A versatile synthetic strategy for the assembly of polyfunctional aromatic metal-ion cages

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Facile new methods of synthesizing derivatised bicyclic amine complexes using a cobalt(III) amine template, with formaldehyde and aromatic ketones or diketones as condensing agents, are described.

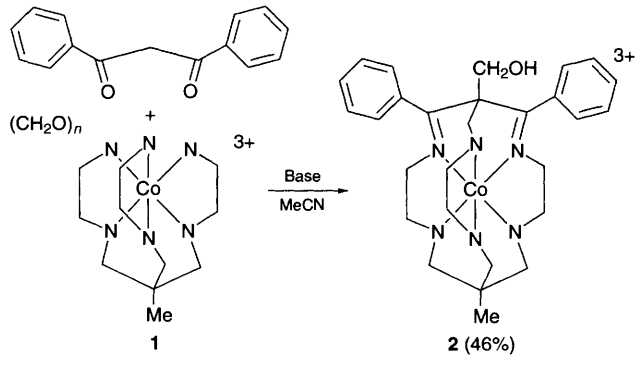
The metal ion encapsulation reaction in the synthesis of $[Co(Me,NO_2\text{-sar})]^{3+}$ {Me,NO_2-sar = 1-methyl-8-nitro-193,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane} from $[Co(sen)]^{3+}$ **1** [sen = 4,4′,4″-ethylidynetris(3-azabutan-1-amine)] is understood to occur in a succession of steps whereby formaldehyde condenses at a deprotonated amine site to generate a metal-ion activated imine which then condenses with the deprotonated carbon acid $MeNO_2$.[1] It has also been found that in non-aqueous solvents relatively weak carbon acids like higher aldehydes and N-alkylated 4-picoline and 4-methylquinoline can be used as effective capping reagents.[2–4]

These results prompted an investigation of other carbon acids like malonic acid diester,[5] acetophenone and dibenzoylmethane in the presence of formaldehyde as a means (shown in Scheme 1) of forming a cage cap. The aromatic reagents provide new substituents which could be further derivatised, and which might be extended to incorporate photoactive reagents for use as fluorescent probes or for energy capture and transfer.

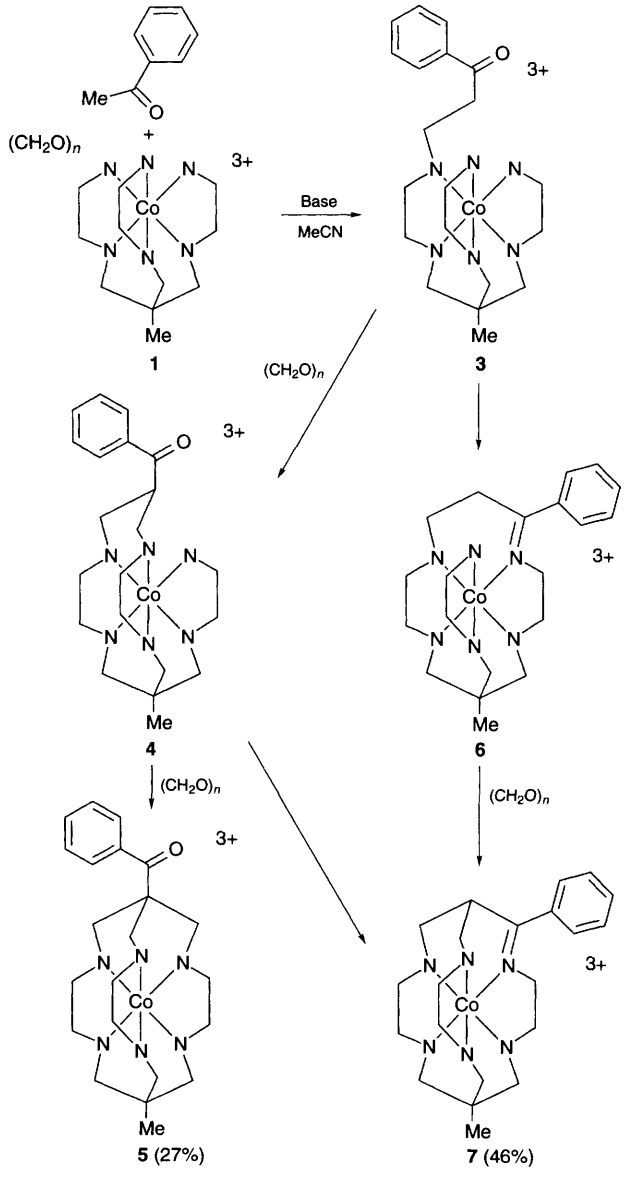
The reactions were carried out in acetonitrile solution in the presence of diisopropylethylamine, using equimolar amounts of $[Co(sen)]^{3+}$ **1** and acetophenone or dibenzoylmethane, and a small excess of paraformaldehyde. After 4 h at 20 °C the mixtures were diluted with water and the products isolated after cation exchange chromatography on SP-Sephadex C-25 resin using 0.2 mol dm^{-3} K_2SO_4 as eluent. Only one cage product (**2**† in Scheme 1) was identified from the dibenzoylmethane–paraformaldehyde mixture, but the two main bicyclic products **5**† and **7**† (in Scheme 2) were isolated when the reagents were acetophenone and paraformaldehyde.

Microanalytical data,‡ IR and UV–VIS spectra,‡ coupled with ^{13}C and ^1H NMR spectra‡ showed clearly that dibenzoylmethane and formaldehyde had condensed with $[Co(sen)]^{3+}$ to give the encapsulated product **2**, in which both carbonyl groups and one formaldehyde molecule were involved in the diimine cap formation. In this condensation it is likely that a methanimine forms first, followed by the addition of the carbanion of the β-diketone at the activated imine carbon atom. Subsequently the two ketone groups condense with the remaining deprotonated primary amine groups of $[Co(sen)]^{3+}$ **1**. This path is preferred because the β-diketone alone does not appear to condense with the complex ion under the basic conditions employed. An additional CH_2O molecule has also reacted with the tertiary carbon atom in the cap, as a result of activation by the two imine groups, to yield an apical $-CH_2OH$ substituent.

For the acetophenone chemistry two paths are evident to yield the C_3 symmetric apically substituted cage **5**,‡ and the less symmetrical meridionally substituted imine cage **7**.‡ It is also



Scheme 1

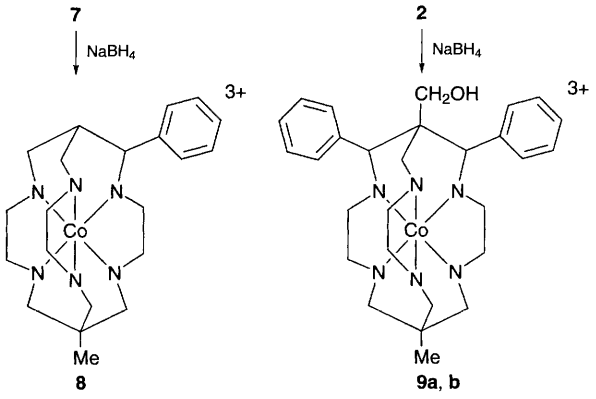


Scheme 2

likely in this instance that the carbanion reacts intermolecularly with a preformed methanime complex of **1** to give **3**, followed in one course by intramolecular condensations with two other methanimines to give **4** and **5** in succession. The second pathway involves a process analogous to the dibenzoylmethane condensation where the ketone in **4** reacts directly with the remaining deprotonated primary amine site to give the imine complex **7**. It is also possible that **7** arises from **3** *via* intermediate **6**.

The imine sites of the cage complexes **7** and **2** were efficiently hydrogenated with $NaBH_4$ to give only one isomer of the saturated analogue **8**‡ and two isomers of **9**‡ respectively (Scheme 3). These isomers arise from the chirality induced at the benzyl carbon atom on reduction but their configurations have not yet been determined.

The encapsulation reactions involving the ketonic carbon acids acetophenone and dibenzoylmethane demonstrate a versatile means of attaching aromatic substituents to the cage assembly, both at apical (**5**) and meridional (**8**, **9**) positions. A wide range of accessible acetyl aromatics ensures an extensive choice for the substituents of **5** and **8**, which can include both photoactive donor and acceptor groups, It is also likely that this strategy may be expanded to include other templates such as $[Co(en)_3]^{3+}$ (en = ethane-1,2-diamine) and $[Co(tame)_2]^{3+}$ [tame = ethylidynetris(methanime)] so that two types of substituent each having a different function could be incorporated in the same cage molecule, or the metal-based chromophore electron properties may be changed by distending or deforming the cavity.[6]



Scheme 3

Footnotes

† **2** = {1-hydroxymethyl-8-methyl-2,14-diphenyl-3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosa-2,13-diene}cobalt(III), **5** = {1-benzoyl-8-methyl-3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosane}cobalt(III), **7** = {8-methyl-2-phenyl-3,6,10,13,16,19-hexaazabicyclo[6.6.6]icosa-2-ene}cobalt(III).

‡ *Data*: for **2**, Calc. for $C_{28}H_{40}CoCl_3N_6O{\cdot}3H_2O$: C, 48.3; H, 6.7; N, 12.1; Cl, 15.3; Co, 8.5. Found: C, 48.6; H, 6.8; N, 12.1; Cl, 15.6; Co, 8.5%. IR (KBr): $\nu_{C=N}$ 1614 cm^{-1}. UV–VIS [H_2O, λ_{max}/nm (ε/dm^3 mol^{-1} cm^{-1})]: 250 (28190), 294(sh) (7150), 335(sh) (533), 468 (238). $^{13}C\{^1H\}$ NMR (75.4 MHz in D_2O, δ in ppm *vs.* $SiMe_4$ with δ CH_3CN at 1.3): 20.3 (CH_3), 41.1 (C_qCH_3), 51.5, 51.9, 52.2, 52.6, 53.7, 54.5, 54.5, 55.5, 56.1, 58.0, 58.0 (CH_2, C_qCH_2OH), 67.5 (CH_2OH), 129.1, 129.7, 129.7, 130.1, 131.9, 133.1, 133.6, 135.1 (phenyl), 189.7, 195.6 (N=C). ^1H NMR (500 MHz in D_2O): consistent with assigned structure, four AB quartets (cap CH_2), three ABCD multiplets (en CH_2) AB quartet (CH_2OH), singlet (CH_3), multiplets (phenyl).

For **5**, **7**, **8**, **9a**, **9b**, microanalytical and spectroscopic data were all consistent with their structures. $^{13}C\{H\}$ NMR of **5** (Cl_3 salt in D_2O, δ NaTPS at −1.1): Ph–C=O form, 20.4 (CH_3), 43.0 (C_qCH_3), 52.2, 55.4, 55.6, 55.7 (CH_2), 59.3 (C_qCO), 128.4, 130.1 (phenyl *o,m*), 134.0 (phenyl *p*), 137.8 (phenyl C_q), 203.0 (C=O): Ph–$C(OH)_2$ form, 20.5 (CH_3), 42.6 (C_qCH_3), 51.4, 54.9, 55.1, 55.8 (CH_2), 54.6 [$C_qC(OH)_2$], 98.0 [$C(OH)_2$], 128.7, 129.5 (phenyl *o,m*), 130.5 (phenyl *p*), 140.9 (phenyl C_q). **7** ($ZnCl_4$ salt in D_2O, δ NaTPS at −1.1): 21.4 (CH_3), 42.2 (C_qCH_3), 48.7, 49.6, 53.1, 53.3, 55.7, 55.8, 55.9, 56.1, 56.3, 57.1, 58.6, 59.3, (CH_2, CH), 129.9, 130.9 (phenyl *o,m*), 135.0 (phenyl *p*), 133.4 (phenyl C_q), 190.9 (N=C). $^{13}C\{H\}$ NMR data for **8**, **9a**, **9b** were consistent with the saturated cage structures shown in Scheme 3.

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