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Azetidines as intermediates in polyamine synthesis – structure and reactions of a quadridentate ligand incorporating an azetidine ring

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Reaction of the tris(benzene sulfonate) of 1,1,1-tris-(hydroxymethyl)ethane with neat 1,2-ethanediamine under relatively mild conditions leads to formation in good yield (60%) of a quadridentate amine incorporating a four-membered, azetidine ring, the nature of the tetramine being established by determination of the crystal structures of two of its cobalt(III) complexes and the reactivity of the azetidine ring being explored in further reactions with 1,2-ethanediamine.

In the synthesis of elaborate polyamine ligands by the reaction of simpler polyamines with polyalkylating agents,[1,2] it is common to observe products arising from cyclisation processes, even despite the use of the neat amine as solvent in order to maximise the rates of intermolecular reactions competing with intramolecular cyclisation. Specifically, in comparing reactions involving 1,2- *vs.* 1,3-diamines,[2] it is found that cyclisation is far more prominent with the former than the latter, a result which may be rationalised as a result of the higher rates of formation of smaller rings (relative to further intermolecular substitution processes). Most of these cases, however, concern only 6- *vs.* 7- or 7- *vs.* 8-membered rings, despite the facts that formation of smaller rings would, at least in some instances, appear possible and, in particular, that there are reasons to expect similar rates for formation of 4- and 7-membered rings.[3]

The reaction of various electrophilic derivatives of 1,1,1-tris(hydroxymethyl)ethane with 1,2-ethanediamine has long been known as a pathway to the sexidentate amine, "sen" (**1**, Fig. 1),[1,4–6] with a side product of the reaction being identified[6] as the (2′-aminoethylamino)methyl-functionalised derivative of the diazepam resulting from both nitrogen atoms of a diamine molecule reacting with separate alkylating sites (**2**, Fig. 1). The two ligands can be easily distinguished by formation of their complexes with cobalt(III) chloride, since the hexamine gives a yellow, tripositive complex ion involving a CoN_6 coordination unit while the tetramine gives a purple, unipositive cation involving a *cis*-CoN_4Cl_2 unit (though under preparative conditions, **2** has commonly been isolated[6] as the yellow $[Co(\mathbf{2})en]^{3+}$ species). In attempting to conduct syntheses of long chain analogues of sen,[7] however, we observed on several occasions the formation of a ligand which gave a green Co(III) complex, this colour indicating it to be a *trans*-CoN_4Cl_2 species. Since the diazepam derivative could not provide a planar array of its 4 N-donors about Co(III), it was speculated at the time that the ligand present may have been the homologue of the azetidine derivative **3** (Fig. 1), for which such a coordination geometry would appear possible. This remained uncertain, however, as it has been reported that **1** (sen) will in fact provide a green Co(III) species, involving only partial coordination of the ligand, under certain preparative conditions.[1] Though crystals suitable for confirmation of the structure by X-ray diffraction could not be obtained from these earlier green materials, we have now structurally confirmed that an azetidine derivative is formed during the synthesis of sen.

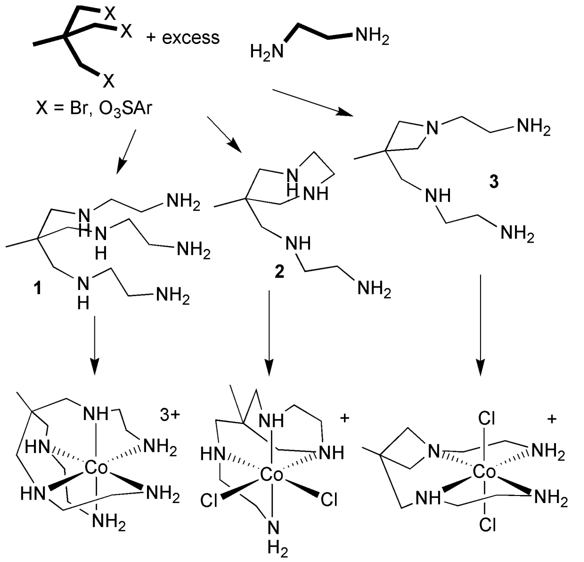

Fig. 1 Possible pathways in the reaction between 1,1,1-tris(hydroxymethyl)ethane derivatives and 1,2-ethanediamine.

Following reaction of 1,1,1-tris(benzenesulfonyloxy)ethane in neat 1,2-ethanediamine at 90 °C for 72 h,† the bulk of the excess diamine was removed by distillation under reduced pressure and the ligands present were then separated by the formation and ion-exchange chromatography of their Co(III) complexes. The bulk product (60% yield) proved to be a green complex that, following its conversion to the slightly soluble perchlorate salt, **4**, was characterised by an X-ray, crystal structure determination (Fig. 2(a)). ‡ The structure confirms the presence of the azetidine ring as in **3**, with the dimensions of the Co(III) coordination environment being generally unremarkable,[8] the longest Co–N bond being that to the tertiary azetidine N, though the elongation is relatively small compared to that observed for tertiary donors in cage amine systems.[9] The azetidine ring itself shows appreciable distortions of the geometry of the simple heterocycle[10] but is little different from that of azetidinium species[11] or that of the azetidine ring in a very closely related Co(III) complex.[12] Its presence in the quadridentate ligand renders it, once coordination stabilises the secondary nitrogen atom to inversion, a resolvable chiral ligand of the "232 tet" type, the space group ($P2_12_12_1$) indicating **4** to crystallise as a "racemic mixture", with the particular crystal taken for the structure solution being one in which the chiral coordinated nitrogen atom has the *R* configuration and the two 5-membered chelate rings have the δ conformation, as shown in Fig. 2(a).

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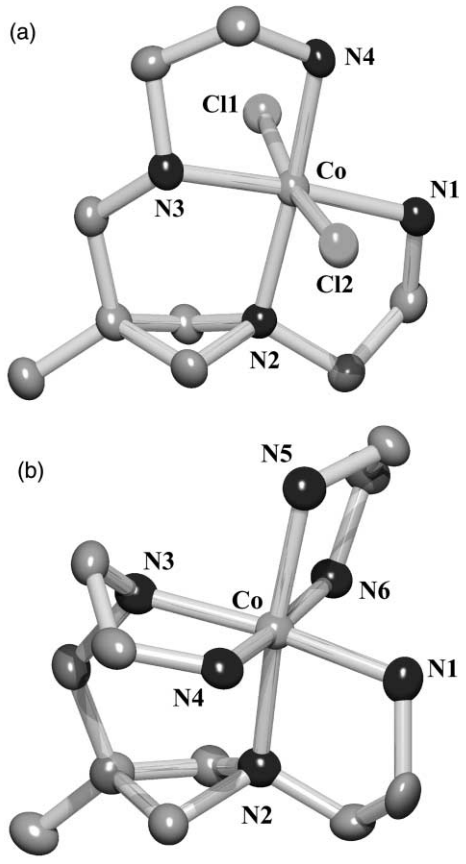

Fig. 2 (a) View of the Co(III) cation present in **4**, ellipsoids drawn at the 60% probability level; counter ion omitted for clarity. Selected bond lengths (Å) and angles (°): Co–N1 1.975(2), Co–N2 1.990(2), Co–N3 1.957(2), Co–N4 1.954(2), Co–Cl1 2.2558(7), Co–Cl2 2.2614(8); N1–Co–N2 86.48(9), N2–Co–N3 89.11(9), N3–Co–N4 86.48(10), N4–Co–N1 97.93(10), Cl1–Co–Cl2 171.20(3). (b) View of the Co(III) cation present in **5**, chloride counter ions and water molecules of hydration omitted, ellipsoids drawn at the 60% probability level. Selected bond lengths (Å) and angles (°): Co–N1 1.953(6), Co–N2 1.989(6), Co–N3 2.004(6), Co–N4 1.984(6), Co–N5 1.983(6), Co–N6 1.992(6); N1–Co–N2 85.9(2), N1–Co–N4 88.0(2), N1–Co–N5 91.4(2), N1–Co–N6 91.0(3), N2–Co–N3 91.7(2), N2–Co–N4 96.6(2), N2–Co–N6 89.7(2), N3–Co–N4 84.3(2), N3–Co–N5 92.0(2), N3–Co–N6 97.1(2), N4–Co–N5 90.7(2), N5–CoN6 82.9(2).

The coordination chemistry of azetidine has been little explored[12–15] but it is known in the case of its more widely studied homologue, aziridine, that metal ion coordination can stabilise a strained ring towards nucleophilic ring opening.[16] Thus, it is not surprising to find that whereas the complex **4** reacts with 1,2-ethanediamine to give a reddish-yellow species $[Co(\mathbf{3})en]^{3+}$ (isolated and structurally characterised (Fig. 2(b)) as the chloride **5**) in which the azetidine ring is retained and the ligand is bound as a quadridentate with the secondary (asymmetric) nitrogen donor rather than the tertiary occupying the “angular” site, extended heating of the reaction mixture from which **3** is isolable at a higher temperature (120 °C) led to the complete loss of **3** and the detection of **1** and **2** only in the product mixture. These results imply that **3** may be an intermediate in the formation of sen from the original trisulfonate and, given the yield of **3** obtained under the conditions described herein, that the pathway **3** ⟶ **1** must in fact be the dominant route. A plausible rationalisation of what now is known of these ligand syntheses is that the initial step of the reaction must involve the displacement of two sulfonate groups by one nitrogen atom of an ethanediamine molecule. This would give an azetidine ring which could subsequently undergo ring expansion (giving **2**) by intramolecular reaction with a pendent amine group or an intermolecular ring opening by ethanediamine (to give **1**). The azetidine formation would appear to parallel that in the formation of some very closely related thiaether–amine ligands,[12] though these species have been reported not to undergo nucleophilic ring-opening reactions with diamines. Since azetidine ring opening by ammonia does appear to occur under forcing conditions,[14] it is clearly a reaction which is sensitive to minor structural variations in the reactants, perhaps owing to differences in ring strain.

Acknowledgements

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Notes and references

† Synthesis and isolation: 1,1,1-tris(benzenesulfonyloxy)ethane (54 g, 0.1 mol) and 1,2-ethanediamine (en; 300 mL) were heated under a nitrogen atmosphere at 90 °C for 72 h. After cooling, excess diamine was distilled out under reduced pressure, a solution of NaOH (12.3 g, 0.31 mol) in methanol (150 mL) added, and sodium benzenesulfonate then filtered off. Cobalt chloride (32 g, 0.13 mol) in methanol (300 mL) and glacial acetic acid (12 g) were added to the filtrate, and the mixture was aerated for 10 h. After adding concentrated HCl (35 mL), the solvents were removed under reduced pressure and the residue dissolved in water (1 L). Chromatography on Dowex 50W × 2 cation exchange resin using 2 mol L^{-1} HCl as eluant revealed 4 components, F1, F2, F3 and F4. Pink F1 was Co^{2+}, orange F3 was largely $[Co(en)_3]^{3+}$ and green F4 contained too little material for it to be conveniently isolated. The eluate containing the major, green product F2 was evaporated down to a volume of 50 mL before $NaClO_4$ was added to precipitate the complex **4** (yield, 25 g, 60%). It was recrystallised by slow cooling of its solution in hot, dilute HCl.

A solution of **4** and excess en in DMSO was heated at 60 °C for 60 min. Cation exchange chromatography of the orange product mixture provided $[Co(en)_3]^{3+}$ and $[Co(\mathbf{3})en]^{3+}$ as the only materials present in significant amounts. The latter was isolated as its chloride (trihydrate) **5**, which was recrystallised from dilute HCl by vapour diffusion of ethanol.

The 200 MHz ^1H NMR spectra (D_2O solvent) of the diamagnetic complexes **4** and **5** were complicated, as expected from the low symmetry of the complexes, but both showed multiplets, δ 3.5–3.7, attributable to two superimposed AB system methylene resonances of the azetidine ring. Reduction of **4** to its labile Co(II) form by addition of $NaBH_4$ to its solution in dilute HCl allowed isolation of the hydrochloride of **3** *via* ion exchange chromatography.

‡ X-Ray crystallography: data were collected on a Nonius-Kappa-CCD area detector diffractometer using graphite-monochromated Mo-K_α radiation ($\lambda = 0.7107_3$ Å), and were processed with DENZO-SMN.[17] The structures were solved by direct methods with SHELXS-97[18] and subsequent Fourier-difference synthesis, and refined by full-matrix least-squares on F^2 with SHELXL-97.[19] Absorption effects were empirically corrected with the program DELABS from PLATON.[20] All non-hydrogen atoms have been refined with anisotropic displacement parameters. The absolute structure of **4** was determined from the value of Flack's parameter,[21] −0.010(14). The hydrogen atoms bound to nitrogen atoms have been found on the Fourier-difference map, whereas all other hydrogen atoms were introduced at calculated positions except those of the water molecules in **5**. All of them have been treated as riding atoms with an isotropic displacement factor equal to 1.2 (NH, NH_2, CH_2) or 1.5 (CH_3) times that of the parent atom. The molecular plots were drawn using SHELXTL,[22] all calculations being performed on a Silicon Graphics R5000 workstation. Crystal data for **4**: $C_9H_{22}Cl_3CoN_4O_4$, $M = 415.59$, orthorhombic, space group $P2_12_12_1$, $a = 9.3136(8)$, $b = 12.2253(10)$, $c = 14.0044(6)$ Å; $V = 1594.6(2)$ Å^3, $Z = 4$; $D_c = 1.731$ g cm^{-3}, $F(000) = 856$, $\mu_{Mo} = 1.598$ mm^{-1}, $T = 100(2)$ K, 2667 observed reflections [$I > 2\sigma(I)$] out of 2800 unique reflections collected [$R_{int} = 0.051$], 191 parameters, $R_1 = 0.026$ [$I > 2\sigma(I)$], $wR_2 = 0.061$ (all data), $S = 1.020$, $\Delta\rho_{max} = 0.214$ e Å^{-3}. For **5**: $C_{11}H_{36}Cl_3CoN_6O_3$, $M = 465.74$, triclinic, space group $P\bar{1}$, $a = 7.9455(6)$, $b = 8.2960(7)$, $c = 16.7784(11)$ Å; $\alpha = 101.991(4)$, $\beta = 94.963(4)$, $\gamma = 110.356(4)$°; $V = 999.0(1)$ Å^3, $Z = 2$; $D_c = 1.548$ g cm^{-3}, $F(000) = 492$, $\mu_{Mo} = 1.283$ mm^{-1}, $T = 100(2)$ K, 2639 observed reflections [$I > 2\sigma(I)$] out of 3290 unique reflections collected [$R_{int} = 0.061$], 219 parameters, $R_1 = 0.079$ [$I > 2\sigma(I)$], $wR_2 = 0.176$ (all data), $S = 1.008$, $\Delta\rho_{max} = 0.863$ e Å^{-3}. CCDC reference numbers 177443 and 177444. See http://www.rsc.org/suppdata/dt/b2/b200382a/ for crystallographic data in CIF or other electronic format.

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