(+)-*syn*-Benzotriborneol an Enantiopure C_3-Symmetric Receptor for Water

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Content of Supporting Information

(10 pages)

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Experimental

Materials. Triol **1** was prepared following procedures previously reported in: a) F. Fabris, L. Bellotto and O. De Lucchi *Tetrahedron Lett.* 2003, **44**, 1211-1213; b) F. Fabris, L. Pellizzaro, C. Zonta and O. De Lucchi *Eur. J. Org. Chem.* 2007, 283-291.
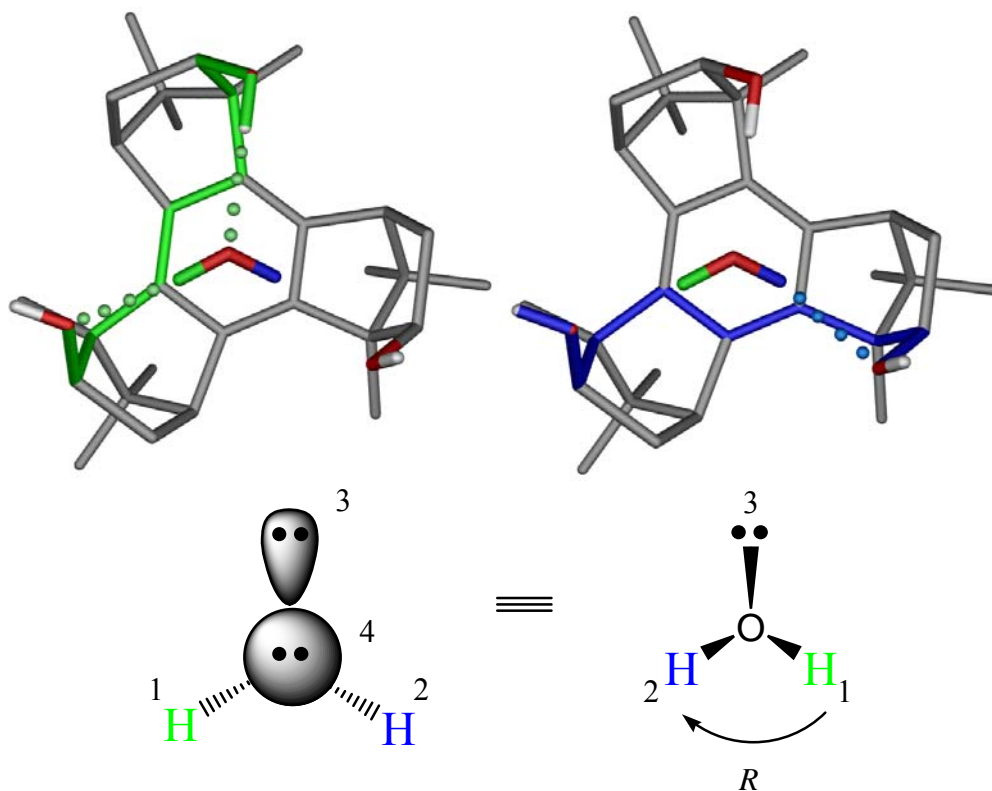
Simultaneous Thermogravimetry and Differential Scanning Calorimetry. The TG/DSC were carried out with a Netzsch STA 409/C employing a nitrogen atmosphere and a heating rate of 15 °C min^{-1} in the temperature range 25–330 °C.

Nuclear Magnetic Resonance Experiments.

^{1}H NMR titration was recorded at 298 K with a Bruker Avance, operating at 300 MHz. Variable Temperature experiments were performed on a Inova 600 instrument. The δ values in ppm are relative to TMS.

Electron Spray Experiments. Experiments were carried out using an Agilent HPLC with ESI Ion Trap.
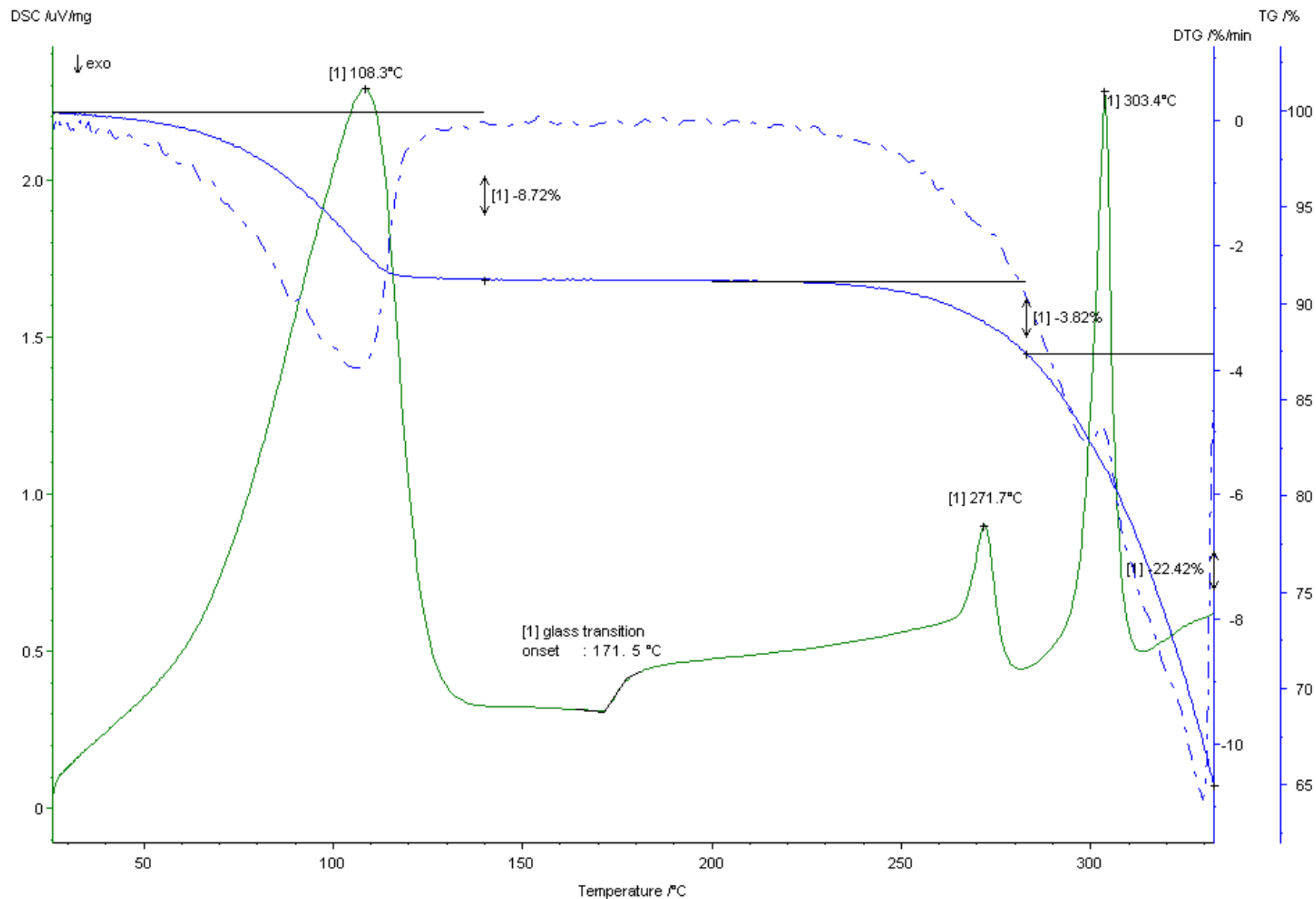
Determination of the Absolute Configuration of the Oxygen Atom of the Water Included in the (+)-syn-Benzotriborneol 1.[1]

[1] E. L. Eliel, S. H. Wilen. "Stereochemistry of Organic Compounds", Wiley: New York, **1994**, pag. 103-112.
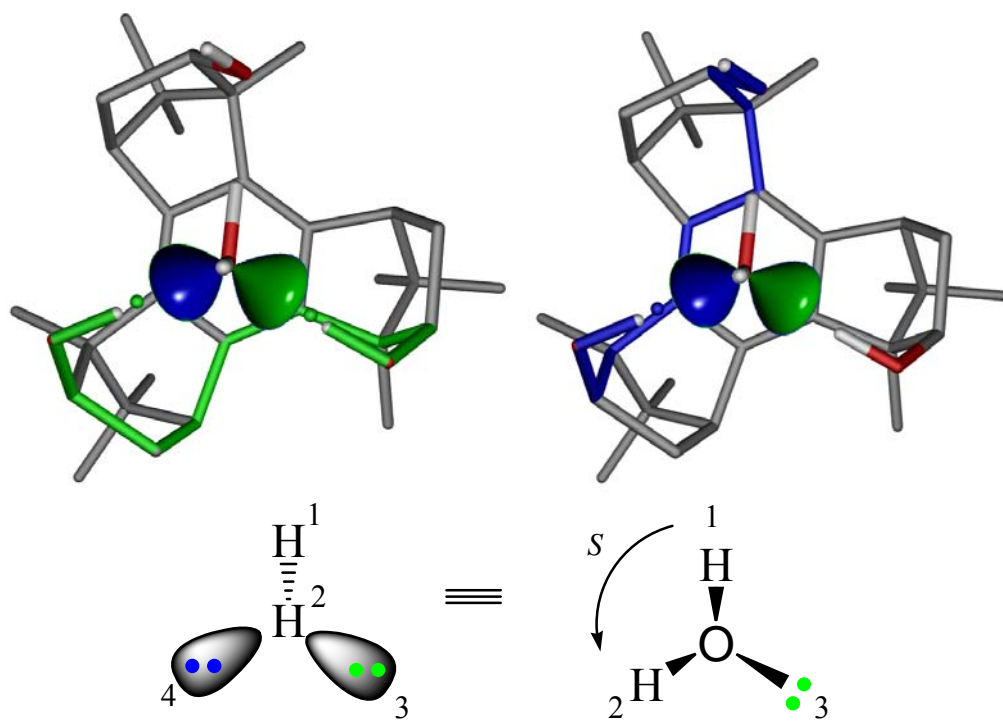
Simultaneous Thermogravimetry and Differential Scanning Calorimetry of Crushed Crystals

DSC / TGA Calculations

Average molar enthalpy for the release of 2.5 H_2O from triol **1**·2.5H_2O ($C_{30}H_{47}O_{5.5}$) = 495.69 Da:

182 Jg^{-1} = 90.22 kJ mol^{-1}

Average molar enthalpy for the release of 1 H_2O:

90.22 $kJmol^{-1}$/2.5 = 36.1 $kJmol^{-1}$

Figure 3

Average molar enthalpy for the release of 1 H_2O from triol **1**·H_2O ($C_{30}H_{44}O_4$) = 468.66 Da:

172.6 Jg^{-1} = 80.89 kJ mol^{-1} = average molar enthalpy for the release of H_2O:

Triol **1**·2.5H_2O ($C_{30}H_{47}O_{5.5}$) = 495.69 Da

2.5 H_2O ($H_5O_{2.5}$) = 45.04 Da

1.5 H_2O ($H_3O_{1.5}$) = 27.02 Da

1 H_2O (H_2O) = 18.02 Da

Theoretical first loss of external water (1.5 eq.) = 27.02/495.69*100 = 5.45%

Theoretical second loss of internal water (1.0 eq.) = 18.02/495.69*100 = 3.64%

Theoretical second loss of whole water (2.5 eq.) = 45.04/495.69*100 = 9.09% (3% error)

ESI-MS Experiment: (+)-*syn*-Benzotriborneol 1/H$_2$O in CH$_3$CN (0.1% HCOOH)

Display Report - Selected Window All Analyses

Operator: Administrator   **Instrument:** LC-MSD-Trap-SL   **Print Date:** 03/01/2010 12:06:37 PM

+MS, 0.4-1.8min #(24-126)

Intens.
x10^7

468.9

472.8

470.8

478.0

488.9

499.8

m/z

MSD Trap Report v5.2 (A4-Opt2)   Page 1 of 1   Agilent Technologies
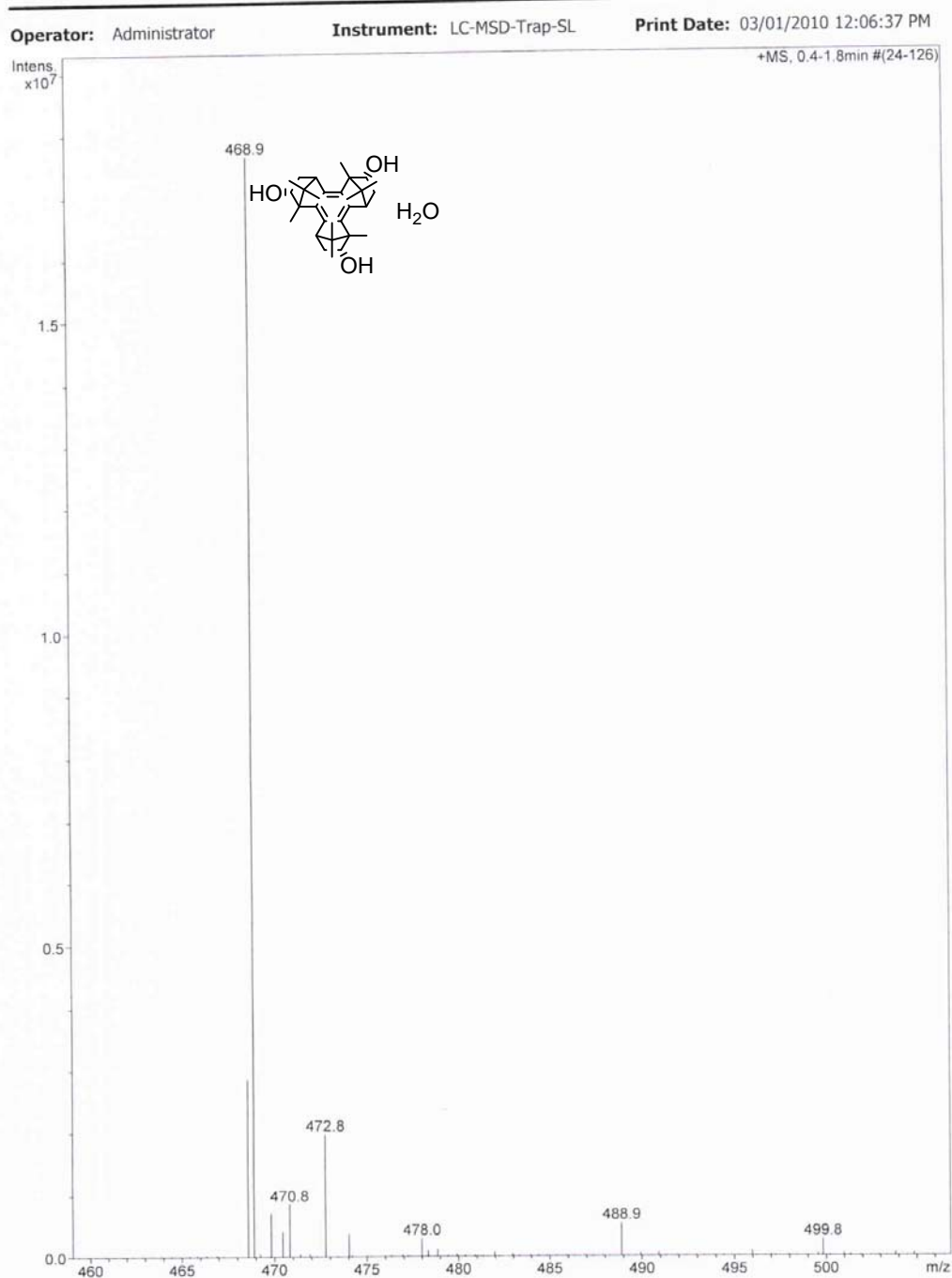
Neutron diffraction: P6$_5$22 vs P6$_5$ space group

Both the X-ray and the neutron diffraction structures have been refined in space group P6$_5$22. Only the latter technique allows an unambiguous location of the H-atoms. It has to be noted that in space group P6$_5$22 the half-occupied HO3D atom is at 0.84 Å from its own (y, x, 5/3-z) symmetry equivalent. In principle, the system would be more rigorously described in space group P6$_5$ with two ligands and five, fully occupied, water molecules as the asymmetric unit. Incidentally, space groups P6$_5$22 and P6$_5$ share the same (000l: $l = 6n$) systematic absence condition. The two complexes in P6$_5$ would be related by the non-crystallographic symmetry (y, x, 5/3-z). As for the population parameters of the H-atoms on hydroxyls and water molecules in the two complexes, the two limiting possibilities (*i* and *ii*) outlined below can be envisaged.

(i)   The H-bonding scheme depicted in Fig. 1A would occur in one complex with full occupancy for the H-atoms, concomitantly with the H-bonding scheme depicted in Fig. 1B in the other complex, again with full occupancy for the H-atoms. In this way, the O3 hydroxyl of the first complex would act as the H-bond donor to O3 of the second complex which, in turn would be H-bond donor to the water molecule in the central cavity.

(ii)   In both complexes the H-atoms would be split on two sites with half occupancy, as basically found for the single complex in the higher symmetry structure. However, their population would be correlated in that the H-bonding scheme depicted in Fig. 1A of the paper would occur in one complex concomitantly with the H-bonding scheme depicted in Fig. 1B in the other complex, and vice versa. In this way, the O3 hydroxyl would act alternatively as the H-bond donor and acceptor to/from its pseudo-symmetric equivalent in the second complex, without the occurrence of short H···H intermolecular contacts.

The dataset provided by the neutron diffraction experiment is not large enough (in terms of number of independent reflections) to carry out a fully anisotropic refinement of the double complex in space group P6$_5$, as the number of parameters to be refined would be about 1500. However, the likely population parameters of the split H-atoms have been deduced by a full-matrix least-squares refinement with all atoms isotropic (679 parameters against 5671 independent data). In order to minimize the bias exerted by the isotropic displacement parameters on the population parameters (as the two items are to some extent correlated), for all of the split H-atoms a common isotropic displacement parameter was set up as a free variable, which refined to the value of 0.049(1) Å^2, whereas the population parameters of the split H-atoms were allowed to freely refine, with the only restraint that for each pair of split H-atoms bonded to the same O-atom the sum of the population parameters should be 1.0. The pairs of population parameters of the split H-atoms converged to

values ranging from 0.61(3) / 0.39(3) to 0.44(3) / 0.56(3). By taking into account the correlation of the sites according to the two H-bonding schemes outlined above in (ii), the averaged populations of the split H-atoms would be 0.52 for the occurrence of the H-bonding scheme of Fig. 1A in the first complex and the H-bonding scheme of Fig. 1B in the second complex, and 0.48 for the occurrence of the H-bonding scheme of Fig. 1B in the first complex and the H-bonding scheme of Fig. 1A in the second complex.

On these bases, the limiting possibility described in (i) can be ruled out, and each of the two independent complexes in space group $P6_5$ can be considered basically equivalent, in terms of population parameters of the split H-atoms, to the single complex in space group $P6_522$ as it has been described in the article.

NMR and ITC binding experiments

All the sample solution were prepared in a MBraun glove-box. Concentration of water in the sample have been measured using dichloroethane as internal standard in the stock solution.

NMR binding experiments:

A 2.5 ml sample of dried host of known concentration (10^{-3} – 10^{-4} M) was prepared in the desired anhydrous deuterated solvent. 0.5 ml of this solution was added in the NMR tube, and a ^{1}H NMR spectrum was recorded. 5 µl of water were then added in the remaining 2.0 ml of host concentration. This procedure allows to keep during the titration the concentration of the host constant. Aliquots of this solution were added successively to the NMR tube containing the host solution. Concentration of water in the NMR tube after each addition were calculated using integrals. The resulting signals (δ1, δ2, δ3) were fitted to a 1:1 binding model to yield the association constant, the bound chemical shifts in the HG complex.

Binding values are difficult to interpret. This is due for the following reasons:

- high affinity of the host for water: small variations in the water content in the host at the beginning of the titration have dramatic influences in the final binding values,
- low solubility of the triol in anhydrous organic solvents. This is due to the formation of aggregates (dimers between the OHs),
- observed chemical shifts changes are small due to the lack of functional groups owning large magnetical anisotropy.

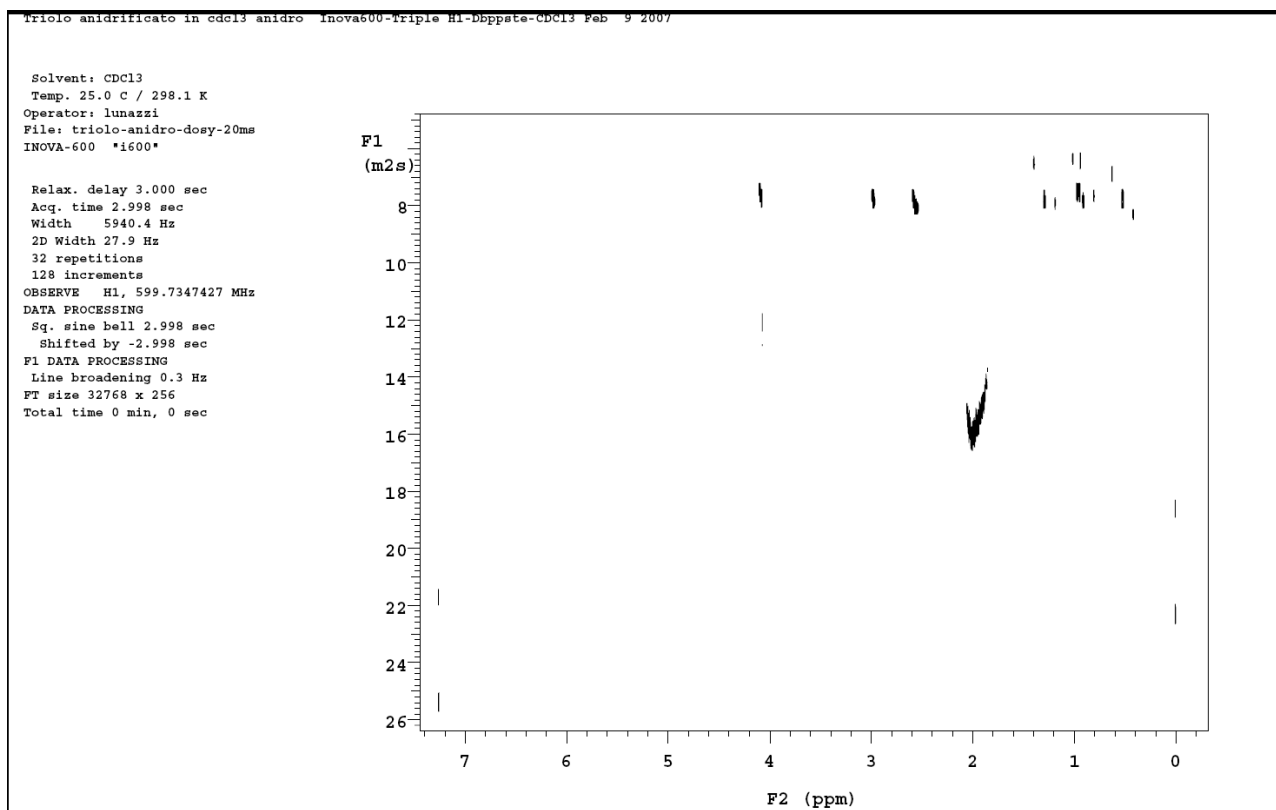Table S1. Binding constant and proton labelling scheme.
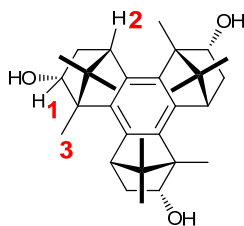
Exp	[1] mM	Guest	[Guest] mM	Solvent	K^a M^{-1}	$\delta 1^b$ ppm	$\Delta\delta 1^c$ ppm	$\Delta\delta 2^c$ ppm	$\Delta\delta 3^c$ ppm
1	0.8	H_2O	10	$CDCl_3$	nd	4.116	nd	nd	nd
2	3.0	H_2O	60	$CDCl_3$	$7\ 10^5$	4.067	0.134	0.049	0.047
3	5.0	MeOH	62	$CDCl_3$	20	4.066	0.08	0.037	0.037
4	5.0	MeOH	62	$CDCl_3$	48	4.074	0.084	0.042	0.042
5	4.8	Et_2O	48	$CDCl_3$	nd	4.053	nd	nd	nd
6	4.7	Et_2O	48	$CDCl_3$	nd	4.064	nd	nd	nd
7	2.0	H_2O	56	CD_3CN	nd	4.052	nd	nd	nd

nd Not determined due to small variations of chemical shifts or/and small binding constants. a) Experimental values have been fitted to a 1:1 binding isotherm. b) ppm of signal 1 at the beginning of titration: these are indicative of the presence of water in the solvent. c) Induced changes in chemical shifts arising from complexation.

DOSY experiments

Performed DOSY experiment does not allow for a distinction among the processes related to hydrogen exchange and binding.

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Triolo anidrificato in cdcl3 anidro  Inova600-Triple H1-Dbppste-CDCl3 Feb  9 2007

  Solvent: CDCl3
  Temp. 25.0 C / 298.1 K
  Operator: lunazzi
  File: triolo-anidro-dosy-20ms
  INOVA-600  "i600"

  Relax. delay 3.000 sec
  Acq. time 2.998 sec
  Width    5940.4 Hz
  2D Width 27.9 Hz
  32 repetitions
  128 increments
  OBSERVE   H1, 599.7347427 MHz
  DATA PROCESSING
  Sq. sine bell 2.998 sec
   Shifted by -2.998 sec
  F1 DATA PROCESSING
   Line broadening 0.3 Hz
  FT size 32768 x 256
  Total time 0 min, 0 sec
```

ITC binding experiments:

Sample have been prepared similarly to the NMR studies in the $10^{-4} - 10^{-5}$ molar concentration. However, thermal information were not sufficient to distinguish among the process due to water dilution or complexation with triol.

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