A New Strategy for the Metal Template Synthesis of Organic Metal Ion Cages

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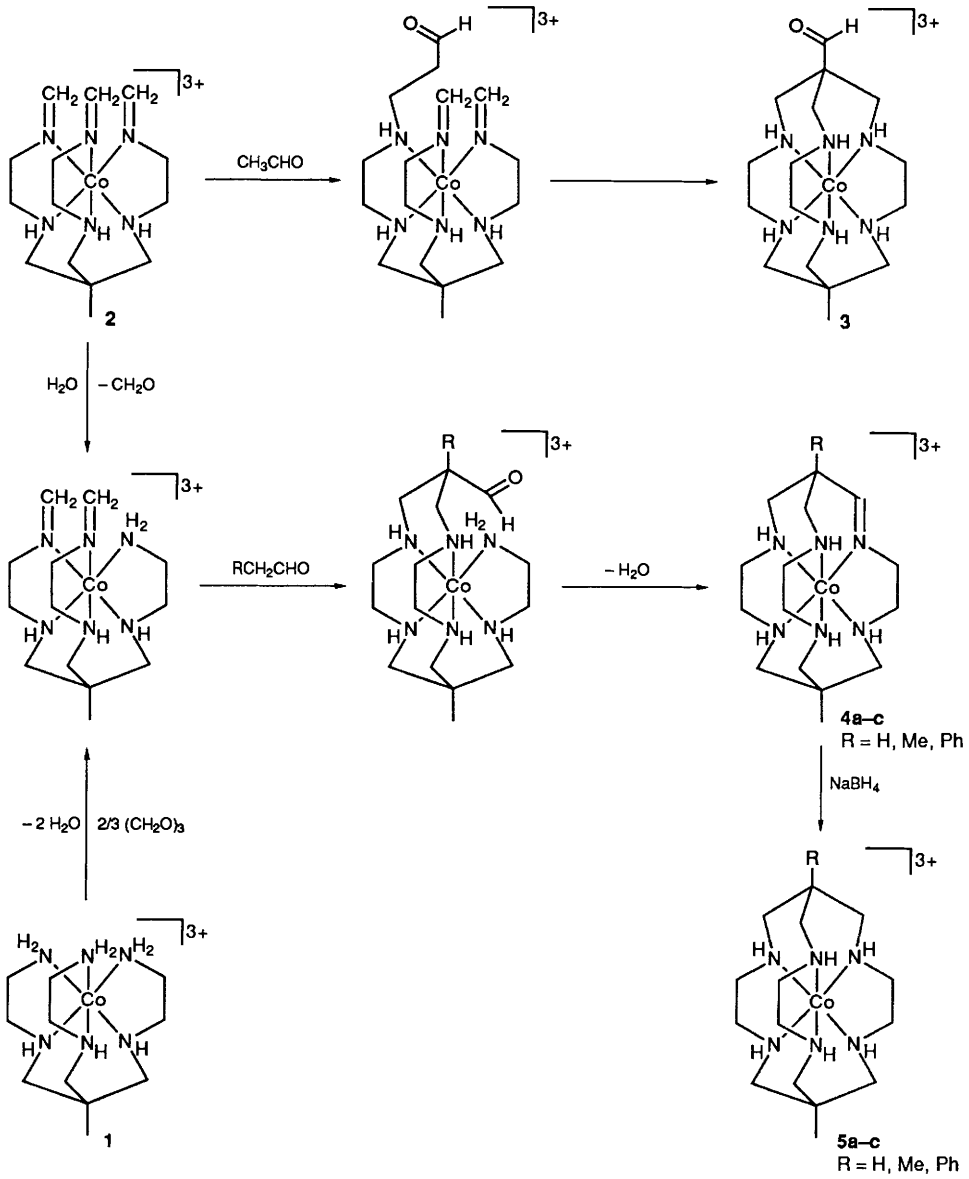
High yield template syntheses of hexa-azabicycloeicosanes and related imines are described arising from non-aqueous condensations of mixed aldehydes with the 4,4′,4″-ethylidyne-tris(3-azabutan-1-amine)cobalt(III) ion in basic media.

Multidentate macrocyclic and macropolycyclic molecules have captured much attention because of their ability to alter in a dramatic way the physical and chemical properties of metal ions upon complexation.[1] One of the problems in these studies is devising efficient syntheses of such large ring systems in which entropy effects limit rapid cyclisation rates and yields are often small.[1,2] Metal-ion template syntheses help to overcome these difficulties and there are good examples of such syntheses in the literature.[3–7] Here we describe a new strategy to achieve macrobicyclic amine ligands that encapsulate metal ions.

Connected with a programme to synthesize aza-cryptates that contain group 5 elements in the framework of the encapsulating ligand, we recently reported the synthesis of a stable triimine precursor $[Co(sim)]^{3+}$, **2**, [sim = 6,6′,6″-ethylidynetris(2,5-diaza-hex-1-ene)] obtained by reacting $[Co(sen)]^{3+}$ **1** [sen = 4,4′,4″-ethylidynetris(3-azabutan-1-amine)] and paraformaldehyde.[8] In this paper we demonstrate



Scheme 1

that the condensation between the primary amine functions of $[Co(sen)]^{3+}$ **1**, is not confined to formaldehyde only. A number of new cage complexes can be synthesized in surprisingly high yields when the above mentioned reaction is conducted in the presence of another primary aldehyde. The new strategy of co-condensing aldehydes around the metal centre of cobalt amine complexes seems to be generally applicable.

In attempts to synthesize cage molecules that have a functional group attached to the encapsulating ligand, $[Co(sim)]^{3+}$ **2**, was treated with acetaldehyde in acetonitrile in the presence of triethylamine. It was expected that the aliphatic protons of the aldehyde molecule would be sequentially deprotonated, each time generating a powerful nucleophile that would attack the *exo*-imino groups of **2** and ultimately lead to the formation of the desired target molecule $[Co(CH_3,CHO\text{-}sar)]^{3+}$ **3**, (CH_3,CHO-sar = 1-formyl-8-methyl-3,6,10,13,16,19-hexa-azabicyclo[6.6.6]eicosane) (Scheme 1). After 30 min, the reaction was quenched with aqueous hydrochloric acid and ion-exchange chromatography (SP Sephadex C25, 0.1 M K_2SO_4) allowed the separation and isolation of two compounds. One of these was identified as the desired aldehyde substituted cage molecule **3** by its ^{13}C NMR spectrum† and elemental microanalysis as the trichloride salt. A ^{13}C NMR spectrum of the second product showed eleven resonances for methylene carbon atoms and one at 184.3 ppm, typical of an imine C-atom, however, it is more than 7 ppm downfield from the resonance of the starting material.[8] The product was assigned the structure of the imine cage molecule

† $^{13}C\{H\}$ NMR (75.43 MHz in D_2O; δ in ppm *vs.* internal dioxane at 67.6 ppm) **3**: 20.49, 43.00, 50.98, 52.80, 55.47, 55.54, 55.68, 90.81; **4a**: 21.08, 41.79, 43.92, 47.33, 47.83, 52.66, 52.88, 55.14, 55.33, 55.56, 56.03, 56.82, 58.84, 61.46, 184.3; **4b**: 19.10, 21.17, 41.91, 49.37, 52.60, 53.01, 53.30, 54.00, 55.17, 55.25, 55.49, 56.07, 56.88, 58.98, 61.63, 188.28; **4c**: 21.19, 41.90, 52.75, 53.21, 54.46, 55.03, 55.09, 55.55, 56.12, 56.30, 56.87, 58.64, 62.11, 127.79, 130.34, 130.83, 136.77, 187.39; **5a**: 20.35 (CH_3), 38.55 (*C*H), 43.13 (C_q), 50.17, 55.38, 55.80 (double intensity) (CH_2); **5b**: 20.38 (CH_3), 43.14 (C_q), 55.46 (C_q–CH_2), 55.88 (CH_2–CH_2); **5c**: 21.26 (CH_3), 43.99 (C_q–CH_3), 49.99 (C_q–C_6H_5), 55.93, 56.34, 56.74, 57.08 (CH_2), 127.97, 130.60, 131.22, 139.14 (C_6H_5).

4a, which was confirmed by converting it into the symmetrical saturated derivative **5a** by reduction with $NaBH_4$ (Scheme 1). The ^{13}C NMR data† of the product so obtained were identical with those of the $[Co(CH_3\text{-sar})]^{3+}$, **5a**, ($CH_3$-sar = 1-methyl-3,6,10,13,16,19-hexa-azabicyclo[6.6.6]icosane) a molecule which was synthesized by a more devious process previously.[9]

The experimental results implied that in the course of the reaction one of the original three imine bonds in **2** was cleaved by reaction with H_2O, present in the reaction solution and originating from the water of crystallisation of the starting material and water eliminated by the imine formation. The intermediate thus formed then condensed twice with a molecule of acetaldehyde as outlined above. This was followed by an intramolecular condensation of the aldehyde group with the now vacant amine function[10] to give the cage molecule **4a** (Scheme 1).

This intriguing observation led directly to experiments, where $[Co(sen)]^{3+}$, **1**, was deliberately treated with only two equivalents of formaldehyde but in the presence of another primary aldehyde. By this route, the cage molecule **4a** was synthesized in *ca.* 70% yield and small amounts of **3** were detected as a by-product. The results imply a much faster condensation of the primary amine groups of **1** with formaldehyde compared with acetaldehyde. The route also leads to very efficient condensation of the reactants, since the treatment of **1** with formaldehyde and propanal yielded quantitatively **4b**, which was then readily reduced to give $[Co\{(CH_3)_2\text{-sar}\}]^{3+}$ **5b**, {$(CH_3)_2$-sar = 1,8-dimethyl-3,6,10,13,16,19-hexa-azabicyclo-[6.6.6]eicosane}. The new strategy is not confined to attaching only alkyl groups to the cage molecule. The phenyl substituted imine cage **4c** was prepared in a similar manner using benzylaldehyde as a reagent, which as expected gave $[Co(C_6H_5,CH_3\text{-sar})]^{3+}$, **5c**, ($C_6H_5$,$CH_3$-sar = 1-phenyl-8-methyl-3,6,10,13,16,19-hexa-azabicyclo[6.6.6]eicosane) upon reduction with $NaBH_4$.

In a typical experiment at *ca.* 23 °C $[Co(sen)]Cl_3$ **1** (0.003 mol), was dissolved in acetonitrile (30 ml) by stirring with an excess of $NaClO_4 \cdot H_2O$ (5g), followed by addition of $(CH_2O)_3$ (0.002 mol), the second aldehyde (0.006–0.009 mol) and NEt_3 (0.003 mol). Purification and isolation of the cage molecules were achieved by cation-exchange chromatography. The reductions of the yellow complexes **4a–c** were conducted in aqueous solution yielding the saturated orange complexes **5a–c**, which were characterized by satisfactory elemental microanalyses and by their ^1H and ^{13}C NMR spectra.† Owing to the gain in symmetry upon conversion of **4** to **5** the spectra simplified tremendously. This effect was particularly striking in the case of **4b**, where, owing to the high symmetry of the reaction product $[Co(CH_3)_2\text{-sar})]^{3+}$ **5b**, the number of observed signals was reduced from 16 **4b** to 4 **5b**. ^1H NMR spectra of the imine complexes **4** were not especially informative and showed overlapping spin systems even at a spectrometer frequency of 500 MHz. Characteristically the reduced molecules **5** showed AB patterns for the cap methylene protons and ABXY **5a**, **5c** or AA'BB' **5b** for the protons of the ethylenediamine moiety.

The metal-ion cages of this size and type are characterized by high stability and unusually high electron exchange rates.[11] Clearly many new derivatives can be made by the new route. The formyl substituent is ideal for tying long chain aliphatic amines to the cage in order to insert the cages into membranes and to make micelles. The free cages may be effective metal detoxifying agents and there are possibilities for using paramagnetic cage complexes as NMR imaging agents. Also the phenyl substituents can be derivatized readily themselves and interesting possibilities arise for photocyclic reactions and energy transformation.

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References

1 K. B. Mertes and J.-M. Lehn, in *Comprehensive Coordination Chemistry*, ed. G. Wilkinson, Pergamon Press, 1987, vol. 2, p. 915.
2 A. M. Sargeson, *Chem. Br.*, 1979, **15**, 23.
3 N. F. Curtis, *Coord. Chem. Rev. 3*, 1968, 3.
4 V. L. Goedken and S.-M. Peng, *J. Chem. Soc., Chem. Commun.*, 1973, 62.
5 J. E. Parks, B. E. Wagner and R. H. Holm, *Inorg. Chem.*, 1971, **10**, 2472.
6 D. R. Boston and N. J. Rose, *J. Am. Chem. Soc.*, 1973, **95**, 4163.
7 A. M. Sargeson, *Pure Appl. Chem.*, 1984, **56**, 1603 and references cited therein.
8 A. Höhn, R. J. Geue, A. M. Sargeson and A. C. Willis, *J. Chem. Soc., Chem. Commun.*, 1989, 1648.
9 I. I. Creaser, J. D. Lydon, A. M. Sargeson, E. Horn and M. R. Snow, *J. Am. Chem. Soc.*, 1984, **106**, 5729.
10 A. R. Gainsford, R. D. Pizer, A. M. Sargeson and P. O. Whimp, *J. Am. Chem. Soc.*, 1981, **103**, 792.
11 P. Bernhard and A. M. Sargeson, *Inorg. Chem.*, 1987, **26**, 4122.