Novel Cationic Surfactants derived from Metal Ion Cage Complexes: Potential Anthelmintic Agents

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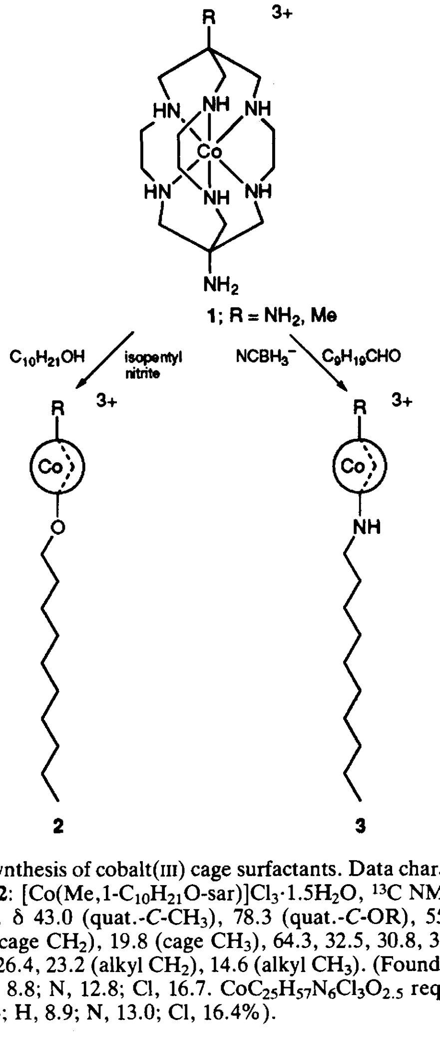
The synthesis of stable highly charged cationic detergents derived from metal ion cage complexes is described along with some of their properties and effects on helminth membranes.

Cationic surfactants derived from quaternary ammonium salts (+1 charge) have a spectrum of biological activity which includes antibacterial and immunosuppressant properties.[1,2] However, there appears to be relatively little exploration of the synthesis and properties of analogous molecules with higher charges on the head group which are soluble in water.[3] Such molecules can be made by efficient template reactions using metal ion complexes and we report here some simple syntheses and aspects of the biological activity of such molecules, especially their effects on some biological membranes.

Sarcophagine complexes (for example Scheme 1) arise from



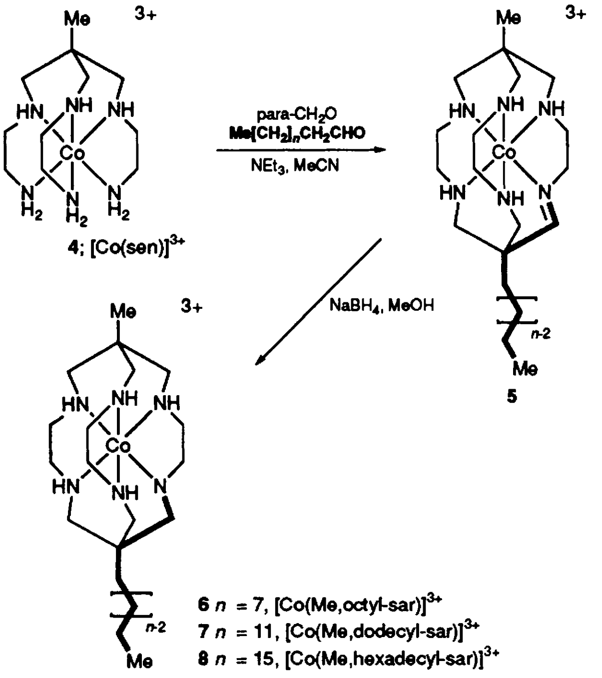
Scheme 1 Synthesis of cobalt(III) cage surfactants. Data characterising compound **2**: $[Co(Me,1\text{-}C_{10}H_{21}O\text{-}sar)]Cl_3{\cdot}1.5H_2O$, ^{13}C NMR (D_2O, 50.3 MHz). δ 43.0 (quat.-C-CH_3), 78.3 (quat.-C-OR), 55.6, 55.6, 54.6, 52.8 (cage CH_2), 19.8 (cage CH_3), 64.3, 32.5, 30.8, 30.3, 30.2, 30.2, 29.9, 26.4, 23.2 (alkyl CH_2), 14.6 (alkyl CH_3). (Found: Co, 9.8; C, 46.5; H, 8.8; N, 12.8; Cl, 16.7. $CoC_{25}H_{57}N_6Cl_3O_{2.5}$ requires Co, 9.1; C, 46.4; H, 8.9; N, 13.0; Cl, 16.4%).

an efficient template synthesis of the organic framework around the metal centre[3–5] and they are noted for their extraordinary thermodynamic and kinetic stability. For example, the rate of loss of the metal ion from the cage is dramatically slower ($\geqslant 10^{10}$ fold) than for simple metal chelate complexes. Moreover, the synthesis is stereospecific and the metal complexes may be isolated as chiral molecules from the chiral template.

At this stage, the primary molecules studied have been cobalt(III) complexes, simply because they are so robust. Using the bridgehead amine group of compound **1**, it is a relatively easy matter to tie a paraffin aldehyde to the amine by reductive alkylation or to substitute an alcohol *via* diazotisation of the amine group, as shown in Scheme 1. However, an even more stable detergent of this type has now been made directly in a template reaction which couples the cage formation with the addition of the paraffin tail (Scheme 2).

Paraffin substituted cage complexes were obtained in good yields (50–60%) from a two-step process (Scheme 2). Paraformaldehyde and a long chain aldehyde were condensed with the $[Co(sen)]^{3+}$ template (compound **4**) in the presence of base to afford an imine cage complex **5**. The intermediate was isolated after chromatography on silica gel and treated with $NaBH_4$ to obtain the fully saturated cage complex (**6–8**). The desired product was purified by chromatography on silica gel and crystallized from aqueous solution.

Aqueous solutions of the surfactant compounds (**2**, **3**, **6**, **7**, **8**) generate a persistent foam when shaken, a feature common to detergents. Conductimetric and surface tension studies[6]



Scheme 2 Template synthesis of cobalt(III) cage surfactants. Data characterising compound **7** $[Co(Me,1\text{-}[CH_2]_{11}CH_3\text{-}sar)]Cl_3{\cdot}H_2O$, ^{13}C NMR (D_2O, 73.54 MHz). δ 43.1, 46.1 (quat.-C), 54.4, 55.1, 55.7, 55.8 (cage CH_2), 20.2 (cage CH_3), 23.5, 23.6, 30.3, 30.6, 30.7, 31.3, 32.8, 35.6 (alkyl CH_2), 14.9 (alkyl CH_3). (Found: Co, 8.8; C, 48.8; H, 9.6; N, 12.6; Cl, 15.6. $CoC_{27}H_{62}N_6Cl_3O$ requires Co, 8.8; C, 48.5; H, 9.4; N, 12.6; Cl, 15.9%).

have shown that the dodecyl substituted complex **7** formed micelles in H_2O when the concentration of surfactant exceeded $(1\text{–}2) \times 10^{-3}$ mol dm^{-3} (at 25 °C). The molecules are also efficient wetting agents.

The lethal effect of one of these reagents on a rat tapeworm is demonstrated in Fig. 1. The tapeworm, *Hymenolepis diminuta,* incubated in a physiological salt solution (plate 1) was treated with complex **2** (R = Me) at a concentration of 10^{-3} mol dm^{-1}. After 30 s (plate 2) the orange molecule was clearly absorbed onto the surface of the worm and after *ca.* 8 min (plate 3) the worm lost motility. At this point, small cream coloured fragments were observed in the medium surrounding the now dead worm and plate 4 shows a magnified view of these fragments of teguments. In two hours, the solution became opaque with the fragments from the dead parasite. Clearly, the molecule has caused disintegration of the membranous outer structures of the tapeworm. A likely mechanism for this effect is simply destabilisation of the tegumental membrane bilayer through a combination of the large size and high charge of the head group which is able to alter the curvature and charge distribution of the bilayer dramatically compared with the normal biological surfactants. The molecules are active (at the level 10^{-3}–10^{-4} mol dm^{-3}) against other cestodes and also parasitic nematodes and trematodes but appear less active against analogous free living nematodes. *In vivo* studies of their efficacy are also being carried out and preliminary results show that while the tapeworms are affected, the hosts (rats) do not seem stressed. Moreover, the molecule was not absorbed from the gut and passed through the alimentary tract quantitatively (^{57}Co tracer study).[7] This lack of absorption is a characteristic of the highly charged cationic complexes and in this respect the molecules differ considerably from surfactants such as cetylpyridinium chloride and cetyltrimethylammonium chloride which are absorbed readily into the whole animal.[2]

Many variations of such surfactants are possible. Two tails can be added, one at each end or bifurcated at one end of the

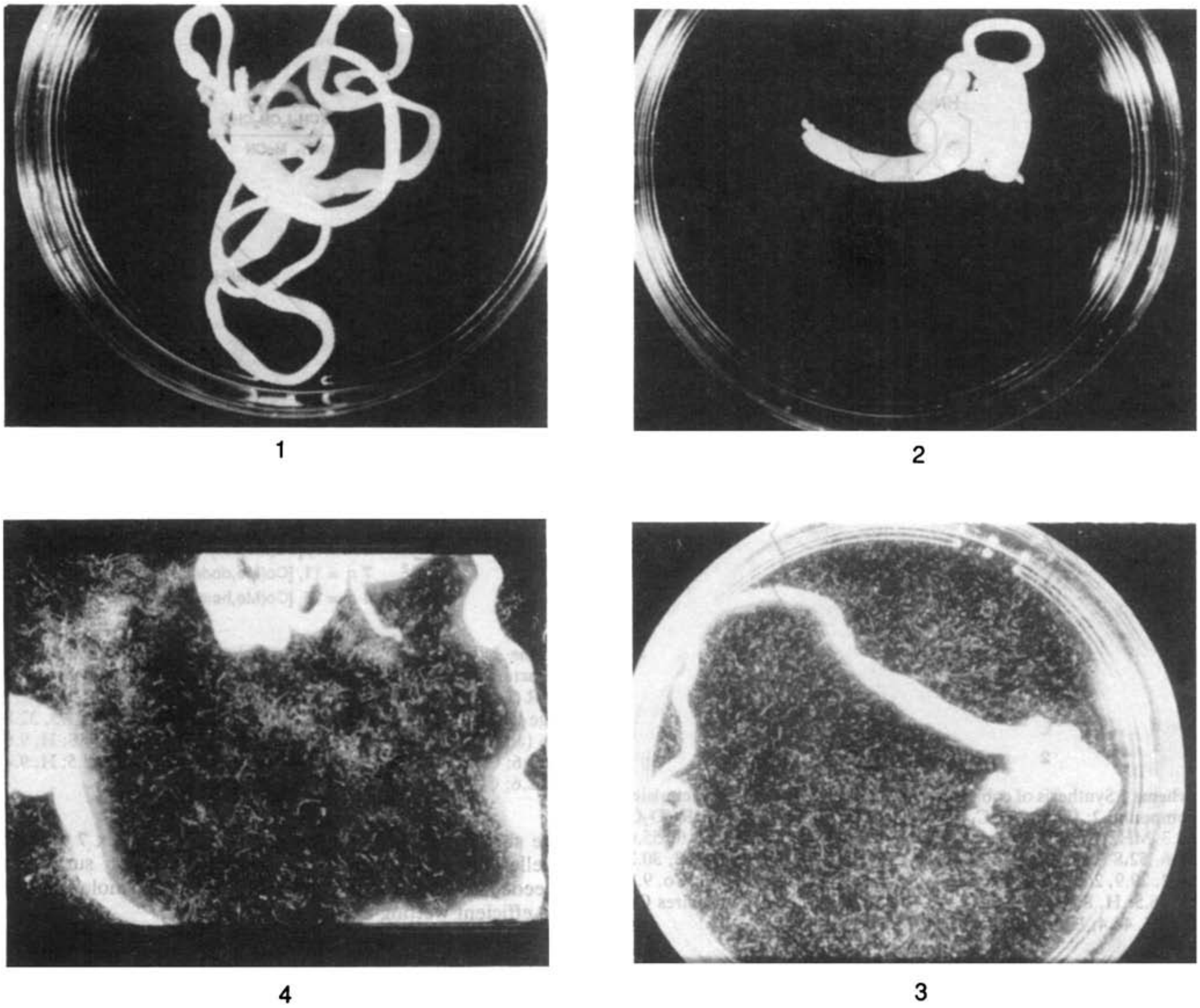


Fig. 1 The lethal effects of the decyl substituted cobalt(III) cage surfactant **2** on the cestode, *Hymenolepis diminuta.* The tapeworm was initially in an uncoiled state sustained in a buffered physiological saline solution[10] prior to administering the cage complex (10^{-3} mol dm^{-3}). Plate 2 after 30 s; plate 3 after 8 min; plate 4, magnified view of the disintegrated worm (8 min).

cage. A photo-active group[8] can be added on one side and a paraffin tail on the other side of the cage. The metal ion can be altered. So far, di-, tri- and tetra-valent metal ions have been installed in the cage[5] including $Co^{III,II}$, $Mn^{III,II}$, $Fe^{III,II}$ $Ni^{III,II}$, Cr^{III}, Cu^{II}, Zn^{II}, Cd^{II}, Hg^{II}, Ga^{III}, In^{III}, V^{IV}, Ru^{II}, Pt^{IV}, Rh^{III} and Ir^{III}. Both 2+ and 3+ surfactants are accessible by this route. Moreover, there are several redox couples accessible which span *ca.* −0.4 to +0.9 V (*vs.* normal hydrogen electrode) and the complexes also undergo rapid electron transfer reactions.[9] In short, these reagents have many possible applications in membrane chemistry both biological and artificial.

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