Unprecedented role of water in self-assembly of potential molecular tweezers

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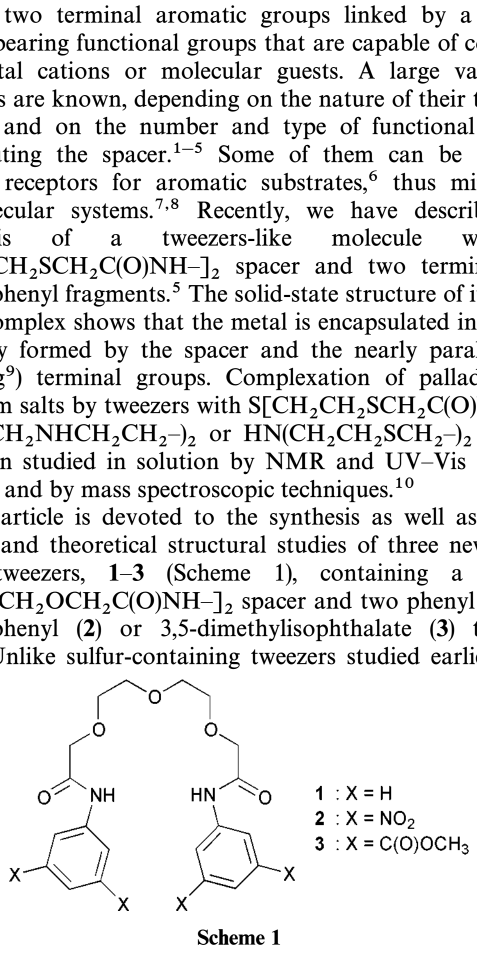
The X-ray structures of three potential molecular tweezers, $C_{20}H_{24}N_2O_5$ (**1**), $C_{20}H_{20}N_6O_{13}$ (**2**) and $C_{28}H_{32}N_2O_{13}$ (**3**), differing only by the substituents on the terminal aromatic moieties, display three as yet unreported arrays. Hydrogen bonding with co-crystallized water molecules as well as van der Waals interactions between terminal aromatic moieties lead to specific packing patterns, namely: (i) a membrane-like architecture of associated molecular tapes in $\mathbf{1} \cdot 2H_2O$, (ii) coupled right-handed and left-handed helices in $\mathbf{2} \cdot H_2O$ and (iii) a stepped arrangement provided by a back-to-back pairing in $(\mathbf{3})_2 \cdot H_2O$. Molecular modelling of individual molecules *in vacuo* shows that the most stable conformers of **1**–**3** intrinsically display attractive interactions between the terminal aromatic groups, which stabilize a pseudocavity suitable for incorporation of a guest compound.

Molecular tweezers represent a family of host molecules possessing two terminal aromatic groups linked by a flexible spacer bearing functional groups that are capable of complexing metal cations or molecular guests. A large variety of tweezers are known, depending on the nature of their terminal groups and on the number and type of functional groups constituting the spacer.[1–5] Some of them can be used as abiotic receptors for aromatic substrates,[6] thus mimicking biomolecular systems.[7,8] Recently, we have described the synthesis of a tweezers-like molecule with a $S[CH_2CH_2SCH_2C(O)NH–]_2$ spacer and two terminal 3,5-dinitrophenyl fragments.[5] The solid-state structure of its palladium complex shows that the metal is encapsulated in a pseudocavity formed by the spacer and the nearly parallel (π-π stacking[9]) terminal groups. Complexation of palladium or platinum salts by tweezers with $S[CH_2CH_2SCH_2C(O)NH–]_2$, $S(CH_2CH_2NHCH_2CH_2–)_2$ or $HN(CH_2CH_2SCH_2–)_2$ spacers has been studied in solution by NMR and UV–Vis spectroscopies, and by mass spectroscopic techniques.[10]

This article is devoted to the synthesis as well as experimental and theoretical structural studies of three new molecular tweezers, **1**–**3** (Scheme 1), containing a flexible $O[CH_2CH_2OCH_2C(O)NH–]_2$ spacer and two phenyl (**1**), 3,5-dinitrophenyl (**2**) or 3,5-dimethylisophthalate (**3**) terminal units. Unlike sulfur-containing tweezers studied earlier, molecules **1**–**3** might be more appropriate ligands for the complexation of hard metal cations and for the fixation of molecular guests *via* hydrogen bonds.[11–13]



Scheme 1

The three compounds have been crystallized at ambient temperature and in air by slow evaporation of acetone (**1**), toluene (**2**) and dimethylsulfoxide (**3**) solutions, respectively. Unexpectedly, water molecules absorbed during the crystallization process are present in the crystals. The water molecules play a role as guest and/or cement leading to three different infinite arrays: (i) a membrane-like architecture of associated molecular tapes in $\mathbf{1} \cdot 2H_2O$, (ii) coupled right-handed and left-handed helices in $\mathbf{2} \cdot H_2O$ and (iii) a stepped arrangement provided by a back-to-back pairing in $(\mathbf{3})_2 \cdot H_2O$. Structure **2** is of particular interest, since supramolecular helical strands paired through hydrogen bonds, to our knowledge, have never been described in the literature. In order to determine whether molecules **1**–**3** are intrinsically preorganized for incorporation of the guest species, we performed conformational sampling using the Monte–Carlo method coupled with molecular mechanics calculations.

Results and discussion

Compounds **1**–**3** were obtained in good yields using the classical condensation between acid chlorides and amines. The amide groups in **1**–**3** are all in the typical *trans* conformation suitable to give intra- and intermolecular hydrogen bonds with oxygens of the polyether spacer and with co-crystallized water molecules. The ligand-to-water ratio varies as a function of the nature of the terminal group of the tweezers; it is equal to 1 : 2 in **1**, 1 : 1 in **2** and 2 : 1 in **3**. The observed ratios are related to the variation in size of the aromatic groups and to the modification of their electronic factors due to different substituents.[9,14] All water molecules are involved in hydrogen bonds and the three compounds present clear-cut structural differences.

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The diffraction study shows that in **1** · 2H_2O the ligand **1** adopts a tweezers-like conformation, unfortunately the two phenyl rings are not stacked, their planes are turned by 59.8(1)° with regard to one another. This corroborates observations made elsewhere.[9,14] The heteroatoms of **1** surround the first water molecule O1w, whereas O2w links together [O1w $\subset$ **1**] units. Molecule O1w is held inside **1** through three hydrogen bonds, involving the two amide NH and one ether O: O1w···N1, O1w···N2 and O1w···O3 are equal to 3.036(2), 3.004(2) and 2.954(2) Å, respectively. Owing to these hydrogen bonds, the carbonyl groups are in an *exo–exo* orientation and are available for interaction with the second water molecule O2w (Fig. 1). O2w forms strong hydrogen bonds both with O1w and with two carbonyl oxygens, each from centrosymmetrically equivalent molecules: O2w···O1w = 2.724(2), O2w···O1 = 2.773(2) and O2w···O5 = 2.782(2) Å. Thus, the [O1w $\subset$ **1**] units are linked together by O2w, which plays a key role in this two-component self-assembly.[15–18] This results in the formation of a molecular tape best formulated as $\{[H_2O \subset \mathbf{1}] \cdot H_2O\}_n$ [Fig. 2(A)]. The tapes are disposed in layers shifted by the value *c*/2. In the successive layers, the tapes are alternately all oriented in either the [110] or the [$\bar{1}$10] direction. This structure can be considered as a model of a lamellar double layer system.[19] The phenyl groups of a tape are turned outwards to produce a hydrophobic rim, whereas spacers and water molecules are in hydrophilic association. The membrane-like structures are packed along the *c* axis [Fig. 2(B)]. Weak CH···π[20] and CH···O[21] interactions within each tape and between tapes stabilize the self-assembly.

In the crystal structure of **2** water also acts as the cement. The water molecule in [**2** · H_2O] forms three hydrogen bonds, with one ether oxygen, one NH group, and a carbonyl oxygen from an equivalent of **2** obtained by inversion [Ow···O3 = 2.836(3), Ow···N2 = 3.074(3), Ow···O1 = 2.985(3) Å]. Thus, a $[\mathbf{2} \cdot H_2O]_2$ dimer is formed; it is stabilized by six hydrogen bonds. The hydrogen bonds as well as intermolecular interactions induce a helical conformation of **2**. The two individual molecules of the dimer constitute two complete and independent loops, that is an elementary step of a helix; one is left-handed, the other right-handed (Fig. 3). The two dinitrophenyl groups of each loop appear here almost face-to-face; they are tilted with a dihedral angle of 26.7(1)°. The packing of successive $[\mathbf{2} \cdot H_2O]_2$ dimeric units exhibits interesting features. Each loop is in tight contact with its neighbour along the *a* axis. The successive loops are in contact through oxygens of the nitro groups [O13···O8 = 2.847(4) Å]. This molecular juxtaposition draws infinite helices linked by pairs *via* hydrogen bonds (Fig. 4). Each strand of a pair is obtained from the other by inversion. Since the two strands are not interweaved, we propose to designate it as a "pseudo-

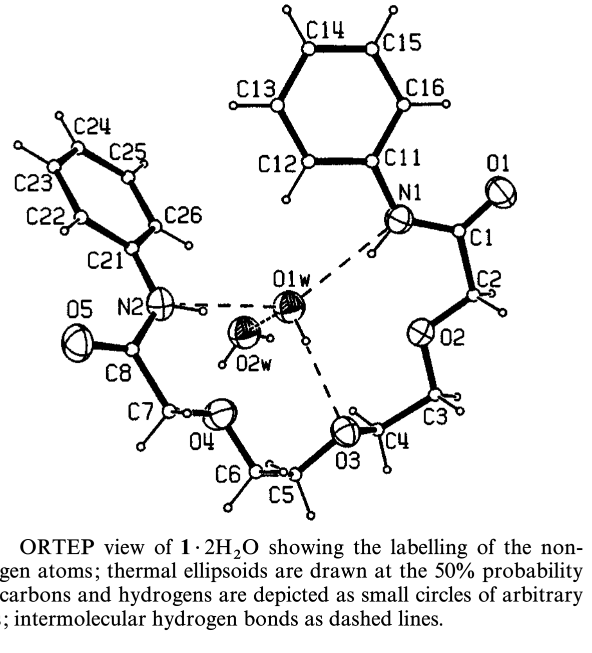

Fig. 1 ORTEP view of **1** · 2H_2O showing the labelling of the non-hydrogen atoms; thermal ellipsoids are drawn at the 50% probability level; carbons and hydrogens are depicted as small circles of arbitrary radius; intermolecular hydrogen bonds as dashed lines.

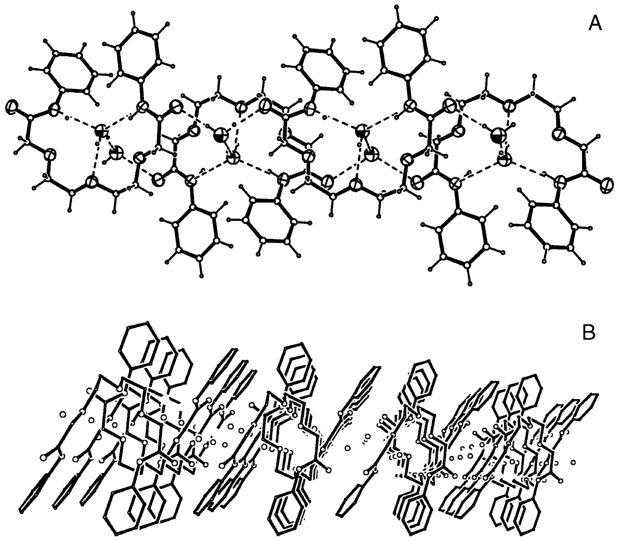

Fig. 2 (A) ORTEP view of the molecular tape $\{[H_2O \subset \mathbf{1}] \cdot H_2O\}_n$ showing four units. The ellipsoids of the water O atoms are represented with octant shading. Carbons and hydrogens are depicted as small circles of arbitrary radius. (B) Partial crystal packing with three tapes of four units each along the *a* axis showing the membranar system displayed in **1** · 2H_2O. The water O atoms (discrete circles) appear inside and between the ligands. Hydrogen atoms are omitted.

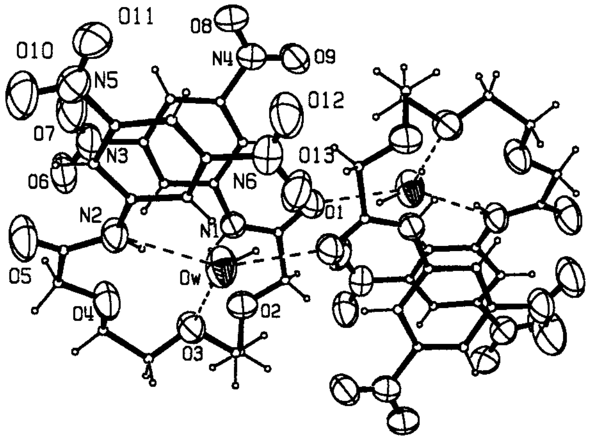

Fig. 3 Top view of the centrosymmetric $[H_2O \subset \mathbf{2}]_2$ unit showing the helical conformation of **2** and the intermolecular hydrogen bond network with the heteroatoms labeled. Drawing parameters are similar to those in Fig. 1 with the ellipsoids of the water O atoms represented with octant shading.

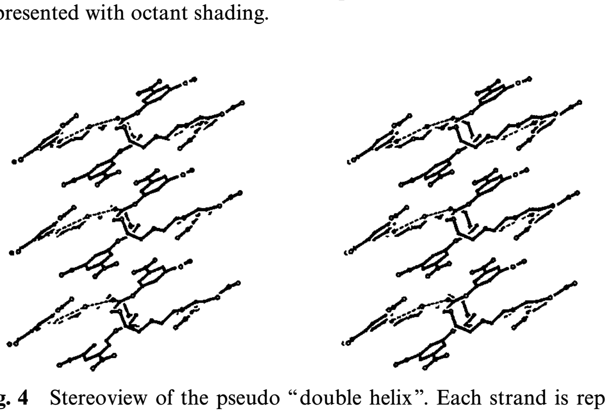

Fig. 4 Stereoview of the pseudo "double helix". Each strand is represented by three successive molecules translated along the *a* axis. Hydrogen atoms are omitted.

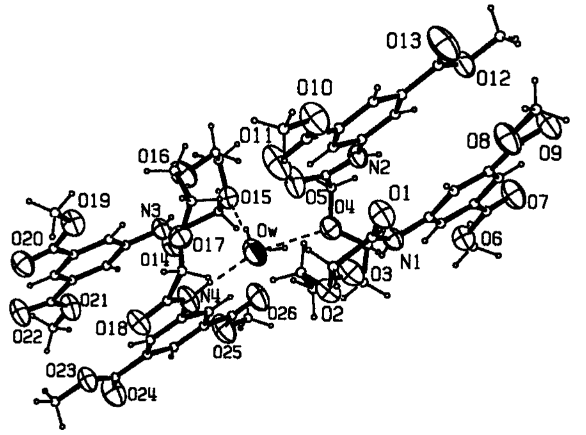

Fig. 5 ORTEP view of a $[3]_2 \cdot H_2O$ entity with the hydrogen bonds between the water molecule and the heteroatoms as dashed lines. Drawing parameters are as in Fig. 1 and 3.

double helix". Theobserved assembly is stabilized by intra- and interstrand forces of the CH···O type.[21]

The asymmetric unit of **3** contains one water and two ligand molecules. Both ligands are approximately symmetry-related. They are held together in a back-to-back fashion by the water owing to three hydrogen bonds: Ow···O4 = 2.777(4), Ow···O15 = 2.832(4) and Ow···N4 = 2.846(4) Å (Fig. 5). The two ligands of the $[3]_2 \cdot H_2O$ entity exhibit the expected tweezers-like configuration with rather strained spacers. The observed values of the intramolecular N···N distances are smallest in $[3]_2 \cdot H_2O$, 4.132(4) and 3.621(4) Å compared to 5.508(2) Å in $\{[H_2O \subset \mathbf{1}] \cdot H_2O\}_n$ and 5.546(4) Å in $[\mathbf{2} \cdot H_2O]$. The amide groups are in a typical *trans* conformation as in **1** and **2**. The planes of the four terminal aromatic groups are all nearly parallel with interplanar angles between 1.2 and 5.6°. For each ligand, the distance between the planes of the aromatic fragments is almost identical: 3.481(3) and 3.401(3) Å, the aromatic moieties being shifted with regard to one another. The different $[3]_2 \cdot H_2O$ entities are linked through hydrogen bonds (NH···O, CH···O and CH···N) and CH···π interactions.[9,20,21] This bonding network results in linear aggregates consisting of stair-like packed units (Fig. 6).

Molecules **1**, **2** and **3** differ simply in that the *meta* positions on the aromatic end groups are occupied by either two hydrogens, two nitro groups or two methylcarboxylate groups. As the bulkiness of the aromatic groups increases, the number of water molecules present decreases. No water molecule is complexed by **3**, the water molecules simply link pairs of ligands. This allows offset face-to-face π-stacking interactions. In the other two compounds, water is each time complexed by the ligand; the conformations of **1** and **2** are stabilized by electronic factors due to the substituents on the aromatic systems, strong hydrogen bonds including the water molecules and, in the case of **1**, CH···π interactions. The packing in $[\mathbf{2} \cdot H_2O]$ displays an original helical self-assembly that, to our knowledge, has never been reported so far.[22] It differs from the helical structures found in helicates, where strands are assembled by metal ion complexation with suitable ligands, and from double helices formed by diols and pyridine derivatives.[23–29] Nonchiral linear molecules tend to form helical structures but not extended arrays.[30] So far only a few helical arrays promoted by neutral substrates have been structurally characterized.[31–33]

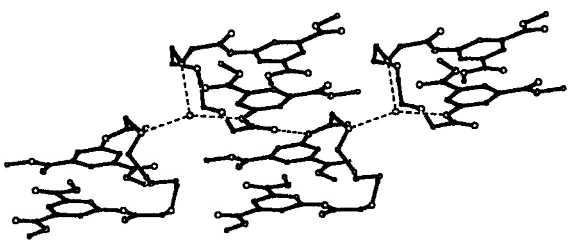

Fig. 6 View of two adjacent $[3]_2 \cdot H_2O$ entities showing the π-stacking. The two entities are linked through the O···HN hydrogen bond [2.969(4) Å] shown as a dashed line at the center of the drawing.

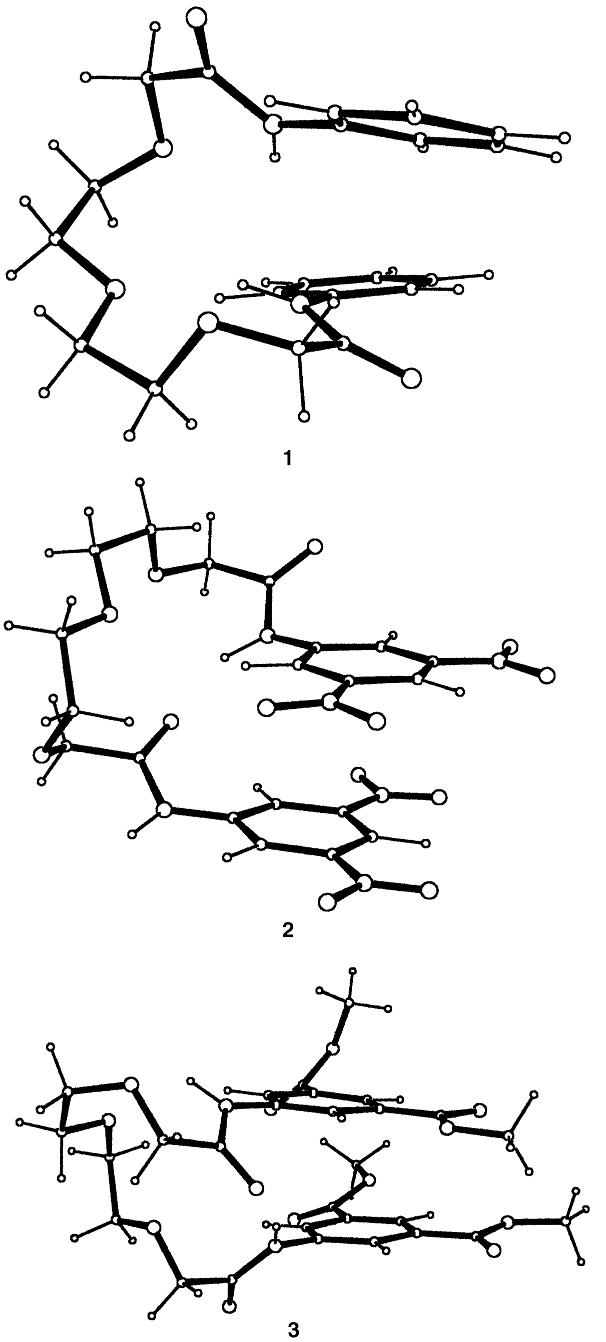

Fig. 7 Lowest-energy conformations of **1**, **2** and **3** (from top to bottom) obtained in a Monte–Carlo conformational search.

From the structures of molecules **1**–**3** in the solid state it is not clear whether they were initially pre-organized or became "tweezers" only under the influence of a guest. To shed light on the conformational behaviour of the studied molecules, a Monte–Carlo conformational search has been performed on uncomplexed **1**–**3** molecules using the AMBER* force field incorporated in the MacroModel 5.5 program.[34] In these calculations, the program generates, for a given molecule, a number of different conformers (1000 by default), whose energies are then minimized in molecular mechanics calculations. In such a way, for each molecule, we have observed a number of low energy conformers stabilized by intramolecular carbonyl-O···H–N and/or ether-O···H–N hydrogen bonds, and having different "in-out" orientations of amide groups and conformations of the polyether spacer. The lowest energy structures of **1**–**3** have pseudocavities suitable for encapsulation of the guest species, *i.e.* these molecules are intrinsically pre-organized as tweezers. Mutual orientation of the two terminal aromatic fragments is similar to that found experimentally for the solid state structures. Thus, the two phenyl groups in **1** are well separated both in the solid state (Figs. 1 and 2) and *in vacuo* (Fig. 7). The most stable gas phase conformers of **2** and **3** display a pseudo-stacking of their terminal groups, as in the X-ray structures: the planes of the aromatic fragments are almost parallel and shifted one with respect to other (Fig. 7). Thus, the intrinsic conformational properties of **1**–**3** are an important factor governing their "tweezers" behaviour in the complexes with cationic or neutral guests.

Conclusion

Three differently functionalized variants of potential tweezers have been studied. These molecules form two-component self-assembled superstructures in the solid state. The process is driven by the coordination of water molecules and the stacking of the aromatic fragments. Theoretical calculations show that interactions between two terminal aromatic groups in uncomplexed tweezers is an important factor affecting their conformational behaviour in complexes with neutral guests. No stacking is observed for **1**, either in the gas phase or in the solid state. A membrane-type assembly is observed in $\{[H_2O \subset \mathbf{1}]\cdot H_2O\}_n$. Free molecules **2** and **3**, for which strong attractive interactions between the two terminal groups are observed *in vacuo*, display stacking effects in their complexes with water in the solid state. Both **1** and **2** exhibit a helical conformation due to the presence of a water molecule in their hydrophilic cavity; this results in formation of infinite helical arrays in **2**. Appropriate choice of substituents in the aromatic fragments may lead to different helical supramolecular species. Studies of compounds obtained by hydrolysis of the ester functions of **3** are, therefore, under way.

Experimental

All reactions were carried out under argon. The solvents were freshly distilled, benzene from sodium, diethyl ether and THF from sodium–benzophenone. Other chemicals were of reagent grade and used without further purification, unless otherwise indicated. ^{1}H and ^{13}C NMR spectra were recorded at ambient temperature on either Bruker WP200 or AC200 spectrometers using the solvent as an internal standard. IR spectra were recorded on a Bruker IFS25 spectrometer. Mass spectra were obtained by the fast atom bombardment (FAB) method; nitrobenzyl alcohol was used as the matrix. Column chromatography was performed on Merck silica 60 (particle size 0.040–0.063 or 0.063–0.200 mm). Elemental analyses were performed by the Service de Microanalyse de l'Institut de Chimie de Strasbourg.

X-Ray structure analyses were recorded on a Philips PW1100/16 diffractometer with Cu-Kα radiation (graphite monochromator, $\lambda = 1.541\,84$ Å) at 173(2) K for **1**, and on an Enraf–Nonius CAD-4 diffractometer, graphite monochromated Cu-Kα radiation at 294(2) K for **2** and **3**. The structures were solved by direct methods using the MOLEN package[35] for **1**, the SDP-VAX (Enraf–Nonius) program system[35] for **2** and **3**. They were refined by full-matrix least-squares on F with anisotropic displacement parameters for the non-H atoms; the minimized function was $\Sigma w(|F_0| - |F_c|)^2$. Neutral atom scattering factors were taken from the usual source,[36] and the effects of anomalous dispersion were included in F_c.[36]

Calculations on the free molecules **1**–**3** *in vacuo* were performed using the AMBER* force field incorporated in the MacroModel 5.5 program.[34] The most stable conformers of **1**–**3** were obtained in a 1000 step Monte–Carlo conformational search. In order to ascertain the force field effects on the conformational equilibrium of studied molecules, the Monte–Carlo calculations on molecule **2** were repeated using AMBER* coupled with electrostatic potential atomic charges (ESP charges) calculated *ab initio* (6-31G*) for the $(NO_2)_2C_6H_3NHC(O)CH_2OCH_3$ fragment.

General synthetic procedures

1–**3** were obtained by a straightforward synthesis involving the condensation of the appropriate aromatic amines with tetraglycolic acid dichloride. 3,6,9-Trioxaundecanedioic acid (tetraglycolic acid purchased from Fluka was purified as described elsewhere[37]) was used as the starting chemical to prepare the three compounds. It was first converted in its dichloride derivative. Condensation of the dichloride with the appropriate amine in a stoichiometric amount in the presence of K_2CO_3 to capture the evolving HCl led to the desired products.

The synthesis of the dichloride was conducted in the dark and under argon: a solution of oxalyl chloride (27.4 g, 0.2 mol) in benzene (50 mL) was added to a suspension of 3,6,9-trioxaundecanedioic acid (19.5 g, 90 mmol) in benzene (130 mL) with pyridine (4 drops). The mixture was stirred at room temperature for 20 h. The pale yellow solution of the dichloride was then quickly filtered over celite and the filtrate reduced under vacuum. The yellow oil (even below −78 °C) obtained was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.72 (A_2X_2, 8H, OCH_2CH_2O), 4.50 (s, 4H, OCH_2CO).

***N,N′*-Bisphenyl-3,6,9-trioxaundecanedicarboxamide (1).** **1** was obtained as a colourless crystalline solid during purification of the tetraglycolic acid. ^{1}H NMR (200 MHz, $CDCl_3$): δ 3.79 (A_2B_2, 8H, OCH_2CH_2O), 4.08 (s, 4H, OCH_2CO), 7.07–7.54 [m, 10H, ArH: 7.07–7.15 (m, 2H); 7.27–7.34 (m, 4H); 7.48–7.54 (m, 4H)], 8.55 (s, 2H, NH); IR (KBr): ν 3384 (N–H), 1654 (C=O) cm^{-1}; elem. anal. for $C_{20}H_{24}N_2O_5 \cdot 2H_2O$ (408.46): calcd C 58.81, H 6.91, N 6.86; found C 59.07, H 6.66, N 6.73%.

***N,N′*-Bis(3,5-dinitrophenyl)-3,6,9-trioxaundecanedicarboxamide (2).** Under an argon atmosphere 3,5-dinitroaniline (4.58 g, 25 mmol) and K_2CO_3 (3.59 g, 26 mmol) were mixed in diethyl ether (250 mL); then a solution of 3,6,9-trioxaundecanedioic acid dichloride (3.37 g, 13 mmol) in diethyl ether (100 mL) was added dropwise. The mixture was stirred at room temperature for 60 h. The resulting yellow solid was filtered, washed successively with diethyl ether and water, before being dried under vacuum. **2** was obtained as a yellow solid (3.2 g, 45%) after purification by column chromatography (eluent CH_2Cl_2–CH_3OH gradient 100 : 0 until 98.5 : 1.5). ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 3.70 (A_2B_2, 8H, OCH_2CH_2O), 4.19 (s, 4H, OCH_2CO), 8.47 (t, 2H, ArH, $J = 2.1$ Hz), 8.93 (d, 4H, ArH, $J = 2.1$ Hz), 11.30 (s br, 2H, NH); ^{13}C NMR (50 MHz, DMSO-d$_6$): δ 69.62 (CH_2), 70.14

(CH_2), 70.31 (CH_2), 112.46 (2 ArCH), 118.93 (4 ArCH), 140.46 (2 ArC), 148.01 (4 ArC), 169.80 (CH_2CO); IR (KBr) $\nu = 3434$, 3311 (N–H), 1696 (C=O), 1540, 1345 (NO_2) cm^{-1}; MS (FAB): m/z 553.0 $[M + H]^+$ (552.1 calcd for $C_{20}H_{20}N_6O_{13}$); elem. anal. for $C_{20}H_{20}N_6O_{13} \cdot H_2O$ (570.43): calcd C 42.11, H 3.89, N 14.73; found C 42.04, H 3.81, N 14.58%.

***N,N′*-Bis(dimethylisophthalate)-3,6,9-trioxaundecanedicarboxamide (3).** Dropwise addition of 3,6,9-trioxaundecanedioic acid dichloride (7.38 g, 28 mmol) in THF (100 mL) to 5-aminoisophthalic acid dimethyl ester (12.05 g, 57.6 mmol) and K_2CO_3 (8.31 g, 60 mmol) in THF (200 mL) gives **3** (5.1 g, 30%) as a beige solid having no accurate melting point. ^{1}H NMR (200 MHz, DMSO-d$_6$): δ 3.70 (A_2B_2, 8H, OCH_2CH_2O), 3.87 (s, 12H, OCH_3), 4.11 (s, 4H, OCH_2CO), 8.10 (t, 2H, ArH, $J = 1.5$ Hz), 8.45 (d, 4H, ArH, $J = 1.5$ Hz), 10.04 (s br, 2H, NH); IR (KBr) ν 3313 (N–H), 1727 (C=O) cm^{-1}; MS (FAB): m/z 605.1 $[M + H]^+$ (604.2 calcd for $C_{28}H_{32}N_2O_{13}$); elem. anal. for $2C_{28}H_{32}N_2O_{13} \cdot H_2O$ (1227.16): calcd C 54.81, H 5.42, N 4.57; found C 55.44, H 5.54, N 4.42.

X-Ray structure analyses

1 $\cdot 2H_2O$. Colourless prisms, monoclinic, $P2_1/c$, (C_{2h}^5) (no. 14), $a = 11.726(3)$, $b = 8.518(3)$, $c = 20.943(6)$ Å, $\beta = 91.31(2)°$, $U = 2091(2)$ Å^3, $Z = 4$, μ(Cu-Kα) = 7.81 cm^{-1}. All hydrogen atoms were localized and introduced as fixed contributions with isotropic thermal parameters set to 1.3 times those of the atoms to which they were bonded. $R = 0.034$, $Rw = 0.047$, for 2111 observed reflections ($F_0^2 > 3\sigma(F_0^2)$). The weighting scheme was defined by the Killean and Lawrence method with terms of 0.02 and 3.0.[38]

2 $\cdot H_2O$. Pale yellow prisms, monoclinic, $P2_1/c$, (C_{2h}^5) (no. 14), $a = 7.994(1)$, $b = 21.670(3)$, $c = 14.741(3)$ Å, $\beta = 101.91(1)°$, $U = 2499(1)$ Å^3, $Z = 4$, μ(Cu-Kα) = 10.88 cm^{-1}. All hydrogen atoms were located on difference Fourier syntheses maps and included as fixed contributions with isotropic thermal parameters 1.3 times those of the atoms to which they were bonded. Anisotropic temperature factors for all non-hydrogen atoms; $R = 0.049$, $Rw = 0.045$, for 3267 reflections ($F_0^2 > 3\sigma(F_0^2)$).

3 $\cdot 0.5H_2O$. Pale yellow prisms, triclinic, $P\bar{1}$, (C_i^1) (no. 2), $a = 11.318(2)$, $b = 24.444(5)$, $c = 11.069(1)$ Å, $\alpha = 96.17(1)$, $\beta = 101.24(1)$, $\gamma = 77.23(2)°$; $U = 2923(1)$ Å^3, $Z = 2$, asymmetric unit formula 2 ($C_{28}H_{32}N_2O_{13}$)$\cdot H_2O$, μ(Cu-Kα) = 9.12 cm^{-1}. The Killean and Lawrence method with terms of 0.02 and 0.4 was used to define the weights.[38] Final $R = 0.052$, $Rw = 0.059$, for 6597 reflections ($F_0^2 > 3\sigma(F_0^2)$). Anisotropic temperature factors were used for all non-hydrogen atoms. Hydrogen atom treatment: included in difference map or calculated positions ($d_{C-H} = 0.95$ Å). An ether O of one ligand showed a large thermal motion. This was treated as a disorder over two alternative positions.

CCDC reference number 440/177. See http://www.rsc.org/suppdata/nj/b0/b001127o/ for crystallographic files in .cif format.

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