Anion control of isomerism, crystal packing and binding properties in a mononuclear zinc complex

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Abstract

The coordination chemistry of the tetradentate pyridyl N-donor ligand cis-3,5-bis-[2-pyridinyleneamin]-trans-hydroxycyclohexane (DDOP) has been investigated with zinc(II) nitrate and triflate. The resulting complexes, [Zn(DDOP)(H2O)(NO3)](NO3) (1), and [Zn(DDOP)(H2O)(OTf)](OTf) (2) differ not only in their counterions, but also the arrangement of the axial ligands and their solid state hydrogen bonded networks. Isothermal titration calorimetry was used to assess the difference in binding properties exhibited by the two zinc complexes at physiological pH in an aqueous environment. A series of coordinating amino acids were found to preferentially bind to the mononuclear zinc triflate (1) complex over the corresponding nitrate (2) assembly, with histidine exhibiting a two centre binding mode.

Keywords: Zinc complex; Amino acid binding; Anion control; Crystal engineering

1. Introduction

The influence of anions and solvents over supramolecular architectures is an important factor in coordination chemistry. While in many synthetic supramolecular assemblies the components are chosen such that metal–ligand bonding dominates weaker supramolecular forces, facilitating prediction and design of a single metallo-supramolecular aggregate [1–3], in other systems a diverse range of molecular architectures can result from closer competition between coordinative, hydrogen bonding, and hydrophobic interactions [4–6]. A striking example has been provided by a range of silver thiomethylterpyridine complexes, where changes of solvent and anion controlled the formation of monomeric, dimeric, pentanuclear and polymeric coordination complexes [7]. In a similar vein, our recent studies of the bidentate amino ligand cis-3,5-diamino-trans-hydroxycyclohexane (DAHC) and its O-derivatives have allowed the description of solvent and anion control over complex shape and nuclearity in copper(II) coordination chemistry [8,9].

Anions are also capable of influencing the behaviour of coordination compounds in solution. For molecular recognition to occur in some systems, potential substrates compete directly with the coordinated anion and the solvent sphere to bind with the metal centre. Consequently, zinc enzyme biomimetic systems have generally utilized non-coordinating anions such as perchlorate and triflate to avoid competition between anion and substrate [10]. Such systems typically consist of macrocyclic zinc complexes and have recently been exploited as hosts for various substrates ranging from phosphates [10,11] to amino acids [12]. Mononuclear zinc centres encapsulated within a
hydrophobic core have been shown to promote binding in aqueous environments.

Herein, we describe the synthesis and structure of mononuclear, octahedral zinc(II) complexes of the tetradentate DAHC derivative cis-3,5-bis[(2-pyridinyleneamin)-trans-hydroxycyclohexane (DDOP) [13], with both nitrate and triflate as anions. Complexation of a series of amino acid substrates with these complexes was examined using isothermal titration calorimetry, revealing that the nature of the counterion has an important influence not only upon the solid state supramolecular architecture, but also upon interactions with other molecules in solution.

2. Results and discussion

2.1. Ligand/complex design overview

DDOP is synthesised from DAHC by a simple Schiff base derivatisation using 2-pyridinecarbaldehyde [13], yielding a more highly pre-organised ligand with a tetradentate (or bis-bidentate) donor set. The aromatic rings increase the system’s rigidity, strengthening the hand of the ligand and reducing the influence of anions, solvent and metal centres on the outcome of the complexation. Furthermore, they provide a hydrophobic surface capable of participating in π-stacking or other van der Waals interactions.

Despite the rigidity of the donor set, the conformational flexibility of the cyclohexane backbone gives this derivative two possible coordination modes depending upon the preferences of the metal centre (Scheme 1); either a dinucleating, bis-bidentate chelator with tetrahedral metal centres, or a tetradentate mononucleating coordination pocket for octahedral, square pyramidal or square planar centres. In the mononuclear case, coordination of an octahedral metal centre leaves two vacant coordination sites which may be filled by solvent molecules, counterions or other co-ligands. In this way, the use of various anions and solvents may influence the shape, hydrogen bonding and packing properties of the complex, or allow bridging to form multinuclear aggregates; while the hydrophobic environment around the zinc centre may encourage substrate binding in aqueous environments.

2.2. Synthesis and crystal structure

Complexes 1 and 2 were synthesised in high yields by simply mixing the ligand with a small excess of the appropriate zinc(II) salt in methanol, and crystallising by slow diffusion of diethyl ether into the methanolic solution. Predictably, the highly preorganised nature of the tetradentate coordination pocket resulted in similar mononuclear complexes. Interestingly, however, there is one significant difference between the two complexes. In 1, the water ligand is arranged anti to the DDOP alcohol group, whereas in 2 it is arranged syn (Fig. 1).

In most other respects, the geometries of the two complexes are highly similar. Both show a slight opening of the ligand “arms” away from a parallel orientation, as demonstrated by a large N–Zn–N angle between the pyridyl nitrogens, and a smaller angle between the imine nitrogens (Table 1). Significantly shorter bond lengths show that axial ligation is stronger to the softer water O-donor than to the harder anions, with this effect being more pronounced in the triflate complex, 2, and both complexes have an O–Zn–O angle that deviates from the ideal 180°. However, in 2 the equatorial Zn–N bond lengths are slightly longer than in 1, while Zn–O distances are shorter.
Furthermore, the Zn atom is substantially displaced (0.131 Å) from the N4 plane in 2, while in 1 it is almost perfectly coplanar (0.006 Å displacement).

The change in position of the water ligand observed in 2 has a significant impact on the long range ordering of the crystal structure, with a change from a 2-dimensional hydrogen bonded network in 1 to isolated hydrogen bonded dimers in 2. In 1, hydrogen bonded layers of complex cations and nitrate counterions run parallel to the crystallographic ab plane (Fig. 2). These layers are constructed by hydrogen bonds between the water ligand of one cation and the nitrato ligand of the next, and further interactions between nitrate counterions, DDOP alcohol groups and water ligands (for distances and angles see Table 2). Association of the layers to form the crystal may occur through π-stacking interactions, with aromatic systems from alternate layers taking an alignment close to that of a classic slipped π–π stack [14], with a long centroid–centroid distance (3.97 Å) and shorter atom to atom contacts (3.52 Å).

In 2, the hydrogen bonded dimers consist of two complex cations and two triflate counterions, while the shorter D...O distances and near-ideal (180°) D–H...A angles imply that the hydrogen bonds are stronger in this system (Table 2). Each cation has its water ligand and DDOP alcohol group bridged by hydrogen bonding interactions with two oxygens from a triflate anion to form a “half-dimer”; these halves are connected by hydrogen bonds between the water ligands and DDOP alcohol groups of the two complex cations. The participation of the water ligand in two strong hydrogen bonding interactions explains the relatively large displacement of the zinc atom from the N4 plane, with the hydrogen bonds and strong Zn–O coordinate bond acting to pull the metal centre out of position in the absence of any counteracting hydrogen bonds to the coordinated triflate anion. This apparent influence of hydrogen bonding over the metal coordination environment suggests that it may be a factor in the positioning of the water ligand. For example, the wider separation of the oxygens in the triflate anion (≈2.4 Å compared with 2.1 Å) may allow it to form a strong hydrogen bonded bridge between the alcohol group and water ligand in 2, making the syn arrangement more favourable. Another factor may be the larger size of the triflate anion, which

![Diagram of complex cations in [Zn-DDOP(NO3)(H2O)]NO3 (1, left), and [Zn-DDOP(OTf)(H2O)]OTf (2, right), showing the anti and syn arrangements of the water ligand respectively. C is grey; F, pale blue; N, blue; O, red; S, yellow; Zn, blue grey. Hydrogen atoms are omitted for clarity. This colour scheme is retained in all figures. (For interpretation of references in colour in this figure legend, the reader is referred to the web version of this article.]

Table 1
Selected bond lengths and angles in [Zn-DDOP(H2O)(NO3)]NO3 (1) and [Zn-DDOP(H2O)(OTf)]OTf (2)

<table>
<thead>
<tr>
<th>Bond distances (Å)</th>
<th>Compound 1</th>
<th>Compound 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DDOP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N(1)-Zn</td>
<td>2.110(2)</td>
<td>N(1)-Zn</td>
</tr>
<tr>
<td>N(2)-Zn</td>
<td>2.136(2)</td>
<td>N(2)-Zn</td>
</tr>
<tr>
<td>N(3)-Zn</td>
<td>2.136(2)</td>
<td>N(3)-Zn</td>
</tr>
<tr>
<td>N(4)-Zn</td>
<td>2.125(2)</td>
<td>N(4)-Zn</td>
</tr>
<tr>
<td>Water ligand</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(2)-Zn</td>
<td>2.173(2)</td>
<td>O(4)-Zn</td>
</tr>
<tr>
<td>Coordinated anion</td>
<td></td>
<td></td>
</tr>
<tr>
<td>O(6)-Zn</td>
<td>2.280(2)</td>
<td>O(1)-Zn</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond angles (°)</th>
<th>Compound 1</th>
<th>Compound 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyridyl-N</td>
<td>N(4)-Zn–N(3)</td>
<td>113.77(8)</td>
</tr>
<tr>
<td>Imine-N</td>
<td>N(1)-Zn–N(2)</td>
<td>88.77(8)</td>
</tr>
<tr>
<td>Oxygen</td>
<td>O(2)-Zn–O(6)</td>
<td>164.67(8)</td>
</tr>
</tbody>
</table>
in the anti arrangement could make an unfavourable steric clash with the DDOP cyclohexane backbone.

2.3. Solution chemistry

The overall structure of 1 and 2, with four equatorial N-donors and an axial water ligand, is reminiscent of the zinc cyclams. $^1$H NMR measurements in deuterated methanol indicated that the basic mononuclear, tetradentate chelated structure of the cations was retained upon dissolution, as revealed by the cyclohexane protons which provide an excellent conformational probe. This, coupled with the hydrophobic surface offered by the aromatic system, suggested that these molecules had potential as molecular recognition agents. Using isothermal titration calorimetry (ITC) [16] we analyzed the binding properties of the two metal complexes against a series of amino acids. Serine, tyrosine and histidine offered an interesting spectrum of coordinating amino acids to gauge the effect of the nitrate and triflate on the metal centre’s ability to bind the substrates. In all cases it was shown that binding constants to the triflate complex 2 were considerably higher than the corresponding nitrate complex 1. In both the serine and tyrosine binding experiments the interactions were highly endothermic. This phenomenon is characteristic of hydrophobic interactions through the expulsion of solvent/counter anions from the receptor surface and substrate environs. For example, serine, when complexed with 2 afforded an endothermic interaction, $\Delta H = +0.94$ kcal mol$^{-1}$. The nitrate species 1, gives a smaller positive $\Delta H$ of $\approx 0.85$ kcal mol$^{-1}$. The substantially lower endothermic interaction observed could be assigned to the ineffective expulsion of the strongly coordinating nitrate anion.

However, for both complex 1 and 2, the ITC traces (Fig. 3) indicate the coordination of two histidine amino acids to the zinc metal centre. While binding of the first histidine is endothermic (for complex 2, $\Delta H \approx +0.94$ kcal
mol$^{-1}$), binding of the second is an exothermic process (for complex 2, $\Delta H \approx -5.1$ kcal mol$^{-1}$). It appears that binding must occur above and below the planar platform via the imidazole moiety, giving an octahedral species reminiscent of the 6-coordinate iron centre observed in some haemoglobin[17]. This is because: (i) zinc has previously been shown to form 6-coordinate imidazole complexes in aqueous solution [18]; while (ii) any 5-coordinate possibilities would first require hydrolysis of one arm of the DDOP ligand to free a donor site, or, improbably, dissociation of this tetradeionate chelating ligand. It should be noted that Schiff bases are generally considered relatively stable to hydrolysis [19], and furthermore such a transformation would be endothermic [20]. The two centre binding observed with histidine is probably due to the higher affinity for zinc of the softer imidazole N-donor, which unlike the carboxylic acid O-donors of the other amino acids is capable of displacing water as well as the counterions. The two complexes were also tested against a series of phosphates, but the binding constants were negligible. The large solvent exposed areas around the metal centre probably contribute to the poor affinity of these polar substrates. Improved hydrophobic shielding would potentially increase the binding affinity for more hydrophilic substrates.

3. Conclusions

A change of anion from nitrate to triflate induces a change in the positioning of the coordinated anion in an octahedral zinc(II) complex. This change appears to result from the triflate anion’s larger size and contrasting hydrogen bonding properties, which in the solid state favour formation of a syn complex, with a corresponding change from a 2D hydrogen bonded network to isolated hydrogen bonded dimers. In addition, the non-coordinating nature of the triflate anion in solution increases the ability of the zinc complex to bind amino acid substrates, giving it the potential for further development as a molecular recognition agent.

4. Experimental

4.1. Materials, methods and instrumentation

The ligand DDOP was synthesised by reaction of cis-3,5-diamino-trans-hydroxycyclohexane with 2-pyridinecarbaldehyde[13]. All other reagents and solvents were purchased (Fisher/Lancaster/Riedel-de Haën/Aldrich) as AR grade and used without further purification. Deuterated solvents were obtained from Aldrich. All complexations were performed in the ambient atmosphere. Infra-red spectra were measured with Jasco FTIR-410 and Bruker TENSOR 27 spectrometers and $^1$H NMR measurements were performed using Bruker DPX-400 and Avance-400 spectrometers. X-ray diffraction data were collected using Nonius Kappa CCD and Bruker CCD-1000 diffractometers with Mo K$\alpha$ radiation and a graphite monochromator. Isothermal titration calorimetry was performed using Microcal MCS and VP-ITC titration microcalorimeters.

4.2. Preparation of $\left[\text{Zn(DDOP)}(\text{H}_2\text{O})(\text{NO}_3)\right](\text{NO}_3)$ (1)

Zn(NO$_3$)$_2$·6H$_2$O (0.0675 g, 0.227 mmol) in methanol (5 mL) was added to a solution of DDOP (0.070 g, 0.226 mmol) in methanol (20 mL) and the resulting clear, colourless solution was stirred for 2 h at room temperature.
Evaporation of solvent in vacuo to a volume of \( \approx 4 \) mL, followed by diffusion of ether into the methanolic solution yielded 1 as large colourless crystals in around 24 h (0.0714 g, 0.138 mmol, 61\%). \(^1\)H NMR (400 MHz, CD\(_3\)OD): \( \delta \) 9.09 (d, 2H), 8.80 (s, 2H), 8.23 (ptd, 2H), 8.08 (d, 2H), 7.97 (m, 2H), 4.50 (m, 2H), 4.22 (tt, 1H), 2.16 (m, 4H), 1.93 (ptd, 2H). IR (KBr disc) cm\(^{-1}\): 3415 s, 1496 w, 1462 m, 1442 s, 1413 m, 1406 s, 1370 s, 1349 s, 1314 s, 1275 m, 1262 m, 1230 s, 781 m.

4.3. Preparation of \([\text{Zn}(\text{DDOP})(\text{H}_2\text{O})(\text{OTf})] \cdot (\text{OTf})\) (2)

Zn(CF\(_3\)SO\(_3\))\(_2 \cdot 6\)H\(_2\)O (0.103 g, 0.283 mmol) in methanol (2.5 mL). After stirring for around 1 h at room temperature, diffusion of ether into the methanolic solution yielded colourless crystals of 2 in less than 24 h (0.138 g, 0.20 mmol, 85\%). \(^1\)H NMR (400 MHz, CD\(_3\)OD): \( \delta \) 9.09 (d, 2H), 8.80 (s, 2H), 7.97 (m, 2H), 4.50 (m, 2H), 4.22 (tt, 1H), 2.16 (m, 4H), 1.93 (ptd, 2H). IR (KBr disc) cm\(^{-1}\): 2922 w, 1641 m, 1603 m, 1385 s, 1329 s, 1068 m, 781 m.

4.4. Single-crystal structure determination

Suitable single crystals of 1 and 2 were mounted on the end of a thin glass fiber using Fomblin oil or epoxy glue. X-ray diffraction intensity data were measured at 150 K on a Nonius Kappa-CCD diffractometer, 1, and at 193 K on a Bruker CCD-1000 diffractometer, 2, in both cases using molybdenum radiation \([\lambda(\text{Mo K} \alpha) = 0.7107 \text{ Å}]\). Structure solution and refinement for 1 was carried out with SHELXS-97 [21] and SHELXL-97 [22] via WinGX [23], and for 2 with SHELXTL [24]. Corrections for incident and diffracted beam absorption effects were applied using empirical methods [25]. Both compounds crystallized in the space group P2\(_1\)/n, as determined by systematic absences in the intensity data, intensity statistics and the successful solution and refinement of the structures. Both structures were solved by a combination of the Patterson method and difference Fourier syntheses and refined against \(F^2\) by the full-matrix least-squares technique, with all non-hydrogen atoms refined anisotropically. Hydrogen atoms of alcohol groups and water ligands were found objectively on a Fourier difference map and were refined in the isotropic approximation, while other hydrogen atoms were calculated using the riding model. Crystal data, data collection parameters and refinement statistics for 1 and 2 are listed in Table 3.

4.5. Isothermal titration calorimetry

Isothermal titration calorimetry (ITC) experiments were used to measure the binding of the two complexes to various substrates, and were performed at 25 °C (298 K) using Microcal MCS and VP-ITC titration microcalorimeters. In order to minimize mixing heat effects caused by differences in solution composition, the substrates and zinc complexes were both dissolved in freshly prepared HEPES buffer (pH = 7.4) before each titration experiment. All solutions prior to experiments were degassed before being added to the calorimeter cell. The substrates, at a concentration of 5.0 mM, were injected in 10 \( \mu \)L increments into the reaction cell (cell volume 1.31–1.41 mL) containing \( 0.25 \) mM, until there occurred a saturation of the macrocyclic cavity. A 250 \( \mu \)L injection syringe with \( 310–400 \) rpm stirring was used to give a series of 10 injections at 3-min intervals. Control experiments for heats of mixing and dilution were performed under identical conditions and used for data correction in subsequent analysis. Table 3: Crystallographic data for compounds 1 and 2.

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical formula</td>
<td>C(<em>{18})H(</em>{22})N(<em>{6})O(</em>{8})Zn</td>
<td>C(<em>{20})H(</em>{22})F(<em>{6})N(</em>{4})O(<em>{8})S(</em>{2})Zn</td>
</tr>
<tr>
<td>Crystal system</td>
<td>monoclinic</td>
<td>monoclinic</td>
</tr>
<tr>
<td>Space group</td>
<td>( P2_1/n )</td>
<td>( P2_1/n )</td>
</tr>
<tr>
<td>Formula weight</td>
<td>515.79</td>
<td>689.91</td>
</tr>
<tr>
<td>Temperature (K)</td>
<td>150(2)</td>
<td>193(2)</td>
</tr>
<tr>
<td>( \rho_{\text{calc}} ) (g cm(^{-3}))</td>
<td>1.657</td>
<td>1.687</td>
</tr>
<tr>
<td>Number of parameters</td>
<td>306</td>
<td>382</td>
</tr>
<tr>
<td>Goodness-of-fit on ( R^2 )</td>
<td>1.040</td>
<td>0.986</td>
</tr>
<tr>
<td>Final ( R ) indices ([R &gt; 2\sigma(R)])</td>
<td>( R_1 = 0.0406 ), ( wR_1 = 0.0343 )</td>
<td>( R_1 = 0.0381 ), ( wR_1 = 0.0882 )</td>
</tr>
<tr>
<td>( R )-indices (all data)</td>
<td>( R_1 = 0.0577 ), ( wR_1 = 0.0418 )</td>
<td>( R_1 = 0.0598 ), ( wR_1 = 0.0929 )</td>
</tr>
<tr>
<td>Maximum, minimum ( \Delta \rho ) (e Å(^{-3}))</td>
<td>0.876, –0.652</td>
<td>0.501, –0.455</td>
</tr>
</tbody>
</table>

\( a = \sum |F_o| - |F_c| / \sum |F_o|, wR_2 = (\sum [w(F_o^2 - F_c^2)^2] / \sum [w(F_o^2)^2])^{1/2} \).

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**Appendix A. Supplementary data**

Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with...
the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 606809 (compound 2) -606810 (compound 1). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk; http://www.ccdc.cam.ac.uk]. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.poly.2006.06.044.

References