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ORIGINAL PAPER

Synthesis, NMR Studies and Crystal Structure of Cryptand 4,7,10,16,21-Pentaoxa-1,13-diazabicyclo[11.5.5]tricosane, $[H(3.1.1)\cdot(H_2O)_3]Cl$

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Abstract The cryptand 4,7,10,16,21-pentaoxa-1,13-diazabicyclo[11.5.5]tricosane (3.1.1, **I**) has been synthesized, the crystal structure of the triaquo-hydrochloride salt has been determined by single crystal X-ray crystallography and the ^{1}H- and ^{13}C-NMR chemical shifts have been assigned for the protonated ligand. $[(C_{16}H_{33}N_2O_5)\cdot(H_2O)_3]Cl$, (**I**), is triclinic with space group $P\bar{1}$ and cell constants: $a = 9.957(3)$ Å, $b = 10.557(5)$ Å, $c = 11.324(3)$ Å, $\alpha = 95.917(8)°$, $\beta = 105.574(8)°$, $\gamma = 107.506(9)°$, $V = 1071.4(3)$ Å^3 and $Z = 2$. In the solid state the cryptand is monoprotonated and holds a water molecule near the central cavity using the hydrogen bonds N13–H13 to O1S, O1S–H1S2 to N1 and O1S–H1S1 to ether oxygen atom O7. Pairs of cryptand molecules are linked by a hydrogen bond network, (O21···H2S2–O2S–H2S1···Cl1)$_2$(μ-H3S1–O3S–H3S2)$_2$, that interacts with an ether oxygen (O21, O21A) in each ligand molecule.

Keywords Cryptand · Crystal structure · NMR spectra · Hydrogen bonds · Hydrate

Introduction

Macrobicyclic ligands, or cryptands, have been studied extensively since their introduction by Lehn and co-workers [1], in part, because they form stable complexes with alkali- and alkaline-earth cations as well as some heavy metal ions [2]. The original family of cryptands, shown in Fig. 1, consisted of ligands with three polyethoxy(ethyl) strands joined at nitrogen bridgehead atoms and were given trivial names indicating the number of ether oxygen atoms in each bridge (e.g., 2.1.1 has $a = 2$, $b = c = 1$) [3]. All members of the family of cryptands with a, b, $c = 1$–3 have been reported [4–7] except for 3.1.1 (**I**), shown in Scheme 1, although the bicyclic diamide precursor (**V**) [8] and analogous compounds with *N*-methyl donor atoms instead of oxygen in the 12-membered ring are known [9, 10]. Cryptand 3.1.1 is a constitutional isomer of 2.2.1 with the same donor atom set (N_2O_5), that differs in the size of the macrocyclic rings that comprise each ligand, i.e., 12/18/18 for 3.1.1 compared to 15/15/18 for 2.2.1. Cryptand 3.1.1 should be of interest because a previous comparison of the constitutional isomers 2.2.2 (18/18/18) and 3.2.1 (21/18/15) showed differences in the complexation selectivity among alkali- and alkaline-earth cations (7). The present study reports the synthesis of the title compound, the X-ray crystal structure of the monoprotonated hydrate of the hydrochloride salt and the assignment of the ^{1}H- and ^{13}C-NMR spectra of the monoprotonated cryptand.

Experimental

General Procedures and Materials

All reagents in this study were used as received from commercial suppliers. Solvents were distilled and stored over molecular sieves. ^{1}H NMR and ^{13}C NMR spectra were obtained at room temperature on a Varian Mercury VX-300 MHz spectrometer. Assignments were made using ^{1}H and ^{13}C 1-D experiments and COSY, HSQC and

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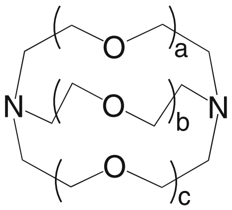
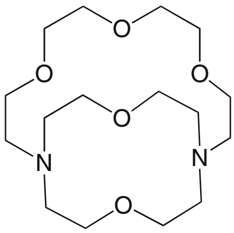


Fig. 1 Schematic structure of diazapolyoxa-cryptands



Scheme 1 Structure of 4,7,10,16,21-pentaoxa-1,13-diazabicyclo[11.5.5]-tricosane (cryptand 3.1.1, **I**)

HMBC 2-D experiments. Chemical shifts are referenced to the residual proton ($\delta = 7.26$ ppm) and ^{13}C ($\delta = 77.23$ ppm) signals of the solvent, $CDCl_3$ [11]. ESI mass spectra were recorded using a Micromass Q-Tof instrument in the positive ion mode.

*Synthesis of 4,7,10,16,21-Pentaoxa-1, 13-diazabicyclo[11.5.5]tricosane), Cryptand 3.1.1(**I**)*

The synthesis of **I** was performed under high-dilution conditions according to the general procedure described by Lehn et al. [4], as shown in Scheme 2. 4.951 g (25.6 mmol) of **II** and 4.251 g (25.7 mmol) of diglycolyl chloride, each dissolved in 300 mL of toluene, were added synchronously from separate dropping funnels to 900 mL of toluene containing 5.795 g (57.3 mmol) of $(C_2H_5)_3N$ in a 5 L Morton round-bottomed flask over a period of 7 h. The reaction mixture was filtered, and after ~2/3 of the solvent was removed, the diamide (**III**) crystallized from solution (4.353 g, 58.6%). 1.38 g (4.75 mmol) of the recovered solid was dissolved in 55 mL of THF, the solution cooled in an ice bath, and 1.4 g (36.9 mmol) of $LiAlH_4$ was added carefully. The solution was then heated at reflux for 7 h. The product (ESI–MS; m/z = 263, (M + H) was purified by extraction from water (pH ~ 10, Et_4NOH) into $CHCl_3$ (3 × 100 mL) yielding 1.122 g (90.2%) of cyclic diamine **IV**. The high-dilution condensation reaction was repeated using 0.710 g (2.71 mmol) of **IV** and 0.504 g (2.95 mmol) of diglycolyl chloride, each dissolved in 300 mL of toluene, added synchronously to 400 mL of toluene containing 0.726 g (7.17 mmol) of Et_3N over a period of 8.0 h. The macrobicyclic diamide (**V**) was purified by column chromatography on alumina using 5–7% MeOH in $CHCl_3$ as the eluent to give 0.46 g (oil, 47%), ESI–MS, 383.2 (M + Na). 20 mL of 1.0 M $BH_3{\cdot}THF$ (20 mmol) was placed in a flask cooled in an ice bath; then 0.40 g (1.11 mmol) of diamide (**V**), dissolved in 25 mL of THF, was added slowly. The mixture was refluxed for 2 h then stirred at room temperature for 36 h. The flask was cooled in an ice bath, excess BH_3 was quenched using water, and the solvent was removed. Then, in the same flask, 10 mL of 6 N HCl was added and was heated at 60 °C for 2 h. The acidic solution was removed, water added and the product was obtained by adjusting the pH to ~10 with $(C_2H_5)_4NOH$ and extraction into $CHCl_3$ (3 × 100 mL). During the initial stage of solvent removal a white precipitate formed (0.092 g) that was removed by filtration. Removal of the remaining solvent gave an oil (0.250 g). The ESI–MS of the solid and oil fractions of the product showed the same peaks, 333.2 (M + H), 355.2 (M + Na), 167.2 (M + 2H), and were combined. The ^{1}H- and ^{13}C-NMR chemical shifts and peak assignments for (**I**) are given in Table 1.

*X-Ray Structure Determination of (4,7,10,16,21-Pentaoxa-1,13-diazabicyclo-[11.5.5]tri-cosane) (**I**)*

Crystals suitable for X-ray crystallography were obtained by adding hexanes to a solution of **I** dissolved in a minimal volume of $CHCl_3$ and placing this solution in a freezer for 1 week. The molecular structure and atom-numbering scheme of the title compound (**I**) are illustrated in Fig. 2. Intensity data for this compound were collected using a diffractometer with a Bruker APEX ccd area detector [12, 13] and graphite-monochromated Mo Kα radiation ($\lambda = 0.71073$ Å). Cell parameters were determined from a non-linear least-squares fit of 5584 peaks in the range $2.26 < \theta < 28.24°$. A total of 10996 data were measured in the range $1.91 < \theta < 26.00°$ using ω oscillation frames. The data were corrected for absorption by the semi-empirical method [14] and were merged to form a set of 4,174 independent data with $R_{\text{int}} = 0.0404$ and a coverage of 99.5%. The triclinic space group $P\bar{1}$ was determined by statistical tests and verified by subsequent refinement. The structure was solved by direct methods and refined by full-matrix least-squares methods on F^2 [15, 16]. The positions of hydrogen atoms bonded to carbon were initially determined by geometry and were refined by a riding model. Hydrogen atoms bonded to N13 and the water oxygen atoms (O1S, O2S, O3S) were located by a difference Fourier synthesis and refined independently. Non-hydrogen atoms were refined with anisotropic displacement parameters. Hydrogen atom displacement parameters were set to 1.2 times the displacement parameters of the bonded atoms. Parameters were refined, with restraints on the O–H bond distances for H(1S2) and H(3S2), to give $wR(F^2) = 0.1367$ and $S = 1.038$ for weights of $w = 1/[\sigma^2\ (F^2) + (0.0700\ P)^2 + 0.5000\ P]$, where $P = [F_o^2 + 2F_c^2]/3$. The final $R(F)$ was 0.0576 for the 3349 observed, $[F > 4\sigma(F)]$, data. Crystal data and refinement details are presented in Table 2.

Scheme 2 Synthesis of cryptand 3.1.1 (**I**)

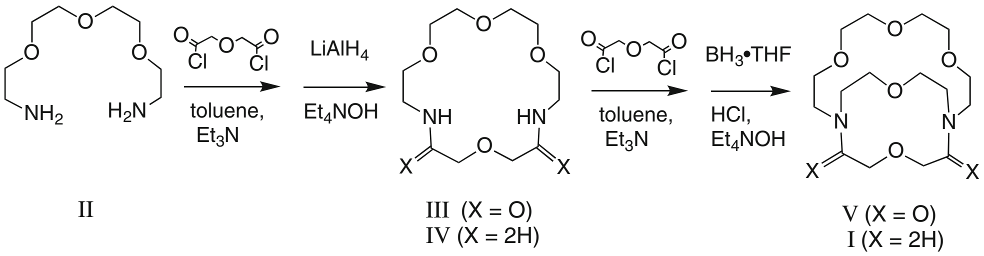


Table 1 ^{1}H- and ^{13}C-NMR chemical shifts δ(ppm) and results of COSY, HSQC and HMBC experiments

C[a]	^{1}H δ(ppm)[b]	COSY (H–H)	^{13}C δ(ppm)	HSQC (C–H)	HMBC (C(−)$_n$H)
2(12)	3.20 4H, t	3.20–3.86	61.6	61.6–3.20	61.6–3.30
3(11)	3.86 4H, m	–	66.8	66.8–3.86	66.8–3.20,3.62
5(9)	3.62 4H, s	–	69.8	69.8–3.62	69.8–3.62
6(8)	3.62 4H, s	–	70.4	70.4–3.62	70.4-3.62
14(18,19,23)	3.30 8H, m	3.30–3.78,4.04	57.4	57.4–3.30	57.4–3.20,4.02
15(17,20,22)	3.78 4H, dt	3.78–4.02	66.3	66.3–3.78	66.3–3.30
15(17,20,22)	4.02 4H, m	–	66.3	66.3–4.02	" "

s singlet, *t* triplet, *dt* doublet of triplets, *m* multiplet

[a] Carbon number from Fig. 2

[b] Chemical shift, number of equivalent protons, resonance multiplicity

Results and Discussion

The synthesis followed existing literature procedures; however, the isolation of the monohydrochloride product probably resulted from incomplete neutralization of $H_2(3.1.1)^{2+}$ that was formed during the hydrolysis of the bis-borane adduct with aqueous HCl. The first protonation constant for the related cryptand, 2.1.1, is between 10.64 and 11.32 [17]. Therefore, if **I** has similar protonation constants, at pH ~ 10 most of the cryptand is likely to be present as $[H(3.1.1)^{+}]$, Cl^{-} during the extraction step.

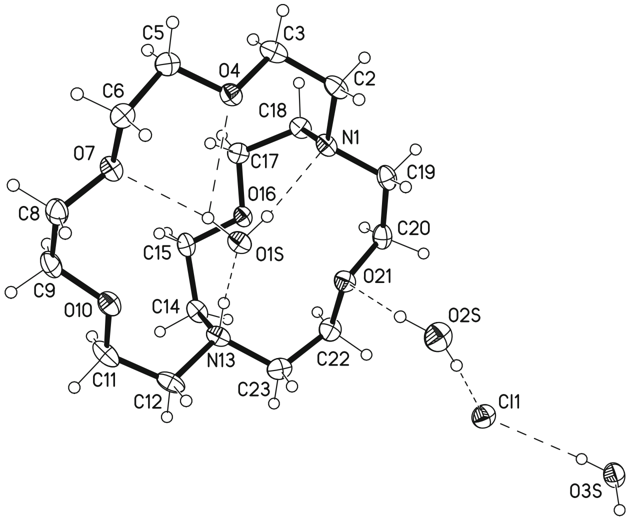


Fig. 2 Atom labeling scheme for 3.1.1. Displacement ellipsoids are shown at the 50% probability level

The ^{13}C-NMR spectra in $CDCl_3$ showed only six peaks, which is consistent with the approximate C_{2v} symmetry expected for 3.1.1 in solution. The proton spectrum also has the appropriate number of peaks, but is complicated is several ways. Considering the chemical shifts, $\delta_{3.1.1,\mathrm{ave}} = 3.2_5$ for N*CH*$_2$, which is significantly downfield compared to $\delta_{\mathrm{ave}} \sim 2.7$ for the analogous protons in 2.1.1, 2.2.1, 2.2.2 and 3.2.2 [4]. Likewise, for NCH_2*CH*$_2$O $\delta_{3.1.1,\mathrm{ave}} = 3.8_9$ compared to ~3.6 for the analogous protons in other cryptands. In the case of the singlet for *OCH*$_2$*CH*$_2$*O*, $\delta_{3.1.1} = 3.6_2$ is close to the value of ~3.7 for the other cryptands [4]. The downfield shifts for 3.1.1 decrease as the protons become further removed from the nitrogen atom. However, if one compares the $\delta_{3.1.1}$ values (3.2_5, 3.8_9, 3.6_2) to the corresponding values of δ_{ave} (3.1_7, 3.8_8, 3.5_9) for the bis(*N*-BH_3) adducts of cryptands 2.1.1, 2.2.1, 2.2.2 and 3.2.2 [4] the downfield shifts compared with 3.1.1 almost disappear. In view of the electron withdrawing properties of the BH_3 groups for the adjacent nitrogen [18], the values and pattern of $\delta_{3.1.1}$ values are consistent with the presence of a proton on one of the nitrogen atoms. The splitting multiplicities in 3.1.1 are also of interest. In the longer bridge the singlet (O*CH*$_2$*CH*$_2$O) and pair of triplets (N*CH*$_2$*CH*$_2$O) are the same as found for the other cryptands and the corresponding bis-N·BH_3 adducts [4], indicating that axial-equatorial interconversion for these ethylene linkages is fast on the NMR time scale. However, the

Table 2 Crystal data and structure refinement for cryptand 3.1.1 (**I**)

CCDC deposit no.	832360
Color/shape	Colorless plate, 0.40 × 0.18 × 0.03 mm,
Empirical formula	$C_{16}H_{39}ClN_2O_8$
Formula weight	422.94
Temperature (K)	100(2)
Crystal system, space group	Triclinic, $P\bar{1}$
Unit cell dimensions	
a (Å)	9.957(3)
b (Å)	10.557(3)
c (Å)	11.324(3)
α (°)	95.917(8)
β (°)	105.574(8)
γ (°)	107.506(9)
Volume (Å^3)	1071.4(5)
Z, density, calculated (g/cm^3)	2, 1.311
Absorption coefficient (mm^{-1})	0.221
θ range for data collection, deg	1.91–26.00
Data measured	10996
Independent/observed data	4174 [$R_{int} = 0.0404$]/3349 [$I > 2\sigma(I)$]
Data/restraints/parameters	4174/2/265
Goodness-of-fit on F^2	1.038
$wR2$ (all data)	0.1367
$R1$(observed data)	0.0576
Largest diff. peak and hole (e/Å^3)	0.538 and −0.230

$wR2 = \{\Sigma[w(F_o^2 - F_c^2)^2]/\Sigma[w(F_o^2)^2]\}^{1/2}$

$R1 = \Sigma||F_o|-|F_c||/\Sigma|F_o|$

Table 3 Hydrogen bond lengths (Å) and angles (°) for (**I**)

D–H···A	d(D–H)	d(H···A)	d(D···A)	<(DHA)
N(13)–H(13)···O(1S)	0.91(3)	1.84(3)	2.750(3)	171(3)
O(1S)–H(1S1)···O(7)	0.83(3)	2.19(3)	3.016(3)	169(3)
O(1S)–H(1S1)···O(4)	0.83(3)	2.55(3)	3.041(2)	119(2)
O(1S)–H(1S2)···N(1)	0.851(10)	2.180(11)	3.027(3)	174(3)
O(2S)–H(2S1)···Cl(1)	1.00(3)	2.18(3)	3.174(2)	171(3)
O(2S)–H(2S2)···O(21)	0.93(3)	2.05(3)	2.906(3)	153(3)
O(3S)–H(3S1)···Cl(1)	0.83(3)	2.37(3)	3.202(2)	175(3)
O(3S)–H(3S2)···Cl(1)#1	0.855(10)	2.352(11)	3.200(2)	172(3)

Symmetry transformations used to generate equivalent atoms: #1 $-x + 2, -y, -z + 2$

increased splitting multiplicity for the NCH_2CH_2O segments in the 12-membered ring shows that these conformational changes are restricted, at least at room temperature. These findings are consistent with those expected for a protonated, possibly hydrated, form of 3.1.1.

The structure of **I**, shown in Fig. 2, reveals that the ligand crystallizes as the tris-aquo-monohydrochoride complex. One water molecule is present near the center of the 18-membered ring defined by the heteroatoms N1,O4,O7,O10,N13 and O21 on the side of the ring opposite to the short bridging segment containing O16. The oxygen atom of the water is 0.720(4) Å distant from this plane and is held in place by three strong hydrogen bonds (see Table 3) involving N1, N13 and O7. The proton of N13 (H13) forms a hydrogen bond to the oxygen of the water molecule while one of the hydrogen atoms on water (H1S2) forms an H-bond with N1. The other hydrogen on water (H1S1) forms a strong hydrogen bond to ether oxygen O7. In addition, H1S1, forms a weak hydrogen bond with O4, with an O1S–H1S1···O4 angle of 119(2)°. Although structures of a number of protonated cryptands are known, only a few of these involve the monoprotonated ligands [19, 20]. In each case a water molecule is held in an 18-membered macrocyclic ring of the ligand cavity by three H-bonds involving alternating heteroatoms; one with N–H and two from H(water) to ether O, similar to the situation found with **I**. One 18-membered ring of 3.1.1 forms an approximate plane defined by heteroatoms N1,O4,O7,O10,N13,O21 (mean dev. = 0.2837 Å). This plane has a dihedral angle of 90.2°(3) with the plane defined by N1, O16, and N13 of the other bridging segment. The torsion angle sequence for the X–C–C–Y segments (X, Y = O, N) around this 18-membered ring is $(aga)_6$, where g and a indicate gauche and antiperiplanar torsion angles, respectively [21, 22]. This conformation has alternating heteroatoms on opposite sides of the heteroatom plane (i.e., N1,N13,O7 and O4,O10,O21). This conformation, with approximate D_{3d} symmetry, is also found for 18-membered crown and diaza-crown ether complexes with several metal ions [23]. The similar symmetry of the planar 18-membered ring in 3.1.1 provides alternating heteroatoms (NH, N, O) suitably placed for H-bond interactions with water and complementarity of H-bond sites between the monoprotonated cryptand, $H(3.1.1)^+$, and water. Two molecules of 3.1.1 are linked together via an H-bond network utilizing O21···H(OS2)H···Cl^-···H(OS3)H subunits, as shown in Fig. 3. A similar $(Cl^-)_2(HOH)_4$ bridged network has been found with $H_2(2.1.1)^{2+}$ [24]; however, in that case there was no interaction of the network with the cryptand O or N atoms.

Supporting Information Available

X-ray crystallographic files, in CIF format, for the structure determination of (I) (CCDC 832360) have been deposited with the Cambridge Crystallographic Data Center, CCDC: 26091. Copies of this information may be obtained free of

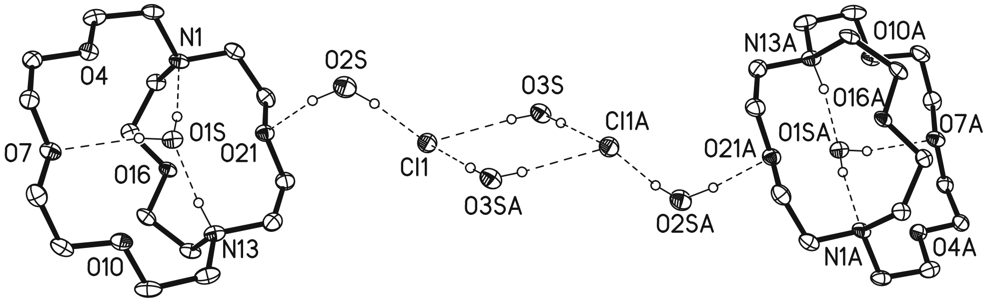


Fig. 3 Hydrogen bond network for H(3.1.1)$^+$ with H_2O and Cl^-

charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ (fax: +44-1223-336033; email: deposit@ccdc.cam.ac.uk or at www: http://www.ccdc.cam.ac.uk).

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