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Crown Ethers with Pendant Primary Amino-Group for Complexation of Dopamine

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Abstract: Two novel 18-6 crown ethers (compounds **6** and **8**) derived from a common 6-amino-6-deoxy-α-D-glucopyranoside framework were prepared and successfully tested for their ability to extract dopamine perchlorate from an aqueous medium. The pendant primary amino-group of these hosts was found essential to interact with one of the phenolic function of dopamine.

Several syntheses of chiral azacrown ethers incorporating asymmetric carbohydrate units into the macrocyclic ring have been reported over the last decade[1]. More recently, much attention has been paid to potential *in vivo* applications of achiral macrocyclic tetraaza-complexing agents for tumour targeting[2] or cancer therapy[3]. As for earlier ligands developed by Lehn and co-workers[4], the role of pendant donors attached to the macrocyclic cavity *via* a suitable spacer has been emphasized for enhancing the *in vitro* kinetic or/and stability of their complexes with yttrium or gadolinium. The recent synthesis of a stable dinuclear complex formed from a 26 membered proton-ionizable crown of 3,5-disubstituted 1*H*-pyrazole and homoveratrylamine[5] prompted us to examine five readily available macrocycles (**3~7**) derived from a common 6-deoxy-α-D-glucopyranoside framework for their complexing ability towards dopamine salts as *guests*. We decided to synthesize first the 6-deoxy-4-*O*-methyl crown ether **3** from **1**[6], with the simplest sugar-framework to minimize supplementary interactions between the *guest* and the chiral moiety of the *host*. The 6-azido-6-deoxy sugar **4** was further cyclized in neat dimethylacetylenedicarboxylate to give the triazole **5** in a very good yield:

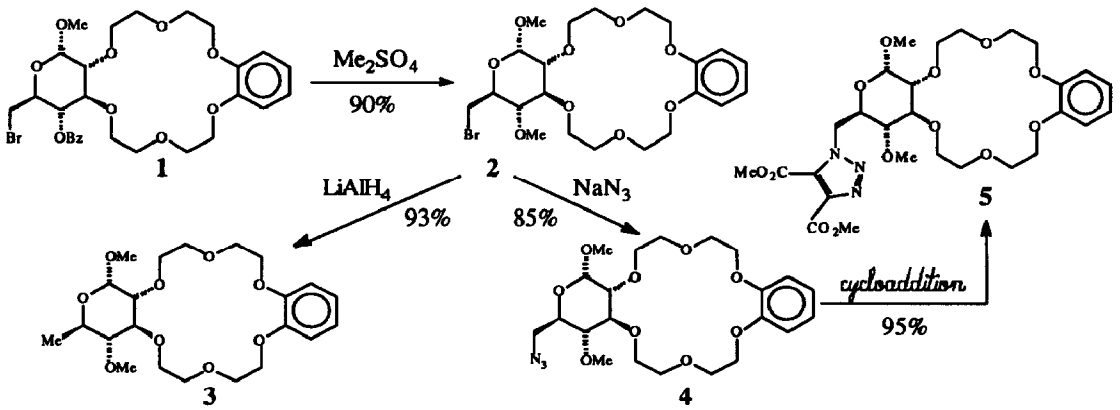
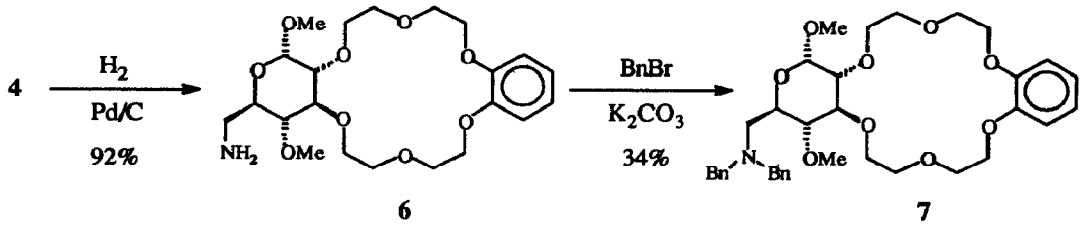


Fig. 1 - Synthesis of crown ethers **2~5** from **1**

The 6-azido-6-deoxy macrocycle **4** was also catalytically reduced to give the primary amine **6**, which was finally dibenzylated to **7**:



6 **7**

Fig. 2 - Synthesis of crown ethers **6** and **7** from **4**

Simple monoplate partitioning[7] (*cf.* our liquid-liquid extraction conditions[8]) showed that only host **6** could extract dopamine as its perchlorate salt from D_2O in a rough 1:1 stoichiometry, stressing the role of the primary amino group as side-arm in lateral interaction[9]. Finally, no crown ether could be detected in the aqueous phase in spite of the fair water-solublity of the corresponding isolated hydrochloride of **6**. Neither the more sterically hindered tertiary amine **7**, nor the less basic triazole **5**, were found to complex dopamine at any level in the same conditions. In order to refine our understanding of the phenomena and to try to collect suitable crystals for X-ray analysis, we synthesized a more lipophilic analogue of **6** by incorporating a 2,3-*ortho*-naphtalene unit into the macrocycle. The resulting crown ether **8**[10] was found to complex dopamine perchlorate in a similar manner; this complexation might be depicted as follows:

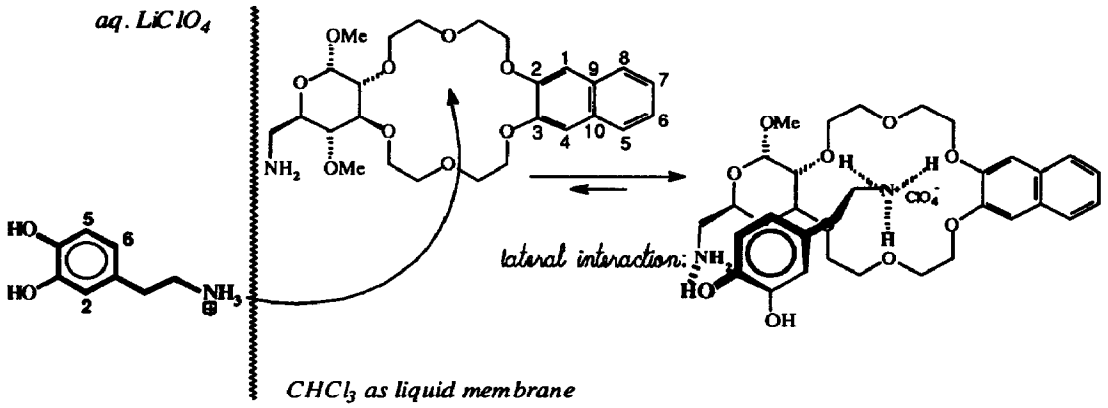


Fig. 3 - Extraction and complexation of aqueous dopamine by crown ether **8** in $CHCl_3$

As for host **6**, the formation of the complex and its stoichiometry could be ascertained by comparison of the ^1H NMR-spectrum of **8** with those resulting from liquid-liquid distribution experiments[8]. Noticeable alterations induced by complexation on the signals of the *host*, with an obvious similarity with these of the

isolated hydrochloride of **8** in $CDCl_3$, suggested an important conformation modification of the sugar moiety and a likely proton-transfer from the catechol moiety of dopamine to the amino-group of the crown ether. Assuming that complexation occurs probably preferentially on the β-face[11,12], a single aromatic proton of the the naphtalen ring (H-1 or H-4) might fall alternately under the unshielding influence of the phenyl ring of the *guest*. On the contrary, the failure to split of the corresponding *pseudo*-singlet (integrating for two protons at 7.1 ppm) into two separated broad singlets (as it could be observed for instance with 2-phenylethylamine perchlorate) is a sound argument in favor of the absence of π-stacking interactions with the aromatic system of the *guest* maintained at the opposite side by the amino-group of the *host*. In addition, H-5 and H-6 of dopamine were significantly downfield moved (~0.85 ppm) by comparison with a similarly designed weak complex with dicyclohexyl-18-crown-6 in $CDCl_3$:

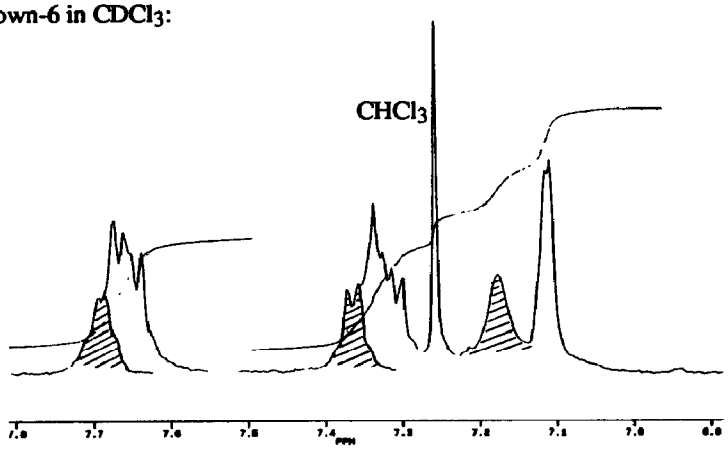


Fig. 4 - ^1H NMR-spectra (6.9~7.8 ppm) of the isolated complex between host **8** and dopamine perchlorate at 250 MHz (the signals of dopamine have been hachted for more legibility)

As shown in figure 4, it was possible to decompose the signals into a part due to dopamine and a second part due to the crown ether. The integration confirmed the validity of this decomposition. Finally, the extraction constant K_e could be estimated to be ~60 at rt by integration of appropriate ^1H NMR-peaks[13]. Other attempts *with* Li_2CO_3 (1.5 eq.) and *without* $LiClO_4$ failed to extract the dopamine-zwitterion into $CDCl_3$. However, the treatment of **8** with dopamine hydrochloride at room temperature, using acetonitrile as solvent[5], yielded white crystals (41%), which were submitted to FAB-MS analysis. A weak molecular ion peak *m/z* = 661 (MH^+ + dopamine, 0.2%), corresponding to the 1:1 complex was clearly observed beside the protonated macrocycle's peak (MH^+, 508, 10.5%) and the dopamine cation's peak ($M'H^+$, 154, 100%).

All these facts confirm the hypothesis that such synthetic receptors with pending primary group are able to recognize and to extract a catecholamine from an aqueous medium by combination of central and lateral interactions. Compounds **6**, **8**, and related structures[14] will be investigated for the transport of various biogenic amines through artificial liquid membranes[15] or the *in vitro* vectorization of catecholamines across blood-brain-barrier models[16].

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8. Typical liquid-liquid extraction experiment: 0.02 mM of the host were dissolved in 1.0 mL of $CDCl_3$ and shaken for 1 min at rt with 1.0 mL of D_2O containing 11.4 mg (3 eq) of dopamine hydrochloride and eventually 107 mg (1 mM) of $LiClO_4$. The two phases were allowed to settle for 30 min at rt in the dark, the organic layer carefully separed, dried over a few crystals of anhydrous Na_2SO_4, filtered and its ^1H NMR-spectrum immediately taken at 300 K.
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10. All new compounds displayed satisfactory spectral and analytical data in full agreement with their structures. For instance, **8**: $[\alpha]_D$ +36.5 (c = 1, $CHCl_3$); MS (CI): *m/z* 508 (MH^+); ^{13}C NMR **8**, HCl (DMSO-d_6): δ (ppm): 148.7 (C-2/C-3 ar), 129.0 (C-9/C-10 ar), 126.3 (C-5/C-8 ar), 124.0 (C-6/C-7 ar), 107.7 (C-1/C-4 ar), 97.1 (C-1), 81.1 (C-4), 80.3 (C-3), 79.6 (C-2), 72.2, 70.7, 70.4, 69.5 (4 x OCH_2), 68.95 (C-6), 68.85, 68.8 (4 x OCH_2), 66.9 (C-5), 60.0 (OMe), 55.2 (OMe); ^1H RMN ($CDCl_3/D_2O$) δ (ppm): 2.7 (dd, 1H, H-6, J_{gem} 10.7, $J_{5\text{-}6}$ 4.0), 3.95 (m, 2H, H-4/H-6'), 3.3 (dd, 1H, H-2, $J_{1\text{-}2}$ 3.7), 3.32 (s, 3H, OMe), 3.4 (m, 1H, H-5, $J_{4\text{-}5}$ 9.5, $J_{5\text{-}6'}$ ~2), 3.5 (s, 3H, OMe), 3.55 (*pseudo*-t, 1H, H-3, $J_{3\text{-}4}$ 9.2), 3.65-4.25 (m, 16H, 8 x OCH_2), 4.7 (d, 1H, H-1), 7.1 (s, 2H, H-1/H-4 ar), 7.3 (dd, 2H, H-6/H-7 ar), 7.65 (dd, 2H, H-5/H-8 ar).
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