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Synthesis of the New Asymmetric Tripodal Amine Ligand abap: Crystal Structure of $[Co(abap)(O_2NO)](ClO_4)_2$ and Stability and Reactivity of $[Co(abap)(OH_2)_2]^{3+}$ toward Phosphate Esters[1]

Rachel L. Fanshawe and Allan G. Blackman*

Department of Chemistry, University of Otago, P.O. Box 56, Dunedin, New Zealand

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Cobalt(III) complexes of the type $[Co(N_4)(OH_2)_2]^{3+}$ have been found to be effective reagents for the hydrolysis of organic esters,[2] peptides,[3] amides,[4] nitriles,[5] and phosphate esters[6] at neutral pH. The rates of these hydrolysis reactions depend markedly on the nature of the N_4 ligand system,[7] and the *trans* form of the complex appears to be inactive.[8] Interest has focused on Co(III) complexes of the tripodal tetraamine ligands tren and trpn, in which the aqua ligands are constrained in a *cis* orientation. Studies by Milburn and co-workers[9] and subsequent investigations by Chin's group[10] have shown $[Co(trpn)(OH_2)_2]^{3+}$ (**1**) to be extraordinarily reactive as a hydrolytic agent for activated and cyclic phosphate mono- and diesters. These studies have shown **1** to be much more reactive in such hydrolysis reactions than the tren complex $[Co(tren)(OH_2)_2]^{3+}$ (**2**).[11,12] This difference in reactivity has been ascribed in part to the greater flexibility of the trpn ligand, which allows facile intramolecular attack of coordinated hydroxide at the phosphorus center of the bound ester.[12] Crystal structural data suggest that **1** is better able to accommodate formation of the strained four-membered phosphato chelate ring by opening the *trans* angle to *ca.* 100°.[13] However an attempt to hydrolyze the phosphate ester linkage in vitamins B_{12} and B_{12a} (pD 5 and pD 7, 25−45 °C)[14] resulted in reduction of **1** to Co(II) *via* oxidative N-dealkylation of the coordinated trpn ligand.[15] In contrast, **2** was stable toward decomposition under all conditions studied. The low stability of **1** and the (relatively) low reactivity of **2** preclude their use in biological hydrolysis reactions.

We herein report the synthesis of the new asymmetric tripodal tetraamine ligand abap. We have also prepared and characterized Co(III) complexes of abap and detail preliminary results on the stability and reactivity of the diaqua complex toward phosphate esters. $abap{\cdot}4HCl{\cdot}2.5H_2O$ was synthesized as follows. To a melt of diphthaloyldipropylenetriamine[16] (27.7 g, 71 mmol) at 155 °C was added solid (2-bromoethyl)phthalimide[17] (18 g, 71 mmol) in portions over 10 min. The mixture was stirred at 160−170 °C for 45 min and allowed to cool. The solid mass was ground to a powder and refluxed in 8M HCl (300 mL) for 11 h. After cooling in ice and removal of phthalic acid, the filtrate was reduced to dryness (rotavap). The crude product was dissolved in water (*ca.* 80 mL), the mixture filtered (Celite), and the filtrate added dropwise with stirring to EtOH (500 mL). The resulting precipitate was removed by filtration and suspended in hot EtOH (*ca.* 270 mL). Water (65 mL) was added,

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(1) Abbreviations used: trpn = tris(3-aminopropyl)amine; tren = tris(2-aminoethyl)amine; abap = *N*-(2-aminoethyl)-*N,N*-bis(3-aminopropyl)-amine.

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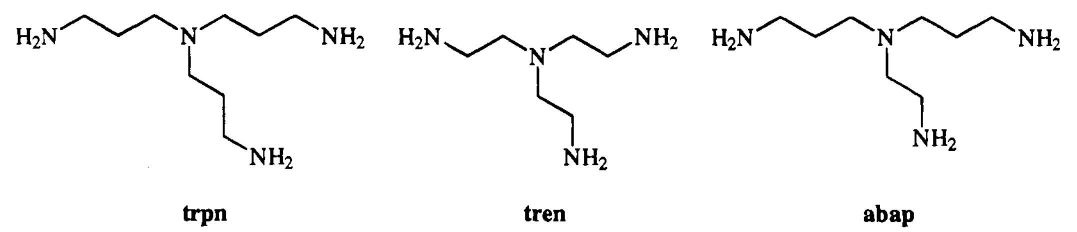

Figure 1. Structures of the tripodal amine ligands.

followed by another portion of EtOH (250 mL). Cooling in ice gave the pure product as white crystals (8.7 g, 34%).[18]

Co(III) complexes of abap were prepared by air oxidation of Co(II) species. This contrasts with reported syntheses of trpn complexes, where a stronger oxidant (PbO_2) is required[19] and suggests the resulting Co(III) abap complexes should be less prone to reduction. Air oxidation of a solution of $Co(ClO_4)_2{\cdot}6H_2O$, ligand, and $NaNO_2$ gave the peroxo-bridged dimer $[(abap)(NO_2)CoO_2Co(NO_2)(abap)]^{2+}$ (**3**).[20] Acid hydrolysis of **3** in dilute aqueous HNO_3 and addition of $NaClO_4$ gave $[Co(abap)(O_2NO)](ClO_4)_2$ (**4**) in good yield.[21] A ^{13}C NMR spectrum of the product in D_2O showed peaks attributable to both possible geometric isomers of the hydrolysis product of **4** (below) but recrystallization from dilute aqueous HNO_3/$NaClO_4$ afforded isomerically pure **4**. X-ray structural analysis of **4** confirmed the presence of a chelating NO_3^- ligand.[22] Such species are rare in Co(III) chemistry, with only $[Co(bipy)_2(O_2NO)](NO_3)(OH){\cdot}4H_2O$ having been previously synthesized in aqueous solution.[23] Figure 2 shows an ORTEP diagram of the $[Co(abap)(O_2NO)]^{2+}$ cation. The usual octahedral geometry about the Co(III) atom is severely distorted by the chelating NO_3^-, with the angle O1−Co1−O2 being 66.1°. This angle is smaller than that observed in both $Co(O_2NO)_3$ (68°)[24] and $[Co(bipy)_2(O_2NO)](NO_3)(OH){\cdot}4H_2O$ (70°)[23] and is also smaller than the corresponding angle in a number of the structurally related $[Co(N_4)(O_2CO)]^{2+}$ complexes.[25] This distortion causes the N−Co−N bond angle in the equatorial plane to open to >90°, and as found in the trpn system, this angle is opened significantly (97.6°).[13] Within the nitrate ligand, the *exo* N−O bond (N2−O3) is significantly shorter than the others, a feature observed previously in $Co(O_2NO)_3$[24] and $[Co(bipy)_2(O_2NO)]^{2+}$.[23]

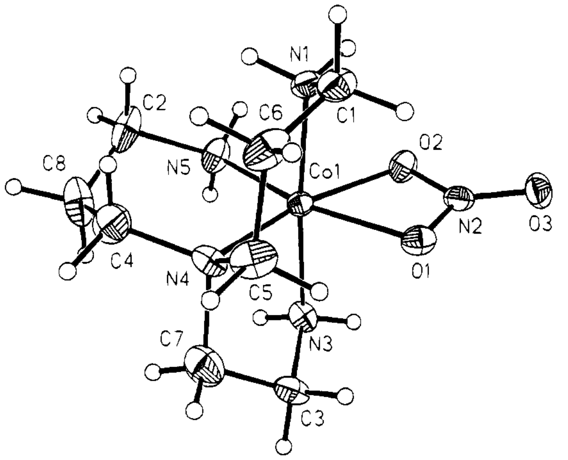

Figure 2. ORTEP view of the cation of **4** with thermal ellipsoids drawn at the 50% probability level. Selected bond distances (Å) and angles (deg): Co1−N1 1.959(5), Co1−N3 1.946(5), Co1−N4 1.968(5), Co1−N5 1.927(5), Co1−O1 1.956(4), Co1−O2 1.950(4), N2−O1 1.284(6), N2−O2 1.287(6), N2−O3 1.195(6); O1-Co1−O2 66.1(2), O2-Co1−N5 96.4(2), N5-Co1−N4 97.6(2), N4-Co1−O1 99.9(2), O2-Co1−N4 166.0(2), O1-Co1−N5 162.5(2), N1-Co1−N3 175.1(2).

On dissolution in water, **4** is hydrolyzed rapidly to $[Co(abap)(OH_2)_2]^{3+}$ (**5**). Attempts to isolate solid **5** using noncoordinating anions (ClO_4^-, $CF_3SO_3^-$, PF_6^-) were unsuccessful. Potentiometric titration of solutions of **5** at 25.0 °C gave pK_a values for the bound waters of 5.15 and 7.01. Preliminary studies have shown **5** promotes hydrolysis of both mono- and bis(*p*-nitrophenyl) phosphate in aqueous solution at pH 5−7. Reaction of **5** with the monoester in D_2O was monitored by ^{31}P NMR spectroscopy at pD 6.5. Spectra obtained immediately after mixing clearly showed 2 peaks (δ 7.3, 7.7 ppm; chemical shifts relative to external H_3PO_4, δ 0.0 ppm) in a 6:1 ratio, assigned to the two possible geometric isomers of the monodentate coordinated phosphate ester. Subsequent spectra showed decay of these over time to give one peak at δ 23.8 ppm assigned to the chelated phosphato complex $[Co(abap)(O_2PO_2)]^+$.[26] UV/vis spectroscopy (400 nm) confirmed liberation of the *p*-nitrophenolate ion. Rate data for the reaction of **5** with bis(*p*-nitrophenyl) phosphate (BNPP) were obtained spectrophotometrically at varying [H^+] by monitoring the absorbance increase at 400 nm (50 °C, [Co] = 0.01 M, initial [BNPP] = 1.67×10^{-5} M). Values of k_{obs} at pH 5.95, 6.44, and 6.86 were 4.1×10^{-3}, 5.0×10^{-3}, and 4.5×10^{-3} s^{-1}, respectively. These results show **5** to be much more reactive toward BNPP than **2** (70−100 times faster) and to be comparable in reactivity

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(18) Anal. Calcd (found) for $C_8H_{22}N_4{\cdot}4HCl{\cdot}2.5H_2O$: C, 26.31 (26.00); H, 8.56 (8.14); N, 15.35 (14.85); Cl, 38.83 (38.90). ^1H NMR (D_2O): δ 3.53 (m, 4H), 3.37 (m, 4H), 3.12 (t, 4H), 2.16 (m, 4H). ^{13}C NMR (D_2O): δ 51.7, 50.5, 37.7, 35.0, 22.9.

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(20) Preparation of $[(abap)(NO_2)CoO_2Co(NO_2)(abap)](ClO_4)_2$: To a solution of $abap{\cdot}4HCl{\cdot}2.5H_2O$ (4 g, 11 mmol) in aqueous NaOH (80.0 mL, 0.5 M) were added $Co(ClO_4)_2{\cdot}6H_2O$ (4 g, 11 mmol) in water (12 mL), $NaNO_2$ (1.08 g, 16 mmol) in water (12 mL) and solid $NaClO_4{\cdot}H_2O$ (9.2 g, 65 mmol). Air was bubbled through the solution for 1.5 h, and the resulting brown precipitate was removed by filtration, washed with EtOH and then Et_2O, and air-dried (3.6 g, 95 %). Anal. Calcd (found) for $C_{16}H_{44}Cl_2Co_2N_{10}O_{14}{\cdot}H_2O$: C, 23.80 (23.74); H, 5.74 (5.68); N, 17.35 (17.42); Cl, 8.78 (8.99). [***Caution***: Perchlorate salts should be handled with care.]

(21) Preparation of $[Co(abap)O_2NO](ClO_4)_2$: A solution of the peroxo dimer (1.0 g) in HNO_3 (20 mL, 5 M) was stirred at room temperature for 1 h and then reduced to near dryness (rotavap). The resulting purple solid was dissolved in the minimum of hot water and reprecipitated by addition of excess $NaClO_4$. The solid was recrystallized from cold nitric acid (3 M) by adding $NaClO_4$ and cooling in ice. The pure product was washed with MeOH and dried in vacuo (0.76 g, 61%). Crystals suitable for X-ray study were obtained on addition of MeOH to the filtrate and storage of the solution for 2 weeks. Analytical and NMR data obtained using the crystallographic sample were identical to those of the bulk material. Anal. Calcd (found) for $C_8H_{22}Cl_2CoN_5O_{11}$: C, 19.44 (19.23); H, 4.49 (4.25); N, 14.18 (14.25); Cl, 14.35 (14.39).

(22) Crystal data (−142 °C) for $C_8H_{22}Cl_2CoN_5O_{11}$: orthorhombic, *Pbca*, $a = 15.592(3)$ Å, $b = 11.925(2)$ Å, $c = 18.616(4)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 3461.4(12)$ Å^3, $Z = 8$, $d_{calcd} = 1.896$ g cm^{-3}. Refinement of the structure converged with R1 = 0.0551 for 1930 reflections with $F_o > 4\sigma(F_o)$ and wR2 = 0.1203 for all 3050 data.

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to both **1** (2−4 times slower) and $[Co(cyclen)(OH_2)_2]^{3+}$ (**6**) (approximately equal).[12]

As expected, **5** proved to be more stable toward reduction to Co^{2+} than **1**. ^1H NMR spectra of a solution of **5** in 0.08 M $DClO_4$ held at 48 °C obtained over 5 days showed a slight change in the appearance of the methylene protons (possibly due to isomerization of the complex) but no Co^{2+}-induced line broadening was detected over this time. The UV/vis spectrum of the final solution showed no features due to Co(II) species, and a chemical test for Co^{2+} (SCN^-) proved negative. A solution of **5** (0.02 M) in 1 M $HClO_4$ also showed no change in its UV/vis spectrum over 36 h at 25 °C. Under acidic conditions, **1** was found to decompose.[14,15a]

The enhanced stability of **5** relative to **1** and observations of its reactivity toward phosphate esters are encouraging. The presence of the ethylene arm in the abap ligand apparently confers stability on **5** due to the formation of a rigid five-membered chelate ring, while the propylene arms allow sufficient flexibility for the complex to react with phosphate esters at rates comparable to those for **1**. We are currently investigating the reactivity of **5** toward a number of activated and unactivated phosphate esters.

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Supplementary Material Available: Text giving structure solution details and listings of crystal data, structure refinement parameters, all atomic coordinates, isotropic thermal parameters, bond lengths, bond angles, and anisotropic thermal parameters for **4** (6 pages). Ordering information is given on any current masthead page.

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