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Short Communication

A Convenient Route to 24-Membered Macrocycles Incorporating Two EDTA Units

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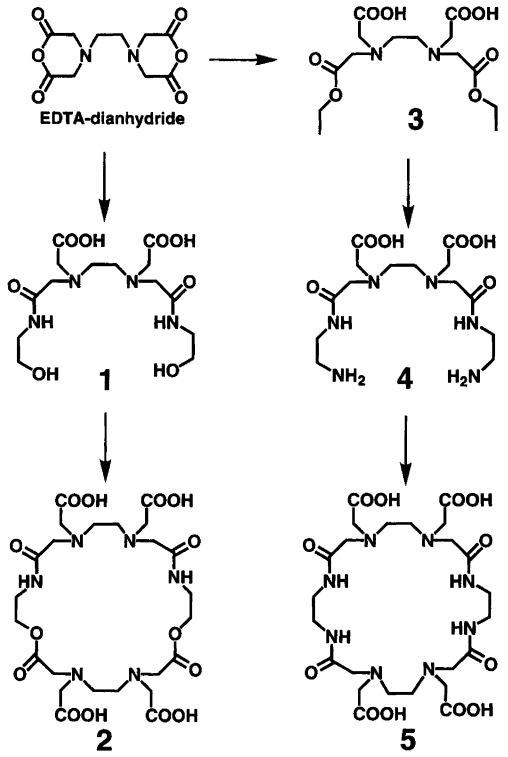
For the last 50 years ethylenediaminetetraacetic acid, EDTA, has been widely used owing to this ligand's ability to form stable complexes with almost all metal ions. *N,N'*-diesters[1] and diamides[2] of EDTA have been prepared from EDTA dianhydride[3] and shown to be good ligands. An interesting development has been ring-closure reactions between EDTA-dianhydride and polyethyleneglycols,[4] and recently the preparation of **5** from EDTA dianhydride and ethylenediamine was described by Inoue *et al.*[5] The bis-manganese(II)[5] and bis-cobalt(II)[6] complexes of **5** were prepared, and both complexes were shown to be symmetric, the two metal ions being crystallographically equivalent.[6]

Working in the same field, we focused on the syntheses of precursors that would allow controlled ring-closure reactions. Compound **1** was prepared in quantitative yield from EDTA dianhydride and 2-aminoethanol in cold DMF, and subsequent ring closure at 65 °C gave the new asymmetric macrocycle **2**. As the direct reaction between ethylenediamine and EDTA dianhydride also gives rise to a 12-membered ring incorporating a single EDTA unit[4] as well as linear oligomers, we prepared the precursor **4** via ammonolysis of **3**. Compound **4** was then ring-closed with EDTA dianhydride to give **5** as the only product.



Scheme 1.

Results and discussion

The ligands **1–5** were prepared in good yield and characterized by NMR, mass spectrometry and elemental analysis. Complexometric titrations[7] against standard Cu(II) and Co(II) solutions confirmed that **1**, **3** and **4** give rise to 1:1 complexes and that with **2** and **5** bis-metal complexes are formed.

In some mass spectra of **2** there was evidence of a MW 1269 ion corresponding to an EDTA tetramer. To study the possible formation of larger oligomers, the ring-closure reaction between **1** and EDTA dianhydride was carried out in 0.06, 0.12 and 0.18 M concentrations. The product obtained at 0.18 M was further fractionated by allowing 2/3 of the product to crystallize at −20 °C; the rest was precipitated with ether. To obtain comparable mass spectra a 5% solution of each product was pre-

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Table 1. Complexation results obtained from MS.

Salts added to H_6L	Complexes detected by FAB+ MS		
$NaHCO_3$	$[Na_4H_3L]^+$	$[Na_5H_2L]^+$	$[Na_6HL]^+$
$Eu(NO_3)_3$	$[EuH_4L]^+$	$[Eu_2HL]^+$	
$Cu(NO_3)_2$	$[CuH_5L]^+]^+$	$[Cu_2H_3L]^+$	
$Mn(NO_3)_2$	$[MnH_5L]^+$	$[Mn_2H_3L]^+$	
$Mn(NO_3)_2$ and $NaHCO_3$	$[Mn_2H_3L]^+$	$[Mn_2NaH_2L]^+$	$[Mn_2Na_2HL]^+$
$Mn(NO_3)_2$ and $Ca(NO_3)_2$	$[MnH_5L]^+$	$[Mn_2H_3L]^+$	$[MnCaH^3L]^+$
$Mn(NO_3)_2$ and $Cu(NO_3)_2$	$[MnH_5L]^+$	$[CuH_5L]^+$	$[MnCuH_3L]^+$

pared in a 1:4 water–glycerol matrix. For all four products the MW 1269 peak amounted to 1.5–2.5% of the MW 634 peak, and there was no significant trend in the ratios between the two peaks. This indicates that cluster ions are largely responsible for the MW 1269 peaks, and that the formation of larger oligomers is negligible.

As we hitherto have been unable to obtain macrocrystalline metal complexes of **2**, we also turned to mass spectroscopy for evidence of complexation. By dissolving various metal nitrates in a 0.1 M solution of **2** and recording the mass spectra of the resulting solutions, we were in most cases able to obtain such evidence. When the solutions were neutralized with $NaHCO_3$, Na^+ further contributed to ionisation of the complexes. The results are given in Table 1, where H_6L corresponds to **2**. Most interesting is the evidence of bis-complexes in which **2** coordinates two different metal ions. As the two coordination sites of the macrocycle are slightly different, it should be well suited for the study of such mixed complexes.

Experimental

Compound **1**, *N,N'*-1,2-ethanediylglycine-bis(*N*-(carboxymethyl)-1,1'di(2-hydroxy)ethyl amide, was prepared by adding 19.21 g EDTA dianhydride, 0.075 mol, to 9.16 g dry 2-aminoethanol, 0.15 mol, in 500 mL cold dry *N,N'*-dimethylformamide, DMF.† The heat of reaction caused the temperature to rise to 25°C, and after 30 min the formation of **1** was complete. The product could be isolated in almost quantitative yield as a fine white powder by precipitation with ether; however, it was extremely hygroscopic and hydrated to a sticky oil upon exposure to air. For the subsequent ring-closure reaction it was thus kept in solution. ^{1}H NMR (D_2O):δ 3.93 (s, 4 H), 3.81 (s, 4 h), 3.77 (t, 4 H, J = 5.5 Hz), 3.49 (t, 4 H, J = 5.5 Hz), 3.41 (s, 4 H). ^{13}C NMR (D_2O):δ 172.1, 169.0, 59.8, 56.4, 56.1, 51.4, 41.5. MS *m/z* 377 (FAB −).

Compound **2**, 2,9,14,21-tetraoxo-1,10-dioxa-4,7,13,16,19-hexaazacyclotetracosane-4,7,16,19-tetraacetic acid, was prepared by adding 19.21 g of EDTA dianhydride, 0.075 mol, to a solution of 28.37 g of **1**, 0.075 mol, in 500 mL of DMF and refluxing at 65°C for 24 h. The product was isolated by precipitation with 1 L of ether and filtered off and washed with ether. Overnight drying at 60°C, 0.1 mmHg gave 43.3 g of **2**, 91% as off-white powder. The last traces of DMF can be removed by adding an aqueous product solution to a large excess of absolute ethanol, filtering and drying at 60°C, 0.1 mmHg. ^{1}H NMR (D_2O):δ 4.41 (m, 4 H), 4.11 (s, 4 H), 3.91 (s, 4 H), 3.89 (s, 4 H), 3.79 (m, 4 H), 3.66 (s, 4 H), 3.64 (s, 4 H), 3.41 (s, 4 H). ^{13}C NMR (D_2O):δ 174.8, 174.5, 172.2, 171.5, 66.7, 59.0, 58.6, 57.0, 54.0, 53.7, 40.7. MS *m/z* 635 (FAB +).

Compound **3**, *N,N'*-1,2-ethanediylglycine-bis(*N*-(carboxymethyl)-1,1'-diethyl ester, was prepared by refluxing 25.6 g of EDTA dianhydride, 0.1 mol, in 500 mL of dry ethanol for 90 min. 350 mL ethanol was removed on a rotary evaporator, and the product was precipitated from the remnant by overnight standing at −15°C. It was collected by filtration, washed with ether and dried at 0.1 mmHg, first at room temperature, and subsequently at 50°C. Yield 27.1 g, 78% white powder m.p. 67–70°C. ^{1}H NMR (D_2O):δ 4.28 (q, 4 H, J = 7.1 Hz), 4.02 (s, 4 H), 3.82 (s, 4 H), 3.35 (s, 4 H), 1.29 (t, 6 H, J = 7.1 Hz). ^{13}C NMR (D_2O):δ 175.9, 172.6, 65.5, 58.7, 57.4, 53.8, 15.9. MS 349 (FAB +).

Compound **4**, *N,N'*-1,2-ethanediylglycine-bis(*N*-(carboxymethyl)-1,1'-di(2-amino)ethyl amide was made by dissolving 17.4 g of **3**, 0.05 mol, in 75 mL of dry 1,2-diaminethane. After 3 days standing at room temperature 1,2-diaminoethane was removed in several steps. Initially distillation at 0.1 mmHg was employed; the viscous oil that remained was precipitated in a 1:1 absolute ethanol/ether mixture, redissolved in water and again precipitated by addition to a 1:1 mixture of absolute ethanol/ether. The product was filtered off and dried overnight at 100°C, 0.1 mmHg. Yield 14.1 g, 75%, as a white powder. ^{1}H NMR (D_2O):δ 3.41 (t, 4 H, J = 5.8 Hz), 3.19 (s, 4 H), 3.10 (s, 4 H), 3.02 (t, 4 H, J = 5.8 Hz), 2.62 (s, 4 H). ^{13}C NMR (D_2O):δ 180.0, 176.3, 60.6, 59.7, 54.2, 40.4, 38.1. MS *m/z* 377 (FAB +).

Compound **5**, 6,11,18,23-tetraoxo-1,4,7,10,13,16,19,22-octaazacyclotetracosane-1,4,7,10-tetraacetic acid, was prepared as the trisodium salt by dissolving 3.76 g of **4**, 0.010 mol, in a mixture of 20 mL of water and 5 mL of triethylamine at 50°C. EDTA dianhydride, 2.56 g, 0.010 mol, was added and the flask was vigorously shaken for a few minutes until all dianhydride had reacted. The solvents were removed on a rotary evaporator, and to the remaining oil was added 30 mL of 1 M NaOH, 0.030 mol. Water was distilled off under reduced pressure, and the product was finally dried overnight at 90°C,

† The DMF used for this reaction should contain no more than 10–20 ppm water. This was best achieved by prolonged standing over 4 Å molecular sieves. As an alternative we refluxed 500 mL DMF, water < 500 ppm with 5 g EDTA dianhydride and 3.5 g $CuSO_4H_2O$ for 24 h at 60°C. Subsequent distillation below 60°C gave a product with a water content below 20 ppm measured by Karl Fischer titration.

0.1 mmHg. This gave 6.84 g, 98%, of the white trisodium salt of the title compound. ^{1}H NMR (D_2O):δ 3.24 (m, 4 H), 3.20 (m, 8 H), 3.11 (m, 4 H), 3.07 (m, 8 H), 2.62 (m, 8 H). ^{13}C NMR (D_2O):δ 178.0, 173.4, 58.6, 57.9, 52.3, 38.5. MS *m/z* 679, 699, 721 di-, tri- and tetrasodium salts (FAB +).

With correction for water, all compounds gave C, H and N elemental analyses within 0.4%. Only **3** produced a well defined melting point; the other compounds slowly decomposed upon heating; **1** above 70°C, **2** above 110°C, **4** and **5** above 130°C.

Nomenclature. Compound **5** C.A. (141585-32-2) is named as in C.A.; 6,11,18,23-tetraoxo-1,4,7,10,13,16,19,22-octaazacyclotetracosane-1,4,13,16-tetraacetic acid.

Compound **2** is named accordingly as 6,11,18,23-tetraoxo-7,22-dioxa-1,4,10,13,16,19-hexaazacyclotetracosane-1,10,13,16-tetraacetic acid.

Compound **3** (17619-53-3) is listed in C.A. as a derivative of glycine; *N,N'*-1,2-ethanediylglycine-bis(*N*-(carboxymethyl)-1,1'-diethyl ester).

Compounds **1** and **4** are named accordingly as *N,N'*-1,2-ethanediylglycine-bis(*N*-(carboxymethyl)-1,1'-di(2-hydroxy)ethyl amide and *N,N'*-1,2-ethanediylglycine-bis-(*N*-(carboxymethyl)-1,1'-di(2-amino)ethyl amide.

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