Synthesis of 1,2-Bis(1,4,7,10-tetra-azadodecanyl)ethane, a Double-ring Fully Saturated Macrocycle containing 12-Membered Tetra-aza Subunits

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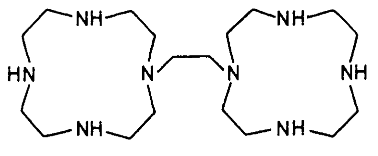
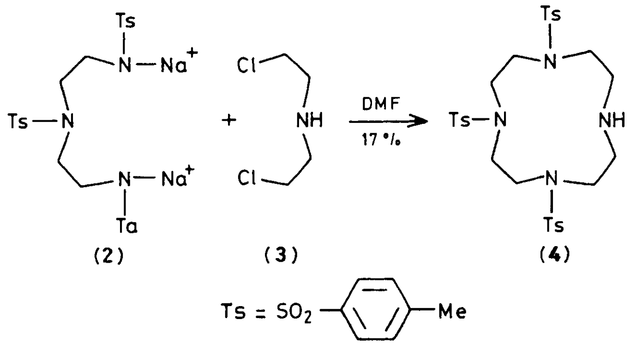
The title compound, a fully saturated bimacrocycle (**1**), has been obtained through a procedure involving the protection of all but one of the amino nitrogen atoms of each tetra-aza ring which are then bridged by an ethylenic segment; (**1**) behaves as a dinucleating ligand, forming a dicopper(II) complex in which there is a weak ferromagnetic interaction between the metal atoms.

The synthesis of bimacrocycles, *i.e.* molecules containing two covalently linked, potentially chelating subunits, has received much attention in recent years. One such class of compounds involves a linkage between one nitrogen atom from each ring, the remaining heteroatoms of each macrocyclic sub-unit being O[1] or S.[2] We describe here the preparation of an N–N bridged bimacrocycle, containing fully saturated tetra-aza subunits, (**1**). Our procedure involved the initial synthesis of a 12-membered tetra-aza ring containing all but one protected amine nitrogen atoms, (**4**).

Compound (**4**) was obtained in moderate yield by reaction of the disodium salt of the tri-*p*-toluenesulphonated diethylenetriamine (**2**)[3] with bis(chloroethyl)amine (**3**)† in dimethylformamide (DMF) at room temperature (3 days, continuous stirring, 1.3×10^{-1} mol dm^{-3} concentrations). The product was obtained as a crystalline precipitate on addition of water (0.6 dm^3). Two protected sub-units, (**4**), can be linked together by an ethylenic chain between nitrogen bridgeheads, *via* two different pathways (see Scheme 1). The first method involved reaction with oxalyl chloride (in CH_2Cl_2, in the presence of Et_3N), followed by reduction of the amido groups with $LiAlH_4$. The other bridging procedure involved reaction with di-*p*-toluenesulphonated ethylene glycol in MeCN, in the presence of Na_2CO_3 (reflux, 4 days). The bimacrocycle (**5**) was finally deprotected by acid hydrolysis (96% H_2SO_4, 100 °C). The polyammonium salt thus obtained was treated with concentrated NaOH, then extracted with $CHCl_3$, to give polyamine (**1**) [yield of deprotection process 43%, overall yield based on (**4**) 6.6% (pathway a) and 6.9% (pathway b); m.p. 153—156 °C; *m/z* 372; ^{13}C n.m.r. ($CDCl_3$): δ 45.00, 45.73, 46.72, 51.94, and 53.01].

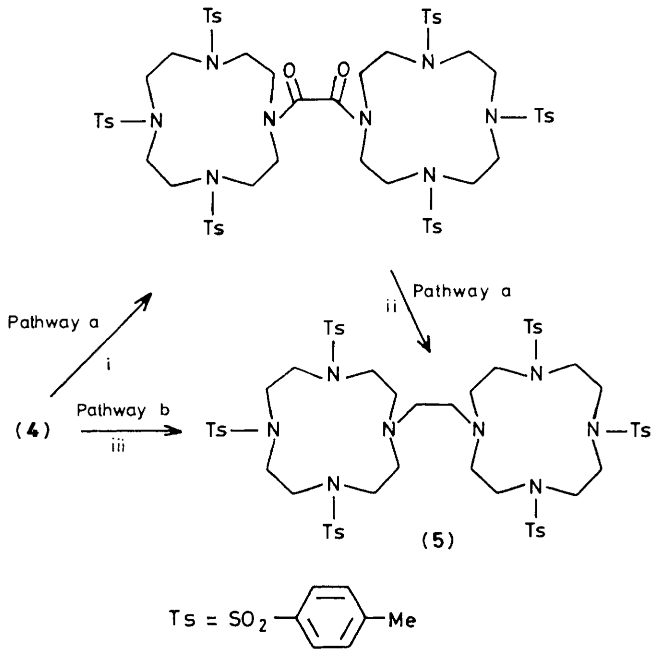


(**1**)



$$\mathrm{LH}_i^{i+} + \mathrm{H}^+ \rightleftharpoons \mathrm{LH}_{(i+1)}^{(i+1)+} \qquad (1)$$

In aqueous solution the bimacrocycle (**1**) behaves as quite a strong poly-base, as far as the first three protonation steps are concerned [log K_i values for the stepwise equilibria represented in equation (1) are 10.07, 9.34, 8.38, and 2.28; the fifth and further protonation steps should have log K_i < 2]. The first two steps presumably involve amine nitrogen atoms of separate rings, while after the addition of the third proton strong effects of mutual electrostatic repulsion between ammonium groups seem to be present. The tendency of (**1**) to co-ordinate metal ions was tested by titrating with standard NaOH a solution containing (**1**), Cu^{2+} (2 equiv.), and a strong acid (8 equiv.). Progressive addition of base made the colour



Scheme 1. i, ClCOCl, CH_2Cl_2, 91%; ii, $LiAlH_4$, tetrahydrofuran, 17%; iii, $TsO[CH_2]_2OTs$, MeCN, Na_2CO_3, 16%.

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† Bis(chloroethyl)amine dihydrochloride was obtained from diethanolamine and thionyl chloride, in chloroform and recrystallized from ethanol–petroleum. The free base was obtained immediately before use by dissolving the dihydrochloride in water and adding a slight excess of NaOH: bis(chloroethyl)amine separated as an oily layer, which was treated with NaOH pellets several times, to remove water.

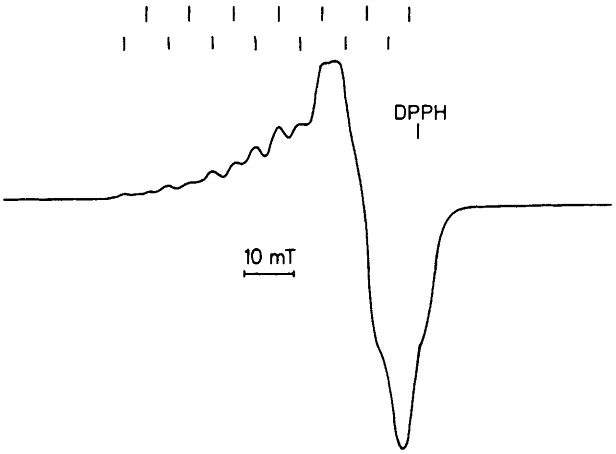

Figure 1. E.s.r. spectrum (X-band) of a 10^{-3} mol dm^{-3} frozen (77 K) solution of $Cu_2(\mathbf{1})(ClO_4)_4$ in DMF. DPPH = Diphenylpicrylhydrazyl.

turn blue–violet and the solution remained buffered in the pH range 2.5—3; after the addition of 8 equiv. of standard base an abrupt change in the pH was observed. This behaviour is consistent with the full co-ordination by the two tetra-aza loops in the bimacrocycle of two Cu^{2+} ions. A dimetallic complex of formula $Cu_2(\mathbf{1})(ClO_4)_4$ can be isolated as a microcrystalline solid by mixing hot ethanolic solutions of copper(II) perchlorate and (**1**). Metal-to-metal effects have been investigated using e.s.r. spectroscopy: Figure 1 shows the e.s.r. spectrum (X-band) of a 1.0×10^{-3} mol dm^{-3} solution of $Cu_2(\mathbf{1})(ClO_4)_4$ in DMF, frozen at 77 K. The spectrum shows the presence of two septets, which originate from coupling of the two copper nuclei ($A_{\parallel}$ = 9.0 mT). The two septets are separated by 4.8 mT, owing to the zero field splitting $2D_{\parallel}$, and centred at g = 2.21. Present spectral features are indicative of the presence of a ferromagnetic interaction between the two copper atoms, to produce a triplet state. Similar behaviour has been found using dimethyl sulphoxide or water as the solvent.

Compound (**1**) is the first fully saturated bimacrocycle with N–N bridged tetra-aza sub-units to be reported.‡ The preliminary investigation described here indicates that it behaves as an excellent dinucleating agent. The reported synthetic procedure has potential for the production of bimacrocycles of the same class, in which the size of the macrocyclic sub-unit and/or the length of the bridging chain can be varied.

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‡ A class of bimacrocycles containing N–N linked 14-membered tetra-aza sub-units has been obtained through a template reaction using Cu^{2+} or Ni^{2+}, diacetylpyridine, and a branched hexamine (ref. 4); however, the rings are unsaturated and the free ligand cannot be obtained through demetallation. A fully saturated bimacrocycle in which two 14-membered cyclam-like moieties are linked through a C–C covalent bond has been obtained as a side product in the synthesis of cyclam (ref. 5).