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MACROTRICYCLIC AND MACROPENTACYCLIC DITOPIC RECEPTOR MOLECULES. SYNTHESIS, CRYSTAL STRUCTURE AND SUBSTRATE BINDING.

Jean-Paul Behr[a], *Marc Bergdoll*[b], *Bernard Chevrier*[b], *Philippe Dumas*[b], *Jean-Marie Lehn*[a] *and Dino Moras*[b]

[a]*Institut Le Bel, 4 rue Blaise Pascal and* [b]*IBMC, 15 rue Descartes, 67000 Strasbourg, France.*

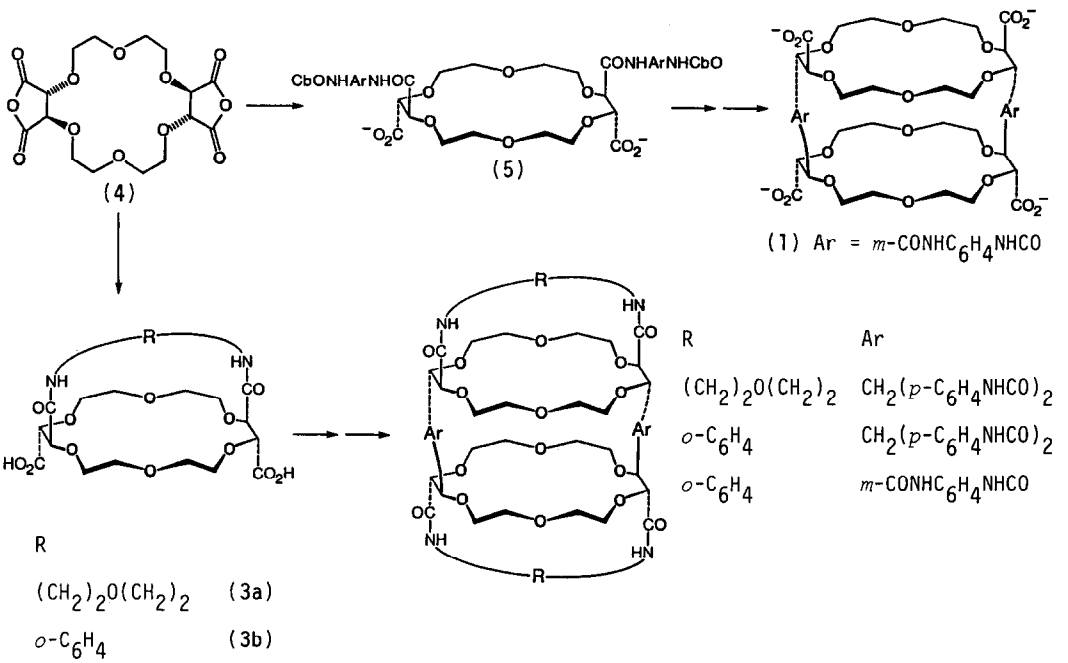
Abstract. A macrotricyclic (1), three macropentacyclic (2a-c) and a macrobicyclic (3b) receptor molecules have been synthesized, via a particularly efficient route for (2b) and (2c). The crystal structures of (1), (2b) and (3b) have been determined and related to some results on their ability to bind ammonium cations.

Coreceptor molecules, which contain two or more binding subunits, may complex either several singly bound substrates or a multiply bound polyfunctional substrate. Thus, ditopic coreptors which bind terminal diammonium and dicarboxylate substrates have been described[1]. If such species are constructed so as to contain a large central molecular cavity, the bound substrates might interact with each other, resulting eventually in regulation, cooperativity, allostery or cocatalysis phenomena. In order the substrates be bound in a specific orientation, the design and synthesis of coreceptor molecules with directional binding subunits is required.

We describe here the synthesis, the structures and some substrate binding features of four coreceptor molecules (**1**), (**2a-c**) and of the macrobicycle (**3b**), based on a tetrafunctional 18-O_6 macrocyclic subunit described earlier[2] which binds both metallic and organic cations[3].

Macrotricyclic Coreceptor (**1**). Stereoselective opening[4] of the dianhydride (**4**) with 1,3 diaminobenzene followed by deprotection of the resulting syn-compound (**5**) and high dilution condensation of the corresponding diamine thus obtained with (**4**), gave the macrotricyclic tetracarboxylate (**1**)[5]. The crystal structure of its bis-ethanolammonium complex (Fig. 1)[6] confirmed the structure and showed the $HOCH_2CH_2NH_3^+$ ions to be anchored on each macrocyclic subunit by the $-NH_3^+$ group as expected[3,7], but located outside the central "cavity" which was closed by contact between the two benzene rings in the bridges.

Macropentacyclic Coreceptors (**2a-c**). Since this orientational preference of substrate binding appeared to be a general behaviour of open face discriminated syn-dicarboxylic diamido compounds[8], we sought a building block for which substrate binding would be sterically forbidden on one face and therefore directed to the other face of the macrocyclic receptor site. The capped macrobicyclic cryptand (**3a**)[9] was activated and condensed with the more rigid and bent diamine, p-dianilinomethane under high dilution conditions to give the macropentacycle (**2a**)[10]. Proton NMR studies (200 MHz; CD_3OD/CD_2Cl_2) 1/9 showed that (**2a**) formed 2/1 and 1/1 complexes with mono and diammonium cations respectively.



In order to gain ready access to such a subunit, direct stereoselective capping of (4) by a diamine of appropriate length was explored. The rigid and short 1,2-diaminobenzene appeared suitable for two reasons: a) formation of the anti-substituted[4] capped derivative would be sterically hindered; b) since the tetrasubstituted species such as (5) studied so far showed axial arrangement of all four groups (ref. 4,7 and Fig. 1), capping by a diamine shorter than the diameter of the macrocycle, would be transmitted through the tartaric acid fragments as divergent functionalities on the other side of the ring (see also in [3]); consequently, the walls of a ditopic receptor of type (2) constructed from such a subunit might be prevented from collapsing as was the case for (1) (Fig. 1).

Indeed, after careful exploration of the experimental conditions, the high dilution reaction of (4) with 1,2-diaminobenzene proceeded quantitatively and stereoselectively to give the macrobicycle (3b)[11]. The crystal structure of (3b) (Fig. 2)[12] showed that a substrate may bind only on the face of the macrocycle opposite to the bridge introduced. Furthermore, four oxygens to the strainless polyether ring point towards the complexing face ($g^+g^+g^-g^+g^+g^-$ C-C framework) and, as expected, the pending carboxylic groups are divergent (~ 35° angular deviation from the axis perpendicular to the ring mean plane).

The diacid (3b) was activated with PCl_5 and the resulting crude acid chloride was condensed in a [2+2] high dilution reaction with p-dianilinomethane or 1,3-diaminobenzene to give the macropentacyclic molecules (2b) and (2c) respectively (~ 40% yield from (4))[13].

The crystal structure of (2b) (Fig. 3)[14] showed that as expected (see above) and in contrast to (1) (Fig. 1), a central cavity was now present in the macropentacyclic system. The macrobicyclic subunits are related by C_2 symmetry and have a shape similar to that of (3b); a tightly bound water molecule is found hydrogen bonded to each unit ($CONH\cdots OH_2$ and $O\cdots H_2O$ distances range from 2.80 to 3.05 Å).

Binding of ammonium cations to (**2a-c**) was detected by ^{1}H-NMR shifts on addition of the substrates (200 MHz; CD_3OD/CD_2Cl_2 1/9). (**2b**) and (**2c**) formed weak complexes with primary ammonium ions, but strong 1/1 association occured with terminal diammonium ions of appropriate length ($H_3N^+CH_2CH_2$-p-C_6H_4-$CH_2CH_2NH_3^+$), giving slow exchange spectra. Competition experiments showed that (**2a**) was binding about ten times stronger than (**2b**).

The lower binding ability of macropentacycles (2) compared to the basic tetrasubstituted macrocycle[3,4,9], may result from three factors: the moderate deformation of the [18]-O_6 ring itself; a large separation between the bound cation and the external anion imposed by the thickness of the "walls" of the receptor molecules (2); and the energy required for desolvating the binding sites. A desolvated receptor might strongly bind other neutral, hydrogen bonding substrates. Building an internal anionic site into the lateral subunits may much increase the binding ability of these large macropentacyclic ditopic receptor molecules and enhance in particular their ability to complex two cationic substrates.

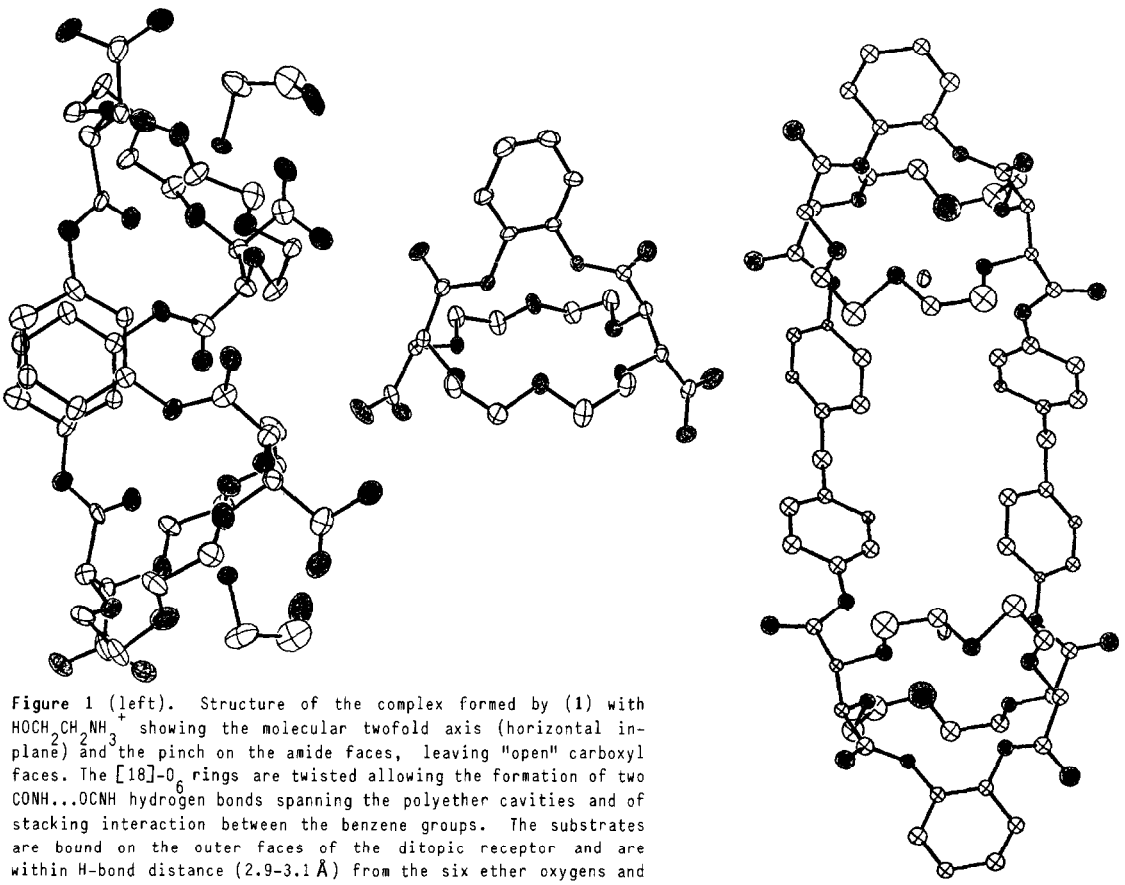


Figure 1 (left). Structure of the complex formed by (**1**) with $HOCH_2CH_2NH_3^+$ showing the molecular twofold axis (horizontal in-plane) and the pinch on the amide faces, leaving "open" carboxyl faces. The [18]-O_6 rings are twisted allowing the formation of two CONH...OCNH hydrogen bonds spanning the polyether cavities and of stacking interaction between the benzene groups. The substrates are bound on the outer faces of the ditopic receptor and are within H-bond distance (2.9-3.1 Å) from the six ether oxygens and from two lateral carbonyl groups.

Figure 2 (middle). Molecular structure of the macrobicycle (**3b**). The structure is stabilized internally by cyclic HN-CO-C-O hydrogen bonding[4], and intermolecularly through a water molecule forming two HNCO..H_2O and two COOH..OH_2 hydrogen bonds.

Figure 3 (right). Structure of the pentacyclic ditopic receptor (**2b**). The molecule has a boat-like shape; a water molecule is strongly bound on top of each macrobicyclic subunit.

References and Notes

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5. The dianhydride (4) was allowed to react with the monoprotected 1,3-diaminobenzene (obtained in 60% yield from the diamine and N-methylmorpholine plus benzyl chloroformiate in CH_2Cl_2 at 0°C) in presence of N-methylmorpholine in CH_2Cl_2 at 0°C. The desired syn-dicarboxylic macrocycle was isolated in 90% yield by extraction into a neutral buffered aqueous solution followed by acid precipitation. The amine protecting group was quantitatively removed with HBr/AcOH. Equimolar amounts (1mM/20 ml CH_2Cl_2) of the resulting diamine ($NHEt_3^+$ salt) and of (4) were simultaneously added over 3 hours to a strongly stirred solution of N-methylmorpholine (4mM) in 50 ml CH_2Cl_2. (1) was isolated in 20% yield by semi-preparative HPLC (RPC18, 20% MeOH in 10^{-2}M $HCO_2^-NH_4^+$ aqueous buffer). ^{1}H-NMR (CD_3OH, NMe_4^+ salt): 3.4-4.0 (m, 32H, OCH_2); 4.25, 4.35 (bd, 2x4H, CH); 7.0, 7.2, 7.8 (t, d, s, 2H, 4H, 2H, 1,3-C_6H_4).
6. *Space group $P6_122$, with a=b=25.70, c=23.04Å, Z=6; the structure was started by using the atomic coordinates of the isomorphous Rb^+ complex (solved by the heavy atom technique). The highly hydrated crystals were unstable and isotropic refinement led to R=.13 for 2038 reflections having $I > 3\sigma(I)$.*
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9. J.P. Behr, C.J. Burrows, R. Heng, J.M. Lehn, Tetrahedron Letters 215 (1985).
10. (**3a**) was converted to the diacid chloride (2.2 equiv. PCl_5 in CH_2Cl_2, 1 hour, room temp.); .02M solutions (5 ml in CH_2Cl_4) of this compound and of p-dianilino methane plus 2.2 equiv. of N-methyl morpholine were added separately over 2 hours into 50 ml of strongly stirred CH_2Cl_2. Acid extraction followed by chromatography over silica (.1 MeOH in $CHCl_3$) yielded (**2a**) (20%). ^{1}H-NMR(CD_2Cl_2): 3.2-39 (m, 52H, OCH_2, NCH_2, CH_2Benz); 4.25, 4.35 (d,2x4H, J=1.6Hz,CH); 6.95,7.55 (d, 2x8H, 1.4-C_6H_4); 7.4 (bt, 4H, $NHCH_2$); 9.1 (s, 4H, NH).
11. 0.5M solutions of (4) and of 1,2-diaminobenzene in CH_2Cl_2 were added to ten volumes of dry, mechanically stirred CH_2Cl_2. After filtration and solvent removal, 95% of (**3b**) cristallized out. ^{1}H-NMR($CDCl_3/CD_3OD$): 3.3-3.7 (m, 16H, OCH_2); 4.30, 4.35 (d, 2x2H, J=2.0Hz, CH); 7.1, 7.65 (m, 2x2H, 1,2-C_6H_4); 8.7 (s, 2H, NH). No tertiary amine was added in this case.
12. *Space group $P3_121$, with a=b=8.68, c=29.76Å, Z=3; the structure was solved by direct methods (MULTAN 82) and refined anisotropically to R=.055 using 901 independent reflections.*
13. (**3b**) was converted to the diacidchloride (2.2 equiv. PCl_5 in CH_2Cl_2, 30 min., room temp.); .02M solutions (10ml in CH_2Cl_2) of this compound and of p-dianilinomethane (or 1,3 diaminobenzene) plus 2.2 equiv. of N-methylmorpholine were added separately over 5 hours into 150 ml of strongly stirred CH_2Cl_2. Acid extraction followed by HPLC (silica, 3% CH_3OH/CH_2Cl_2) yielded (**2b**) or (**2c**)) (about 40% from (4))a5; the major side product (30%) was the trimer as shown by mass spectroscopy. ^{1}H-NMR($CDCl_3$).(**2b**): 3.4-3.9 (m, 32H, OCH_2); 3.95 (s, 4H, CH_2 benz); 4.40, 4.45 (d, 2x4H, J=1.9Hz, CH); 7.25,7.85 (m, 2x4H, 1,2 benzenediamide); 7.30, 7.75 (d, 2x8H, 1,4 C_6H_4); 8.45, 9.7 (s, 2x4H, NH); (**2c**): 3.5-4.3 (m, 32H, OCH_2); 4.35, 4.65 (d, 2x4H, J=3.6Hz, CH); 7.0, 7.25, 7.65 (t, dd, bt, 2H, 4H, 2H, 1,3 benzenediamide); 7.3, 7.8 (m, 2x4H, 1,2 benzenediamide); 8.5, 9.2 (s, 2x4H,NH).
14. Space group C_2, with a=29.21, b=8.74, c=17.35Å, β=92.16°, Z=2; the structure was solved using molecular replacement methods with the known structure[12] of (**3b**) as model. Isotropic refinement led to R=.11 for 1435 significant reflections.

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