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Structures of aza-macrocyclic ligands with polyphosphonated dangling groups

Deyuan Kong [a,*], Jennifer McBee [b], LeAnthony Holliness [c], Abraham Clearfield [c]

[a] Chevron Tech. Com., Energy Tech. 35-1204, Richmond, CA 94801, United States
[b] Department of Chemistry, University of California, Berkeley, CA 94720-1460, United States
[c] Department of Chemistry, Texas A&M University, College Station, TX 77842-30012, United States

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Abstract

Two phosphonated hexaaza-macrocycles with 24- and 26-membered rings have been synthesized via a Mannich reaction and characterized. The novel crystal structures of the macrocyclic ligands show the extended 3-D hydrogen bonded structure in their solid states. These ligands have unusual ring conformations with two or four pendent arms wrapping around the macrocycle with alternating up and down orders. Strong hydrogen bonding between the protonated phosphonate groups and the deprotonated phosphonated groups was observed in those structures together with the complicated solvent hydrogen bonding networks.

In the last few decades, polyazamacrocycles with phosphonate dangling groups have been researched. The interest in these complexes stems from their various uses in biological systems. DOTP (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetramethylenephosphonic acid) is one such studied polyazamacrocycle. This tetraaza macrocycle embodies the numerous areas of study for the synthesized polyazamacrocylces and their various chelates researched herein.

Many trivalent lanthanide cation chelates of DOTP have been researched with the purpose of acting as a contrast agent in magnetic resonance imaging (MRI) technique.[6,7] The gadolinium chelate of DOTP serves as the most common contrast agent for functional MRI. This allows for the enhancement of the solvent water proton relaxation rates in the tissue. Not only do the chelates bind metal ions to a monoclonal antibody in radioimmune therapy, they can also be used to decrease the toxicity in NMR topography.

The polyazamacrocycle chelates can be used in the determination of certain cation levels in cells and tissues. The size of the macrocycle ring is selective toward different metal cations in biological systems, with examples including triaza derivatives for measuring the Mg^{2+} level and tetraaza derivatives for measuring the Ca^{2+} level.[1]

One application of the phosphonated macrocycles is the creation of multi-dimensional Zr-layered compounds and the creation of new ion-exchange compounds.[2,3] Once the phosponate pendent groups have been linked to the zirconium ions, the variable ring size of the macrocycles generates suitable cavities for many ions to access.

The hexaaza-macrocycle BMXD has been synthesized and examined as mentioned previously.[4,5] A new 18-membered hexaaza-macrocyclic ligand with four pendent methylenephosphonates has been synthesized via the Mannich reaction, which includes two pyridyl rings in the macrocycle.[6] PBNXD and PKM1 are synthesized by Mannich reaction of presynthesized polyamine–KTM1(KTM1 = 3,6,9,16,19,22-hexaazatricyclo-[22.2.2.2^{11,14}]-triaconta-1(27),11(30),12,14(29),24(28),25-hexaene) and BNXD (BNXD = 3,7,10,18,22,25-hexaazatricyclo-[25.3.1.1^{12,16}]-dotriaconta-1(31),12(32),13,15,27,29-hexaene), then by recrystallization at hot HCl to give the pure product. Detailed synthesis and

* Corresponding author. Tel.: +1 510 242 1654.
E-mail address: deyk@chevron.com (D. Kong).

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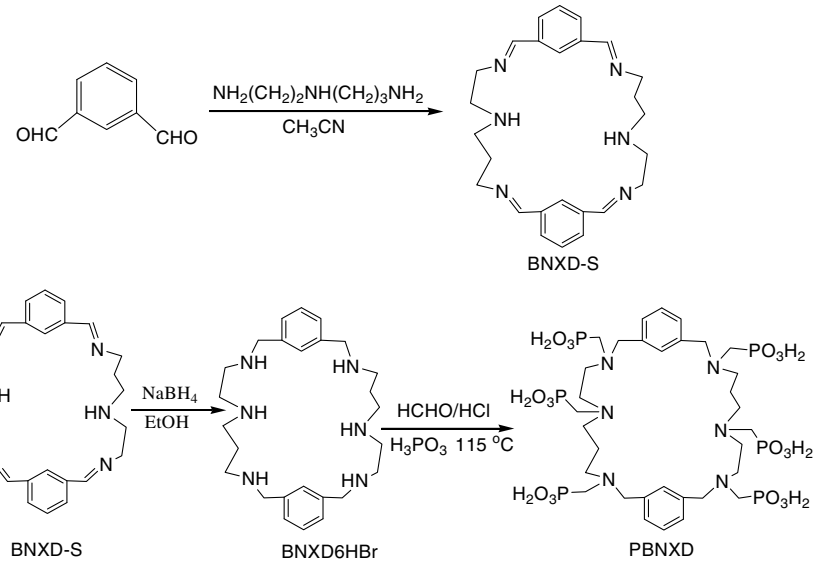

Scheme 1.

analysis are provided in Supplementary data. Scheme 1 shows as the general synthetic route. The ion-exchanger method for purification did not work for those polyphosphonic acid compounds. PKTM1 crystallized in the triclinic crystal system, space group P-1 with two molecules in one unit cell.

Figure 1 gives the ORTEP diagram of this molecule with the atom labeling scheme. Two chlorine atoms and five water molecules are located in the lattice for charge balance and hydrogen bond packing. The two benzene rings are parallel to each other and four phosphonate groups extend out from the macrocyclic ring. The two central phosponate groups bend over the ring to form a discrete packing mode. The shortest P–O bonds are 1.49 Å which are assumed to be unprotonated P=O double bonds. Also, for hydrogen bonded to oxygen of a phosphonate group, the ideal P–OH bond is in the range of 1.56–1.58 Å. The monoprotonated P–O (PO_3H^-) bonds are in the range of 1.50–1.51 Å. The disordered atoms bonded to P4, O10 and O11, and P1:O1 are not considered to be protonated even with longer bond lengths of around 1.6 Å. The six phosphonate groups donated four protons in total, but all nitrogen atoms of macrocycle are protonated. All the hydrogen atoms associated with nitrogen atoms were located in the Fourier map at suitable distances. The two additional positive charges are compensated with two chlorine anions indicating that HCl was the recrystallizing agent. In one unit cell, two molecules are connected with square-like hydrogen bonds through O–H···Cl (O1w–H···Cl1 3.127 Å and O5w–H···Cl1 3.208 Å [symmetry code $x+1$, y, z]) which forms a dimer as depicted in Figure 2. The

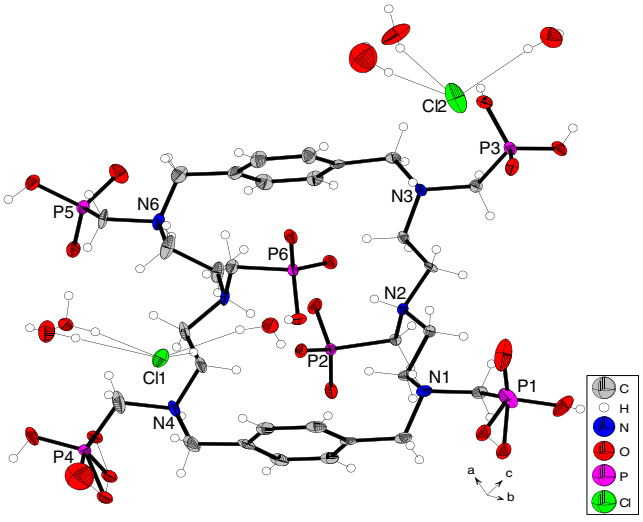

Fig. 1. ORTEP representation of PKTM1 with atomic labeling (the dashed lines are hydrogen bonds).

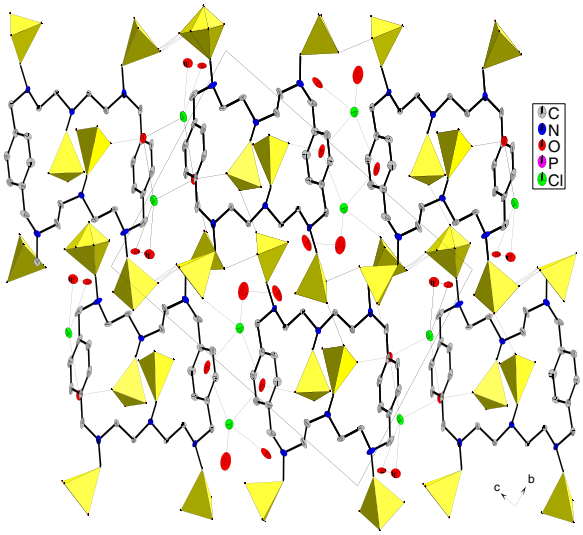

Fig. 2. Unit cell packing of the PKTM1 along *bc* plane (the yellow tetrahedron represents CPO_3 group, hydrogen atoms are omitted for clarity. Dashed lines represent hydrogen bonds).

strong intermolecular hydrogen bonding between the protonated P–OH and deprotonated O–P groups: O12–H···O6 2.487(5) Å, O7–H···O13 2.444(5) Å, O9–H···O18 2.448(5) Å connect the molecule in the *bc* plane forming infinite polymer chains. The pendent groups which are located in the center of the triethylene chain are further hydrogen bonded with the water molecules through O17–H···O1w 2.684(5) Å and O3w–H···O4 2.612(5) Å to complete the 2-dimensional network. The intramolecular hydrogen bonds between the protonated nitrogen atoms and phosphonate groups also provided the strong folding force for the present wrapping conformation. Other clathrated water molecules are hydrogen bonded toward each other or with phosphonated groups to provide additional lattice energy to stabilize the whole structure.

A small amount of PBNXD powder was recrystallized in a mixed solution of HBr in water and layered with methanol. Block-shaped crystals suitable for X-ray diffraction grew in two months. The crystals are monoclinic, space group $P2_1/c$ with two bromide anions and two hydronium cations and 21/2 water molecules. The unit cell is centrosymmetric with two differently oriented molecules. Both of them adopt the chair conformation with the twisted macrocycle skeleton and two C2–N1–C1–C13# −131.5(6)°; N2–C10–C11–N3 −78.1(6)°; C14–N4–o antiparallel benzene rings with torsion angles of C15–C16 −133.2(5)° and C17–N5–C18–C19 48.1(6)°, respectively. The structure of the PBNXD could be described as a pair of molecules forming a helical ring system. These two molecules are connected with the strong intermolecular hydrogen bonding between the terminal P═O and deprotonated phosphonated groups [O(9)–H···O(11)# 2.461(8) Å, $1-x$, $1-y$, $-z$; O(14)–H···O(1)# 2.506(7) Å, $-x$, $1-y$, $-1-z$] along ⟨0 1 1⟩ plane. All nitrogen atoms are protonated and form intramolecular hydrogen bonds with the deprotonated phosphonate groups as shown in Figure 3. This strong H-bonding forces the molecule to twist and form a more tight packing type. [N(1)–H···O(6)# 2.700(6) Å, $1-x$, $1-y$, $-z-1$; N(2)–H···O(4)# 2.692(6) Å, $1-x$, $1-y$, $-z-1$; N(3)–H···O(4)# 2.639(6) Å, $1-x$, $1-y$, $-z-1$; N(4)–H···O(16) 2.725(6) Å; N(5)–H···O(17)# 2.661(6) Å, $-x$, $1-y$, $-z$; N(6)–H···O(17)# 2.669(6) Å, $-x$, $1-y$, $-z$] O(5)–H···O(8)# 2.777(8) Å, $1-x$, $1-y$, $-1-z$; O(18)–H···O(15)# 2.536(6) Å, $-x$, $1-y$, $-z$; Four of the six phosphonate pendent arms form PO_3H^- groups carrying one negative charge and the other two form PO_3H^- groups carrying two disordered negative charges, in total, six protons have been transferred. Three trends of P–O bond distances are observed in the structure. The longest P–O bond lengths of 1.55–1.59 Å are defined as the protonated PO–H groups. Bond distances of the terminal P═O are in the range of 1.48–1.49 Å. Only four P–O bond lengths are close to 1.53 Å which are assigned as one negative charged O–P–O (PO_3H^-) groups with one disordered hydrogen atom between each other which is consistent with the above IR discussion for the absence of characteristic vibration bands of PO_3[3,7] This conclusion is supported by the very short D–A contacts between O(14)···O(1) and O(11)···O(9). Six protons have been located on the nitrogen atoms of the macrocycle ring. Two more charges are balanced by hydronium cations. All hydronium molecules are connected by hydrogen bonds between each other, or with bromide ions and pendent phosphonate groups which form a more complicated hydrogen bonding network as depicted in Figure 4. The bromine atoms are heavily disordered, especially Br2 which is disordered in four positions with occupancy refinement to the ratio at 7:30:30:30, which also gave a satisfactory hydrogen bonding between the disordered positions and water molecules.

Preliminary reaction of these phosphonic acids with $ZrOCl_2$ appears to produce layers with the crown ethers between the layers. More detailed studies will be performed and reported upon.

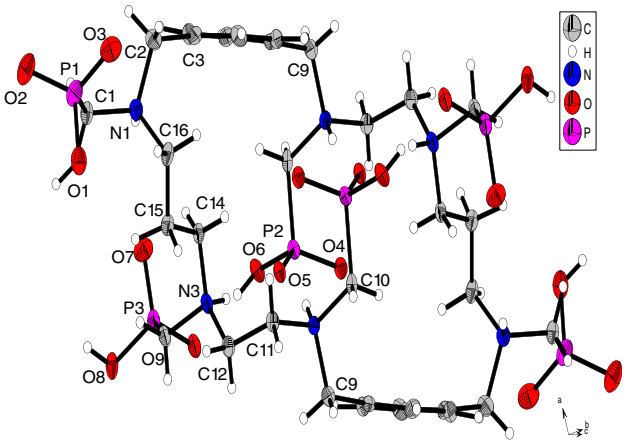

Fig. 3. ORTEP structure of PBNXD dimer (all solvent molecules, hydrogen and bromine atoms are omitted for clarity, dashed lines are hydrogen bonds).

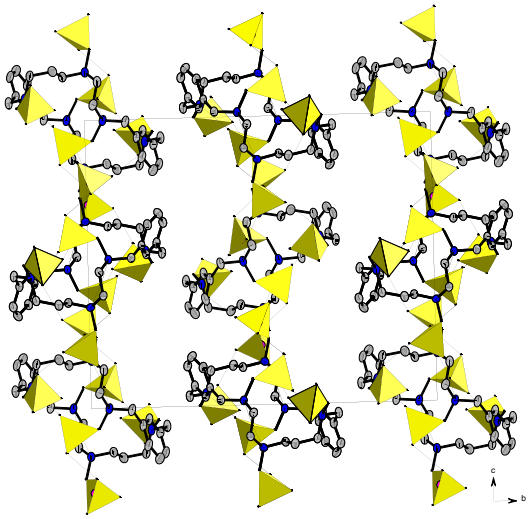

Fig. 4. Unit cell packing of PBNXD viewed along *a* axis (the yellow tetrahedron represents CPO_3 group, the dashed lines are hydrogen bonds, all solvents and bromine atoms are omitted for clarity).

Crystallographic data: Atomic coordinates, bond angles, bond distances and thermal parameters associated to four compounds have been deposited at the Cambridge Crystallographic Data Center. Data are available from the CCDC, 12 Union Road, and Cambridge CB2 1EZ, UK on request with CIF deposition codes: 249360-249363. Email: deposition@ccdc.cam.ac.uk, fax: +44 (0) 1223 33603.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.03.085.

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