Studies of the Protonation in Aqueous Solution of 1-Thia-4,7-diazacyclononane, 1-Thia-4,8-diazacyclodecane and 5-Thia-2,8-diazanonane

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The acid–base properties of 1-thia-4,7-diazacyclononane, 1-thia-4,8-diazacyclodecane and of 5-thia-2,8-diazanonane have been investigated in aqueous solution (25 °C, 0.1 mol dm^{-3} KNO_3) by pH potentiometry, adiabatic calorimetry and ^1H NMR spectroscopy. The cyclic diamines show a less effective solvation by water in the first protonation step with respect to the open-chain diamine. The presence of an internal hydrogen bond in the first protonation step of 1-thia-4,8-diazacyclodecane is evidenced.

Small macrocyclic polyamines such as triaza-,[1] oxadiaza-[2] and thiadiaza-cycloalkanes[3] combine a macrocyclic rigid structure with the incorporation of saturated nitrogen donors and exhibit a remarkable size-match selectivity towards small 3d-transition-metal ions.[4] Their acid–base properties have usually been determined in connection with metal-ion complexing abilities, so that the data are mostly limited to log K^H protonation constants. A complete thermodynamic study is only available for 1,4,7-triazacyclononane ([9]aneN_3).[1b] A proper assessment of the influence of inductive effects, solvation, hydrogen bonding and ring rigidity on the observed global amine basicity, as expressed by log K^H values, necessitates the knowledge of $-\Delta H^\circ$ and $T\Delta S^\circ$ values.

For that reason the acid–base properties of 1-thia-4,7-diazacyclononane ([9]aneN_2S) and 1-thia-4,8-diazacyclodecane ([10]aneN_2S) and of the open chain 5-thia-2,8-diazanonane (tdan) were studied by pH potentiometry and calorimetry. Although the protonation sequence of [9]aneN_2S and [10]aneN_2S is not ambiguous, their ^1H NMR titration profiles are also reported. The protonation constants for [9]aneN_2S have already been determined by Hancock and co-workers.[3]

Experimental

Materials.—1-Thia-4,7-diazacyclononane di(hydrobromide) and 1-thia-4,8-diazacyclodecane di(hydrobromide) were prepared as described.[5] 5-Thia-2,8-diazanonane–nitric acid (1/2) was prepared by reaction of 2-(methylamino)ethyl bromide hydrobromide (219 g, 1 mol) with an alkaline methanolic solution (400 cm^3) containing potassium sulfide (0.5 mol) at 60 °C for 2 h. After separation of the precipitate of KBr and evaporation of the solvent, the remaining oil was fractionated [b.p. 98 °C, 1 mmHg (*ca.* 133 Pa)]. The amine was converted into its dinitrate salt with a cold aqueous nitric acid solution and recrystallized from boiling water (57.6 g, 42%), m.p. 113 °C (Found: C, 13.1; H, 6.7; N, 20.3. $C_6H_{18}N_4O_6S$ requires C, 13.1; H, 6.6; N, 20.4%); δ_H(360 MHz; solvent D_2O; standard sodium 3-trimethylsilylpropane-1-sulfonate) 2.753 (6 H, s, 2 CH_3), 2.919 (4 H, t, 2 SCH_2), 3.289 (4 H, t, 2 NCH_2) and 4.771 (4 H, s, 2 $^+NH_2$).

Distilled and deionized water (Milli-Q quality, conductivity <0.05 μS cm^{-1}) was used throughout for all solutions. Deuterium oxide (Janssen Chimica, 99.8 atom % D) was used as solvent in the ^1H NMR measurements. Carbonate-free (<0.5%) potassium hydroxide solutions (*ca.* 0.250 mol dm^{-3}) were prepared from Titrisol ampoules (Merck) and were standardized by titration with potassium hydrogenphthalate (Janssen Chimica, p.a.). Stock solutions of nitric acid were standardized with the KOH solution. All solutions for the potentiometric and calorimetric titrations were made up to an ionic strength of 0.1 mol dm^{-3} with potassium nitrate (Merck, p.a.).

Potentiometric Measurements.—The potentiometric measurements were carried out using a titration system, equipped with a Radiometer PHM84 pH-meter, a Scott T-100 burette (total volume 5.000 cm^3) and a personal computer. The pH-meter was fitted with a Radiometer G2040C glass electrode and a K4040 calomel reference electrode with a second salt bridge filled with 0.1 mol dm^{-3} KNO_3 solution. A Radiometer TTA-80 titration assembly was used with a thermostatted vessel (maximum volume 50 cm^3) and a mechanical stirrer. All titrations were performed at 25 ± 0.05 °C under an atmosphere of argon, presaturated with water vapour by bubbling through a 0.1 mol dm^{-3} KNO_3 solution. The program TITRATE,[6] slightly modified, was used to monitor the whole titration.

The electrode system was calibrated by titrations of nitric acid (40.00 cm^3, 0.0125 mol dm^{-3}) with standard potassium hydroxide titrant solution (*ca.* 0.250 mol dm^{-3}). The titration data were processed using Gran's method[7] in order to calculate the standard cell potential (E°), the dissociation constant of water (K_w), together with the coefficients of correction terms for changes in the liquid-junction potential in a strong acid medium, a_j ($-\log[H^+] < 2.5$) and for the non-linear electrode response in a strong alkaline medium, b_j ($-\log[H^+] > 11.5$). The pK_w value was found to be 13.78 in accord with literature values,[8] $a_j = -296$ mV dm^3 mol^{-1} and $b_j = 159$ mV dm^3 mol^{-1}. The electromotive force readings were converted into pH values (pH = $-\log[H^+]$) using equation (1). pH Values

$$pH = (E^\circ - E + a_j[H^+] + b_jK_w[H^+]^{-1})/0.059\,16 \quad (1)$$

were obtained by successive approximations taking $[H^+]$ as zero at the start.

Solutions of the ligands contained an excess of mineral acid (40.00 cm^3, *ca.* 0.160 mmol ligand, *ca.* 0.400 mmol H^+) and were titrated in duplicate with the KOH titrant.

Calorimetric Measurements.—The calorimetric titrations were performed in a Tronac model 1250 isoperibol calorimeter. A glass Dewar titration vessel (25 cm^3) and a precision Hamilton burette (2.500 cm^3, delivery rate 0.0885 cm^3 min^{-1})

Table 1 Summary of the results of the check upon the calorimetric system (25 °C, I = 0.1 mol dm^{-3} KNO_3) and comparison with literature values

Equilibrium	$-\Delta H^{\circ}$/kJ mol^{-1} Experimental[a]	Literature
$H^+ + OH^- \rightleftharpoons H_2O$	56.6	56.4[b]
$H^+ + Tris \rightleftharpoons HTris^+$	47.5	47.5[c]
		47.8[d]
$H^+ + GlyO^- \rightleftharpoons Gly$	44.8	44.4[e]

[a] $\Delta H^{\circ} \pm 0.1$ kJ mol^{-1}. [b] Ref. 9, I = 0.1 mol dm^{-3}. [c] Ref. 8. [d] Ref. 10, I = 0.5 mol dm^{-3}. [e] Ref. 8.

were used. The temperature of the water-bath (CTB-1005R, 95 dm^3) was kept accurately at 25 ± 0.0002 °C by means of a precision temperature controller (PTC-41). The calorimeter was interfaced to a computer by a Tronac model 900 computer interface. The data acquisition was performed by a software package (FS101 program) purchased from Tronac. After a series of data selections and transformations, a two-dimensional array of added titrant volume (cm^3) *versus* overall reaction heat (kJ) was obtained. In a typical calorimetric run, a solution of the fully protonated ligand in a slight excess of mineral acid (25.00 cm^3, *ca.* 0.300 mmol ligand, *ca.* 0.700 mmol H^+; total ionic strength 0.1 mol dm^{-3}) was titrated with a KOH titrant solution (1.018 mol dm^{-3}). Heats of dilution for the titrant in 25.00 cm^3 KNO_3 solution (0.1 mol dm^{-3}) were also determined. The calorimetric system and the software were tested by determining the formation enthalpy of water and the protonation enthalpies of tris(hydroxymethyl)aminomethane (Tris) and of glycine (Gly). These results are shown in Table 1, together with the reported literature values.

^{1}H *NMR Measurements.*—The proton nuclear magnetic resonance spectra were recorded with a Brüker WH-360 spectrometer at an ambient temperature of 33 °C. The values of the chemical shifts (δ) were measured with respect to sodium 3-trimethylsilylpropane-1-sulfonate and are reported with a precision of 0.001 ppm.

The concentration of the ligand solutions was 0.020 mol dm^{-3} and the pa_D was adjusted with a concentrated NaOD solution [Janssen Chimica, 40% (w/w) D_2O] ($pa_D = -\log a_D$, where a_D is the activity of the D^+ ion in D_2O). A Radiometer GK2301C combination electrode fitted to a PHM84 pH-meter was used and calibrated at 25 °C with a potassium hydrogenphthalate buffer (pa_H = 4.008) and a borax buffer (pa_H = 9.18). The pH-meter readings in the D_2O solution were converted into the pa_D scale using $pa_D = pa_H + 0.4$.[11] The pa_D scale was converted into the pc_H scale (where $pc_H = -\log[H^+]$ in 0.1 mol dm^{-3} KNO_3 solution) using $pc_H = pa_D - 0.51$ [0.51 is half the difference between pK_{D_2O} (14.8)* and pK_w (13.78) (I = 0.1 mol dm^{-3})].

Calculations.—The overall protonation constants of the ligands were calculated with the program SUPERQUAD.[14] The error in the pH values was taken as 0.002 pH, whereas the error in the added titrant volume was 0.005 cm^3. The overall protonation enthalpies were calculated with a laboratory-written BASIC program CALO, which was a modified version of the earlier program KALO.[15] The program CALO will be described elsewhere. The calculations on the ^{1}H NMR data were performed as indicated in the Discussion.

Results and Discussion

Thermochemical Studies.—The thermodynamic data for the stepwise protonation of the ligands investigated at 25 °C in 0.1 mol dm^{-3} KNO_3 are reported in Table 2. The values for log K_1^H are in the usual range for secondary amines, except for [10]aneN$_2$S which has an exceptionally high value.

Table 2 Thermodynamic data for the stepwise diamine protonation at 25 °C and I = 0.1 mol dm^{-3} KNO_3[a]

Diamine	n	$\log K_n^H$	$-\Delta H_n^{\circ}$/kJ mol^{-1}	$T\Delta S_n^{\circ}$/kJ mol^{-1}
tdan	1	9.91	46.9	9.6
	2	8.94	47.5	3.5
[9]aneN$_2$S	1	9.89	37.8	18.6
		9.67[b]		
	2	4.18	32.6	−8.8
		3.98[b]		
[10]aneN$_2$S	1	12.0	56.1	12.4
	2	3.25	22.9	−4.4

[a] log K_n^H ±0.02, ΔH° ±0.2 kJ mol^{-1}, $T\Delta S^{\circ}$ ±0.3 kJ mol^{-1}. [b] Ref. 3, I = 0.1 mol dm^{-3} $NaNO_3$.

Although the first protonation constant for [9]aneN$_2$S is similar to that for tdan, the protonation heat ΔH_1° for the former is much less exothermic, while its entropy change $T\Delta S_1^{\circ}$ is more favourable. These differences can be explained by a less-efficient electrostatic solvation of the HL^+ ligand form of the cyclic diamine relative to the open-chain one.[16]

The first protonation step of [10]aneN$_2$S is 18.4 kJ mol^{-1} more exothermic than for [9]aneN$_2$S and 9.2 kJ mol^{-1} more exothermic than for tdan. The change in inductive $+I$ effect on the amino groups of [10]aneN$_2$S cannot account for these large differences. It is more likely that the high value of $-\Delta H_1^{\circ}$ results from the formation of an internal $^+$N–H ••• N hydrogen bond, which gives an extra stabilization to the HL^+ form of [10]aneN$_2$S. The less positive $T\Delta S_1^{\circ}$ value then reflects the greater rigidity of the HL^+ ion.

There are no literature data on the thermodynamic protonation functions ΔH_1° and $T\Delta S_1^{\circ}$ for [10]aneN$_3$ and [10]aneN$_2$O, which could be used for comparison with [10]aneN$_2$S. The compound [10]aneN$_3$, however, also shows an exceptionally high value of log K_1^H (12.02, I = 0.1 mol dm^{-3}),[1c] which can be attributed to the formation of an internal $^+$N–H ••• N bond. The lack of agreement in the values of log K_1^H reported for [10]aneN$_2$O (9.56 at I = 0.1 mol dm^{-3} $NaNO_3$;[2c] 10.09 at I = 0.1 mol dm^{-3} KNO_3),[2d] which might be due to the different ionic background, makes a conclusion premature.

The value of log K_2^H for [9]aneN$_2$S and [10]aneN$_2$S is much lower than that for the open chain tdan. This decrease in basicity is a consequence of a larger electrostatic repulsion between the two neighbouring ammonium groups in the ring. This also causes a ring stiffening, making $T\Delta S_2^{\circ}$ negative.

The value of $-\Delta H_2^{\circ}$ for [10]aneN$_2$S is lower than that for [9]aneN$_2$S, as the internal hydrogen bond in the HL^+ form of the former must be broken at the second protonation step.

^{1}H *NMR Studies.*—Table 3 summarizes the results of the ^{1}H NMR study of the protonation of [9]aneN$_2$S and [10]aneN$_2$S in aqueous solution. The quantitative approach of Sudmeir and Reilley[17] was used, which is based on the changes in the chemical shifts of non-labile methylenic protons upon protonation of basic groups in their vicinity.

The deshielding of the methylenic protons in a polyamine when a neighbouring basic site becomes protonated is expressed by equation (2), where δ_i^0 is the chemical shift of the ith

$$\Delta\delta_i = \delta_i^{obs} - \delta_i^0 = \sum_{j=1}^{N} C_{ij} f_j \qquad (2)$$

methylenic proton of the fully deprotonated ligand and δ_i^{obs} is the observed chemical shift of the same proton when n mol of

* Mean of two literature values: 14.71 (ref. 12) and 14.87 (ref. 13).

Table 3 Calculated shielding constants (ppm) for protonation of [9]aneN$_2$S and [10]aneN$_2$S in aqueous solution

Diamine	Medium[a]	C_N[b]	$C_{N'}$[c]	$C_{N+N'}$[d]
[9]aneN$_2$S	Alkaline	0.67	0.20	0.68
	Acidic	0.91	0.52	1.40
[10]aneN$_2$S	Alkaline	—	—	—
	Acidic	0.86	0.46	—
			0.54	
Sudmeier–Reilley values[e]		0.75	0.35	1.10

[a] Different shielding constants are obtained depending on the pa_D of the solution. [b] C_N is the shielding constant for the methylenic protons in α position to a nitrogen atom: protons b in [9]aneN$_2$S and [10]aneN$_2$S. [c] $C_{N'}$ is the shielding constant for the methylenic protons in β position to a nitrogen atom: protons c in [9]aneN$_2$S and c and d in [10]aneN$_2$S. [d] $C_{N+N'}$ is the shielding constant for the methylenic protons in both α and β positions to two equivalent nitrogen atoms: protons a in [9]aneN$_2$S. [e] Ref. 17, reference values.

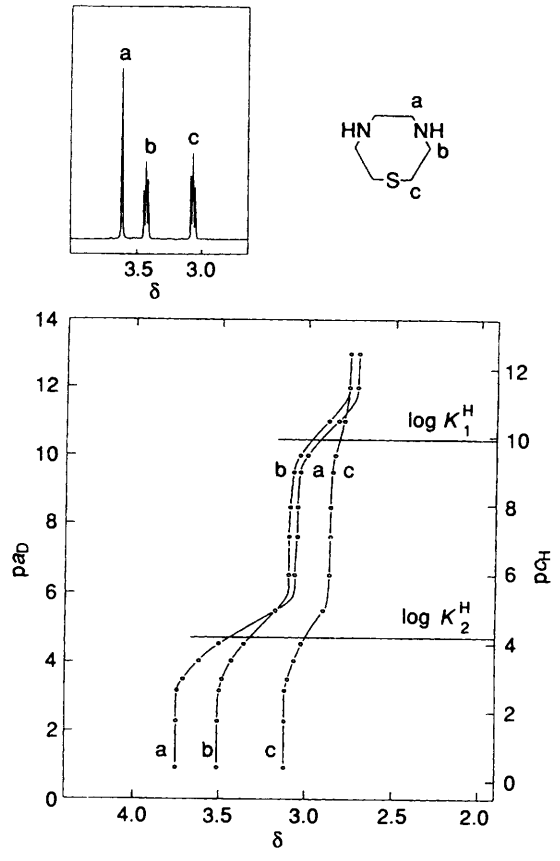

Fig. 1 Proton NMR spectrum of [9]aneN$_2$S at pa_D = 4.04 and titration curves of δ^{obs} *versus* pa_D

acid are added per mol of ligand; f_j is the protonation degree of the jth basic group, out of a total of N different basic groups, and C_{ij} is the shielding constant of the ith methylenic proton by the neighbouring jth basic group. When the unprotonated polyamine is titrated with strong acid relation (3) also holds,

$$n = \sum_{j=1}^{N} \alpha_j f_j \qquad (3)$$

where n is the number of moles of acid added per mol of ligand and α_j represents the number of equivalent basic groups of type j. Both [9]aneN$_2$S and [10]aneN$_2$S contain two identical secondary amino groups, thus $N = 1$ and $\alpha_1 = 2$. Since the

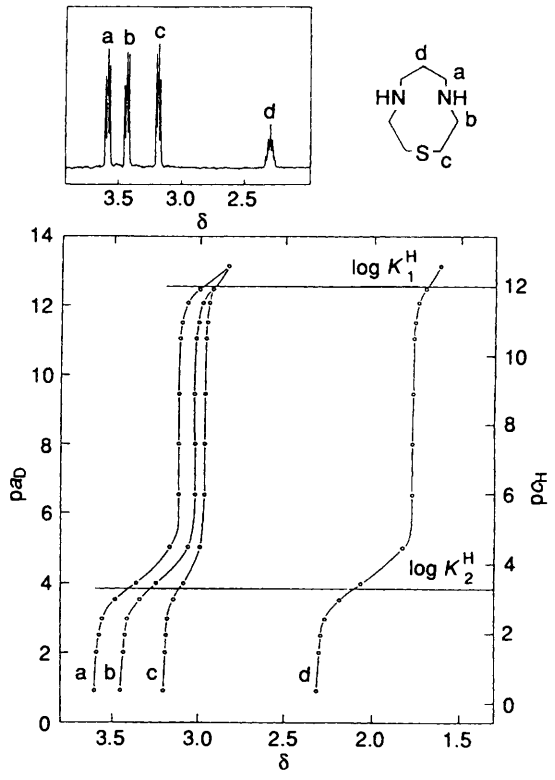

Fig. 2 Proton NMR spectrum of [10]aneN$_2$S at pa_D = 1.99 and titration curves of δ^{obs} *versus* pa_D

two amino groups are separately protonated, their protonation degree f_j can be calculated exactly using equation (3) at any titration point with the known values of n.

The ^{1}H NMR titration curves and the ^{1}H NMR spectra are shown in Fig. 1 for [9]aneN$_2$S and in Fig. 2 for [10]aneN$_2$S. The assignment of the observed resonances to the different non-labile methylenic protons has already been communicated[5] and is indicated in the figures. The shielding constants were calculated from the observed changes in chemical shifts at each protonation step, giving values for alkaline and acid media. The results are given in Table 3.

Two observations can be made. First, the individual values for C_N, $C_{N'}$, and $C_{N+N'}$ differ noticeably from the reference values, and are higher in acid than in alkaline media, at least for [9]aneN$_2$S. This can be attributed to conformational changes in the ligands as they become more protonated. Different low-energy conformations may result from the need to minimize electrostatic charge repulsion in the cyclic polyammonium ions.[18] Secondly, the alkaline C_{N+N} value for [9]aneN$_2$S, calculated from the change in chemical shift of the b methylenic protons, is much lower than the sum of C_N and $C_{N'}$ (0.87 ppm) calculated with the corresponding change for the a and c protons. This indicates that the assumed additivity in equation (2) for the deshielding of the methylenic protons is dependent on the protonation degree of the polyamine. It is then surprising that the additivity rule holds best for the fully protonated form of [9]aneN$_2$S with maximum charge repulsion.

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