# Borylated Lyxofuranosides as Selective Host Molecules for Amines

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Abstract: *Borylated lyxofuranosides 3a,b serve as heterotopic host molecules for primary amines, multi-point binding occurring at the "inside" position due to synergistic effects.*

A wide variety of host molecules have been designed for the molecular recognition of amine hydrochlorides, but those capable of recognizing neutral primary amines are rare.[1] We recently proposed that compounds containing several donor sites as well as sigma-bonded metal centers with an empty orbital should be ideal receptors for primary amines, this being due to the possibility of multi-point binding based on synergistic effects (reversible nitrogen-metal dative bonds and simultaneous H-bonding).[2] Indeed, boron-containing crown ethers such as 1 were shown to undergo this unusual type of molecular recognition.[2] In this letter we demonstrate that such heterotopic behavior is also possible in very different situations, specifically in the interaction of borylated carbohydrates with amines.

1 (L$_2$ = glycolate, catecholate)   2
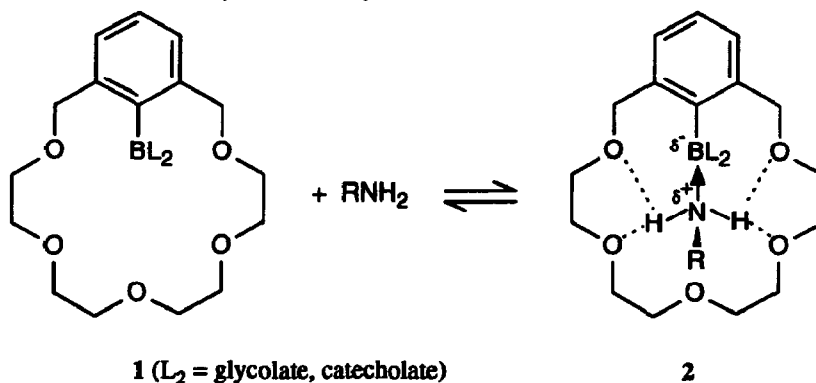
The borylated lyxofuranoside 3a was prepared from D-lyxose according to the method of Dahlhoff[3] and was then transformed into the phenyl analog 3b in two simple steps.[4]

3a   3b
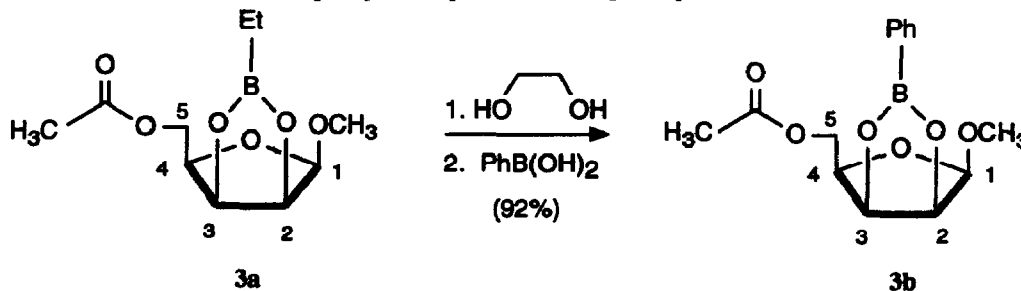
We speculated that binding of an amine from the "inside" of these concave/convex molecules could lead to multi-point interaction according to 5, whereas "outside" binding would simply constitute classical dative bond formation[5] according to 4.
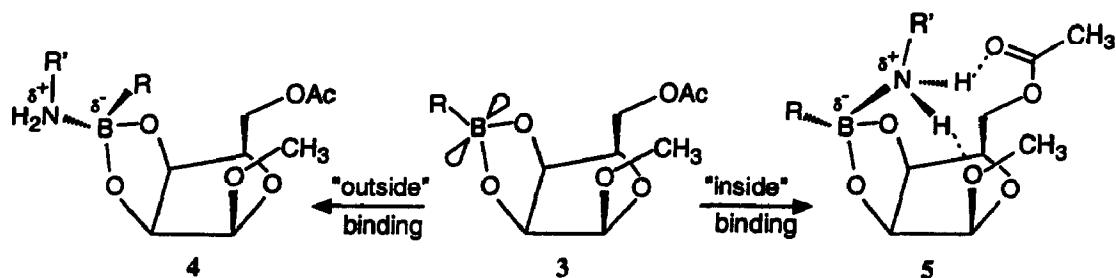
Upon treating **3a** with benzylamine, crystals were obtained.[4] The X-ray structural analysis[6] (Fig. 1) shows that "inside" binding pertains, and that synergistic effects are indeed operating. As a consequence of nitrogen-boron σ-bond formation the amine takes on ammonium ion character, which in turn makes hydrogen bonding of one of the amine hydrogen atoms to the methoxy oxygen atom energetically favorable (Fig. 1a). Interestingly, the acetoxy function does not participate in H-bonding with the second hydrogen of the PhCH$_2$NH$_2$ entity as originally anticipated (cf. **5**). Rather, the latter forms a hydrogen bond with one of the oxygen ligands of boron in such a way that a dimer is formed in the solid state (Fig. 1b). Indeed, formation of an ate-complex is expected to lead to increased negative charge (electron density) at these oxygen ligands, increasing their ability to participate in H-bonding.[7]
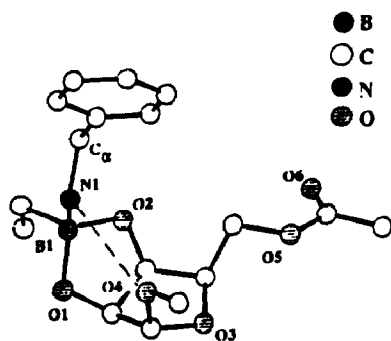

Fig. 1a   Partial crystal structure of
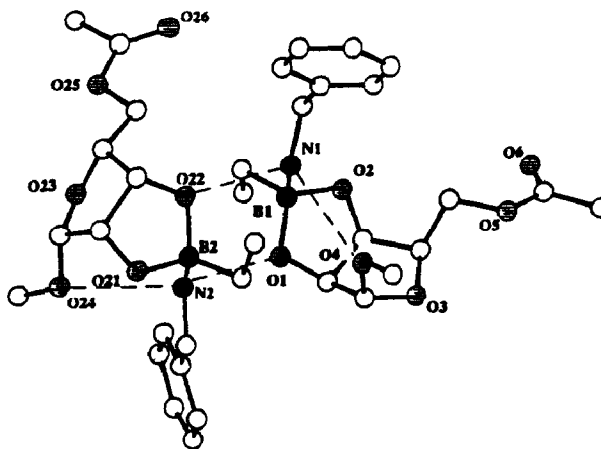3a/PhCH$_2$NH$_2$
(N1 - O4 = 2.98 Å)

Fig. 1b   Crystal structure of
3a/PhCH$_2$NH$_2$ (dimer)
(N2 - O24 = 2.95 Å; N1 - O22 =
2.98 Å; N2 - O1 = 2.83 Å)

A 1 : 1 mixture of **3a** (or **3b**) and a primary amine RNH_2 in $CDCl_3$ gave rise to characteristic shifts in the ^{11}B- and ^{13}C-NMR spectra (Table 1). For example, the ^{11}B-NMR signal of host **3b** (δ = 35.3 ppm, $BF_3 \cdot OEt_2$ external standard) shifts upfield to 27.1 ppm ($\Delta\delta$ = -8.2 ppm) upon additon of one part $PhCH_2NH_2$, indicating the presence of tetra-coordinate boron.[8] However, the shift is less than previously observed for the crown ether **1** ($\Delta\delta$ = 21 ppm).[2] Thus, **3b** (and **3a**) does not bind primary amines as strongly as **1** (which, for example, binds 97% of benzylamine in a typical 1 : 1 experiment).[2] Indeed, whereas it was possible to perform 1 : 1 : 1 competition experiments with **1** and two different amines by "freezing out" two distinct sets of host/guest NMR signals,[2] similar experiments with **3a,b** showed rapid exchange phenomena even at low temperatures.[4] Furthermore, the ^{13}C-NMR shifts in the case of **3a,b**/RNH_2 turned out to be small in the carbohydrate portion (the largest effects occurring at the anomeric C-atom), so that NMR titrations for the determination of the binding constants K are not precise or reliable enough. Nevertheless, the $\Delta\delta$([11]B)-values in Table 1 clearly show that the binding affinity decreases in the order n-$PrNH_2$ > $PhCH_2NH_2$ > $PhCH(CH_3)NH_2$, which is also oberserved for host **1**.[4] Due to the relatively low binding capacity of **3a,b** and the dynamic behavior of the guest/host systems resulting thereof, it was not possible to examine potential enantioselective molecular recognition using such chiral amines as (+)- and (-)-α-methylbenzylamine. In view of the X-ray structure (Fig. 1), the degree of enantioselection would be expected to be low anyway. For this purpose host molecules with spatially extended cavities and more electrophilic metal centers would be required. The ^{1}H- and ^{13}C-NMR signals of the acetoxy group are not influenced at all by amine adduct formation, which means that acetoxy participation as indicated in **5** is unlikely in solution as well .

Table 1. NMR Data of **3a**/RNH_2 and **3b**/RNH_2 in $CDCl_3$ ([11]B: 64MHz; [13]C: 100MHz)

		$\Delta\delta$ [11]B [ppm]	$\Delta\delta$ [13]C OCH_3 [ppm]	$\Delta\delta$ [13]C C5 [ppm]	$\Delta\delta$ [13]C C1 [ppm]
3a	n-$PrNH_2$	-13.7	-0.06	+0.38	+0.74
	($\pm$)-sec-$BuNH_2$	-2.9	-0.17	+0.01	+0.04
	$PhCH_2NH_2$	-8.3	-0.21	+0.22	+0.30
	($\pm$)-α-$PhCH(CH_3)NH_2$	-0.7	-0.17	-0.05	+0.03
3b	n-$PrNH_2$	-14.0	+0.15	+0.49	+0.94
	$PhCH_2NH_2$	-8.2	+0.02	+0.27	+0.52
	($\pm$)-α-$PhCH(CH_3)NH_2$	-1.6	-0.08	+0.02	+0.01

In summary, the present work demonstrates that borylated lyxofuranosides are heterotopic hosts for primary amines, i. e., they constitute another rare example (besides **1**)[2] of multi-point binding of a primary amine function. Since borylated (or otherwise metalated) sugars are easily accessible,[3] more elaborate and efficient host molecules can be envisioned for amines, nucleoside bases and other donor molecules.

Acknowledgement

References and Notes

1. Vögtle, F. *Supramolecular Chemistry*, Wiley: Chichester, England, 1991; Lehn, J.-M. *Angew. Chem.* **1990**, *107*, 1347; *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1304; Anderson, H. L.; Hunter, C. A.; Meah, M. N.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5780-5789; Kugimiya, S.-I. *Chem. Soc., Chem. Commun.* **1990**, 432-434; Danks, I. P.; Lane, T. G.; Sutherland, I. O.; Yap, M. *Tetrahedron*, **1992**, *48*, 7679; Kickham, J. E.; Loeb, S. J.; Murphy, S. L. *J. A. Chem. Soc.* **1993**, *115*, 7031-7032.

2. Reetz, M. T.; Niemeyer, C. M.; Hermes, M.; Goddard, R. *Angew. Chem.* **1992**, *104*, 1054-1056; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 1017-1019; see also Reetz, M. T.; Niemeyer, C. M.; Harms, K. *Angew. Chem.* **1991**, *103*, 1515-1517; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1472-1474; Reetz, M. T.; Niemeyer, C. M.; Harms, K. *Angew. Chem.* **1991**, *103*, 1517-1519; *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1474-1476.

3. Dahlhoff, W. V. *Liebigs Ann. Chem.* **1990**, 1093-1096.

4. Huff, J. *Dissertation*, Universität Marburg, 1993.

5. Brown, H. C.; Johannesen, R. B. *J. Am. Chem. Soc.* **1953**, *75*, 16.

6. X-ray analysis of 3a/PhCH$_2$NH$_2$: C$_{17}$H$_{26}$BNO$_6$, M$_r$ = 351.2 gmol^{-1}, green-yellow crystals, crystal size 0.25 x 0.46 x 0.70 mm, a = 9.061(3), b = 20.185(6), c = 10.199(2) Å, β = 92.14(1)°, V = 1864.0 Å^3. T = 100 K, d$_{cal}$ = 1.25 gcm^{-3}, μ = 0.87 cm^{-1}, Z = 4, monoclinic, space group P2$_1$ [No. 4], Enraf-Nonius CAD4 diffractometer, λ = 0.71069 Å, scan mode ω-2θ, 4641 measured reflections (±h,+k,+l) [(sinθ)/λ]$_{max}$ = 0.65 Å^{-1}, 4617 independent reflections, 3964 observed reflections [I>2σ(I)], structure solved by direct methods (SHELXS-86, Sheldrick, G. M. *Acta Crystallogr.* **1990**, *A46*, 467-473), refined by leastsquares (GFMLX, a modified version of ORFLS, Busing, W. R.; Martin, K. O.; Levy, H. A. Report ORNL-TM-305, Oak Ridge National Laboratory, Oak Ridge, TN, U.S.A. 1962), H atoms refined isotropically, absolute configuration could not be determined, R = 0.066, R$_w$ = 0.079 for 450 refined parameters, residual electron density 0.34 eÅ^{-3}. Atomic coordinates and e.s.d.'s have been deposited at the Cambridge Crystallographic Data Centre.

7. Although organic chemists place the negative charge in borate ions R$_4$B$^{\ominus}$ on boron, it resides in fact to a large extent in the ligands R. A similar situation pertains in the case of the positive charge of RNH$_3^{\oplus}$ and (CH$_3$)$_4$N$^{\oplus}$, which is not localized on nitrogen, but distributed over the four substituents. See MO calculations in: Reetz, M. T.; Knauf, T.; Minet, U.; Bingel, G. *Angew. Chem.* **1988**, *100*, 1422-1424; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 1373-1374.

8. Wrackmeyer, B. in *Annual Reports of NMR Spectroscopy*, Webb, G. A. Ed.; Academic Press: New York, Vol. 2, 1988.