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Molecular Recognition of Anionic Substrates. Crystal Structures of the Supramolecular Inclusion Complexes of Terephthalate and Isophthalate Dianions with a Bis-intercaland Receptor Molecule

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Abstract. Molecular recognition of flat substrates requires the design of receptor molecules containing complementary flat units. If two such units are incorporated into a macrocyclic framework, a face to face inclusion of a planar substrate may take place, leading to an intercalative supramolecular structure. The water-soluble macrocyclic bis-intercaland receptor **1**.4H$^+$, containing two naphthalene subunits, linked by two positively charged oxy-bis-ethylamine binding sites, is able to bind strongly flat organic anions. The crystal structures of the terephthalate **2** and isophthalate **3** inclusion complexes are reported here. Complex **2**, triclinic, *P-1*(N°2), $a = 7.717(3)$, $b = 10.625(6)$, $c = 16.238(9)$ Å, $\alpha = 99.00(7)$, $\beta = 99.70(6)$, $\gamma = 109.46(4)°$, $Z = 1$. Complex **3**, triclinic, *P1* (N°1), $a = 7.513(10)$, $b = 10.640(9)$, $c = 16.164(10)$ Å, $\alpha = 98.81(5)$, $\beta = 99.77(10)$, $\gamma = 109.36(12)°$, $Z = 1$. Comparison of the environment (water molecules, anions and macrocycle) in the two X-ray structures highlights the formation of a similar organized assembly with the two different substrates.

Key words: anionic substrates, molecular recognition, cryptates, crystal structures, H-bonds, intercalation, inclusion complex

Supplementary Data relating to this article are deposited with the British Library as Supplementary Publication No. 82245 (38 pages).

1. Introduction

In recent years, several reports from our laboratories have been devoted to the selective binding of flat organic substrates by bis-intercaland type macrocyclic receptor molecules. Our approach rests on the design of molecules containing two

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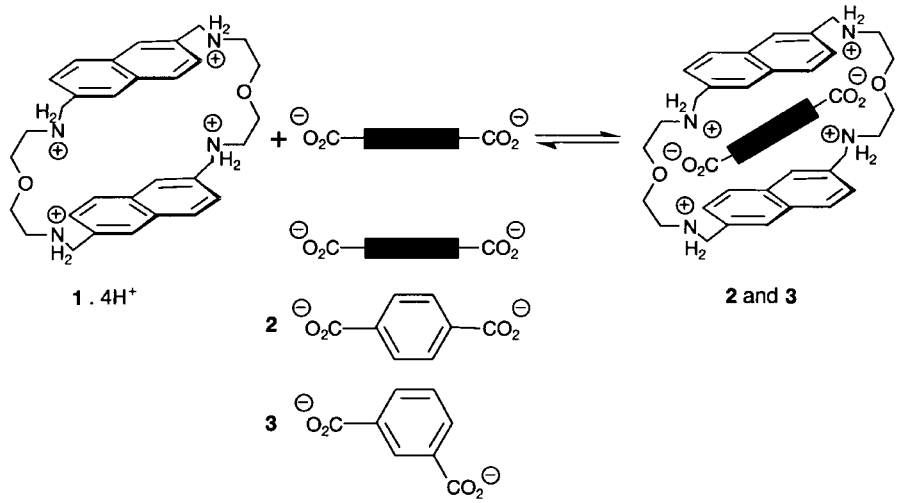

Scheme 1. Formation of the intercalative complexes **2** and **3** between the bis-naphthalene receptor **1** and the substrates terephthalate and isophthalate respectively.

flat residues of sufficient area positioned at a distance suitable for the intercalation of planar substrates. We have shown that macrocycles containing two intercaland groups derived from porphyrin [1, 2], diazapyrene [3], phenazine [4], acridine [5–11], phenanthridine [12–14] and naphthalene [15] bind planar substrates such as aromatic dicarboxylates or nucleosides and nucleotides. In the complexes formed with anionic substrates, both intercalative (stacking) and electrostatic interactions are in principle operative. The 1 : 1 stoichiometry, always observed, and, depending on the cases, the shielding effects in NMR spectra, the hypochromism in the UV/VIS absorption and the variations of the intensity of fluorescence emission suggest a sandwich type structure for the complexes, the substrates being located between the two flat subunits of the receptors. The intercalation of a nitrobenzene molecule between the two diazapyrene diimide groups of a cyclo bis-intercaland macrocycle was confirmed in the solid state by X-ray crystallography [3]. It was highly desirable to obtain firm structural data for complexes of planar anionic substrates, where both intercalation and electrostatic interactions contributed to the molecular recognition process. We have now succeeded in obtaining crystals suitable for X-ray structure determination and we herewith report the crystal structures of two supramolecular species **2** and **3** resulting from the binding of terephthalate and isophthalate dianions by a bis-naphthalene macrocyclic receptor, **1** (Scheme 1).

2. Experimental

2.1. REAGENTS

All commercially available chemicals employed were reagent grade and used without further purification. Melting points were determined on an Electrothermal digital melting-point apparatus. Proton NMR spectra were recorded on a Bruker AC 200 spectrometer, using TMS as an internal standard. The microanalyses were performed at the Service Régional de Microanalyse de l'Université Pierre et Marie Curie (Paris).

Naphthalene-2,6-dicarbaldehyde was prepared as previously described [15] from commercially available (Aldrich) dimethyl naphthalene-2,6-dicarboxylate ($LiAlH_4$ reduction followed by Swern oxidation).

2,2′-Oxybis(ethylamine) was obtained from its dihydrochloride (Aldrich) by treatment with NaOH in methanol.

2.2. PREPARATION OF 2,8,19,25-TETRAAZA 5,22-DIOXO[9,9] (2,6) NAPHTHALENOPHANE-1,8,18,25-TETRAENE (**4**)

A solution of 2,2′-oxybis(ethylamine) (170 mg, 1.63 mmol) in CH_3CN (75 mL) was added dropwise, at room temperature and under N_2, to a well-stirred solution of naphthalene-2,6-dicarbaldehyde (302 mg, 1.62 mmol) in CH_3CN (100 mL). The mixture was stirred at room temperature for 2 days. The white precipitate was filtered off, washed with $CHCl_3$ and dissolved in $CHCl_3$/MeOH 20/1. The insoluble solid was removed by filtration and the solvents were evaporated to give **4** (310 mg, 76% yield) which was used without further purification; ^{1}H-NMR ($CDCl_3/CD_3OD$ 20/1): 8.14 (s, 4H), 7.50 (d, J = 8.5 Hz, 4H), 7.36 (s, 4H), 7.24 (d, J = 8.5 Hz, 4H), 3.75 (s, 16 H).

2.3. PREPARATION OF 2,8,19,25-TETRAAZA 5,22-DIOXO[9,9] (2,6) NAPHTHALENOPHANE (**1**.4H$^+$)

$NaBH_4$ (0.56 g, 14.9 mmol) was added to a solution of tetraimine **4** (300 mg, 0.595 mmol) in CH_2Cl_2/MeOH 3/2 (50 mL). After 3 h of refluxing and cooling at room temperature, water (3 mL) and aqueous NaOH solution (10 mol.dm^{-3}, 0.5 mL) were added. The solvents were evaporated under vacuum at 40°C and the residue was dissolved in a minimum volume of hot THF. The insoluble materials were removed by filtration and, after cooling, a saturated solution of HCl in THF (3 mL) was added. The precipitate was filtered off, washed with THF and with CH_2Cl_2/MeOH 3/2 and then dissolved in water. After a new filtration, the water was evaporated and the residue was dried under vacuum to give **1**.4H$^+$ as a white powder (380 mg, 97% yield). ^{1}H-NMR (DCl 0.01N): 7.67 (s, 4H), 7.62 (d, J = 8.4 Hz, 4H), 7.28 (d, J = 8.4 Hz, 4H), 4.16 (s, 8H), 3.77 (t, J = 4.6 Hz, 8H), 3.34 (t, J =

4.5 Hz, 8H). Anal. Calcd. for $C_{32}H_{44}N_4O_2Cl_4$: C, 58.36; H, 6.73; N, 8.51. Found: C, 58.31; H, 6.68; N, 8.40.

2.4. BINDING CONSTANT DETERMINATION

The fluorescence spectra ($\lambda_{exc} = 300$ nm) were recorded on a Fluoromax (Spex) spectrophotometer at ca 25°C. The titration experiments were performed as follows: to an aqueous solution of **1**.4H$^+$ (5×10^{-6} mol.dm^{-3}) in cacodylate buffer (10 mM) were added aliquots of a mixture of the substrate diluted in an aqueous solution of **1**.4H$^+$ (5×10^{-6} mol.dm^{-3}) in cacodylate buffer (10 mM). In this manner the concentration of the receptor **1** was left constant while the concentration of the substrate varied. The data were analysed by a non-linear least-squares curve fitting procedure.

2.5. CRYSTAL STRUCTURE DETERMINATION OF TEREPHTHALATE **2** AND ISOPHTHALATE **3** DIANION CRYPTATES

Suitable crystals of the terephthalate and isophthalate complexes **2** and **3** (Scheme 1) were obtained by diffusion of acetone into an aqueous solution of the complexes.

Crystal data and details concerning data collection and structure refinement are given in Table I. The lattice parameters and intensity data were measured on an Enraf-Nonius Cad4 diffractometer. The cell constants were obtained from the least-squares refinement of the setting angles of 24 reflections [$10.6° < \theta < 11.8°$] for **2** and [$6.7 < \theta < 11.8°$] for **3**. Three standard reflections were measured every three hours to monitor instrument and crystal stability. No significant decay was observed. Both structures were solved by direct methods with the program SHELXS-86 [16] and refined on F^2 for all reflections by a least-squares method, using SHELXL-93 [17]. All hydrogen atoms for compound **2** were located on difference Fourier syntheses, including those of the water molecules present in the crystal structure. They were introduced in the refinement cycles with an isotropic thermal factor equivalent to 1.3 that of the bonded atom. For compound **3**, all the hydrogen atoms of the macrocyclic receptor and the dianion were located on difference Fourier syntheses, but only 11 hydrogen atoms for the 10 water molecules could be determined. H-atoms of the [macrocycle/dianion] were included in the refinement at their ideal positions (C—H = 0.97 Å, N—H = 0.90 Å) and assigned an isotropic thermal parameter of 1.3 that of the bonded atom, whereas the H-atoms of water molecules, located from the $\Delta\rho$ were fixed during the subsequent calculations.

The list of atomic coordinates and anisotropic thermal parameters of non hydrogen atoms, bond lengths and angles, atomic coordinates of hydrogen atoms have been deposited with the British Library as Supplementary material (36 pages).

Table I. Crystal data and selected experimental details for the terephthalate **2** and isophthalate **3** complexes

	Terephthalate **2**	Isophthalate **3**
Formula	$[C_{32}H_{44}N_4O_2]^{4+}$, $[C_8H_4O_4]^{2-}$, $2Cl^-$, $10H_2O$	$[C_{32}H_{44}N_4O_2]^{4+}$, $[C_8H_4O_4]^{2-}$, $2Cl^-$, $10H_2O$
Formula weight	931.88	931.88
Temperature/°K	293(2)	293(2)
Wavelength/Å	MoKα, 0.71070	MoKα, 0.71070
Crystal system	Triclinic	Triclinic
Space group	P-1 (No. 2)	P1 (No. 1)
a/Å	7.717(3)	7.513(10)
b/Å	10.625(6)	10.640(9)
c/Å	16.238(9)	16.164(10)
α/°	99.00(7)	98.81(5)
β/°	99.70(6)	99.77(10)
γ/°	109.46(4)	109.36(12)
V/Å^3	1204.6(11)	1170(2)
Z	1	1
Dcalc/gcm^{-3}	1.285	1.322
μ/mm^{-1}	0.204	0.210
F(000)	498	498
Crystal dimensions/mm	0.3 × 0.5 × 0.5	0.3 × 0.4 × 0.5
Scan mode	$\theta/2\theta$	$\theta/2\theta$
θ range for data collection	2.09 to 24.99°	2.08 to 24.97°
Index range	$-9 \le h \le 9$, $-12 \le k \le 12$, $0 \le l \le 19$	$-8 \le h \le 8$, $-12 \le k \le 12$, $0 \le l \le 19$
Reflections collected	4380	4318
Independent reflections	4215 [R (int) = 0.0254]	4269 [R (int) = 0.0476]
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	4211/0/382	4260/3/559
Goodness-of-fit on F^2	1.031	1.046
Final R indices	$R1$ = 0.0385, w$R2$ = 0.0979 for 3160 [I > 2σ(I)]	$R1$ = 0.0629, w$R2$ = 0.1635 for 2831 [I > 2σ(I)]
R indices for all data	$R1$ = 0.0625, w$R2$ = 0.1115	$R1$ = 0.1225, w$R2$ = 0.2016
Largest peak in final diff. map	0.240 and −0.198 e.Å^{-3}	0.588 and −0.275 e.Å^{-3}

3. Results and Discussion

3.1. LIGAND SYNTHESIS AND BINDING CONSTANTS

The macrocycle **1** was prepared according to the methodology previously used to obtain the polyaza analogue containing diethylenetriamine bridges [15]. It was isolated as its tetrachlorhydrate **1**.4H$^+$, 4Cl$^-$ (97% yield) following $NaBH_4$ reduction of the corresponding tetraimine **4**. The latter was readily obtained (76% yield) via the 2 + 2 condensation between 2,2′-oxybis(ethylamine) and naphthalene-2,6-dicarbaldehyde. Due to the rigidity of the naphthalene unit the formation of the 1 + 1 species was not observed.

Like its polyaza analogue [15], compound **1** is soluble in acidic aqueous solution. It delineates a flat-walled molecular cavity suitable for inclusion of planar organic substrates, in aqueous solution, by a combination of stacking, electrostatic and hydrophobic effects.

The complexation between **1**.4H$^+$ and the planar substrates was monitored by fluorescence spectroscopy. Upon addition of the substrate the fluorescence intensity of **1**.4H$^+$ decreased steadily and reached a limiting value at high proportion of substrate. The titration experiments were analyzed by a non-linear least squares curve fitting procedure. In every case the stoichiometry of the complexes formed was found to be 1 : 1 and the binding constants K_s were determined. Selected values of log K_s for the sodium salts of the substrates are the following; maleate: 3.4; fumarate: 4.4; isophthalate: 5.6; terephthalate: 5.65 (standard deviation ± 0.2). They are close to those obtained with the polyaza cyclo-bis-intercaland analogue and the same trends are observed [15]. In particular the very strong binding of the iso and terephthalate anions reveals a significant complementarity between these planar dianionic substrates and the flat faced receptors as it will be confirmed by the similarity of the crystal structures of the two inclusion complexes **2** and **3**. Weaker binding of terephthalate was observed for a macrobicyclic polyamine presenting less structural complementarity with this substrate, despite the higher positive charge of the receptor [18]. Thus both electrostatic and structural factors contribute to the stability of complexation.

3.2. MOLECULAR STRUCTURES

Both complexes **2** and **3** with included terephthalate and isophthalate anions, crystallize in the same triclinic cell, containing a single molecular complex, with a 1 : 1 host-guest ratio. A center of symmetry exists in the terephthalate case. In both structures, the four positive charges of the receptor are balanced by the phthalate dianion, plus 2 chloride anions. Ten water molecules cocrystallize in each cell (Figures 1 and 2).

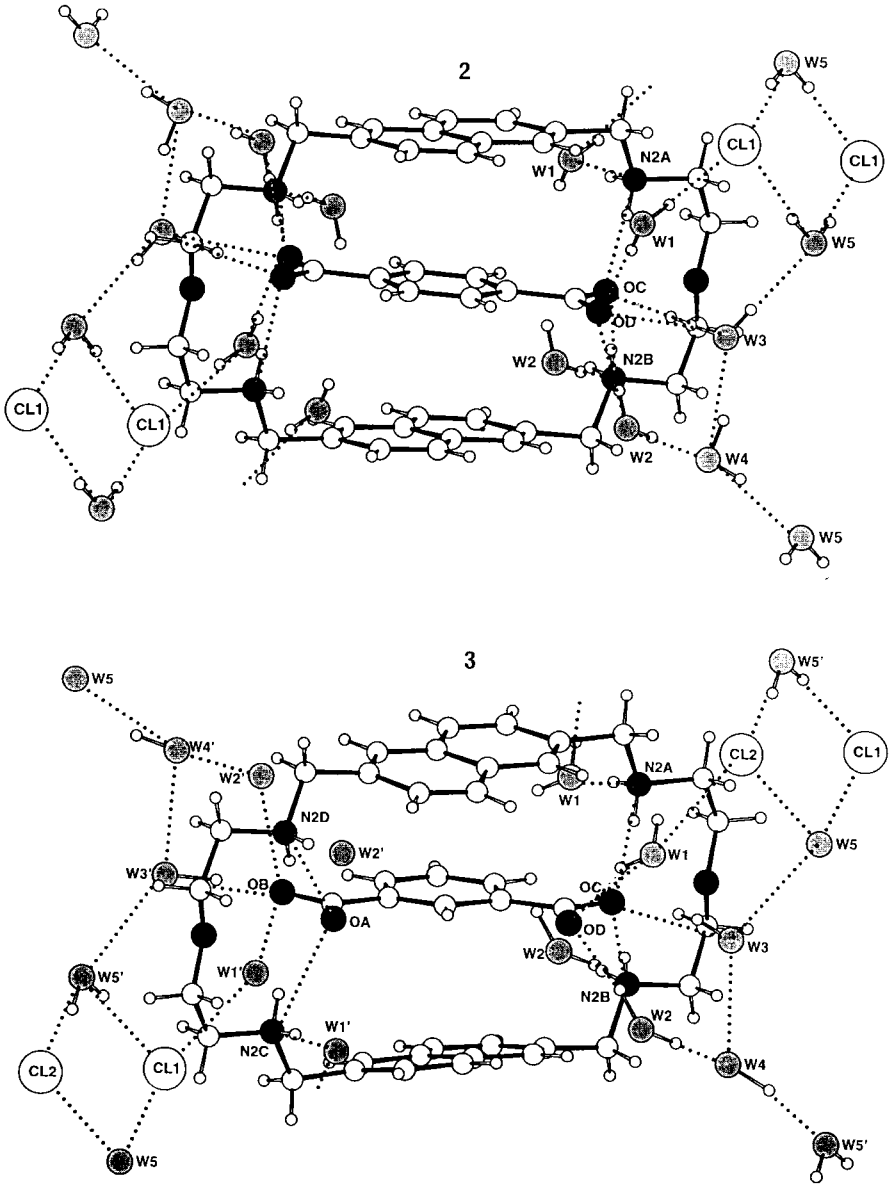

Figure 1. Comparison of the hydration networks in the two inclusion complexes **2** and **3** between the bis-naphthalene receptor **1** and the substrate terephthalate and isophthalate respectively. Hydrogen bonds are represented by dotted lines.

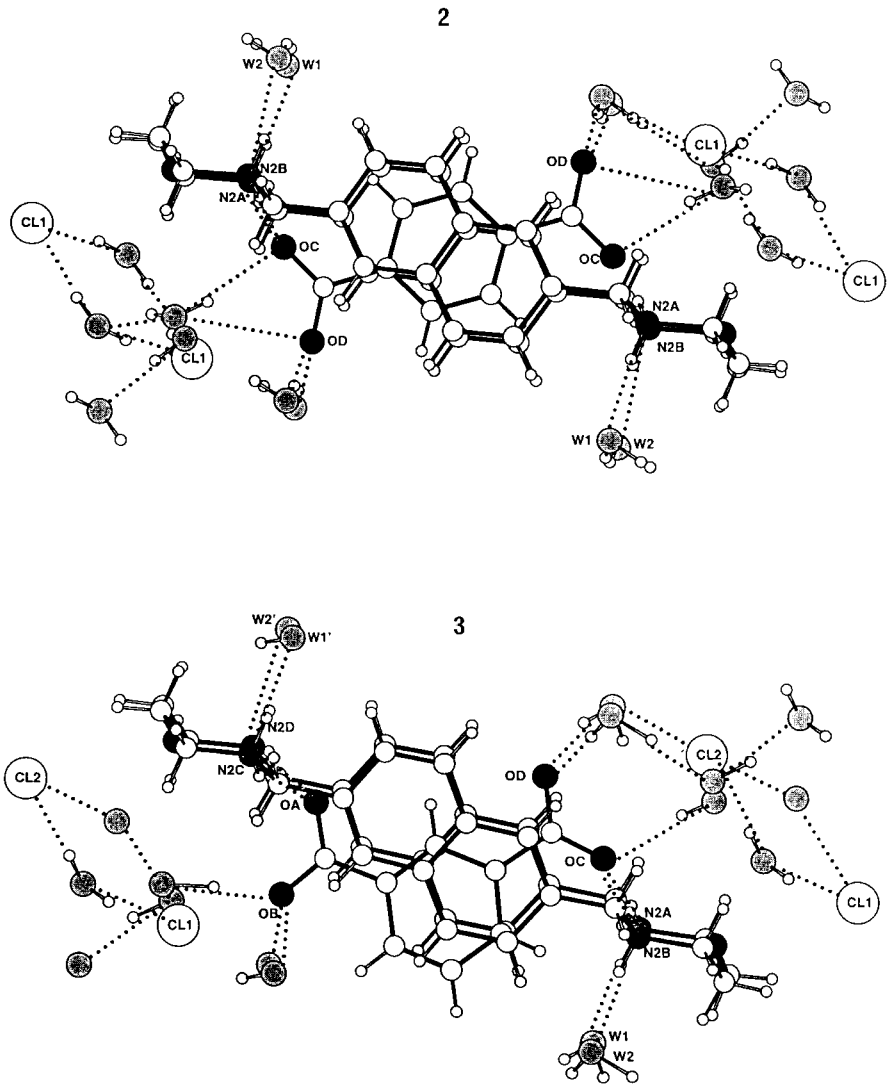

Figure 2. Representation of the inclusion complexes **2** (terephthalate) and **3** (isophthalate) viewed normal to the plane of the naphthalene unit; the macrocyclic receptor is surrounded by chloride ions and water molecules.

3.2.1. *Receptor/Substrate Interaction*

The dicarboxylate substrate, terephthalate as well as isophthalate, is intercalated between the two naphthalene units of the macrocyclic receptor (Figure 3). The terephthalate dianion is planar, and its plane is parallel (angular lag: 0.8°) to the macrocyclic aromatic units, at a van der Waals contact distance of 3.4 Å. When the ligand includes the isophthalate dianion, also rigorously planar, its shape is slightly

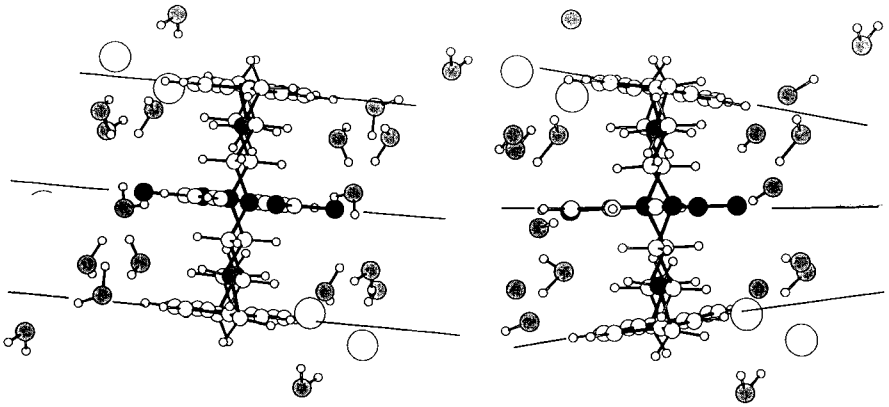

Figure 3. View of the complexes **2** (terephthalate) and **3** (isophthalate) along the O ··· O axis of the bridges of the macrocyclic receptor **1**.

modified, with the two naphthalene units forming a dihedral angle of 17.5°. The substrate is inserted halfway with a tilt angle of 9.3 and 8.2° with respect to each naphthalene plane. The shortest distance is 6.1 Å [C(4)–C(14)] and the largest 7.2 Å [C(9)–C(19)] (Figure 4). The organic anion interacts with its ligand by stacking contact of their aromatic parts, and by hydrogen bonding between the protonated nitrogens of the ligand and one of the oxygens of each carboxylate group. The second oxygen is linked only to water molecules (see Table II and Figures 1 and 2). Compared to the terephthalate cryptate, the isophthalate substrate achieves inclusion by gliding in the central plane so that the anionic oxygens stay close to their previous position (Figure 4); the phenylene center of the anion moves by 1.6 Å, the oxygen atoms only from 0 to 0.7 Å. The isophthalate aromatic core sticks out of the cavity, the two naphthalene walls being further apart on this hydrophobic side. There is no observed disorder, neither by rotational motion of the substrate in its plane, nor by its statistical stacking in different orientations.

3.2.2. *Hydrogen-bond networks and environment*

A striking result, pointed out by the comparison of both crystal structures **2** and **3**, is the conservation of the environment of the macrocyclic complex and the similarity of complicated hydrogen bond networks (Table III). The halogen ions occupy the same positions, and are H-bonded only to water molecules. Hydrogen bonds between the protonated nitrogens and water molecules W1 and W2 (average 2.77 ± 0.1 Å and < N—H ··· W 165° ± 10°), bind the macrocycle to the environment (Figure 2). The hydrogen bonds link the same water molecules with distances between 2.70 to 2.89 Å, thus forming an identical water network. The only difference between the two structures is a water W3 sharing a hydrogen atom between the two oxygen atoms [O(C) and O(D)] for the terephthalate carboxylate

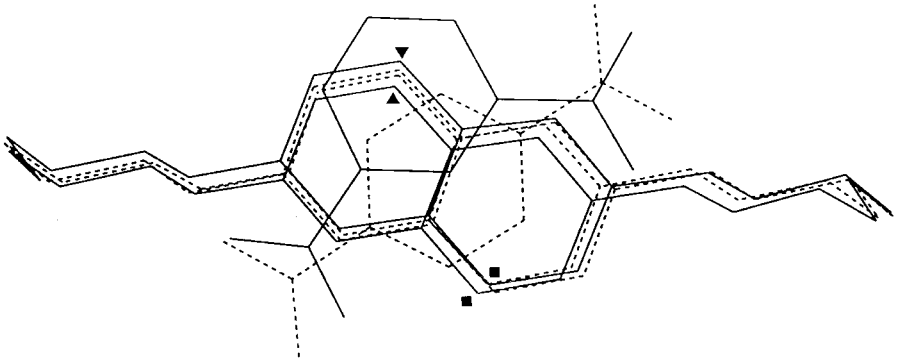

Figure 4. Superimposition of the complexes **2** and **3** on the naphthalene units, pointing out the displacement of the isophthalate dianion with respect to the terephthalate one. Dashed lines: **2** terephthalate substrate; full lines: **3** isophthalate substrate; ■ carbons C4 and C14, ▼ carbons C9 and C19.

Table II. Macrocycle – substrate interactions (Å,°)

Oxygens	Terephthalate			Isophthalate		
O(A)				N(2C)(i)	2.938	153
O(A)				N(2D)(i)	2.866	157
O(C)	N(2A)(i)	2.852	173	N(2A)(i)	2.918	173
O(C)	N(2B)(i)	2.842	176	N(2B)(i)	2.881	175
O(B)				W(1′)(ii)	2.786	146
O(B)				W(2′)(ii)	2.785	174
O(D)	W(1)(i)	2.748	175	W(1)(i)	2.850	153
O(D)	W(2)(i)	2.751	173	W(2)(i)	2.756	178
O(C)	W(3)(i)	2.896	169	W(3)(i)	2.833	158
O(D)	W(3)(i)	3.195	136			
O(B)				W(3′)(ii)	2.732	174

(i) = x, y, z; (ii) = x, y, $1 + z$.

group, whereas a single H-bond occurs in the isophthalate structure [O(C)] (Figure 1).

4. Conclusion

The water-soluble protonated macrocyclic bis-intercaland receptor **1**.4H$^+$ displays strong binding of flat organic substrates. The study of the crystal structure of the cryptates of terephthalate and isophthalate anions reveals great similarity in spite of the different geometries of the polar H-bond acceptor groups of the dianion. The environment of the supramolecular edifice seems to make an important contribution to the stabilization of the assembly [water/chloride anions/macrocycle].

Table III. Stable hydrogen-bonding network common to the crystal structures of both complexes **2** and **3**. Distances (Å) between chloride, water and macrocycle

Terephthalate			Isophthalate		
			Cl(1)	W(1)(i)	3.074
			Cl(1)	W(5)(i)	3.133
			Cl(1)	W(5′)(i′)	3.171
Cl(1)	W(1)(i)	3.101	Cl(2)	W(1)(i)	3.128
Cl(1)	W(5)(i)	3.134	Cl(2)	W(5)(i)	3.099
Cl(1)	W(5)(i′)	3.136	Cl(2)	W(5′)(ii)	3.135
N(2A)	W(1)(iii)	2.764	N(2A)	W(1)(iii)	2.761
N(2B)	W(2)(iii)	2.761	N(2B)	W(2)(iii)	2.772
			N(2C)	W(1′)(iV)	2.787
			N(2D)	W(2′)(iV)	2.756
W(2)	W(4)(i)	2.789	W(2)	W(4)(i)	2.887
W(3)	W(4)(i)	2.725	W(3)	W(4)(i)	2.705
W(3)	W(5)(i)	2.871	W(3)	W(5)(i)	2.872
W(4)	W(5)(V)	2.815	W(4)	W(5′)(i)	2.839
			W(5)	W(4′)(Vi)	2.815
			W(2′)	W(4′)(i)	2.749
			W(3′)	W(4′)(i)	2.750
			W(4′)	W(5)(iii)	2.814
			W(3′)	W(5′)(iii)	2.891
			W(4′)	W(5)(iii)	2.814

(i) = x, y, z; (i′) = $-x, -y, -z$; (ii) = $x, -1+y, z$; (iii) = $1+x, y, z$
(iv) = $-1+x, y, 1+z$; (v) = $-x, 1-y, -z$; (vi) = $-1+x, y, z$.

This suggests that the organization of the water framework around and within the macrocycle plays a significant role.

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