Template formation of a macrocyclic pendant-arm ligand by intramolecular alkylation: crystal structure of the cobalt(III) complex of 1,4-bis(carboxymethyl)cyclam

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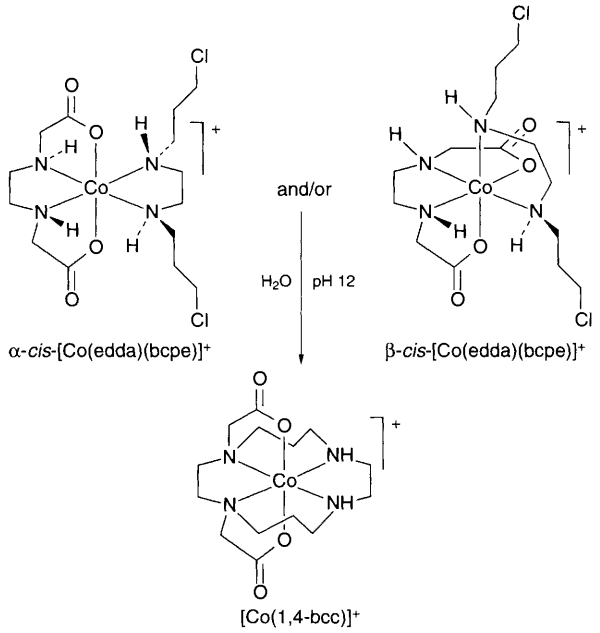
A cobalt(III) complex containing the tetradentate ligand edda and a bidentate diamine ligand which bears 3-chloropropyl groups on the nitrogen atoms undergoes efficient intramolecular alkylation in basic solution to form a complex containing the cyclam tetraaza macrocycle with two coordinated *N*-carboxymethyl pendant arms, characterised by an X-ray crystal structure of the perchlorate salt.

Metal complexes containing saturated polyaza macrocyclic ligands bearing pendant donor functions, often *N*-carboxymethyl groups, appear in a wide range of applications, including MRI imaging agents and other therapeutic agents requiring bifunctional chelates.[1] Pendant-arm chelating macrocycles also form a class of ligand intermediate between simple macrocycles and fully encapsulating ligands with a three-dimensional framework.[2] The pendant-arm macrocycles are usually synthesised prior to coordination. Fully alkylated ligands (containing only tertiary nitrogens) can be relatively straightforward to prepare, whereas the partially alkylated macrocycles (containing both secondary and tertiary nitrogens) are more difficult to achieve.[3] Problems arise from low yields and the formation of mixtures of partially alkylated products. The macrocycles may also form as mixtures of isomers and indeed some geometric isomers have proved to be inaccessible.[4] We describe here an intramolecular alkylation reaction of a cobalt(III) complex which produces a new substituted cyclam, 1,4-*N*,*N*′-bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane (1,4-bcc) bearing pendant, coordinating carboxymethyl groups on two adjacent nitrogen atoms. The efficient cyclisation proceeds with excellent control of the regio- and stereochemistry.†

The alkylating groups are contained in the chelating ligand *N*,*N*′-bis(3-chloropropyl)ethylenediamine (bcpe). The substrate for the intramolecular alkylation reaction is coordinated *N*,*N*′-ethylenediaminediacetate (edda). The precursor cobalt complex $[Co(edda)(bcpe)]^+$ containing the two acyclic ligands is prepared from $[Co(edda)(H_2O)_2]^+$[5] and bcpe in aqueous solution. Two geometrical isomers, the α- and β-*cis* forms (Scheme 1), can be separated by ion-exchange chromatography and are isolated as the perchlorate salts. The major, α-*cis* isomer contains the four nitrogen donors in a square-planar arrangement with the two carboxyl groups *trans*. Six diastereomers (three pairs of enantiomers) are possible for the α-*cis* isomer, depending on the configurations at cobalt (Δ or Λ) and at the two secondary nitrogen centres in the coordinated bcpe ligand [(*R*) or (*S*)]. Two pairs (*R*,*R*) and (*S*,*S*) contain a twofold axis of symmetry (C_2), while the last pair (*R*,*S*) contains no symmetry elements (C_1). The α-*cis* isomer, formed in 41% yield, was characterised by elemental analysis and ^1H and $^{13}C\{^1H\}$ NMR spectroscopy. The sample obtained directly from chromatography shows 7 peaks in the $^{13}C\{^1H\}$ NMR spectrum indicating that the major product is just one of the racemic pairs of C_2 isomers. This is presumed to be the diastereomer [Δ(*R*,*R*) and its enantiomer Λ(*S*,*S*)] which has the least steric interactions between the chloropropyl and carboxymethyl groups. The C_1 pair of enantiomers (characterised by 14 peaks in the spectrum) is present as a minor component, with an approximately 2 : 1 ratio of the C_2 to C_1 pairs. Epimerisation of the secondary nitrogen centres occurs in solution, and repeated recrystallisation resulted in isolation of the major (C_2) diastereomer in pure form.

The intramolecular alkylation reaction takes place upon stirring either α- or β-*cis*-[Co(edda)(bcpe)]Cl in basic aqueous solution maintained at pH 12. The reaction produces 2 moles of HCl and is judged to be complete when the pH no longer drops, after *ca.* 4 d at room temp. Each chloropropyl group on the bcpe ligand alkylates an adjacent secondary nitrogen atom on the edda ligand to form the macrocyclic ligand 1,4-*N*,*N*′-bis(carboxymethyl)-1,4,8,11-tetraazacyclotetradecane (1,4-bcc). The product, $[Co(1,4\text{-bcc})]^+$, is isolated as the ClO_4^- salt after ion-exchange chromatography (yield 83%) and contains the 14-membered cyclam macrocycle with the four nitrogen atoms coordinated in the equatorial plane. The two carboxymethyl groups from the edda fragment are retained on adjacent nitrogen atoms and coordinate through *trans* oxygen atoms. Elemental analysis, ^1H and $^{13}C\{^1H\}$ NMR spectroscopy and an X-ray crystal structure determination‡ confirm the formulation of the product. The macrocyclic complex retains the C_2 symmetry of the α-*cis* precursor and shows the expected 7 peaks in the $^{13}C\{^1H\}$ NMR spectrum.

The coordination geometry around the cobalt ion in $[Co(1,4\text{-bcc})]ClO_4$ is close to octahedral (Fig. 1), with no large distortions. The Co–N(3) and Co–N(4) bond lengths involving the tertiary nitrogens (av. 1.961 Å) are slightly shorter than those to the secondary nitrogens, Co–N(1) and Co–N(2) (av.



Scheme 1

1.977 Å). The cyclam macrocycle adopts the commonly observed *trans*-III conformation.[6]

The inherent kinetic stability imparted by the bis(pendant arm) macrocycle is manifested in the electrochemical reduction to the cobalt(II) complex. Cyclic voltammetry of [Co(1,4-bcc)]ClO_4 in aqueous solution shows a reversible couple at −0.49 V *vs.* Ag/AgCl (ΔE_p = 61 mV, i_{pc}/i_{pa} = 1.0, E^0 = −0.29 V), in contrast to the acyclic precursor α-*cis*-[Co(edda)(bcpe)]ClO_4 which exhibits completely irreversible reduction (E_p = −0.37 V *vs.* Ag/AgCl).

Alkylations of coordinated amines are not readily accomplished due to the requirement for initial deprotonation of the nitrogen in order to reveal a nucleophilic lone pair. Reactions involving an external alkylating agent have only been accomplished in non-aqueous solution and usually require a large excess of the alkylating agent.[7] Examples of alkylations of acyclic chelating amine ligands to form macrocyclic complexes are rare and have had to rely on the more acidic aryl amines for which a relatively high concentration of the deprotonated amine can be achieved.[8] The chemistry reported here takes place in aqueous solution and involves the use of a less acidic alkyl amine as substrate. This has been achieved by exploiting the intramolecular nature of the alkylation reaction which allows preorganisation of the acyclic components in the coordination sphere. The reaction proceeds at appreciable rates despite only very low concentrations of the deprotonated amine.

The 14-membered cyclam ring adopts a single conformation in the product, and epimerisation of the secondary nitrogen centres in the bcpe ligand during the reaction allows the alkylation step to produce this preferred conformation. The size of the macrocycle formed is important. The complex α-*cis*-[Co(edda)(bce)]$^+$ [bce = *N*,*N*′-bis(2-chloroethyl)ethylenediamine] which contains 2-chloroethyl groups in place of 3-chloropropyl groups undergoes a single alkylation to give a hexadentate acyclic ligand, but a second alkylation which would form a macrocycle does not occur.[9] The potential product, a 12-membered tetraaza macrocycle (cyclen) with two pendant *N*-carboxymethyl groups, would be too sterically restricted to accommodate the cobalt(III) ion in the equatorial plane.[10]

The β-*cis* isomer of [Co(edda)(bcpe)]$^+$ can also serve as a precursor to the macrocyclic complex and in this case isomerisation must occur as part of the reaction sequence. We have improved the utility of the method for producing the bis(pendant arm) cyclam derivative by developing a 'one-pot' process for the preparation of [Co(1,4-bcc)]$^+$ directly from H[Co(edda)Cl_2] without the requirement for the intermediate complexes [Co(edda)$(OH_2)_2$]$^+$ and [Co(edda)(bcpe)]$^+$ to be isolated or purified. Gentle warming of H[Co(edda)Cl_2] in aqueous solution, followed by the addition of bcpe/charcoal, filtration, addition of NaOH to achieve pH 12 then allowing the reaction to proceed as for the direct synthesis gives the product in 57% isolated yield.

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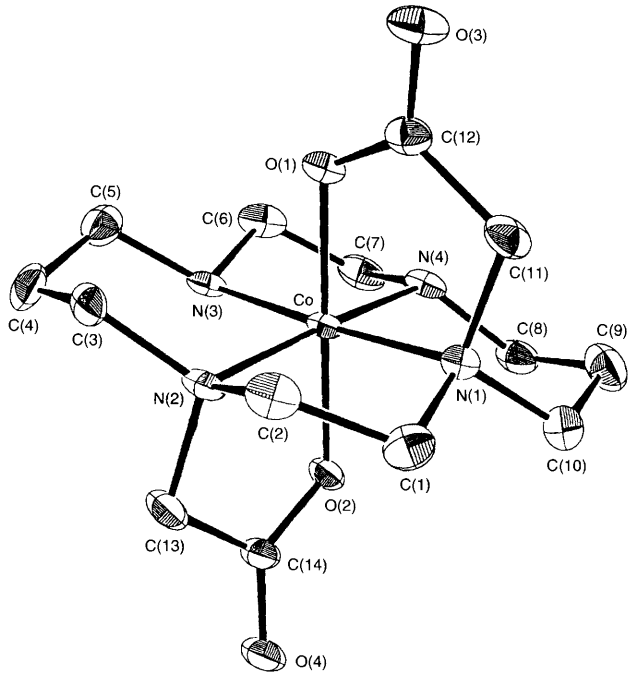

Fig. 1 Molecular structure of [Co(1,4-bcc)]ClO_4. Important bond lengths (Å) and bond angles (°): Co–O(1) 1.892(3), Co–O(2) 1.887(3), Co–N(1) 1.974(4), Co–N(2) 1.980(4), Co–N(3) 1.962(4), Co–N(4) 1.960(4), O(2)–Co–O(1) 178.04(13), O(2)–Co–N(4) 89.1(2), O(1)–Co–N(4) 92.1(2), O(2)–Co–N(3) 92.18(14), O(1)–Co–N(3) 89.44(14), N(4)–Co–N(3) 86.5(2), O(2)–Co–N(1) 91.21(13), O(1)–Co–N(1) 87.18(13), N(4)–Co–N(1) 92.5(2), N(3)–Co–N(1) 176.4(2), O(2)–Co–N(2) 87.11(14), O(1)–Co–N(2) 91.71(13), N(4)–Co–N(2) 176.2(2), N(3)–Co–N(2) 92.9(2), N(1)–Co–N(2) 88.3(2).

Footnotes

† The organic synthesis of 1,8-bcc, a geometrical isomer of the new ligand, has been reported in 16% yield beginning from cyclam (ref. 4).

‡ *Crystal data* for [Co(1,4-bcc)]ClO_4: $C_{14}H_{26}ClCoN_4O_8$, M = 472.77, monoclinic, space group $P2_1/c$, a = 7.692(2), b = 13.860(12), c = 17.385(6) Å, β = 96.45(3)°, U = 1842(2) Å^3, $F(000)$ = 984, D_c = 1.705 g cm^{-1}, Z = 4, μ(Mo-Kα, λ = 0.71069 Å) = 11.30 cm^{-1}. Intensity data were collected to a 2θ limit of 50° on a Nonius CAD-4 diffractometer and corrected for Lorentz, polarisation and absorption effects. The structure was solved from Patterson and heavy-atom electron density maps and refined by full-matrix least-squares analysis. All non-hydrogen atoms were allowed to assume anisotropic motion, and hydrogen atoms were located. Refinement converged to R = 0.0424 (R_w = 0.0892) for 3229 reflections for which $I > 2\sigma(I)$.

Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/61.

References

1 R. B. Lauffer, *Chem. Rev.*, 1987, **87**, 901; D. Parker, *Chem. Soc. Rev.*, 1990, **19**, 271.
2 G. A. Lawrance and P. G. Lye, *Comments Inorg. Chem.*, 1994, **15**, 339; P. V. Bernhardt and G. A. Lawrance, *Coord. Chem. Rev.*, 1990, **104**, 297.
3 T. A. Kaden, *Top. Curr. Chem.*, 1984, **121**, 157.
4 I. M. Helps, D. Parker, J. R. Morphy and J. Chapman, *Tetrahedron*, 1989, **45**, 219.
5 K. Kuroda and K. Watanabe, *Bull. Chem. Soc. Jpn.*, 1971, **44**, 1034.
6 R. J. Restivo, G. Ferguson, R. W. Hay and D. P. Piplani, *J. Chem. Soc., Dalton Trans.*, 1978, 1131.
7 F. Wagner, M. T. Mocella, M. J. D'Aniello Jr., A. H.-J. Wang and E. K. Barefield, *J. Am. Chem. Soc.*, 1974, **96**, 2625.
8 G. J. Grant and D. J. Royer, *J. Am. Chem. Soc.*, 1981, **103**, 867; C. W. G. Ansell, M. K. Cooper, K. P. Dancey, P. A. Duckworth, K. Hendrick, M. McPartlin and P. A. Tasker, *J. Chem. Soc., Chem. Commun.*, 1985, 439.
9 D. C. Ware, D. M. Tonei, H. R. Palmer and P. J. Brothers, unpublished work.
10 Y. Hung, L. Y. Martin, S. C. Jackels, A. M. Tait and D. H. Busch, *J. Am. Chem. Soc.*, 1977, **99**, 4029.

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