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Ca^{2+} metal ion adducts with cytosine, cytidine and cytidine 5'-monophosphate. A comprehensive study of calcium reactivity towards building units of nucleic acids.

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This manuscript is dedicated to Prof. Miguel Julve to celebrate his 60th birthday.

Six new Ca(II) adducts of formulae $[Ca(cyt)_2(H_2O)_4][ClO_4]_2 \cdot 2cyt \cdot 2H_2O$ (**1**), $[Ca_2(cyt)_2(H_2O)_4(ClO_4)_4]$ (**2**), $[Ca_2(cyt)_4(H_2O)_4Cl_2]Cl_2$ (**3**), $[Ca(H_2cyd)_2(H_2O)_4][ClO_4]_2 \cdot 3H_2O$ (**4**), $[Ca(H_2cyd)_2(H_2O)_4]Cl_2 \cdot 3H_2O$ (**5**) and $[Ca_2(CMP)_2(H_2O)_{11}] \cdot 5H_2O$ (**6**) [cyt = cytosine, H_2cyd = cytidine, CMP = cytidine 5'-monophosphate] have been synthesized and structurally characterized. They reveal classical as well as uncommon structures, with H_2cyd and CMP showing unprecedented binding sites for the calcium ion. The structure of compound **1** consists of monomeric $[Ca(cyt)_2(H_2O)_4]^{2+}$ cations, uncoordinated ClO_4^- anions as well as lattice nucleobases molecules. The structures of compounds **2** and **3** contain either neutral (**2**) or cationic (**3**) dinuclear entities. They have in common a bis-μ-carboxilate bridged $[Ca_2(cyt)_2]^{4+}$ dinuclear core, where each cytosine molecule shows coordination simultaneously through O2-N3. The coordination sphere of each calcium ion in **2** is completed by two *cis* water molecules and two ClO_4^- groups, the latter either in a mono- or bis-monodentate fashion. In the structure of **3**, the dinuclear entities are cationic due to the direct metal-coordination of only two Cl^- anions over four, the remaining two being engaged as counterions in hydrogen bonds with the metal complex. The coordination sphere of each calcium ion in **3** is completed by two *trans* water molecules and an additional cytosine molecule, coordinated this time *via* O2 only. Compounds **4** and **5** are, like **1** and **3**, ionic salts. They share the same $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ cationic unit, and differ by the supramolecular packing motif generated with the aid of water molecules of crystallization and the specific counterions in each case [ClO_4^- in **4** and Cl^- in **5**]. The structure of compound **6** consists of neutral $[Ca_2(CMP)_2(H_2O)_{11}]$ asymmetric moieties and crystallization water molecules. Each dimer contains two Ca(II) ions in a slightly different coordination environment and two CMP di-anions exhibiting the chelating coordination mode through the ribose O2' and O3' hydroxyl groups and interacting with a calcium ion each. One of them is further coordinated *via* the nucleobase O2 oxygen atom toward the exogenous calcium ion, thus building up the dinuclear unit. The lack of coordination of Ca^{2+} ions towards phosphate groups observed in **6** is unusual.

Introduction

Studies on metal ion-nucleic acid interactions have been of great interest since metal ions play a crucial role in the structure and function of nucleic acid and genetic information transfer.[1-4] Both experimental and theoretical studies have been performed on these systems.[1-10]

The coordinative site depend on the nature of the metal ion, and is non-innocent, generating a stabilizing or destabilizing effect on DNA, correlated to its ability to supports or prevents the formation of base pairing. Generally, metal ions bounded to

phosphate groups stabilize the double helical structure of the DNA while base-binding destabilize this structure.[1-3] Furthermore, at high metal concentrations, an excessive charge neutralization in the helix promotes the formation of further hydrogen-bonding base pairs not so stable as the Watson–Crick ones, and mispairing is often chosen. On the other hand, metal ions compete with the hydrogens involved in H-bonds for the electron donor sites on nucleobases and, as a consequence of hydrogen displacements, metals can built crosslinks between strands.[3-4]

The simultaneous picture of structure, stability and electronic properties of the studied systems obtained through detailed computational analysis is extremely useful in order to have a better insight in their biochemical functions. However it is still important to increase records of experimental data, when possible, in physiological DNA and RNA. For this purpose, many research efforts, based on crystallographic studies, have been dedicated to the rational design, preparation and characterization of bio-mimetic systems based on the interaction of fragments or constituents of DNA, as nucleobases and their derivatives, with a wide range of metal ions.[1-5,11-14]

On the other hand, new generations of metal complexes containing biomolecules, such as amino acids, peptides, proteins, *etc.* have emerged in supramolecular coordination chemistry as nonthreatening building blocks, useful to develop new materials with tailored architectures and properties. The intrinsic self-assembling features of these molecules offer the possibility to achieve a fine control over the structure of the material at the nanoscale level. The incorporation of transition metal ions into pre-organized structures allows the introduction of addressable functionality and properties.[15-16] Among molecules from the biological world, key constituents of nucleic acids, such as nucleobases, and related nucleosides and nucleotides, have accessible nitrogen and oxygen electron lone pairs, which allow these molecules to be suitable candidates to act as multidentate organic ligands. Their rich metal binding and H-bonding capabilities, together with the rigidity of their molecular structures, make them ideal bio-linkers for constructing topologically diverse families of coordination compounds potentially useful in the field of nanotechnology.[17-26]

Then, motivated by the importance of the topic, with the aim to contribute rationalizing the reactivity of the Ca^{2+} ion towards a series of related nucleobase - nucleoside - nucleotide ligands, we set out to explore its behaviour towards cytosine (cyt), cytidine (H_2cyd) and cytidine 5'-monophosphate (CMP) in the presence of either chloride or perchlorate anions.

In reference to the alkaline-earth metal ions, many X-ray structures of compounds containing Mg^{2+}, Ca^{2+} and Ba^{2+} with nucleic acids constituents have been reported.[27-34] Focusing on Mg(II) and Ba(II), three structures are known. One of Mg^{2+} with the nucleobase cytosine,[27] and two of Ba^{2+} with cytidine-5'-phosphate and uridine-5'-phosphate[28]. The binding mode of the Mg^{2+} metal ion with base atoms in cytosine is unidentate *via* O(2). Ba^{2+} exhibits the expected coordination to phosphate group together with bind to O2' and O3' atoms of the sugar moiety. From these results it is evident that the Mg^{2+} ion shows, with cytosine, a behavior similar to that of Mn^{2+} and Co^{2+} and Ni^{2+}, giving rise to compounds in which the nucleobase is coordinated *via* O(2).[29] Few examples of Ca^{2+} adducts with nucleotides, have been structurally studied.[30-33] In these compounds Ca^{2+} cations are bound to phosphate anions. Remarkable exceptions are given by two compounds where Ca^{2+}, in addition to the coordination through the phosphate group, is bound to O3' of the sugar moiety and to the exocyclic O(2) atom of the nucleobase of deoxythymidine-5'-monophosphate,[33] and to O2' and O3' atoms of the sugar in the adduct with guanosine-5'-monophosphate.[32]

As far as we know, no example of adducts of Ca^{2+} with nucleosides have been reported in literature. Limiting our attention to nucleobases, only one Ca^{2+} compound and cytosine, is known,[34] containing N(3)-O(2) and O(2) bridge co-ordination modes simultaneously.

In the present work we report our first results concerning synthesis and X-ray structure analyses of six new adducts of Ca^{2+}. Among them there are the first isolated cytidine-containing calcium(II) complexes. They exhibit a rare and unpredictable binding to the sugar moieties both with the cytidine and CMP. This occurs in water, without sugar deprotonation and, with CMP, no-binding of the phosphate group is observed.

Table 1. Crystal Data and Structure Refinement for Compounds **1-6**

Compound	**1**	**2**	**3**	**4**	**5**	**6**
empirical formula	$C_{41}H_{38}Cl_2CoN_5O_3P$	$C_4H_9Cl_2CaN_3O_{11}$	$C_8H_{14}Cl_2CaN_6O_4$	$C_{72}H_{160}Cl_8Ca_4N_{24}O_{100}$	$C_{36}H_{80}Cl_4Ca_2N_{12}O_{34}$	$C_{18}H_{56}P_2Ca_2N_6O_{32}$
Z	1	2	2	8	1	2
T, K	296(2)	296(2)	296(2)	100(2)	296(2)	296(2)
fw	791.52	386.12	369.23	3406.15	1447.08	1010.79
Crystal system	Triclinic	Triclinic	Triclinic	Tetragonal	Triclinic	Monoclinic
Space group	*P-1*	*P-1*	*P-1*	$I4_122$	*P1*	$P2_1$
a , Å	6.966(3)	7.042(2)	9.487(2)	21.7076(9)	12.2222(5)	12.298(2)
b , Å	10.138(2)	10.068(3)	9.650(2)	21.7076(9)	12.6202(3)	8.762(2)
c , Å	13.113(3)	10.415(3)	9.796(2)	59.216(4)	12.6332(3)	19.691(2)
α, deg	70.48(2)	63.28(2)	84.51(2)	90	103.712(1)	90
β , deg	86.08(3)	83.44(2)	88.01(2)	90	109.206(1)	102.16(1)
γ , deg	71.43(3)	86.87(2)	62.17(2)	90	108.164(1)	90
D_c, g cm^{-3}	1.590	1.957	1.553	1.622	1.485	1.618
μ, mm^{-1}	0.444	0.950	0.759	0.437	0.438	0.463
$^aR1$ [$I > 2\sigma(I)$]	0.0740	0.0435	0.0452	0.0597	0.0409	0.0437
$^{b,c}wR2$	0.1810	0.1252	0.0893	0.1704	0.1178	0.1262
Flack parameter				0.10(5)	0.013(19)	0.02(4)

$^aR1=\sum||F_o|-|F_c||/\sum|F_o|$. $^bwR2=\{\sum[w(F_o^2-F_c^2)^2]/[(w(F_o^2)^2]\}^{1/2}$. $^cw = 1/[\sigma^2(F_o^2) + (aP)^2+bP]$ with $P = [F_o^2+2F_c^2]/3$, $a = 0.1056$ (**1**), 0.0771 (**2**), 0.0262 (**3**), 0.1206 (**4**), 0.0902 (**5**), 0.0971 (**6**) and $b = 0.2953$ (**1**), 0.9575 (**2**), 1.0909 (**3**), 21.4898 (**4**), 0.0450 (**5**) and 0.3138 (**6**).

Results and discussion

Structure of $[Ca(cyt)_2(H_2O)_4](ClO_4)_2 \cdot 2cyt \cdot 2H_2O$ (1).

Compound **1** consists of monomeric $[Ca(cyt)_2(H_2O)_4]^{2+}$ moieties, uncoordinated ClO_4^- anions and nucleobases and crystallization water molecules (Fig. 1). It is isostructural with the related Mg(II),[27] Mn(II), Co(II) and Ni(II) compounds.[29] The Ca^{2+} ion lies on an inversion centre and is hexacoordinated in an octahedral environment, being linked to four water and two cytosine molecules *trans*-coordinated *via* oxygen atoms. The octahedral geometry around Ca(1) may be described as slightly elongated, the best equatorial plane being defined by O(1W), O(1Wa), O(2), O(2a) set of atoms. The Ca-$O_{(eq)}$ [2.303(4) (4), 2.380(4) Å] and Ca-$O(2W)_{ax}$ [2.343(4) Å] distances (Table S1) are longer than those found in the magnesium compound as well as those found in manganese, cobalt and nickel compounds, but they are in the same range found in the reported example of Ca-cyt compound.[34]

Four hydrogen bonds, in which coordinated water molecules and N(1) and N(1a) nitrogen atoms are involved, contribute to the stabilization of the structure. Two uncoordinated cytosine molecules are joined to the coordinated ones by hydrogen bonds in such a way as to form two base pairs. Two crystallization water molecules and two perchlorate anions are linked to each other and are also linked to the $[Ca(cyt)_2(H_2O)_4]^{2+}$ ion and to the base pairs so as to form two

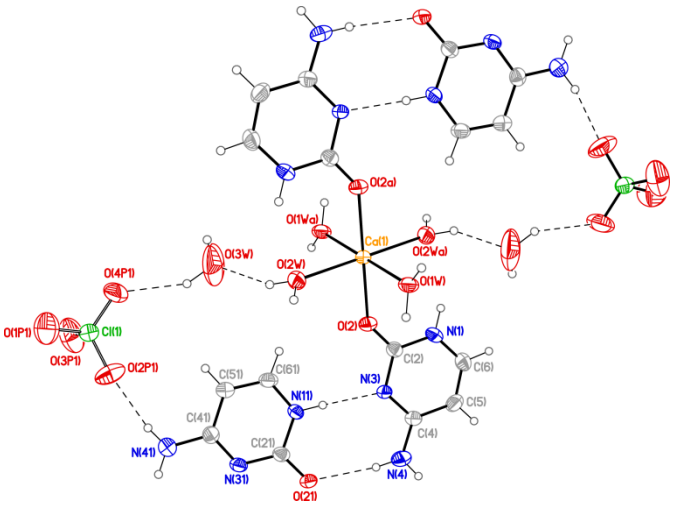

Fig.1 ORTEP drawing of the structure of **1** with atoms numbering scheme. (Thermal ellipsoids are plotted at 30% probability). [Symmetry code: (a) - *x*, - *y*, - *z*].

rings (Fig. 1) (See Table S7). The formation of these rings, most likely, stabilizes this structure giving rise to an unusual hexacoordination for Ca^{2+}. The coordination exhibited in the other compounds hereunder reported, in which no base-pairs are formed, is thoroughly altered. The bond lengths and angles in the cytosine ligand are in agreement with those reported in the literature.[27,29,34]

In the crystal packing further hydrogen bonds involving O21 oxygen atom and N3 nitrogen atoms of the non-coordinated cyt and water molecules together with parallel-displaced π-stacked arrangement of the uncoordinated cytosine nucleobase rings and coordinated and non-coordinated cyt rings occur (Figure 2). The average inter-ring C–C distance is 3.46 Å, and the angles between the centroid-centroid vectors from the facing nucleobase rings and their normal (θ) are 36.5(1) and 41.6(1)°.

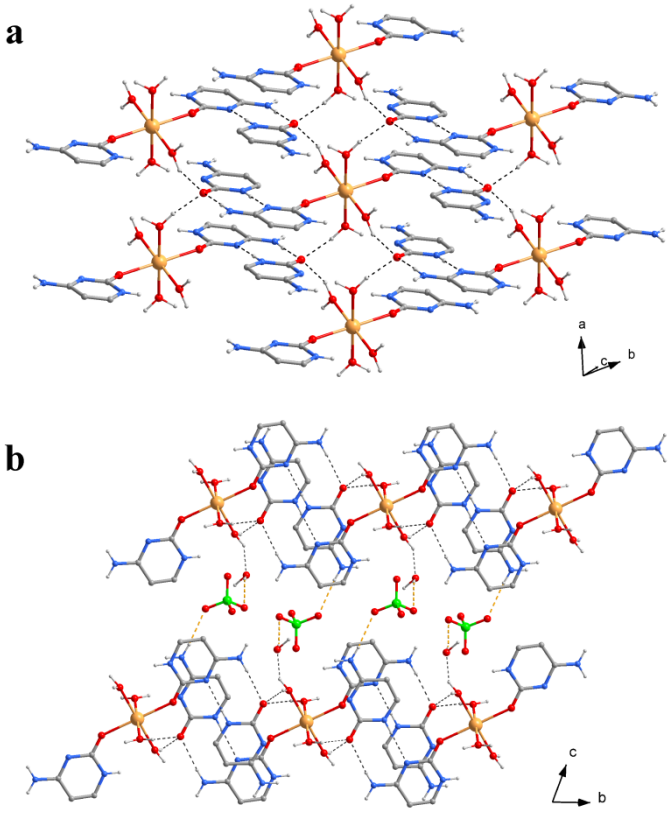

Fig.2 View along *c* crystallographic axes of crystal packing of **1**.

Structures of $[Ca_2(cyt)_2(H_2O)_4(ClO_4)_4]$ (2) and $[Ca_2(cyt)_4(H_2O)_4Cl_2]Cl_2$ (3).

Compounds **2** and **3** contain neutral (**2**) or cationic (**3**) dinuclear entities with two crystallographically equivalent Ca^{2+} ions, being related by an inversion center, bridged by two nucleobases. In the dimers present in the molecular structure of **2**, Ca^{2+} ions are octacoordinated in an highly distorted environment, being linked to two water and two cytosine molecules acting as bridging ligands, coordinated in a μ_2 fashion *via* oxygen atoms O(2) and, simultaneously, *via* nitrogen atom N3. Also four perchlorate anions are directly linked to the metal ions both in mono- and bidentate coordination mode (Figure 3).

In the structure of **3**, the dinuclear entities are cationic due to the direct coordination of two chloride anions (Figure 4a). Furthermore the two chloride counterions interacts, indirectly, with dinucler moieties by means of H-bonds involving coordinated water molecules (Figure 5).

In **3** the coordination sphere of each Ca^{2+} ion is completed by a molecule of nucleobase, coordinated with oxygen atoms O(2). The resulting coordination geometry around the Ca^{2+} is pentagonal-bipyramidal. The basal plane is defined by the chloride atom Cl(1), three oxygen atoms of three cytosine base, namely the μ_2-coordinated oxygen atoms O(21) and O(21a) and the monodentate O(2) atom of the peripheral cytosine, and the nitrogen atom N(3) of the bidentate nucleobase, as shown in Fig.4. The two axial positions are occupied by the water oxygen atoms.

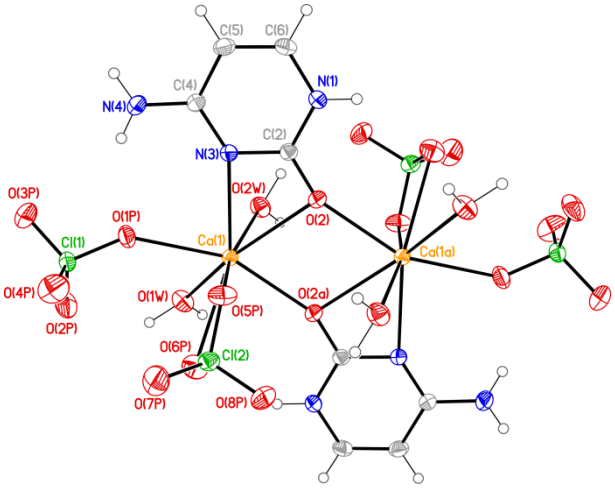

Fig.3 ORTEP drawing of the structure of **2** with atoms numbering scheme. (Thermal ellipsoids are plotted at 30% probability). [Symmetry code: (a) - *x*, - *y*, - *z*].

The bidentate chelation mode of cyt ligand has been found in $\{[Ca(cyt)Cl_2]\cdot H_2O\}_n$ (**3a**)[34], the unique structurally characterized compound of Ca^{2+} with this nucleobase, but, despite the similarity with **2** and **3**, the previously reported compound **3a** show a chain motif. Compound **3** is different with respect to the previous known compound because of the further coordination of a monodentate nucleobase and a water molecule replacing a coordinated chloride in **3a**, eluding the polymerization.

The Ca–N3 [2.555(3) (**2**), 2.573(4) Å (**3**)] and the $Ca–O2_{bridging}$ distances for **2** and **3** [Ca–O(2) 2.540(3) and Ca–O(2a) 2.323(3)

Å, (a): -*x*, -*y*, -*z*; (**2**), Ca–O(21) 2.524(3) and Ca–O(21a) 2.404(3) Å, (a): -*x*, -*y*, -*z* + 1; (**3**)] (see Figs 3 and 4 and Tables S2 and S3) are in the same range found in **3a**.

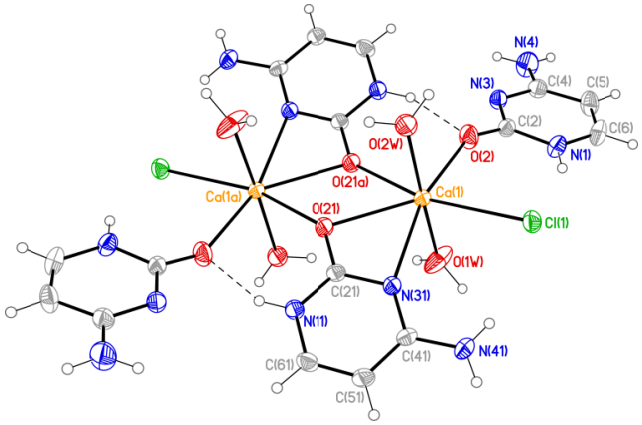

Fig.4 ORTEP drawing of the structure of **3** with atoms numbering scheme. (Thermal ellipsoids are plotted at 30% probability). [Symmetry code: (a) - *x*, - *y*, - *z* + 1].

In **3** the Ca-O(2) distance related to the monodentate cyt is 2.312(3) Å shorter than that found for the bridging cyt, as expected. The Ca–O_{water} bond lengths are slightly longer in **2** [2.396(3) and 2.421(3) Å] in respect to those found in **3** [2.327(3) and 2.356(3) Å]. The monodentate perchlorate anion in **2** exhibits a shorter bond distance [2.423(3) Å] in respect to those observed for the bidentate one [2.521(3) and 2.722(4) Å]. The Ca-Cl bond length in **3** [2.817(2) Å] is in agreement with those found in previous reported compounds[34].

The terminal cyt rings in **3** are tilted, bent around the *trans* conformation with a dihedral angle with chelating cyt of 24.32°(1) (Fig. 5b).

The intramolecular Ca(1)–Ca(1a) distances (*r*) are 3.977(1) and 4.158(1) Å in **2** and **3** respectively. The shortest intermolecular Ca(1)–Ca(1b) separations are 7.042(1) and 6.542(1) Å (b = -1 + *x*, *y*, *z* (**2**); -*x*, 1-*y*, 1-*z* (**3**)).

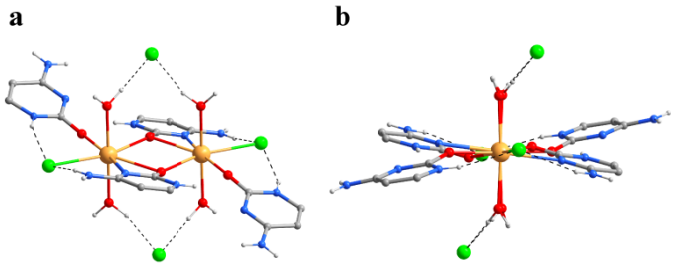

Fig.5 a) Front view b) side view of the indirect interactions to the dinuclear core of chloride atoms in **3**.

In the crystal packing of **2** the monodentate perchlorate anions interact with the $–NH_2$ groups of adjacent dimers, building double H-bonds bridges (Fig. 6). Further H-bonds interactions involving perchlorate anions and water molecules stabilize the whole lattice (see Table S8).

In the crystal packing of **3** two hydrogen bonds contribute to the stabilization of the dimers (Fig.5) involving both chloride anions (see Table 7) and coordinated water molecules, leading to layers lying in the *bc* crystallographic plane (Figure 7). In addition, parallel-displaced π-stacked arrangement of the chelating cytosine nucleobase rings exists. The average inter-ring C–C distance is 3.40 Å, and the angle between the centroid-centroid vector from the facing nucleobase rings and their normal (θ) is 32.3(1)°.

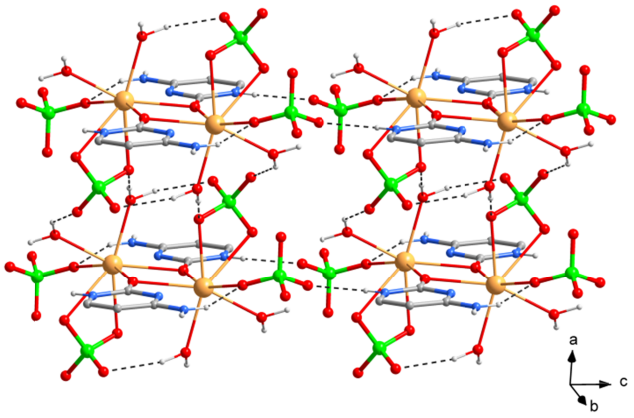

Fig.6 Perspective view of the crystal packing of **2**.

The influence of the anions is pretty evident comparing **2** and **3.** It is worth noting that they contend with monodentate cyt for the coordination toward Ca^{2+}. Keeping in mind the 1:1 M/L molar ratio used in the preparation of both compounds, and the common dimeric core $[Ca_2(cyt)_2(H_2O)_4X_2]^{2+}$ (where X = ClO_4^- (**2**) and Cl^-(**3**)), it is evident that **3** is formed because of the ligand cyt succeeds in the competition with chloride. It can be realized that monodentate cyt ligand appears to be less coordinative than ClO_4^- anion but definitively more efficient of Cl^- in binding Ca^{2+} ion.

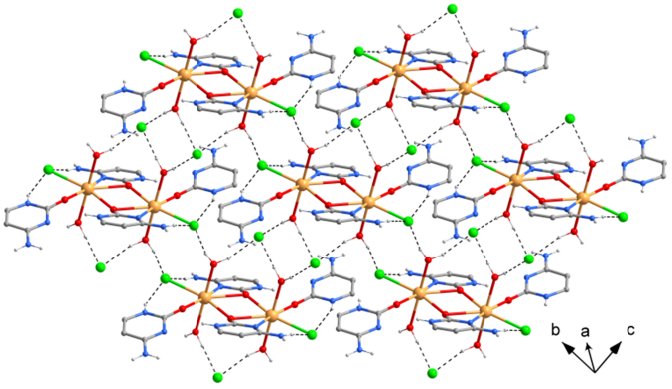

Fig.7 Perspective view of the crystal packing in **3.**

Structures of $[Ca(H_2cyd)_2(H_2O)_4](ClO_4)_2 \cdot 3H_2O$ (4) and $[Ca(H_2cyd)_2(H_2O)_4]Cl_2 \cdot 3H_2O$ (5).

Compounds **4** and **5** are constructed by $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ cationic units, perchlorate (**4**)/chloride (**5**) as counterions and crystallization water molecules. In the asymmetric unit two crystallographically non-equivalent cationic units are present. The asymmetric cationic entity with atom numbering scheme are depicted in Fig. 8 and Fig. 9, for **4** and **5**, respectively.

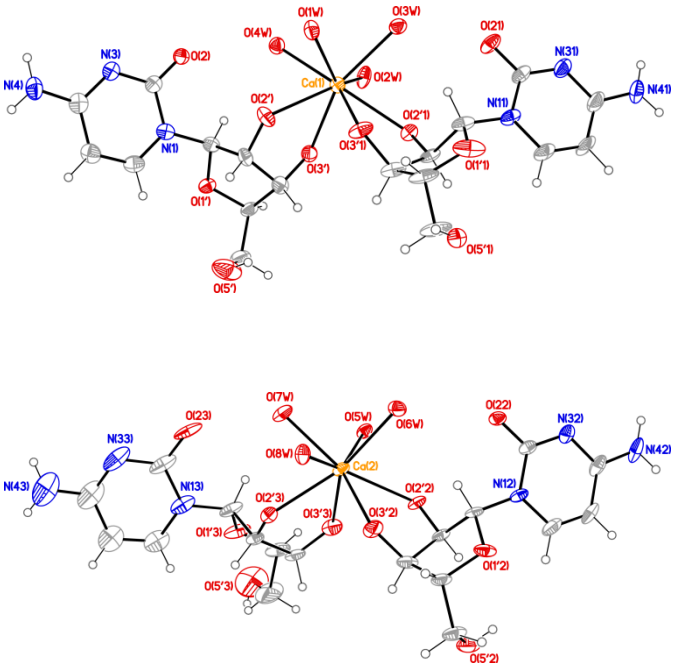

Fig. 8 ORTEP drawing of the cationic $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ units in **4** with atoms numbering scheme. (Thermal ellipsoids are plotted at 30% probability).

The mononuclear $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ unit contains two H_2cyd neutral ligands chelating the metal ion through the O(2') and O(3') hydroxyl groups of ribonucleosides. Consequently, the Ca(1) and Ca(2) atoms result involved in the formation of five-membered chelate rings. The coordination around Ca^{2+} ions is completed by four oxygen atoms of water molecules. Both in **4** and **5** structures, each calcium(II) results octacoordinated, with highly distorted geometry. In **4** Ca(1) lie in a plane defined by O(1w), O(3w), O(2') and O(3'), atoms, quite perpendicular (91.3°) to the plane defined by O(2w), O(4w), O(2'1), O(3'1) set of atoms. Concerning the environment of Ca(2), O(5w), O(7w), O(2'2) and O(3'2) set of atoms define the equatorial plane containing the metal ion. The other four atoms, O(6w), O(8w), O(2'3) and O(3'3) hardly define a good plane with significant deviations up to 0.197(1) Å]. The Ca-O(2') bond lengths in **4** [mean value of 2.469(3) Å] (see Table S4) are quite similar to those observed for Ca-O(3') [mean value of 2.460(3) Å] except the Ca(1)-O(2'1) [2.531(3)] that is somewhat longer. The Ca-O_{water} distances are very similar to each other varying in the range Å 2.413(3)-2.483(3).

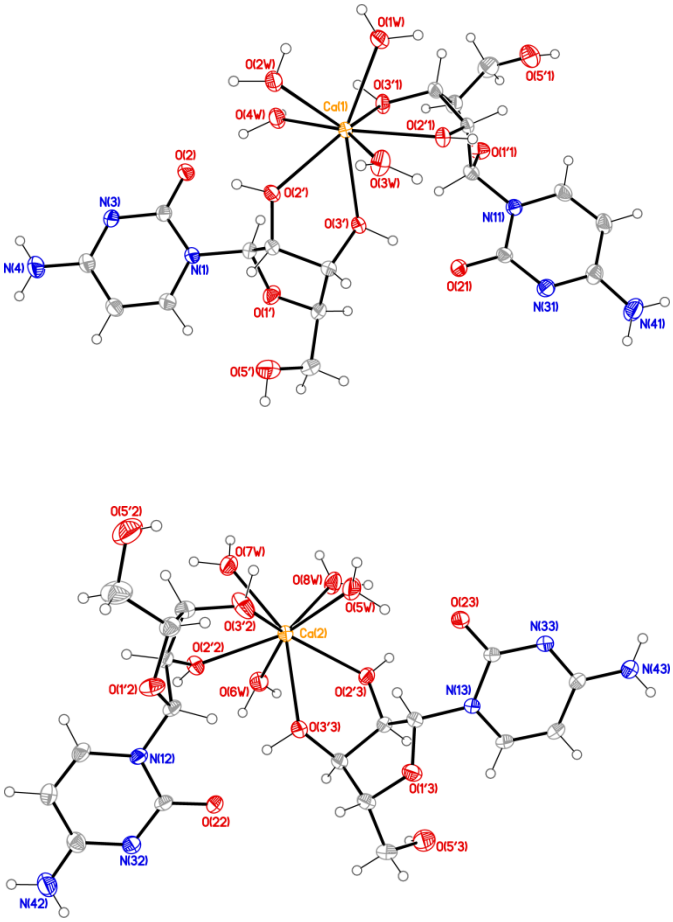

Fig. 9 ORTEP drawing of the cationic $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ units in **5** with atoms numbering scheme. (Thermal ellipsoids are plotted at 30% probability).

In **5** the coordination geometry around each Ca(II) may be considered as derived by a pentagonal bipyramid with an axial position split. The equatorial positions are defined by O(2'), O(2'1) and O(3'1), and O(2'3), O(2'2), O(3'2) set of atoms from two H_2cyd molecules, for Ca(1) and Ca(2), respectively and two oxygen atoms of water molecules [O(3w) and O(4w), for Ca(1)], [O(5w) and O(6w), for Ca(2)]. An axial position is filled by O(3') [Ca(1)] and O(3'3) [Ca(2)] oxygen atoms. The split axial positions are occupied by O(1w) and O(2w), for Ca(1), O(7w) and O(8w), for Ca(2). Unlike in **4**, in compound **5** structure the Ca-O(3') bond lengths [mean value of 2.525(2) Å]

are longer than those for Ca-O(2') [mean value of 2.435(2) Å] and Ca-O_{water} [range 2.386(2)-2.462(2) Å] (see Table S5).
In both structures the pyrimidine rings from the nucleobase are planar and exhibit an *anti*-disposition. The ribose moiety is puckered with a C2'-*endo* conformation and its absolute configuration is C(1')*R*, C(2')*R*, C(3')*R*, C(4')*R*.
Although the chelation through the O(2') and O(3') hydroxyl groups of ribonucleosides towards Ca^{2+} ions is known,[32] it is still rare. On the other hand, even that, to the best of our knowledge, no examples of nucleoside and Ca^{2+} adducts exist in literature, the chelating coordination mode in **4** and **5** is most likely the favourite binding way due to the chelate effect.
In the crystal packing of **4** an extended network of hydrogen bonds together with very efficient stacking interactions contribute to stabilize the whole lattice. Because of thermal and static disorder, it was not possible to clearly define the positions of some of non-coordinated perchlorate and crystallization water molecules. Our best model contains only a disordered perchlorate anion, lying on a twofold axis, interacting with cationic entities by means of host-guest interactions.

In addition, these wheel supramolecular systems, are stabilized by intra- and intermolecular hydrogen bonds involving coordinated water molecules and the O(2) oxygen atoms of the pyrimidine rings pointing toward the center of the cavities [$O_{water}\cdots O_{anions}$ distances varying in the range of 2.84(2)-3.14(1) Å]. Each wheel includes perchlorate anions, that act as templating ions, showing receptor properties through multiple H-bonding interactions toward anions, which occupy the centers of the tetranuclear motifs.
These *tetranuclear* wheels contain eight H_2cyd molecule as in the *octanuclear* Cu(II) cytidine complex,[23b] where, other than the different nature of metal ions, the dissimilar nuclearity is likely due to the deprotonation of cytidine that support the unusual O(2') bridging coordination mode observed in the Cu(II) polynuclear compound.
Neighboring tetranuclear wheels lead to layers in the *ab* plane with a AB stacking sequence running along the crystallographic *b*-axis, likely interacting by further H-bonds and built up to a porous 3D motif (total potential solvent and anion accessible voids of 29% of the volume of the unit cell) (Fig. 11).

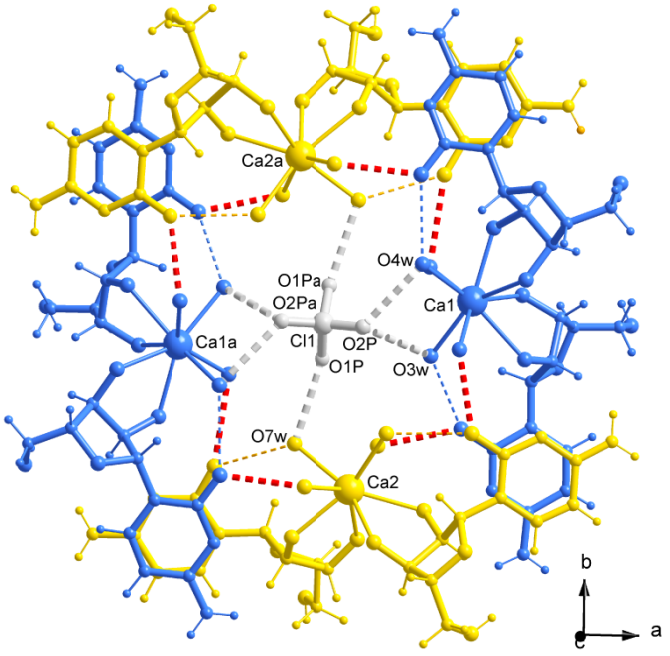

Fig.10 View along *c* crystallographic axes of the supramolecular wheel motif in **4**. [Symmetry code: (a) - *x* + 1, - *y* + 1, *z*].

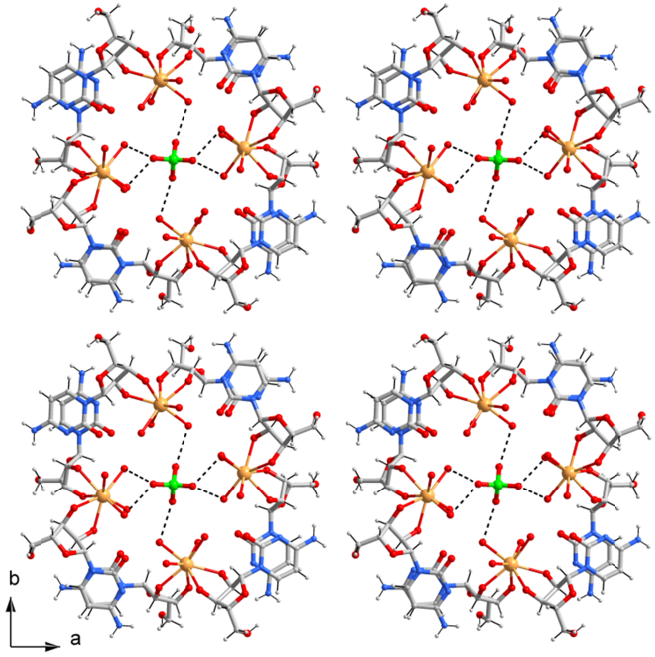

Fig.11 View along *c* crystallographic axes of the layers of tetranuclear pseudo-wheels in **4**.

As shown in Fig.10, four cationic $Ca(H_2cyd)_2(H_2O)_4^{2+}$ units are arranged in a wheel supramolecular shape, built up through π interactions between cytosine rings lying in a parallel *face-to-face* fashion at interplanar distances of 3.36(1) and 3.50(1) Å. The average inter-ring C–C distance is 3.45 Å, and the angle between the centroid-centroid vector from the facing nucleobase rings and their normal (θ) of 7.46(1) and 12.38(1)°.

The resulting overall packing suggests the occurrence of a number of crystallization water molecules, placed inside and outside of the wheels affected by thermal and static disorder.
The different nature, size and shape of the counterions in **5** are the main reasons to a pretty dissimilar crystal packing in respect to **4**.
In **5** concerted stacking interactions between pyrimidine rings (Fig. 12) and H-bonds lead to an overall 1D motif.

As shown in Fig.13, adjacent cationic $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ units are arranged in stranded base-stacked ribbons, in which pyrimidine bases are aligned parallel to one another with interplanar distances of 3.44(1) and 3.55(1) Å and an average inter-ring C–C distance of 3.45 Å.

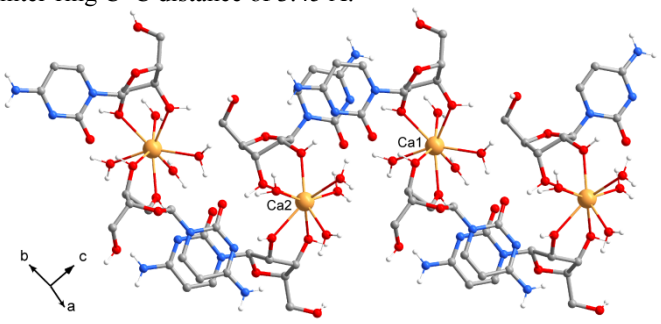

Fig.12 Perspective view of stacking interactions between pyrimidine rings leading to an overall 1D motif in **5.**

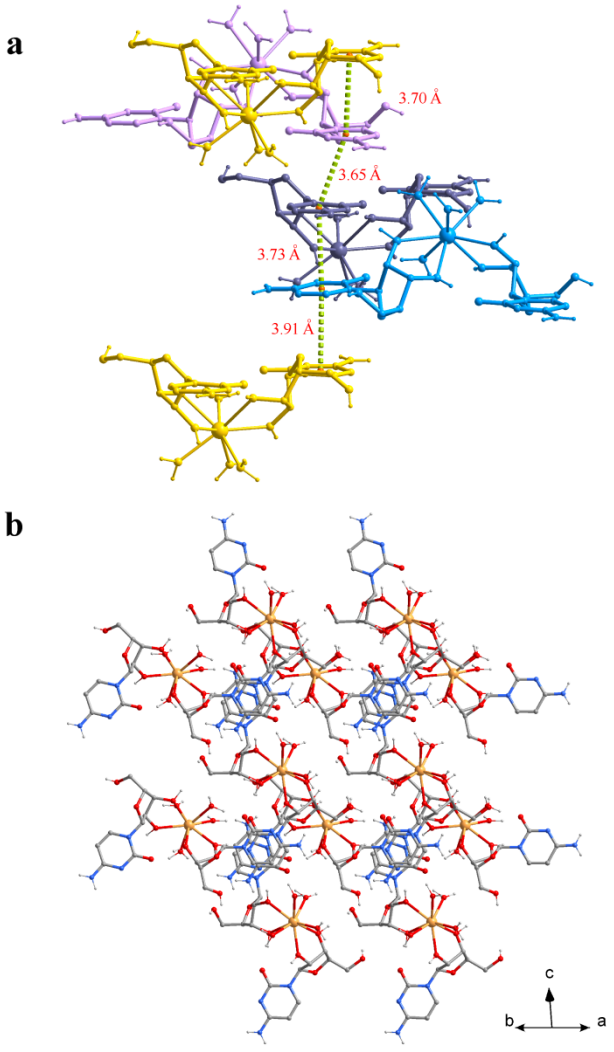

Fig. 13. (a) Side view and (b) top view of adjacent cationic $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ units arranged in stranded base-stacked ribbons motif in **5**.

The angles between the centroid-centroid vector from the facing nucleobase rings and their normal (θ) are 19.5(1) and 24.68(1)°. These values clearly indicate a larger off-set of pyrimidine rings with respect to those observed in **4**. As in compound **4**, within the cationic entities, the oxygen atoms O(2) of the nucleobase are involved in intramolecular H-bonds, acting as acceptors towards coordinated water molecules or O(3') oxygen atoms of the sugar moieties [O(2)···O(4w) and O(21)···O(3') for Ca(1) units, O(23)···O(5w) and O(22)···O(3'3) for Ca(2) units] (Fig. 9). Their surroundings, characterized by an extended network of intermolecular H-bonds, involving chloride anions, coordinated and lattice water molecules, together with oxygen and nitrogen atoms of H_2cyd ligands, also contribute to stabilize the chain motif (see Table S10).

Structure of $[Ca_2(CMP)_2(H_2O)_{11}]\cdot 5H_2O$ (6).

The structure of compound **6** consists of neutral $[Ca_2(CMP)_2(H_2O)_{11}]$ moieties and crystallization water molecules. Each molecule contains two Ca^{2+} ions, and two CMP anions exhibiting different coordination mode, together with eleven coordinated water molecules (Figure 14). Remarkably no coordination of Ca^{2+} ions towards phosphate groups occurs.

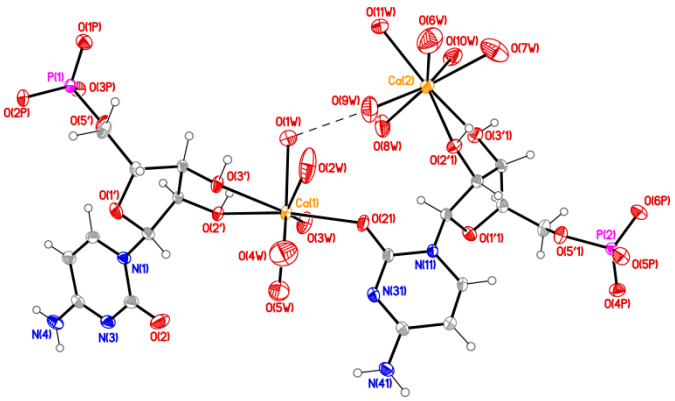

Fig.14 ORTEP drawing of the $Ca_2(CMP)_2(H_2O)_{11}$ molecules in **6** with atom numbering scheme. (Thermal ellipsoids are plotted at 30% probability)**.**

One of the CMP ligand acts as bridge, chelating through the O(2') and O(3') hydroxyl groups of the ribose at Ca(2) and, simultaneously, coordinating *via* O(2) at Ca(1) of the nucleobase. The other CMP ligand chelate Ca(1) through the O(2') and O(3') atoms. Consequently the two bridged Ca^{2+} ions are crystallographically not equivalent.

Each Ca^{2+} ion is octacoordinated Ca(1) is linked to oxygen atom O(2) of the pyrimidine base of the bridging CMP anion and O(2') and O(3') of the ribose of the auxiliary CMP, having completed the coordination environment by five solvent

molecules. Ca(2) is linked only to a chelating CMP ligand and to six water molecules (Fig. 13).

The coordination geometry around Ca(1) may be described as derived by a highly distorted pentagonal bipyramid with equatorial positions defined by O(1W), O(2W), O(3W), O(4W) and O(5W) set of atoms, an axial position defined by O(21) oxygen atom of the coordinated nucleobase and the second one split in two positions, defined by O(2') and O(3') hydroxyl groups. In regards to Ca(2) surrounding, no ideal geometry can be found: the oxygen atoms O(2'1) and O(3'1) of CMP are on the opposite side of the O(11w) oxygen atom, but the other five oxygen atoms of water molecules hardly define a plane. The Ca-O_{water} bond lengths vary in the range 2.370(5) - 2.608(5) Å. The Ca-O(2') bond lengths [mean value of 2.540(2) Å] are longer than those for Ca-O(3') [mean value of 2.404(4) Å]. Meaningfully the Ca(1) - O(21) bond length is the shortest one [2.361(2) Å] (see Table S6).

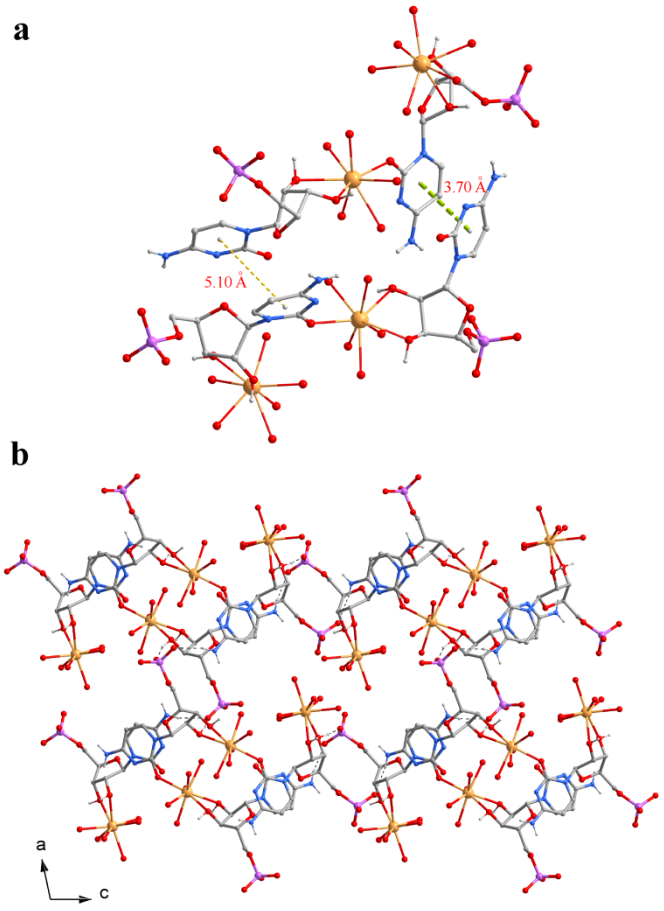

Fig.15 (a) View along *a* crystallographic axes of two adjacent molecules in **6** interconnected by π-interactions; (b) packing view showing parallel face-to-face interactions between pyrimidine rings, to give a 1D ribbon-like supramolecular motif.

In the whole molecule the pyrimidine rings from the nucleobase are planar and exhibit a conformation *anti* with respect to the sugar ring. The ribose moiety is puckered with a C2'-*endo* and *gauche-gauche* conformation about the C4'-C5' bond. Its absolute configuration is C(1')*R*, C(2')*R*, C(3')*R*, C(4')*R*.

Intramolecular H-bonds among O(1W) and O(9W) water molecules from the Ca(1) and Ca(2) coordination spheres, respectively (Fig. 14), contribute to enhance the stability of dimers. In the crystal packing of **6**, the $[Ca_2(CMP)_2(H_2O)_{11}]$ molecules are joined by stacking interactions between pyrimidine rings, arranged in a offset parallel face-to-face mode giving rise to a 1D ribbon-like motif (Fig. 15). The observed interplanar distances among aromatic rings vary in the range 3.48(1) – 3.70(1) Å. The angle between the centroid-centroid vector from the closest facing nucleobase rings and their normal (θ) is of 19.9° (Fig. 15b). H-bond interactions, involving crystallization water molecules and oxygen atoms of the phosphate groups, ensure the cohesion between chains (see Table S11).

The lack of Ca^{2+} ions coordination towards phosphate groups observed in **6** demonstrates that the binding mode through chelation *via* the O(2') and O(3') hydroxyl groups, observed also in the structures of compounds **4** and **5**, is a "credible" coordination mode towards Ca^{2+} ions even in presence of the phosphate groups. In other words, the O(2') site competes with the phosphate group for the coordination and, sometimes, can succeed, which is, most likely, due to the chelate effect. Furthermore, compound **6** represents the first evidence of Ca^{2+} ion coordinated to nucleobase and ribose moiety, while the phosphate group, surprisingly, is only "endorsed" to engage H-bonds interactions.

Conclusions

In the present work we have reported the synthesis and X-ray structure analysis of six new adducts of Ca^{2+} with cytosine (compounds **1**-**3**), cytidine (compounds **4**-**5**) and cytidine 5'-monophosphate (compound **6**). These nucleic acid constituents show similarities, offering more and more possibilities for coordination from cyt to H_2cyd and CMP. There are many structural studies on cyt, H_2cyd and CMP compounds with transition metal ions, but very few of those with alkaline earth metal ions remain. In particular, restricting ourselves to the Ca^{2+} ion, only a structure of a cytosine compound, where the nucleobase coordinates, as chelating ligand, *via* N3-O2, and, simultaneously, *via* O2, giving rise to a chain motif, is known. Compounds **2** and **3** confirm this coordination mode, even if they are dinuclear species in which the different nature, size and shape of anions play an active role in the overall structures. Interestingly, compound **2** was obtained in mixture with the mononuclear compound **1**. In the structure of **1**, Ca^{2+} exhibits an atypical hexa-coordination, that is most likely driven by the formation of supramolecular assemblies containing crystallization water molecules and *non-innocent* perchlorate anions. Fascinatingly, the motif is analogues to those previously

reported for Mg(II), Mn(II), Co(II) and Ni(II), despite the different nature of the metal ions involved.[27,29]

Cytidine Ca(II) compounds (**4-5**) are substantially different if compared to those of cytosine. In this case, both using perchlorate or chloride as counterions, analogous structural units are obtained. These units contain $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ moieties, where neutral cytidine molecules coordinate *via* O(2') and O(3') atoms of the ribose. As far as we are aware, they are the first isolated cytidine-containing calcium(II) complexes. It is noteworthy as, although containing similar structural units, they show a different crystal packing. Both are packed by means of stacking interactions between the pyrimidine rings and hydrogen bonds in which perchlorate (**4**) or chloride (**5**) anions are involved, but the resulting motif is totally different. In **4**, four cationic $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ units are arranged, by means of stacking interactions between the pyrimidine rings, in a wheel - like supramolecular system. Each pseudo-wheel shows receptor properties through multiple H-bonding interactions toward perchlorate anions, acting as template agent, which occupy the centers of the tetranuclear motifs. On the contrary, in the structure of **5**, depending on the different size and shape of the chloride anions, a 1D supramolecular motif is formed.

Finally, also cytidine 5'-monophosphate Ca(II) compound (**6**) exhibits the O(2'), O(3') chelating coordination mode observed in the cytidine compounds, but, in addition, the monodentate one *via* O(2) of the nucleobase. Therefore, it became similar to the corresponding CMP Ba(II) compound. However, despite what observed for Ba(II) ion,[28] no-coordination of Ca(II) ions to phosphate groups, that are merely engaged in H-bonds interactions, is present. Compound **6** represents the first evidence of Ca^{2+} coordination to nucleobase and ribose moiety without involvement of phosphate groups. Then, the donor sites competition of the nucleoside cytidine towards metal ions is a never-ending story, being still active and fruitful even in presence of the favourite winner as the phosphate group.

The outcomes reported are certainly not predictive for nucleic acids behaviour in their biologically environment, due to the presence in them of more stable hydrogen bonds, electrostatic interactions and steric hindrances, that may prevent the metal ions, in the hydrated form, to reach the likely binding sites. However, the results reported in this work, can contribute to a better knowledge of the ground rules relating donor sites of DNA and RNA bricks with metal ions. Indeed, it is really surprising to see that the sugar moieties in the cytidine and, even more so, in CMP, is always linked. Noteworthy, this binding mode occurs: i) in water ii) with no sugar deprotonation and, what is astonishing is that, the phosphate group, "chooses" to be engaged, exclusively, in hydrogen bonds.

Experimental Section

Materials and equipment.

The cyt, H2cyd and cytidine 5'-monophosphate disodium salt (CMP) ligands were purchased of reagent grade and used without further purification. The elemental analysis (C, H, N) were performed on a Perkin-Elmer 2400 elemental analyzer. The IR spectra of compounds **1-6** were recorded with a Nicolet 5700 FTIR spectrometer with pressed KBr pellets in the 4000–500 cm^{-1} region.

Synthesis of $[Ca(cyt)_2(H_2O)_4](ClO_4)_2 \cdot 2cyt \cdot 2H_2O$ (1) and **$[Ca_2(cyt)_2(H_2O)_4(ClO_4)_4]$ (2).** An aqueous solution (5 mL) of cyt (0.2 mmol, 0.023 g) obtained after gently warming to facilitate the base dissolution, was added to an aqueous solution (5 mL) of $Ca(ClO_4)_2 \cdot 4H_2O$ (0.2 mmol, 0.062 g) dropwise under stirring at room temperature. The resulting colourless solution gave X-ray quality colourless tiny needles of **1** in mixture with irregular parallelepipeds of **2** upon slow evaporation after two weeks. The solids were recovered by filtration, and air dried. Crystals of **1** and **2** were separated by hand (compound **1** was the minor product of the reaction that gave crystals of **2** as main product). All attempts to obtain compound **1** in a higher yield, starting from the M:L ratio 1:4 or 1:2, were unsuccessful and constantly the unreacted cytosine nucleobase precipitate as colourless plate crystals. Analytical data for **1**: Anal. Calcd for $C_{16}H_{32}CaCl_2N_{12}O_{18}$ (**1**): C 24.28; H 4.08; N 21.24 Found: C 24.29, H 4.04, N 21.14; IR (KBr): ν = 3521 (O–H), 1715, 1632, 1605 cm^{-1} (C=O). Analytical data for **2**: Anal. Calcd for $C_8H_{18}Ca_2N_6O_{22}Cl_4$ (**2**): C, 12.44; H, 2.35; N, 10.88% Found: C, 12.13; H, 2.33; N, 10.77%.; IR (KBr): ν = 3474 (O–H), 1648, 1607 cm^{-1} (C=O).

Synthesis of $[Ca_2(cyt)_4(H_2O)_4Cl_2]Cl_2$ (3). An aqueous solution (5 mL) of cyt (0.2 mmol, 0.022 g) obtained after gently warming (T = 40 °C), was added to an aqueous solution (5 mL) of $CaCl_2 \cdot 2H_2O$ (0.2 mmol, 0.030 g), dropwise under stirring at room temperature. The resulting colourless solution gave X-ray quality colourless irregular parallelepipeds of **3** upon slow evaporation after two weeks together with traces of plate-like crystals of compound of formula $\{[Ca(cyt)Cl_2] \cdot H_2O\}_n$ (**3a**) previously reported.[34] The solid was recovered by filtration, air dried and crystals of **3** were separated by hand (70% yield). It is worth to point out that, when the reaction solution was heated at 80 °C, crystals of **3a** were precipitated with a good yield. Their structure was confirmed by determination of cell parameters of a selected plate-like crystal. Anal. Calcd for $C_{16}H_{28}Ca_2N_{12}O_8Cl_4$ (**3**): C, 26.02; H, 3.82; N, 22.76%. Found: C, 26.09; H, 3.75; N, 22.67%.; IR (KBr): ν = 3432 (O–H), 1718, 1678, 1623 cm^{-1} (C=O).

Synthesis of $[Ca(H_2Cyd)_2(H_2O)_4](ClO_4)_2 \cdot 3H_2O$ (4) and $[Ca(H_2Cyd)_2(H_2O)_4]Cl_2 \cdot 3H_2O$ (5). An aqueous solution (10 mL) of $CaX_2 \cdot yH_2O$ [where X = ClO_4^-, y = 4 (**4**), Cl^-, y = 2 (**5**)] (0.2 mmol, 0.062 g (**4**), 0.2 mmol, 0.030 g (**5**)) was added to an aqueous solution (10 mL) of H_2Cyd (0.5 mmol, 0.100 g) under stirring at room temperature (pH = 5). The colourless reaction mixture was further stirred for 30 min under gentle warming and then left to slowly evaporate at room temperature. After three days in the reaction vessel, X-ray quality colourless rhombuses crystals of **4** (**5**) appeared. The solid was recovered by filtration and air dried (70% (**4**), 60% (**5**) yield). Anal. Calcd for $C_{18}H_{40}CaN_6O_{25}Cl_2$ (**4**): C, 25.39; H, 4.73; N, 9.87%. Found: C, 25.96; H, 4.71; N, 10.09%. IR (KBr): 3478 (O–H), 1741, 1624 cm^{-1} (C=O). Anal. Calcd for

$C_{18}H_{40}CaN_6O_{17}Cl_2$ (**5**): C, 29.88; H, 5.57; N, 11.62%. Found: C, 30.00; H, 5.26; N, 11.66%. IR (KBr): 3520 (O–H), 1752, 1603 cm^{-1} (C=O).

Synthesis of $[Ca_2(CMP)_2(H_2O)_{11}]\cdot 5H_2O$ (6). An aqueous solution (10 mL) of $Na_2CMP\cdot 6H_2O$ (0.2 mmol, 0.074 g) was added to an aqueous solution (10 mL) of $CaCl_2\cdot 2H_2O$ (0.2 mmol, 0.030 g) dropwise under stirring at room temperature. The colourless reaction mixture was further stirred for 20 min under gentle warming and then, after two weeks, upon slow evaporation at room temperature X-ray quality colourless prisms of **6** appeared. The same product has been obtained starting from $Ca(ClO_4)_2\cdot 4H_2O$ as source of Ca^{2+} ions and running with the same reaction conditions (70% yield). (**6**) Anal. Calcd for $C_{18}H_{56}Ca_2N_6O_{32}P_2$: C, 21.39; H, 5.58; N, 8.31%. Found: C, 21.08; H, 5.69; N, 8.21%. IR (KBr): 3410 (O–H), 1638, 1603 cm^{-1} (C=O), 1070, 1113 cm^{-1} (P=O).

X-ray crystallography. Single-crystal X-ray diffraction data of **1-6** were generally collected at room temperature on either a Bruker R3m/V automatic four-circle (**1-3**) or a Bruker-Nonius X8APEXII CCD area detector diffractometer (**4-6**) using graphite-monochromated Mo-Kα radiation (λ = 0.71073 Å); data for compound **4** were collected at 100 K. Lorentz-polarization and empirical absorption corrections through the Ψ-scan program[35] were applied to compounds **1-3**. All calculations for data reduction, structure solution, and refinement for **4-6** were performed through the SAINT[36] and SADABS[37] programs. The structures were solved by direct methods and subsequently completed by Fourier recycling using the SHELXTL software package.[38] All non-hydrogen atoms were refined anisotropically. In compounds **1** and **4** two sets for oxygen atoms of the perchlorate anion have been modelled with refined occupancy factors. A double position has been refined also for the O(5') oxygen atom of a ligand in **4** and for the lattice molecule O(16)w in **5**.

The hydrogen atoms were set in calculated positions and refined as riding atoms. The hydrogen atoms on water molecules, when assigned, were refined with restraints on O-H distances and H-O-H angles. In compound **4** the contribution to the diffraction pattern from the perchlorate anions and the water molecules of crystallization (96 molecules of H_2O and 56 perchlorate anions located in the voids of the lattice that amount to 29 % percentage void volume of the unit cell), were subtracted from the observed data by using the SQUEEZE method, as implemented in PLATON.[39] The residual agreement factors for reflections with $I > 2\sigma(I)$ for **4** were $R_1 = 0.0771$ and $wR_2 = 0.2157$ before SQUEEZE whereas they were and $R_1 = 0.0597$ and $wR_2 = 0.1704$ after SQUEEZE. The final formulation of the compound is in agreement with the residual electron density and volume.

The final geometrical calculations and the graphical manipulations were carried out with PARST97[39] and DIAMOND[40] programs, respectively. The crystal data are presented in Table 1.

Acknowledgements

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Notes and references

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†Electronic Supplementary Information (ESI) available: Tables S1-S6 of selected bond lengths and angles and Tables S7-S11 of hydrogen bonds for **1-3** and **5-6**. CIF files for **1-6** complexes. CCDC 989699-989704. For ESI and crystallographic data in CIF or other electronic format see. DOI: /10.1039/b000000x.

1 C. Hsiao, E. Tannenbaum, H. VanDeusen, E. Hershkovitz, G. Perng, A. R. Tannenbaum and L. Dean Williams, *Metal Ion–Nucleic Acid Interactions*, ed. Hud Nicholas V., Royal Society of Chemistry, 2009, pp. 1-38.

2 B. Lippert *Metal Ion–Nucleic Acid Interactions*, ed. Hud Nicholas V., Royal Society of Chemistry, pp. 39-74.

3 (a) G. L. Eichhorn, *Adv. Inorg. Biochem.*, 1981, **3**, 1; (b) N. Hadjiliadis and E. Sletten, *Metal-complexes–DNA interactions*, Blackwell Publishing Ltd, John Wiley & Sons Ltd., 2009.

4 (a) S. I. Nakano, M. Fujimoto, H. Hara and N. Sugimoto, *Nucleic Acids Res.*, 1999, **27**, 2957; (b) D. Armentano, G. De Munno, L. Di Donna, A. Napoli, G. Sindona, G. Giorgi and L. Salvini, *J. Am. Soc. Mass Spectrom.* 2004, **15**, 268-279.

5 (a) S. Sikova and S. Rowan, *Chem. Soc. Rev.*, 2005, **34**, 9; (b) J. A. R. Navarro and B. Lippert, *Coord. Chem. Rev.*, 2001, **22**, 219.

6 P.-H. Qin, W.-C. Lu, P.-J. Guo, W. Qin, L.-Z. Zhao, and W. Song, *J. Theor. Comput. Chem.*, 2012, **11**, 1183-1199.

7 J. E. Šponer, V. Sychrovský, P. Hobza, and J. Šponer, *Phys. Chem. Chem. Phys.,* 2004*,* **6**, 2772-2780.

8 J. V. Burda, J. Šponer, and P. Hobza, *J. Phys. Chem.* 1996, **100**, 7250-7255.

9 A. S. Petrov, G. R. Pack, and G. Lamm, *J. Phys. Chem. B,* 2004, **108**, 6072-6081.

10 J. E. Šponer, J. V. Burda, J. Leszczynki, and J. Šponer, *Computational Studies of RNA and DNA*, Chapter 15 *Interactions of Metals Cations with Nucleic Acids and their Building Units,* J. Šponer and F. Lankas (eds.), © 2006 Springer, Netherlands, pp. 389–410.

11 (a) B. Lippert, *Progress in Inorganic Chemistry*, ed. K. D. Karlin, John Wiley and Sons, New York, 2005, vol. 54, pp. 385-447. (b) B. Lippert, *Coord. Chem. Rev.*, 2000, **200-202**, 487-516.

12 (a) P. K. Ganguli, T. Theophanides, *Inorg. Chim. Acta*, 1981, **55**, L43; (b) G. Wilkinson, R. D. Gillard., J. A. McCleverty, *Comprehensive Coordination Chemistry*, Pergamon Press, Oxford, 1987, vol. 4, p. 635; (c) A. Marzotto, D. A. Clemente, A. Ciccarese, and G. Valle, *J. Crystallogr. Spectrosc. Res.,* 1993, **23**, 119; (d) E. Bugella-Altamirano, D. Choquesillo-Lazarte, J. M. González-Pérez, M. J. Sánchez-Moreno, R. Marín-Sánchez, J. D. Martín-Ramos, B. Covelo,

R. Carballo, A. Castiñeiras, and J. Niclós-Gutiérrez, *Inorg. Chim. Acta* 2002, **339**, 160.

13 (a) H. Siegel, *Chem. Soc. Rev.* 1993, **22**, 255; (b) M. Palaniandavar, I. Somasundaram, M. Lakshminarayanan, and H. Manohar, *J. Chem. Soc. Dalton Trans.* 1996, 1333; (c) M. Sabat, B. Lippert, A. Siegel, H. Siegel, *Metal Ions Biol. Syst*., 1996, **33**, 143; (d) M. Sabat, A. Siegel, H. Siegel, *Metal Ions Biol. Syst*., 1996, **32**, 521; (e) R. Bau, M. Sabat, and B. Lippert, *Cispl. Chem Bioche. Lead. Antican. Drug*, 1999, 319; (f) W. Bruning, E. Freisinger, M. Sabat, R. K. O. Siegel, and B. Lippert*, Chem. Eur. J.*, 2002, **8**, 4681; (g) D. Gupta, M. Huelsekopf, M. Morell Cerda, R. Ludwig, and B. Lippert, *Inorg. Chem.* 2004, **43**, 3386.

14 (a) C. L. Coulter, *J. Am. Chem. Soc.* 1973, **95**, 570; (b) K. Ogawa, M. Kumiashi, K. I. Tomita, and S. Shirotake, *Acta Crystallogr.* 1973, **B36**, 1793; (c) J. Pandit, T. P. Seshadri, and M. A. Viswamitra, *Acta Crystallogr.* 1983, **C39**, 342; G. H. Borodi, A. Hernanz, I. Bratu, M. Pop, and R. Navarro, *Acta Cryst*. 2001, **E57**, m514; (d) A. E. Gibson, C. Price, W. Clegg, and A. Houlton*, J. Chem. Soc., Dalton Trans*. 2002, 131.

15 (a) H. Yang, K. L Metera, and H. F. Sleiman, *Coord. Chem. Rev.,* 2010, **254**, 2403; (b) A. Singh, M. Tolev, M. Meng, K. Klenin, O. Plietzsch, C. I. Schilling, T. Muller, M. Nieger, S. W. Wenzel, and C. Richert, *Angew. Chem. Int. Ed.,* 2011, **50**, 3227; (c) T. J. Bandy, A. Brewer, J. R. Burns, G. Marth, T. N. Nguyen, and E. Stulz, *Chem. Soc. Rev.* 2011, **40**, 138; (d) J.-L. H. A. Duprey, Y. Takezawa, and M. Shionoya, *Angew. Chem. Int. Ed.* 2013, **52**, 1212.

16 (a) R. A. Smaldone, R. S. Forgan, H. Furukawa, J. J. Gassensmith, A. M. Z. Slawin, O. M. Yaghi, and J. F. Stoddart, *Angew. Chem. Int. Ed.*, 2010, **49**, 46; (b) I. Imaz, M. Rubio-Martínez, J. An, I. Solé-Font, N. L. Rosi, and D. Maspoch, *Chem. Commun.*, 2011, **47**, 7287; (c) Y. Q. Y. Liu, and Z. Tang, *Chem. Eur. J.* 2012, **18**, 4 ; (d) H. L. Zheng, X. Zhu, X. Guo, and J. Y. Liu, *Solid State Sciences*, 2013, **18**, 42.

17 S. Verma, A. K. Mishra and A. Kumar, *Acc. Chem. Res*., 2010, **43**, 79–91.

18 (a) E. Sletten, *Acta Crystallogr., Sect. B: Struct. Crystallogr. Cryst. Chem.*, 1969, **B25**, 1480–1491; (b) P. X. Rojas-Gonzàlez, A. Castineiras, J. M. Gonzàlez-Pérez, D. Choquesillo-Lazarte and J. Nicolòs-Gutiérrez, *Inorg. Chem.*, 2002, **41**, 6190–6192; (b) J. Y. An, R. P. Fiorella, S. J. Geib and N. L. Rosi, *J. Am. Chem. Soc.*, 2009, **131**, 8401–8403.

19 (a) P. I. Vestues and E. Sletten, *Inorg. Chem*., 1981, **52**, 269–274; (b) C. S. Purohit and S. Verma, *J. Am. Chem. Soc*., 2006, **128**, 400–401; (c) C. S. Purohit and S. Verma, *J. Am. Chem. Soc*., 2007, **129**, 3488–3489.

20 K. Gillen, R. Jensen and N. Davidson, *J. Am. Chem. Soc.,* 1964, **86**, 2792–2796.

21 J. An, S. J. Geib and N. L. Rosi, *J. Am. Chem. Soc*., 2010, **132**, 38–39.

22 J. P. Garcia-Teran, O. Castillo, A. Luque, U. Garcia-Couceiro, P. Roman and L. Lezama, *Inorg. Chem*., 2004, **43**, 4549–4551.

23 E. C. Yang, H. K. Zhao, B. Ding, X. G. Wang and X. J. Zhao, *New J. Chem.*, 2007, **31**, 1887–1890.

24 C. S. Purohit, A. K. Mishra and S. Verma, *Inorg. Chem*., 2007, **46**, 8493–8495.

25 T. F. Mastropietro, D. Armentano, E. Grisolia, C. Zanchini, M. Julve, F. Lloret, and G. De Munno, *Dalton Trans*. 2008, 514.

26 D. Armentano, T. F. Mastropietro, M. Julve, R. Rossi, P. Rossi, and G. De Munno, *J. Am. Chem. Soc*. 2007, **129**, 2740; b) D. Armentano, N. Marino, T. F. Mastropietro, J. Martinez-Lillo, J. Cano, M. Julve, F. Lloret, and G. De Munno, *Inorg. Chem*., 2008, **47**, 10229; (c) N. Marino, D. Armentano, T. F. Mastropietro, M. Julve, F. Lloret, and G. De Munno, *Cryst. Growth Des*., 2010, **10**, 1757-1761.

27 M. A. Geday, G. De Munno, M. Medaglia, J. Anastassopoulou, and T. Theophanides, *Angew. Chem. Int. Ed. Engl.* 1997, **36**, 511.

28 (a) E. Shefter, and K.N. Trueblood *Acta Crystallogr.,* 1965, **18,** 1067; (b) J. Hogle, M. Sundaralingam, and J.H.Y.Lin, *Acta Crystallogr., Sect. B,* 1980, **36**, 564.

29 (a) G. De Munno, M. Medaglia, D. Armentano, J. Anastassopoulou, and T. Theophanides, *J. Chem. Soc. Dalton Trans.* 2000, **10**, 1625; (b) T. F. Mastropietro, D. Armentano, N. Marino, G. De Munno, J. Anastassopoulou, and T. Theophanides, *Cryst. Growth Des.* 2007, **7**, 609; structure of compound with formula $[Ni(cyt)_2(H_2O)_4](ClO_4)_2{\cdot}2H_2O$ has been reported as private communication.

30 (a) H. Einspahr, W. J. Cook, C. E. Bugg *ACA, Ser.2,* 1981, **9,** 32; (b) H. Einspahr, W. J. Cook, C. E. Bugg, *Biochemistry,* 1981, **20,** 5788; (c) T. Sato *Acta Crystallogr., Sect.C,* 1984, **40**, 738.

31 B. Hingerty, E. Subramanian, S. D. Stellman, T. Sato, S. B. Broyde, R. Langridge, *Acta Crystallogr., Sect.B,* 1976, **32**, 2998.

32 S. Mangani, P. Orioli, *Chem. Commun.,* 1985, 780.

33 T. Sato, *Acta Crystallogr., Sect.C,* 1984, **40**, 736.

34 K. Ogawa, M. Kumihashi, K.-I. Tomita, S. Shirotake, *Acta Crystallogr., Sect.B,* 1980, **36**, 1793.

35 A. C. T. North, D. C. Philips, F. S. Mathews, *Acta Crystallogr., Sect A,* 1968, **24**, 351.

36 *SAINT*, version 6.45, Bruker Analytical X-ray Systems, Madison, WI, 2003.

37 G. M. Sheldrick, *SADABS Program for Absorption Correction,* version 2.10, Analytical X-ray Systems, Madison, WI, 2003.

38 (a) G. M. Sheldrick, *Acta Crystallogr.* **2008**, *A64*, 112-122; (b) *SHELXTL*, Bruker Analytical X-ray Instruments, version 6.14 Madison, WI, 2003.

39 A. L. Spek, *Acta Cryst.* 2009, **D65**, 148-155.

40 *DIAMOND* 2.1d, Crystal Impact GbR,CRYSTALIMPACT K; Brandeburg&H. PutzGBR, Bonn, Germany, 2000.

Ca^{2+} metal ion adducts with cytosine, cytidine and cytidine 5'-monophosphate. A comprehensive study of calcium reactivity towards building units of nucleic acids.

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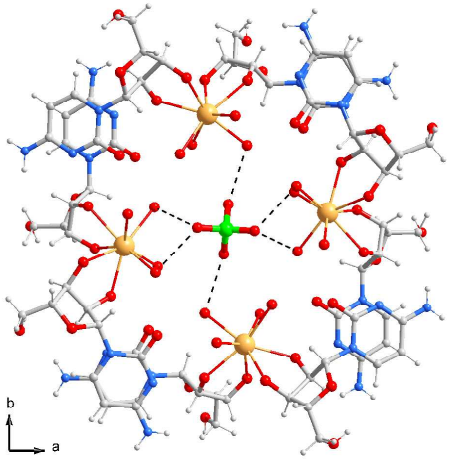
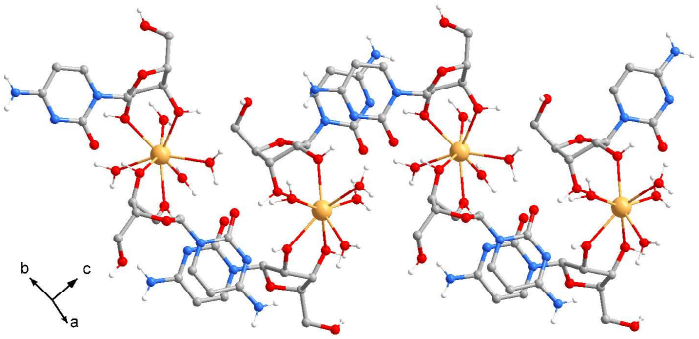
This manuscript is dedicated to Prof. Miguel Julve to celebrate his 60th birthday.

Six new Ca(II) adducts of formulae $[Ca(cyt)_2(H_2O)_4][ClO_4]_2\cdot 2cyt\cdot 2H_2O$ (**1**), $[Ca_2(cyt)_2(H_2O)_4(ClO_4)_4]$ (**2**), $[Ca_2(cyt)_4(H_2O)_4Cl_2]Cl_2$ (**3**), $[Ca(H_2cyd)_2(H_2O)_4][ClO_4]_2\cdot 3H_2O$ (**4**), $[Ca(H_2cyd)_2(H_2O)_4]Cl_2\cdot 3H_2O$ (**5**) and $[Ca_2(CMP)_2(H_2O)_{11}]\cdot 5H_2O$ (**6**) [cyt = cytosine, H_2cyd = cytidine, CMP = cytidine 5'-monophosphate] have been synthesized and structurally characterized. They reveal classical as well as uncommon structures, with H_2cyd and CMP showing unprecedented binding sites for the calcium ion. The structure of compound **1** consists of monomeric $[Ca(cyt)_2(H_2O)_4]^{2+}$ cations, uncoordinated ClO_4^- anions as well as lattice nucleobases molecules. The structures of compounds **2** and **3** contain either neutral (**2**) or cationic (**3**) dinuclear entities with a bis-μ-carboxilate bridged $[Ca_2(cyt)_2]^{4+}$ dinuclear core, where each cytosine molecule shows coordination simultaneously through O2 - N3. Compounds **4** and **5** are ionic salts. They share the same $[Ca(H_2cyd)_2(H_2O)_4]^{2+}$ cationic unit, and differ by the supramolecular packing motif generated with the aid of water molecules of crystallization and the specific counterions in each case [ClO_4^- in **4** and Cl^- in **5**] (see picture below). The structure of compound **6** consists of neutral $[Ca_2(CMP)_2(H_2O)_{11}]$ asymmetric dimers and crystallization water molecules. The lack of coordination of Ca^{2+} ions towards phosphate groups observed in **6** is unusual.



$[Ca(H_2cyd)_2(H_2O)_4][ClO_4]_2\cdot 3H_2O$



$[Ca(H_2cyd)_2(H_2O)_4]Cl_2\cdot 3H_2O$