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PAPER

(+)-*syn*-Benzotriborneol an enantiopure C_3-symmetric receptor for water†

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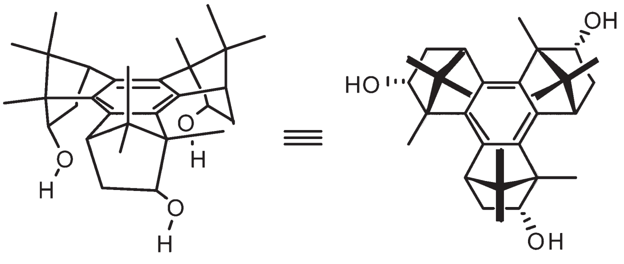
(+)-*syn*-Benzotriborneol forms stable complexes with one molecule of water. This is due to the ability of the host to form three hydrogen bonds with water, to act simultaneously as a hydrogen-bond acceptor and donor, and to a perfect geometrical match between the pair. We report experimental (X-ray and neutron diffraction, VT NMR, DSC, TGA) and stereochemical studies carried out to elucidate and quantify the molecular and thermodynamic aspects of this supramolecular complex.

Introduction

Because water is ubiquitous on Earth, biological binding events are often regulated by displacement of water molecules.[1] For this reason the interactions of water molecules with organic compounds have been the subject of extensive experimental and theoretical research.[2] These studies gave more insight into determination of the thermodynamic and structural parameters which govern water binding. Following this approach, the design and synthesis of a suitable receptor for water, combined with the use of the tools of physical organic chemistry, could furnish more experimental data on the thermodynamics involved in water recognition. This information can be readily transferred to biology and chemistry for the understanding of molecular phenomena at binding interfaces. The design of a receptor for water has attracted attention since the beginning of supramolecular chemistry. However, to the best of our knowledge, few systems have been reported to bind water in solution and, because most of these systems were not specifically designed for this purpose, their measured binding thermodynamic parameters are relatively small.[3] Indeed, the design of a host for a water molecule is not trivial. In order to stabilize a single water molecule as a guest, a host should be designed with optimal geometry to link efficiently both the hydrogen atoms and the lone pairs. Thermodynamically, the host should be structured to entrap water sufficiently well to override the entropic cost of freezing the molecule in the receptor.[4]

In the quest to design new supramolecular motifs, in recent years we have studied the synthesis[5] and recognition properties[6,7] of a new class of molecules belonging to the C_3 symmetry class.[8] In particular, we have been interested in the recognition properties of the enantiopure synthetic triterpene (+)-*syn*-benzotriborneol **1** (Scheme 1).[7] Our interest in the study of a water receptor arose from the observation that the C_3-symmetric rigid enantiopure **1** obtained from water-containing solutions differs in physical and spectroscopic properties from samples of the same compound obtained from anhydrous solutions.[9] In particular, harsh conditions were required to dry a solution of the triol **1**. This peculiar behaviour was rationalized with the help of molecular dynamic studies, which showed a high time of residence of water, around 750 ps, inside the cavity of **1** due to a perfect match between the water molecule and the host triol.[9]



1 **1**

Scheme 1 (+)-*syn*-Benzotriborneol **1**.

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† Electronic supplementary information (ESI) available: Materials and methods, Mills–Nixon effect, determination of the absolute configuration of the oxygen atom of the water included in the triol, DSC and TGA curves, binding constant calculations by titration of **1** with H_2O in $CDCl_3$, ESI-MS, neutron diffraction. CCDC reference numbers 690687 and 793277. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob06774a

Herein we report experimental and theoretical studies carried out to elucidate the nature of the complex. The peculiarity of water required the development of a multi-faceted study which involves the use of various analytical techniques to elucidate and quantify the molecular aspects of this interaction.

Results and discussion

X-ray and neutron diffraction analysis

Geometrical information on the affinity of triol **1** for water has been obtained from an X-ray diffraction analysis of crystals grown from a wet acetone solution by slow evaporation.† The asymmetric unit, in the hexagonal space group $P6_522$, is composed of one molecule of triol **1** and three water molecules, one of which (O2W) has half occupancy as it lies on a crystallographic special position. The three hydroxyl groups, located on one side of **1**, define a cavity with O···O distances in the range 4.69–4.80 Å. As expected, one water molecule (O1W) occupies the centre of the cavity. The distances between O1W and each of the three hydroxyl oxygen atoms, in the range 2.777(3)–2.892(3) Å, are appropriate for the occurrence of three hydrogen bonds. In addition, the O1 and O3 hydroxyls are at H-bonding distance from the additional co-crystallized water molecules O2W and O3W, which surround the triol and, in turn, are also H-bonded to symmetry-related water molecules and hydroxyl groups. The identification of all the H-bond donors and acceptors in such a complex network requires the unambiguous location of the H atoms on each water and hydroxyl group, a task that could not be achieved in our X-ray diffraction analysis.

Fortunately, crystals large enough for a neutron diffraction analysis were subsequently grown. The neutron diffraction data, collected at 20 K at the Institut Laue-Langevin (Grenoble), allowed the location and anisotropic refinement of all H atoms. The refined site occupation factors of the H atoms bound to oxygens for the hydroxyl groups O1–H01A and O2–H02A, and for the H atoms on O2W and O3W, being in the range 0.93(4)–1.00(5), are all very close to unity. By contrast, two positions were found for the H atom bound to O3, namely H03C and H03D, with occupation factors of 0.52(3) and 0.47(4), respectively. The O1W water molecule in the central cavity of the triol carries H1WA with nearly full occupation [0.94(5)] and a second H atom disordered over two positions, labelled as H1WC and H1WD, with occupancy factors of 0.50(4) and 0.47(3), respectively. The partial occupancy sites for the H atoms on O3 and O1W are correlated in that H03D cannot occur concomitantly with H1WC, as these two H atoms would be only 0.98 Å apart.

Table 1 H-bond parameters (Å and °) for the neutron diffraction structure of $\mathbf{1}\cdot 2.5\ H_2O$

D–H···A	Distance (D–H)	Distance (H···A)	Distance (D···A)	Angle (D–H···A)
O1–H01A···O3W	0.950(13)	1.804(12)	2.737(9)	166.7(9)
O2–H02A···O1W	0.960(13)	1.875(11)	2.824(8)	169.2(9)
O3–H03D···O1W	1.000(19)	1.891(18)	2.866(9)	163.8(15)
O3–H03C···O3#1[a]	0.98(3)	1.732(18)	2.707(15)	175.2(18)
O1W–H1WA···O1	0.981(12)	1.786(11)	2.767(9)	176.9(11)
O1W–H1WC···O3	0.91(3)	1.96(2)	2.866(9)	171.8(19)
O2W–H2WA···O2	0.956(12)	1.819(11)	2.773(7)	175.1(10)
O3W–H3WA···O3#2[a]	0.940(16)	1.929(12)	2.856(9)	168.0(10)
O3W–H3WB···O2W#3[a]	0.956(14)	1.895(12)	2.841(9)	169.5(11)

[a] Symmetry transformations used to generate equivalent atoms: #1 *y*, *x*, −*z* + 5/3; #2 *y*, *x* + 1, −*z* + 5/3; #3 *x* − 1, *y*, *z*

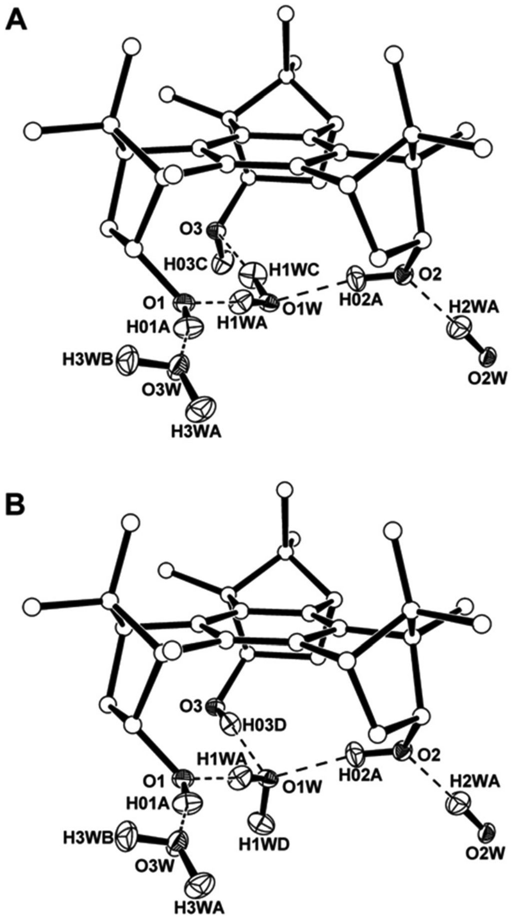

Fig. 1 Neutron diffraction structure of $\mathbf{1}\cdot 2.5\ H_2O$. The two alternative H-bonding schemes arising from the occurrence of statistically disordered H atoms on O1W and O3 are shown in **A** and **B**, respectively. H atoms on carbons are omitted for clarity. Displacement ellipsoids for O and H atoms are drawn at the 30% probability level. H-bonds are indicated by dashed lines. H atom labels ending with A or B designate fully occupied sites, those ending with C or D sites with fractional occupancy. The second H atom on O2W, the symmetry-generated equivalent of H2WA, is not shown.

Based on these observations and on the geometrical parameters reported in Table 1, the two H-bonding schemes shown in Fig. 1 can be built. In both arrangements O1W acts as the H-bonding donor to O1 and as the acceptor from O2. However, in one case O1W is also H-bonding donor to O3, whereas in the other case O1W accepts the H-bond from O3, with the H1WD atom protruding out of the cavity but not involved in any H-bond.

Symmetry-related water molecules and hydroxyl groups give rise to a network of hydrogen bonds. This network produces in the overall packing a layered structure arising from the amphiphilic character of the molecule (Fig. 2).

In the central aromatic ring the phenomenon of bond length alternation is observed. The exocyclic bond distances are in the

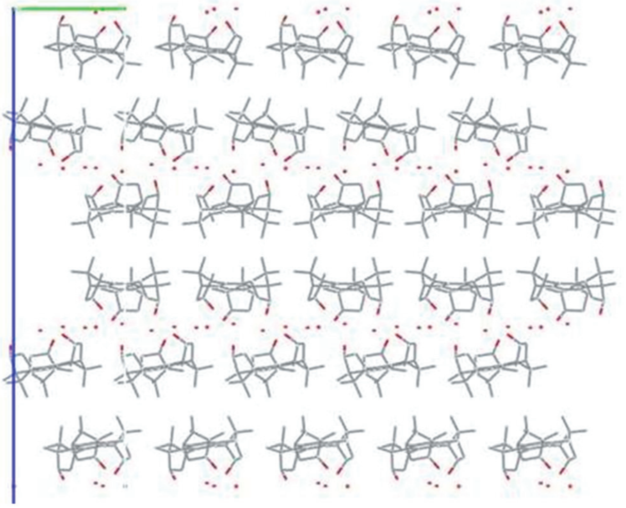

Fig. 2 Crystal packing as viewed down the *a* axis. Oxygen atoms are indicated in red.

range 1.366(4)–1.376(4) Å, while those of the endocyclic bonds are in the range 1.412(4)–1.423(4) Å, with an average difference of 0.047 Å in line with other examples.[7c]

Thermogravimetric analysis

The diffraction results give added weight to the structures found in the molecular dynamics simulations,[9] thus confirming that the receptor is perfectly designed for the complexation of water. To evaluate the thermodynamics of the association process, we studied the thermal stability of the complex by means of Differential Scanning Calorimetry (DSC) and Thermo Gravimetric Analysis (TGA) (Fig. 3 and ESI†).

The TGA experiment using crystals of **1** in the temperature range between 40 and 130 °C showed a weight loss of 8.72% (see ESI†). This value was close to the theoretical 9.28% calculated for the 2.5 water molecules in the crystal structure. The DSC plot indicates that this process required 90.2 kJ mol^{-1}, an average of 36.1 kJ mol^{-1} per water molecule. The loss of water from the crystal seemed not to be a stepwise process discriminating between inner and outer molecules, and for this reason we performed thermogravimetric analysis using triol **1** in powder form. This sample, which was prepared by evaporation at reduced pressure of a solution of triol **1** in wet acetone, displays in the TGA experiment a weight loss of 2.74% in the temperature range between 40 and 150 °C (Fig. 3a). This value was close to the theoretical 3.50% calculated for one water molecule. The DSC plot (Fig. 3b) indicates that this process required 80.9 kJ mol^{-1} per water molecule; a value in line with other water receptors which use three hydrogen bonds.[10]

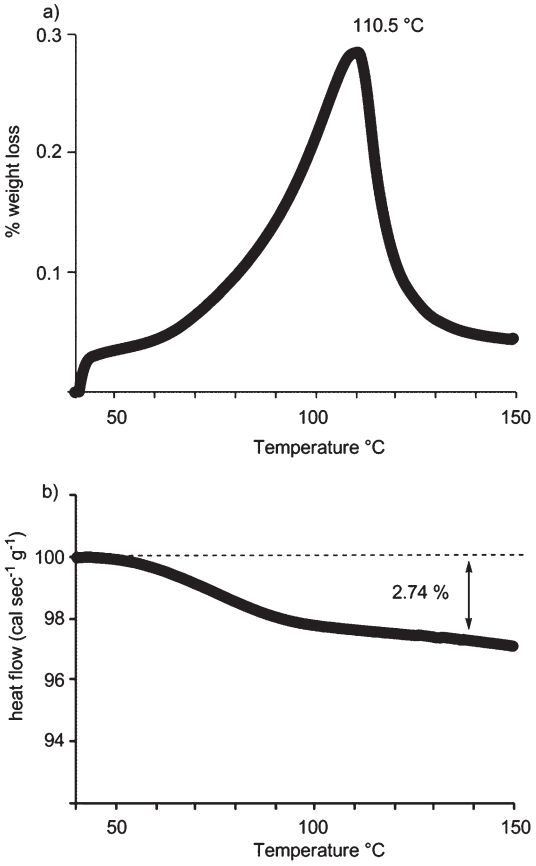

Fig. 3 (a) Thermogravimetric plot showing the weight loss of **1** on increasing temperature, (b) DSC plot exhibiting one endothermic peak for the loss of one water molecule.

In-solution analysis

The association of **1** with water was confirmed in solution by Electron Spray Ionization Mass Spectroscopy (ESI-MS†). The wet solution of **1** in acetonitrile, containing 0.1% of formic acid was injected into the analyser, which revealed a peak at m/z = 469, corresponding to the protonated **1**·water complex. While Isothermal Titration Calorimetry (ITC) and ^{1}H-NMR binding experiments did not furnish reliable values for the binding constant of water,‡ more interesting results were obtained performing in solution Variable Temperature ^{1}H-NMR experiments. A carefully dried sample of **1** was dissolved in dry $CDCl_3$ (4 Å molecular sieves), and the NMR tube was sealed to avoid any poisoning from air moisture. The ^{1}H-NMR spectrum at +25 °C exhibits a broad singlet at 1.94 ppm, due to the three hydroxyl signals of **1** merged with the residual peak of H_2O still present in the solvent (about 50% with respect to the triol **1**). On lowering the temperature this signal broadens and moves downfield, reaches coalescence at about −10 °C, and eventually splits into two almost equivalent signals at −50 °C (Fig. 4).

The energy barrier involved in the dynamic process is estimated to be 49 kJ mol^{-1} at the coalescence temperature (−10 °C).[11] The two separated signals at low temperature could be attributed to the formation of the $\mathbf{1}\cdot H_2O$ complex and to the uncomplexed **1**. Due to the presence of hydrogen bonds between the water molecule and the three OH groups of the receptor, the low field signal could be attributed to the $\mathbf{1}\cdot H_2O$ complex, and the high field one to the free receptor. In this framework, the observed barrier corresponds to the transfer of the water from the complex to a molecule of free receptor **1**, and *vice versa*. It should be noted that the two signals are both singlets. This is due to the fact that the water molecule, at this temperature, is fluxional in the cavity, thus the chemical shifts of the three

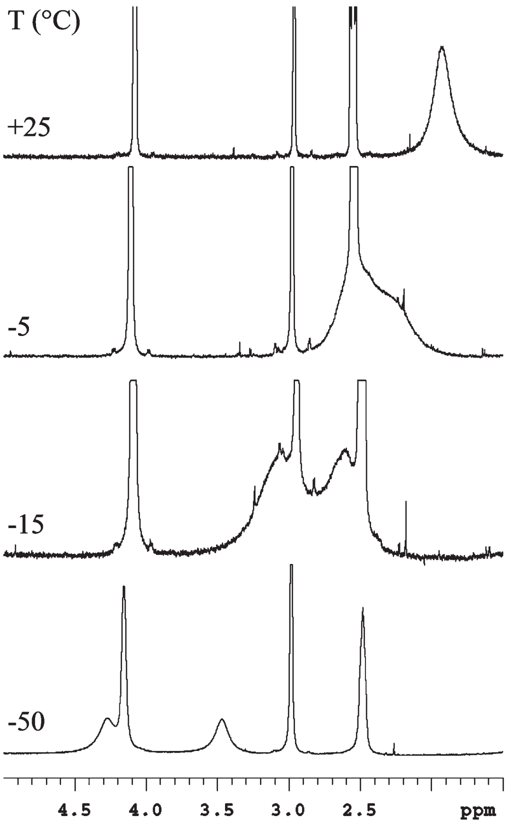

Fig. 4 VT NMR spectra in $CDCl_3$ (600 MHz) of triol **1**.

hydroxyls are averaged into a single signal. In other words, when the water is complexed within the triol **1**, its movement inside the cavity and the exchange of the hydrogens are not frozen.

Stereochemical analysis

Owing to the peculiar position of water in the centre of the three hydroxyls of triol **1**, the oxygen atom (O1W) becomes a stereogenic centre.[12] The absolute configuration must be assessed differently depending on whether water is bound to **1** with two hydrogen atoms and a lone pair (Fig. 1A), or with two lone pairs and a hydrogen atom (Fig. 1B). In the first case, the lowest priority (4), is assigned to the uncoordinated lone pair. The hydrogen-bonded lone pair (3) is the third substituent in priority.§ In order to discriminate between the two hydrogens, the hierarchical digraph, as defined by Cahn, Ingold and Prelog, has been built, and the resulting highest priority pathway is indicated in green and blue in Fig. 5. The highest priority hydrogen is characterized by a pathway (in green) leading to a hydroxyl hydrogen bound to the central water. By contrast, the blue hydrogen pathway ends with an unconnected hydroxyl hydrogen. Hence the green hydrogen is higher in priority than the blue one, assigning the absolute configuration *R* to the central oxygen atom (Fig. 5and ESI†).

In the case of water bound to **1** with two lone pairs the absolute configuration is *S*.

Attempts to determine experimentally whether the triol **1** is able to discriminate between the two binding modes failed.

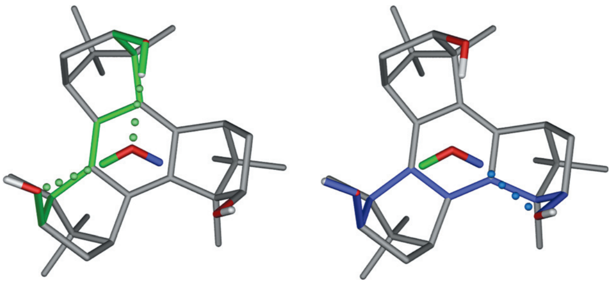

Fig. 5 Highest priority pathways for the two hydrogens of water for the structure in Fig. 1A.

While the two bonding sites are nearly equally populated in the crystals,† fast dynamic processes occurring in the NMR timescale do not allow differentiation between the two binding modes in solution.

Conclusions

In summary, an organic molecule displaying an exceptional affinity to a single water molecule is reported. The water molecule is held inside the cavity of the (+)-*syn*-benzotriborneol **1** by three hydrogen bonds as shown by complementary X-ray and neutron diffraction analysis. In the crystals, the water molecules are kept inside the cavities in two distinct, nearly equally populated, binding modes in which the host acts simultaneously as a hydrogen-bond acceptor and donor. Thermogravimetric and in-solution analyses have yielded exceptionally high values for the thermodynamics of the association process confirming a perfect geometrical match between the pair.

Experimental section

X-ray diffraction

Diffraction data for $\mathbf{1}\cdot 2.5\ H_2O$ were collected at room temperature with a Philips PW1100 diffractometer in the θ–2θ scan mode up to $2\theta = 120°$, using graphite monochromated CuKα radiation ($\lambda = 1.54178$ Å). Intensities were corrected for Lorentz and polarization effects, not for absorption. The structure was solved by use of the SIR 2002[13] program. The water molecule O2W lies on a (x, x, 5/6) special position with half occupancy. Refinement was carried out on F^2 by full-matrix block least-squares, with use of all data, by application of the SHELXL 97[14] program with all non-H atoms anisotropic, and their positional parameters and the anisotropic displacement parameters being allowed to refine in alternate cycles. The positions of H atoms on hydroxyl groups and water molecules were tentatively calculated on the basis of possible hydrogen bonding considerations, whereas the remaining H atoms were placed at idealized positions. The positional parameters of the H atoms bonded to the water molecules were refined with the O–H distances restrained to 0.82(1) Å. All other H atoms were refined as riding, with U_{iso} set equal to 1.2 (or 1.5 for the hydroxyl and the methyl groups) times the U_{eq} of the parent atom. Crystallographic data: $C_{30}H_{42}O_3\cdot 2.5\ H_2O$, $M_r = 495.7$, crystal dimensions 0.60 × 0.45 × 0.20 mm^3, hexagonal, space group $P6_522$, unit cell dimensions $a = b = 10.913(2)$ Å, $c = 81.73(3)$ Å, $\gamma = 120°$, $V = 8429(3)$ Å^3,

$Z = 12$, $\rho_{\mathrm{calc}} = 1.172$ Mg m^{-3}, $\mu = 0.626$ mm^{-1}, $\lambda = 1.54178$ Å, $T = 293(2)$ K, $2\theta_{\max} = 120°$. In total 4993 reflections were collected, of which 4196 were independent ($R_{\mathrm{int}} = 0.028$). Data/restraints/parameters: 4196/12/341. $R_1 = 0.050$ [on $F \geq 4\sigma(F)$], w$R_2 = 0.150$ (on F^2, all data); min/max residual electron density −0.18/0.19 e Å^{-3}. The choice of space group $P6_522$, rather than its enantiomorph $P6_122$, was based upon the known stereochemistry of **1**.[7]

Neutron diffraction

The neutron diffraction data were collected at 20 K on the H11 thermal neutron beamline of the Institut Laue-Langevin in Grenoble, using the D19 diffractometer with the new horizontally-curved position-sensitive detector, subtending 30 degrees vertically and 120 degrees horizontally.[15] A significant challenge was posed by the 81 Å-long *c* axis, which requires on one hand the use of a long wavelength to minimize overlap of the diffraction peaks, but on the other hand use of a short wavelength if the number of independent reflections necessary to refine the structure anisotropically is to be collected. A reasonable compromise was found by the use of neutrons at 1.46 Å, from a flat Cu220 monochromator. The vertical and horizontal divergence of the beam from the monochromator were reduced as far as reasonable with slits, to reduce overlap. Because of the very high quality and unusually large crystal, volume 42 mm^3, counting statistics were excellent for almost all Bragg peaks to the edge of the detector, and in fact a much shorter wavelength could have been used were it not for the long *c* axis. Long omega step-scans at a number of phi and chi positions allowed the unique reflections to be accessed with considerable redundancy, and between each long scan, a number of strong reflections were monitored in a shorter scan, and (as usual in neutron diffraction) there was no significant change in intensity. Absorption corrections (Gaussian integration) were necessary because of the large H content and crystal size.

The positional parameters of the non-H atoms, as obtained from the X-ray diffraction analysis, were taken as the starting structural model for the refinement, which was carried out with the SHELXL97[14] program. Coherent scattering lengths for C, H and O were as tabulated in ref. 16. By alternating cycles of least-squares refinement with difference Fourier maps, all H atoms were located. Then, anisotropic refinement of all atoms, including hydrogens, was performed by full-matrix least squares on F^2. The sum of the occupancies of H atoms disordered over two sites was restrained to the occupancy of the O atom to which they are bonded. It has to be noted that a large shift/e.s.d. (1.207) characterized the site occupation factor of the H atom on the O2 water molecule, which nonetheless remained unchanged at the value of 1.00(5) throughout the last 10 cycles of refinement. As the second largest shift/e.s.d. in the final cycle of refinement was 0.004, we are confident that the structure was refined to convergence.

Neutron diffraction crystallographic data: $C_{30}H_{42}O_3 \cdot 2.5\ H_2O$, $M_r = 495.7$, crystal dimensions $4.0 \times 4.0 \times 2.7$ mm^3, hexagonal, space group $P6_522$, unit cell dimensions $a = b = 10.8602(10)$ Å, $c = 81.052(10)$ Å, $\gamma = 120°$, $V = 8278.8\ (15)$ Å^3, $Z = 12$, $\rho_{\mathrm{calc}} = 1.191$ Mg m^{-3}, $\mu = 0.368$ mm^{-1}, $\lambda = 1.4597$ Å, $T = 20(2)$ K, $2\theta_{\max} = 123.7°$. In total 14 723 reflections were collected, of which 4878 were independent ($R_{\mathrm{int}} = 0.141$). Data/restraints/parameters: 4878/4/775. $R_1 = 0.0795$ [on $F \geq 4\sigma(F)$], w$R_2 = 0.2031$ (on F^2, all data); min/max residual in the final difference Fourier map −0.95/0.87 fm Å^{-3}.

CCDC 690687 and 793277 contain the supplementary (X-ray and neutron, respectively) crystallographic data for this paper.

Acknowledgements

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Notes and references

‡ In order to evaluate the strength of this interaction in solution, the binding constant of triol **1** with water was measured by means of ITC and ^{1}H-NMR complexation experiments in a solvent of low polarity (deuterochloroform).[17] While ITC failed to furnish any appreciable thermal information in the range of concentration studied, the results of ^{1}H-NMR using water and methanol as guests furnished values difficult to reproduce. This is due to the strong dependence of the measurement on the initial concentration of water.

§ The geometry of the crystal structure shows that the uncoordinated lone pair is directed outside the cavity, as justified by the electrostatic repulsion with the π system of the aromatic ring.

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