SUPPORTING INFORMATION

Zinc(II) Complexes of Constrained Antiviral Macrocycles

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Contents

1. Synthesis and Characterisation of Phosphato Complexes

Synthesis of [3,14-dimethyl-2,6,13,17-tetra*aza*tricyclo(16.4.0.0$^{7.12}$)docosane]zinc(II) diphosphate (S1). (40.6 mg, 0.07 mmol, 68.5%). Zinc(II)-hexyl-Me$_2$-cyclam dichloride **(5)** (37.10 mg, 0.08 mmol) was dissolved in distilled water (10 mL) and stirred at room temperature. Silver hexafluorophosphate (20.23 mg, 0.08 mmol, 1 mol. equiv.) was added and an immediate white precipitate was formed. The mixture was stirred at room temperature for 1 h and the solution filtered to remove the precipitate. Sodium ammonium phosphate tetrahydrate was added (33.45 mg, 0.16 mmol, mol. equiv.) and stirred at room temperature for 16 h. The solution was filtered and the solvent removed under reduced pressure with further drying under vacuum. The product was a white powder and crystals formed from a methanolic solution with diffusion of diethyl ether. ν_{max} (K/Br)cm^{-1} H-bonding (br) 3421; NH 3224; P=O 1400; P-O 1084; P-F 841, 742; O-P-O 482; *m/z* (ESI) 497.2 [M]$^+$.

Synthesis of [2,13-bis(1-naphthylmethyl)-5,16-dimethyl-2,6,13,17-tetra*aza*-tricyclo(16.4.0.0$^{7.12}$)docosane]zinc(II) diphosphate (S2). (11 mg, 0.01 mmol, 31.5%). Zinc(II)-naphthyl-hexyl-Me$_2$-cyclam dichloride (30 mg, 0.04 mmol) was dissolved in HPLC Grade MeOH (5 mL) and stirred at room temperature. Silver hexafluoro-phosphate (10.12 mg, 0.04 mmol, 1 mol. equiv.) was added and an immediate white precipitate was formed. The mixture was stirred for 1 h and the resulting pink solution was separated under centrifugal force, 4000 rpm, 30 min. Sodium ammonium phosphate tetrahydrate was added (7.0 mg, 0.04 mmol, 1 mol. equiv.) and refluxed under argon for 16 h. The solution was separated under centrifugal force, 4000 rpm, 10 min, then decanted and filtered. The solvent was removed under reduced pressure with further drying under vacuum. ν_{max} (K/Br)cm^{-1} H-bonding (br) 3440; NH 3224; P=O 1400; P-O 1205, 1142, 1082; P-F 839; O-P-O 557; *m/z* (ESI) 763.2 [M+2H]$^+$.

The molecular structure of complex **S1** was determined by single-crystal X-ray diffraction and structure determination was carried out at 150 K. Complex **S1** did not crystallise in the expected structure and is shown in Figure S1. Mass spectrometry identified the molecular ion as the diphosphate structure, (*m/z* 497.2, $[M]^+$), but crystals formed of the dimer with a shared phosphate group between two zinc 5-coordinate centres. Problems were encountered with refinement of the structure thought to be due to the presence of a disordered zinc atom. The structure exhibits a peak close to one of the Zn atoms which suggests that the Zn is positionally disordered over two sites, one (the major occupancy) where it is coordinated to the phosphate, and the other (minor occupancy) when it is coordinated to a chloride. The chloride site is similarly disordered. The chloride must be acting as either a 6^{th} ligand or counter ion for charge balance. As complex **S1** was synthesised from complex **(5)**, the presence of chloride suggests that not all chloride was removed prior to addition of phosphate. Complex **S1** crystallised as 2 separate 5-coordinate zinc macrocycles, bound to a shared phosphate through zinc-oxygen bonds. Only cell dimensions are available and these are listed in Table S1.

A phosphate-bound zinc cyclen structure determined by Kimura *et al.*[1] shows trimeric zinc(II) complexes with apparent stability of the bound phosphate thought to be due to additional hydrogen bonding between a pendant –OH group and a phosphate oxygen. The lack of additional hydrogen-bonding in complex x may be related to the problematic synthesis, and latterly, evidence of decomposition of the product.

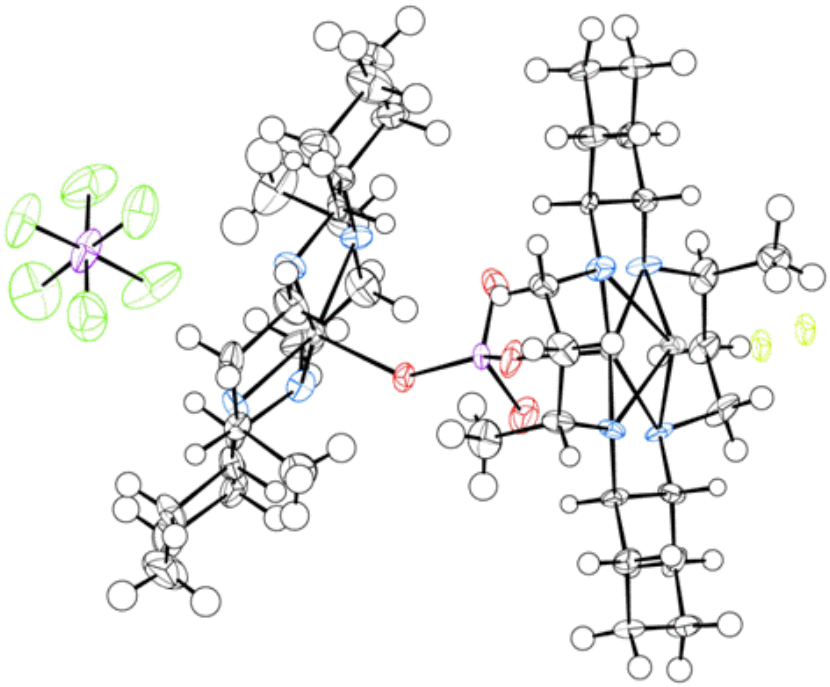


Figure S1. Low resolution x-ray structure of the Zn(II)-HMC phosphate complex, **(S1)**

Table S1. X-ray crystallographic data (cell dimensions) for Zn(II)-(constrained cyclam)$_2$-phosphato complex **(S1)**

Formula	$C_{48}H_{92}N_8O_4P_1Zn_2$
a / Å	21.2436(14)
b / Å	16.3400(11)
c / Å	17.2105(12)
α / °	90
β / °	108.902(4)
γ / °	90
Cell vol. / Å^3	5652.0(8)

2. Spectral Data and crystal packing diagrams for Zn(II) constrained-cyclam complexes

Infrared Spectroscopy

The infrared spectrum of Zn(II)-hexyl-Me_2-cyclam(diacetate) (**3**), was recorded at room temperature as a KBr disc and shows three weak absorption bands (546, 526, 488 cm^{-1}) in the 400-600 cm^{-1} region, indicating a *trans*- arrangement of the unidentate ligand.[2] The *cis*- complex would be expected to show more bands and more splitting in this region due to lower symmetry. The infrared spectral data of this complex appear to be consistent with the *trans*- configuration. The spectrum obtained for the chloride complex **(5)** also shows three bands in this region, although the second band at 528 cm^{-1} is very weak. These bands are not seen for the phosphate complex **(S1)** as the ν_4 strong O-P-O stretch found in this region splits into two bands at 482 cm^{-1} and 559 cm^{-1} and masks any weak signals. The splitting of the band indicates a reduction in symmetry from the free phosphate ion and suggests the phosphate is coordinated. Absorption bands for all three complexes are listed in Table S2. Spectra obtained for the Zn(II)-NHMC phosphate complex **(S2)** also shows three weak absorption bands in the 400-600 cm^{-1} region that may infer *trans*- geometry of the acetate ligands. The chloride species gives similar results and the phosphate analogue revealed a strong O-P-O vibrational stretch that may overlap weak signals found in this region. Absorption bands for each complex are listed in Table S3.

Table S2. Infrared absorption bands in 400-600 cm^{-1} region for Zn(II)-constrained cyclam, **(3)** acetato, **(5)** chlorido and **(S1)** phosphato complexes.

Complex	Band 1 (cm^{-1})	Band 2 (cm^{-1})	Band 3 (cm^{-1})
(3)	546	526	488
(5)	546	528	490
(S1) (O-P-O)	559		482

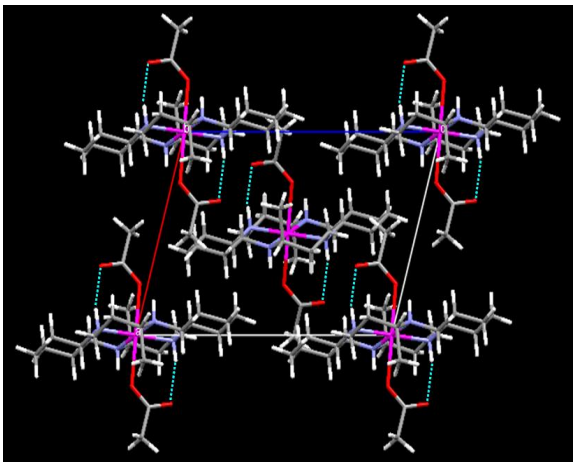
Table S3. Infrared absorption bands in 400-600 cm^{-1} region for Zn(II)-NHMC, **(4)** acetato, **(6)** chlorido and **(S2)** phosphato complexes.

Complex	Band 1 (cm^{-1})	Band 2 (cm^{-1})	Band 3 (cm^{-1})
(4)	479	508	561
(6)	486	507	559
(S2) (O-P-O)	557		480

NMR Spectroscopy

Zn-HMC phosphato complex, (S1). On acquiring a ^{1}H spectrum of complex **(S1)** before and after all 2D data was collected, there was evidence of new signals appearing. It is believed some decomposition of the product in the solution has occurred and may indicate that the phosphate complex is less stable than the acetate **(3)** and chloride **(5)** species.

(a)



(b)

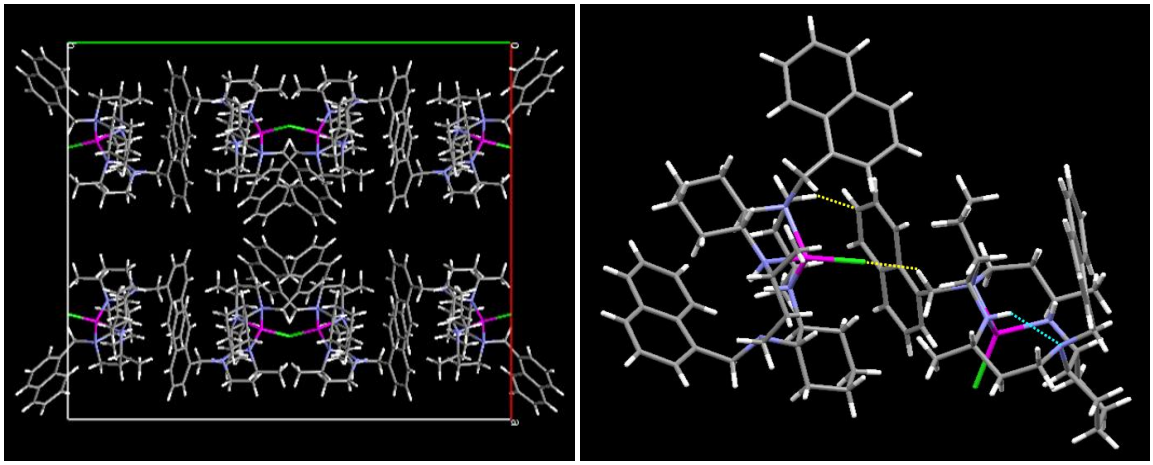


Figure S3. (a) Crystal packing of Zn(II)-constrained cyclam acetato complex, **(3).** Hydrogen bonding is seen between NH protons and oxygen atoms of axial acetates. The macrocycle is in the trans-III configuration. (b) Crystal packing of Zn(II)-constrained cyclam chlorido complex, **(6)** projected along the c axis of the unit cell and rotated by 90˚. Hydrogen bonds are shown (cyan) between an unbound nitrogen and a protonated nitrogen of the macrocycle. Short contacts (yellow) are seen between chlorido ligands of one macrocycle and methylene protons of the naphthyl of a neighbouring macrocycle. Short contacts also form between protons of the hexyl rings with carbon atoms of the aryl rings.

3. References

[1] T. Koike, S. Kajitani, I. Nakamura, E. Kimura, and M. Shiro, *J. Am. Chem. Soc.*, 1995, **117**, 1210.

[2] K. Nakamoto, 'Infrared and Raman Spectra of Inorganic and Coordination Compounds, John Wiley & Sons, 1997.