FULL PAPER

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Synthesis and complexation properties of ditopic ligands built from a macrocyclic and an open chain chelator moiety

Liselotte Siegfried, Marcus Honecker, Andreas Schlageter and Thomas A. Kaden
Department of Chemistry, Spitalstr. 51, 4056 Basel, Switzerland. E-mail: th.kaden@.unibas.ch

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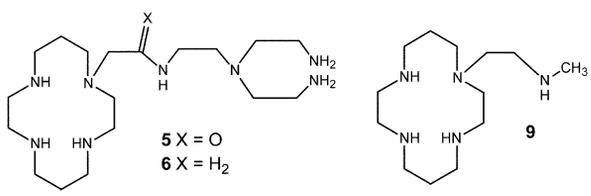
Two heteroditopic ligands **5** and **6**, containing the macrocyclic unit cyclam and the open chain ligand 2,2′,2″-triaminotriethylamine (tren), as well as the pendant macrocycle 1-(2-methylaminoethyl)-1,4,8,11-tetraazacyclotetradecane **9**, were synthesized. Their complexation potential towards Cu^{2+} and Ni^{2+} was studied using potentiometric pH-measurement and spectrophotometric titrations, from which the stability constants and thus the existence range of the species were determined. Both ligands **5** and **6** form a series of mononuclear MLH_n ($n = 3, 2, 1, 0$) and dinuclear M_2LH_p ($p = 0, -1, -2$) species, and in some cases also dimeric complexes $(ML)_2H_m$ ($m = 2, 1, 0$). Using **9** for comparison purposes, the structures of the species observed with ligands **5** and **6** can be deduced from their spectral properties. Thus in the complexes MLH_n, the metal ion is always bound by the macrocyclic ring, whereas in the species M_2LH_p one metal is coordinated by the macrocycle and the other by the tren unit. Kinetic measurements show that the metal ion first binds to the more reactive open chain unit but then it is transferred to the cyclam moiety, which gives the thermodynamically most stable compound. In the heterodinuclear species the sequence of addition of the metal ions determines where they are bound. The first metal ion is always coordinated by the macrocycle, whereas the second one is bound by the tren moiety, so that it is possible to selectively prepare the two isomers.

Introduction

There has been a continuing interest in dinuclear metal complexes,[1] since with them one can study metal–metal interactions through their magnetic properties, the role of distance between two metal centers in regard of their redox potentials and the rate of electron exchange. In addition they can be used as models for metallo enzymes containing two or more metal ions,[2] such as urease,[3] alkaline phosphates,[4] superoxide dismutase (SOD),[5] or laccase.[6] Many ligands developed for this purpose are homoditopic, *i.e.* consist of two equal binding sites for the two metal ions, which allows to prepare homodinuclear complexes, but makes it difficult to synthesize heterodinuclear species. In some cases a chromatographic separation has been necessary to isolate complexes with two different metal ions.[7]

More interesting are heteroditopic ligands,[8] which offer two different binding sites for metal ions and thus allow a simpler synthesis of heterodinuclear complexes[1,9] or mononuclear species in which the metal ion is bound only at one site and leaves the other one free. Such heterodinuclear complexes have, for example, been used to mimic SOD.[10]

There are many examples of homo- and ditopic ligands in which two macrocyclic rings have been linked together[7,11] or in which large rings have been built so that they can accommodate two metal ions.[12] Because of the specific properties of macrocyclic ligands, which generally form thermodynamically and kinetically very stable complexes compared to open chain chelators, which give labile species upon complexation, we have synthesized new ditopic systems by combining these two structural elements in one molecule. In this first project we have prepared compounds **5** and **6**, which contain the well-known tetraazamacrocycle cyclam combined with the open chain ligand tren. A combination of cyclam linked through a 1,4-xylyl group to tren has previously been described[13] and the authors have used this system to make a Cu^{2+}/Ni^{2+} heterodinuclear species which is able to translocate anions driven by a redox process. In our case we have not used a rigid bridge unit but have coupled the two units through a flexible ethylene chain, which allows the two metal ions to come closer to each other. For comparison purpose we also have synthesised ligand **9**, in which a 2-methylaminoethyl side chain mimics the beginning of the tren unit.



Experimental

Materials and methods. All reagents and solvents obtained from commercial sources were used without further purification. Infrared spectra as KBr-pellets (1–3%) were measured on a ATI Matteson Genesis Series FTIR™. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker AC250 or Bruker AC400 spectrometer. Reported chemical shifts are relative either to TMS ($CDCl_3$) or sodium 3-(trimethylsilyl)propylsulfonate (D_2O). Elemental analyses were performed either by the analytical laboratory of Ciba–Geigy AG or of the Institute for Organic Chemistry of the University of Basle. Electrospray-MS were run on a Finnigan MAT, FAB-MS on a VG-70–35, LD-TOF-MS on a PerSeptive Biosystems instrument with a Voyager BioSpectrometry workstation.

4,8,11-Tris(*tert*-butyloxycarbamoyl)-1,4,8,11-tetraazacyclotetradecane[14] (**1**) and 1,4,8-tritosyl-1,4,8,11-tetraazacyclotetradecane[15] (**7**) were prepared according to the literature.

4,8,11-Tris(*tert*-butyloxycarbamoyl)-1,4,8,11-tetraazacyclotetradec-1-yl)acetic acid (2). A solution of **1** (3.01 g, 6 mmol)), *N*-ethyldiisopropylamine (4 ml) and iodoacetic acid (1.46 g, 7.8 mmol) in $CHCl_3$ (15 ml) and MeOH (5 ml) was refluxed for 18 h. After evaporation of the solvent the crude product was flash-chromatographed on silica gel (350 g) using first CH_2Cl_2–MeOH (6 : 1, 3 l), then MeOH (1.5 l) as eluent. In the last fraction we obtained **2** as a white foam (2.5 g, yield 74.6%). ^{1}H NMR ($CDCl_3$): δ 1.4 (s, 27H, $C(CH_3)$), 1.6–1.9 (m, 4H, 2 $C–CH_2–C$), 2.42–2.95 (m, 4H, $N–(CH_2)_2N–CH_2–COOH$), 2.95–3.5 (m, 14H, 7 $N–CH_2–$); ^{13}C NMR ($CDCl_3$): δ 29.07 (CH_3), 48.94, 47.86, 47.72, 47.07 ($N–CH_2–$), 80.29 ($O–C(CH_3)_3$, 156.1 ($N–COOC$, $N–CH_2–COOH$). MS (FAB): *m*/*z* 560 (M + 1), 559 (M^+), 459 (M^+ − Boc), 359 (M^+ − 2Boc), 259 (M^+ − 3Boc).

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Compound 3. To a solution of **2** (1.18 g, 2 mmol) in CH_2Cl_2 (7 ml), *N*-hydroxysuccinimide (509 mg, 4.4 mmol) was added under N_2 atmosphere After cooling the solution to 0 °C *N*,*N*-dicyclohexylcarbodiimide (498 mg, 2.4 mmol) was added and the solution was kept at 0 °C for 3 h. Then tren (3 ml, 20 mmol) dissolved in CH_2Cl_2 (10 ml) was mixed with the previous solution and the mixture was left for 2 h at 0 °C, then for 18 h at r.t. The precipitate was filtered off and the filtrate evaporated to dryness. The oil was taken up in CH_3CN (10 ml) and kept at −18 °C for 1 h, whereby a precipitate formed. After filtration the solution was evaporated and the residue taken up with CH_2Cl_2 (10 ml) and extracted with NaOH (2 × 10 ml, 2 M). The organic phase was dried and evaporated leaving a pale yellow foam (1.19 g, 94%). ^{1}H NMR ($CDCl_3$): δ 2.0–1.0 (m + s, 31H, 3 C(CH_3)$_3$ + 2 C–CH_2–C), 2.8–2.5 (3 m, 7 N–CH_2–), 3.6–3.0 (m, 8 CO–N–CH_2– and N–CH_2–CONH); ^{13}C NMR ($CDCl_3$): δ 25.47, 25.34 (CH_2–*C*H_2–CH_2), 28.80 (CH_3), 40.07, 54.24 (N–*C*H_2CON), 57.74 (N–CH_2–), 80.16, 80.18, 80.22, 80.30 (O–*C*(CH_3)$_3$, 155.93, 157.35 (N–*C*OOC, R*C*ON).

Compound 4. Compound **3** (940 mg, 1.37 mmol) in dry CH_2Cl_2 (70 ml) was treated with di-*tert*-butyloxydicarbamate (745 mg, 3.42 mmol) in CH_2Cl_2 (30 ml). After 2 h at r.t. the solvent was rotatory evaporated and the crude product was purified by flash-chromatography on silica gel (135 g) using CH_2Cl_2–MeOH (9 : 1) as eluent to give **4** (770 mg, 63.6%). ^{1}H NMR ($CDCl_3$): δ 1.45 (s, 45H, 5 C(CH_3)$_3$); 1.6–1.95 (m, 4H, 2 C–CH_2–C), 2.45–2.75 (m, 10H, N–CH_2–); 3.1–3.5 (m, 20H, 10 O=C–N–CH_2–); ^{13}C NMR ($CDCl_3$): δ 25.95, 25.64 (CH_2–*C*H_2–CH_2), 28.48 (CH_3), 47.46, 47.71, 48.98 (N–CH_2–), 53.9 (N–*C*H_2–CO–N), 79.77, 79.9 (O–*C*(CH_3)$_3$), 155.6, 156.2 (N–*C*OOC). MS (FAB): *m*/*z* 888 (M + 1), 787 (M + 1 − Boc).

Compound 5. To compound **4** (600 mg, 0.67 mmol) dissolved in CH_2Cl_2 (5 ml) a solution of trifluoroacetic acid in CH_2Cl_2 (20 ml, 1 : 1 mixture) was added dropwise. After 20 min diethyl ether (40 ml) was added whereby a precipitate formed. The reaction mixture was kept overnight at −18 °C to allow complete precipitation, then the solvent was decanted off and the residue dried *in vacuo*. The triflate (540 mg, 81.8%) was dissolved in a little water and converted into the hydrochloride using Dowex (2 × 8) ion exchanger in the chloride form in the batch mode. After filtration of the ion exchanger and evaporation of the solvent the residue was washed twice with MeOH and recrystallized from H_2O–MeOH (1 : 20) with addition of a few drops of conc. HCl. ^{1}H NMR (D_2O): δ 2.12, 1.92 (2 quint, 4H, 2 C–CH_2–C), 3.7–2.7 (m, 33H, 15 N–CH_2– + MeOH). ^{13}C NMR 173.9, 173.70 (N–C=O), 49.34 (MeOH), 34.01–55.91 (N–CH_2–, 15 signals); 22.64, 22.04 (C–*C*H_2–C); IR (KBr)/cm^{-1}: 1685 (–CONH), 3002, 3064, 3142 (NH^+); Anal. Calc. for $C_{18}H_{49}N_8OCl_7$·1.5H_2O·MeOH (700.881): C, 32.56; H, 8.05; N, 15.99%. Found: C, 32.52; H, 7.89; N, 16.30%.

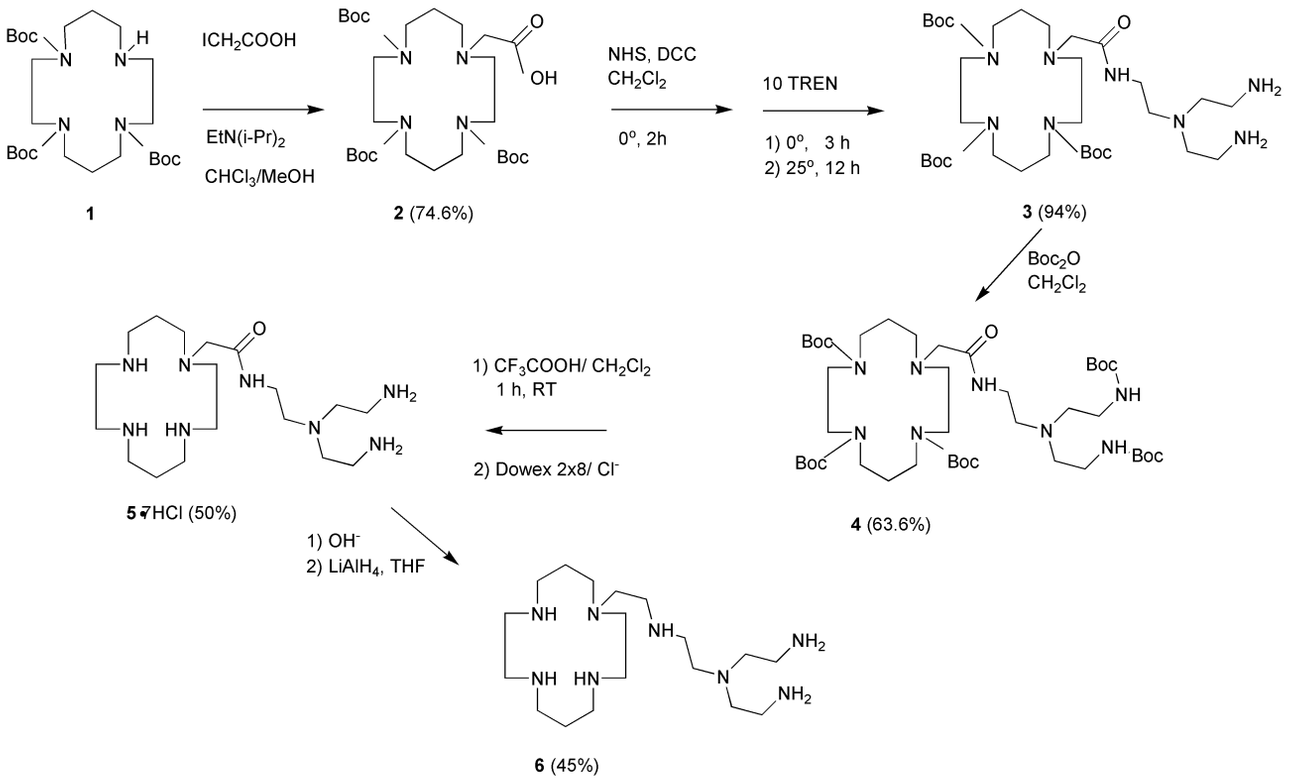
Compound 6. Compound **5** (260 mg, 0.67 mmol) as free base (obtained through exchange of chloride ions by hydroxide with a Dowex ion exchanger) was suspended in dry THF (20 ml) and treated under Ar atmosphere with $LiAlH_4$ (15 ml, 1 M in THF) then heated to reflux for 16 h. After cooling to r.t. the excess of $LiAlH_4$ was destroyed by careful addition of water until no H_2 evolution was observed. The precipitate was stirred for 1 h, then filtered off and washed with H_2O. The filtrate was rotatory evaporated. The residue was taken up in MeOH–CH_2Cl_2, filtered again and rotatory evaporated. Finally the residue was taken up in MeOH and the hydrochloride was precipitated by addition of 36% HCl (0.6 ml), then filtered and dried. For further purification an aqueous solution of the hydrochloride was chromatographed on Sephadex G15 (Pharmacia). The eluate was evaporated, the residue taken up in MeOH and the hydrochloride was crystallized at −18 °C. Yield: 230 mg (45%). ^{1}H NMR (D_2O); δ 2.12, 1.92 (2 quint, 4H, 2 C–CH_2–C), 3.25 (s, 6H, MeOH), (3.55–2.55 (m, 32H, 16 N–CH_2–). Anal. Calc. for $C_{18}H_{52}N_8Cl_8$·2H_2O·2MeOH (764.41): C, 31.43; H, 8.44; N, 14.66; O, 8.37%. Found: C 31.88; H 7.89; N 14.99; O 8.41%.

1,4,8-Tritosyl-11-[2-(methyltosylamino)ethyl]-1,4,8,11-tetraazacylotetradecane (8). To a solution of **7** (3.5 g, 5.3 mmol) and *N*,*O*-ditosyl-*N*-methylethanolamine (2.36 g, 6.9 mmol) in $CHCl_3$–MeOH (17.5 ml, 3 : 1), *N*-ethyldiisopropylamine (3.5 ml, 20.5 mmol) was added and the reaction mixture was heated to reflux for 7 days. After evaporation of the solvent the crude product was taken up in $CHCl_3$ and flash-chromatographed on silica with $CHCl_3$–ethyl acetate (first 20 : 1, then 10 : 1). The fractions containing the product (R_f = 0.5 in $CHCl_3$–ethyl acetate = 5 : 1) were rotatory evaporated and the product dried *in vacuo* at 50 °C. Yield 2.44 g (52.9%). ^{1}H NMR ($CDCl_3$): δ 1.76, 1.93 (2 quintets, 4H, 2 C–CH_2–C), 2.42, 2.43 (2 s, 12H, aryl–CH_3), 2.54–2.67 (m, 6H, CH_2–N), 2.71 (s, 3H, CH_3N), 2.98–3.31 (m, 14H, TsN–CH_2–), 7.27–7.38 (m, 8H, Ar-H), 7.62–7.72 (m, 8H, Ar-H). ^{13}C NMR ($CDCl_3$): δ 21.5 (aryl–*C*H_3), 27.0, 27.9 (C*C*H_2C), 35.7 (N*C*H_3), 47.7–54.1 (10 signals, NCH_2), 127.28, 127.37, 127.40 (SO_2C*C*H), 129.82, 129.85 (CH_3C*C*H), 134.1, 135.0, 135.1, 135.2 ((CH_3*C*), 143.47, 143.55, 143.60 (SO_2C). FAB-MS (nitrobenzyl alcohol): *m*/*z* 874 ([M + H])$^+$, 718 ([M − Ts])$^+$, 689 ([M − NMeTs])$^+$, 675 ([M − CH_2N-MeTs])$^+$, 562 ([M − H − 2Ts])$^+$, 520 ([M − CH_2NMeTs − Ts])$^+$, 408 ([M − 3Ts])$^+$, 379 ([M − NMeTs − Ts])$^+$, 365 ([M − CH_2NMeTs − 2Ts])$^+$, 253 ([M − 4Ts])$^+$, 212 ([CH_2CH_2NMeTs])$^+$, 210 ([M − CH_2NMeTs − 3Ts])$^+$, 91 ([C_7H_7])$^+$. IR (KBr): 1598 cm^{-1} (w, aromatic ring), 1340, 1159 (s, SO_2).

1-[2-(Methylamino)ethyl]-1,4,8,11-tetraazacyclotetradecane (9). A mixture of **8** (2.38 g, 2.7 mmol) in anisole (10.7 ml) and trifluoromethane sulfonic acid (20.1 ml) was heated to 70 °C for 19 h under N_2. After cooling to 0 °C diethyl ether was added in portions until no further precipitation took place. The solid was filtered off, washed with ether and run through a Dowex (2 × 8) column in the OH^--form. The fractions containing the product (which can be identified by reaction with $CuCl_2$) were collected and rotatory evaporated. Yield 0.53 g (70.0%). For further purification the product was recrystallized from acetonitrile. Mp. 81–82 °C. ^{1}H NMR ($CDCl_3$): δ 1.61–1.84 (m, 4H, CCH_2C), 2.33–2.89 (m, 23H, NCH_2, NCH_3 (2.43, s)). ^{13}C NMR ($CDCl_3$): δ 26.1, 28.1 (C*C*H_2C), 36.5 (NCH_3), 47.5–54.8 (NCH_2). Anal. Calc. for $C_{13}H_{31}N_5$·0.17H_2O: C, 59.94; H, 12.13; N, 26.89. Found: C, 60.06; H, 11.92; N, 26.82%.

Cu^{2+} Complexes of 5. To a solution of **5** ditriflate (370 mg, 0.7 mmol) and $Cu(ClO_4)_2$·6H_2O (740 mg, 1.75 mmol) in H_2O (5 ml), NaOH was added to reach pH = 6. After 2 h the pH was increased to 8 and the precipitated $Cu(OH)_2$ was filtered off. The reaction mixture was concentrated and put on a Sephadex G15 (Pharmacia) column (3 × 50 cm), from which two distinctly separated bands were obtained. The first fraction was the 1 : 1 complex (110 mg, yield 20.3%) as indicated by the absorption spectrum and the FAB-MS. The second fraction still contained some free Cu^{2+} and thus was re-chromatographed. The last part of the band was collected, made alkaline, filtered and then brought to pH = 6. After addition of $NaClO_4$ (2 ml) the solution was evaporated and the solid was extracted with nitromethane (3 × 10 ml) to give the 2 : 1 complex (130 mg, yield 20.6%). MS (FAB) of $CuL(CF_3COO)_2$: *m*/*z* 562 ($M^+ - CF_3COO^-$); 448 ($M^+ - 2CF_3COO^-$); 387 ($M^+ - 2CF_3COO^- - Cu^{2+}$). MS (FAB) of $Cu_2L(ClO_4)_4$: *m*/*z* 909 (M^+), 711 ($M^+ - 2ClO_4^-$), 612 ($M^+ - 3ClO_4^-$), 513 ($M^+ - 4ClO_4^-$).

Cu^{2+} Complex of 6. A solution of **6** (225 mg, 0.29 mmol) and $CuSO_4$·5H_2O (130 mg, 0.52 mmol) in H_2O (20 ml) was treated with NaOH (2.6 ml, 0.5 M) and left at r.t. for 2 h. After concentration the mixture was chromatographed (4 × 50 cm) on



Scheme 1

Sephadex G15 (Pharmacia). The first fraction was collected, treated with H_2S until no CuS further precipitation occurred. The excess of H_2S was eliminated by bubbling N_2 through the solution. The pH was then brought to 0.3 and the solution was filtered from CuS. The Cl^- ions were exchanged by OH^- on a Dowex (2 × 8) column. Thereafter the pH was adjusted to 2.3 with HNO_3 and the solution used in this form. ESI/MS (0.3 ml complex solution + 10 ml MeOH): *m/z* 684 (M^+; $CuL{\cdot}4HNO_3$) 100%, 621 (M^+; $CuL{\cdot}3HNO_3$) 25%, 588 (M^+; $CuL{\cdot}2HNO_3$) 12%.

Measurements

Potentiometric titrations were carried out with our fully automated setup connected online with a 286-PC and consists of a burette (Metrohm 655), a pH-meter (Metrohm 605) and the program TITFIT as described previously.[16] Experimental conditions: [ML] = 0.8–1.5 × 10^{-3} M, 25 °C, I = 0.5 M (KNO_3), pH range 3 to 11, 70–100 points per titration curve, 2–4 replicates, log K_w =13.86, combined glass electrode (Metrohm), calibrated with buffer (pH 4.00 and 7.00). The calculations were done with the program TITFIT[17] and the constants are mixed activity (a_H) concentration constants.

Spectrophotometric titrations were carried out with an ATI Unicam UV4 instrument, with the program SPECTRATE,[18] using 1 cm quartz cuvettes. Experimental conditions: 25 °C and I = 0.5 M (KNO_3). Buffers were 0.02 M 2,6-lutidine-3-sulfonic-acid, 0.02 M CES, 0.02 M MES, 0.02 M *N*-methylmorpholine, [NaOH] = 0.4 M, added in aliquots of 0.003–0.01 ml, waiting time after each addition 60 s. Typical concentrations: [ML] = 0.8–4 × 10^{-3} M, pH range 3 to 11, 40–50 spectra per titration, 2–4 replicates, combined glass electrode (Metrohm), calibrated with buffer (pH 4.00 and 7.00). The calculations were done with the program SPECFIT[19] and the resulting constants are mixed activity (a_H) concentration constants.

Complex formation kinetics were carried out at 25.0 ± 0.1 °C using a KinTec Minimixer stopped-flow instrument with a 2 cm cell, connected to a J&M Tidas MMS16 VIS500/1 photodiode array with a range 300–1000 nm. The spectra were recorded with the program Kinspec235.[20] Typical concentrations were: [L] = 1.0 × 10^{-3} M, [Cu^{2+}] = 1.0 or 2.0 × 10^{-3} M, c_{buffer} = 0.04 M 2,6-lutidine-3-sulfonic acid, ionic strength I = 0.5 M (KNO_3), pH 4.17, 4.56, 4.96. The rate constants of the single experiments were calculated with the program SPECFIT.[19] The *k*-values reported are means of three experiments.

Results and discussion

The syntheses of the ditopic ligands **5** and **6** (Scheme 1) starts with the trifold Boc-protected tetraazamacrocycle **1**, which is selectively alkylated with iodoacetic acid to give **2**. The carboxylic group, activated through formation of the *N*-hydroxysuccinimide ester, is then reacted with one amino group of tren, present in large excess to favour monoacylation. Since it was difficult to purify compound **3**, we decided to introduce two additional Boc groups on the tren moiety to give **4**, which could then be flash-chromatographed because of the lower polarity.

One-pot experiments in which compound **4** was first reduced with $BH_3{\cdot}S(CH_3)_2$ and then treated with hydrochloric acid, showed that N-methyl derivatives were present in the product as impurities and that they could not be separated from the desired compound. So a two step sequence was used. First the Boc groups were cleaved off with trifluoroacetic acid to give **5** and then the amide function was reduced with $LiAlH_4$ to produce **6**. Thus with this sequence it was possible to obtain two interesting new ligands at once. In addition, for comparison purposes, we prepared also compound **9**, which contains the macrocyclic moiety with the beginning of the side chain of tren.

Spectral properties

The spectra of the mononuclear complexes of ligands **5**, **6** and **9** with Cu^{2+} or Ni^{2+}, as well as those of the homo- and heterodinuclear complexes of **5** and **6** with Cu^{2+} and Ni^{2+} are given in Table 1.

The qualitative results are:

(1) At low pH the mononuclear Cu^{2+} and Ni^{2+} complexes of **6** and **9** show the typical absorption spectra of square planar species,[21] in which the metal ion is bound by the four nitrogens of the macrocycle. In contrast the spectra of the complexes with

Table 1 Absorption maxima (nm) and molar absorptivities (M^{-1} cm^{-1}) of the mono- and dinuclear complexes of **5**, **6** and **9**

Metal ion	pH	**5**	**6**	**9**
Cu^{2+}	2	558 (122)	524 (187)	530 (151)
	5	562 (134)	582 (129)	621 (142)
Ni^{2+}	2	400 (sh), 525 (10), 800 (sh)	456 (25), 350 (sh)	463 (29)
	7	356 (60), 524 (16), ~900 (sh)	359 (sh), 528 (19)	345 (20), 525 (12)
Cu^{2+}/Cu^{2+}	8	595 (163)	833 (162)	
Ni^{2+}/Ni^{2+}	8	400 (sh), 540 (18), 850 (14)	330 (sh), 462 (55), 510 (28)	
Ni^{2+}/Cu^{2+}	8	660 (64), 800 (sh)	469 (65), 660 (120), 830 (sh)	
Cu^{2+}/Ni^{2+}	8	572 (160)	548 (152)	

5 are distinctly different. In the case of Ni^{2+} a pseudo-octahedral geometry seems to be present,[21] in the case of Cu^{2+} the value of λ_{max} = 558 nm indicates axial coordination in addition to the N_4-donor set.

(2) At higher pH the mononuclear complexes of **6** and **9** show a drastic change in their spectral properties, whereas those of **5** remain nearly constant.

(3) Addition of a second metal ion to the mononuclear species of **5** and **6** changes the spectral pattern, thus indicating that the second metal ion is coordinated by the tren moiety.

(4) For the heterodinuclear complexes with Cu^{2+} and Ni^{2+} the spectra differ upon the sequence of metal ion addition. In the case of **5**, if Cu^{2+} is added first it binds to the macrocyclic unit, as indicated by a band at 572 nm, whereas Ni^{2+} as the second metal ion must coordinate at the tren unit giving bands of low intensity. If, however, Ni^{2+} is the first metal ion added, it binds to the macrocycle with a band of low intensity and the Cu^{2+} ion, coordinated to the tren moiety, shows a spectrum with λ_{max} = 660 nm and a shoulder at ~800 nm. In the case of **6** we have a similar situation. If Cu^{2+} is added first it absorbs at 548 nm, which is typical for the Cu^{2+}–macrocyclic chromophore, whereas if Ni^{2+} is first added the Cu^{2+} must bind to the tren unit with λ_{max} = 660 nm with a shoulder at ~830 and 469 nm for the band of Ni^{2+} in the macrocycle. These findings confirm the results of Fabbrizzi *et al.*,[13] who also observed that with their xylyl bridged ligand the first metal ion added goes to the macrocyclic ring.

To better understand the properties and complexation potential of the new ligands **5** and **6** quantitative studies using potentiometric and spectrophotometric titrations have been performed whereby the results of the complexes with **9** were used for comparison.

Cu^{2+} and Ni^{2+} complexes of 9. The potentiometric and spectrophotometric studies of the Cu^{2+} and Ni^{2+} complexes with **9** revealed that different protonated species are present in aqueous solution and that in some instances drastic spectral changes are coupled with the protonation/deprotonation steps.

The potentiometric titration of the Cu^{2+} complex shows a first buffer region at about 4.5 corresponding to one H^+ per complex, followed by a second around pH 6, which, however, involves only 0.5 protons per complex. The titration curves were thus fitted with a model based on eqns. (1) and (2) and gave the constants collected in Table 2.

$$[MLH]^{3+} \rightleftharpoons [ML]^{2+} + H^+ : K_1 \quad (1)$$

$$2[MLH]^{2+} \rightleftharpoons [(ML)_2H_{-1}]^{3+} + H^+ : K_2 \quad (2)$$

The same equilibria were also used to fit the spectrophotometric titrations of the Cu^{2+} system (Fig. 1) and the constants shown in Table 2 are very close to the potentiometric values.

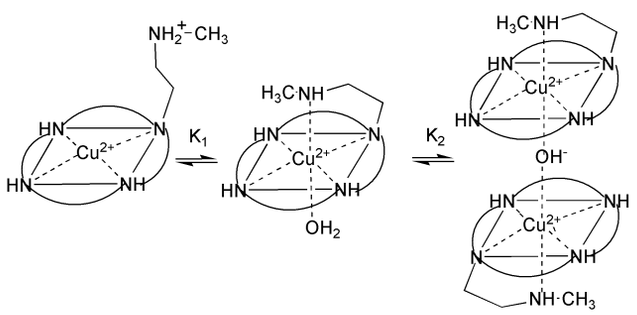
In the case of the spectrophotometric titrations of the Ni^{2+} complex only the first deprotonation was observed. Thus the measurements were fitted using eqn. (1) and the $\log K_1$ value is given in Table 2.

The results can be understood using Scheme 2. At low pH the metal ion is coordinated by the macrocycle in a square planar geometry and the amino group of the side chain is protonated.

Table 2 Potentiometrically and spectrophotometrically determined $\log K$, values and spectral properties of the Cu^{2+} and Ni^{2+} complexes with **9** at 25 °C and I = 0.5 M (KNO_3)

		Cu^{2+}, pot.	Cu^{2+}, spec.	Ni^{2+}, spec.
$[MLH]^{3+}$		[b]	[b]	[b]
	$\lambda_{max}/\varepsilon$ [a]		530/150	462/28
$[ML]^{2+}$	$\log K_1$	4.54(2)	4.50(2)	4.68(1)
	$\lambda_{max}/\varepsilon$ [a]		623/140	344/20, 532/12
$[(ML)_2H_{-1}]^{3+}$	$\log K_2$	−3.5(1)	−3.7(1)	
	$\lambda_{max}/\varepsilon$ [a]		615/ 320	

[a] λ_{max} in nm and ε in M^{-1} cm^{-1}. [b] Fully formed.



Scheme 2

Increasing the pH the ammonium group deprotonates and the amino group acts as an additional donor to bind in the axial position of the metal ion. For Cu^{2+} this is accompanied by a shift of the absorption maximum from 530 to 623 nm, whereas for Ni^{2+} the spectrum changes from one typical for square planar geometry (λ_{max} = 462 nm) to one corresponding to a pseudo-octahedral chromophore (λ_{max} = 344 and 532 nm). The reaction is similar to that proposed by Fabbrizzi and coworkers[22] for the analogous compound with an aminoethyl side chain. The second equilibrium, although observed by these authors, but not explained on a molecular basis, consists in a hydrolysis step with concomitant dimerisation to give a μ-hydroxo bridged species (see Scheme 2). The small change in the absorption spectrum of the Cu^{2+} complex indicates that the geometry remains nearly constant.

Cu^{2+} Complexes of 5. Ligand **5** was obtained on the way in the synthesis of **6**. Because of its amide group, **5** is less stable than **6**, especially in alkaline solution. Thus the complexation study of the mononuclear species could be run only to about pH 8.

The spectrophotometric titrations of the 1 : 1 metal to ligand ratio reveal two protonated mononuclear species (eqns. (3) and (4)) with $\log K$ values of 3.96 and 6.69 (Table 3), which are due to successive deprotonations of the ammonium groups of the side chain. In fact the spectral changes from $[MLH_2]^{4+}$ to $[MLH]^{3+}$ and $[ML]^{2+}$ are relatively small, the λ_{max} being 555 (127), 567 (149) and 568 nm (153 M^{-1} cm^{-1}), respectively, and indicate that the chromophore is not changed.

$$[MLH_2]^{4+} \rightleftharpoons [MLH]^{3+} + H^+ : K_3 \quad (3)$$

$$[MLH]^{3+} \rightleftharpoons [ML]^{2+} + H^+ : K_4 \quad (4)$$

Table 3 Spectrophotometrically determined log K, values and spectral properties of the Cu^{2+} complexes with **5** at 25 °C and $I = 0.5$ M (KNO_3)

Species	i	log K_i	λ_{max} [a]	ε [a]
$[MLH_2]^{4+}$		[b]	555	127
$[MLH]^{3+}$	3	3.96(1)	567	149
$[ML]^{2+}$	4	6.69(4)	568	153
$[M_2L]^{4+}$	5	−5.05(4)	590	242
$[M_2LH_{-1}]^{3+}$	6	9.05(4)	597	228
$[M_2LH_{-2}]^{2+}$	7	10.59(5)	659	228

[a] λ_{max} in nm and ε in M^{-1} cm^{-1}. [b] Fully formed.

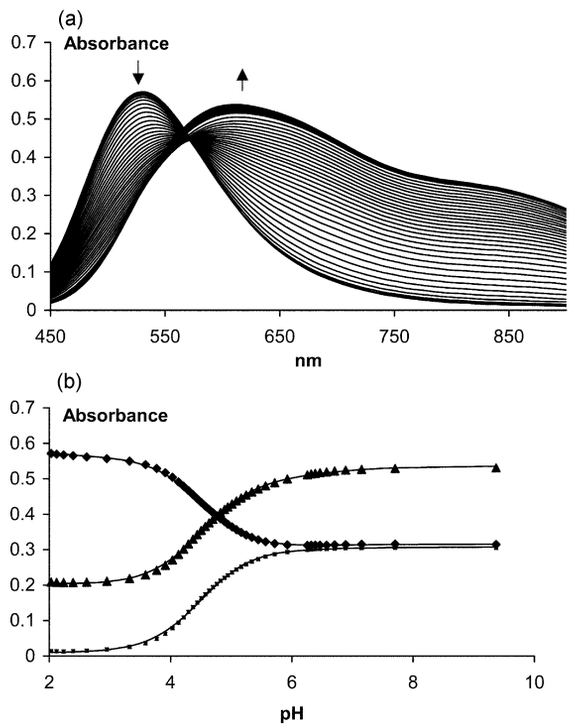


Fig. 1 (a) Spectrophotometric titration of Cu(**9**). [Cu(**9**)] = 3.82×10^{-3} M, titrated with increments of 0.008 ml of NaOH (0.4 M) up to a total volume of 0.264 ml and 0.001 ml up to 0.009 ml, respectively. (b) Fit of the data at different wavelengths: (■) experimental, (—) calculated curve at 860 nm; (▲) experimental, (—) calculated curve at 630 nm; (◆) experimental, (—) calculated curve at 530 nm.

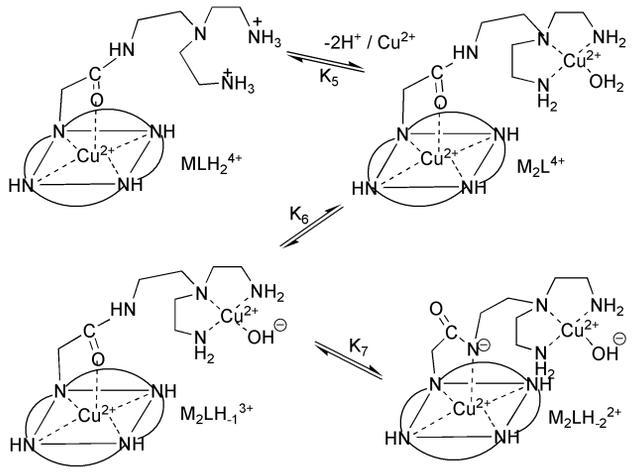
$$[MLH_2]^{4+} + M^{2+} \rightleftharpoons [M_2L]^{4+} + 2H^+ : K_5 \qquad (5)$$

$$[M_2L]^{4+} \rightleftharpoons [M_2LH_{-1}]^{3+} + H^+ : K_6 \qquad (6)$$

$$[M_2LH_{-1}]^{3+} \rightleftharpoons [M_2LH_{-2}]^{2+} + H^+ : K_7 \qquad (7)$$

It is, however, interesting to note that λ_{max} of $[MLH_2]^{4+}$ is 555 nm, which is distinctly different from the values of $[MLH]^{3+}$ with **9** (530 nm) and $[MLH_3]^{5+}$ with **6** (536 nm), in which the metal ion is coordinated by the four nitrogens of the macrocycle. We therefore suggest that in $[MLH_2]^{4+}$ and also in $[MLH]^{3+}$ and $[ML]^{2+}$ with ligand **5** the carbonyl oxygen of the amide group is involved in coordination as shown in Scheme 3, to give a pentacoordinated Cu^{2+} complex. Similar observations on O-coordination of the amide group have been made previously in a macrocyclic complex carrying an amide side chain.[23]

The 2 : 1 mixture of Cu^{2+} and ligand **5** is more stable than the 1 : 1 mixture so the complexation study could be extended to higher pH values (Fig. 2). A series of complexes $[M_2LH_n]^{(4+n)+}$ (n = 0, −1, −2) (eqns. (5)–(7)) were observed with a minor change in λ_{max} on going from $[M_2L]^{4+}$ (590 nm) to $[M_2LH_{-1}]^{3+}$ (597 nm), but a major shift on going from $[M_2LH_{-1}]^{3+}$ (597 nm)



Scheme 3

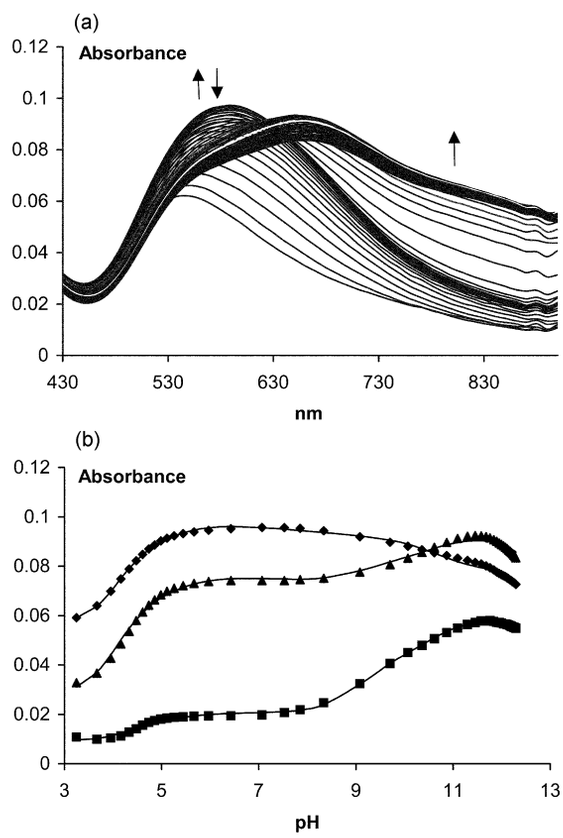


Fig. 2 (a) Spectrophotometric titration of Cu_2(**5**). [Cu_2(**5**)] = 7.87×10^{-4} M, titrated with increments of 0.01 ml of NaOH (0.4 M) up to a total volume of 0.45 ml. (b) Fit of the data at different wavelengths: (■) experimental, (—), calculated curve at 870 nm; (▲) experimental, (—) calculated curve at 670 nm; (◆) experimental, (—) calculated curve at 570 nm.

to $[M_2LH_{-2}]^{2+}$ (659 nm). This latter spectral change is an indication that at pH >10.5 the amide group deprotonates and coordinates to one of the Cu^{2+} ions. The formation of the dinuclear complex (log K_5) can be compared to the complexation of $dienH_2^{2+}$ with Cu^{2+}, for which we can calculate a log K value of −4.18.[24] The deprotonation of $[M_2L]^{4+}$ to $[M_2LH_{-1}]^{3+}$ with log K_6 = 9.05 is also comparable with the hydrolysis of $Cu(dien)^{2+}$ (log K = 9.39).[24] So the sequence $[M_2L]^{4+}$, $[M_2LH_{-1}]^{3+}$ and $[M_2LH_{-2}]^{2+}$ can be described on a molecular basis by Scheme 3.

Cu^{2+} Complexes of 6. The ditopic ligand **6** can bind up to two equivalents of Cu^{2+} to give a series of mononuclear species $[MLH_n]$ (n = 3, 2), which can dimerize to $[(ML)_2H_m]$ (m = 3, 2, 1,

Table 4 Potentiometrically and spectrophotometrically determined log K, values and spectral properties of the Cu^{2+} complexes with **6** at 25 °C and $I = 0.5$ M (KNO_3)

Species	i	log K_i, pot.	log K_i, spec.	λ_{max} (ε) [a]
$[MLH_3]^{5+}$		[b]	[b]	536 (132)
$[MLH_2]^{4+}$	8	4.74(2)	4.79(2)	586 (130)
$[M_2L_2H_3]^{7+}$	9	−4.22(5)	−3.7(2) [d]	583 (287)
$[M_2L_2H_2]^{6+}$	10	8.80(2)	[c]	
$[M_2L_2H]^{5+}$	11	9.55(2)	[c]	
$[M_2L_2]^{4+}$	12	10.15(3)	[c]	
$[M_2L_2H_{-1}]^{3+}$	13	11.60(7)	[c]	
$[M_2LH]^{5+}$	14	4.27(1)	[c]	
$[M_2L]^{4+}$	5	−4.48(2)	−4.47(2)	831 (172), 680 (sh), 530 (143)
$[M_2LH_{-1}]^{3+}$	6	9.02(2)	9.07(2)	820 (179), 670 (172), 535 (143)
$[M_2LH_{-2}]^{2+}$	7	11.25(5)	[c]	

[a] λ_{max} in nm and ε in M^{-1} cm^{-1}. [b] Fully formed. [c] Could not be determined spectrophotometrically. [d] Rough estimate, since it takes into account also the following step, which could not be determined spectrophotometrically.

0, −1), and a series of dinuclear complexes $[M_2LH_p]$ (p = 1, 0, −1, −2). The complexation was studied by potentiometric and spectrophotometric titrations, each method allowing to determine the existence and stability of this or that species. The final picture of the complexation obtained by the two methods is consistent and described by equilibria (eqns. (8)–(13)) for the 1 : 1 species and by eqns. (14)–(17) for the dinuclear complexes.

$$[MLH_3]^{5+} \rightleftharpoons [MLH_2]^{4+} + H^+ : K_8 \quad (8)$$

$$2[MLH_2]^{4+} \rightleftharpoons [(ML)_2H_3]^{7+} + H^+ : K_9 \quad (9)$$

$$[(ML)_2H_3]^{7+} \rightleftharpoons [(ML)_2H_2]^{6+} + H^+ : K_{10} \quad (10)$$

$$[(ML)_2H_2]^{6+} \rightleftharpoons [(ML)_2H]^{5+} + H^+ : K_{11} \quad (11)$$

$$[(ML)_2H]^{5+} \rightleftharpoons [(ML)_2]^{4+} + H^+ : K_{12} \quad (12)$$

$$[(ML)_2]^{4+} \rightleftharpoons [(ML)_2H_{-1}]^{3+} + H^+ : K_{13} \quad (13)$$

$$[MLH_2]^{4+} + M^{2+} \rightleftharpoons [M_2L]^{4+} + 2H^+ : K_5 \quad (14)$$

$$[M_2LH]^{5+} \rightleftharpoons [M_2L]^{4+} + H^+ : K_{14} \quad (15)$$

$$[M_2L]^{4+} \rightleftharpoons [M_2LH_{-1}]^{3+} + H^+ : K_6 \quad (16)$$

$$[M_2LH_{-1}]^{3+} \rightleftharpoons [M_2LH_{-2}]^{2+} + H^+ : K_7 \quad (17)$$

Whereas potentiometry allows to determine all of the 1 : 1 species, spectrophotometric titrations only can detect the species $[MLH_3]^{5+}$, $[MLH_2]^{4+}$ and $[(ML)_2H_3]^{7+}$, the remaining dimeric protonated species having electronic spectra very similar to each other (Table 4).

The change in the spectrum on going from $[MLH_3]^{5+}$ to $[MLH_2]^{4+}$ and the value of log K_8 are similar to the results found for ligand **9** (Table 2) and indicate that here too the amino group of the side chain can bind in an axial position of the metal ion. In this case there are still two protons bound by the other amino groups of the tren moiety. The somewhat smaller shift of the absorption maximum for ligand **6** compared to ligand **9** is probably due to steric reasons. The absorption of the 1 : 1 mixture remains nearly constant at 580 nm for $[(ML)_2H_2]^{6+}$, $[(ML)_2H]^{5+}$ and $[(ML)_2]^{4+}$, since deprotonations occur from the ammonium groups of the side chain (Scheme 2). The small changes due to these deprotonations are the main reason that the log K values cannot be determined by spectrophotometry. It is interesting to note that the Cu^{2+} complex of ligand **6** behaves in its first deprotonations similarly to the complex of ligand **9**. In both cases the side chain amino group coordinates around pH 4.7 and this pseudo-octahedral complex dimerizes through a μ-hydroxo bridge.

The 2 : 1 species obtained when the ligand is titrated in the presence of two equivalents of Cu^{2+} have the following stoichiometries $[M_2LH]^{5+}$, $[M_2L]^{4+}$, $[M_2LH_{-1}]^{3+}$ and $[M_2LH_{-2}]^{2+}$, indicating that both metal ions can hydrolyze to give a monohydroxo species $[M_2LH_{-1}]^{3+}$, in which the OH^- is bound by the Cu^{2+} in the tren unit and at higher pH a dihydroxo complex $[M_2LH_{-2}]^{2+}$, with a second OH^- bound by the Cu^{2+} in the macrocycle (Scheme 4). This can be infered if one compares the two deprotonation steps with the value of the hydrolysis of $[Cu(tren)]^{2+}$, which is 9.01[25] or 9.17[26] according to the literature.

The binding of the two Cu^{2+} is very different. Whereas the first Cu^{2+} binds to the macrocycle at very low pH and does not dissociate when acid is added to it, the second Cu^{2+} is coordinated around pH 4–5 and is labile against acid. The stability of the second Cu^{2+}, defined by eqn. (14), and can be compared to the complexation of the diprotonated form of tren with Cu^{2+} (eqn. (18)), for which log $K = -1.14$.[26]

$$[trenH_2]^{2+} + Cu^{2+} \rightleftharpoons [Cu(tren)]^{2+} + 2H^+ \quad (18)$$

The lower stability for binding of the second Cu^{2+} by ligand **6** compared to tren is certainly due to the fact that one amino group of the tren is involved in the axial coordination of the first Cu^{2+} and therefore not directly available for the second Cu^{2+} ion.

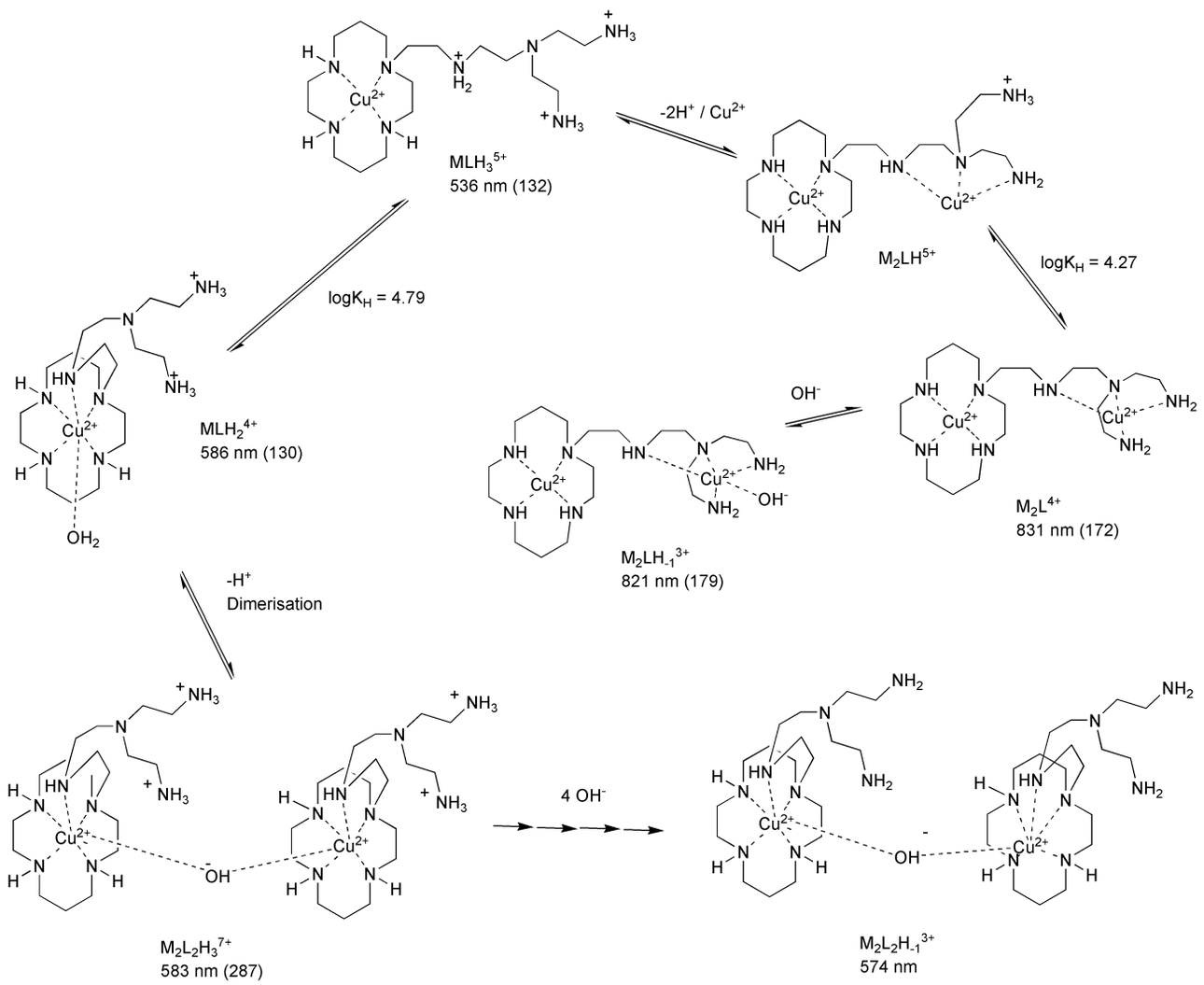
The formation of $[M_2LH]^{5+}$ also reflects the properties of $[Cu(tren)]^{2+}$, which in fact can be protonated to $[Cu(trenH)]^{3+}$ with log $K = 4.06$,[27] a value which nicely compares to log K_{14} = 4.27.

Not only the potentiometric study but also the spectral properties of the system clearly indicate that the second Cu^{2+} is bound by the tren unit (Fig. 3). So the long wavelength bands in the spectrum of $[M_2L]^{4+}$ are practically the same as those in $[Cu(tren)]^{2+}$,[28] whereas the band at 520 nm corresponding to the Cu^{2+} in the cyclam ring remains intact. Only minor changes are observed, when the hydrolysed species $[M_2LH_{-1}]^{3+}$ is formed.

Heterodinuclear $Cu^{2+}Ni^{2+}$ complexes with 6

In order to illustrate the ability of ligand **6** to bind selectively two metal ions we have titrated the complex in which Ni^{2+} is bound to the macrocycle in the presence of one equivalent of Cu^{2+}, as well as that, in which Cu^{2+} is coordinated by the macrocycle in the presence of one equivalent of Ni^{2+}.

In the first case the spectrophotometric titration very clearly shows that at pH below 4 the Ni(cyclam) unit is already present and that by increasing the pH above 4 the Cu^{2+} then reacts giving a species with a spectrum very similar to the sum of that of $[Ni(cyclam)]^{2+}$ and of $[Cu(tren)]^{2+}$ (Fig. 4). The quantitative fitting of the potentiometric pH-titrations gives a series of protonated and hydroxylated species with the stoichiometry



Scheme 4

Table 5 Potentiometrically determined log K, values and spectral properties for the isomeric dinuclear Cu^{2+}/Ni^{2+} complexes with **6** at 25 °C and $I = 0.5$ M (KNO_3)

Species[a]	i	log K_i, pot.	λ_{max} (ε) [b]
$[CuLH_3]^{5+}$		[c]	526 (148)
$[NiLH_3]^{5+}$		[c]	469 (53)
$[CuLH_2]^{4+}$	8	4.80(2)	550 (135)
$[NiCuLH]^{5+}$	14	−4.30(2)	660 (97), 470 (53)
$[CuNiL]^{4+}$	5	−8.53(5)	550 (150), 790 (sh)
$[NiCuL]^{4+}$	5	-4.51(3)	832 (127), 680 (sh), 470 (65)
$[CuNiLH_{-1}]^{3+}$	6	9.76(2)	550 (153), 810 (sh)
$[NiCuLH_{-1}]^{3+}$	6	8.77(2)	817 (126), 670 (123), 470 (65)
$[NiCuLH_{-2}]^{5+}$	7	11.66(3)	817 (128), 670 (126), 480 (51)
$[(CuNiL)_2H_{-1}]^{7+}$	15	−5.00(3)	550 (291), 800 (sh)
$[(NiCuL)_2H_{-1}]^{7+}$	15	−6.03(3)	818 (201), 620 (sh), 470 (136)

[a] $[MM'LH_n]$: M in the macrocycle and M′ in the tren unit. [b] λ_{max} in nm and ε in M^{-1} cm^{-1}. [c] Fully formed.

$[NiCuLH_n]^{(4+n)+}$ (n = 1, 0, −1, −2) (Table 5). The log K_H = 3.86 for $[NiCuLH]^{5+}$ (Table 5) is very close to that of $[Cu_2LH]^{5+}$ and $[Cu(trenH)]^{3+}$ (see above) indicating that in this complex it is the Cu^{2+} in the tren unit which gives a protonated species. After formation of the 2 : 1 complex hydrolysis takes place at higher pH. The three systems $[Cu_2L]^{4+}$, $[CuNiL]^{4+}$ and $[NiCuL]^{4+}$ (see below) all give the species $[M_2LH_{-1}]^{3+}$ and sometimes $[M_2LH_{-2}]^{2+}$. The first OH^--addition corresponds to the hydroxylation of the metal bound by the tren unit. In fact $[Cu_2L]^{4+}$ and $[NiCuL]^{4+}$ have very similar log K_H values (Table 4 and 5), which in addition are very close to the value reported in the literature for $[Cu(tren)]^{2+}$ (log K_H = 9.01 [25] or 9.17 [26]). In the case of $[CuNiL]^{4+}$ the log K_H value for the hydrolysis is distinctly higher, which is expected if Ni^{2+} is bound by the tren unit and comparable to the literature value log K_H = 9.8 [26] for $[Ni(tren)]^{2+}$. It is more difficult to propose a structure for $[M_2LH_{-2}]^{2+}$, since the second OH^- group can either coordinate to the metal ion in the macrocycle or again to that in the tren unit.

Of interest is the $[M_4L_2H_{-1}]^{7+}$, which is found in these systems (eqn. (19)). It must be a species with a λ-hydroxo bridge between the two dinuclear complexes and we propose that this takes place between the metal ions bound by the tren unit.

$$2[M_2L]^{4+} \rightleftharpoons [M_4L_2H_{-1}]^{7+} + H^+ : K_{15} \qquad (19)$$

In the second case with Cu^{2+} in the macrocycle and one additional equivalent of Ni^{2+} the evolution of the spectra as a function of pH is completely different (Fig. 5). At the beginning we have the typical absorption of the $[Cu(cyclam)]^{2+}$ chromophore with λ_{max} = 524 nm. At pH ~ 4 there is a shift to λ_{max} = 550 nm, which indicates that the nitrogen of the side chain is axially binding to the Cu^{2+} (see above with **9**). Then when Ni^{2+} starts to bind (pH ~7) there are small changes at about 360 nm and 570 nm, which are expected for an octahedral Ni^{2+} chromophore.

Kinetics of the Cu^{2+} binding

Equilibrium studies described above clearly show that the first metal ion added to ligand **6** always binds to the macrocyclic unit, which gives the thermodynamically most stable complex.

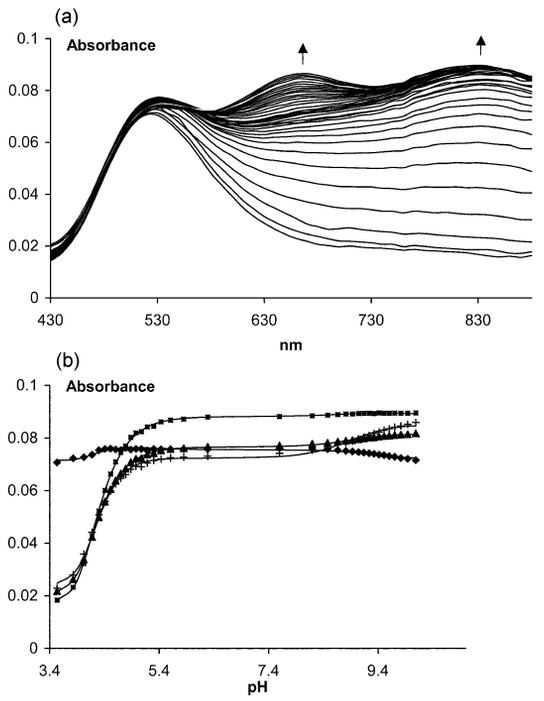


Fig. 3 (a) Spectrophotometric titration of Cu_2(**6**). [Cu_2(**6**)] = 5×10^{-4} M, titrated with increments of 0.007 ml of NaOH (0.4 M) up to a total volume of 0.28 ml. (b) Fit of the data at different wavelengths: (■) experimental, (—) calculated curve at 830 nm; (▲) experimental, (—) calculated curve at 730 nm; (+) experimental, (—) calculated curve at 680 nm, (◆) experimental, (—) calculated curve at 520 nm.

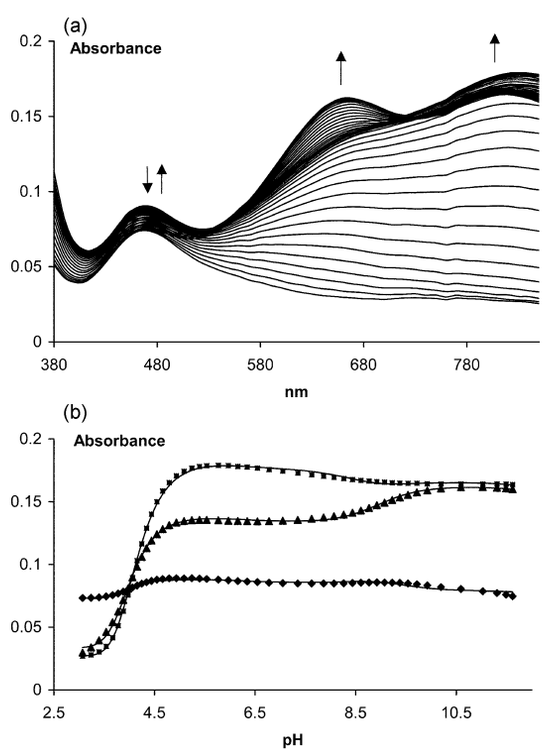


Fig. 4 (a) Spectrophotometric titration of Ni(**6**) in the presence of one equivalent of Cu^{2+}. [Ni(**6**)] = 1.6×10^{-3} M, titrated with increments of NaOH (0.4 M) up to a total volume of 0.352 ml. (b) Fit of the data at different wavelengths: (■) experimental, (—) calculated curve at 830 nm; (▲) experimental, (—) calculated curve at 660 nm; (◆) experimental, (—) calculated curve at 460 nm.

The second metal ion added is thus found in the open chain tren moiety. It was therefore interesting to look also at the kinetics of complex formation, in particular to find out how mechanistically the Cu^{2+} binding takes place.

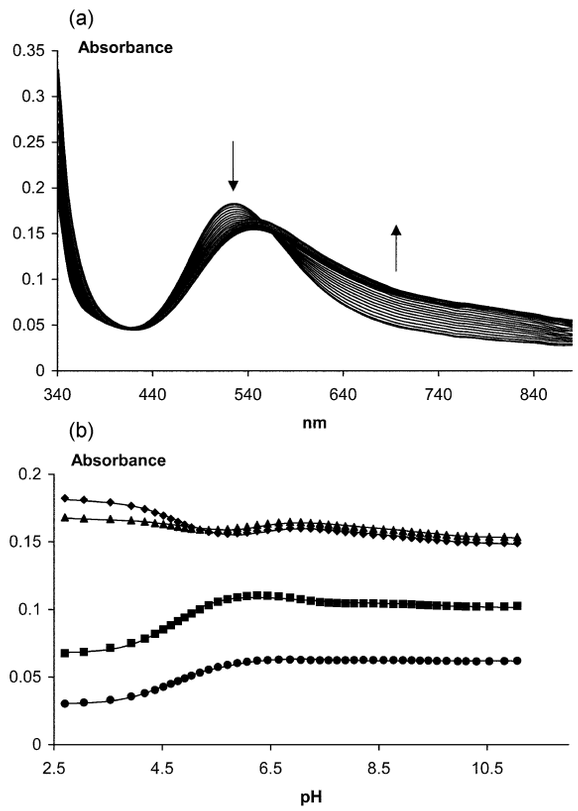


Fig. 5 (a) Spectrophotometric titration of Cu(**6**) in the presence of one equivalent of Ni^{2+}. [Cu(**6**)] = 1.22×10^{-3} M, titrated with different increments of NaOH (0.4 M) up to a total volume of 0.39 ml. (b) Fit of the data at different wavelengths: (●) experimental, (—) calculated curve at 836 nm; (■) experimental, (—) calculated curve at 644 nm; (▲) experimental, (—) calculated curve at 550 nm; (◆) experimental, (—) calculated curve at 528 nm.

For this we have studied the kinetics of complex formation of **6** with Cu^{2+} using the stopped-flow photodiode array technique, which allows to rapidly mix the reactants and follow the spectral changes of the reaction as a function of time. Reacting **6** with one equivalent of Cu^{2+} at pH = 4.96 gives a complicated sequence of reaction steps (Fig. 6), which were analyzed with the computer program SPECFIT.[19] The program indicates through the number of eigenvalues that beside Cu^{2+} we need at least three couloured species to fit the data, *i.e.* two intermediates and the final product.

In a relatively fast bimolecular reaction between Cu^{2+} and the protonated ligand a first intermediate CuL′, which has a spectrum typical for a CuN_3-chromophore, is formed. Thereafter CuL′ interconverts to a second intermediate CuL″, with an absorption spectrum very similar to that of $[Cu(tren)]^{2+}$.

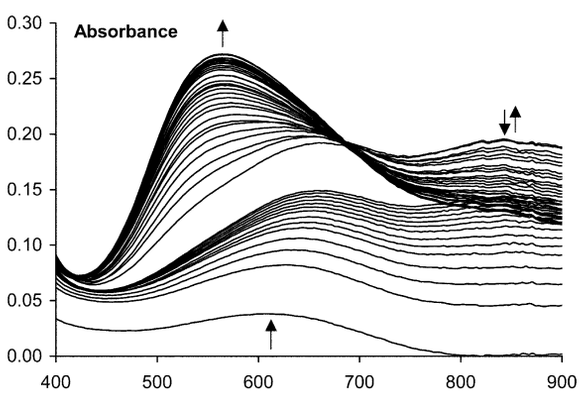
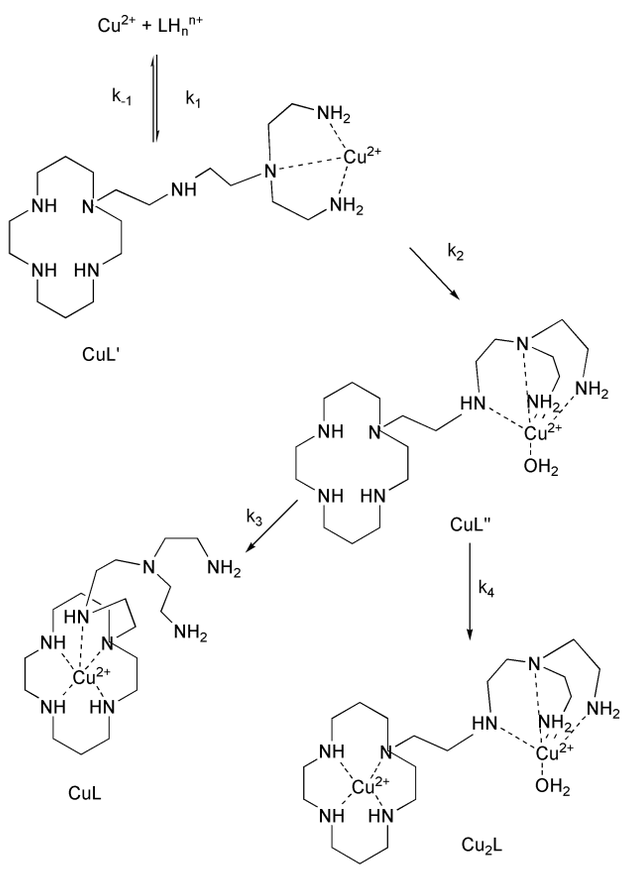


Fig. 6 Kinetics of complex formation of **6** with Cu^{2+}. [L] = 10^{-3} M, [Cu^{2+}] = 10^{-3} M, pH 4.96. Total acquisition time 180 s.

Finally CuL″ reacts to give the end product with an absorption maximum at 524 nm, corresponding to a complex with a Cu^{2+} in the macrocyclic unit. The reaction sequence can thus be written as eqn. (20), from which SPECFIT calculates $k_1 = 3.1(3) \times$

$$Cu^{2+} + LH_n^{n+} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} CuL' \xrightarrow{k_2} CuL'' \xrightarrow{k_3} [CuL]^{2+} \quad (20)$$

10^4 mol^{-1} dm^3 s^{-1}, $k_2 = 4.2(3)$ s^{-1}, $k_3 = 1.54(2) \times 10^{-2}$ s^{-1} at pH = 4.96. At lower pH values a similar sequence as the one described at pH 4.96 is observed, but the formation of CuL′ is less pronounced, so that we postulate a pH dependent equilibrium for the first step of the reaction (k_{-1}). Mechanistically the reaction proceeds in such a way that the Cu^{2+} is rapidly complexed by three nitrogens of the ligand. We can assume that the less sterically hindered two primary and the tertiary nitrogens are probably involved, whereby an intermediate with a structure similar to $[Cu(dien)]^{2+}$ is formed (Scheme 5). This species interconverts into a second intermediate with a spectrum typical for $[Cu(tren)]^{2+}$, which then slowly transfers the Cu^{2+} ion from the tren moiety to the macrocyclic ring thus giving the thermodynamically most stable species. The here observed interesting sequence of reactions in the complexation process is a direct consequence of the higher reactivity of the open chain part of the ligand (tren unit) compared to the well-known lower reactivity of the tetraaza macrocycle towards metal ions.



Scheme 5

If one reacts **6** with two equivalents of Cu^{2+} at pH 4.93 one observes a reaction sequence, which can be described again by eqn. (20) to which, however, a further step eqn. (21) must be added to give the 2 : 1 species.

$$CuL'' + Cu^{2+} \xrightarrow{K_4} [Cu_2L]^{4+} \quad (21)$$

The value $k_4 = 42.2$ (4) mol^{-1} dm^3 s^{-1} at pH = 4.93, obtained by fitting this step is very comparable with the rate of complexation of cyclam with Cu^{2+} at the same pH.[29]

In conclusion we can say that **6** is an interesting ditopic ligand able to bind Cu^{2+} or Ni^{2+} in two completely different environments and thus can induce very different and specific properties to the two metal centres. In addition it is also able to coordinate two different metal ions such as Cu^{2+} and Ni^{2+} in a selective way, the first being coordinated by the macrocyclic unit, the second by the tren moiety. Finally a subtle balance between thermodynamical and kinetic properties determines the mechanism of complex formation in so far that the more reactive open chain binding site first coordinates the metal ion to transfer it to the macrocyclic unit, which gives the thermodynamically more stable species.

Acknowledgements

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