# Pyruvate Imine Cobalt(III) Complex as a Reagent for Metal Encapsulation

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A cobalt(III) complex of pyruvate imine has been shown to be an effective nucleophile in condensing with formaldehyde and $Co(sen)^{3+}$ ion [sen = tris(4-amino-2-azabutyl)-1-ethane] to synthesise a functionalised sarcophagine type cage (sarcophagine = 3,6,10,13,16-hexa-azabicyclo[6.6.6]eicosane) for a cobalt(III) ion.

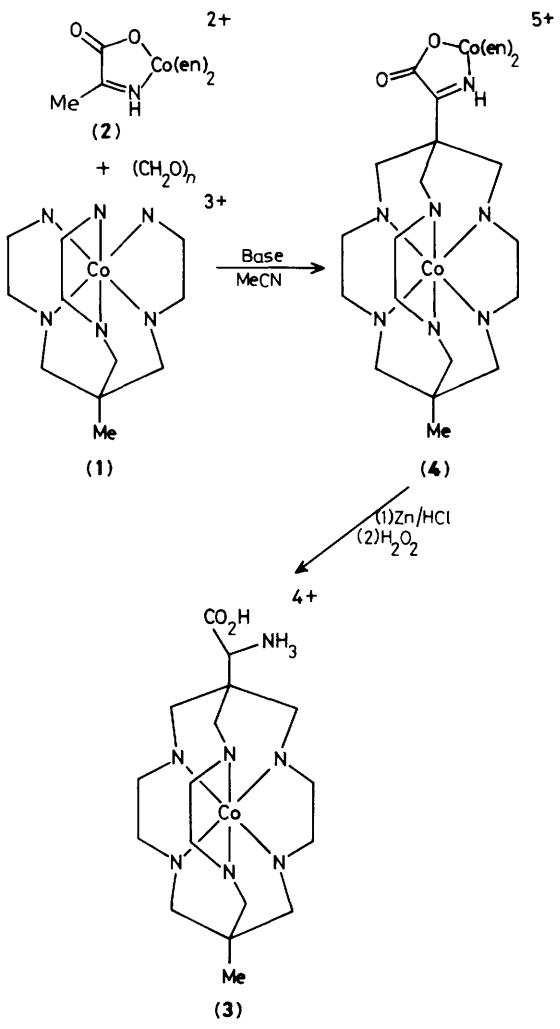
The template condensation of $[Co(sen)]^{3+}$ (**1**) [sen = tris(4-amino-2-azabutyl)-1-ethane] with formaldehyde and nitromethane leads to the formation of a hexa-azamacrobicyclic $Co^{III}$ complex $[Co(NO_2Mesar)]^{3+}$ (sar = sarcophagine = 3,6,10,13,16-hexa-azabicyclo[6.6.6]eicosane).[1] Recent work has shown that the metal ion encapsulation reaction can be conducted in non-aqueous solvents and it has been found that under such conditions much weaker carbon acids can be used as effective capping reagents. For example, *N*-alkylated γ-picoline derivatives have been use to produce functionalised cage complexes.[2]

The methyl group of the pyruvate imine complex (**2**) exchanges its protons in basic $D_2O$. It also reacts rapidly with formaldehyde at pH 10 to give the tris(hydroxymethyl) derivative.[3] These properties indicated that the methyl group could be utilised for the metal ion encapsulation reaction since the metal ion both activates the methyl group and protects the pyruvate imine functionality. This possibility is particularly attractive since the product, following reduction of the imine and decomposition of the external complex, would be a novel cage substituted amino acid.

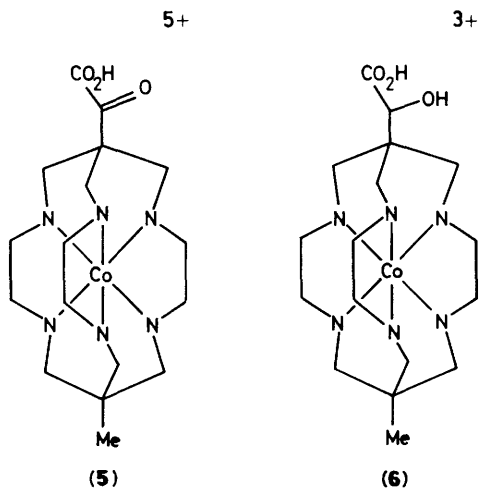
The trifluoromethanesulphonate salts of (**1**) and (**2**) were dissolved in acetonitrile and reacted with paraformaldehyde in the presence of di-isopropylethylamine. After 6 h the reaction mixture was diluted with 0.1 M HCl, reduced by the addition of zinc dust, and re-oxidised with hydrogen peroxide. Chromatography on Sephadex SP-C25 resin (eluent: 0.2 M $NaH_2PO_4$) yielded the bicyclic complex (**3**) (Scheme 1), in ~27% yield.

Alternatively, the reaction mixture was quenched with acetic acid and adsorbed on Sephadex SP-C25 resin. Elution with 0.15 M $K_2SO_4$ allows the separation of the intensely coloured binuclear species (**4**) (deprotonated at the imine nitrogen). After desalting and acidification an orange complex (**4**) was isolated as its perchlorate salt. This appears to be the least soluble of the diastereoisomers. It was readily reduced (Zn/HCl) and reoxidised ($H_2O_2$) to give (**3**).

The products were characterised by satisfactory elemental analyses and n.m.r. spectra. The $^1H$ n.m.r. spectrum (200 MHz) of complex (**3**) is typical of such cage compounds with a singlet due to the α-proton of the amino acid at δ 4.12. The $^{13}C$ n.m.r. spectrum is relatively simple, in fact typical of most such cage compounds,† with substituent signals at δ 58 and 169. The $^1H$ n.m.r. spectrum of (**4**) is featureless, with the ethylenediamine envelope of the external complex overlapping with the broad cage resonances. The $^{13}C$ n.m.r. spectrum of (**4**) is complex, as the cage loses symmetry as a result of restricted rotation of the bulky substituent. The substituent signals are at δ 184 ($-CO_2-$); 172 (–C=NH–); 47.2, 46.7, 45.9, 45.4 ($CH_2$).




Scheme 1




† $^{13}C$ N.m.r. chemical shifts of amino acid cage carbons (**3**): δ 50.7, 55.4, 55.4, 55.4 ($CH_2$); 42.8 (Me–C–); 45.6 (R–C–); 19.9 ($CH_3$).

The amino acid (**3**) is a product of reduction, initially of the imine (to amine) and then of the external cobalt(III) [to cobalt(II)], followed by dissociation of the external metal ion. It should be possible to find reduction conditions that will give products in which the amino acid is still co-ordinated to the external cobalt(III) ion. Also, the keto acid (**5**) and hydroxy acid (**6**) cages become accessible if the external cobalt(III) ion is reduced before the ligand.

These new cage functionalities have a great deal of potential for elaboration, especially to tie peptides to the cages. Such elaboration may allow the cages to target relatively specific biological sites for imaging or radiation treatment.

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