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Synthesis of the New Thia–Aza Cage 12,17-Dimethyl-5-thia-1,9,12,17-tetraazabicyclo[7.5.5]nonadecane. Thermodynamic Studies on Protonation and Copper(II) Complex Formation

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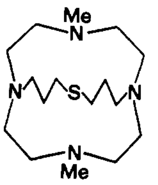
The synthesis of the new thia–aza cage 12,17-dimethyl-5-thia-1,9,12,17-tetraazabicyclo[7.5.5]nonadecane (L) and of its Cu(II) complex are described. The thermodynamic parameters $\Delta G°$, $\Delta H°$, and $\Delta S°$ relative to protonation and complex formation equilibria have been determined by potentiometry, continuous-titration calorimetry, and batch microcalorimetry at 25 °C in 0.15 mol dm^{-3} NaCl. The cage (L) behaves as a strong diprotic base (log k_1 = 11.91; log k_2 = 8.78); in both protonation steps the high basicity is due to a very favorable enthalpic term: $\Delta H°_1 = -13.3$ kcal mol^{-1}; $\Delta H°_2 = -11.5$ kcal mol^{-1}. pH–^{13}C NMR studies indicate that minor conformational changes take place on protonation. The stability of the $[\mathrm{CuL}]^{2+}$ complex (log k = 18.2) is due to a favorable enthalpic term ($\Delta H° = -14.0$ kcal mol^{-1}) and to a very favorable entropic term ($T\Delta S° = 10.8$ kcal mol^{-1}). The electronic spectra of the Cu(II) complexes show the same features both in the solid state and in solution and are diagnostic of a distorted square-pyramidal structure.

Introduction

In recent years an ever increasing interest has been devoted to the chemistry of macrocyclic compounds.[2] Among these compounds the so called "cryptands"[3] form one of the most interesting and studied groups. In previous papers[4,5] we have reported the cage pentaazamacrobicycloalkane 12,17-dimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (L1) and its ligational properties toward metal ions. Continuing this series of studies on cagelike macrocycles we now report the synthesis of the new thia–aza cage 12,17-dimethyl-5-thia-1,9,12,17-tetraazabicyclo-[7.5.5]nonadecane (L) and its ligational behavior toward protons (basicity) and the Cu(II) ion.



L

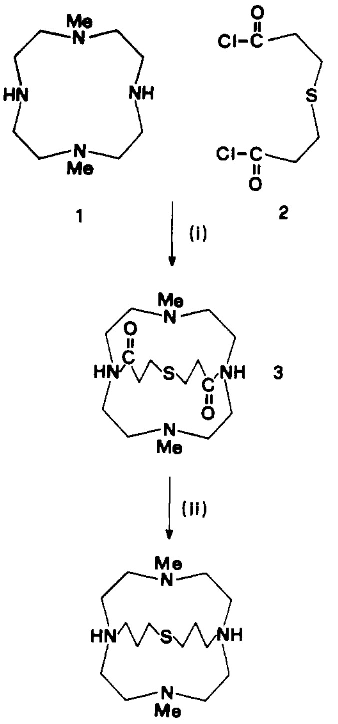
Experimental Section

Ligand Synthesis (L) (Scheme I). The macrocycle 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (**1**) has been prepared as previously described.[6]

3,3′-Thiodipropionic Acid Chloride (2). A 3.56-g (0.02-mol) sample of 3,3′-thiodipropionic acid was treated with 48 g (0.4 mol) of thionyl chloride at 45–50 °C for 20 h. The unreacted $SOCl_2$ was removed under reduced pressure, and the resulting yellowish oil was used without further purifications.

Bicyclic Thiodiamide (3). A 4.0-g (0.018-mol) sample of **2** in 500 cm^3 of dry benzene and 4.6 g (0.023 mol) of 1,7-dimethyl-1,4,7,10-tetraazacyclododecane (**1**) in 500 cm^3 of dry benzene containing 4.0 g (0.04 mol) of triethylamine were added simultaneously to 500 cm^3 of dry benzene, under mechanical stirring, over a period of 7 h at room temperature. The reaction mixture was then filtered and evaporated to dryness on a rotary evaporator. The white crystalline product obtained was recrystallized from absolute ethanol. Yield: 5.1 g (75%). Mp: 268–270 °C. Anal. Calcd for $C_{16}H_{30}N_4O_2S$: C, 56.10; H, 8.82; N, 16.35. Found: C, 56.1; H, 9.0; N, 16.2.

Scheme I[a]



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[a] (i) Dry benzene–triethylamine at room temperature for 7 h, yield 75%; (ii) dry THF and diborane at 0 °C with warmup and reflux for 6 h, yield 68%.

12,17-Dimethyl-5-thia-1,9,12,17-tetraazabicyclo[7.5.5]nonadecane (L). A 0.04-mol sample of diborane (50 cm^3 THF solution) were added dropwise in nitrogen atmosphere to a suspension of 1.7 g (5 mmol) of **3** in 15 cm^3 of dry THF cooled at ice temperature. The addition was made over a period of 30 min. After removal of the cooling bath the reaction mixture was allowed to warm up at room temperature and then refluxed for 6 h. The resulting solution was cooled to 0 °C, and the excess of diborane was destroyed with methanol (30 cm^3) and water (10 cm^3). The solution was then evaporated to dryness. The white solid obtained was dissolved in a $HCl/H_2O/MeOH$ mixture (3/9/30 cm^3) and refluxed for

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4 h. The solution was made alkaline by addition of a concentrated NaOH solution. The white solid separated was filtered off and sublimed in vacuo at 80 °C. Yield: 6.2 g (68%). Mp: 140–142 °C. Anal. Calcd for $C_{16}H_{34}N_4S$: C, 61.09; H, 10.89; N, 17.81. Found: C, 61.2; H, 11.2; N, 17.9.

(L)·2HClO$_4$ was obtained by adding a slight excess of $HClO_4$ in EtOH to an ethanol solution of the free ligand cooled at 0 °C. The white crystalline product was filtered off, washed with ethanol, and dried in vacuo. Anal. Calcd for $C_{16}H_{36}N_4O_8SCl_2$: C, 37.28; H, 7.04; N, 10.87. Found: C, 37.3; H, 7.2; N, 10.8.

Spectroscopy. Proton-decoupled ^{13}C NMR spectra were recorded with a Varian FT-80A spectrometer operating at 20.0 MHz using water with 15% (w/w) D_2O as solvent; chemical shifts are reported in ppm from $SiMe_4$ with dioxane as secondary reference standard [δ(dioxane) = δ-($SiMe_4$) + 67.4 ppm]. The electronic spectra were recorded on a Perkin-Elmer Lambda 9 spectrophotometer.

Copper Complex. A solution of $Cu(ClO_4)_2$ (0.15 mmol) in methanol (5 cm^3) was added to a solution of the ligand (0.15 mmol) in methanol (5 cm^3). The blue crystals that immediately formed were filtered off, washed with ethanol/methanol (3.5 cm^3, 1:1 v/v), and dried under vacuum. (*Caution*! Perchlorate salts of metal complexes can be explosive and must be handled with care. Compounds should not be heated as solids.) Anal. Calcd for $C_{16}H_{34}N_4O_8SCl_2Cu$: C, 33.31; H, 5.94; N, 9.71. Found: C, 33.4; H, 6.1; N, 9.7.

Materials. All potentiometric and calorimetric measurements were carried out in 0.15 mol dm^{-3} NaCl as an inert ionic medium using commercial NaCl (Merck Suprapur) without further purification. Standardized CO_2-free solutions of NaOH, used in the potentiometric and calorimetric measurements, were prepared according to standard procedures.[7]

Protonation and Complex Formation Constant. The potentiometric titrations were carried out with a fully automatic apparatus as described in ref 8. The experimental values of the emf were not corrected for the liquid-junction potential. Two titration curves (111 data points) have been used to determine the basicity constants of L. Due to the long time required for chemical equilibrium to be attained in the reaction between Cu(II) and the cage L, a batchwise potentiometric procedure was used to determine the stability constant of $[CuL]^{2+}$. The procedure and its application to macrocyclic Ni(II) complexes have been described in ref 9. Twelve different aqueous solutions of the ionic medium, containing different amounts of ligand (L) (concentration range 9.4×10^{-4}–1.1×10^{-3} mol dm^{-3}), Cu^{2+} ion as perchlorate salt (concentration range 9.0×10^{-4}–1.0×10^{-3} mol dm^{-3}), and hydrochloric acid, were prepared in separate bottles. The solutions were maintained at 25 °C, and the magnitude of $-\log [H^+]$ for each solution was measured periodically until a constant value was reached. In order to ascertain that equilibrium had been reached, the concentration of $[CuL]^{2+}$ was spectrophotometrically monitored over a period of 2 weeks. The computer program SUPERQUAD[10] was used to process all the potentiometric data and to calculate the basicity and complex stability constants.

Enthalpy of Protonation and Complex Formation. The enthalpies of protonation of L were determined with an LKB calorimeter (Model 8700) by employing the continuous-titration technique. The apparatus and the experimental procedure have already been reported.[11] The calorimetric system was controlled by an Apple II Europlus microcomputer, equipped with a 9-in. video display and one minifloppy disk driver. A computer program was written in Basic,[12] with some routines in assembler, to monitor for each titration point the voltage of the unbalanced Wheatstone bridge, the time, and the volume of the titrant added. The experimental collected data, stored on the floppy disk, were further processed to determine the stepwise enthalpy of reaction. The enthalpy of ionization of water was determined by adding NaOH solution to a solution of HCl contained in the calorimetric vessel. The measured value, −13.50 (3) kcal mol^{-1}, was in agreement with the accepted literature value.[13] Because of the slowness of the formation reaction the enthalpy of the Cu(II)–L complex was determined by using a model 10700-2 LKB batch microcalorimeter. A full description of the apparatus, its calibration, and the calorimetric procedure has already been reported.[14] In a typical experiment an aqueous solution of Cu^{2+} and a solution of the neutralized ligand were mixed. The reaction was considered to be complete when no further heat effect could be detected, the reaction time being typically 40–50 min. Under the reaction conditions and with employment of the determined stability constants, the species present and their percentages at equilibrium before and after mixing were calculated by means of the DISPOL[15] computer program. The only significant species present at equilibrium before and after mixing were the free nonprotonated ligand and the complex $[CuL]^{2+}$, respectively. Blank experiments were carried out to correct for the enthalpy of dilution of the NaOH solution.

Table I. Thermodynamic Quantities of Protonation and Cu(II) Complex Formation of L in Aqueous Solution at 25 °C in 0.15 mol dm^{-3} NaCl (Standard State 1 mol dm^{-3})

reaction	log *K*	$-\Delta G°$, kcal mol^{-1}	$-\Delta H°$, kcal mol^{-1}	$T\Delta S°$, kcal mol^{-1}
$L + H^+ = HL^+$	11.91 (4)[a]	16.24 (5)	13.3 (1)	2.9 (1)
$HL^+ + H^+ = H_2L^{2+}$	8.78 (4)	11.98 (5)	11.5 (1)	0.5 (1)
$Cu^{2+} + L = [CuL]^{2+}$	18.2 (1)	24.8 (1)	14.0 (1)	10.8 (1)

[a] Values in parentheses are standard deviations in the last significant figure.

Results and Discussion

Protonation. Both in the solid state and in aqueous solution macrocycle L can take up at most two protons. The diperchlorate salt of L has been isolated and characterized (see Experimental Section). In aqueous solution macrocycle L behaves as a strong base in both protonation steps, the observed thermodynamic parameters being reported in Table I. Both $|\Delta G°|$ and $|\Delta H°|$ values for the stepwise protonation reactions are unexpectedly high for tertiary nitrogen atoms.[16] In the first protonation step L is more basic than monocycle **1** (see scheme I), which contains two secondary and two tertiary nitrogen atoms.[6] The high basicity of L in the first protonation step is entirely due to a very favorable enthalpic term ($\Delta H_1° = -13.3$ kcal mol^{-1}; see Table I), in other words, the added hydrogen ion should interact very strongly with the nitrogen atoms to form the monoprotonated species $(HL)^+$. The first protonation step of L, where only tertiary nitrogen atoms are involved, is much more exothermic than the corresponding reaction for both linear and monocyclic tertiary polyamines.[16,17] The above considerations indicate that the hydrogen atom of the $-NH^+$ group should be well embedded within the electron density of all the nitrogen atoms. In the case of the parent cage L1 the first proton is so strongly bound that it can not be removed in 3 mol dm^{-3} KOH. The base L1 is stronger than OH^- in aqueous solution. ^1H NMR and crystal structure analyses have demonstrated that in the species $(HL1)^+$ the hydrogen ion is rapidly exchanged with the bulk solvent and bound through hydrogen bonding to three nitrogen atoms. This arrangement makes the species exceptionally stable from the thermodynamic point of view. The cage L, in which one sulfur atom has replaced the secondary nitrogen –NH– in L1, is less basic in aqueous solution than L1, and its basicity is measurable. Nevertheless, this basicity is very high for a compound having only tertiary nitrogens. Even in the second protonation step L behaves as a relatively strong base, and also in this step the basicity is essentially enthalpic in origin, the heat of reaction (−11.5 kcal mol^{-1}) being comparable with those found for the second protonation step of polyaza macrocycles having only secondary amino groups.[17] In order to better understand the protonation behavior of L, a ^{13}C NMR/pH study was carried out. In Figure 1 the chemical shifts (ppm) of the carbon atoms of L as a function of pH are shown. The assignment

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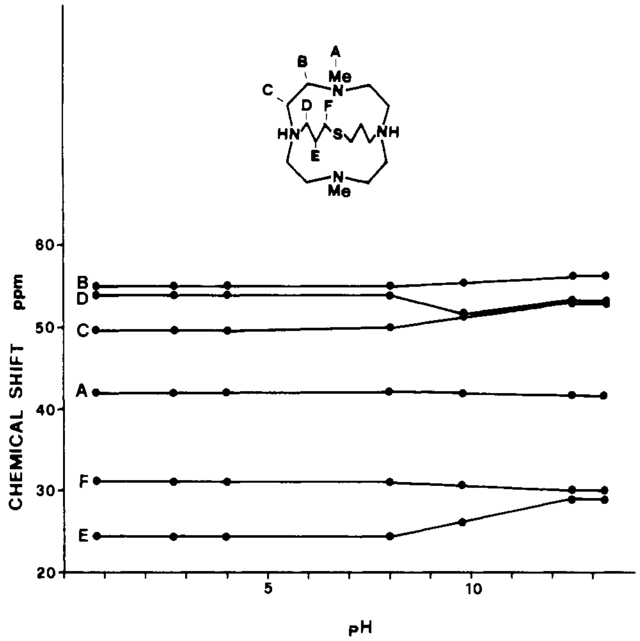

Figure 1. ^{13}C NMR chemical shift variation (ppm) as a function of pH for L.

of the peak at 42.2 ppm to methyl carbons A is confirmed by the APT technique.[18] The central carbon atoms E of the propylenic chains are assigned to the highest field peak at 24.4 ppm. The tentative assignment of the remaining signals has been made on the basis of the relative intensities and by comparing them with the spectrum of the related cage L1.[3] The overall pH range investigated can be divided into three parts: (i) In the first part (pH >12.5), where the cage L can be considered to be essentially unprotonated, the spectrum consists of five signals since the peaks of carbon atoms C and D coincide and does not undergo any further change at higher pH. (ii) In the second part (pH range 8–12.5) the most important species present is the monoprotonated species $[HL]^+$. Only in this part we have modest changes in the ^{13}C NMR spectrum with pH; carbon atoms C and D show downfield and upfield shifts, respectively, as the pH is increased. These shifts are rather small and may be due to some conformational changes as the cage is diprotonated. The largest change in chemical shift is that of carbon E, which shows an upfield shift of 5 ppm as the cage becomes more protonated. This shift may be due to conformational rearrangements and/or to the so-called "β effect".[19,20] It should be noted that also the C and B carbon atoms show a slightly upfield shift as the degree of protonation increases. (iii) In the last part of the pH range investigated (pH range 1–8), where the cage L is present as the diprotonated species $[H_2L]^{2+}$, the ^{13}C spectrum consists of six signals, indicating C_{2v} symmetry for the above species, possibly time averaged among lower symmetry conformers and/or tautomers. In this pH range no change in the spectrum with pH is observed. From the ^{13}C NMR/pH studies on L the following conclusions may therefore be drawn: the protonation of cage L produces only small conformational changes, and the carbon atoms E, C, and B in β-position with respect to the protonation sites show upfield shifts.

Copper(II) Complex. A solid compound of stoichiometry $CuL(ClO_4)_2$ was isolated (see Experimental Section); the electronic spectra of the compound in the solid state and in solution are essentially the same (solid 10 900, 15 000, 31 400 cm^{-1}; aqueous solution 10 900 (ϵ = 164), 15 100 (ϵ = 221), 35 900 cm^{-1} (ϵ = 1372)) and are diagnostic of a distorted square-pyramidal structure.[21] The complex $[CuL][ClO_4]_2$ shows a great inertness toward strong acid solutions: it does not undergo appreciable decomposition over a period of days in a 5 mol dm^{-3} $HClO_4$ solution at room temperature. A similar behavior has been already found for the Cu(II) complex of the parent cage (L1),[4] for which the X-ray analysis has shown the Cu(II) ion wholly enclosed by the cage and five-coordinated. The formation of $[CuL]^{2+}$ is also relatively slow (see Experimental Section). All these evidences seem to indicate that the Cu(II) ion is incapsulated in the cage cavity. The thermodynamic properties for the formation of the Cu(II) complex with the cage (L) are given in Table I. The discussion of these results will be made assuming that the metal ion is located inside the cage cavity. To our knowledge these results are the first complete set of thermodynamic parameters ($\Delta G°$, $\Delta H°$, and $\Delta S°$) relative to the formation equilibrium between Cu(II) and a thia–aza cage. It can be seen that the stability of the $[CuL]^+$ complex is only moderately high; it is more interesting to note that a large contribution to this stability comes from the entropic term, which is extremely favorable (see Table I). The formation reaction is in the whole exothermic, but the observed value (−14.0 kcal mol^{-1}) is not large compared with those for the formation of many Cu(II)–polyaza macrocyclic complexes.[8,22] These results indicate that unfavorable contributions to the enthalpy of reaction, such as ligand conformational changes and desolvation, should play an important role in the overall enthalpy of formation of the $[CuL]^{2+}$ complex. The extremely favorable entropic term to $[CuL]^{2+}$ complex formation can be interpreted in terms of cage preorientation and large release of solvent molecules as a consequence of the incapsulation of the Cu(II) ion in the cage cavity. In conclusion, the thermodynamic parameters measured for the formation reaction of $[CuL]^{2+}$ strongly support the hypothesis that the metal ion is located inside the cavity.

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Registry No. **1**, 90281-17-7; **2**, 18733-39-6; **3**, 104422-13-1; L, 104422-14-2; (L)·2HClO$_4$, 104422-15-3; CuL(ClO$_4$)$_2$, 104422-17-5; 3,3′-thiodipropionic acid, 111-17-1.

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