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Physical Image vs. Structure Relation. Part 3 [1]. Basic Properties and Protonation Mechanism of Some Tetraaza Macrocyclic Ligands

DARIUSZ SROCZYŃSKI and ANDRZEJ GRZEJDZIAK
Department of General and Inorganic Chemistry, University of Łódź, 90-136 Łódź 1, P.O. Box 376, Poland

RYSZARD B. NAZARSKI*
Department of Organic Chemistry, University of Łódź, 90-136 Łódź 1, P.O. Box 376, Poland

Abstract. The protonation constants, log K, for 1,4,7,11-tetraazacyclotetradecane (isocyclam, **2**), 1-(2-aminoethyl)-1,4,8,11-tetraazacyclotetradecane (scorpiand, **3**), 5,12-dimethyl-1,4,8,11-tetraazacyclotetradecane (Me_2cyclam, **4**) and 5,5,7,12,14,14-hexamethyl-1,4,8,11-tetraazacyclotetradecane (Me_6cyclam, **5**) were determined pH-metrically. Attempts of correlation of the calculated enthalpy of protonation in the gas phase (AM1 method) with experimental values of the protonation constants for ligands **1**, **2**, **4–7** were done {1,4,8,11-tetraazacyclotetradecane, cyclam, **1**; 1,4,7,10-tetraazacyclotetradecane, cyclen, **6**; 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane, (N-Me)$_4$cyclam, **7**}. Extensive NMR pH-titrations, i.e., determination of pH vs. chemical shifts (^{1}H and/or ^{13}C) plots, (δ_X = f(pH), allowed to suggest the most likely protonation schemes of all nitrogen atoms in the cyclic polyamines **1–3**. The possibility of the formation-breaking of the intramolecular hydrogen bonds, as well as the change of conformation of these polybasic macrocycles during protonation-deprotonation steps, has been considered on the basis of the supplementary theoretical calculations (MMX/STO-3G study).

Key words: protonation sequence, tetraaza macrocycles, multidentate ligands, 14-membered rings, MM studies, AM1 method, *ab initio* STO-3G calculations, NMR titration spectroscopy, protonation shift, polyammonium cations structure, intramolecular hydrogen bonding, basic properties.

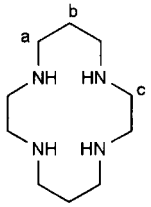
1. Introduction

The cyclic tetraamines and their complexes with metal ions have been extensively investigated for about three decades [2–4]. It seems to be strange, but our knowledge about this protonation mechanism is still unsatisfactory. Although the values of stepwise protonation constants have been determined for many of these amines, the protonation sequence of the nitrogen atoms has not been thoroughly explained yet. Cyclic polyamines can also stabilize unusually high and low oxidation states of the metal cations [5]. Such complexes are used as catalysts in organic synthesis, electron-carrier systems and chemical current sources.

* Author for correspondence (e-mail: rynaz@chemul.uni.lodz.pl).

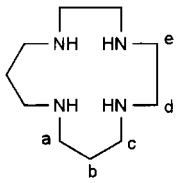
In order to describe quantitatively the metal ion–ligand equilibria existing in protic solvents, it is necessary to know the acid-base properties of the macrocyclic ligands, i.e., their protonation constants.

The main purpose of our study was to investigate the basic properties of the compounds **2–5**, the attempt of correlation of the calculated enthalpy of protonation reaction of macrocycles **1**, **2**, **4–7** in the gas phase with experimental values of the protonation constants and the determination of the protonation sequence of the nitrogen donor atoms for the multidentate ligands **1–3** using NMR pH-titrations. (The characters and numbers around the formulas listed below, refer to the signal assignments of the NMR spectra; Section 3.2.)



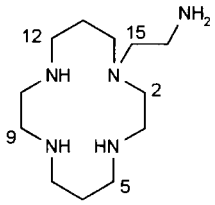
cyclam

1



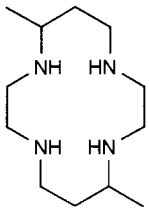
isocyclam

2



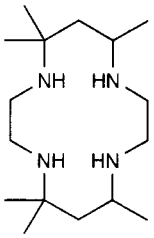
scorpiand

3



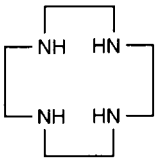
Me$_2$*cyclam*

4



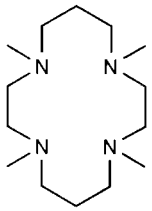
Me$_6$*cyclam*

5



cyclen

6



(N-*Me*)$_4$*cyclam*

7

2. Experimental and Computational

2.1. MATERIALS

Cyclam (Fluka) was used as received. Isocyclam was obtained following the literature procedure [6], with some modifications. Scorpiand was prepared according to the method of Pallavicini *et al*. [7]. Both synthesized ligands were fully characterized by ^{1}H and ^{13}C NMR techniques. The purity of all compounds were checked by pH-titration. The ligands **4** and **5** were kindly supplied by Prof. L. Fabbrizzi, Universita di Pavia (Italy).

2.2. POTENTIOMETRIC MEASUREMENTS

The potentiometric titrations were carried out in a sealed vessel thermostated at 293.0 ± 0.1 K. The pH of the solutions were measured by using digital pH-meter N5172 (TelEko, Poland) and the combined EsAgP-301 WM electrode (Euro-Sensor, Poland). Before measurements the electrode was calibrated with respect to the aqueous buffer solutions (Aldrich). The solutions of the ligands with a composition of $c_{\mathbf{L}} + 5c_{\mathbf{L}}$ HNO_3 ($c_{\mathbf{L}} = 1 - 5 \times 10^{-3}$ mol dm^{-3}) were titrated with CO_2-free KOH standard solution. Constant ionic strength $\mu = 0.1$, was adjusted by the addition of KNO_3. The values of the protonation constants were calculated by means of the program based on the PKAS [8] and MINIGLASS [9] algorithms.

2.3. THEORETICAL INVESTIGATIONS

2.3.1. *AM1 Calculations*

The structures **1**, **2** and **4–7** were initially optimized by means of molecular mechanics (MM+ force field, Polak–Ribiere algorithm; HyperChem package [10]). Then full optimization of the geometry with semiempirical AM1 method (MOPAC 6.0 [11]) were done. The solvation shell consisting of 14 molecules of H_2O (HyperChem, Periodic Box option) was built and a similar calculation was done. The heat of formation values of particular protonated forms of the ligands obtained $[H_m\mathbf{L}]^{m+}$ (m = 0–2, **L** = ligand) were used in the calculation of the enthalpy of protonation reaction, ΔH, in gas phase.

2.3.2. Ab Initio *Calculations*

Molecular modeling studies (MMX force field, PCMODEL program [12]) on isolated polyamine ligands **1** and **2** as well as the respective cations $[H_m\mathbf{1}]^{m+}$ and $[H_m\mathbf{2}]^{m+}$, were performed. Structures corresponding to low-energy conformations, found in a Saunders type procedure [13], were used as starting geometries in further *ab initio* geometry optimizations at STO-3G level of theory (final RMS gradient $\leq$0.2 kJ mol^{-1} A^{-1}; HyperChem).

Table I. Values of the successive protonation constants of the investigated ligands in aqueous solutions, μ = 0.1 (0.1 mol dm^{-3} KNO_3), T = 293 K

	Cyclam [17]	Isocyclam (lit. [18])	Scorpiand	Me_2cyclam	Me_6cyclam
log K_{01}	10.92	11.45 (11.29)	10.45	11.77	9.89
log K_{12}	10.51	10.35 (10.19)	8.50	9.89	6.41
log K_{23}	2.65	4.14 (4.32)	6.34_5	2.90	2.66
log K_{34}	1.62	2.29 (<2)	2.95_5	1.56	2.29
log K_{45}	–	–	2.18	–	–

2.4. NMR MEASUREMENTS

The 199.98 MHz ^{1}H and 50.29 MHz ^{13}C NMR spectra at different pH values were recorded in 5-mm ca. 294 K on a Varian Gemini 200 BB spectrometer. Solutions of the ligand **1** (0.032 ± 0.006 mol dm^{-3}) and **2** (0.12 ± 0.03 mol dm^{-3}) for the measurements were made up in D_2O (99.9 atom% D) and nA (or pD) were adjusted by adding the appropriate amounts of concentrated DNO_3 (and/or CO_2-free NaOD) solutions in D_2O (99.5 atom% D); all deuterated products were purchased from Polatom (Świerk, Poland). Relatively high concentrated solutions of these ligands were employed to obtain good ^{13}C NMR signals. The operational pD was determined by the same procedure as described in Section 2.2, but without control of the ionic strength of the samples; sodium error corrections [14] were also not made. The final pH was calculated from the measured pD values using the empirical equation, pH = pD − 0.41 [14–16]. For ligand **3**, solutions in H_2O (≈ 0.01 mol dm^{-3}) were used for the ^{13}C NMR pH-titrations; small amounts of D_2O were added only for locking. All chemical shifts (δ_X) were referenced to $SiMe_4$ in an external capillary; bulk susceptibility corrections were not made.

The resonance signals assignments, concerning polyamines **1** and **2**, have been made on the basis of two-dimensional C,H-COSY correlation experiments (Varian Gemini 200 BB) at the different pH values studied. In the case of ligand **3**, corresponding 2D spectra (H,H-COSY, C,H-COSY, TOCSY, and ROESY) were recorded in H_2O solution (pH 10.76) at a probe temperature with a Bruker DRX 500 instrument operating at 500.13/125.76 MHz in the NMR Laboratory of the Polish Academy of Sciences (Łódź).

3. Result and Discussion

3.1. ACID-BASE PROPERTIES

The calculated values of the protonation constants for the ligands **2–5** are given in Table I. In the case of compounds **3–5** such data were determined for the first time.

The values of log K obtained are typical for cyclic tetraamines. The values of the K_{01} and K_{12} constants are high and the values of the last two are ca. 2–3 log

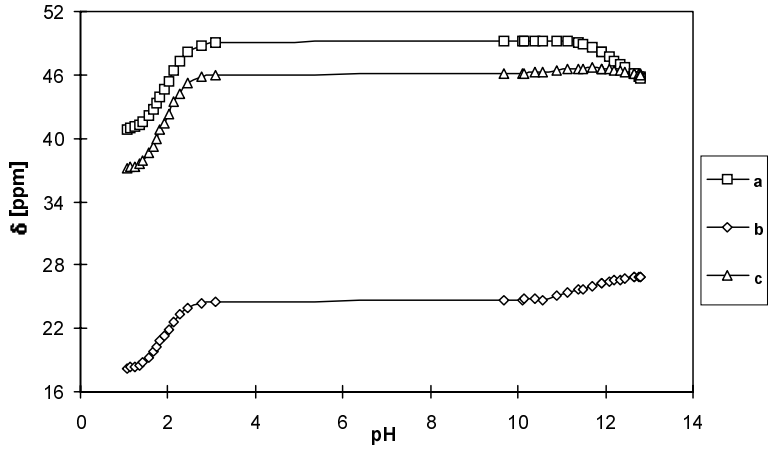


Figure 1. ^{13}C NMR titration curves, δ_C vs. pH, of cyclam **1**.

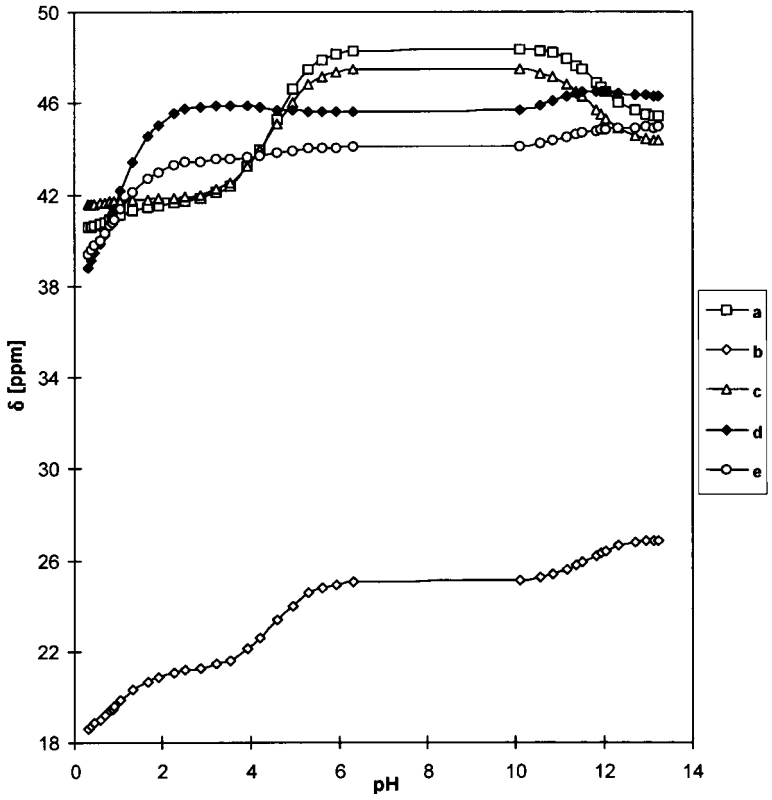


Figure 2. ^{13}C NMR titration curves, δ_C vs. pH, of isocyclam **2**.

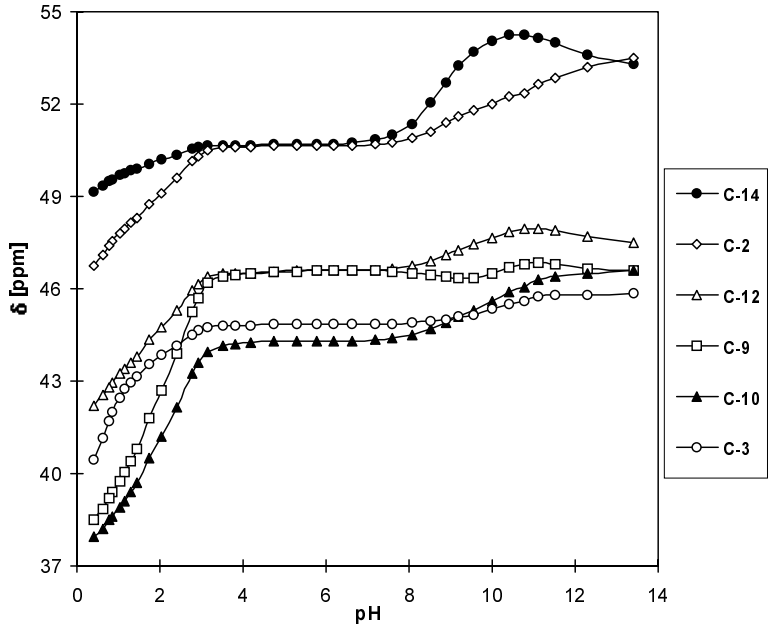


Figure 3. ^{13}C NMR titration curves, δ_C vs. pH, of scorpiand **3**. Part 1.

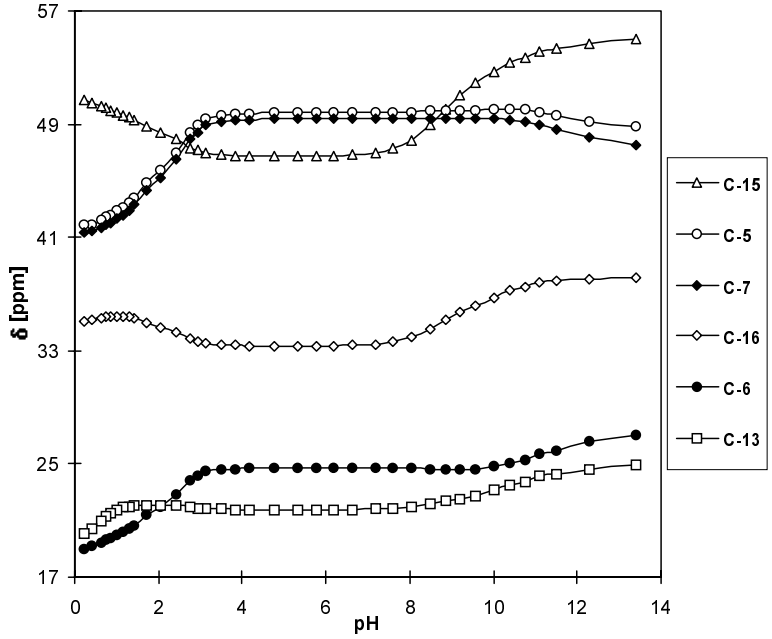


Figure 4. ^{13}C NMR titration curves, δ_C vs. pH, of scorpiand **3**. Part 2.

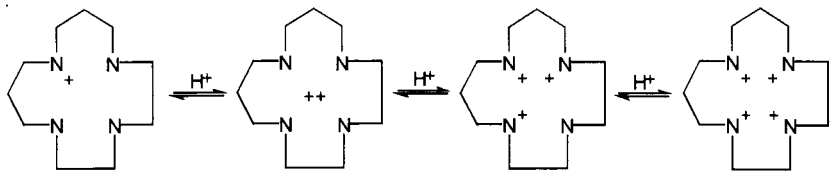
units. K_{23} for the scorpiand refers to the protonation of the nitrogen atom of the pendant aminoethyl group [19]. Thus, it is possible to compare K_{34} and K_{45} of the scorpiand with K_{23} and K_{34} of the other ligands.

The difference between the log K_{12} and log K_{23} values can be possibly explained by the formation of the intramolecular hydrogen bonds with participation of one or two protons attached to nitrogen donor atoms. One can see (Table I) that the cyclam-type ring is the ligand system in which hydrogen bonding is the strongest (the lowest values of log K_{23}). In the case of isocyclam, with an unsymmetrical assemblage of donor atoms, the hydrogen bonds are probably weaker and hence the log K_{23} value is greater.

For the macrocyclic ligands **1**, **2**, **4–7** the semiempirical AM1 calculation were done. The obtained values of the heat of formation of particular protonated forms of the ligands $[H_m\mathbf{L}]^{m+}$ (m = 0–2), with and without the solvation shell of 14 H_2O molecules, were used in the calculation of the enthalpy reaction, (ΔH, of protonation processes in the gas phase). In order to find the correlation between ΔH and experimental values log K, among all the possible reactions paths, the lowest value of ΔH were selected. Literature log K values for cyclen and (N-Me)$_4$cyclam were taken from [20] and [17], respectively. In both cases correlations did not occur. In general the changes of the enthalpy of protonation in the gas phase do not correspond to changes of the protonation constants. The correlation should occur when a sufficient number of the H_2O molecules are taken into consideration in the calculations. In this case additional solvation of the tetraazacyclic cations occurs which disperses positive charge on the amine hydrogen atoms and to a greater extent stabilizes the whole macrosystem. The results of our calculations show that 14 molecules of H_2O are too small in order to simulate the solvation shell and hence correlation has failed.

3.2. NMR AND *ab initio* INVESTIGATIONS [21]

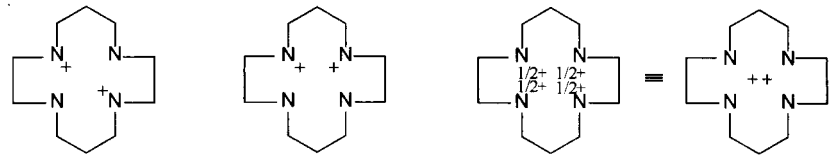
The full interpretation of the 1D and 2D NMR spectra, especially difficult in the case of the extremely complex scorpiand $[H_m\mathbf{3}]^{m+}$ (m = 0–5) species [19], and establishing of the chemical shifts vs. pH (or number of moles of acid, nA, added per mole of ligand) plots (i.e., δ_X = f[pH (or nA)] where X = ^{1}H and/or ^{13}C nucleus; see Figures 1–4, for the most informative titration diagrams [22]) allowed us to suggest the most likely protonation schemes of all the nitrogen atoms in the studied macrocycles **1–3**. Such a sequence, elucidated unambiguously by means of NMR pH-titrations (^{1}H, ^{13}C, and $^1J_{CH}$ data vs. pH/nA plots) for the isocyclam system, was presented recently [23]; see also scheme below. (Labile amine hydrogen atoms are omitted for clarity. Moreover, crosses in the middle of the $[H_2\mathbf{2}]^{2+}$ (in reality $[D_2\mathbf{2}]^{2+}$) ion formula signify schematically the positive charge spread over all four nitrogenous basic centers of the 14-membered heterocycle.)



$[H_1\mathbf{2}]^{1+}$ $[H_2\mathbf{2}]^{2+}$ $[H_3\mathbf{2}]^{3+}$ $[H_4\mathbf{2}]^{4+}$

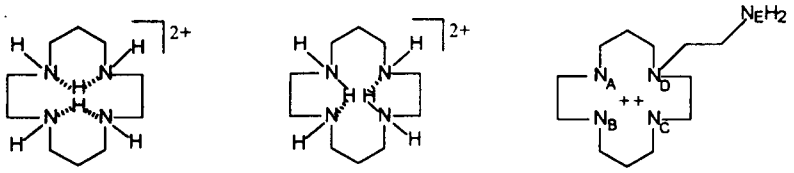
Despite the higher concentrations of ligand solutions used in the NMR investigations, the inflections of the titration curves (Figures 1–4) fit quantitatively to the potentiometrically obtained log K values (Section 3.1). The case of log K_{23} for the isocyclam system is the most representative; one-acid-equivalent point of inflection in the δ_C vs. pH curves are very well observed at pH $\approx$ 4.6 (Figure 2, the **a–c** nuclei).

Among all the investigated tetraaza macrocycles the nature of the different protonation states of cyclam, and especially its diammonium cation $[H_2\mathbf{1}]^{2+}$, were determined the most precisely. The ^{1}H and ^{13}C NMR pH-titration data allowed three descriptions of this partially protonated intermediate, i.e., using formula **A**, **B** or **C**. Obviously, the **A**-type objects formerly suggested [15, 16, 24] and **B**-type ones (less probable due to the closer proximity of positively charged atoms) should have participated in the tautomeric equilibrium involving two or four species, respectively.



A-$[H_2\mathbf{1}]^{2+}$ **B**-$[H_2\mathbf{1}]^{2+}$ **C**-$[H_2\mathbf{1}]^{2+}$

Theoretical calculation (MMX/STO-3G joint approach, gas-phase approximation) results enabled us to choose the structure of the ion $[H_2\mathbf{1}]^{2+}$. Two bridged structures with intramolecular hydrogen bonds corresponding to global (form **D**, two symmetrical H-bonds) and local energy minimum (form **E**, two unsymmetrical H-bonds; total energy difference $\Delta E_{\mathbf{E-D}}$ = 63.4 kJ mol^{-1}) were obtained, respectively. Thus, **C**-type lodging for the two protons is the most probable. According to the time-averaged NMR pH-titration data (e.g., Figure 1), such a charge delocalization characterizes all charged forms of system **1**. It can therefore be inferred that a protonation scheme of the cyclam system involves four species $[H_m\mathbf{1}]^{m+}$ (m = 1–4) with symmetrically delocalized charge.



D-$[H_2\mathbf{1}]^{2+}$ **E**-$[H_2\mathbf{1}]^{2+}$ **F**-$[H_2\mathbf{3}]^{2+}$

E = -1585556.4 kJ mol^{-1} (STO-3G) E = -1585493.0 kJ mol^{-1} (STO-3G) (alternative structure)

The probable structures of scorpiand cations $[H_m\mathbf{3}]^{m+}$ (m = 1–5) with the localized charge, and a full protonation sequence for this macrocycle were reported previously [19]. The N_C atom is protonated first, then N_A, N_E, N_B, and N_D; for denotation, see formula **F**-$[H_2\mathbf{3}]^{2+}$. The character of the observed inflections in δ_C = f(pH) titration curves (Figures 3 and 4) as well as an additional ^{13}C spin-lattice T_1 relaxation-time data confirmed the correctness of tentative ^{13}C NMR assignments within the isolated —N$(CH_2)_z$N— (z = 2, 3) spin systems, throughout the pH-range explored. However, 'anomalous' δ_C variations below pH 3 (i.e., downfield protonation shifts [25] concerning the side arm aminoethyl group (Figure 4, the C-15 and C-16 nuclei)) and the broadening of several ^{13}C resonances at pH $\approx$ 2.5, remained unexplained to date [23]. In view of the above results obtained for model tetraaza macrocyclic ligands **1** and **2**, some participation of the alternative schematic structure of type **F** with charge delocalized around centrally situated nitrogen atoms, can now be suggested for the ion $[H_2\mathbf{3}]^{2+}$.

One finding of this work seems to be worth noting. The unexpected decrease of δ_C values for all α-carbons of the —N$(CH_2)_3$N— fragments were observed for the studied ligands **1–3** under basic conditions (pH > 10–11; Figures 1–4). From the δ_C = f(nA) plots it can be seen that these downfield protonation shifts concern the deprotonation of the corresponding mono- or diprotonated species with free polyamine liberation. Our preliminary STO-3G calculations indicate that this phenomenon (inherent to this type of tetraaza macrocycles?) is due to the change of the hydrogen-bond bridging, i.e., disruption and subsequent formation of new intramolecular H-bond(s), and simultaneous alteration in the ring conformation. However, the lack of corresponding changes in the δ_H = f(pH/nA) plots is very striking. On the other hand, a quite similar situation was observed recently for some azaparacyclophanes containing also two propylenediamine fragments [16]. Undoubtedly, this problem demands further deeper study.

Acknowledgement

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References

1. For Parts 1 and 2, see refs. 26 and 27, respectively.
2. R. Bhula, P. Osvath, and D. C. Weatherburn: *Coord. Chem. Rev.* **91**, 89 (1988).
3. P. V. Bernhardt and G. A. Lawrance: *Coord. Chem. Rev.* **104**, 297 (1990).
4. A. E. Martell and R. D. Hancock: *Metal Complexes in Aqueous Solutions*, Plenum Press, New York (1996).
5. K. B. Yatsimirskii: *Zh. Neorg. Khim.* **36**, 2010 (1991).
6. L. Sabatini and L. Fabbrizzi: *Inorg. Chem.* **18**, 438 (1979).
7. P. S. Pallavicini, A. Perotti, A. Poggi, B. Seghi, and L. Fabbrizzi: *J. Am. Chem. Soc.* **109**, 5139 (1987).
8. R. J. Motekaitis and A. E. Martell: *Can. J. Chem.* **60**, 168 (1982).
9. A. Izquierdo and J. L. Beltran: *Anal. Chim. Acta* **181**, 87 (1986).
10. HyperChem® for Windows, Release 4.5, Publication HC45-00-01-00, May 1995, Hypercube, Inc., Waterloo, Ontario, Canada N2L 3X2.
11. J. J. P. Stewart: *J. Computer-Aided Mol. Design* **4**, 1 (1990).
12. PCMODEL, Molecular Modeling Software for the IBM PC/XT/AT and Compatibles, Serena Software, Bloomington, IN 47402-3076, USA.
13. M. Saunders: *J. Am. Chem. Soc.* **109**, 3150 (1987).
14. A. K. Covington, M. Paabo, R. A. Robinson, and R. G. Bates: *Anal. Chem.* **40**, 700 (1968), and references therein.
15. J. Costa and R. Delgado: *Inorg. Chem.* **32**, 5257 (1993), and refs. therein.
16. A. Bianchi, B. Escuder, E. García-Espana, S. V. Luis, V. Marcelino, J. F. Miravet, and J. A. Ramírez: *J. Chem. Soc., Perkin Trans. 2* 1253 (1994).
17. A. Grzejdziak: *Monatsh. Chem.* **125**, 107 (1994).
18. A. P. Leugger, L. Hertli, and T. A. Kaden: *Helv. Chim. Acta* **61**, 2296 (1978).
19. R. B. Nazarski, D. Sroczyński, P. Urbaniak, J. Dziegieć, and A. Grzejdziak: *36th IUPAC Congress*, Geneva, August 17–22, 1997, poster SB-I16; *Chimia* **51**, 432 (1997).
20. M. Kodama and E. Kimura: *J. Chem. Soc., Dalton Trans.* 327 (1980).
21. The detailed structural studies, especially concerning the NMR resonance assignments for the complex scorpiand systems, will be published soon.
22. In certain pH intervals signal assignments for objects **2** and **3** are tentative due to crossover of the titration curves, which does not influence the proposed protonation schemes.
23. R. B. Nazarski and D. Sroczyński: *Symposium on Application of Magnetic Resonance in Chemistry and Related Areas*, Warsaw, June 24–26, 1998, poster P32.
24. M. Micheloni, P. Paoletti, and A. Vacca: *J. Chem. Soc., Perkin Trans. 2* 945 (1978).
25. H.-O. Kalinowski, S. Berger, and S. Braun: *Carbon-13 NMR Spectroscopy*, John Wiley, Chichester, 1988, pp. 222–226.
26. M. Cygler, K. Dobrynin, M. J. Grabowski, R. B. Nazarski, and R. Skowroński: *J. Chem. Soc., Perkin Trans. 2* 1495 (1985).
27. R. B. Nazarski and R. Skowroński: *J. Chem. Soc., Perkin Trans. 1* 1603 (1989).