ChemComm

Structures of $[Co(\textsc{ii})(L)(NO_3)(HOCH_3)_n]BPh_4$ ($n = 4, 5$) complexes (L = *cis,cis*-1,3,5-triaminocyclohexane-based ligand): structural 'snapshots' of anion binding to a metal centre

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Received (in Cambridge, UK) 16th June 1999, Accepted 15th July 1999

The crystal structures of $[Co(\textsc{ii})(L)(NO_3)(HOCH_3)_n]BPh_4$ {L = *cis,cis*-1,3,5-tri[(4-*tert*-butylphenyl)propenylideneamino]cyclohexane} complexes demonstrate the role of solvent molecules in the stabilisation of anions within a solvated cavity: the structures can be compared with bicarbonate binding in the active site of carbonic anhydrase.

Small molecule metal complexes have long been used successfully to mimic the immediate metal coordination sphere of metal ions in metalloproteins. Some of the most successful model complexes, especially models of myoglobin,[1] have attempted to model not only the metal and its surrounding ligands but also other active site features. Such models have the potential to provide chemical clues about the mechanistic roles of these features which are remote from the immediate metal coordination sphere. Of late, we have been interested in preparing small molecule complexes which mimic both primary and secondary coordination spheres of the metal ion in the zinc-containing metalloenzyme human carbonic anhydrase II (CA). CA (and its catalytically competent Co(II)-substituted form) is of significant interest since it catalyses the hydration of carbon dioxide at near diffusion-limited rates. The enzyme's active site can be described as a 15 Å deep cleft with a metal ion coordinated by three histidine residues at the 'bottom' of the cleft. There are several amino acid residues remote from the primary coordination sphere of the metal which are critical in maintaining the high catalytic efficiency of the enzyme.[2] Another feature of the active site are chains of hydrogen-bonded water molecules extending from the metal to the 'top' of the cavity; studies show that the active site water molecules have important roles to play in proton transfer and in substrate binding.[3] To model these remote active site features in a synthetic complex requires a ligand design which combines an N_3 face-capping coordination geometry with a rigid 'superstructure', *e.g.* derivatised cyclodextrins[4] and derivatised trispyrazolylborate complexes.[5]

We have previously reported the use of propenylidene derivatives of *cis,cis*-triaminocyclohexane ligands (abbreviation: protach) in the modelling of CA.[6] The protach ligand system provides a face-capping N_3 coordination environment on one 'face' of the metal and surrounds the other 'face' with a rigid, hydrophobic superstructure (Fig. 1). We have shown that this superstructure is capable of encapsulating several solvent molecules, modelling the solvated active site cavity seen in CA.[7] In this paper we report two new structures using the protach-based ligand system (4-*tert*-butylphenylprotach). These structures exhibit different degrees of nitrate solvation within the structures' cavities. One structure shows the nitrate coordinated to the metal centre [cobalt(II)], whereas the other structure of the same metal–ligand complex—crystallised under different conditions—shows the nitrate solvated by methanol molecules at the 'top' of the cavity.

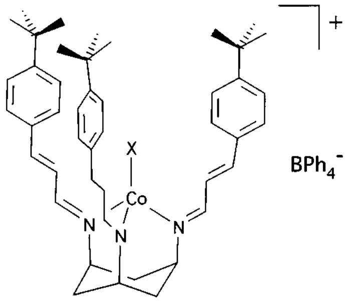

Fig. 1 Metal ligand complex used in this study (X = NO_3).

Condensation of 4-*tert*-butylcinnamaldehyde with *cis*-1,3,5-triaminocyclohexane gave the ligand *cis,cis*-1,3,5-tri[(4-*tert*-butylphenyl)propenylideneamino]cyclohexane (L) in 58% yield. Addition of L to $Co(NO_3)_2\cdot 6H_2O$ in CH_2Cl_2–CH_3OH (*ca.* 10/90 v/v) solution gave, after slow evaporation of the solvent, crystals of $[Co(L)(HOCH_3)_3](NO_3)(HOCH_3)_2(BPh_4)$ **1** in 65% yield. Repeating the procedure with CH_2Cl_2–CH_3OH (*ca.* 30/70 v/v) solution gave crystals of $[Co(L)(NO_3)(HOCH_3)]$-$(HOCH_3)_3(CH_2Cl_2)_2(BPh_4)$ **2** in 74% yield. Satisfactory analyses were obtained for the fully desolvated complexes of **1** and **2**. The crystals of both **1** and **2** rapidly lost all solvent *in vacuo*.

The structures of **1** and **2** were determined by single crystal X-ray diffraction.† The structure of **1** (Fig. 2) shows the cobalt atom in a near octahedral co-ordination geometry, with L co-ordinating in the expected face-capping fashion. The phenylpropenylidene 'arms' of the ligand form a rigid cavity around the metal's remaining co-ordination sites, which are occupied by three methanol molecules. All three co-ordinated methanol molecules are involved in hydrogen bonding with either other methanol molecules or the nitrate anion in the cavity. The OH groups of two coordinated methanol molecules, O(2) and O(3),

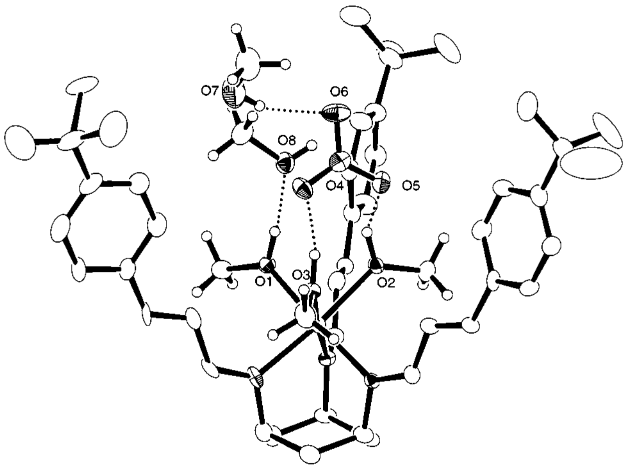

Fig. 2 ORTEP[9] representation of **1** (30% probability ellipsoids). Co(1)–O(1) 2.140(6), Co(1)–O(3) 2.134(6), Co(1)–O(2) 2.161(6), O(1)···O(8) 2.690(9) Å, O(1)–H(1)···O(8) 144.7°, O(2)···O(5) 2.769(9) Å, O(2)–H(2)···O(5) 140.2°, O(3)···O(4) 2.672(9) Å, O(2)–H(2)···O(5) 164.2°, O(7)···O(6) 3.055(12) Å, O(7)–H(7)···O(6) 168.2°, O(8)···O(5)* 3.005(9) Å, O(8)–H(8)···O(5)* 161.5°, Tetraphenylborate anion and hydrogen atoms on L are not shown for clarity.

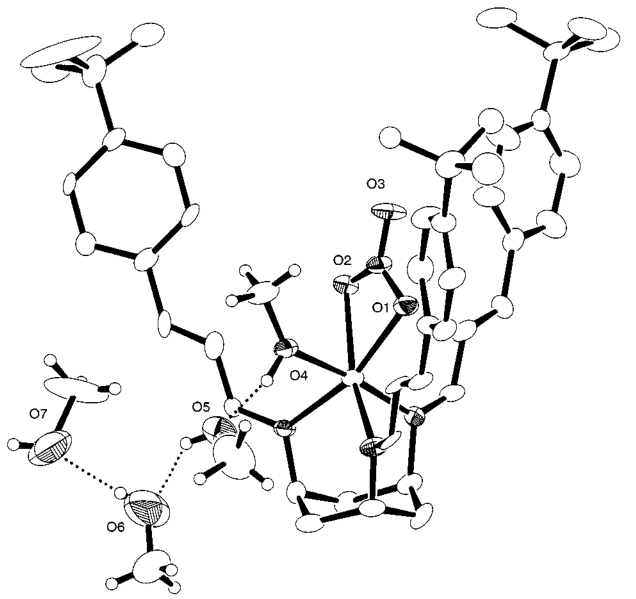

Fig. 3 ORTEP[9] representation of **2** (30% probability elipsoids). Co(1)–O(1) 2.145(11), Co(1)–O(2) 2.244(9), Co(1)–O(4) 2.153(11), O(4)···O(5) 2.602(18) Å, O(4)–H(4)···O(5) 168.3°, O(5)···O(6) 2.73(2) Å, O(5)–H(5)···O(6) 145.1°, O(6)···O(7) 2.54(3) Å, O(6)–H(6)···O(7) 136.2°. Tetraphenylborate anion, dichloromethane molecules and hydrogen atoms on L are not shown for clarity.

are hydrogen-bonded to two oxygen atoms of the nitrate, O(5) and O(4) respectively. The third nitrate oxygen atom, O(6), is hydrogen-bonded to two further methanol molecules, O(7) and O(8)*, at the 'top' of the cavity. The third coordinating methanol molecule, O(1), is hydrogen-bonded to another methanol molecule, O(8); this methanol molecule forms a hydrogen bond to an oxygen of the nitrate anion, O(6)*, of an adjacent asymmetric unit. Accordingly, the two cobalt complex cations form a pseudo-dimer. A tetraphenylborate anion completes the structure.

The structure of **2** (Fig. 3) shows the cobalt atom in a near octahedral co-ordination geometry with L co-ordinating in a face-capping fashion. As before, the phenyl propenylidene 'arms' of the ligand form a rigid cavity around the metal ion's remaining co-ordination sites, which are occupied by the oxygen atom of one methanol molecule and an η^2-nitrate. The oxygen atom of the coordinated methanol molecule, O(4), is hydrogen-bonded to a chain of three further hydrogen bonded methanol molecules, O(5), O(6) and O(7). The nitrate anion is not involved in any hydrogen bonding. A tetraphenylborate anion and two dichloromethane solvent molecules complete the structure. The cobalt coordination geometry matches closely with that of cobalt in the structure of Co-substituted CA (HCO_3^-); in the protein structure the cobalt has a bidentate bicarbonate ligand (analogous to nitrate in the model complex) and a water molecule occupying the sixth coordination site (analogous to methanol).[8]

The structures of **1** and **2** demonstrate the ability of the complexes to encapsulate solvent molecules. These solvent molecules are involved in extensive hydrogen-bonding interactions. It appears that by controlling the concentration of methanol in the crystallising solvent it is possible to control the degree of methanol incorporation in the complexes; this is a powerful tool to study the effects of solvent on the solvation of anions within the cavity of the complex. Comparison of the two structures (see Fig. 4) shows two possible structural 'snapshots' of nitrate binding to cobalt through a shell of solvent molecules. The structure of **1** illustrates one possible stage along the binding pathway in which the nitrate ion forms hydrogen-bond interactions with coordinated solvent molecules. There are parallels between our models and the binding of bicarbonate in the Co-substituted form of CA. By analogy it is possible that the transfer of bicarbonate in and out of the active site is stabilised by similar hydrogen-bond interactions between metal-bound water molecules and bicarbonate. Such interactions could be important in facilitating rapid transfer of bicarbonate in and out of the hydrophobic active site. In other words, bicarbonate binding through a hydrophobic active site can be achieved without extensive desolvation of the bicarbonate, and also binding can be achieved with relatively little reorganisation of solvent molecules.

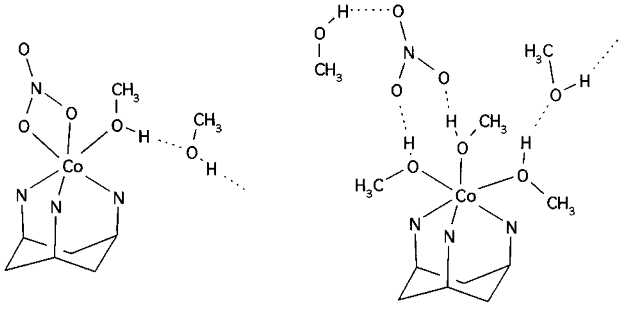

Fig. 4 Schematic comparison of nitrate–metal interactions in **1** (right) and **2** (left). Phenylpropenylidene groups, tetraphenylborate anions and dichloromethane molecules are not shown for clarity.

C. J. B. acknowledges the EPSRC for the provision of a maintenance grant.

Notes and references

† *Crystal data* for **1**: $C_{74}H_{97}BCoN_4O_8$, M = 1240.30, a = 16.491(8), b = 19.048(11), c = 12.838(6) Å, α = 98.79(5), β = 97.26(4), γ = 114.35(4)°, V = 3549(3) Å^3, triclinic, space group $P\bar{1}$, (no. 2), Z = 2, T = 150 K, final $R1$ = 0.063, $wR2$ = 0.225 for 8918 reflections, GoF (on F^2) = 1.023, Δ/σ (max.) = 0.00.

Crystal data for **2**: $C_{75}H_{97}BCl_4CoN_4O_7$, M = 1378.11, a = 10.393(4), b = 16.811(5), c = 21.737(5) Å, β = 97.21(2)°, V = 3768(2) Å^3, monoclinic, space group $P2_1$ (no. 4), Z = 2, T = 150 K, final $R1$ = 0.064, $wR2$ = 0.232 for 5138 reflections, GoF (on F^2) = 1.025, Δ/σ (max.) = 0.00.

Both structures were solved using direct methods with SHELXS. Full matrix refinement on F^2 with SHELXL 93.[10] Hydrogen atoms involved in hydrogen bonding were placed in fixed positions near appropriate peaks in a Fourier difference map. CCDC 182/1332. See http://www.rsc.org/suppdata/cc/1999/1647/ for crystallographic files in .cif format.

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Communication 9/04802B