13. Polyamines XIV. Protonation Equilibria of Linear Tetraamines Containing two Ethylenediamine Residues

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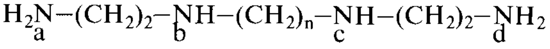
(12.XI.81)

Summary

The syntheses of the linear tetraamines $H_2N-(CH_2)_2-NH-(CH_2)_n-NH-(CH_2)_2-NH_2$ (n = 4 and 5) are described. The protonation of the homologous tetraamines for n = 2, 3, 4, 5, 6 and 8, as well as of *N*-methylethylenediamine, was investigated using potentiometric and calorimetric measurements. The results obtained are discussed taking into consideration the substituent effect on the basicity of the aminic N-atoms.

Introduction. - A simple series of linear N-ligands in which the distance between the N-atoms is varied is represented by the tetraamines 2, n, 2-tet of type **I**.



$$H_2\underset{a}{N}-(CH_2)_2-\underset{b}{N}H-(CH_2)_n-\underset{c}{N}H-(CH_2)_2-\underset{d}{N}H_2$$

I

They contain two ethylenediamine molecules connected by an alkylene chain of n methylene groups through two N-atoms. By variation of n, it is possible to vary the size of a chelate ring in the (1:1)-complexes ML. Because of the presence of two ethylenediamine residues, which are powerful ligands toward divalent 3d- and 10d-cations [1] [2] [3], one expects the formation of stable complexes. While the ligands 2,2,2- and 2,3,2-tet have been investigated [4] [5] [6], the effect of a further increase of n on the stability of the complexes has never been followed up. This is partly due to difficulties in the syntheses of 2,4,2- and 2,5,2-tet, which have been first obtained by us. However, the higher homologues with n ⩾ 6 are easily obtained by methods developed by *van Alphen* [7].

In this paper the measured protonation constants, as well as the thermodynamic functions ΔG, ΔH and ΔS, obtained from direct calorimetric measurements, are used to discuss the protonation equilibria of the ligands of type **I** for n = 2, 3, 4, 5, 6 and 8. Our data for the ligand *N*-methylethylenediamine are used for comparison purposes.

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[1]) Some results are taken from the thesis of *P. B.*, ETH Zürich, 1977.

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All measurements are made under the same experimental conditions, *i.e.* $T=25\,^{\circ}C$ and an ionic strength $I=1$ (KNO_3). The measured pH is defined in the following way: $pH=-\log[H]$, in which [H] is given in $mol \cdot dm^{-3}$.

Results and Discussions. - The protonation constants obtained ($K_p=[H_pL]/([H][H_{p-1}L])$) are given in *Table 1* together with the corresponding thermodynamic quantities. The literature values, given in *Tables 1, 2* and *3* are also reported for comparison purposes. The observed differences are expected in consideration of the different ionic medium or/and temperature of the measurements.

The values for $\log K_p$ and ΔH_p for *N*-methylethylenediamine can be compared with those calculated using *Equations 1* and *2* [8] [9]. Both relationships contain a term (A or B) which is

$$\log K_p = A - \Sigma_i (1/2)^{r-3} \delta_i + S \tag{1}$$

$$-\Delta H_p = B - \Sigma_i \delta_{i,r} \tag{2}$$

Table 1. *Protonation constants and thermodynamic data valid at 25 °C and $I-1(KNO_3)$* (K_p values in $dm^3 \cdot mol^{-1}$, ΔG_p and ΔH_p in $kcal \cdot mol^{-1}$ and ΔS_p in $cal \cdot mol^{-1} \cdot K^{-1}$)

Ligand	Equilibrium	p	$\log K_p$ (± 0.03)	ΔG_p (± 0.1)	ΔH_p (± 0.1)	ΔS_p (± 0.5)
men[a])	$L+H^+ \rightleftarrows HL^+$	1	10.25	-14.0	-11.0	10.1
	$HL^+ + H^+ \rightleftarrows H_2L^{2+}$	2	7.42	-10.1	-10.16	0.0
2,2,2-tet[b])	$L+H^+ \rightleftarrows HL^+$	1	10.07	-13.7	-10.9	9.5
	$HL^+ + H^+ \rightleftarrows H_2L^{2+}$	2	9.50	-13.0	-11.2	6.0
	$H_2L^{2+} + H^+ \rightleftarrows H_3L^{3+}$	3	7.15	-9.8	-10.2	-1.2
	$H_3L^{3+} + H^+ \rightleftarrows H_4L^{4+}$	4	4.02	-8.3	-8.0	-8.5
2,3,2-tet[c])	$L+H^+ \rightleftarrows HL^+$	1	10.28	-14.2	-11.1	10.4
	$HL^+ + H^+ \rightleftarrows H_2L^{2+}$	2	9.51	-13.0	-11.1	6.4
	$H_2L^{2+} + H^+ \rightleftarrows H_3L^{3+}$	3	7.35	-10.0	-10.8	-2.7
	$H_3L^{3+} + H^+ \rightleftarrows H_4L^{4+}$	4	6.08	-8.3	-9.8	-3.0
2,4,2-tet	$L+H^+ \rightleftarrows HL^+$	1	10.40	-14.2	-11.3	9.6
	$HL^+ + H^+ \rightleftarrows HL^{2+}$	2	9.68	-13.2	-11.5	5.7
	$H_2L^{2+} + H^+ \rightleftarrows H_3L^{3+}$	3	7.60	-10.4	-10.9	-1.6
	$H_3L^{3+} + H^+ \rightleftarrows H_4L^{4+}$	4	6.80	-9.2	-10.5	-4.3
2,5,2-tet	$L+H^+ \rightleftarrows HL^+$	1	10.47	-14.3	-11.34	10.0
	$HL^+ + H^+ \rightleftarrows H_2L^{2+}$	2	9.79	-13.4	-11.5	6.3
	$H_2L^{2+} + H^+ \rightleftarrows H_3L^{3+}$	3	7.69	-10.5	-11.0	-1.6
	$H_3L^{3+} + H^+ \rightleftarrows H_4L^{4+}$	4	7.01	-9.6	-10.8	-4.4
2,6,2-tet	$L+H^+ \rightleftarrows HL^+$	1	10.60	-14.5	-11.6	9.6
	$HL^+ + H^+ \rightleftarrows H_2L^{2+}$	2	9.925	-13.5	-11.5	6.8
	$H_2L^{2+} + H^+ \rightleftarrows H_3L^{3+}$	3	7.755	-10.6	-11.15	-1.9
	$H_3L^{3+} + H^+ \rightleftarrows H_4L^{4+}$	4	7.13	-9.7	-11.0	-4.4
2,8,2-tet	$L+H^+ \rightleftarrows HL^+$	1	10.57	-14.4	-11.8	8.9
	$HL^+ + H^+ \rightleftarrows H_2L^+$	2	10.04	-13.7	-11.6	7.2
	$H_2L^{2+} + H^+ \rightleftarrows H_3L^{3+}$	3	7.79	-10.62	-11.1	-1.6
	$H_3L^{3+} + H^+ \rightleftarrows H_4L^{4+}$	4	7.23	-9.86	-11.1	-4.0

[a]) $\log K_p = 10.14$ (p = 1) and 7.26 (p = 2) at 25 °C and $[KNO_3] = 1$ M [10].

[b]) $\log K_p = 10.25$ (p = 1), 9.50 (p = 2), 7.28 (p = 3) and 6.02 (p = 4) at 25 °C and I = 0.5 (KCl) [13].

[c]) $-\Delta H_p = 10.96$ (p = 1), 11.33 (p = 2), 10.03 (p = 3) and 9.18 (p = 4) at 25 °C and I = 0.5 (KCl) [5].

characteristic of the basic group considered to be protonated and the quantities δ_i or $\delta_{i,r}$ representing the substituent effect of the different atoms present in the base: they are normally known for 20 resp. 25 °C and ionic strengths $I \rightarrow 0$. The number r is the number of atoms between the basic atom and the substituent atom considered, increased by 1. The statistical term S takes into consideration the presence of equivalent atoms in the base and in the conjugated acid. For the case considered, the values of A are 10.77 ± 0.2 for a primary (N_I) and 11.15 ± 0.2 for a secondary (N_{II}) N-atom. The value of δ_i is 0.8 for a N_I, 0.9 for a N_{II}, 3.6 for a quaternary positive-charged N-atom and zero for the C-atoms [8]. The calculated values for the first protonation: $L + H^+ \rightarrow HL^+$ are different for the reaction at N_I ($\log K = 10.77 - 0.9 = 9.87$) and at N_{II} ($\log K = 11.17 - 0.8 = 10.35$). For the second step, the influence of the protonated ammonium group is considered as giving different values for the protonation at N_I ($\log K = 10.77 - 3.6 = 7.17$) or at N_{II} ($\log K = 11.15 - 3.6 = 7.55$). The comparison with the experimental values $\log K_1 = 10.25$ and $\log K_2 = 7.42$ shows that the protonation is likely to take place at both N-atoms simultanously in each step. Because the experimental ionic strength is equal 1, and the values of A and B are affected by a large error (± 0.2) an exact assignment of the amounts of the different species is not possible. Similar calculations with *Equation 2* and the corresponding $\delta_{i,n}$ give the following results: for the first protonation: $\Delta H = -11.99$ (N_I) and -10.65 (N_{II}) $\mathrm{kcal \cdot mol^{-1}}$ and for the second protonation: $\Delta H = -11.01$ (N_I) and -9.67 (N_{II}) $\mathrm{kcal \cdot mol^{-1}}$. For the full protonation one obtains $-11.99 + (-9.67) = -20.66$ instead of the experimental value -21.15 $\mathrm{kcal \cdot mol^{-1}}$ with a discrepancy of 2.5%. These values show that for HL^+ a tautomeric equilibrium should exist. *Paoletti et al.* [10] using only similar calorimetric data for the same diamine have also concluded the presence of the two possible forms of HL^+ in nearly equal amounts.

Plots of the experimental values of $\log K_p$, ΔH_p and ΔS_p for the tetraamines *vs.* n are shown in *Figures 1-3*, respectively. The calculations performed as discussed above give two series of values for K_1 which correspond to a protonation of N_I or N_{II}, respectively. The comparison with the experimental values *(Fig. 1)* supports the idea that the first-protonation step for 2,2,2-tet occurs mainly to a primary N-atom (N_I) but as n is increased also the secondary N-atom (N_{II}) is involved. This supposition for the more basic N_{II}-atom seems reasonable because on increasing n the mutual influence between the two ethylenediamine residues diminishes. In the series of tetraamines of type **I** this effect would become more important as the two N_{II}-atoms are closer to each other thus making protonation of 2,2,2-tet the least favored. This can be seen from the corresponding calculated values for the logarithm of the micro-constants, *i.e.*, 10.06 for N_I and 9.64 for N_{II}. The mutual influence between the two ethylenediamine residues decreases as n increases. For 2,8,2-tet it is negligible and each residue behaves as an *N*-methylethylenediamine unit in which the first protonation should occur mainly at N_{II} with $\log K_1 = 10.62$ against 10.16 for N_I.

After the second-protonation step, because of the electrical repulsion between the two positive charges, the species H_2L^{2+} is expected to be protonated at the two more remote (primary) N-atoms. However, as n is increased because of the higher

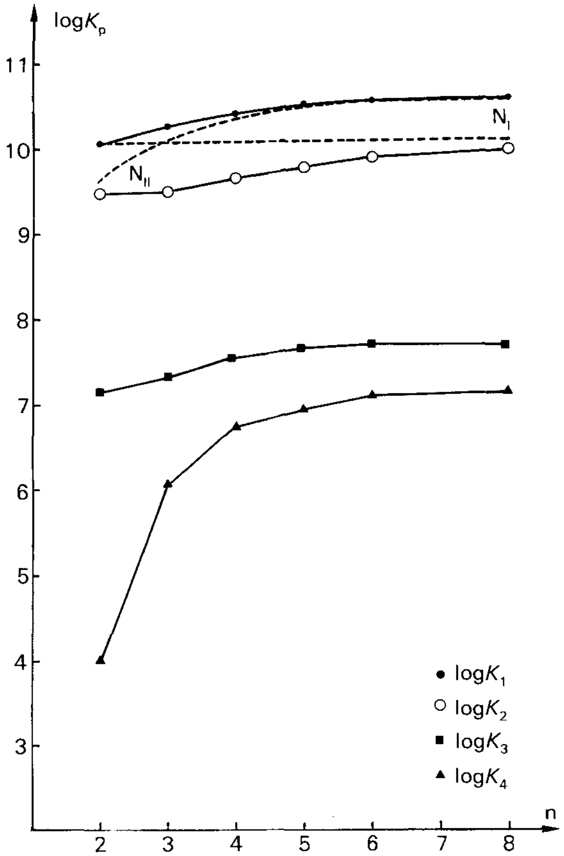


Fig. 1. *The logarithm of* K_p (p = 1, 2, 3 and 4; [dm^3 · mol^{-1}]) *of 2,n,2-tet* vs. *the number n* (Dotted curves correspond to $\log K_I$ calculated with *Eqn. 1* for the protonation of a primary (N_I) or of a secondary (N_{II}) N-atom)

basicity of the secondary N-atom, partial protonation at the latter basic atom occurs. In principle, if all the terms in *Equation 1* for the ionic strength considered where known, it would be possible to calculate the protonation constants of each single basic atom [11]. For each tetraamine, using the numbering a, b, c and d for the N-atoms in **I**, four different values for K_1K_2 are expected which correspond to the protonation in the positions a and b, a and c, a and d as well as b and c, *i.e.* $K_1K_2(\mathrm{a,b})$, $K_1K_2(\mathrm{a,c})$, $K_1K_2(\mathrm{a,d})$ and $K_1K_2(\mathrm{b,c})$. The expected value for K_1K_2 is then given by the following relation:

$$K_1K_2 = K_1K_2(\mathrm{a,b}) + K_1K_2(\mathrm{a,c}) + K_1K_2(\mathrm{a,d}) + K_1K_2(\mathrm{b,c}) \qquad (3)$$

Using the values given by *Clark & Perrin* [8], it is possible to see that for n = 2 $K_1K_2(\mathrm{a,b})$ and $K_1K_2(\mathrm{b,c})$ are 1000 times lower in magnitude than the other two terms and therefore the corresponding species are present in a 1000 time lower concentration respect to the other species and are negligible. For the molar ratio of the species $H_2L(a,c)^{2+}$ and $H_2L(a,d)^{2+}$ one obtains 0.285 and 0.715, respectively. For 2,8,2-tet also the species protonated at the positions b and c should be considered, giving for the three species the following molar ratio: (a,c) 0.40, (a,d) 0.07 and (b,c) 0.53. The calculated values for $\log K_1K_2$ (n=2: 19.57, n=8: 20.70) are in reasonable agreement with the experimental values (n=2: 19.57 and n=8: 20.60).

The third-protonation step gives H_3L^{3+} and would probably correspond for 2,2,2-tet(2,8,2-tet) to the formation of a species in which one $N_{II}(N_I)$ remains unprotonated. The values for $\log K_3$ obtained, with consideration of the more stable tautomeric forms for H_2L^{2+}, are for 2,2,2-tet: 6.5 (exp. 7.15) and for 2,8,2-tet: 7.47 (exper. 7.79). The last protonation step gives for 2,2,2-tet: $\log K_4=3{,}2$ (exper. 4.02) and for 2,8,2-tet: 6.8 (exper. 7.23). The large discrepancies for some of these values are mainly due to differences in the ionic strength used in our measurements and that at which the δ_i values of *Equation 1* (I→0) have been estimated. This causes large changes of $\log K_p$ as can be seen by comparing the values of $\log K_3$ and K_4 for different ionic strengths (see *Table 2*). They are mainly due to the different effect of the ionic medium on the activity of species with increasing ionic charge. The $\log K_p$ values at I=0.1 agree with those predicted by *Equation 1*, within the error of A.

On the other hand, the enthalpy values ΔH_p for each ligand and for the different protonation steps are very similar in magnitude. The graphical representation of these data *(Fig. 2)* shows that the variations in ΔH_p are much smaller than those of $\log K_p$. Therefore, the assignment of the values to an equilibrium involving the protonation of a given N-atom (a, b, c and d) is much more difficult. Furthermore the enthalpies of protonation of H_2L^{2+} and H_3L^{3+} depend strongly on the ionic strength. This appears evident from the values for 2,2,2-tet given in *Table 3*. Nevertheless the values obtained for the first step, which are less dependent on the ionic strength, are in agreement with the above interpretation.

The values for the entropy of protonation show that within the estimated error of ±0.5 cal $mol^{-1} \cdot K^{-1}$, similar changes are obtained for each step *(Fig. 3)*. Therefore the more important factor determining this quantity is the charge of the species and not the spatial charge distribution on the protonated amine with exception of ΔS_4 for 2,2,2-tet. Only the formation of HL^+ and H_2L^{2+} is accompanied by an entropy gain ($\Delta S>0$), which could correspond to an increase of the number of species (free H_2O molecules). An increase of charge on the species formed increases also their electrical field with immobilization of a larger number of dipolar solvent

Table 2. *Protonation constants of 2,2,2-, 2,3,2- and 2,6,2-tet at different ionic strengths and 25°C*

		2,2,2-tet			2,3,2-tet		2,6,2-tet	
	I	0.1 [4] [12]	0.5 [13]	1.0	0.1 [14]	1.0	0.1 [14]	1.0
$H^+ + L \rightleftarrows HL^+$	$\log K_1$	9.8	9.85	10.02	10.16	10.39	10.41	10.66
$H^+ + HL^+ \rightleftarrows H_2L^{2+}$	$\log K_2$	9.1	9.31	9.39	9.23	9.58	9.64	10.00
$H^+ + H_2L^{2+} \rightleftarrows H_3L^{3+}$	$\log K_3$	6.57	6.86	7.00	6.88	7.37	7.31	7.78
$H^+ + H_3L^{3+} \rightleftarrows H_4L^{4+}$	$\log K_4$	3.26	3.66	4.00	5.40	6.05	6.60	7.10

Table 3. *ΔH-([kcal · mol^{-1}]) and ΔS-([cal · mol^{-1} · K^{-1}]) values for the protonation of 2,2,2-tet at different ionic strengths and 25°C*

	I = 0.1 [12]		I = 1.0	
	$-\Delta H_p$	ΔS_p	$-\Delta H_p$	ΔS_p
$H^+ + L \rightleftarrows HL^+$	11.01	7.8	10.9	9.6
$H^+ + HL^+ \rightleftarrows H_2L^{2+}$	11.27	3.4	11.2	6.0
$H^+ + H_2L^{2+} \rightleftarrows H_3L^{3+}$	9.53	−2.0	10.2	−1.2
$H^+ + H_3L^{3+} \rightleftarrows H_4L^{4+}$	6.83	−8.1	8.2	−9.0

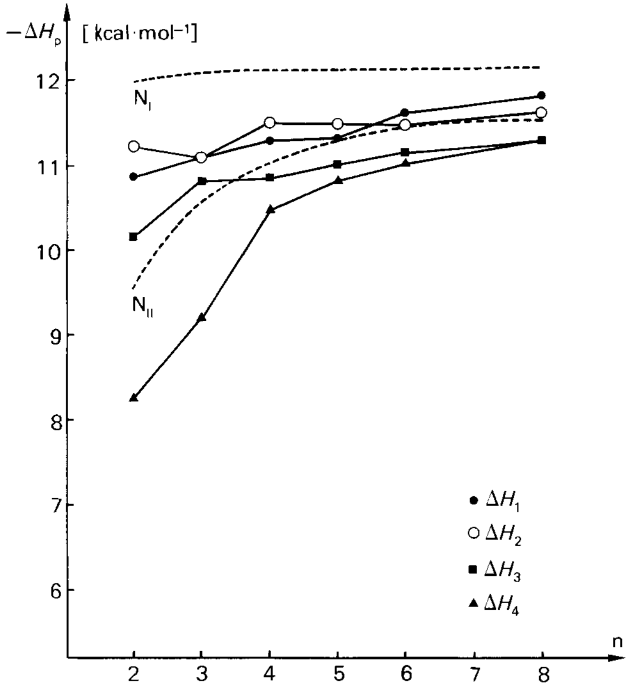


Fig. 2. *Enthalpy of protonation* $-\Delta H_p$[kcal · mol^{-1}] *of 2,n,2-tet* vs. *the number n* (Dotted curves correspond to $-\Delta H_1$ calculated with *Eqn. 2* for protonation of a primary (N_I) or of a secondary (N_{II}) N-atom)

molecules and reduction of the entropy gain. As the association of two species in the gas phase corresponds to a negative reaction entropy of 20–30 cal · mol^{-1} · K^{-1}, *i.e.* to a larger entropy change respect to those of *Table 1*, all values obtained can be attributed to an effective increase in the number of species in solution if all other entropy contributions (conformational, rotational, vibrational, ...) in ΔS or their sum can be neglected. A more detailed discussion is not possible as the standard entropies of the different species in solution are not yet known.

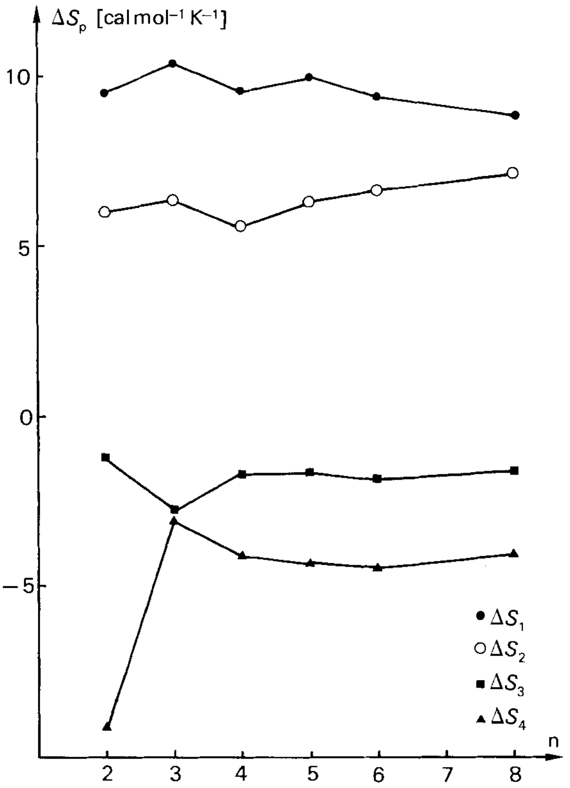
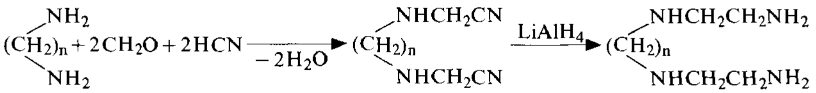


Fig. 3. *Entropy of complex formation of 2, w, 2-tet* vs. *the number n*

Experimental Part

1. Preparation of the ligands. - The method of *van Alphen* has been used in the preparation of the tetraamines of type **I** with n = 3, 6 and 8. This is based on the reaction of an *a,ω*-dibromoalkane with an excess of ethylenediamine in ethanolic solution which occurs on addition of solid KOH. The tetraamines obtained by distillation, after separation of KBr, ethylenediamine and water, were neutralized with HNO_3 and separated as tetrahydronitrates. Because of formation of cyclic products, the same reaction cannot be applied to obtain 2,4,2- and 2,5,2-tet. For this reason we used the reaction below [15] [16].



$$(CH_2)_n\begin{matrix}NH_2\\NH_2\end{matrix} + 2CH_2O + 2HCN \xrightarrow[-2H_2O]{} (CH_2)_n\begin{matrix}NHCH_2CN\\NHCH_2CN\end{matrix} \xrightarrow{LiAlH_4} (CH_2)_n\begin{matrix}NHCH_2CH_2NH_2\\NHCH_2CH_2NH_2\end{matrix}$$

1,4,9,12-Tetraazadodecane tetrahydrochloride. The solution of 1,4-diaminobutane (44 g, 0.5 mol) in 10 ml water was acidified at *ca.* 0° by addition of 85 ml conc. hydrochloric acid (1 mol). A solution of 49 g KCN (1 mol) and 1.5 g $CaCl_2$ in 50 ml water and then an aq. 37.7% solution (80 ml) of formaldehyde were added dropwise at 10°. After standing, the obtained dinitrile was extracted with benzene. The product (35 g) was used without purification. To 5 g $LiAlH_4$ in 150 ml freshly distilled THF were added 3.4 ml 100% sulfuric acid and thereafter 7.8 g dinitrile dissolved in 40 ml THF under stirring at 0°. After standing the excess hydride was carefully destroyed by addition of 20 ml water and 50 ml 12% NaOH-solution. The amine was extracted with $CHCl_3$, and after evaporation of the solvent, was neutralized with dil. HCl-solution and dried. The product, dissolved in the minimum amount of conc. HCl-solution at 50° gave the hydrochloride on cooling. After two recrystallizations the substance was of the necessary purity as shown by alkalimetric titration. Yield of the reduction: 1.1 g (14%). Analysis of the tetrahydrochloride, after drying over $CaCl_2$ in vacuum dessiccator:

$C_8H_{26}Cl_4N_4$	Calc.	C 29.64	H 8.08	N 17.29	Cl 44.98%
(320.12)	Found	,, 29.70	,, 7.98	,, 16.86	,, 43.70%

1,4,10,13-Tetraazatridecane tetrahydrochloride was obtained in the same way.

$C_9H_{28}Cl_4N_4$	Calc.	C 32.35	H 8.40	N 16.80	Cl 42.50%
(334.15)	Found	,, 32.36	,, 8.38	,, 16.64	,, 42.12%

The purity of the products was further checked by alkalimetric titrations and determination of the p*K* values of the tetraprotonic acids. Sometimes a better purification was achieved by elution of the amine through an anion exchanger in the OH^--form or by precipitation of the tetrahydrochloride with HCl-gas from a dry methanolic solution of the amine.

2. Determination of the protonation constants and of the protonation enthalpy. - See [17-19].

The authors wish to express their gratitude to Mr. *B. Rüttimann* for his help in the synthesis and in the measurements. The support of these investigations *(P. B.)* by the *Schweizerischer Nationalfond zur Förderung der wissenschaftlichen Forschung* is gratefully acknowledged.

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