Pendent Arm Formation and Extension accompanying Macrocycle Synthesis – A New Class of Ryongamines?

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Reaction of the Cu^{II} complex of the podand hexamine "sen", $CH_3C(CH_2NHCH_2CH_2NH_2)_3$, with formaldehyde and nitroethane under basic conditions provides, as one of the principal products, a complex containing a new ligand which is not only macrocyclic but which has resulted also from reactions to extend one podand arm, to introduce an aminal bridge and to oxidise one of the donor-*N* atom units to an imine.

Introduction

Formaldehyde has been used in a remarkable variety of reactions with polyamines to give macrocyclic and macropolycylic ligands.[1–3] Aminal formation — in general a useful pathway in macrocycle synthesis[4] — is commonly involved in these reactions, as is carbon-carbon bond formation through carbanion addition to intermediate imines, although for a particular product it is usually either one or the other that is involved. Macrocycle formation from the sexidentate amine ligand $CH_3C(CH_2NHCH_2CH_2NH_2)_3$, "sen",[5] when reacted as its Cu^{II} complex with formaldehyde and nitroethane, appears, however, as we show presently, to involve a competition between these two pathways, leading to a product macrocycle with a pendent arm which is both tied back to the macrocycle by an aminal bridge and elongated as a result of carbanion addition to a presumed imine formed at the terminal amino group. Further, the ligand then appears to have undergone alkylation by formaldehyde at the carbon atom derived from nitroethane in the extended arm, as well as partial oxidation within the macrocyclic ring to convert one N-donor unit to an imine!

For metal ions favouring octahedral coordination, the coordination chemistry of sen has been fairly well characterised[6] but surprisingly little is known of the behaviour of this ligand towards Cu^{II}. Evidence is available,[7] however, that a homologue of sen will bind to Cu^{II} through only four of its six *N*-donor atoms and, given the propensity of Cu^{II} to adopt four coordination even in systems such as those involving potentially sexidentate cage amines,[8] it was anticipated that the widely applied reaction of Cu^{II} tetraamine complexes with formaldehyde and nitroethane to give macrocycles[1–3] might, in this case, lead to a macrocycle with a pendent diamine arm. Such a macrocycle could then be used in the formation of multimetallic complexes through, for example, the formation (and capping) of a tris(bidentate) metal complex from the donor atoms in the pendent arm. There are many possible complications in this system arising from isomerism of the complex ions and thus we have attempted, as a preliminary step, to define precisely the chemistry involved in the reaction of the Cu^{II} complex of sen with nitroethane and formaldehyde. This will be described in detail elsewhere, the present report being of the remarkable structure found (Figure 1) for the leading component found during chromatographic treatment (SP Sephadex cation exchange with 0.3 M sodium citrate as eluent) of the reaction mixture inadvertently prepared with the use of a very large excess of formaldehyde.

Results and Discussion

The ligand structure (inset, Figure 1) shows that two arms of the original sen ligand have indeed become involved in the anticipated cyclisation reaction to give a cyclam-like[9] macrocycle but also that the third arm, singly protonated in the isolated complex, has become involved in elaborate related reactions leading to a partially rigidified pendent arm in which two new functional groups — hydroxyl and nitro — have been added to the diamine entity. Further, a reaction well-known with other metal ion complexes of amines but rarely observed with Cu^{II} [10] has led

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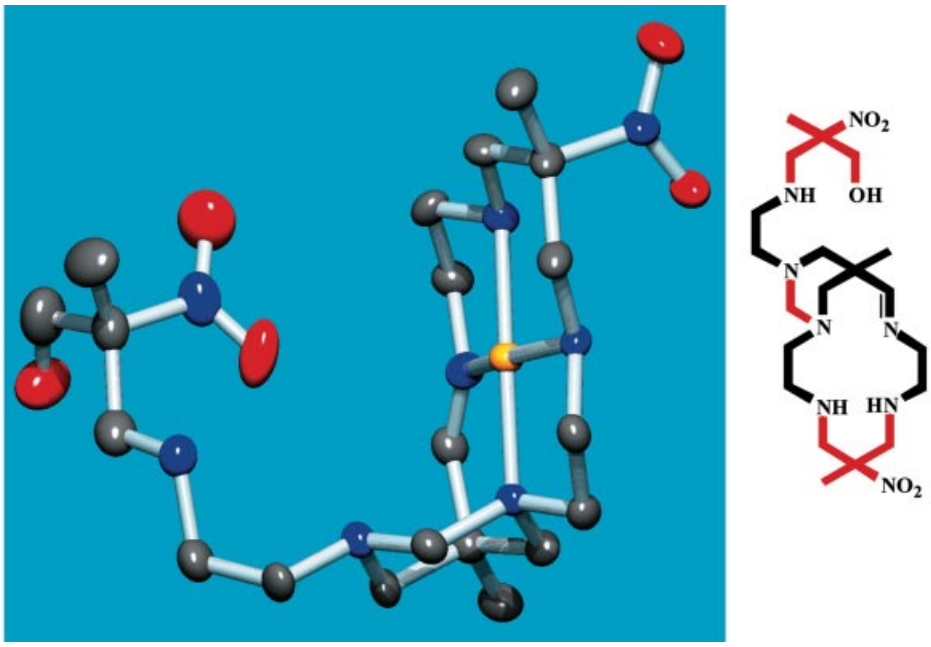

Figure 1. The complex cation found in the crystal lattice of $[Cu(LH)](ClO_4)_3 \cdot 1.5H_2O$; displacement ellipsoids are drawn at the 50% probability level; C = grey, N = blue, O = red, Cu = yellow; hydrogen atoms are not shown and one position only of the disordered parts is represented; inset is the structure of the ligand (L), with the initial sen skeleton shown in black

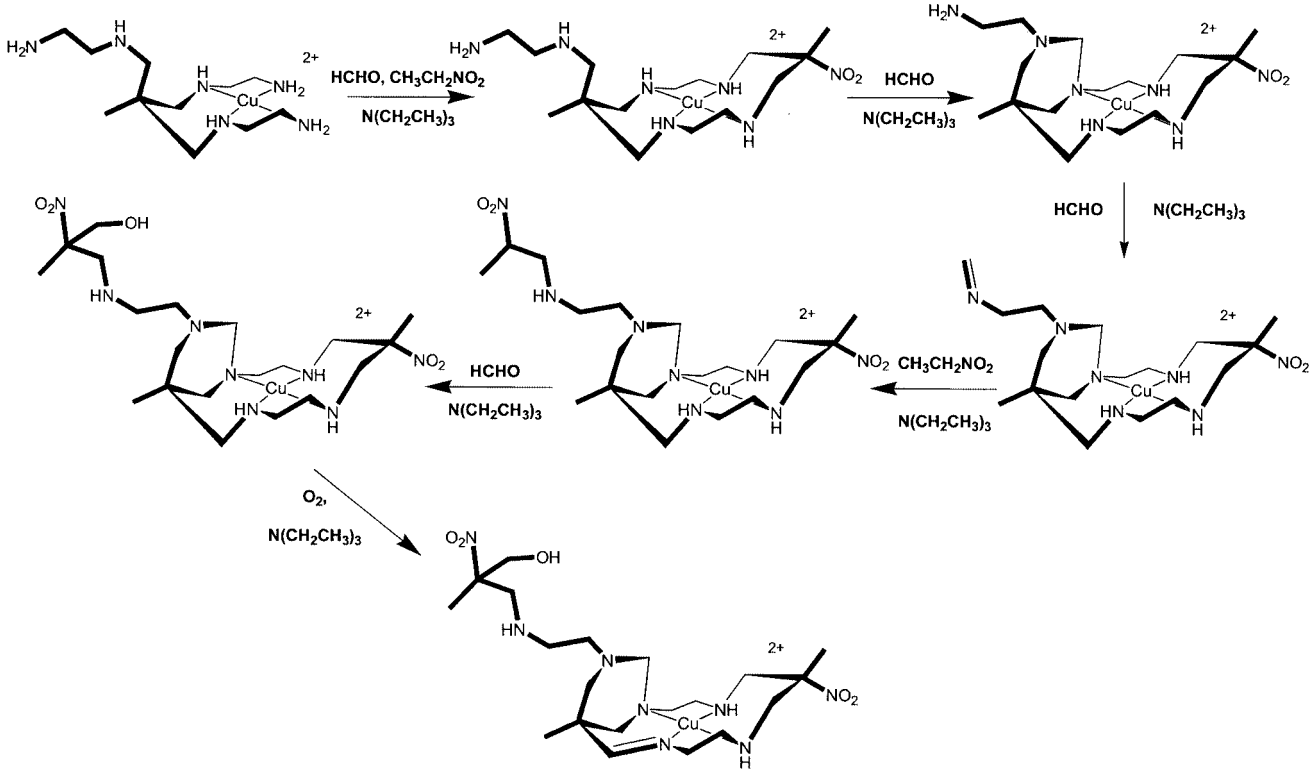

Figure 2. A possible sequence of events involved in the synthesis of a "ryongamine"

to the partial oxidation of the macrocyclic ring, converting one amine donor to an imine. As seen in many related instances,[11] the crystal structure of the complex shows the nitro and methyl substituents on the macrocyclic ring to adopt axial and equatorial orientations, respectively, on the chair six-membered ring formed by the macrocyclisation process. Despite this aspect of stereospecificity, there is disorder associated with the chiral centre generated on the

pendent arm, indicating a complete lack of diastereoselectivity in the crystallisation process. This is perhaps in part a consequence of the rigidification of the pendent arm by aminal formation, giving a six-membered heterocyclic ring, between donor atoms N3 and N6, and which may inhibit any significant interaction between the chiral donor centres on the metal and the chiral centre near the arm terminus. A simplified representation of a possible sequence of events leading to the complex is given in Figure 2. Clearly, reduction of the product complex under acidic conditions can be expected to generate a saturated, chiral octaamine-mono-ol ligand in which a macrocyclic unit has two, very different amino-pendent arms in an *anti* (*trans*) arrangement relative to the macrocycle mean plane. The chemistry involved is a remarkably simple pathway to a ligand of such a sophisticated structure, though the detection of the product was a completely fortuitous consequence of an error made in the quantity of formaldehyde used and a systematic evaluation of procedures to optimise the yield of the complex is now in progress. The prospects are that a wide range of podand ligands might be used in similar reactions and our perception of a resemblance between the structure of the molecule presently described and classical oriental representations of a dragon (see graphical abstract), prompts us to suggest the trivial name "ryongamines" for this class of macrocycle, "ryong" being the romanised form of the Korean word for dragon.

Experimental Section

Synthesis: A methanolic solution of sen was prepared by slurrying sen·6HCl[6b] (1.20 g) with NaOH (0.62 g) in methanol (100 mL) and mixed with $CuCl_2 \cdot 2H_2O$ (0. 70 g) in 1:1 water/methanol (100 mL). The resulting blue-violet solution was filtered to remove some $Cu(OH)_2$ before HCHO (36% aqueous solution, 10 g), nitroethane (0.40 g) and triethylamine (4 g) were added and the mixture then heated at reflux for 12 h. On cooling to room temperature, the reaction mixture was acidifed to pH 6 with acetic acid and taken to dryness under vacuum. The residue was dissolved in water and chromatographed on Na^+-form SP Sephadex C25 with 0.13 M sodium citrate. Separate eluate fractions were absorbed on H^+-form Dowex 50Wx2 and elution with HCl used to recover the complexes as their chlorides after evaporation of the solvents to dryness. The first component thus obtained is the subject of the present communication and was precipitated from water as its perchlorate (50 mg) for the structure determination. $C_{20}H_{44}Cl_3CuN_8O_{18.5}$ (862.5): calcd. C 27.59, H 5.09, N 12.87; found C 27.6, H 6.7, N 12.3.

X-ray Crystallography: Data were collected on a Nonius-Kappa-CCD area detector diffractometer[12] using graphite-monochromated Mo-K_α radiation (λ = 0.71073 Å). The crystal was introduced in a glass capillary with a protecting "Paratone-N" oil (Hampton Research) coating. The unit cell parameters were determined from ten frames, then refined on all data. A 180° -range was scanned with 2° steps during data collection, with a crystal-to-detector distance fixed at 28 mm. The data were processed with DENZO-SMN.[13] The structure was solved by Patterson-map interpretation with SHELXS-97[14] and refined by full-matrix least-squares on F^2 with SHELXL-97.[14] Absorption effects were corrected empirically with the program DELABS from PLATON.[15] The terminal CH_2OH and CH_3 groups of the pendent arm are disordered so that each fragment bears a partially occupied oxygen atom site (occupancies constrained to sum to unity). One perchlorate ion is disordered over two sites sharing three oxygen atoms, the disordered chlorine and oxygen atoms having been refined with occupancy parameters constrained to sum to unity. All non-hydrogen atoms were refined with anisotropic displacement parameters, with some restraints for some oxygen atoms of the pendent arm, perchlorate ions and water molecules. Hydrogen atoms bound to nitrogen atoms were found on a Fourier-difference map and all others were introduced at calculated positions, except those bound to oxygen atoms. All protons were treated as riding atoms with a displacement parameter equal to 1.2 (NH, NH_2, CH, CH_2) or 1.5 (CH_3) times that of the parent atom. The molecular plot was drawn with SHELXTL.[16]

Crystal Data and Refinement Details: $C_{20}H_{44}Cl_3CuN_8O_{18.5}$, M = 862.52, triclinic, space group $P\bar{1}$, a = 11.8592(6), b = 12.3654(11), c = 13.3374(13) Å, α = 78.768(4)°, β = 81.703(6)°, γ = 61.386(5)°, V = 1681.1(2) Å^3, Z = 2, D_c = 1.704 g cm^{-3}, $F(000)$ = 896, μM_o = 0.979 mm^{-1}, T = 100(2) K. Refinement of 484 parameters on 5790 independent reflections out of 11446 measured reflections (R_{int} = 0.066) led to R_1 = 0.073, wR_2 = 0.183, S = 1.013, $\Delta\rho_{max}$ = 1.14 e·Å^{-3}.

CCDC-212644 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

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