Coreceptor–Substrate Binding. Crystal Structures of a Macrotricyclic Ligand and of its Molecular Cryptate with the Cadaverine Dication

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The structure of the complex formed by the macrotricycle (**1**) with the cadaverine dication is a mononuclear-dihapto molecular cryptate-{$^{+}H_3N$–$[CH_2]_5$–NH_3^{+} ⊂ (**1**)}, (**2**), in which the substrate is held inside the coreceptor molecule by simultaneous binding to the macrocyclic subunits; the preferential complexation of this dication results from the structural complementarity between the receptor and the substrate.

Substrate binding to coreceptor molecules yields supramolecular structures in which the binding subunits of the receptor co-operate to give the complexation either of several singly bound substrates or of a multiply bound species.[1,2] When the sub-units are able to bind primary ammonium groups, inclusion complexes of molecular cations may be formed. In particular, macrotricycles of cylindrical type bind diammonium substrates $^{+}H_3N$–A–NH_3^{+}, giving species formulated as molecular cryptates, in which the dication is contained in the central molecular cavity of the receptor and anchored by its

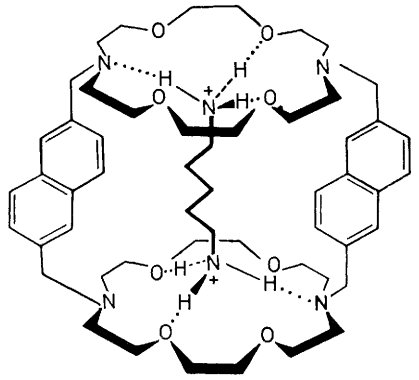
two $-NH_3^+$ groups to the lateral macrocycles.[1,3-6] Remarkable high field shifts of the substrate signals in the proton n.m.r. spectra of these complexes, as well as chain-length dependent binding selectivities[1,3-5] and dynamic rigidity[6] support such a picture.

We now report the crystal structures of both the free bis-2,6-naphthalene macrotricyclic receptor molecule (**1**)[1] and of its complex with the cadaverine dication $^+H_3N-[CH_2]_5-NH_3^+$,[1] as well as some new data on binding selectivities. These results are used to i, confirm the molecular inclusion phenomenon; ii, describe the supramolecular structure resulting from multiple binding between a substrate and a coreceptor molecule; iii, picture the changes occurring on complex formation; and iv, relate the structure and complexation properties.[7]

The solid state structure of the free macrotricycle (**1**) (Figure 1)†§ is centrosymmetric. Its overall shape is a skew cylinder; the bases are formed by the [18]-N_2O_4 macrocycles whose mean planes are parallel and 7.7 Å apart. The naphthalene groups, which constitute the walls, are contained in parallel planes 2.91 Å apart and displaced with respect to each other out of overlap. The four nitrogen bridgeheads as well as the oxygen sites are oriented towards the interior of the molecule, which should facilitate internal substrate binding.

The structure of the complex (**2**) (Figure 2)‡§ confirms the complete inclusion of the substrate molecule, forming a genuine molecular cryptate $\{^+H_3N-[CH_2]_5-NH_3^+ \subset (\mathbf{1})\}$ of the mononuclear-dihapto type, in which the ligand indeed functions as a ditopic coreceptor molecule.[1] The two [18]-N_2O_4 macrocyclic subunits of the macrotricycle co-operate in binding the substrate by its terminal $-NH_3^+$ groups.

The mactrotricycle in the complex has a cylindrical shape, containing an intramolecular cavity inflated with respect to



(**1**) (pentamethylene diammonium substrate removed)
(**2**)

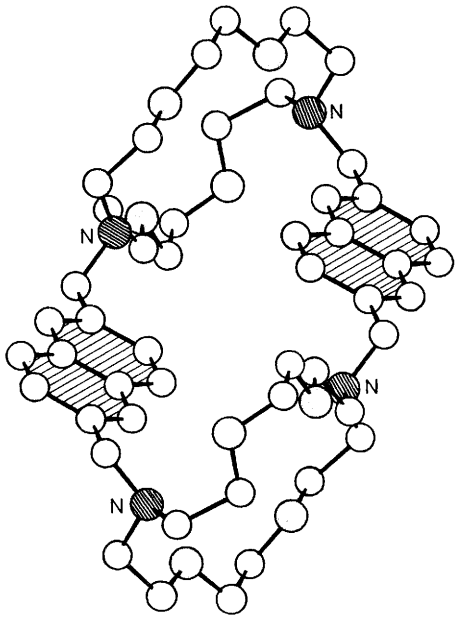


Figure 1. Crystal structure of the macrotricycle (**1**). The N,O heteroatoms and the naphthalene groups are shaded.

that of the free ligand in order to accommodate the tubular substrate (Van der Waals' dimensions: 3.7 × 4 × 7.6 Å). The planes of the naphthalene groups are parallel (interplanar angle *ca* 5°) to each other and 6.5 Å apart, leaving a void in which the substrate is contained (Figure 2a); the naphthalene groups are not exactly superposed but are slightly shifted (*cf.* the side-view Figure 2b). Compared with the free ligand (**1**), the two macrocycles slide on top of each other, maintained by the rigid naphthalene units (Figure 2c). The four nitrogen atoms form a rectangle with N . . . N distances of *ca.* 6.2 and *ca.* 9.3 Å respectively within and between the two macrocycles. The mean planes of the two macrocycles make a dihedral angle of about 28° and are almost perpendicular (*ca.* 80°) to the planes of the naphthalene groups; this distortion of the cylinder yields a non-symmetrical cavity with a smaller (*ca.* 7.5 Å) and a larger (*ca.* 10.0 Å) opening (respectively in front and in the back of Figure 2a, or to the left and to the right of Figure 2b).

The substrate diammonium cation $^+H_3N-[CH_2]_5-NH_3^+$ is strung inside the cavity of the macrotricyclic receptor and

† Crystals of compound (**1**) were grown from tetrahydrofuran (THF). *Crystal data:* $C_{48}H_{68}N_4O_8$, M = 829, monoclinic, space group $P2_1/n$, a = 19.140(4), b = 10.375(1), c = 11.494(1) Å, β = 94.00(2)°, Z = 2 D_c = 1.209 g cm^{-3}, λ(Cu-K_α). The intensities were collected on an automatic four-circle diffractometer, Philips PW1100. The molecules are located on crystallographic centres of symmetry. The structure was solved by direct methods, using a home-made program based on the phase function[8] and the negative quarters.[9] A least squares refinement was based on 2346 reflections with anisotropic temperature factors for the 30 independent heavy atoms. The 34 H atoms of the asymmetric unit were introduced at their theoretical positions. The final R-value is 5.9%.

‡ The first crystals studied were those of the dipicrate salt of (**2**) grown from THF. *Crystal data:* $C_{65}H_{88}N_{12}O_{22}$, M = 1389.4, monoclinic, $P2_1/c$, a = 11.840(2), b = 32.494(7), c = 20.314(4) Å, β = 100.36(2)°, U = 7688 Å^3, Z = 4. After unsuccessful attempts to find the structure by direct methods, isomorphous crystals were grown from THF for the bis(2-bromo-4,6-dinitro)phenolate[10] salt of (**2**). *Crystal data:* $C_{65}H_{88}N_{10}O_{18}Br_2$, M = 1457, monoclinic, $P2_1/c$, a = 11.865(1), b = 32.622(2), c = 20.179(2) Å, β = 100.40(2)°, U = 7682 Å^3, D_m = 1.36, D_c = 1.38 g cm^{-3} (with one molecular entity plus 2 THF solvent molecules per asymmetric unit). For both crystals the intensities were recorded on the PW1100 automatic diffractometer [λ(Cu-K_α)]. As direct and Patterson methods failed, the structure was eventually solved by the interpretation of a Patterson difference synthesis. Least squares refinement was conducted with large blocks (SHELX 76),[11] with anisotropic thermal factors for the bromine atoms, and isotropic ones for the other atoms. Whereas some parts of the complex undergo normal thermal motion (cation), others are highly agitated (part of one macrocycle, THF solvent). Owing to disorder, the NO_2 group in position 6 of the anion could not be localized and the co-ordinates of these atoms were not introduced into the refinement. The final R-factor is 18% for 2386 reflections and 160 introduced atoms (including 61 theoretical H atoms).

§ The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

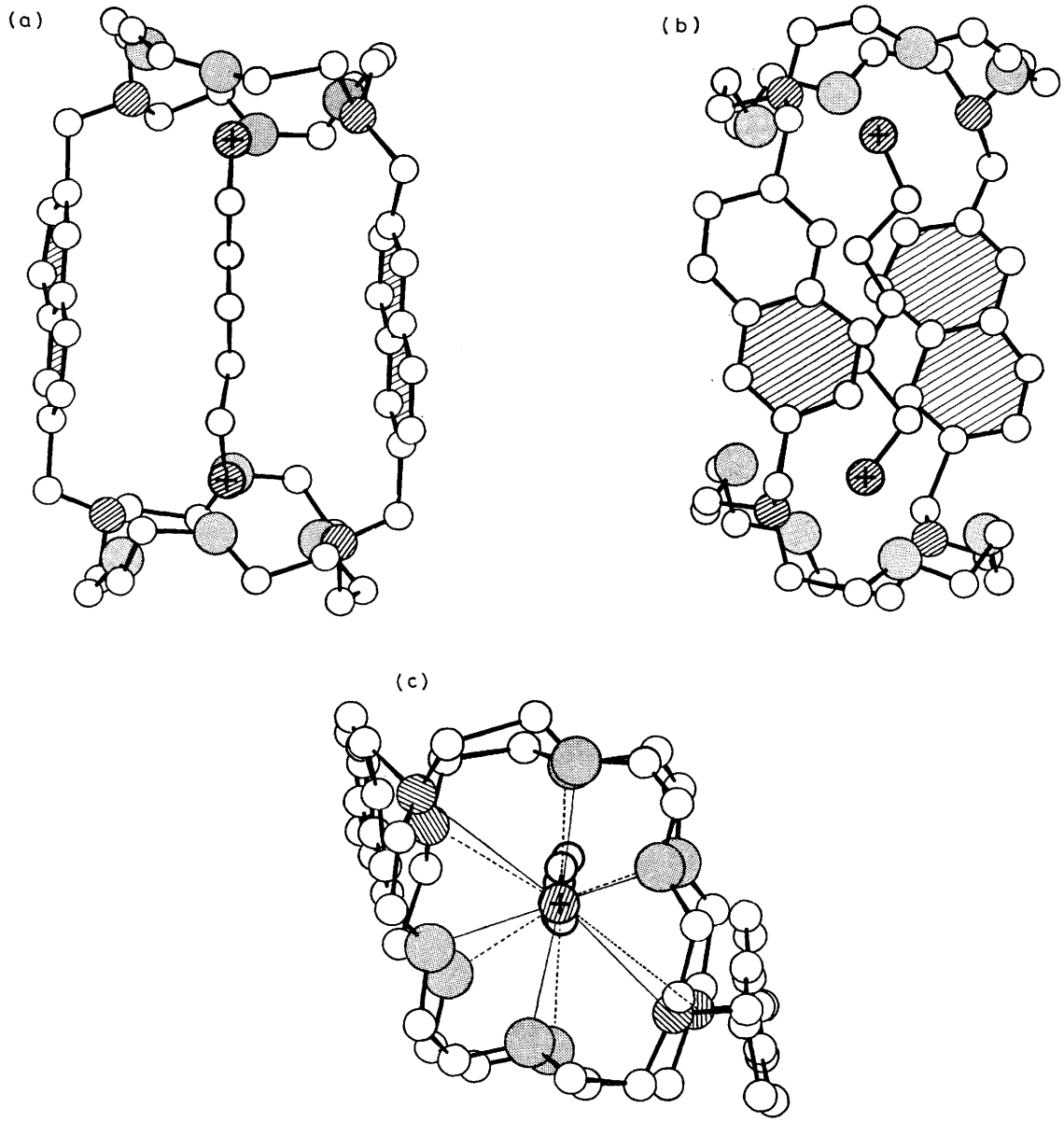


Figure 2. Crystal structure of the molecular cryptate (**2**) formed by the macrotricyclic coreceptor molecule (**1**) with the complementary diammonium substrate $^{+}H_3N$–$[CH_2]_5$–NH_3^{+}; (a) front view, into the cavity; (b) side view; (c) axial view along the substrate chain. Shading conventions as in Figure 1.

fully extended; its plane is nearly parallel to that of the naphthalene groups (interplanar angle of 18°). The terminal $-NH_3^{+}$ groups are tucked in the centre of the macrocycles, about 1 Å from the mean planes of the heteroatoms, and linked to the O and N heteroatoms by N–H^{+} . . . X interactions. Each $-NH_3^{+}$ group is at N . . . X distances of *ca.* 2.8—3.1 Å from the four oxygen atoms and one nitrogen atom of the ring to which it is bound, but *ca.* 0.2 Å further from the other nitrogen atom.

The present data show that there is a structural fit between the receptor (**1**) and the substrate in the {$^{+}H_3N$–$[CH_2]_5$–NH_3^{+} ⊂(**1**)} cryptate (**2**). Chain-length-dependent complexation selectivity towards $^{+}H_3N$–$[CH_2]_n$–NH_3^{+} substrates has been observed for macrotricyclic receptors[1,3–6] in which the binding macrocyclic subunits are maintained at different distances by rigid aromatic bridges. With (**1**) itself, competition experiments have shown¶ that the relative selectivities towards the species with n = 8, 7, 6, 5, and 4 are 1:6:11:32:8, respectively. Thus, the most stable complex is that of the cadaverine cation

¶ Competition experiments have been performed by 200 MHz proton n.m.r. measurements at —58 °C on $CDCl_3$–CD_3OD(9:1) solutions containing equimolar amounts of: i, the complex of (**1**) with a given diammonium dipicrate of chain length n; and ii, the complex of a substrate of different length n' with the reference *N,N'*-dimethyl-[18]-N_2O_4 macrocycle. Since in these conditions substrate exchange is slow, the spectrum contains the characteristic CH_2 signals for each complex [(**1**) + n] and [(**1**) + n'] at equilibrium, shifted at high field by the shielding effect of the naphthalene groups. Simple integration of these signals yields the relative amounts of the two complexes. The same results have been obtained by interchanging substrates n and n' in making up the mixed solution.

($n = 5$), (**2**), whose structure is reported here (Figure 2) and which is also dynamically the most rigid.[6] The putrescine cation ($n = 4$) is less well bound, indicating that (**1**) is able to discriminate between these two biological cations.

On complexation, the separation of the macrocycles, the binding sites, changes by less than 20%, whereas that of the bridging naphthalene groups more than doubles in order to accommodate the substrate. Thus, complexation selectivity rests on rigidity along the recognition direction, but not in the perpendicular directions. Also, the rigidity–flexibility balance of the receptor molecule may provide higher selectivities by the way in which a given substrate is able to reorganize the receptor on binding.

The results above provide a structural basis for receptor–substrate complementarity in linear molecular recognition. The latter requires length-sensing molecular devices, ditopic coreceptors whose two binding subunits are maintained at a distance fitting the substrate to be bound. Recognition of dianionic substrates, like the dicarboxylate anions $^{-}O_2C$–$[CH_2]_n$–CO_2^{-},[12] or of zwitterionic species represents further extensions into the manipulation of supramolecular structures.

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