during the geometry optimizations. Thus, in order to allow comparison of these values to those of other related structures, the angle was kept constant (at 104.813° which is the 6-31G*//6-31G* value of the angle) during the geometry optimizations. [l] The torsion angle H-O-B-NH₃ forced to 180° by symmetry [m] The torsion angle C-O-B-NH₃ forced to 180° by symmetry.

Structure, Formation and Stability of the BH₃ and HO-BH₂ Adducts

Optimized geometries (6-31G*//6-31G*) of the HO-BH₂ adducts 3'a-c (see Scheme 2) resemble those of the corresponding BH₃ adducts (i.e. 2'a-c)[3a] whereas in the case of 3'a', 3'b' and 3'c' the geometries (see Scheme 3) fit best to those of separate 1'a-c[3a] and HO-BH₂ molecules. In the case of 3'a the B(1)-N bond is

longer than that of **2'a** but in both **3'b** and **3'c** the B(1)-N bond is shorter than that of **2'b** or **2'c**. Thus, on the basis of the length of the B(1)-N bond of **2'b-c** and **3'b-c** one could conclude that the boron of an alkoxyborane RO-BH$_2$ can afford a more close contact to the nitrogen of an oxazaborolidine than BH$_3$. Also the comparison of Mulliken ovelaps of the B(1)-N bonds of **2'b-c** and **3'b-c** supports this [e.g. the B(1)-N overlap of **3'b** is 41% higher than that of **2'b** and the corresponding overlap of **3'c** about 10% higher than that of **2'c**, see Table 2].
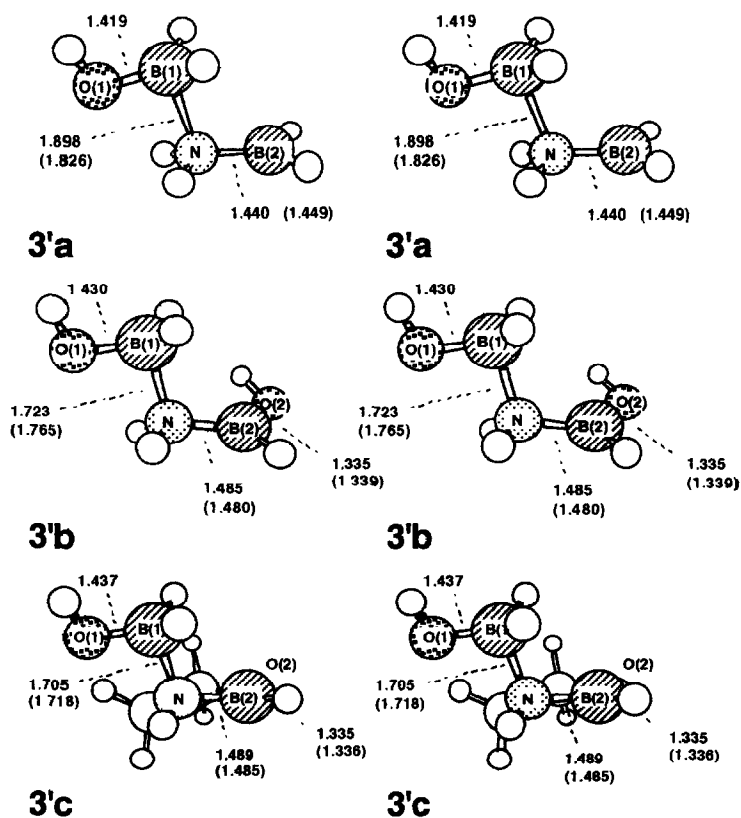
Scheme 2. Stereo representations of the optimized geometries of **3'a-c** (6-31G*//6-31G*). Some of the most important bond lengths are shown. The values in parenthesis are the corresponding bond lengths of the analogs **2'a-c**.

Comparison of lengths of the B(2)-N and B(2)-O(2) bonds of the adducts **2'a-c** and **3'a-c** confirms further, although in an indirect way, the proposed closer B(1)-N contact. Namely, the B(2)-N bond of both **3'b** and **3'c** is longer than the corresponding bonds of the analogs **2'b** and **2'c**. A connection from these differences in the lengths of the B(2)-N and B(2)-O(2) bonds to the B(1)-N interaction can be found by taking into account that coordination of a borane to the nitrogen of an oxazaborolidine disturbs the energetically advantageous

resonance (O-B-N <-> O-B$^-$=N$^+$) giving double bond character to the B(2)-N bond, and consequently, as the double bond character of the B(2)-N bond decreases the bond lengthens.[3a] Furthermore, even though the difference is small, also the B(2)-O(2) bond of **3'b** (or **3'c**) is longer than that of **2'b** (or **2'c**) implying that compensation of the loss of the advantageous resonance (O-B-N <-> O-B$^-$=N$^+$) by another resonance (i.e. O-B-N <-> O$^+$=B$^-$-N) shortening the B(2)-O(2) bond is of higher importance in the case of alkoxyborane adducts [i.e. the more close B(1)-N contact the shorter B(2)-O(2) bond].[3a] Similar conclusions could be drawn by comparing charges of **2'b-c** and **3'b-c** [e.g. B(2) of **3'b-c** is more positive than that of **2'b-c**, see Table 2].
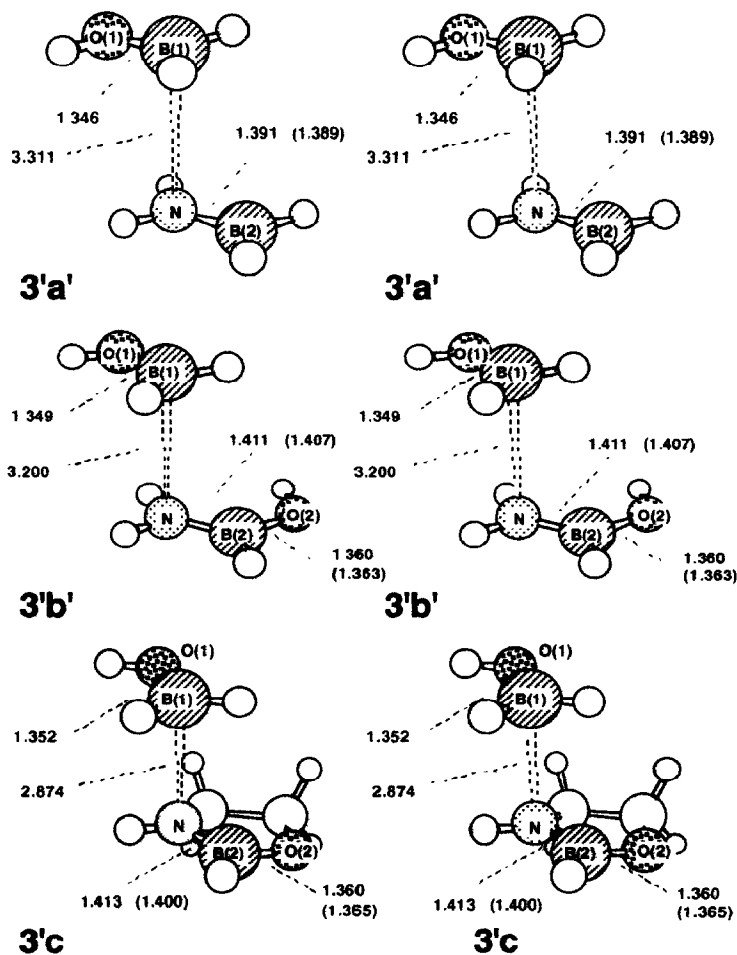
Scheme 3. Stereo representations of the optimized geometries of **3'a'**, **3'b'** and **3'c'** (6-31G*//6-31G*). Some of the most important bond lengths are shown. The values in parenthesis are the corresponding bond lengths of **1'a-c**.

Table 2. Mulliken overlap populations and distances between acidic (A) and basic (B) centers of Lewis acid - base pairs (A⁻-B⁺), HOMO / LUMO energies, and the net atomic charges of B(1), H_{BH_3}, B(2), N, O(1) and O(2) of 1'a-c, 2'a-c, 3'a-c, 3'a', 3'b', 3'c', 4'a-c, HO-BH₂ and MeO-BH₂.[a,b]

Structure	B(1)	$H_{B(1)}$[c]	B(2)	N	O(1)	O(2)	HOMO	LUMO	(A⁻-B⁺) distance	(A⁻-B⁺) overlap
1'a	-	-	+0 265	-0.858	-	-	-11 72	+4.71	-	-
1'b	-	-	+0 545	-0.927	-	-0 694	-11 26	+5.84	-	-
1'c	-	-	+0 551	-0 776	-	-0.585	-10 12	+5 84	-	-
2'a	+0 077	-0.094	+0 346	-0.906	-	-	-11.76	+2 94	1 826	0.161
2'b	+0 098	-0.106	+0.595	-0 940	-	-0 658	-11 54	+4 50	1 765	0 160
2'c	+0.098	-0.114	+0.609	-0.804	-	-0.546	-11.31	+4.28	1.718	0 230
3'a	+0 451	-0.142	+0 347	-0.926	-0.782	-	-10.53	+3 03	1 898	0 166
3'b	+0 457	-0.175	+0 603	-0.940	-0.793	-0 655	-10 27	+4 10	1 723	0 226
3'c	+0 466	-0.170	+0 613	-0.819	-0.804	-0 546	-10.06	+4 18	1 705	0 254
3'a'	+0.354	-0.085	+0 269	-0 865	-0.650	-	-11 86	+4 10	3 311	0.020
3'b'	+0 360	-0.086	+0 556	-0 940	-0 657	-0 691	-11 40	+4.31	3 200	0 026
3'c'	+0 381	-0.093	+0 574	-0 803	-0 664	-0 583	-10 40	+4 67	2 874	0.038
4'a	+0 418	-0.102	+0.418	-0 931	-0.763	-	-11 51	+5 37	-	-
4'b	+0.410	-0.103	+0 740	-0.961	-0.780	-0 789	-11 62	+5 84	-	-
4'c	+0.433	-0 107	+0 779	-0 860	-0 818	-0 633	-11 62	+5.50	-	-
H₃B	+0 123	-0.041	-	-	-	-	-13.47	+2.41	-	-
HO-BH₂[d]	+0.346	-0.080	-	-	-0 641	-	-12 50	+4.07	-	-
HO-BH₂[e]	+0 642	-0.124	-	-	-0.857	-	-11 56	+3.40	-	-
MeO-BH₂[f]	+0.360	-0.086	-	-	-0 517	-	-12 14	+3 98	-	-
MeO-BH₂[g]	+0 420	-0.098	-	-	-0.558	-	-11 00	+3.51	-	-
H₃B•OH₂	+0.160	-0.102	-	-	-	-	-11.80	+4.27	1 814	0.124
HO-BH₂•OH₂	+0 397	-0.098	-	-	-0 678	-	-12.09	+4.91	2 579	0 052
HO-BH₂•OH₂[h]	+0 486	-0.148	-	-	-0 792	-	-10.54	+4.84	1.763	0.168
MeO-BH₂•OH₂	+0 420	-0.109	-	-	-0 550	-	-11 82	+4.80	2 569	0.056
MeO-BH₂•OH₂[i]	+0.500	-0.145	-	-	-0.653	-	-10.23	+4.76	1.754	0.190
H₃B•OMe₂	+0 197	-0.121	-	-	-	-	-11.34	+5.51	1.719	0.180
MeO-BH₂•OMe₂	+0.433	-0 109	-	-	-0 544	-	-11 54	+4 95	2.613	0.050
MeO-BH₂•OMe₂[j]	+0.566	-0.171	-	-	-0.659	-	-9.87	+6.00	1.683	0.218
H₃B•NH₃	+0 104	-0 123	-	-0.933	-	-	-11 12	+4 65	1.683	0.202
HO-BH₂•NH₃	+0.464	-0.161	-	-0.964	-0 779	-	-10.68	+5.00	1.749	0.120
HO-BH₂•NH₃[k]	+0.470	-0.179	-	-0 943	-0 805	-	-9 86	+5 04	1.674	0.224
MeO-BH₂•NH₃	+0.497	-0.155	-	-0.988	-0.631	-	-10.63	+4.86	1 768	0.100
MeO-BH₂•NH₃[l]	+0.486	-0.173	-	-0 943	-0.663	-	-9 64	+5.00	1.672	0.234

[a] Based on 6-31G*//6-31G*. [b] Orbital energies are given in electron volts; distances between acidic and basic centers of Lewis acid - base pairs (A⁻-B⁺) are given in ångströms. [c] An average value of hydrogens of the borane moiety [hydrogens of B(1), see Schemes 2 and 3]. [d] Planar geometry. [e] The plane set on H-O-B perpendicular to that on O-B-H (forced by symmetry) [f] The HC-O-BH2 atoms in the same plane. [g] The plane set on C-O-B perpendicular to that on O-B-H (forced by symmetry). [h] The torsion angle H-O-B-OH₂ forced to 180° by symmetry. [i] The torsion angle C-O-B-OH₂ forced to 180° by symmetry. [j] The torsion angle C-O-B-OMe₂ forced to 180° by symmetry. [k] The torsion angle H-O-B-NH₃ forced to 180° by symmetry. [l] The torsion angle C-O-B-NH₃ forced to 180° by symmetry.

Interesting observations could be made by comparing the charges of B(1), B(2) and hydrogens of B(1) shown in Table 2. As a borane coordinates to the nitrogen of an oxazaborolidine ring both the positive charge of the boron of the oxazaborolidine moiety [B(2)] and the negative charge of hydrogens of the coordinating boron

B(1) increase. In the case of hydrogens of the coordinating BH_3 the negative charge almost triples as a result of the coordination whereas in the case of $HO-BH_2$ the negative charge only doubles (see Table 2). Nevertheless, higher negative charges of hydrogens of B(1) of **3'b** and **3'c** with respect to those of the corresponding BH_3 adducts (**2'b** and **2'c**) imply that the propensity of an alkoxyborane adduct to deliver a hydride would be higher than that of the corresponding BH_3 adduct. Furthermore, on the basis of charges of hydrogens of B(1) shown in Table 2 and other related values reported in the literature,[3a,3c-d] it looks as if alkoxyborane adducts analogous to **3'c** would be the second most potent hydride donating species among those involved in the catalysis [in Table 2 only two borane adducts of NH_3 have equally or more negatively charged hydrogens than **3'c**; the most negative hydrogens were found[3a] in a model of a ketone complex of a borane adduct of an oxazaborolidine (formaldehyde used as a model of a ketone)].

Table 3. Energies of the coordination of H_3B, $HO-BH_2$ and $MeO-BH_2$ to the oxygen of H_2O and Me_2O and to the nitrogen of **1'a-c** and NH_3.

Reaction				3-21G	4-31G	6-31G	4-31G*	6-31G*
						Coordination energies[a]		
1'a	+	H_3B	->	2'a	-46	-21	-16	-23	-20
1'b	+	H_3B	->	2'b	-69	-35	-30	-44	-41
1'c	+	H_3B	->	2'c	-84	-50	-44	-57	-55
1'a	+	H_2B-OH[b]	->	3'a	+25	+43	+45	+56	+57
1'b	+	H_2B-OH[b]	->	3'b	-4	+22	+25	+27	+28
1'c	+	H_2B-OH[b]	->	3'c	-20	+9	+12	+19	+19
1'a	+	H_2B-OH[b]	->	3'a'	-10 [c]	-4 [c]	-3 [c]	-4 [c]	-3 [c]
1'b	+	H_2B-OH[b]	->	3'b'	-17 [c]	-10 [c]	-8 [c]	-6 [c]	-5 [c]
1'c	+	H_2B-OH[b]	->	3'c'	-24	+5	+9	-6 [c]	-5 [c]
H_3N	+	H_3B	->	$H_3N \cdot BH_3$	-149	-110	-103	-103	-99
H_3N	+	H_2B-OH	->	$H_3N \cdot BH_2-OH$	-78	-53	-47	-32	-29
H_3N	+	H_2B-OH	->	$H_3N \cdot BH_2-OH$[d]	-81	-55	-50	-28	-26
H_3N	+	H_2B-OMe	->	$H_3N \cdot BH_2-OMe$	-17	-47	-43	-32	-29
H_3N	+	H_2B-OMe	->	$H_3N \cdot BH_2-OMe$[e]	-84	-53	-50	-34	-31
H_2O	+	H_3B	->	$H_2O \cdot BH_3$	-105	-60	-54	-43	-38
H_2O	+	H_2B-OH	->	$H_2O \cdot BH_2-OH$	-54	-22	-19	-12 [f]	-10 [f]
H_2O	+	H_2B-OH	->	$H_2O \cdot BH_2-OH$[g]	-48	-6	-2	+21	+24
H_2O	+	H_2B-OMe	->	$H_2O \cdot BH_2-OMe$	-57	-23	-20	-16 [f]	-14 [f]
H_2O	+	H_2B-OMe	->	$H_2O \cdot BH_2-OMe$[h]	-51	-5	-1	+17	+20
Me_2O	+	H_3B	->	$Me_2O \cdot BH_3$	-110	-71	-65	-49	-45
Me_2O	+	H_2B-OMe	->	$Me_2O \cdot BH_2-OMe$	-56	-22	-18	-9 [i]	-8 [i]
Me_2O	+	H_2B-OMe	->	$Me_2O \cdot BH_2-OMe$[j]	-58	-20	-16	+13	+16

[a] Complexation energies given in kJ mol⁻¹   [b] Planar geometry   [c] The B(1)-N bond in the optimized geometry was longer than 2.5 Å   [d] The torsion angle H O-B-NH₃ forced to 180° by symmetry   [e] The torsion angle Me-O-B-NH₃ forced to 180° by symmetry   [f] The B OH₂ distance in the optimized geometry was longer than 2.5 Å   [g] The torsion angle H-O-B-OH₂ forced to 180° by symmetry   [h] The torsion angle Me-O-B-OH₂ forced to 180° by symmetry   [i] The B-OMe₂ distance in the optimized geometry was longer than 2.5 Å   [j] The torsion angle Me-O-B-OMe₂ forced to 180° by symmetry.

Comparison of energies of the highest occupied molecular orbitals (HOMO values, see Table 2) support the conclusions drawn by inspecting charges as discussed above. Namely, the HOMO value of **3'c** is 1.25 eV higher (less negative) than that of **2'c**, and the HOMO of these adducts consists mostly of functions of the hydrogens of B(1), the lone pair of O(2) and some density of B(1), i.e. **3'c** should be a more potent hydride donor than **2'c**.

Furthermore, the HOMO energy of 3'c appears to be the lowest one among those of the reactive intermediates shown in Table 2 (two borane adducts of NH_3 have lower values; but, amines are not present in the reaction mixture and therefore these two adducts were calculated only for reference purposes). The most prominent component of LUMO is clearly the $2p_z$ function of B(2) but the LUMO energies of 3'b and 3'c are only slightly lower than the corresponding values of 2'b and 2'c, e.g. the LUMO energy of 3'c is 0.1 eV lower than that of 2'c (in the case of 3'b and 2'b the difference is 0.4 eV). Therefore, as the difference of LUMO energies is so small it would be easy to envision that both of these boranes, i.e. BH_3 and an alkoxyborane, as they coordinate to an oxazaborolidine, would enhance Lewis acidity of the boron of the oxazaborolidine moiety approximately by equal amounts.

Energies of the formation of 3'a-c differ more from those of 2'a-c than could be expected on the basis of rather close structural similarity of these adducts discussed above. The formation of 2'a-c is energetically advantageous whereas the formation of 3'a-c requires energy (e.g. the difference of energies of the formation of 2'c and 3'c is 74 kJ mol^{-1}). This difference, however, diminishes when we include solvent effects, because BH_3 forms more stable complexes with Lewis basic solvents than an alkoxyborane would do; e.g. a BH_3 molecule would be stabilized by 38 kJ mol^{-1} as it coordinates to water $(6\text{-}31g*//6\text{-}31G*)^{3c}$ whereas the corresponding stabilization is only 10 - 14 kJ mol^{-1} in the case of $HO\text{-}BH_2$ and $MeO\text{-}BH_2$ (see Table 3). Closely similar conclusions could be drawn by comparing the corresponding values calculated for Me_2O (see Table 3). Therefore, if the adducts are also expected to be equally stabilized by coordination of a Lewis basic solvent to the boron of the oxazaborolidine ring (as discussed below) one could conclude that the formation of BH_3 adducts of oxazaborolidines should be favored over the alkoxyborane adducts analogous to 3'c by about 40 - 50 kJ mol^{-1}.

Preliminary support for the similar stabilization of borane and alkoxyborane adducts by the coordination of a Lewis basic solvent to the boron of the oxazaborolidine ring mentioned above was provided by inspecting the coordination of water to B(2) of 3'a. Energies of the coordination of water to 3'a, 3'a' and 2'a (water syn to the borane) were -62 kJ mol^{-1}, -61 kJ mol^{-1}, and -60 kJ mol^{-1} (the water complex of 2'a and a number of other closely related models have been studied earlier[3c]). This close similarity could not have been predicted on the basis of an inspection of dipole moments shown in Table 1 as dipole moments of all the models of BH_3 adducts calculated appeared to be considerably higher than those of the corresponding alkoxyborane adducts. On the other hand, the similarity could be understood in the light of one of the observations discussed above. Namely, changing one of the hydrogens of the borane moiety of a BH_3 adduct to an alkoxy group would not affect the Lewis acidity of the boron of the oxazaborolidine ring.

An interesting result was also the observed increase of stability of 3'a' by the coordination of water to B(2). The B(1)-N distance in the water complex of 3'a' was only slightly (0.047 Å) longer than that of the water complex of 3'a [the corresponding difference in the case of 3'a and 3'a' with no solvent coordinated to B(2) was 1.413 Å, see Schemes 2 and 3]. On the basis of this preliminary work it looks as if a Lewis basic solvent could stabilize an alkoxyborane - oxazaborolidine adduct against its decomposition back to the alkoxyborane and oxazaborolidine moieties.

In addition to the lower stability of the alkoxyborane adducts (3'a-c) in comparison to the corresponding BH_3 adducts (2'a-c) they were also very sensitive to conformational changes in the alkoxyborane moiety. When the B(1)-O(1) bonds of 3'a-c were rotated so that the $H\text{-}O(1)\text{-}BH_2$ system became close to a planar arrangement and those geometries were optimized with respect to the total energy the alkoxyborane models $(HO\text{-}BH_2)$ started to repel the oxazaborolidine ones. The optimizations eventually lead to the structures 3'a'-c' (see Scheme 3) in which the distance between the alkoxyborane and oxazaborolidine models is surprisingly long [e.g. the B(1)-N distance is 2.874 Å in the case of 3'c' (see Scheme 3) whereas the corresponding distance in 3'c is 1.705 Å (see Scheme 2)]. The structures of adducts 3'a'-c' also resemble mostly those of the corresponding free borane and oxazaborolidine models (see Scheme 3) although some small changes can be found; e.g. in the case of 3'c' the

B(2)-N bond lengthens 0.013 Å and the B(2)-O(2) bond shortens 0.005 Å (the most significant changes found).

The difference of stabilities of 3'a-c and 3'a'-c' observed could probably be attributed to the different stabilities and Lewis acidities of the corresponding alkoxyboranes. However, an alkoxyborane R-O-BH$_2$ in which a lone pair of the oxygen can interact with the empty π-orbital of the adjacent boron atom (a planar system: the substructure C-O-BH$_2$ forms a planar system; functions representing the lone pairs and the empty π-orbital belong to the same symmetry) would be more stable and also less acidic than the conformer in which the interaction cannot play a role (a nonplanar system: a plane set on the atoms BH$_2$ of the C-O-BH$_2$ system is perpendicular to that set on the atoms C-O-B; functions representing the lone pairs and the empty π-orbital belong to different symmetries); e.g. energy of the planar configuration of HO-BH$_2$ is about 60 kJ mol^{-1} lower than that of the corresponding nonplanar system (on the basis of the 6-31G*//6-31G* energies shown in Table 1). In the case of MeO-BH$_2$ the corresponding difference is about 54 kJ mol^{-1}. Comparison of LUMO energies of these planar and nonplanar configurations of HO-BH$_2$ reveals that LUMO of the nonplanar system resides 0.67 eV lower in energy than the LUMO of the corresponding planar system (see Table 2). In the case of MeO-BH$_2$ the corresponding difference is 0.47 eV (see Table 2). If the LUMO values of these boranes are inspected in a relative scale in which the LUMO of BH$_3$ represents 100 % and that of the most stable (planar) conformer of RO-BH$_2$ system 0 % of Lewis acidity we observe that the less stable (nonplanar) conformers posses acidities of 40 % (HO-BH$_2$) and 30 % (MeO-BH$_2$). As a further evidence for the rationale of the above discussed different behaviour of the planar and nonplanar alkoxyboranes one could consider all the results provided for the adducts of water, Me$_2$O and NH$_3$ to HO-BH$_2$ and MeO-BH$_2$; e.g. in the adduct of Me$_2$O to the planar MeO-BH$_2$ the distance between the boron of MeO-BH$_2$ and the oxygen of Me$_2$O was 2.613 Å and the Mulliken overlap population of the these atoms was 0.050 whereas in the case of the corresponding adduct of the nonplanar MeO-BH$_2$ the distance was 1.754 Å and the overlap 0.190 (see Table 2). In the case of the corresponding adducts of NH$_3$ the B-N bond lengths are not affected much but the Mulliken overlaps in the case of adducts to planar alkoxyboranes are markedly lower than those of the corresponding adducts to nonplanar alkoxyboranes (see Table 2).

As the strength of the B(1)-N interaction in all alkoxyborane adducts to oxazaborolidines turned out to depend drastically on the conformation of the alkoxyborane moiety steric effects arising from the size of the alkoxy group(s) may play a role in the catalysis. In an alkoxyborane adduct of an oxazaborolidine the alkoxy group would have no problem to orient to a direction away from the oxazaborolidine moiety [i.e. the torsion angle R-O-B(1)-N would be close to 180°) whereas in the case of any dialkoxyborane adduct of the oxazaborolidine (dialkoxyborane originating from the catalytic reduction of the ketone) it would be impossible to arrange the alkoxy groups in such a way that both of the torsion angles R-O-B(1)-N would be close to 180° (otherwise the alkoxy groups would overlap). Therefore, it looks obvious that at least one of the alkoxy groups of the dialkoxyborane adduct would be in a configuration in which a lone pair of an oxygen adjacent to B(1) would interact with the 2p$_z$ function of B(1) lowering the Lewis acidity of B(1). Further, it could be easy to predict that N-adducts of dialkoxyboranes formed during the catalytic reduction would be substantially less stable than the corresponding monoalkoxyborane or BH$_3$ adducts.

The above proposed lower stability of dialkoxyborane adducts is interesting in the light of some early experimental observations.[1] Namely, the THF•BH$_3$ / oxazaborolidine system used to reduce ketones converts the borane and ketone to the corresponding dialkoxyborane derivative;[1] i.e. the dialkoxyborane arising from the newly formed chiral alcohol should not play any significant role in the catalytic reduction process. That would be easily understood on the basis of the computational results discussed above as it looks as if the dialkoxyboranes derived from the ketone being reduced would hardly even coordinate to the catalyst in the same way as the corresponding monoalkoxyborane or BH$_3$ are supposed to do. Nevertheless, this does not mean that none of dialkoxyboranes could not serve as a source of hydrogen in an oxazaborolidine catalyzed reduction of carbonyl compounds in general. It has been shown that a catecholborane / oxazaborolidine system can be used to reduce carbonyl

compounds.[1,2] As implied by different type of reaction conditions (the catecholborane / oxazaborolidine based reductions are conducted in about 100° C lower temperatures and reaction times are also much longer than in the case of THF• BH_3 / oxazaborolidine based reductions)[2] the mechanism of the reduction in the case of catecholborane / oxazaborolidine system may not necessarily be exactly the same as that of the THF•BH_3 / oxazaborolidine system. On the basis of the results of this work and those of previous studies on the energetics of the coordination of carbonyl compounds to borane adducts of oxazaborolidines[3a] and stabilization of borane adducts of oxazaborolidines in the presence of Lewis basic solvents[3c] one could predict that neither the catecholborane adduct nor the ketone adduct to the oxazaborolidine would be stable alone but if the borane and the carbonyl compound both coordinate to the the catalyst in a very short time scale, almost in a concerted manner, it would give rise to a formation of a complex which could live long enough for the hydride transfer from the borane to the carbonyl to occur. Nevertheless, more research is needed to assess the merit of this hypothesis.

One of the major concerns of this work was to evaluate the relative energetic advantage of the reactions (a,b and c) shown in Scheme 1. Energies of these reactions estimated by using the models 4'a-c are shown in Table 4.

Table 4. Energies of the regeneration of 1'a-c [reaction (a)][a] and the opening of the four membered ring of 4'a-c giving rise to 3'a-c [reaction (b)].[a]

Reaction				3-21G	4-31G	6-31G	4-31G*	6-31G*
				Energies[b]				
4'a	->	1'a	+ H_2B-OH[c]	+104	+46	+39	+26	+22
4'b	->	1'b	+ H_2B-OH[c]	+105	+45	+40	+21	+17
4'c	->	1'c	+ H_2B-OH[c]	+115	+53	+46	+22	+18
4'a	->	3'a		+129	+89	+84	+82	+78
4'b	->	3'b		+101	+68	+64	+48	+45
4'c	->	3'c		+94	+62	+57	+41	+37

[a] See Scheme 1 [b] Energies given in kJ mol⁻¹. [c] Planar geometry.

On the basis of the energies shown in Table 4 it could be easy to draw a conclusion that regeneration of the catalysts 4 -> 1 + R-O-BH_2 [reaction (a)] would be favored over the rearrangement 4 -> 3 [reaction (b)]; e.g. the energy of the reaction 4'c -> 1'c + HO-BH_2 requires 18 kJ mol⁻¹ whereas the rearrangement 4'c -> 3'c requires about twice as much, i.e. 37 kJ mol⁻¹ (see Table 4). If we correct these energies by the most important solvent effects we decrease the regeneration energy by 10 kJ mol⁻¹ for the stabilization of the alkoxyborane by a Lewis basic solvent coordinating to it [based on the energy of the formation of the complex HO-BH_2•OH_2 (6-31G*//6-31G*), see Table 3] and the rearrangement energy by 24 kJ mol⁻¹ for the stabilizing coordination of a Lewis basic solvent to the boron [B(2)] of the oxazaborolidine moiety (assuming that the adduct 3'c would be stabilized as much as 2'c[3c]). These corrections give an estimate of +8 kJ mol⁻¹ for the regeneration of the catalyst [reaction (a)] and +13 kJ mol⁻¹ for the rearrangement of the bicyclic oxazadiboretane (4) to the corresponding alkoxyborane - solvent adduct [reaction (a) followed by the coordination of the solvent to the boron of the oxazaborolidine]. As these energies are so closely similar one could predict that both of these reactions (a and b) could play a role in the enantioselective reduction of ketones by oxazaborolidines when THF•BH_3 is used as a source of hydrogen. Both the regeneration and rearrangement energies are also very low in comparison to the amount of energy released during the preceding hydride transfer step.[3d] Therefore the hydride transfer should produce clearly all the energy needed for the subsequent catalytic steps.

CONCLUSIONS

The relative energetic advantage of the formation of borane and alkoxyborane adducts of oxazaborolidines calculated suggest that the ease of formation of the adducts would increase in the order: $(RO)_2BH < RO\text{-}BH_2 < BH_3$. On the other hand, a comparison of structural and electronic properties of these adducts revealed that alkoxyborane adducts could in some cases be as good reduction catalysts, or even better, as the corresponding BH_3 adducts, but as the stability of the alkoxyborane adducts appeared to depend strongly on the conformation of the alkoxy substituent it would be difficult to make use of this potential advantage. A Lewis basic solvent (e.g. THF) was found to stabilize equally both the alkoxyborane and BH_3 adducts of oxazaborolidines (water used as a model of a Lewis basic solvent). Nevertheless, as some conformations of the alkoxyborane adducts appeared to decompose back to the corresponding separate alkoxyborane and oxazaborolidine molecules alkoxyborane adducts apparently would need the stabilizing effect provided by a Lewis base (may be either the solvent or the ketone to be reduced) coordinating to the boron of the oxazaborolidine ring more than the corresponding BH_3 adducts.

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REFERENCES AND NOTES

1. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551; (b) Corey, E. J.; Proceedings of the 31th National Organic Symposium, ACS **1989**, 1; (c) Corey, E. J.; *Pure & Appl. Chem.* **1990**, *62*, 1209.

2. (a) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925; (b) Corey, E. J.; Shibata, S.; Bakshi, R. K. *J. Org. Chem.* **1988**, *53*, 2861; (c) Corey, E. J.; Chen, C.-P.; Reichard, G. A. *Tetrahedron Letters* **1989**, *30*, 5547; (d) Corey, E. J.; Link, J. O. *Tetrahedron Letters* **1989**, *30*, 6275; (e) Corey, E. J.; Bakshi, K.; Reichard, G. A. *Tetrahedron Letters* **1990**, *31*, 611; (f) Youn, I. K.; Lee, S. W.; Pak, C. S. *Tetrahedron Letters* **1988**, *29*, 4453; (g) Corey, E. J.; Link, J. O. *J. Am. Chem. Soc.* **1992**, *114*, 1906.

3. (a) Nevalainen, V. *Tetrahedron Asymmetry* **1991**, *2*, 63; (b) ibid. 429; (c) ibid. 827; (d) ibid. 1133; (e) Nevalainen, V. Abstracts of 8th Int. Conf. on Organic Synthesis, Helsinki, IUPAC, **1990**, 317; (f) ibid. 319; (g) ibid. 320; (h) ibid. 316; (i) Nevalainen, V. Proceedings of the 9th Annual Meeting of the Molecular Graphics Society, Uppsala, MGS **1990**.

4. Singh, U. Chandra; Kollman, P. A. School of Pharmacy, Department of Pharmaceutical Chemistry, University of California, San Francisco, CA 94143.

5. 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.

6. Jolly, W. L.; Schmitt, T. *Inorg. Chem.* **1967**, *6*, 344.