Chapter Two

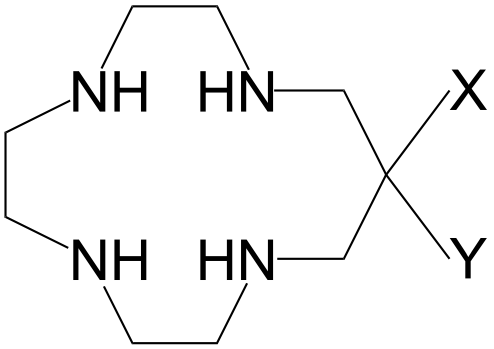
Tetraazacycloalkanes with a Pendant Carboxylate: Synthetic Aspects

2.1 Introduction

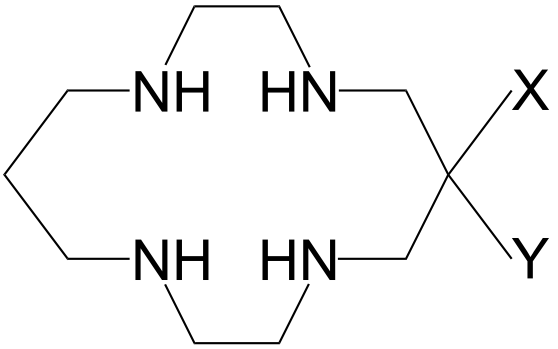
Cyclic polyamines carrying pendant carboxylate groups have been known for some time, but essentially all examples contain -CH_2-COOH pendant groups attached to the initially secondary amines of the macrocycle,[1,2] producing tertiary amines where a pendant is introduced. Up to the maximum of three carboxymethyl groups have been attached to 1,4,7-triazacyclononane,[3] with the 1,4,7-triazacyclononane-1,4,7-triethanoic acid capable of coordinating to a range of metal ions as a sexidentate ligand.[4] Analogues with different size macrocyclic rings have also been prepared.[5] The monosubstituted 1-carboxymethyl-1,4,7-triazacyclononane has been prepared conveniently by reaction of chloroacetic acid with an excess of the macrocycle.[6] For tetraazacycloalkanes, analogues are also known, including 1,4,8,11-tetraazacyclotetradecane-1,4,8,11-tetraethanoic acid,[7] which binds copper ion in the crystal through the four tertiary amines occupying a plane and two pendant carboxylates, one on either side of the plane.[8] By contrast, the smaller ring in 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraethanoic acid leads to binding of copper with the macrocycle folded into a *cis* geometry, and

two pendant carboxylates on the same side of the macrocycle in the other two sites.[9] The ethyl 4,7,11-trimethyl-1,4,7,11-tetraaza cyclotetradecane-1-ethanoate binds copper in a square-based pyramidal geometry, with the carbonyl oxygen of the ester group acting as a donor in the axial site.[10] These examples identify the capacity of pendant carboxylates to act as donors for metal ions in concert with the macrocycle amines, but all are N-pendant macrocycles, with steric crowding of the tertiary nitrogens presumably having an influence on metal ion binding capacity. Syntheses of C-based carboxylate pendant polyazacycloalkanes, which may present different if not superior steric demands, have not been addressed much, and it was this area which attracted our attention.

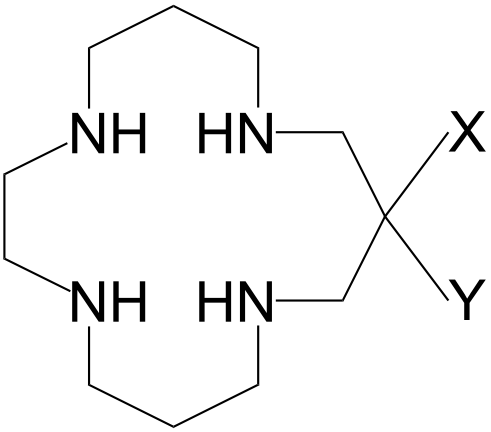
The facile metal directed synthesis of a range of tetraaza-macrocycles with pendant nitro and methyl groups using tetraamines, formaldehyde and nitroethane has been developed in recent years.[1, 11,12,13] Reduction of the pendant nitro groups with zinc and aqueous acid produces macrocycles with pendant primary amines attached directly to the central carbon of a propyl chain of the macrocyclic ring, and the ability of such amines to bind to metal ions has been clearly demonstrated.[14, 15, 16] The parallel chemistry using diethyl malonate as an alternative carbon acid to nitroethane has been explored only briefly,[17,18,19] with one macrocyclic product isolated as a *gem* diester.[17] It is clear that decarboxylation and hydrolysis of *gem* diesters, which is readily accomplished, [20] should produce macrocycles with a carboxylic acid



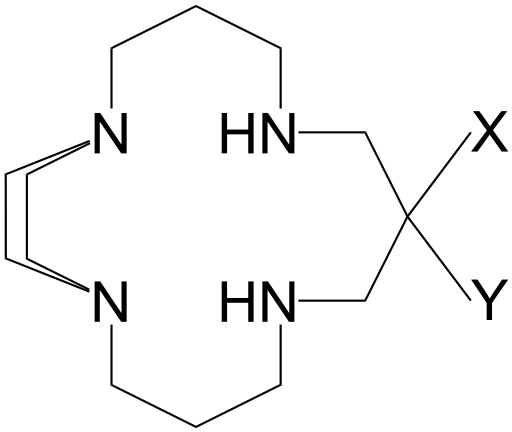
L1 X = Y = COOEt
L6 X = COO^- Y = H
L11 X = NH_2 Y=CH_3



L2 X = Y = COOEt
L7 X =H Y = COO^-
L12 X=NH_2 Y=CH_3



L3 X = Y = COOEt
L8 X = COO^- Y = H
L13 X = NH_2 Y = CH_3



L4 X = COOEt Y = H
L5 X = COOEt Y = COOH
L9 X = COO^- Y = H
L10 X = NO_2 Y = Me
L14 X = NH_2 Y=CH_3

(or carboylate) pendant to the central carbon of a propyl chain in the macrocycles. These pendant groups should, like their primary amine analogues, have the capacity to bind to metal ions. The chemistry providing routes to a series of cyclic tetraamines with a single pendant carboxylate is reported in this chapter. The comparative physical characteristics of copper(II) complexes of analogous nitro and carboxylate pendant macrocycles

is reported, as well as the comparative protonation constants of a series of macrocycles bearing pendant amine or carboxylate groups. The X-ray crystal structure analysis of the copper(II) complex of an ethoxycarbonyl tetraamine (an ester of one of the pendant carboxylate macrocycles) is also described.

2.2 Experimental

2.2.1 Preliminary Macrocycle Syntheses

(Diethyl 1,4,7,10-tetraazacyclotridecane-12,12-dicarboxylate)copper(II) Perchlorate Hemihydrate, [Cu(L1)]$(ClO_4)_2 \cdot 0.5H_2O$

To 3,6-diazaoctane-1,8-diamine (trien, 5g) was added a methanolic solution of $Cu(ClO_4)_2.6H_2O$ (12g in 200 cm^3). The resulting dark blue solution was warmed to approx. 50°C , then diethyl malonate (3 cm^3) and excess formaldehyde (12 cm^3, 38% aqueous solution) were added. After heating for two hours the solution was left to stir overnight. The solution was then diluted to 3 dm^3 with water, filtered and sorbed onto a column of SP Sephadex C25 (Na^+ form) resin (20 x 5 cm). Upon elution, two bands were separated. A blue band eluted with 0.2 mol dm^{-3} $NaClO_4$. This band showed no stability in acid, consistent with it being a non-cyclic byproduct, and on this basis full characterisation was not pursued. An acid-stable major purple/blue band eluted with 0.5 mol dm^{-3} $NaClO_4$. The eluted solution was reduced in volume on a rotary evaporator and left to crystallise. On standing, a dark blue solid precipitated, was collected, washed with alcohol and air dried. Further crops

were obtained after extended periods (0.9 g). (Found C, 30.0; H, 4.9; N, 8.9. $C_{15}H_{31}Cl_2CuN_4O_{12.5}$ requires C, 30.0; H, 5.2; N, 8.3%). Electronic Spectrum (water): λ_{max} 558 (ε 183), 267 nm (4660 dm^3 mol^{-1} cm^{-1}). IR Spectrum (KBr disc): 1725[a] (s, -COOEt), 1751 (w) cm^{-1} . $E_{1/2}$ ($Cu^{II/I}$) -0.64 V (vs Ag/AgCl). ([a] The ν_{sym} in the complex studied is often masked in the IR spectra of the complexes and ligands in this study and hence can often be difficult to distinguish. As such only the more informative and easily distinguished ν_{asym} is reported throughout this study.)

(Diethyl 1,4,8,11-tetraazacyclotetradecane-6,6-dicarboxylate)copper(II) Perchlorate, [Cu(L2)](ClO_4)$_2$

To a solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (8 g) in ethanol (100 cm^3) was added with stirring 3,7-diazanonane-1,9-diamine (2 g) in methanol (10 cm^3), followed by diethyl ether (10 cm^3). The purple-pink precipitate was collected, washed with diethyl ether and dried. To a solution of the above complex (2 g) in methanol (200 cm^3) and water (10 cm^3) was added triethylamine (1.16 g), diethyl malonate (1 g) and formaldehyde (4 cm^3, 38% aq). The solution was refluxed for 18 hours, then left to stir at room temperature for 2 days, diluted to 1 dm^3 with water and loaded onto a column of SP-Sephadex C-25 (Na^+ form) (10 x 25 cm). Two bands were eluted. The first acid-stable band (*ca* 40% of total copper) was eluted with 0.2 mol dm^{-3} $NaClO_4$, reduced in volume by rotary evaporation, and crystallized very slowly following addition of a small amount of perchloric acid, but in very low isolated yield (0.3 g, as a dihydrate diprotonated species) due to high solubility of the hydrolyzed and decarboxylated forms presumably also present. (Found C, 22.8; H, 4.65; N, 6.9.

$C_{16}H_{34}Cl_2CuN_4O_{12}\cdot 2H_2O\cdot 2HClO_4$ requires C, 22.7; H, 4.75; N, 6.65%)

Electronic Spectrum (water): λ_{max} 506 (ε 93 $dm^3\,mol^{-1}\,cm^{-1}$), 254 nm (6940).

IR Spectrum (KBr disc): 1725 cm^{-1} (-COOR). $E_{1/2}$ ($Cu^{II/I}$) -0.88 V (vs Ag/AgCl).

(Diethyl 1,4,8,12-tetraazacyclopentadecane-10,10-dicarboxylate)copper(II) Perchlorate, [Cu(L3)]$(ClO_4)_2$

This complex was prepared essentially as previously described.[17] To (4,7-diaza-decane-1,10-diamine)copper(II) perchlorate (4g) was added triethylamine (2 cm^3), diethyl malonate (4 cm^3) and formaldehyde (38% aqueous solution, 8 cm^3). This solution was stirred at 60°C for four hours, diluted to 3 dm^3 with water, filtered and sorbed onto a column of SP-Sephadex C25 (Na^+ form) resin (20 x 5 cm). The major acid-stable blue band of the diester was separated first, and crystallized slowly following concentration (0.4 g). (Found: C, 31.9; H, 5.5; N, 8.9. $C_{17}H_{36}Cl_2CuN_4O_{13}$ requires C, 31.9: H, 5.7; N, 8.8%). Electronic spectrum (water): λ_{max} 568 (ε 105 $dm^3\,mol^{-1}\,cm^{-1}$), 268 nm (7030). IR (KBr disc): 1726 cm^{-1} (-COOR). $E_{1/2}$ ($Cu^{II/I}$) -0.76 V (vs Ag/AgCl).

Copper(II) Macrocyclic Complexes Based on N,N'-(3-aminopropyl)-1,4-diaza-cyclohexane

To a stirring methanolic solution of copper(II) perchlorate hexahydrate (5 g in 100 cm^3) was added a methanolic solution of N,N'-(3-aminopropyl)-1,4-diazacyclohexane (5 cm^3 in 20 cm^3). Precipitation of the bright purple solid was completed by addition of diethyl ether. The solid was collected, washed with ethanol and air dried. Some 4 g of the solid was suspended in methanol (300 cm^3) to which triethylamine (1.1 cm^3), diethyl malonate (2.1 cm^3), and

formaldehyde (38% aqueous solution, 5 cm^3) were added. The solution was stirred at 60°C for two hours, diluted to 4 dm^3 with water and sorbed onto a column of Sephadex C25 (Na^+ form) resin (10 x 25 cm). Two major bands were separated and identified:

(Ethyl 1,5,9,13-tetraazabicyclo[1.1.2.2]heptadecane-7-carboxylate)copper(II) Perchlorate Hydrate, $[Cu(L4)](ClO_4)_2 \cdot H_2O$

An acid-stable blue band was eluted first with 0.2 mol dm^{-3} $NaClO_4$. The solution was reduced in volume on a rotary evaporator and on standing a dark blue precipitate formed (1.1 g). (Found C, 32.6; H, 5.5; N, 9.2. $C_{16}H_{34}Cl_2CuN_4O_{11}$ requires C,32.4; H, 5.8; N, 9.4%). Electronic Spectrum (water): λ_{max} 579 (ε 270 dm^3 mol^{-1} cm^{-1}), 287nm (7030). IR Spectrum (KBr disc): 1723 cm^{-1} (-COOR). $E_{1/2}$ ($Cu^{II/I}$) -0.58 V (vs Ag/AgCl). Slow evaporation of an aqueous solution of the product afforded single crystals of a quality suitable for X-ray analysis.

(Ethyl hydrogen 1,5,9,13-tetraazabicyclo[1.1.2.2]heptadecane-7,7-dicarboxylate)copper(II) Perchlorate Hydrate, $[Cu(L5)](ClO_4)_2 \cdot H_2O$

A second acid-stable blue band also eluted with 0.2 mol dm^{-3} $NaClO_4$. As it was reduced in volume on the rotary evaporator, a purple/blue solid precipitated. This was collected, washed with alcohol and air dried (0.7 g). (Found C, 33.3; H, 5.5; N, 8.9. $C_{17}H_{32}Cl_2CuN_4O_{12}$ requires C, 33.0; H, 5.2; N, 9.1 %). Electronic Spectrum (water): λ_{max} 576 (ε 242 dm^3 mol^{-1} cm^{-1}), 268 nm (7250). IR Spectrum (KBr disc): 1724 (-COOR), 1749 cm^{-1} (-COOH). $E_{1/2}$ ($Cu^{II/I}$) -0.58 V (vs Ag/AgCl).

2.2.2 Macrocyclic Hydrolysis Products

Hydrolysis and decarboxylation of complexes with *gem* diesters, *gem* acid-esters and hydrolysis of complexes of monoesters can be conveniently achieved by heating (*ca* 80°C) solutions of these complexes in aqueous base (pH > 12) for a period of hours. This is exemplified for several complexes below.

(1,4,8,12-tetraazacyclopentadecane-10-carboxylic acid)copper(II) Perchlorate, [Cu(HL8)]$(ClO_4)_2$

The diester [Cu(L3)]$(ClO_4)_2$ was prepared exactly as described above, and the band off the Sephadex column was reduced in volume on a rotary evaporator and then rediluted to 100 cm^3 with water. The pH was then raised to 12 with aqueous sodium hydroxide, the solution was stirred at 80°C for 4 hours, then diluted to 1 dm^3 with water and sorbed onto a column of Sephadex C25 (Na^+ form) resin (20 x 5 cm). Only one major blue band was observed. This was eluted with 0.2 mol dm^{-3} $NaClO_4$, reduced in volume on a rotary evaporator, treated with a small amount of $HClO_4$, and left to crystallize. On standing, a small amount of a purple solid precipitated. (Found C,25.1; H, 4.7; N,9.6. $C_{12}H_{26}Cl_2CuN_4O_{10}\cdot 1/2HClO_4$ requires C, 25.2; H, 4.7; N, 9.8%) Electronic Spectrum (water): λ_{max} 569 (ε 94 dm^3 mol^{-1} cm^{-1}), 269 nm (6380). IR Spectrum (KBr disc): 1747 cm^{-1} (-COOH). $E_{1/2}$ ($Cu^{II/I}$) -0.75 V (vs Ag/AgCl).

(1,5,9,13-tetraazabicyclo[1.1.2.2]heptadecane-7-carboxylic acid)copper(II) Perchlorate, [Cu(HL9)]$(ClO_4)_2$

Commencing with a concentrated solution of $[Cu(L5)](ClO_4)_2$, reaction was followed exactly as described for the L8 analogue above, with a small amount of purple solid isolated on standing. (Found C,26.7; H, 4.9; N, 8.75. $C_{14}H_{30}Cl_2CuN_4O_{10}{\cdot}HClO_4$ requires C, 26.4; H, 4.9; N, 8.8%). Electronic Spectrum (water): λ_{max} 577 (ε 304 $dm^3\ mol^{-1}\ cm^{-1}$), 288 nm (8700). IR Spectrum (KBr disc): 1748 cm^{-1} (-COOH). $E_{1/2}$ ($Cu^{II/I}$) -0.57 V (vs Ag/AgCl). Samples of the 13-membered (L6) and 14-membered (L7) carboxylate complexes were also isolated, analytically impure due to contamination with sodium perchlorate, but permitting spectroscopic characterisation.

2.2.3 Preparation of Hydrochloride Salts

1,4,7,10-tetrazacyclotridecane-12-carboxylic acid tetrahydrochloride, HL6·4HCl·1/2MeOH

3,6-Diazaoctane-1,8-diamine (trien, 6.4 g) was added to a methanolic solution of $Cu(ClO_4)_2.6H_2O$ (6.7 g in 500 cm^3). The resulting dark blue solution was warmed to approx. 50°C , then diethyl malonate (7 g), triethyl amine (4.4 g) and excess formaldehyde (25 cm^3, 38% aqueous solution) were added. After heating for two hours, the solution was left to stir overnight. The solution was then diluted to 3 dm^3 with water, filtered and sorbed onto a column of SP Sephadex C25 resin (Na^+ form, 50 x 6 cm). Upon elution, two bands were separated. A blue band eluted with 0.2 mol dm^{-3} $NaClO_4$. This band showed no stability in acid, consistent with it being a non cyclic by-product. An acid-stable major purple/blue band eluted with 0.5 mol dm^{-3} $NaClO_4$. The pH of the eluted solution was raised to *ca* 10 with 2.5 mol dm^{-3} and it was stirred at *ca* 70°C for 12 hours. This solution and hydrochloric acid (3 mol dm^{-3}, 100 cm^3) were added

from separate dropping funnels dropwise over one hour to zinc powder (10 g) while stirring. The solution was stirred for a further half hour at 60°C and then filtered to remove copper and any remaining zinc. The solution was diluted to 5 dm^3 with water and sorbed onto a column of Dowex 50Wx2 resin (H^+ form, 5 x 40 cm). The column was washed with 1 mol dm^{-3} HCl until no further evidence of zinc(II) ion elution (i.e. formation of zinc hydroxide on addition of base) was present, and then the product was eluted with 3 mol dm^{-3} HCl (elution of the required macrocycle being indicated by the formation of an acid stable species on addition of base and Cu^{2+} to a small sample of the eluent). The product was taken to dryness on a rotary evaporator, washed with ethanol then diethyl ether, dried in a vacuum desiccator and recrystallised from hot methanol to produce a white free-flowing powder. (Found C, 32.7; H, 7.7; N, 14.8. $C_{10}H_{26}Cl_4N_4O_2.(CH_3OH)_{0.5}$ requires C, 32.2; H, 7.2; N, 14.3%) NMR (D_2O): ^1H, δ 2.9-3.5 (multiplet); ^{13}C, δ 47.0, 47.2, 47.6, 49.0, 175.0 p.p.m.

1,4,8,11-tetraazacyclotetradecane-6-carboxylic acid pentahydrochloride, HL7·5HCl

To a solution of $Cu(ClO_4)_2 \cdot 6H_2O$ (7.9 g) in ethanol (150 cm^3) was added with stirring 3,7-diazanonane-1,9-diamine (3.4 g) in ethanol (30 cm^3), followed by diethyl ether (10 cm^3). The purple-pink precipitate was collected, washed with diethyl ether and dried. To a solution of the above complex (8 g) in methanol (350 cm^3) and water (5 cm^3) was added triethylamine (3 cm^3), diethyl malonate (7 cm^3) and formaldehyde (15 cm^3, 38% aq). The solution was refluxed for 18 hours, diluted to 5 dm^3 with water and loaded onto a column of SP-Sephadex C-25 (Na^+ form) (10 x 25 cm) after addition of acetic acid (5 cm^3). Two acid stable bands were eluted with 0.2 mol dm^{-3} $NaClO_4$, recombined and reduced in volume by rotary evaporation (20 cm^3). This solution was diluted with methanol (400 cm^3), triethylamine (3 cm^3) was added and the mixture was left to stir at 60°C for 12 hours. This was filtered and reduced in volume (50 cm^3) to leave a purple solution. This solution and hydrochloric acid (3 mol dm^{-3}, 100 cm^3) were added from separate dropping funnels dropwise over one hour to zinc powder (10 g) while stirring. The solution was stirred for a further half hour at 60°C and then filtered to remove copper and any remaining zinc. The solution was diluted to 5 dm^3 with water and sorbed onto a column of Dowex 50Wx2 resin (H^+ form, 5 x 40 cm). The column was washed with 1 mol dm^{-3} HCl until no further evidence of zinc(II) ion elution was present, and then the product was eluted with 3 mol dm^{-3} HCl. The solution of product was taken to dryness on a rotary evaporator, washed with ethanol then diethyl ether, dried in a vacuum desiccator and recrystallised from hot methanol to produced a pale yellow free-flowing powder (yield 0.5 g). (Found C, 30.6; H, 7.1; N, 13.8.

$C_{11}H_{31}Cl_5N_4O_2$ requires C, 30.8; H, 6.8; N, 13.1 %) NMR (D_2O): ^1H, δ 2.7-3.9 (multiplet); ^{13}C, δ 25.6, 38.3, 47.2, 47.8, 49.0, 51.6, 177.3 p.p.m.

1,4,8,12-tetraazacyclopentadecane-10-carboxylic acid tetrahydrochloride hydrate, HL8·4HCl·H_2O

(4,7-diazadecane-1,10-diamine)copper(II) perchlorate was prepared by the careful addition of the free polyamine to an equimolar amount of $Cu(ClO_4)_2·6H_2O$ in ethanolic solution followed by collection of the purple solid by filtration. Some 15 g of this solid was suspended in methanol (600 cm^3) and heated under reflux. To this was added diethyl malonate (12 cm^3), triethylamine (4 cm^3) and excess formaldehyde (25 cm^3, 38% aqueous solution) and the solution was left stirring under reflux overnight. The solution was then diluted to 5 dm^3 with water, filtered and sorbed onto a column of SP Sephadex C25 resin (Na^+ form, 50 x 6 cm). Upon elution with 0.2 mol dm^{-3} $NaClO_4$, only one major acid-stable blue band formed with no other acid stable products observed. The pH of the eluted solution was raised to *ca* 10 with 2.5 mol dm^{-3} and it was stirred at *ca* 70°C for 12 hours. This solution and hydrochloric acid (3 mol dm^{-3}, 100 cm^3) were added from separate dropping funnels dropwise over one hour to zinc powder (10 g) while stirring. The solution was stirred for a further half hour at 60°C and then filtered to remove copper and any remaining zinc, then was diluted to 5 dm^{-3} with water and sorbed onto a column of Dowex 50W x 2 resin (H^+ form, 5 x 40 cm). The column was washed with 1 mol dm^{-3} HCl until no further evidence of zinc(II) ion elution was present, and then the product was eluted with 3 mol dm^{-3} HCl. The product was taken to dryness on a rotary evaporator, washed with ethanol

then diethyl ether, dried in a vacuum desiccator and recrystallised from hot methanol to produced a white free-flowing powder (yield 8 g). (Found C, 34.0; H, 8.0; N, 13.1. $C_{12}H_{32}Cl_4N_4O_3$ requires C, 34.1; H, 7.6; N, 13.3%) NMR (D_2O): ^1H, δ 2.2-3.1 (multiplet); ^{13}C, δ 23.0, 42.7, 45.0, 45.4, 45.7, 46.5, 47.7, 175.5 p.p.m.

1,5,9,13-tetraazabicyclo[1.1.2.2]heptadecane-7-carboxylic acid pentahydrochloride, HL9·5HCl·MeOH

(N,N'-(3-aminopropyl)-1,4-diazacyclohexane)copper(II) perchlorate was prepared by the careful addition of the free polyamine to an equimolar amount of $Cu(ClO_4)_2.6H_2O$ in ethanolic solution followed by collection of the dark blue solid by filtration. Some 15 g of this solid was suspended in methanol (600 cm^3) and heated under reflux. To this was added diethyl malonate (12 cm^3), triethylamine (4 cm^3) and excess formaldehyde (25 cm^3, 38% aqueous solution) and the solution left stirring under reflux overnight. The solution was filtered, then diluted to 5 dm^3 with water and sorbed onto a column of SP Sephadex C25 resin (Na^+ form, 50 x 6 cm). Elution with 0.2 mol dm^{-3} $NaClO_4$ resulted in two major blue acid stable bands as well as a non-acid stable product spread across the column. The two spectroscopically similar cyclic bands (ester and hydrolysed product) were recombined and reduced in volume to 300 cm^3 by rotary evaporation. The pH of the solution was raised to *ca* 10 with 2.5 mol dm^{-3} and stirred at *ca* 70°C for 12 hours. This solution and hydrochloric acid (3 mol dm^{-3}, 100 cm^3) were added from separate dropping funnels dropwise over one hour to zinc powder (10 g) while stirring. The solution was stirred for a further half hour at 60°C and then filtered to remove copper and remaining

zinc. The solution was diluted to 5 dm^3 with water and sorbed onto a column of Dowex 50Wx2 resin (H^+ form, 5 x 40 cm). The column was washed with 1 mol dm^{-3} HCl until no further evidence of zinc(II) ion elution was present , and then the product was eluted with 3 mol dm^{-3} HCl. The product was taken to dryness on a rotary evaporator, washed with ethanol then diethyl ether, dried in a vacuum desiccator and recrystallised from hot methanol to produced a white free-flowing powder (yield 10 g). (Found C, 35.5; H, 7.6; N, 11.1. $C_{15}H_{39}Cl_5N_4O_3$ requires C, 35.9; H, 8.1; N, 11.2%) NMR (D_2O): ^1H, δ 2.3 (pentet), 3.3-4.0 (multiplet); ^{13}C, δ 20.5, 45.8, 46.0, 46.2, 51.3, 55.2, 173.3 p.p.m.

12-methyl-1,4,7,10-tetrazacyclotridecane-12-amine pentahydrochloride, HL11·5HCl was prepared as described in the literature and the products identity and purity confirmed by NMR.[16]

7-methyl-1,5,9,13-tetraazabicyclo[1.1.2.2]heptadecane-7-amine pentahydrochloride, L14·5HCl·3H₂O

$Cu(NO_2)_2.3H_2O$ (17.4 g) was dissolved in methanol (350 cm^3) and to this was added a methanolic solution of N,N'-(3-aminopropyl)-1,4-diazacyclohexane (13.2 g in 20 cm^3). To this was added triethylamine (9 cm^3), nitroethane (9 cm^3) and formaldehyde solution (30 cm^3, aq. 38%), and the solution was stirred at 60 °C for two hours and then at room temperature for two days. The solution was diluted to 10 dm^3, then sorbed onto a column of SP Sephadex C25 resin (Na^+ form, 50 x 6 cm). This column was washed with 2 dm^3 of water and then eluted with 0.2 mol dm^{-3} $NaClO_4$, yielding only one major acid stable band. This was collected, acidified by the addition of 10 mol dm^{-3} HCl (100 cm^3) and

zinc powder (10 g) added. The solution was stirred for 3 hours and then filtered to remove copper and excess zinc. The solution was diluted to 5 dm^3 with water and sorbed onto a column of Dowex 50Wx2 resin (H^+ form, 5 x 40 cm). The column was washed with 1 mol dm^{-3} HCl until no further evidence of zinc(II) ion elution was present, and then the product was eluted with 3 mol dm^{-3} HCl. The product was taken to dryness on a rotary evaporator, washed with ethanol then diethyl ether, dried in a vacuum desiccator and recrystallised from hot methanol to produced a white free-flowing powder (yield 12 g). (Found C, 33.3; H, 8.8; N, 13.4. $C_{14}H_{44}Cl_4N_5O_3$ requires C, 33.1; H, 8.7; N, 13.8%) NMR (D_2O): ^1H, δ 1.6 (singlet), 2.3 (pentet), 3.1-3.9 (multiplet); ^{13}C, δ 21.2, 23.9, 47.8, 51.0, 52.5, 55.8, 61.6 p.p.m.

2.2.4 Physical Methods

Electronic spectra were recorded on aqueous solutions using an Hitachi 220A spectrophotometer. IR spectra were recorded on complexes dispersed in KBr discs using a BioRad FTS-7 Fourier-transform spectrometer. Electrochemical measurements were performed with a AMEL Model 473 controller linked to an EG&G PAR Model 303A static mercury drop electrode. A conventional three electrode system, with Ag-AgCl reference electrode and platinum counter electrode, as well as nitrogen purge gas, was employed, with 0.1 mol dm^{-3} $NaClO_4$ as an electrolyte. NMR spectra (in D_2O) were recorded using a Bruker Advance DPX300 with chemical shifts measured versus trimethylsilylpropanoate and cited versus tetramethylsilane. Elemental analysis were performed by the Australian National University Microanalytical Service. Potentiometric titrations were carried out essentially

as described previously [21] using a Metrohm 665 automated burette and an IBM clone computer fitted with a Fylde Scientific pH card connected to a Metrohm combined glass electrode. All measurements were fully automated under control of the IBM clone computer. Titrations were performed at 25.0 ± 0.1°C in constant ionic strength (I = 0.5, KCl) aqueous solutions under nitrogen. Solutions of ligand (6 x 10^{-4} mol dm^{-3}) were titrated with 83 increments (of 4 x 10^{-6} dm^3) of 0.4 mol dm^{-3} NaOH. Equilibrium constants were calculated from potentiometric data with a TURBO BASIC version of the program TITFIT[22]. For each system, each titration was repeated at least three times, with good reproducibility (*ca* ± 0.1 log units) in the determined constants.

2.2.5 X-Ray Crystal Structure Determination

Crystal Data

[Cu(L4)]$(ClO_4)_2$, $C_{16}H_{32}Cl_2CuN_4O_{10}$, *M* 574.9. Monoclinic, space group $P2_1/c$ (C_{2h}^5, No. 14), *a* = 8.968(3), *b* = 8.435(3), *c* = 32.007(11) Å, ß 99.18(3)°, *U* = 2390(1) $Å^3$. D_c (*Z* = 4) = 1.60 g cm^{-3}. *F(000)* = 1196. μ_{Mo} = 11.3 cm^{-1}.

Specimen: 0.26 by 0.30 by 0.17 mm. $A^*_{min,max}$ 1.18, 1.35. [University Of Western Australia]

Structure Determination

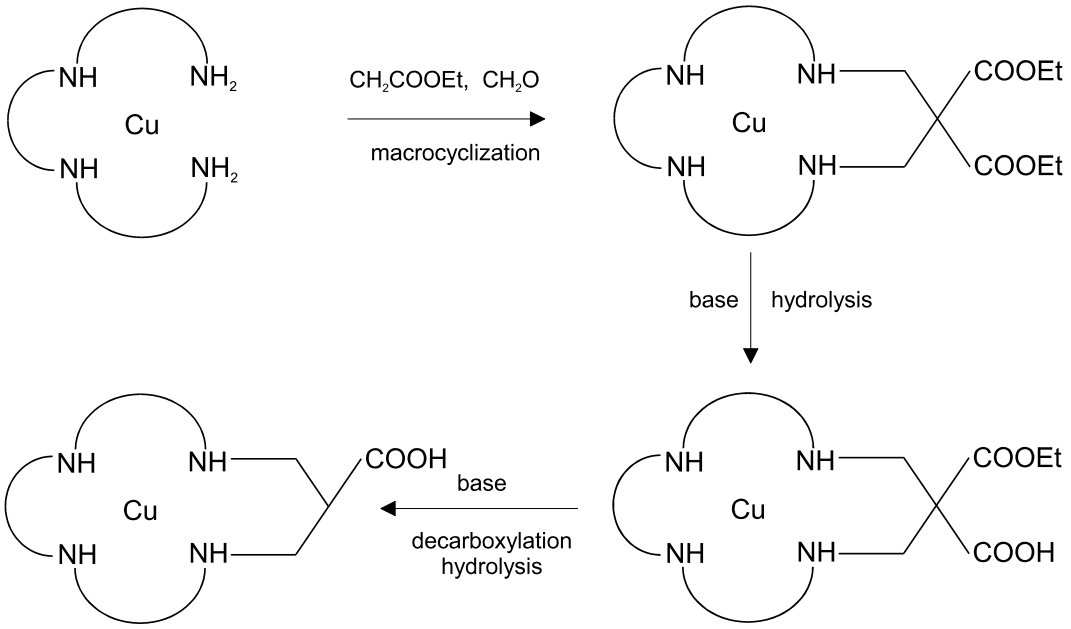
A unique data set was measured at University Of Western Australia by Allan H. White and Brian W. Skelton at *ca* 295 K within the limit $2\theta_{max}$ 50° using a Syntex $P2_1$ four-circle diffractometer [2θ/θ scan mode; monochromatic Mo*K*α radiation (λ = 0.7107_3 Å)], yielding 4239 independent reflections; 2631 of these

with $I > 3\sigma(I)$ were considered 'observed' and used in the full matrix least squares refinement after Gaussian absorption correction and solution of the structure by Patterson methods. Anisotropic thermal parameters were refined for the non-hydrogen atoms; $(x, y, z, U_{iso})_H$ were included, constrained at estimated values. Conventional residuals, R, R_w on $|F|$ at convergence were 0.045, 0.046, statistical weights derivative of $\sigma^2(I) = \sigma^2(I_{diff}) + 0.0004\ \sigma^4(I_{diff})$ being used. Neutral atom scattering factors were employed;[23] computation used the XTAL 3.0 program system [24] implemented by S. R. Hall. The coordinated perchlorate was disordered over two orientations, and was modelled with equal occupancies. Pertinent results are presented and discussed in the following section.

2.3 Results and Discussion

2.3.1 Synthesis and Characterisation of Polyaminoacids and Their Complexes

Condensation reactions of the copper(II) complexes of several polyamines were carried out using diethyl malonate and formaldehyde. The formation of macrocyclic products in the reactions was followed by periodically checking samples of the reaction mixtures for the presence of acid stable species, defined by the sample maintaining its colour on addition of an equal volume of 1 mol dm^{-3} HCl. Acid stability is a characteristic of copper(II) complexes of macrocycles rarely shared by their non-cyclic counterparts, unless the latter are highly sterically constrained,[25] which does not apply in these experiments. The reaction may be defined as shown in Scheme 2.1. The copper(II) ion with its pseudo square planar geometry acts as a template to hold the *cis*-disposed amines in the correct position for the entropically favoured formation of the six-membered ring. The incorporation of -COOR groups into the resulting compounds was clearly shown by strong infrared absorbances in the region between 1700 and 1750 cm^{-1} for acids and esters, with a band observed near 1725 cm^{-1} for the esters and near 1750 cm^{-1} for the acids. Partial ester hydrolysis to form a gem ester acid may occur during formation under the basic conditions employed. Complexes with both acid and ester groups exhibited two distinct bands in the -COOR stretching region.



Scheme 2.1

Although yields of isolated complexes were not high compared with analogous reactions employing nitroalkanes,[12,13] the reactions proceeded with limited amounts of other products apart from starting material isolated. Ester hydrolysis and decarboxylation reactions presumably proceed for some complexes during the slow crystallisation process and relatively high solubility of products contributed to low isolated yields. The $[Cu(L3)]^{2+}$, $[Cu(L4)]^{2+}$ and $[Cu(L5)]^{2+}$ products were recovered in reasonable yield, with $[Cu(L4)]^{2+}$ the only product precipitating as the solution from the chromatographic separation was reduced in volume for these reactions. In contrast, both $[Cu(L1)]^{2+}$ and $[Cu(L2)]^{2+}$ were obtained in poor yield (*ca* 10-20%) with most of the precursor polyamine decomposing during the reaction to form a mixture of intractable and or insoluble products. Attempts to increase the yield by changing reaction conditions were relatively unsuccessful. The only byproduct crystallised, in the case of syntheses of L1 and L3, has been identified previously in the case of L3

as a monoimine (or its hydrated form, an aminol),[17] and species arising from condensation of the precursor polyamine and formaldehyde alone are reasonable though not particularly stable products. Recovery of precursor complex from some reaction mixtures may arise in part from decomposition of such intermediates.

Overall, yields from the condensations using diethyl malonate are clearly lower than the analogous reactions using nitroethane. This effect may be related in part to the lower acidity of diethyl malonate when compared to nitroethane; it has a pK_a approximately five log units lower. This results in there being significantly lower concentrations of the nucleophile $(EtOOC)_2CH^-$ available for reaction with imine intermediates, perhaps permitting other unwanted competing reactions (e.g. with OH^-) to become important.

The variation in the extent to which ester hydrolysis and decarboxylation appear to occur in analogous syntheses is surprising. Although in most cases the diester complex is isolated, the products (L4 and L5 complexes) from reaction with bis(3-aminopropyl)diazacyclohexane have one of the ester groups hydrolysed to the acid form or have undergone decarboxylation. It would seem that decarboxylation must be preceded by hydrolysis of at least one of the ester groups, and the rate of ester hydrolysis and subsequent decarboxylation is probably influenced by axial interaction of ester groups with the copper ion. This can occur for only certain conformations of the secondary amines, and also may be influenced by macrocycle ring size or rigidity. Hydrolysis of

pendant ethoxycarbonyl groups (as part of a -NH-CH_2-COOEt chain) on copper(II) polyamine complexes has been examined recently, with the reactions slightly faster than similar hydrolyses in the absence of copper(II), and some influence of the macrocycle backbone apparent.[10]

The inherent tendency for gem diesters or acid esters to undergo hydrolysis and decarboxylation,[20] as illustrated by the isolation of both $[Cu(L4)]^{2+}$ and $[Cu(L5)]^{2+}$ from the one synthesis, was pursued deliberately to produce complexes of macrocycles with a single pendant carboxylic acid. Ester hydrolysis and decarboxylation in aqueous base proceeds without any noticeable destruction of the macrocycle assembly (from chromatographic monitoring), although facile isolation of the polyaminoacid complexes is diminished substantially by their high solubility. When isolation is achieved from sufficiently basic solution, the deprotonated acid complex is obtained, identified by a shift in the strong infrared absorbance from 1750 cm^{-1} (-COOH) to 1610 cm^{-1} ($-COO^-$). Although the carboxylate anion may be presumed to have the capacity to coordinate in an axial site, this is not anticipated to lead to a strong interaction with the copper(II) ion, although binding of this pendant to metal ions which prefer higher coordination numbers is quite facile and is discussed in later chapters.

The copper complexes of macrocyclic products all have electronic maxima of considerably higher energy than their open chain precursors (typical shift ~20 nm), which is consistent with the stronger ligand field associated with the macrocycles. The copper complexes all showed poorly reversible or irreversible

Cu(II)-Cu(I) couples in cyclic voltammetry experiments. Limited reversibility is typical of (tetraazacycloalkane)copper(II) complexes but not of acyclic analogues,[11] the result of the inability of the relatively rigid macrocycle (when compared with acyclic analogues) to adapt to the preference of the Cu(I) ion for a tetrahedral environment. These general observations regarding physical properties support other evidence for macrocyclisation, confirmed by an X-ray crystal structure analysis.

The crystal structure of $[Cu(L4)](ClO_4)_2$ is illustrative of the family of pendant arm macrocycles described herein. Non-hydrogen atom coordinates appear in Table 2.1, with details of the copper environment appearing in Tables 2.2. This molecule, which has undergone decarboxylation following condensation, contains an introduced -NH-CH_2-CH(COOEt)-CH_2-NH- chain which completes the macrocycle. The six-membered chelate ring incorporating this unit adopts (like the other six-membered ring) a chair conformation with the secondary amines having *RS* conformations, and in this geometry the pendant is displaced away from the axial site of the copper. The 1,4-diazacyclohexane fragment adopts a 'butterfly' conformation, and the copper ion exists in a square-based pyramidal geometry with one perchlorate clearly coordinated [Cu-O 2.30 Å], albeit in a disordered manner, and the other not at a bonding

Table 2.1. Non-hydrogen atom coordinates for $[Cu(L4)](ClO_4)_2$.

Atom	*x*	*y*	*z*	Atom	*x*	*y*	*z*
Cu	0.28131(7)	0.50307(8)	0.63331(2)	C(6b)	0.4661(8)	0.1959(7)	0.6565(2)
C(1)	0.3175(7)	0.7014(8)	0.5433(2)	N(7a)	0.3637(5)	0.3134(5)	0.6709(1)
C(11)	0.4428(8)	0.8206(8)	0.5539(2)	C(8b)	0.4350(6)	0.3984(7)	0.7091(2)
O(1)	0.4369(5)	0.9347(6)	0.5757(1)	C(9b)	0.2270(8)	0.2328(7)	0.6821(2)
O(2)	0.5593(5)	0.7851(6)	0.5354(1)	Cl(1)	-0.0173(2)	0.3003(3)	0.57218(6)
C(12)	0.683(1)	0.901(1)	0.5443(3)	O(11)[a]	0.132(1)	0.332(1)	0.5891(3)
C(13)	0.777(2)	0.864(2)	0.5202(6)	O(12)[a]	-0.071(2)	0.190(2)	0.6016(4)
C(2a)	0.1843(7)	0.7404(7)	0.5649(2)	O(13)[a]	-0.013(2)	0.273(4)	0.5309(5)
N(3a)	0.2169(4)	0.7237(5)	0.6116(1)	O(14)[a]	-0.103(2)	0.437(2)	0.5838(9)
C(4a)	0.0914(6)	0.7991(7)	0.6298(2)	O(11')[a]	0.049(1)	0.402(1)	0.5979(3)
C(5a)	0.1149(7)	0.7984(8)	0.6773(2)	O(12')[a]	0.115(2)	0.189(2)	0.5685(6)
C(6a)	0.0792(7)	0.6424(8)	0.6957(2)	O(13')[a]	-0.084(4)	0.372(3)	0.5388(8)
N(7a)	0.1881(4)	0.5181(5)	0.6887(1)	O(14')[a]	-0.108(2)	0.192(3)	0.5754(8)
C(8a)	0.3292(6)	0.5249(7)	0.7200(1)	Cl(2)	0.6684(1)	0.7652(2)	0.67465(4)
C(9a)	0.1198(7)	0.3608(8)	0.6935(2)	O(21)	0.5095(4)	0.7905(5)	0.6728(1)
C(2b)	0.3678(7)	0.5317(7)	0.5477(2)	O(22)	0.6947(5)	0.6825(5)	0.6379(1)
N(3a)	0.4313(5)	0.4840(5)	0.5921(1)	O(23)	0.7224(4)	0.6709(5)	0.7109(1)
C(4b)	0.5094(8)	0.3274(7)	0.5906(2)	O(24)	0.7465(4)	0.9113(5)	0.6774(1)
C(5b)	0.5789(8)	0.2661(8)	0.6328(2)				

[a] Site occupancy factor 0.5

distance. A view of the molecule, with atom numbering, appears in Figure 2.1. The copper ion is displaced 0.246(1) Å above the mean plane of the nitrogen donors [χ^2, 34; d N(3A, 7A, 3B, 7B), -0.012(5), 0.018(6), 0.014(5), -0.018(5) Å]. The Cu-N distances for the tertiary nitrogens are slightly longer than those for the secondary nitrogens in each section of the structure [2.082(4) *v.* 2.037(4) and 2.062(4) Å *v* 2.035(4).], and somewhat longer overall than the average Cu-N distance [2.037 Å] in an analogue without the additional 'strap'.[12] The crystal structure of the analogous strapped complex aqua(7-methyl-7-nitro-1,5,9,13-tetraazabicyclo[1.1.2.2]- heptadecane)copper(II) perchlorate, $[Cu(L10)](ClO_4)_2 \cdot H_2O$, with nitro and methyl groups pendant to the introduced six-membered chelate ring, has been reported.[13] This molecule adopted an analogous square-pyramidal environment, but with a more tightly bound water molecule in the axial site rather than a perchlorate ion. The copper environment of this complex is compared with the present example in Table 2.2, with torsional angles compared in Table 2.3. The close relationship between the two structures, whose ligands differ only in pendant groups, is apparent.

Electronic maxima for $[Cu(L4)]^{2+}$ and $[Cu(L10)]^{2+}$ [575 and 579 nm respectively] differ only slightly, consistent with the common macrocyclic core, although the $Cu^{II/I}$ couples [-0.58 and -0.67 V *v.* Ag/AgCl respectively] shows some variation as a consequence of the different electron-withdrawing properties of the pendants attached in each complex.[26] The 'strapped' macrocyclic complexes are reduced at a less negative potential than

Fig. 2.1. A view of the molecular cation $[Cu(L4)](ClO_4)_2$, with atom numbering; 20% thermal ellipsoids are shown for the non-hydrogen atoms. Hydrogen atoms have arbitrary radii of 0.1 Å.

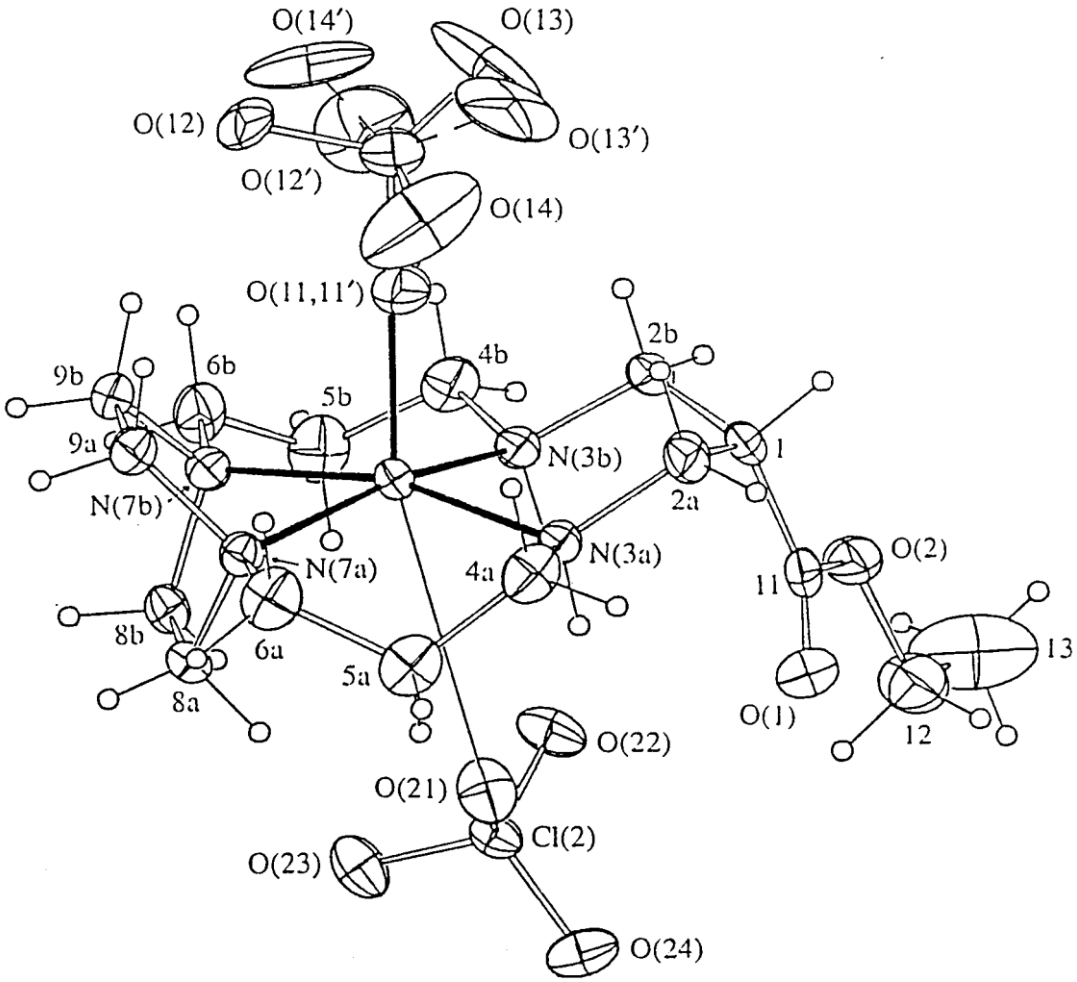


Table 2.2 The square-based pyramidal copper environment in $[Cu(L4)](ClO_4)_2$. The value *r* is the copper-donor atom distance (Å); the other entries in the matrix are the angles (degrees) subtended at the copper by the relevant atoms at the head of the row and column; two values for O relate to two disordered perchlorates of equal occupancy (O-Cu-O 28.1(4)°); values in parentheses are for the analogue L10.

Atom	*r*	N(7B)	N(3B)	N(7A)	N(3A)
O	2.29(1), 2.32(1)	89.6(3), 105.2(3)	86.0(3), 107.2(3)	106.9(3), 89.1(3)	105.0(3), 85.8(3)
	[2.259(8)]	[98.1(3)]	[94.9(3)]	[102.0(3)]	[94.7(3)]
N(3A)	2.037(4)	163.9(2)	91.8(2)	96.0(2)	
	[2.056(8)]	[165.0(3)]	[89.5(3)]	[96.8(4)]	
N(7A)	2.082(4)	72.9(2)	162.5(1)		
	[2.072(9)]	[73.0(3)]	[161.4(3)]		
N(3B)	2.035(4)	96.0(2)			
	[2.044(8)]	[97.1(3)]			
N(7B)	2.062(4)				
	[2.053(8)]				

Table 2.3. Macrocycle torsion angles (degrees) in $[Cu(L4)](ClO_4)_2$.

The two values in each entry are for sections A, B. Atoms are denoted by number; nitrogen is in *underlined*. Values for the analogue L10 appear in parentheses.

Atoms	Angles	Atoms	Angles
2-1-2-3	64.6(6), -66.1(6)	5-6-7-9	-160.2(5), 162.5(5)
	[58, -57]		[-155, 164]
1-2-3-4	167.4(5), -166.8(5)	6-7-8-8'	-177.6(5), 175.7(5)
	[167, -168]		[-177, 176]
2-3-4-5	-176.8(5), -179.7(5)	6-7-9-9'	174.6(4), -175.8(4)
	[-179, -177]		[175, -176]
3-4-5-6	-79.1(6), 77.6(7)	7-8-8'-7'	1.2(6)
	[-80, 77]		[0]
4-5-6-7	68.6(6), -69.6(7)	7-9-9'-7'	0.9(5)
	[68, -73]		[0]
5-6-7-8	81.5(6), -79.2(6)		
	[85, -77]		

'unstrapped' analogues, and display a slightly weaker ligand field, implying some relationship which has been explored more fully for the series of 'unstrapped' complexes.

Comparison of selected physical properties for the carboxylate-pendant series of complexes of the ligands L1, L2 and L3 with those of their analogues carrying nitro substituents[11] proved revealing. A consistent relationship

between both electronic maxima and $Cu^{II/I}$ couple and macrocycle ring size was observed for both series, as illustrated in Figure 2.2.

For each property considered, a turning point occurs at the fourteen-membered ring, consistent with the view that this macrocycle ring size is most appropriate for incorporating copper(II) ion.[27] The electronic spectra of the carboxylate pendant series are very similar to those found for the nitro pendant analogues for 14- and 15-membered rings (Figure 2.2), suggesting that varying the C-pendant groups attached to the ring do not have a significant influence. This is not surprising, as due to the Jahn-Teller effect copper(II) prefers a pseudo-square planar geometry and interactions of different pendants in axial sites (and consequent effects) should be modest, even more so for poorly coordinating nitro or ester groups. The electronic maxima of the 13-membered ring system compounds do differ, which suggests, since the electronic spectrum of the nitro-pendant analogue of L11 does show solvent dependence,[12] some different axial interactions in solution in this case. The $Cu^{II/I}$ couple is consistently *ca* 0.1 V more negative for the carboxylate-substituted series (Figure 2.2), reflecting consistent and different electronic influences of the pendant groups superimposed on a variation with macrocycle ring size.

It has been established that condensations about copper(II) complexes of polyamines using diethyl malonate and formaldehyde in basic solution provide a route to the synthesis of macrocyclic polyamines with pendant

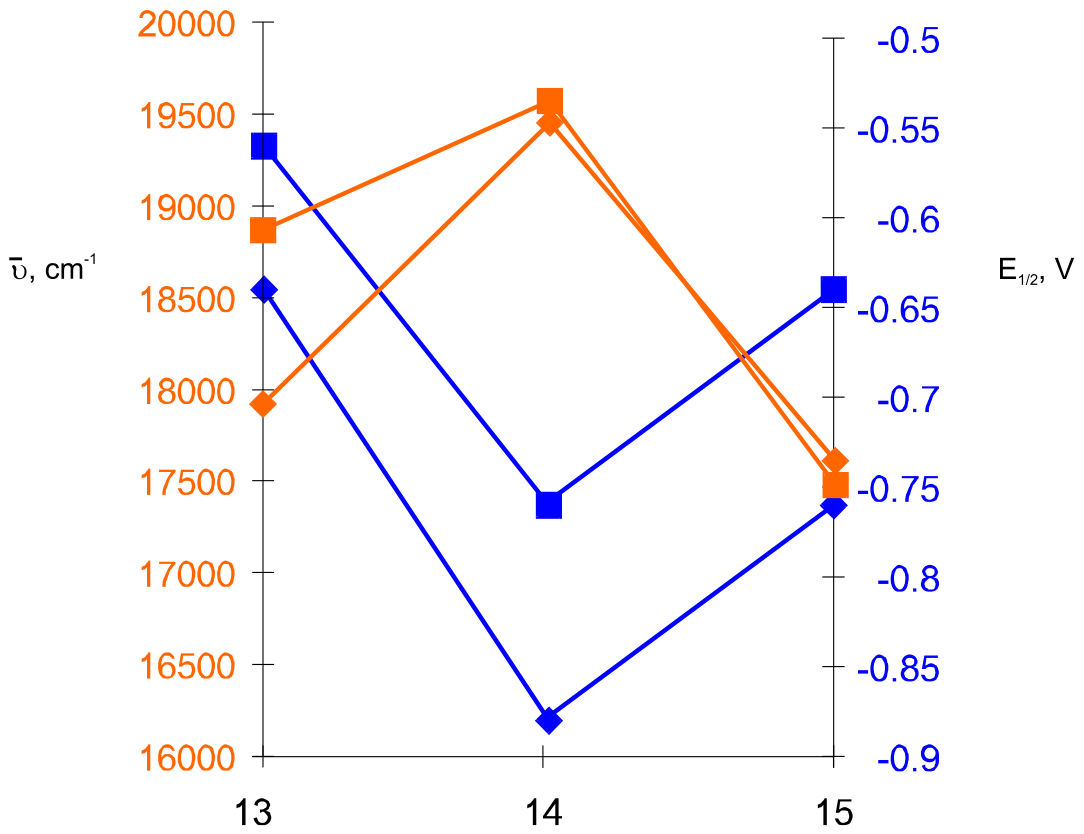


Figure 2.2 Variation in electronic maxima and redox potential of copper(II) monomacrocyclic complexes with macrocyclic ring size, shown for the carboxylic acid pendant (◆) and nitro pendant (■) series

carboxylic acid groups. While this pendant group may not coordinate to the copper(II) ion, it has the potential to coordinate as a fifth donor in an axial position if the molecule were coordinated around a metal ion preferring octahedral geometry, as will be discussed in the next chapter. Such a coordination of a pendant arm carboxylic acid group on cobalt(III) has already been demonstrated for the acyclic ligand 3-(2'-aminoethylamino)-2-[(2"-aminoethylamino)methyl]propanoic acid.[18] Mixed nitrogen and oxygen donor sets will have an effect on metal ion preference as a result of the difference in the affinity of certain metal ions for oxygen and nitrogen donors. The pendant

group is also open to a number of reactions which may convert it to other functional groups.

All copper(II) complexes discussed can be conveniently reduced using zinc and acid to remove the copper ion and complete decarboxylation to produce the hydrochloride salt of the free amino acid. It was found to be unnecessary to isolate the intermediate copper complex of each ligand as a solid. Rather, it was found possible and more convenient to reduce the original solution from the synthesis after chromatography had removed unreacted material and byproducts. Yields were increased by hydrolysis of the copper complex in basic solution before reduction. This is presumably because the monoacid species produced by this process are less prone to decomposition in the vigorous reduction conditions than the *gem* diesters and acid esters produced in the original synthetic step. The yields for the direct reduction procedure were relatively high, and appear to be consistent with the amount produced from reactions where the hydrolysis intermediate was first isolated, suggesting little or no degradation of the macrocycle. Chromatography of the reduction products only yielded macrocyclic species and excess zinc, with no acyclic polyamines detected. The ^{1}H-decoupled ^{13}C spectra of the isolated free ligands are consistent with the expectations based on the symmetry of the macrocycles, and support the high purity of the products. The pendant carboxylic acid group is clearly defined by a peak near 175 ppm in each case (see Figures 2.3 and 2.4), and is further confirmed by the observation of a strong resonance associated with the group near 1750 cm^{-1} in the IR spectrum.

Figure 2.3 The ^{1}H decoupled ^{13}C spectra of L6·4HCl (top) and L7·4HCl (bottom)

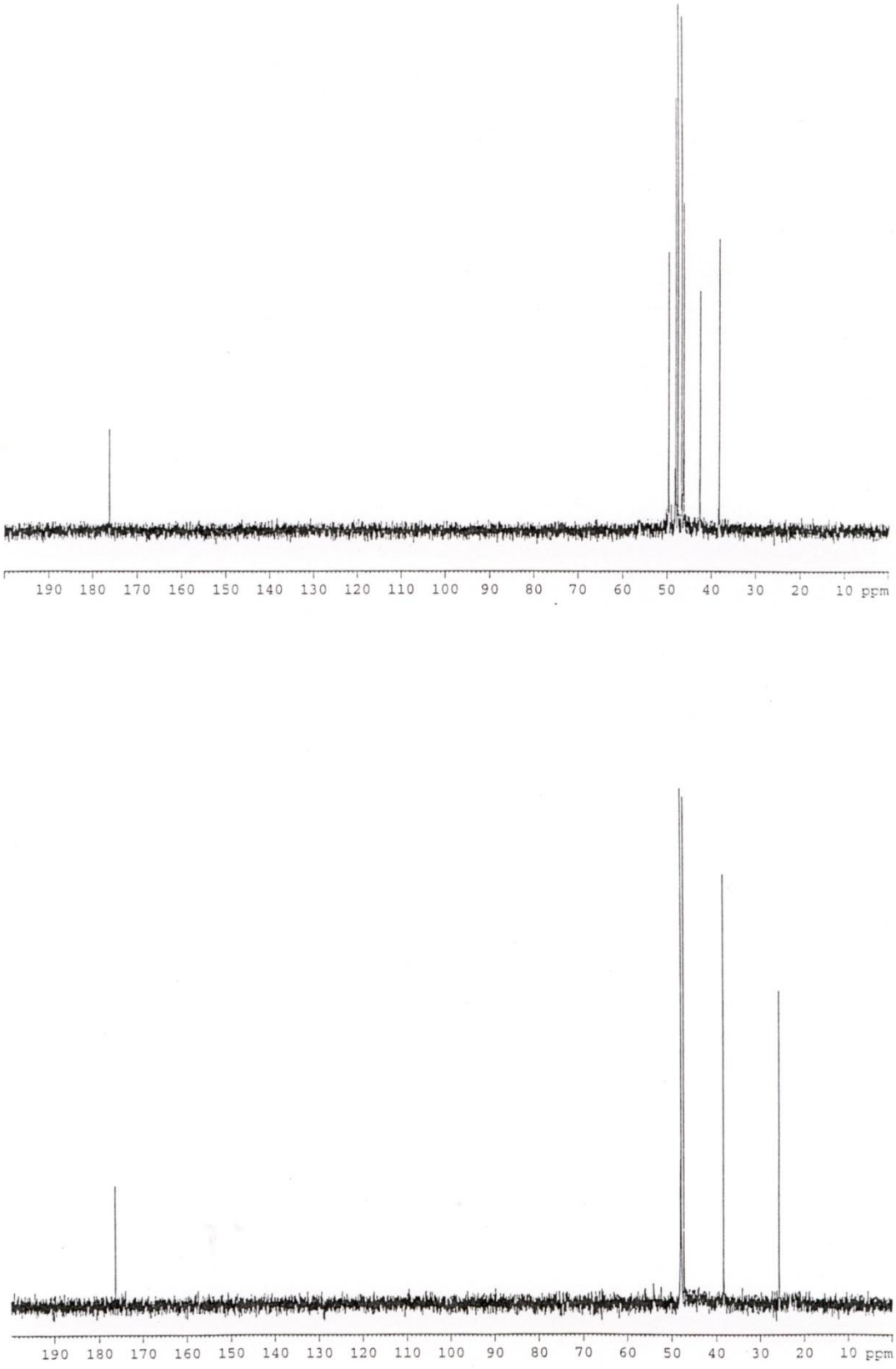
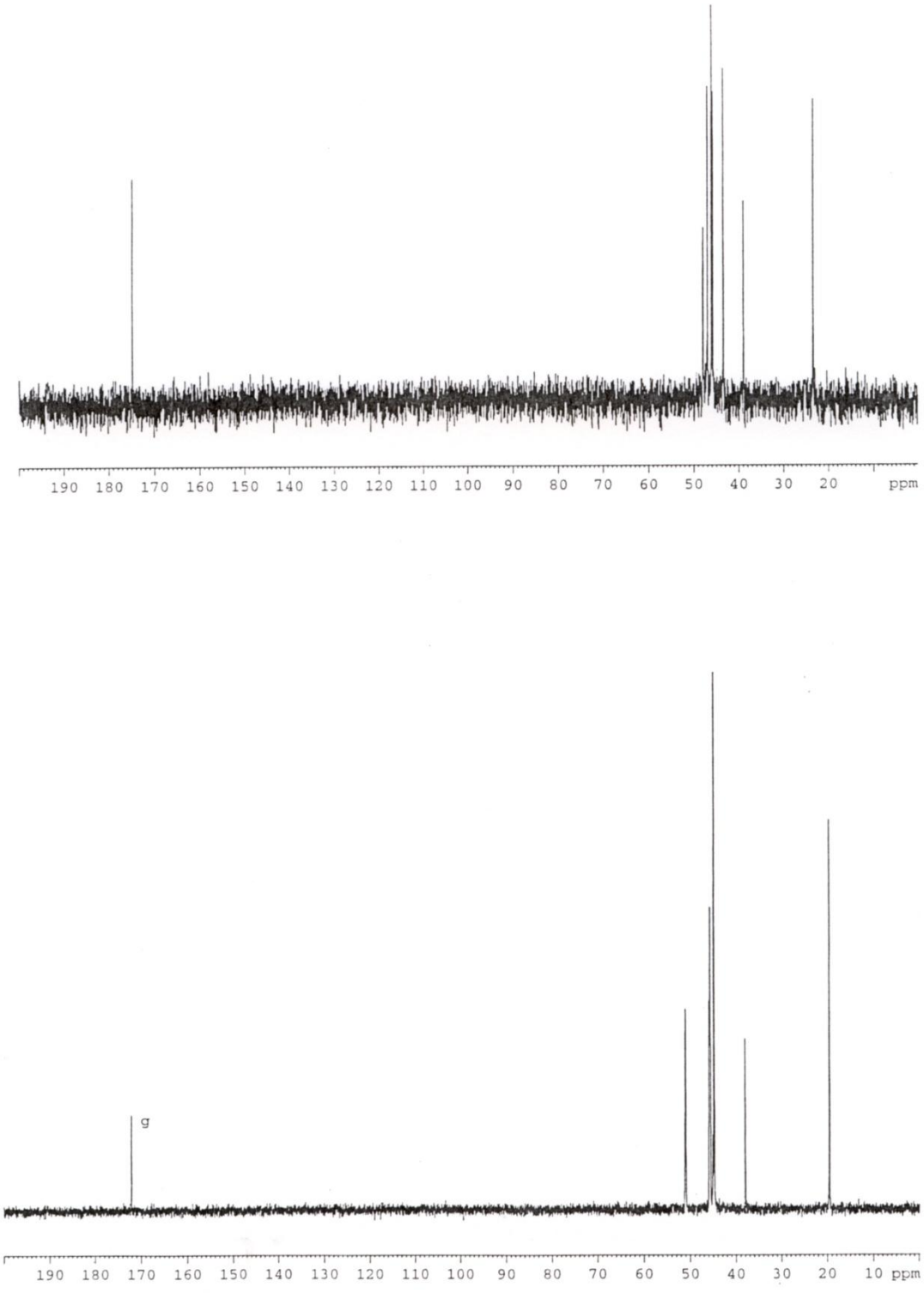


Figure 2.4 The ^{1}H decoupled ^{13}C spectra of L8·4HCl (top) and L9·4HCl (bottom)



2.3.2 Determination of Protonation Constants for the Polyaminoacids

Potentiometric titrations were performed on the hydrochloride salts of the four carboxylate pendant macrocyclic ligands (L6-L9) to determine the protonation constants for these species and to compare these with the values found for the amine pendant analogues (L11-L14). To complete the data set, this involved also the titrations of L11 and L14, with data for L12 and L13 previously reported.. All titrations were modelled successfully for the five protonation steps involved.

The results of titrations are presented in Table 2.4 and illustrated graphically in Figure 2.5. In the data presented in Table 2.4 the ligands are either the neutral pentaamine (L11-L14), or else the deprotonated amino acid (L6-L9). The first and second protonations occur with pK_a values between 11.5 and 8.5 in all ligands, and are associated with proton addition to the secondary amines in the macrocycle ring, with the protons shared between adjacent pairs of amines within the ring.[2, 28] At least in the case of the amine pendant species, there appears to be a relationship between macrocyclic ring size and pK_a values for the first two protonations with a maxima at the 14-membered macrocycle. This is not surprising, since the sharing of a proton must be affected by the spatial relationship of the two amines involved. That the amine pendant plays little or no role in these initial protonations is supported by the similarity in values for the first two protonations of L12 with its 'parent' cyclam, which carries no pendants groups (pK_a 11.6 and 10.2 compared with

Table 2.4

The logarithms of the protonation constants [a] for the C-pendant macrocyclic ligands discussed in this chapter.

	Amine pendant ligands				Carboxylate pendant ligands			
	L11	L12[29]	L13[30]	L14	L6	L7	L8	L9
$H + L \Leftrightarrow HL$	10.45	11.55	11.0	10.6	10.4	10.5	10.45	10.9
$HL + H \Leftrightarrow H_2L$	9.55	10.2	9.5	8.65	10.1	9.7	9.55	9.55
$H_2L + H \Leftrightarrow H_3L$	6.5	5.9	6.1	6.5	7.7	6.55	5.55	4.05
$H_3L + H \Leftrightarrow H_4L$	3.5	~3.6	3.6	~2.6	3.65	3.3	4.2	~2.9
$H_4L + L \Leftrightarrow H_5L$	~0.9	~2.0	<2	~0.9	~1.9	~0.8	~0.9	~2.0

(a) 25 °C, I = 0.5 mol dm^{-3} KCl, standard errors are ±0.5 units.

11.6 and 10.6 for cyclam). The carboxylate pendant macrocycles do not show the same apparent trend, suggesting other masking influences in this system.

The next step in each ligand can tentatively be assigned to the protonation of the pendant. In the case of the amine pendant this is supported by the results found for other macrocyclic species with amine pendants,[31] with all determined pK_a values lying between 5.5 and 6.5. In contrast to the relatively constant nature of the third protonation of the amine pendant species, the carboxylate pendant species show a pronounced decrease in pK_a as macrocyclic ring size is increased and, in the case of L9, macrocyclic rigidity is increased. Assuming that this protonation is associated with the carboxylate itself, it can be suggested that some form of zwitterion is involved. Formation of such ions

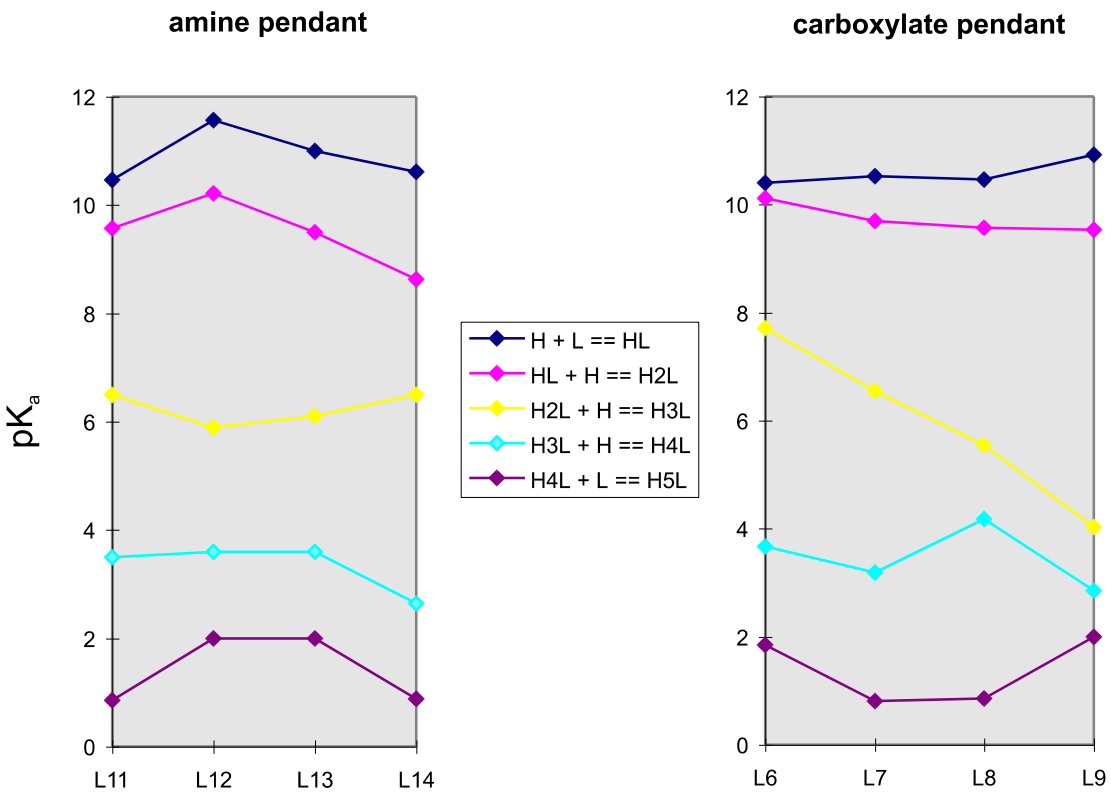


Figure 2.5 Variation in protonation constant with ring size for the ligands discussed in this chapter

could be strongly influenced by the spatial arrangement of the amines and carboxylates involved and the flexibility of the macrocycle. It could also be the formation of such ions which is the cause of the differences seen in the first two protonations for the carboxylate-pendant macrocycles compared with there amine-pendant analogues. It should be noted, however, that any assignment of protonations to specific sites is in the very least speculative. Introduction of the last two protons, presumably into the macrocyclic ring, occurs only with difficulty due to prior protonation in the ring. The results are approximate or estimated because of the difficulties in defining these values in dilute aqueous acid.

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