The X-Ray Structure of 1,4,8,11-Tetraazacyclotetradecane-1,4,8,11-tetraacetic Acid and its Relevance to the Protonation of Polyaza Polycarboxylic Macrocycles†

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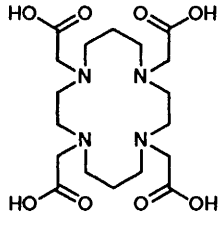
The tetraprotonated form of the macrocyclic ligand teta (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetate) crystallizes in the monoclinic system, space group $P2_1/c$, $a = 7.816(2)$, $b = 14.656(2)$, $c = 11.647(3)$ Å, $\beta = 102.52(4)°$, $Z = 2$. The structure was refined from diffractometer data to an R value of 0.035 and the hydrogen atoms were located unequivocally. In agreement with previous NMR investigations, H_4teta features two protonated nitrogen atoms in the ring and two protonated carboxylate groups. The electrostatic repulsion is thus reduced to a minimum. The tetraaza ring adopts a quadrangular [3434] conformation which is one of the most stable geometric arrangements of the 14-membered cycles. The ligand forms no intramolecular hydrogen bonds but it is involved in intermolecular hydrogen bonds with water molecules.

The chemical and physical properties of polyaza polyacetic macrocycles such as H_4teta (1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraacetic acid) continue to attract considerable interest because of the many intriguing features of this class of ligands. For instance, these ligands form non-labile lanthanide chelates that are exceedingly stable.[1] The kinetic inertness of these chelates has led to the development of contrast agents in NMR imaging.[2,3] The latter are gadolinium(III) complexes that must exhibit a high thermodynamic and kinetic stability in order to reduce the toxicity of the gadolinium ion.

Kinetic studies indicate that the rate of formation of complexes with polyaza polyacetic macrocycles strongly depends upon the degree of protonation of these ligands.[4] The protonation sequence of several macrocyclic ligands has been unravelled by NMR spectroscopy.[5–8] This technique has proved extremely valuable for analysing the protonation scheme of chelating agents provided one can determine independently the NMR shifts that are induced by the addition of a proton at each basic site. Numerous studies[5–8] indicate that the protonation sequence of the tetraaza tetraacetic macrocycles differs from that of their non-cyclic analogues such as H_4edta (ethylenediaminetetraacetic acid). All the nitrogen atoms of the latter are protonated before a proton is attached to any of the carboxylate groups. By contrast, electrostatic repulsion seems to prevent the protonation of more than two nitrogen atoms in the internal cavity of the macrocycles. For instance, NMR investigations[5] indicate that the tetraprotonated form of teta features two NH^+ groups and two protonated carboxylate functions thus leaving two unprotonated nitrogen atoms even at low pH. The present study provides additional evidence in favour of this protonation scheme. We have been able to solve fully the crystallographic structure of the tetraprotonated form of teta and to locate all the hydrogen atoms.



H_4teta

Experimental

Preparation of the Ligand H_4teta.—The tetraprotonated form of teta was obtained as described elsewhere.[5] Slow evaporation of a saturated aqueous solution of this ligand yielded colourless prismatic single crystals.

Crystallography.—X-Ray intensities were recorded with an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Mo-K$\bar{\alpha}$ radiation ($\lambda = 0.710\,73$ Å). Unit-cell dimensions were determined from a least-squares refinement of the angular settings of 25 accurately centred reflections. The space group $P2_1/c$ was unequivocally established from systematic absences. Intensity data were measured in the θ–2θ scan mode. As a check of the stability of the instrument and of the crystal, three standard reflections were recorded at 30 min intervals and anisotropic decay corrections were applied to the data. Intensity data were also corrected for Lorentz polarization and absorption effects. Absorption

† *Supplementary data available:* see Instructions for Authors, *J. Chem. Soc., Dalton Trans.*, 1991, Issue 1, pp. xviii–xxii.

Table 1 Crystallographic data for H_4teta

Formula	$C_{18}H_{32}N_4O_8 \cdot 6H_2O$	Crystal size (mm)	0.35 × 0.45 × 0.40
M	540.57	T/°C	22
Crystal symmetry	Monoclinic	2θ range for lattice constants determination/°	25–45
Space group	$P2_1/c$	Maximum decay correction (%)	6
a/Å	7.816(2)	Range of transmission factors (%)	95.43–99.85
b/Å	14.656(2)	Collection range/°	$4 < 2\theta < 47$
c/Å	11.647(3)	h −9 to +9, k −17 to +17, l −13 to +13	
		No. intensity measurements	7654
β/°	102.52(4)	No. independent observed reflections	2009
U/Å^3	1302(1)	No. data used in refinement [$I > 2\sigma(I)$]	1260
Z	2	Largest Δ/σ	0.01
D_c/g cm^{-3}	1.378	$R = \Sigma(\|F_o\| - \|F_c\|)/\Sigma\|F_o\|$	0.035
F(000)	584	$R' = [\Sigma w(\|F_o\| - \|F_c\|)^2/\Sigma w\|F_o\|^2]^{\frac{1}{2}}$	0.037
μ(Mo-Kα), cm^{-1}	1.105	Merging R	0.028
		Goodness of fit	0.834

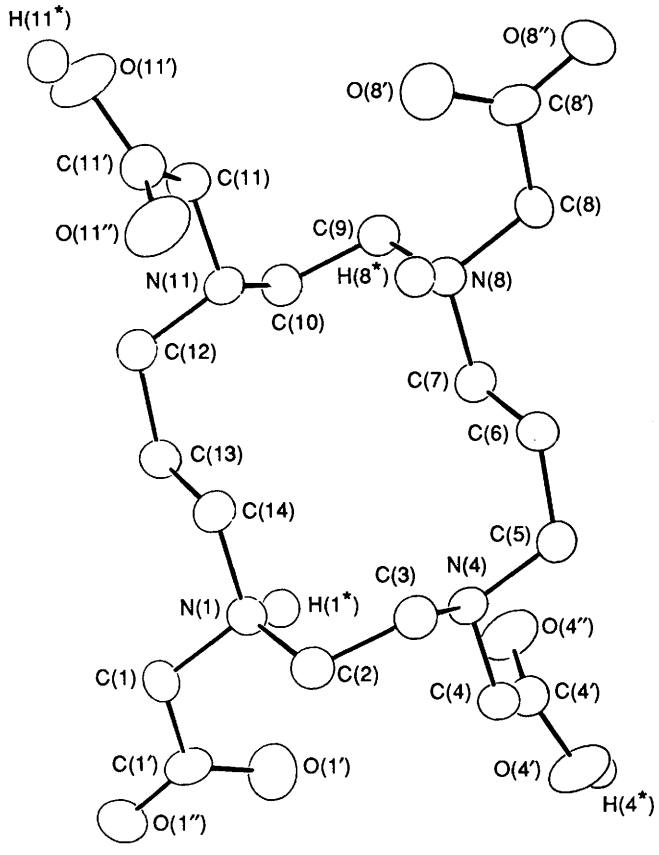


Fig. 1 The molecular structure of tetraprotonated teta and the atom-numbering scheme. Atoms N(8) to C(14) and the two acetate groups of this half of the molecule are centrosymmetrically related to the reference atoms N(1) to C(7) and to the substituents of atoms N(1) and N(4). For sake of clarity, all hydrogen atoms connected to carbon atoms have been omitted. All atoms are depicted as 60% probability ellipsoids

corrections were based on an empirical method which uses a set of scans of reflections with χ values close to 90°.[9] The structure was solved by direct methods, Fourier techniques and full-matrix least-squares calculations [minimizing $\Sigma w(\Delta F)^2$ with unit weights]. All hydrogen atoms even those of the water molecules could be located on successive difference maps calculated at the last stages of refinement. In the last least-squares cycles, non-hydrogen atoms were refined anisotropically while hydrogen atoms were refined isotropically. A secondary extinction coefficient was refined to $g = 8.23 \times 10^{-7}$ with $F_c = F_c/[1 + g(F_c)^2 L_p]$. The maximum and minimum heights in the final Fourier difference map were +0.18 and −0.16 e Å^{-3} respectively. Relevant crystal and experimental data are provided in Table 1. Atomic scattering factors and anomalous dispersion terms were taken from ref. 10. The programs used were part of the Enraf-Nonius SDP-plus package.[11] The atomic coordinates, which include those of the water molecules, are given in Table 2.

Additional material available from the Cambridge Crystallographic Data Centre comprises thermal parameters.

Results and Discussion

The structure of the tetraprotonated form of teta is displayed in Fig. 1 together with the atom labelling. All protons except those bonded to a nitrogen or an oxygen atom have been omitted for clarity. There are two centrosymmetric molecules in the unit cell ($Z = 4$) lying respectively on the inversion centres (0, 0, 0 and 0, ½, ½). The four nitrogen atoms of each molecule are thus coplanar. The ligand H_4teta is a double zwitterion featuring two $NH^+CH_2CO_2^-$ groups and two NCH_2CO_2H groups. In full keeping with the NMR measurements,[5] the two protonated nitrogen atoms are as far as possible from each other, *i.e.* in *trans* positions. The electrostatic repulsion in the ring is thus reduced to a minimum. The two protonated acetate groups are also in *trans* positions and are bonded to the uncharged nitrogen atoms. Two adjacent acetate groups (labelled 8 and 11) are above the plane of the tetraaza ring and the two other acetate groups (labelled 1 and 4) are below that plane. Selected interatomic distances and angles are listed in Table 3. All bond lengths fall within the ranges previously reported.[12] The protonation of only two nitrogen atoms is clearly indicated not only because the attached protons were accurately located in the Fourier maps but also because the C–N distances are longer (mean 1.507 Å) in the case of the charged nitrogen atoms than in the case of the uncharged atoms (mean 1.467 Å). Similarly, the CO_2^- and the CO_2H groups are easily distinguished not only because of the location of the OH functions but also because the two C–O bonds are practically identical in the unprotonated moiety (1.248 and 1.244 Å) while these bonds differ when a proton is attached (1.207 and 1.312 Å).

The tetraaza ring of H_4teta adopts a quadrangular conformation with a methylene group at each corner. In Dale's nomenclature[13] this conformation is labelled [3434] where each number designates the number of bonds between bends. Each bend is a 'genuine corner' with two *gauche* bonds of the same sign between two *anti* bonds (the $ag^{\pm}g^{\pm}a$ sequence in Dale's scheme[13,14]). The same conformation has been reported in the case of the unsubstituted tetraprotonated 1,4,8,11-tetraazacyclotetradecane[12] in the solid state and in the case of 1,4,8,11-tetraoxacyclotetradecane[14] in solution. This conformation belongs to the diamond-lattice type and it is also the most stable geometry of cyclotetradecane itself.[15,16] In the structure

Table 2 Atomic coordinates ($\times 10^4$, $\times 10^3$ for the hydrogen atoms) for H_4teta

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
N(1)	1322(3)	1333(2)	−1056(2)	H(2)	−42(3)	235(2)	−100(2)
C(1)	2775(4)	1909(2)	−1316(3)	H(2′)	−41(3)	203(2)	−231(2)
C(1′)	2912(4)	1896(2)	−2594(3)	H(3)	−210(3)	106(2)	−72(3)
O(1′)	1885(3)	1384(2)	−3274(2)	H(3′)	−298(3)	157(2)	−188(2)
O(1″)	4069(3)	2396(2)	−2839(2)	H(4)	−143(3)	95(2)	−362(2)
C(2)	−405(2)	1807(2)	−1526(2)	H(4′)	−343(4)	73(2)	−380(2)
C(3)	−1974(4)	1206(2)	−1532(3)	H(5)	−330(4)	−84(2)	−246(2)
N(4)	−1959(3)	342(2)	−2162(2)	H(5′)	−450(3)	5(2)	−224(2)
C(4)	−2232(4)	505(2)	−3428(2)	H(6)	−420(3)	−94(2)	−72(2)
C(4′)	−1860(4)	−315(2)	−4117(3)	H(6′)	−327(3)	−5(2)	−16(2)
O(4′)	−2595(3)	−240(2)	−5238(2)	H(7)	−56(3)	−78(2)	−31(2)
O(4″)	−992(3)	−966(2)	−3708(2)	H(7′)	−167(3)	−171(2)	−68(2)
C(5)	−3381(4)	−258(2)	−1966(3)	H(1*)	139(4)	78(2)	−145(3)
C(6)	−3219(4)	−571(2)	−698(3)	H(4*)	−239(5)	−74(3)	−575(3)
C(7)	−1582(4)	−1122(2)	−241(3)	H(W1)	−333(5)	260(3)	34(3)
O(W1)	−3342(3)	2220(2)	919(2)	H(W1′)	−406(4)	240(2)	120(3)
O(W2)	−3529(4)	3303(2)	−1024(2)	H(W2)	−425(5)	312(3)	−162(3)
O(W3)	−1888(3)	562(2)	1788(2)	H(W2′)	−321(5)	382(3)	−104(3)
H(1)	386(4)	169(2)	−83(2)	H(W3)	−228(4)	109(2)	153(3)
H(1′)	260(3)	255(2)	−103(2)	H(W3′)	−115(5)	73(3)	234(3)

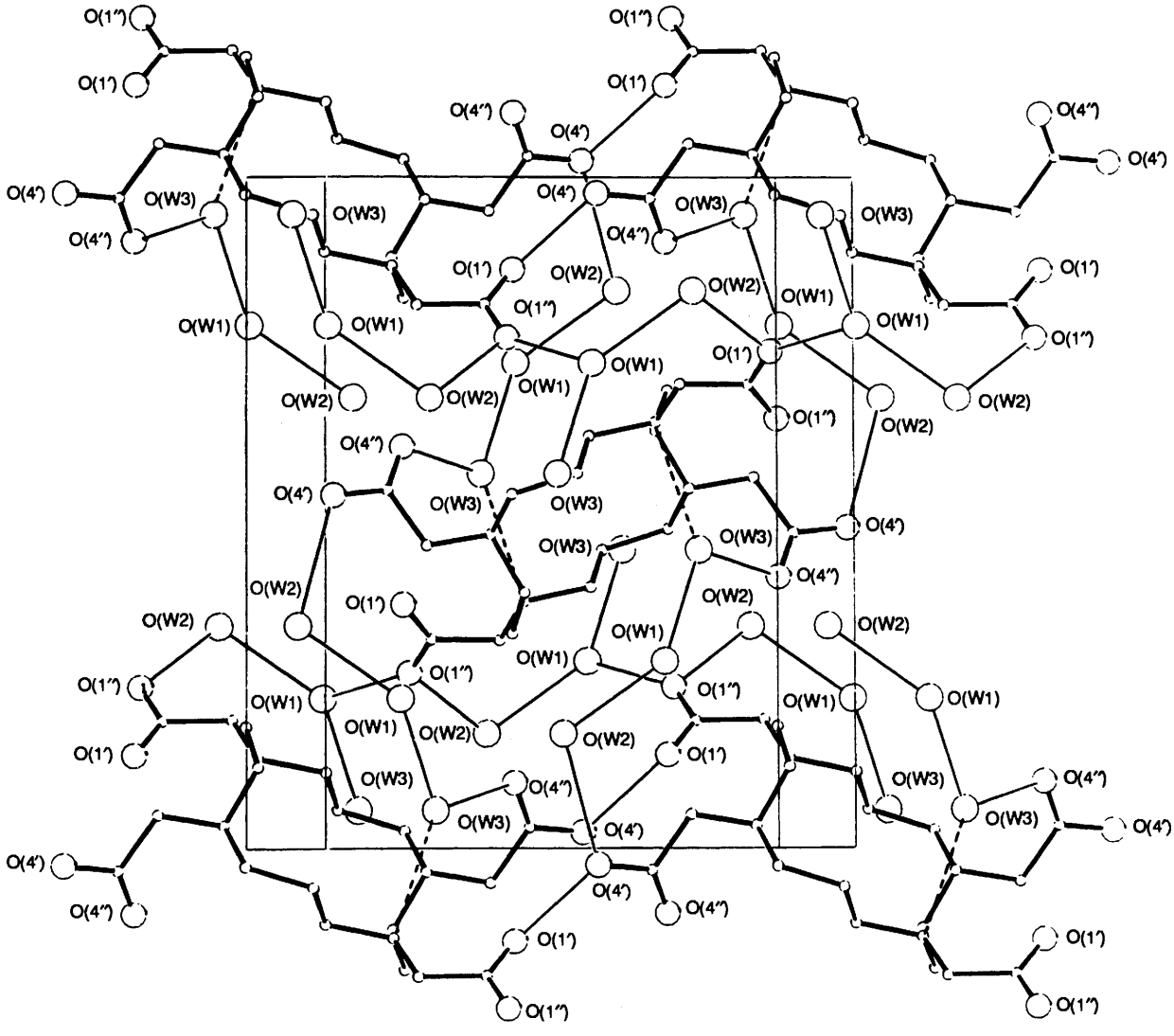


Fig. 2 The crystal packing in the unit cell as a projection on the *bc* plane. Axis *b* is vertical and *c* is horizontal from left to right

depicted in Fig. 1 the two protonated nitrogen atoms of H_4teta are spaced as far apart as possible so as to minimize the electrostatic repulsion. A more compact geometry has been reported in the case of diprotonated 1,4,8,11-tetraazacyclotetradecane.[17] This macrocycle features $ag^{\pm}a$ arrangements that are sterically crowded in cyclic structures[13] but which could be stabilized by two intramolecular hydrogen bonds between adjacent nitrogen atoms. It is also noteworthy that the

Table 3 Intramolecular bond distances (Å), angles (°) and torsion angles (°) with standard deviations in parentheses[a]

C(2)–N(1)	1.510(4)	N(4)–C(3)	1.465(4)
C(2)–C(3)	1.508(5)	C(1)–C(1′)	1.516(5)
N(1)–C(1)	1.498(4)	C(1′)–O(1″)	1.244(4)
N(1)–C(14*i*)	1.513(4)	C(1′)–O(1′)	1.248(4)
N(1)–H(1*)	0.94(4)	C(4)–C(4′)	1.509(5)
C(6)–C(7)	1.509(5)	C(4′)–O(4″)	1.207(4)
C(6)–C(5)	1.525(5)	C(4′)–O(4′)	1.312(4)
C(5)–N(4)	1.474(4)	O(4′)–H(4*)	0.98(5)
N(4)–C(4)	1.463(4)	N(1)–H(1*)	0.94(4)
C(3)–C(2)–N(1)	113.3(3)	C(4)–N(4)–C(3)	110.4(3)
C(2)–N(1)–C(1)	109.0(3)	N(4)–C(3)–C(2)	114.3(3)
C(2)–N(1)–C(14*i*)	111.8(3)	N(1)–C(1)–C(1′)	114.2(3)
C(2)–N(1)–H(1*)	111(2)	C(1)–C(1′)–O(1″)	115.3(3)
C(1)–N(1)–C(14*i*)	111.9(3)	C(1)–C(1′)–O(1″)	117.2(3)
C(1)–N(1)–H(1*)	105(2)	O(1″)–C(1′)–O(1′)	127.5(3)
C(14*i*)–N(1)–H(1*)	108(2)	N(4)–C(4)–C(4′)	113.8(3)
N(1)–C(14*i*)–C(13*i*)	112.4(3)	C(4)–C(4)–O(4″)	125.2(3)
C(7)–C(6)–C(5)	112.8(3)	C(4)–C(4′)–O(4′)	117.3(3)
C(6)–C(5)–N(4)	115.0(3)	O(4″)–C(4′)–O(4′)	123.1(3)
C(5)–N(4)–C(4)	107.7(3)	C(4′)–O(4′)–H(4*)	117(3)
C(5)–N(4)–C(3)	110.5(3)		
C(3)–C(2)–N(1)–C(14*i*)	−67.3(3)	C(6)–C(5)–N(4)–C(3)	−64.5(3)
C(2)–N(1)–C(14*i*)–C(13*i*)	174.6(3)	C(5)–N(4)–C(3)–C(2)	171.1(3)
N(1)–C(14*i*)–C(13*i*)–C(12*i*)	−173.2(3)	N(4)–C(3)–C(2)–N(1)	−54.8(3)
C(7)–C(6)–C(5)–N(4)	−61.3(3)		

[a] Atoms related by the inversion centre at (0, 0, 0) to reference atoms listed in Table 2 are designated by *i*.

Table 4 Hydrogen bond distances (Å) and angles (°)[a]

O(1″) · · · O(W2^{I})	2.836(5)	O(1″) · · · H(W2^{I})–O(W2^{I})	166(5)
O(1″) · · · O(W1^{II})	2.788(4)	O(1″) · · · H(W1^{II})–O(W1^{II})	166(5)
O(1′) · · · O(4^{III})	2.557(4)	O(1′) · · · H(4*^{III})–O(4′^{III})	168(5)
O(4′) · · · O(W2^{IV})	3.023(5)	O(4′) · · · H(W2′^{IV})–O(W2^{IV})	153(5)
O(4″) · · · O(W3)	2.869(4)	O(4″) · · · H(W3′)–O(W3)	170(5)
O(W1) · · · O(W2)	2.742(5)	O(W1) · · · H(W1)–O(W2)	172(5)
O(W1) · · · O(W3)	2.779(5)	O(W1) · · · H(W3)–O(W3)	176(4)

[a] Symmetry codes: I $x + 1, y, z$; II $x + 1, 0.5 - y, z - 0.5$; III $x, y, z - 1$; IV $-x, y - 0.5, 0.5 - z$.

ligand teta would have to rearrange itself after deprotonation in order to form a lanthanide complex such as $[Tb(teta)]^-$.[18] The latter adopts the non-diamond lattice biangular [77] conformation with all carboxylic groups pointing to the same side of the tetraaza ring. The [3434] and [77] geometries may be interconverted by relatively small nuclear displacements and exhibit closely similar conformational energies.[16]

An aspect of particular interest in the solid-state structure of polyaminopolyacetic acids is that they represent cases where both intra- and inter-molecular hydrogen bonds can be formed. For instance, Cotrait[19] and Ladd *et al.*[20] reported that a strong hydrogen bond is formed between each NH^+ group of H_4edta and an unprotonated carboxylic group belonging to the same molecule (N–H^+ · · · O 2.15 Å). A similar structure was tentatively suggested for the diprotonated form of macrocyclic ligands such as teta[5] and it was assumed to be relatively unreactive presumably because it was stabilized by hydrogen bonds.[4] The ligand H_4teta crystallizes with six water molecules. The packing pattern is illustrated in Fig. 2. No intramolecular hydrogen bond is observed but there is a close contact between each NH^+ moiety and one oxygen atom of the acetate group to which it is linked [N(1) · · · O(1′) 2.714 Å]. Intermolecular hydrogen bonds are formed between each NH^+ group and a water molecule labelled W3 in Fig. 2 [N(1)–H(1*) · · · O(W3) 2.059 Å, N(1)–H(1*) · · · O(W3) 162°]. One proton of the W3 water molecule is in turn hydrogen bonded to the closest oxygen atom of a protonated carboxylate group [O(W3)–H(W3) · · · O(4″) 2.059 Å, O(W3)–H(W3) · · · O(4″) 170°]. The other hydrogen atom of the W3 molecule is co-ordinated to the oxygen atom of another water molecule W1 [O(W3)–H(W3) · · · O(W1) 1.919 Å] which is itself hydrogen bonded to a third water of hydration W2 [O(W1)–H(W1) · · · O(W2) 1.871 Å]. Selected hydrogen bond distances and angles are reported in Table 4.

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