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Reversible Dimerisation of Ephedrine-derived Oxazaborolidines

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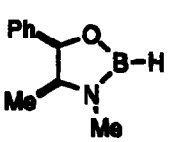
Abstract : *On standing, 4R, 5R-3,4-dimethyl-5-phenyl-1, 3, 2-oxazaborolidine dimerises to a monocyclic species, reverting quantitatively on gentle thermolysis. Related oxazaborolidines show contrasting behaviour.*

Oxazaborolidines have made a remarkable contribution to asymmetric catalysis, inter alia to the borane and catecholborane reduction of ketones[1], Lewis acid-catalysed cycloadditions[2], aldol condensations[3] and organozinc additons to aldehydes[4], and latterly cyanohydrin formation[5]. In this laboratory their application to catalytic asymmetric hydroboration and to the catalytic synthesis of vinylboranes has been demonstrated[6]. In all such work, the emphasis has tended to be on synthetic application, and accompanying structural characterisation of the oxazaborolidine catalysts has been of secondary importance. It has been presumed that the active catalytic species formed are monocyclic and monomeric, and potential association or oligomerisation processes have not generally been discussed, despite being commonplace in organoborane chemistry. Monomer-dimer equilibria (to an unspecified structure) were discussed in Corey's early paper on the oxazaborolidine derived from diphenylprolinol[1], but a different structure related to this oxazaborolidine dimer has been suggested recently[7]. An oxazaborolidine-borane adduct is monomeric in the solid-state by X-ray; this has been assumed to be the form of the catalyst involved in solution-phase asymmetric reduction of ketones[8]. We report a clear-cut example of the reversible dimerisation of an oxazaborolidine involving ring-opening and reclosure, demonstrating the potential complexity of species involved in catalysis.



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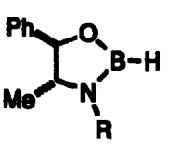
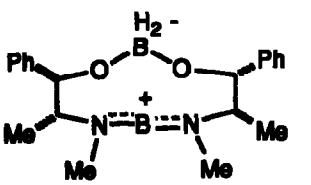


2 R = methyl
3 R = i-propyl



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When borane 1 is prepared from 1R, 2S-ephedrine as previously described[4,6] the product can be distilled in vacuo at 40 °C to give a water-white liquid which is stable under argon for protracted periods. The ^{11}B NMR spectrum clearly shows the expected B-H coupling of 156 Hz, GC/MS indicates a monomeric compound and all other spectroscopic properties are consistent with the simple formulation, including ν(B-H) = 2562 cm^{-1}(neat). Contrasting behaviour is shown by 1R, 2R-ephedrine, following the same protocol. In this latter case, the

distillate of **2** first formed[9] gradually crystallises on standing in an inert atmosphere, and the crystalline material has quite different spectroscopic properties (Table 1) from the original product. Interestingly, the analogue **3** is monomeric and stable[6]. The dimeric species **4** is sufficiently stable in solution for full spectroscopic evaluation, but reverts quantitatively to monomer **2** on gentle thermolysis (120 °C, 180 s). The ^{11}B NMR spectrum is particularly revealing, since there are two separate resonances, but only one strong B-H band in the IR. The ^{1}H NMR of the dimer shows that it is symmetrical, the most interesting feature being the increased ^{3}J coupling in the ephedrine backbone (9.6 vs. 7.0 Hz) which limits the range of reasonable possibilities.

	2	**4**[a]
ν (B-H)	2565 cm^{-1} [b]	2445 cm^{-1} [c]
$[\alpha]^{20}_D$	-58.8 (*c* 0.93, $CHCl_3$)	-125.1 (*c* 1.00 $CHCl_3$)
^{11}B nmr[d]	29.5 (d, J_{B-H} 151 Hz)[e]	8.8 (1B, s) and -6.5 (1B, bs)[f]
^{1}H nmr[g]	7.35 (5H, m, $C_6\underline{H}_5$) 4.90 (1H, d, J 7.02 Hz, $C_6H_5C\underline{H}$) 3.31 (1H, dq, J 6.21, 7.02 Hz, $C_6H_5CHC\underline{H}$) 2.72 (3H, s, $C\underline{H}_3N$) 1.28 (3H, d, J 6.21 Hz, $C_6H_5CHCHC\underline{H}_3$).	7.49 (2H, d, J 6.72 Hz, ortho $C_6\underline{H}_5$) 7.35 (3H, m, meta and para $C_6\underline{H}_5$) 4.67 (1H, d, J 9.62 Hz, $C_6H_5C\underline{H}$) 2.70 (1H, dq, J 6.54, 9.62 Hz, $C_6H_5CHC\underline{H}$) 2.59 (3H, s, $C\underline{H}_3N$) 1.16 (3H, d, J 6.54 Hz, $C_6H_5CHCHC\underline{H}_3$).
^{13}C nmr[h]	142.7 (C ipso), 128.3 (C ortho) 127.5 (C para), 125.3 (C meta) 87.9 ($C_6H_5\underline{C}H$), 64.0 ($C_6H_5C\underline{C}H$) 29.8 (CH_3N), 18.8 ($C_6H_5CHCH\underline{C}H_3$).	140.6 (C ipso), 128.4 (C ortho) 127.9 (C para), 126.6 (C meta) 81.5 ($C_6H_5\underline{C}H$), 69.1 ($C_6H_5C\underline{C}H$) 42.4 (CH_3N), 10.0 ($C_6H_5CHCH\underline{C}H_3$).

Table 1. a: ^{1}H and ^{13}C nmr multiplicity assignments based on a single pseudo-ephedrine unit. b: Thin film on NaCl. c: KBr disc. d: ^{1}H decoupled, 80.21 MHz; the approximate half-width of the low-field signal is 80 Hz, and that of the high-field signal 300 Hz; at 65°C the triplet structure is clearly discerned in the ^{1}H-coupled spectrum of the high-field signal at -6.5 ppm without change in the low-field signal e: C_7D_8 solution. f: C_6D_6 solution. g: 300 MHz, $CDCl_3$ solution. h: 125 MHz, $CDCl_3$ solution.

Some insight into the nature of the crystalline species **4** derived from **2** was obtained from its mass spectrum. A sample of dimer **4** was injected on to a GC-MS column, (injection port 220°C), and eluted only the monomer (m/z 175, M^+). A sample of dimer **4** was mounted in a glass capillary, on a solids probe, and inserted into the EI+ source of the mass spectrometer; the probe was heated ballistically to 250°C.The initial mass spectra that were obtained were of the monomeric oxazaborolidine **2** and consisted of two major ions at m/z 175 (M^+) and m/z 160 ($M-CH_3$)$^+$. However, spectra acquired 10-15 s later also contained an isotope cluster centred at m/z 349 (M_2-H)$^+$. A mixture of dimer **4** and monomer **2** were inserted, *via* the solids probe, into the ion source and then heated (gradient 50°C min^{-1}). The ion currents at m/z 175 and 349 were monitored with time, and displayed three regions. At 100°C, the monomer dominated, and between 100°C and 150°C the spectrum was very weak. Between 150°C and 200°C, the monomer was again dominant, now being formed by cracking of the dimer. Above 200°C, both monomer and dimer ions were strong, consistent with co-evaporation of both components in an equilibrating mixture. The predominant daughter fragment of the monomer is at m/z 160 (M^+-CH_3) and

under these latter conditions there is a strong peak at m/z 364 resulting from methyl capture by the m/z 349 species.

Taken together, these results are consistent with the structure drawn for **4**. Its feasibility was tested by molecular modelling (MMX), minimising first with an allene replacing the N-B-N entity, and then introducing the latter without change in bond angles. The result is shown in Figure 1 ; it is particularly interesting that the Ph and C-Me substituents attain a φ-equatorial conformation, so that the protons observed to possess a large ^3J coupling are mutually axial. The structure is to be compared with that suggested[7] as **6** for the dimeric species formed in the attempted preparation of oxazaborolidine **5**, on the basis of spectroscopic evidence. Recently[10], Nevalainen has extended his ab initio MO studies of oxazaborolidines to encompass the possible aggregated species formed from the parent in the presence and absence of coordinated BH_3. Compounds **7** and **8** were discussed and shown to be energetically viable, with the most stable anti-arrangement of the former 32 KJmol^{-1} the more stable than the most stable anti-arrangement of the latter. Structures corresponding to **4** were not considered, and were not identified in an experimental study where oxazaborolidine **2** was reacted with BH_3, although BH-bridged borane adducts were suggested[11].

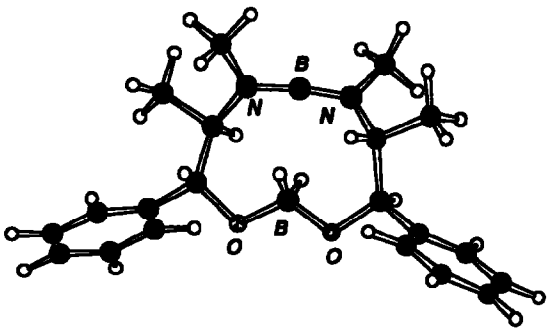
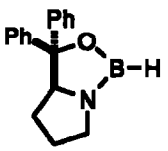


Figure 1 MMX-derived structure for the oxazaborolidine dimer 4. The endocyclic dihedral anglesHC-CH are 164 ± 1 °, giving a predicted vicinal coupling constant of 10.9 Hz (exptl. 9.6 Hz)



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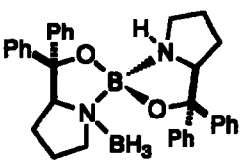

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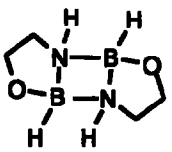

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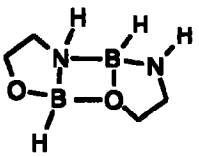

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In summary, these results demonstrate that the structure of oxazaborolidines and related boranes is highly sensitive to substitution in the ring, and that a dimeric species with potential reducing power is easily accessible under the conditions of typical catalytic reactions.

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9. Preparation of **2**: 1R, 2R-2-(N-Methylamino)-1-phenylpropanol (Aldrich), (15g, 97 mmol) was placed in a Schlenk tube. After evacuating and purging with argon (three cycles), tetrahydrofuran (15 ml), was added *via* syringe to afford a partial solution. The reaction was cooled to 0°C and then treated dropwise (cannula) with $BH_3{\cdot}SMe_2$ (Aldrich, 2.0 M solution in thf) 48.5 ml, (97 mmol) over a period of 1.5 h. The reaction mixture was stirred to ambient temperature over a period of 2 h after which one equivalent of H_2 gas had been produced. Solvent was removed *in vacuo* to afford a white foam. The vessel was purged with argon and then heated to 120°C for 2.5 h. after which a further one equivalent of H_2 gas was produced, affording a pale yellow oil. This was transferred to a vacuum jacketed Vigreux column and the product collected at 36°C, 0.05 mmHg as a water white clear mobile oil (15.1g, 95%, $\rho \approx 1.07$ g cm^{-3}). Preparation of 2R,3R,7R,8R-3,4,6,7-tetramethyl-2,8-diphenyl-1,9-dioxa-4,6-diaza-5,10-(5B,10BH_2)-diborecane (**4**) : 4R,5R-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine **2** was stored under argon at ambient temperature for a period of approximately five months, after which a large crystalline mass had formed. A sample of the crystalline mass, *ca.* 0.1 mg, was then used to seed a sample of 4R,5R-3,4-dimethyl-5-phenyl-1,3,2-oxazaborolidine **2** (1g), that had been freshly pyrolysed (100°C, 2 h under argon). This resulted in rapid crystallisation of approximately 30% of the material. The mixture was stored at -30°C, under argon, for 4 d. to complete crystallisation. Subsequent samples were obtained by sublimation of portions of the above crystals in vacuo, mp 99 -102°C.
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