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Proton coordination by polyamine compounds in aqueous solution

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Abstract

The present article is concerned with proton transfer reactions in aqueous solution of open-chain, macrocyclic and macropolycyclic or cage compounds having nitrogen atoms as protonation sites in the molecular framework, although several compounds with additional different donors will be considered. The main purpose of this review is to collect some significant examples of proton transfer processes in order to show how the electronic properties and molecular topology of polyamines affect the thermodynamic parameters of their protonation equilibria.

Keywords: Polyamine compounds; Proton transfer reactions; Thermodynamic parameters

1. Introduction

'*The most general and important reaction in chemistry*' [1] has been defined as the reaction which involves transfer of a proton from one atom to another. This elementary reaction plays a fundamental role in innumerable processes including acid–base neutralization, electrophilic addition, etc. [2,3]. The proton occupies a special position as a promoter in chemical reactions occurring in solution. It is well known that because of its small radius, proton does not exist as an elementary particle in water, but binds to a molecule of water forming a covalent hydronium ion H_3O^+ (primary hydration). The last species through hydrogen bond agglomerates other water molecules forming more hydrated species like $H_9O_4^+$ (secondary hydration) [4]. In spite of the complexity of the proton–water system, we will use the name 'proton' with the meaning of 'proton in aqueous solution'.

Although the literature including thermodynamic data on protonation equilibria in aqueous solution is very vast [5–15], there was not a comprehensive review centered on this topic. The present article is concerned with proton transfer reactions in aqueous solution of open-chain, macrocyclic and macropolycyclic or cage compounds having nitrogen atoms as protonation sites in the molecular framework, although several compounds with additional different donors will be considered. These compounds have been widely employed as receptors for different types of substrates like metal ions and anions. Since polyamines are bases in aqueous solution they give rise to competition between their protonation and complexation reactions. Therefore, the basicity behavior of such compounds in aqueous solution has to be investigated preliminary to any complexation study.

The main purpose of this review is to collect some significant examples of proton transfer processes in order to show how the electronic properties and molecular topology of polyamines affect the thermodynamic parameters of their protonation equilibria.

2. Determination of thermodynamic parameters

The determination of protonation constants of many organic molecules received important consideration during about the first half of the present century owing to the increasing interest in their application as ligands in the new coordination chemistry area. Experimental data obtained in those studies were subjected to graphical analysis [16,17]. More recently, the development in instrumentation, the introduction of glass electrodes for precise and quick measurements of H^+ equilibrium concentration [18], along with the use of more and more efficient computer programs [19,20], have given impulse to the methodical determination of protonation constants, allowing the study of very intricate multiprotic systems. Most of the known protonation constants have been determined by pH-metric methods using glass electrodes [2–23]. Calibration of glass electrodes can be achieved using buffers of specific pH values when only a relative scale of acidity is required, while, for the general use in potentiometric methods, a linear calibration curve of experimental emf readings versus logarithms of the corresponding calculated H^+ concentrations should be obtained by means of strong acid–strong base titrations. Using the last method, there is a reduced range of free H^+ concentrations suitable for calibration, corresponding to ca. $2.5 <$ observed pH < 10.5, because of liquid junction potential in more acidic solutions [18,24–27] and increasing electrode sensitivity to alkali metal cations at higher pH [18]. Procedures for calibration of these electrodes out of this range have been proposed, allowing the potentiometric method using glass electrode to be extended [25,28,29]. Nevertheless, protonation constants smaller than 10^2 or greater than 10^{11} must be evaluated very critically. Indeed many authors prefer to make use of alternative techniques [16,26,27] for determining very small and very large protonation constants. The techniques most widely used instead of glass electrode potentiometric measurements are based on spectrophotometric, nuclear magnetic resonance (NMR), solubility and ion exchange methods. In contrast to potentiometry, sometimes these techniques do not permit the use of inert electrolytes required to keep constant the ionic strength during measurements leading, thus, to rough determination of protonation constants. For constants in the range $10–10^3$ dm^3 mol^{-1} the calorimetric technique is also quite well suited to their determination. The calorimetric method has the advantage that along with the equilibrium constants the corresponding enthalpy changes are also determined [30–34]. The knowledge of enthalpic and entropic contributions of protonation processes is generally very useful in the identification of protonation sites and in the evaluation of solvent effects and, therefore, they are largely sought [35]. Direct calorimetric methods normally produce very accurate values. However, some protonation enthalpies have been determined by van't Hoff analysis of protonation constants at different temperatures. Also, this procedure can furnish reliable ΔH° values provided that a set of highly accurate equilibrium constants, determined under the same experimental conditions in a sufficiently wide range of temperature, is used, and there is no temperature dependency of $\Delta H°$ within this ΔT range. Otherwise corrections for the temperature dependency of $\Delta H°$, by means of the Kirchhoff equation, have to be applied once the heat capacity, ΔC°_p, is known.

Nevertheless, $\Delta H°$ values obtained by van't Hoff analysis of protonation constants require a more critical evaluation.

3. Open-chain polyamines

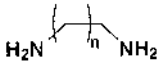
It is well known that in the gas-phase the basicity of ammonia and its methyl derivatives follows the sequence $N(CH_3)_3 > NH(CH_3)_2 > NH_2(CH_3) > NH_3$ [36–38]. Since alkyl groups are electron donating towards electronegative atoms, the replacement of hydrogen atoms by methyl groups in ammonia yields a regular increase in basicity in the gas phase. In aqueous solution, however, the basicity sequence is rather different [39,40]. Reported values for the logarithms of the stepwise basicity constants (298 K, $I = 0.1$ mol dm^{-3}) of these simple amines are as follows: $NH(CH_3)_2$, $\log K = 10.77$, $NH_2(CH_3)$, $\log K = 10.63$, $N(CH_3)_3$, $\log K = 9.82$; NH_3, $\log K = 9.28$, the basicity order being $NH(CH_3)_2 \sim NH_2(CH_3) > N(CH_3)_3 > NH_3$. Since B-strain effects [41] should be discarded due to the regular order observed in the gas phase, the intrinsic acid–base behavior of the water molecules must be responsible of this altered order and, particularly, of the low basicity of trimethylamine in aqueous solution. Water molecules are good hydrogen-bond donors and acceptors and will solvate stronger positively charged ammonium cations than uncharged amines. Therefore, solvation will tend to enhance the basicity of all amines being such an increase greater the larger the number of non-substituted hydrogens in the amines and thus the number of possible hydrogen bonds with the solvent.

This simple and well-known discussion has advanced most of the parameters (inductive effects, strain effects, and hydrogen bonding) for analyzing the acid–base behavior of amines.

With regard to polyamines, apart from the effects above mentioned, electrostatic repulsion between charged ammonium sites will play a predominant role in determining the actual values of the protonation constants and the location of the acidic protons in the compound (protonation pattern).

Extensive work on the thermodynamics of protonation of open-chain polyamines has been performed and a great deal of references can be found in the literature. Stability constant collections and electronic databases in Refs. [5–15], include most of the relevant work performed on this topic. For the purpose of this article, the data for di-, tri-, tetra- and pentaamines have been taken from the excellent critical stability constant review of Martell et al. [9]. Selected bibliography including some of the most relevant contributions to this chemistry is included in Refs. [42–70].

3.1. Unsubstituted open-chain polyamines



n = 1 (1)
n = 2 (2)
n = 3 (3)
n = 4 (4)
n = 5 (5)

An analysis of the basicity constants of the series of diamines ethylenediamine (**1**), propylenediamine (**2**), butylenediamine (**3**), pentamethylenediamine (**4**) and hexamethylenediamine (**5**) can provide a first illustration of the influence of electrostatics effects on polyamine protonation (Table 1a, b)

In (**1**) the difference between the protonation constants of the first and second protonation steps is 2.8 logarithmic units while in (**2**) such a difference is reduced in one logarithmic unit being 1.8 logarithmic units. Thus, the presence in (**2**) of a propylenic spacer between the terminal primary amino groups reduces significantly the electrostatic repulsion between both sites. This effect is much less important on going from propylenediamine to butylenediamine ($\Delta \log K) = 1.3$) and even less significant when passing to the next term pentamethylenediamine (**4**) (($\Delta \log K) =$ 0.9) (Table 1a). Finally, the addition of a further methylene group in the chain does not produce further decreases in the gap between both protonation constants being such a difference the same for (**4**) than for (**5**) (Table 1a, Fig. 1). Indeed, in the case of (**4**) and (**5**) the difference between both constants can be basically attributed to statistical effects. Therefore, the conclusion that can be drawn is that electrostatic repulsions are very significant when two amino groups are separated by an ethylenic chain, this effect being considerably attenuated when the separation is by a propylenic chain and vanishing when the amino groups are linked by a hexamethylenic chain.

The stepwise protonation enthalpies for these processes, shown in Table 1b, also support this behavior. The difference in exothermicity between the first and second protonation steps decreases along the series, disappearing almost completely for (**5**). The inductive effects of the methylene groups and the reduced effect of more distant amino groups are reflected in larger protonation constants and more

Table 1
Logarithms of the stepwise protonation constants and enthalpy terms (kJ mol^{-1}) for the stepwise protonation of diamines (**1**–**5**) [9] where $I = 0.1$ mol dm^{-3} and $T = 298$ K unless otherwise noted

	(**1**)	(**2**)	(**3**)	(**4**)	(**5**)
(a) Logarithms					
Log K_1	9.89	10.56	10.72	10.78	10.97
Log K_2	7.08	8.76	9.44	9.85	10.09
Log β [a]	16.97	19.32	20.16	20.63	21.04
Δ Log K [b]	2.81	1.80	1.28	0.93	0.88
(b) Enthalpy terms (kJ mol^{-1})					
$-\Delta H^\circ_1$	49.7	54.3	56.9[c]	58.1[c]	58.1[c]
$-\Delta H^\circ_2$	45.6	51.0	55.2[c]	56.0[c]	57.3[c]
$\Delta(\Delta H^\circ)$ [d]	4.1	3.3	1.7[c]	2.1[c]	0.8[c]

[a] Log $\beta = \Sigma \log K_i$.
[b] Difference between the stepwise protonation constants
[c] $I = 0.5$ mol dm^{-3}.
[d] Differences between the first and second stepwise protonation enthalpies.

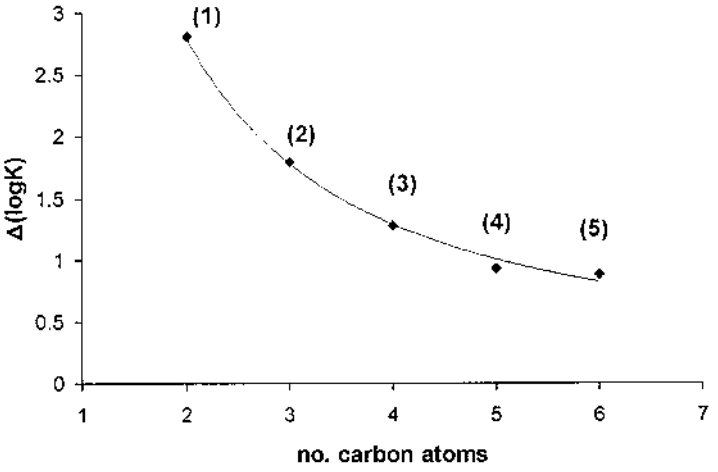
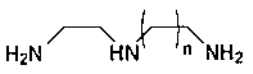
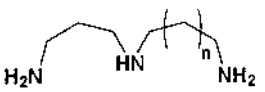


Fig. 1. Plot of the differences between the first and second stepwise protonation constants of diamines (**1**–**5**) vs. the number of carbon atoms in the chain.

exothermic contributions. In Table 1b it can be seen that the enthalpy terms for the first protonation of (**3**), (**4**) and (**5**) are, within the experimental errors reported, almost the same denoting also an attenuation of the latter effect with the number of methylene groups in the chain. Nevertheless, other possible contributions like hydrogen bonding or/and solvation should not be ignored.



n = 1 (**6**)
n = 2 (**7**)
n = 3 (**8**)



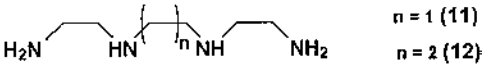
n = 1 (**9**)
n = 2 (**10**)

Triamines like 3-azapentane-1,5-diamine (**6**), usually named dien, 3-azahexane-1,6-diamine (2,3-tri) (**7**), 3-azaheptane-1,7-diamine (2,4-tri) (**8**), 4-azaheptane-1,7-diamine (3,3-tri) (**9**) and 4-azaoctane-1,8-diamine (3,4-tri or spermidine) (**10**) represent a new point to examine since they both display different numbers of methylene groups between the nitrogen atoms and also different kinds of amino groups, primary at the ends and secondary in the middle of the molecule. Table 2a, b present the stepwise protonation constants, cumulative basicity and enthalpy terms for the protonation of these molecules, respectively.

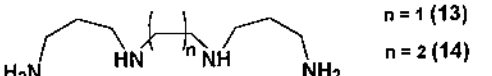
Again the magnitudes of the basicity constants reflect the kind of chains linking the amino groups. In a triamine, the change of an ethylenic chain by a propylenic one, increases the cumulative basicity by more than two orders of magnitude ($\Delta \log \beta$ (**7**)–(**6**) = 2.4, $\Delta \log \beta$ (**10**)–(**8**) = 2.2). However, replacement of a propylenic chain by a butylenic one just increases the overall basicity in about one order

of magnitude ($\Delta \log \beta$ (**8**)–(**7**) = 1.3, $\Delta \log \beta$ (**10**)–(**9**) = 1.0). The grouping of the constants is also reflecting the coulombic repulsion in the molecules. While (**6**) presents two relatively high protonation constants and one much lower (for (**6**), $\log K_1 - \log K_2 = 0.82$, $\log K_3 - \log K_4 = 4.79$), the grouping of constants in the other triamines reveals either a set of two high constants and one last intermediate or three high constants as a function of the length of the hydrocarbon chains between the nitrogen atoms. Although this is not clear cut, (**7**) and (**8**), containing an ethylenic chain, will be representative of the first type while (**9**) and (**10**), with only propylenic and/or butylenic chains, would belong to the second one (Table 2a).

The enthalpic contributions for the protonation of (**6**) are highly exothermic for the first two stages and much less exothermic for the third one. As can be seen in Table 2b, all the other polyamines of the series show a smaller gap between the enthalpies of the second and third protonation steps denoting the lower electrostatic repulsion produced in these molecules upon protonation.



n = 1 (**11**)
n = 2 (**12**)



n = 1 (**13**)
n = 2 (**14**)
n = 3 (**15**)

Table 2
Logarithms of the stepwise protonation constants and enthalpy terms (kJ mol^{-1}) for the stepwise protonation of triamines (**6**–**10**) [9] where $I = 0.1$ mol dm^{-3} and $T = 298$ K

	(**6**)	(**7**)	(**8**)	(**9**)	(**10**)
(a) Logarithms					
Log K_1	9.84	10.21	10.65	10.65	10.89
Log K_2	9.02	9.17	9.42	9.57	9.81
Log K_3	4.23	6.10	6.71	7.69	8.24
Δ Log $K_{1/2}$ [a]	0.8	1.0	1.2	1.1	1.1
Δ Log $K_{2/3}$ [b]	4.8	3.1	2.7	1.9	1.6
Log β [c]	23.09	25.48	26.78	27.91	28.94
(b) Enthalpy terms (kJ mol^{-1})					
$-\Delta H_1^\circ$	46.8	51.0	51.0	51.4	56.4
$-\Delta H_2^\circ$	50.2	50.6	48.5	54.3	53.5
$-\Delta H_3^\circ$	30.0	41.8	41.0	43.9	48.0
$\lvert\Delta(\Delta H^\circ)_{1/2}\rvert$ [d]	3.4	0.4	2.5	3.1	2.9
$\lvert\Delta(\Delta H^\circ)_{2/3}\rvert$ [e]	20.2	8.8	6.5	10.4	4.6

[a] Differences between the first and second protonation constants.
[b] Differences between the second and third protonation constants.
[c] $\log \beta = \Sigma \log K_i$.
[d] Absolute differences between the enthalpy terms of the first and second protonation steps.
[e] Absolute differences between the enthalpy terms of the second and third protonation steps.

Table 3
Logarithms of the stepwise protonation constants, enthalpy terms (kJ mol^{-1}) and entropy terms (kJ mol^{-1}) for the stepwise protonation of tetraamines (**11**–**15**) [9] where $I = 0.1$ mol dm^{-3} and $T = 298$ K

	(**11**)	(**12**)	(**13**)	(**14**)	(**15**)
(a) Logarithms					
Log K_1	9.74	10.08	10.53	10.46	10.80
Log K_2	9.07	9.26	9.77	9.82	10.02
Log K_3	6.59	6.88	8.30	8.54	8.85
Log K_4	3.27	5.45	5.59	7.21	7.96
Δ Log $K_{1/2}$ [a]	0.7	0.7	0.8	0.6	0.8
Δ Log $K_{2/3}$ [b]	2.5	2.4	1.5	1.3	1.2
Δ Log $K_{3/4}$ [c]	3.3	1.4	2.7	1.3	0.9
Log β [d]	28.7	31.7	34.19	36.0	37.6
(b) Enthalpy terms (kJ mol^{-1})					
$-\Delta H_1^\circ$	45.1	46.0	51.7	51.0	54.8
$-\Delta H_2^\circ$	47.2	47.2	51.8	52.3	51.8
$-\Delta H_3^\circ$	39.0	41.8	43.2	48.9	51.8
$-\Delta H_4^\circ$	29.0	38.0	34.1	45.6	48.1
$\lvert\Delta(\Delta H^\circ)_{1/2}\rvert$ [e]	2.1	1.2	0.1	1.3	3.0
$\lvert\Delta(\Delta H^\circ)_{2/3}\rvert$ [f]	6.2	5.4	8.6	3.4	0
$\lvert\Delta(\Delta H^\circ)_{3/4}\rvert$ [g]	10.0	3.8	9.1	3.3	3.7
(c) Entropy terms (kJ mol^{-1})					
$T\Delta S_1^\circ$	10.0	12.5	8.5	8.7	6.2
$T\Delta S_2^\circ$	5.0	6.2	4.0	3.7	5.0
$T\Delta S_3^\circ$	−2.5	0	4.2	0	−1.2
$T\Delta S_4^\circ$	−11.2	−3.7	−1.2	−5.0	−2.5

[a] Differences between the first and second protonation constants.
[b] Differences between the second and third protonation constants.
[c] Differences between the third and fourth protonation constants.
[d] Log $\beta = \Sigma \log K_i$.
[e] Absolute differences between the enthalpy terms of the first and second protonation steps.
[f] Absolute differences between the enthalpy terms of the second and third protonation steps.
[g] Absolute differences between the enthalpy terms of the third and fourth protonation steps.

In Table 3a–c and Fig. 2, the protonation constants and enthalpy terms of tetraamines (**11**–**15**) are shown displaying different sets of ethylenic, propylenic and butylenic hydrocarbon chains [5–10]. As with triamines, these compounds present two distinct kinds of nitrogen atoms, primary at the ends and secondary at the central part of the chain. Therefore, electrostatic repulsions, inductive effects and solvation energies will be the main points to consider in order to analyze the magnitude of the protonation constants and to elucidate possible protonation patterns.

Trien (**11**) with all ethylenic chains displays two large constants, one intermediate constant ($\Delta \log K_{2/3} = 2.5$) and one last low constant for the fourth protonation stage. The first two protonations are accompanied by highly exothermic terms and

favorable entropic terms while the third and fourth stages display reduced exothermic character and negative entropic terms. This means that the first two protons can bind (**11**) without introducing severe repulsion in the molecule. As aforementioned, this implies that protonation is occurring on nitrogen atoms separated by at least four methylene groups and consequently, one of these two protons should be located at the terminal nitrogens. The entry of the third proton necessarily occurs on a nitrogen atom next to one already protonated nitrogen, and therefore a moderate diminution in the binding strength is observed. The binding of the fourth proton implies strong electrostatic repulsion yielding a further decrease in the constant. The higher charge in the molecule is reflected in the thermodynamic parameters: reduced exothermic character and negative entropy due to the greater interaction with the solvent of the tri- or tetra-charged species (Table 3b, c).

The trends of the protonation constants of the remaining members of the series also manifest the coulombic interactions in each protonation stage. For instance, 2,3,2-tet (**12**) presents two large basicity constants and two intermediate ones ($\log K_2 - \log K_3 = 2.4$, $\log K_3 - \log K_4 = 1.4$), whereas 3,2,3-tet (**13**) displays three large constants and one intermediate ($\log K_1 - \log K_3 = 2.3$, $\log K_3 - \log K_4 = 2.7$) (Fig. 2). The arrangement of ethylenic and propylenic chains along these compounds can justify the observed trends. Indeed, in (**12**) the first two protons can bind any nitrogen as long as they do not belong to the same ethylenediamine moiety, the third one will be separated from one of the protonated sites by an ethylenic chain producing a drop in basicity. The situation is similar for the entrance of the last proton. As can be observed in Table 3b, c, the enthalpic terms for (**12**) are more exothermic in the last protonation stages than those of (**11**) and also the entropic contributions are less favorable in accordance with the larger dimensions of (**12**).

In the case of (**13**) three protons bind the polyamine that is least separated by a propylenic chain, and it is the fourth proton, the only one necessarily originating

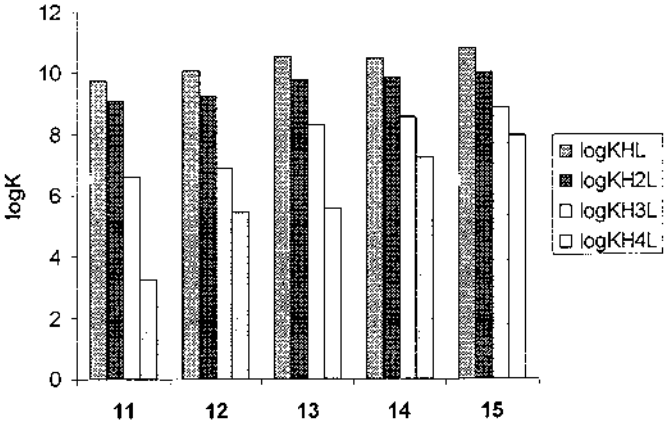


Fig. 2. Bar diagram of the logarithms of the stepwise protonation constants ($\log K$) of tetraamines (**11**–**15**).

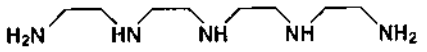
Table 4
Logarithms of the stepwise protonation constants of pentaamines (**16**–**17**) and enthalpy (kJ mol^{-1}) and entropy terms (kJ mol^{-1}) determined at 298 K [9]

	(**16**)	(**17**)		(**16**)		(**16**)
Log K_1	9.70	10.72	$-\Delta H_1^\circ$	45.2	$T\Delta S_1^\circ$	10.0
Log K_2	9.14	10.50	$-\Delta H_2^\circ$	47.2	$T\Delta S_2^\circ$	5.0
Log K_3	8.05	8.94	$-\Delta H_3^\circ$	44.8	$T\Delta S_3^\circ$	1.2
Log K_4	4.70	7.89	$-\Delta H_4^\circ$	33.1	$T\Delta S_4^\circ$	−6.2
Log K_5	2.92	3.96	$-\Delta H_5^\circ$	28.5	$T\Delta S_5^\circ$	−11.2
Δ Log $K_{1/2}$ [a]	0.6	0.2				
Δ Log $K_{2/3}$ [b]	1.1	1.6				
Δ Log $K_{3/4}$ [c]	3.4	1.0				
Δ Log $K_{4/5}$ [d]	1.8	3.9				
Log β [e]	34.5	42.0				
I (mol dm^{-3})	0.1	0.5		0.1		0.1

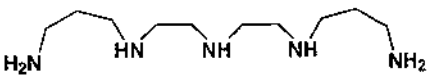
[a] Differences between the first and second protonation constants.
[b] Differences between the second and third protonation constants.
[c] Differences between the third and fourth protonation constants.
[d] Differences between the fourth and fifth protonation constants.
[e] Log $\beta = \Sigma \log K_i$.

repulsion at distance of an ethylenic chain. Thus, the reduction in basicity is produced in the last stage. Again, the thermodynamic terms support the proposed pattern.

Finally, the two largest members of the series 3,3,3-tet or thermine (**14**) and 3,4,3-tet or spermine (**15**), with only propylenic or/and butylenic chains, show much higher basicity constants and exothermic contributions in all their protonation steps (Table 3b, c and Fig. 2). As discussed above, propylenic or butylenic chains very much reduce electrostatic repulsion with respect to ethylenic ones. In fact, the biogenic polyamine spermidine would be almost fully protonated at neutral pH facilitating its well-known physiological role as charge neutralizer of DNA.



(16)



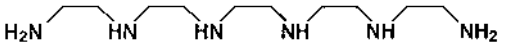
(17)

In Table 4 the protonation constants determined are collected with ionic strength 0.1 M at 298.1 K of polyamines 2,2,2,2-pent (**16**), and 3,2,2,3-pent (**17**), as well as the thermodynamic parameters of the former.

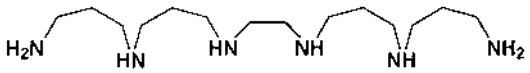
The same arguments advanced to discuss the protonation behavior of tri- and tetraamines hold in this case. 2,2,2,2-Pent (**16**) presents a group of three high constants ($\log K_1 - \log K_3 = 1.7$) and another two constants much more acidic ($\log K_3 - \log K_4 = 3.4$, $\log K_4 - \log K_5 = 1.8$). Three protons can bind this com-

pound in alternate nitrogen atoms without introducing strong repulsion, the last two protonations have to take place adjacent to the already protonated amino groups and as a result a basicity decrease is observed.

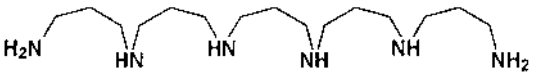
In (**17**) the presence of two propylenic chains at the ends of the molecule reduces considerably the positive charge accumulation and, in the last step a reduction in basicity occurs. The enthalpy an entropy terms of (**16**) agree with this observations and with the general behavior already discussed for other polyamines.



(18)



(19)



(20)

Hexaamines 1,4,7,10,13,16-hexaazaoctadecane (**18**), 1,5,9,12,16,20-hexazacosane (**19**) and 1,5,9,13,17,21-hexaazaheneicosane (**20**) also show the same basicity patterns (Table 5, Fig. 3) . Indeed, (**18**) made up of five ethylenic chains displays three large constants, an intermediate one, and two low constants for the last two protonation steps. (**19**) with four propylenic chains and an ethylenic one symmetrically distributed, shows five relatively large constants and an intermediate one for its sixth protonation step while (**20**), made up of just propylenic chains, shows a high basicity in all its six protonation steps. Again here, electrostatic considerations explain the observed trends. The fourth protonation on (**18**) has to occur on a nitrogen neighbor to an already protonated site and thus, yield a reduction in

Table 5
Stepwise protonation constants for hexaamines (**18**–**20**) and enthalpy terms (kJ mol^{-1}) for (**19**) determined at 298.1 K

	(**18**)	(**19**)	(**20**)		(**19**)
Log K_1	10.41	10.83	10.10	$-\Delta H_1^\circ$	54.9
Log K_2	9.37	10.15	10.10	$-\Delta H_2^\circ$	49.9
Log K_3	8.99	9.30	9.30	$-\Delta H_3^\circ$	48.7
Log K_4	7.02	8.45	8.70	$-\Delta H_4^\circ$	50.1
Log K_5	4.32	7.30	7.70	$-\Delta H_5^\circ$	46.4
Log K_6	2.72	4.98	7.00	$-\Delta H_6^\circ$	39.8
Log β[a]	42.8	51.0	52.9		
I (mol dm^{-3})	0.15	0.1	0.1		
Ref.	[71]	[72]	[73]		

[a] Log $\beta = \Sigma$ og K_i.

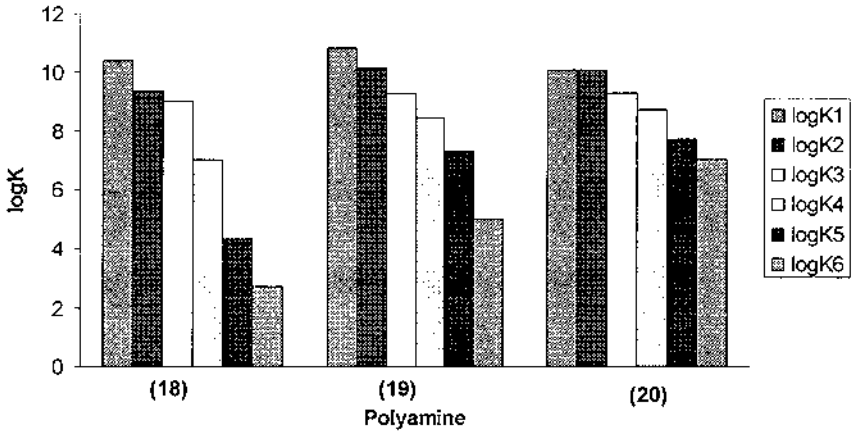


Fig. 3. Bar diagram of the logarithms of the stepwise protonation constants (log K) of hexaamines (**18**–**20**).

basicity. In the other two polyamines the propylenic chains enhance their basicity remarkably, the only difference between them is in the last protonation step. The thermodynamic parameters for (**19**) also support the proposed mechanism since highly favorable enthalpies are observed for all the steps except for the last one in which protonation occurs on nitrogen atoms separated by an ethylenic chain.

The behavior described for these compounds may be summarised in Fig. 4, where the overall biscuits of all tri- tetra-, penta- and hexaamines are plotted against the total number of atoms in the various molecules described. Such a plot gives a straight line and supports the idea of a common protonation mechanism for all of them in which electrostatic repulsion plays the major role.

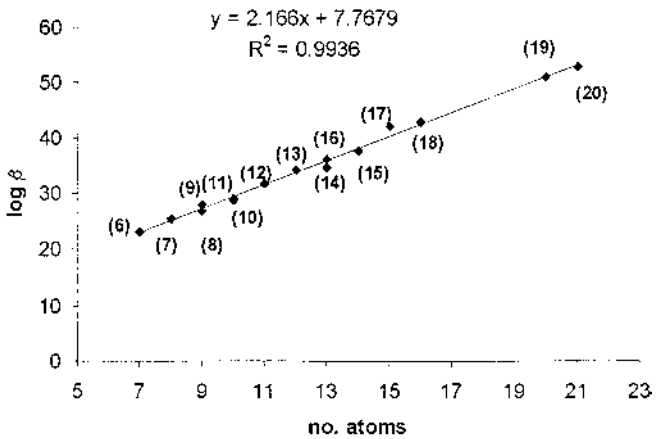


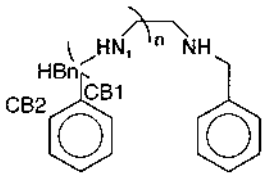
Fig. 4. Plot of the logarithms of the overall basicities ($\log \beta = \Sigma \log K_i$) of polyamines (**6**–**20**) as a function of the number of atoms in the different molecules.

Table 6
Stepwise protonation constants for polyamines (**21**–**25**) where $I = 0.15$ mol dm^{-3} at 298 K [74]

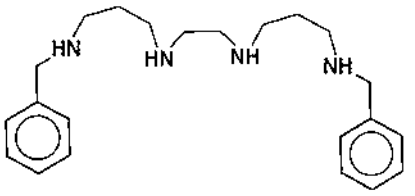
	(**21**)	(**22**)	(**23**)	(**24**)	(**25**)
Log K_1	9.11	9.38	9.30	9.68	9.85
Log K_2	6.23	8.29	8.62	8.87	8.89
Log K_3		3.99	6.41	7.37	7.99
Log K_4			3.77	4.90	4.93
Log K_5					2.75
Log β [a]	15.3	21.7	28.1	30.8	34.4

[a] Log $\beta = \Sigma \log K_i$.

3.2. Terminally methylated and benzylated polyamines



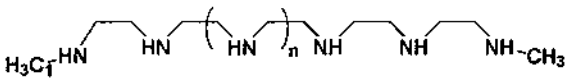
n = 1 (**21**)
n = 2 (**22**)
n = 3 (**23**)
n = 4 (**25**)



(**24**)

Recently the series of α,ω-dibenzylated polyamines (**21**–**25**) have been synthesized and their protonation behavior characterized by potentiometric and NMR techniques [74]. The stepwise protonation constants are presented in Table 6.

The basicity of these compounds follows the general trends discussed for the related non-benzylated polyamine (**1**), (**6**), (**11**), (**13**) and (**16**). The main difference rests on the lower constants the compounds (**21**–**24**) display with respect to their non-benzylated counterparts. However, as it can be seen in Fig. 5, the cumulative basicities of pentaamines (**25**) and (**16**) are rather similar. Therefore, for the di- tri and tetraamines, the substitution of the terminal primary nitrogen atoms by benzylated secondary nitrogens reduces the global basicity of the compounds. These differences become smaller as the size increases and for pentaamines such an effect is no longer observed.



n = 1 (**26**)
n = 2 (**27**)
n = 3 (**28**)
n = 4 (**29**)
n = 6 (**30**)

A few years ago in order to check the existence of macrocyclic effect in the so-called large polyazacycloalkanes, namely saturated macrocycles with more than six nitrogen donors, the synthesis of the series of open-chain terminally methylated polyamines 1,16-dimethyl-1,4,7,10,13,16-hexaazahexadecane (**26**), 1,19-dimethyl-1,4,7,10,13,16,19-heptaazanonadecane (**27**), 1,22-dimethyl-1,4,7,10,13,16,19,22-octaazadocosane (**28**), 1,25-dimethyl-1,4,7,10,13,16,19,22,25-nonaazapentacosane (**29**) and 1,28-dimethyl-1,4,7,10,13,16,19,22,25,28-decaazaoctacosane (**30**) was carried out. These polyamines are believed to be appropriate counterparts of the cyclic ligands since they display the same number and kind of nitrogen atoms, as well as the same overall number of atoms in the molecule [75,76].

The logarithms of the stepwise protonation constants for these polyamines, presented in Table 7 and in Fig. 6, show different sequences for the polyamines with even and odd number of nitrogen atoms. The first ones take up $k/2$ protons ($k =$ total number of nitrogen atoms in the molecule) without great repulsion between positive charges. The $(k/2+1)$th proton will be placed next to one ammonium group, which would considerably increase electrostatic repulsion and, therefore, yield a drop in basicity. All the other protons will bind nitrogens located between two ammonium groups producing a further basicity decrease. This situation will yield, as observed in Fig. 6, two groups of constants separated by an intermediate constant. Polyamines with an odd number of nitrogens show a slightly different protonation pattern. For these compounds the intermediate situation does not occur and just two groups of constants are observed. The first $(k/2+1)$th constants are much more basic than the following ones, since, in the latter, the protons would be placed between protonated nitrogens. As will be mentioned later, these trends are reverted in macrocyclic polyazalkanes with all ethylenic chains. Cyclic polyamines with odd numbers of nitrogens follow the pattern of open-chain

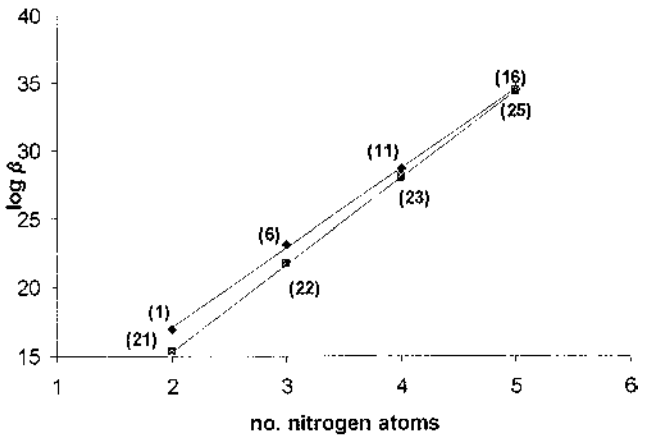


Fig. 5. Plot of the overall basicities of polyamines (**1**), (**6**), (**11**) and (**16**) and of α,ω-dibenzylated polyamines (**21**–**25**) containing only ethylenic chains vs. the number of nitrogen atoms.

Table 7
Logarithms of the stepwise protonation constants for polyamines (**26**–**30**) where $I = 0.15$ mol dm^{-3} and $T = 298$ K [75,76]

	(**26**)	(**27**)	(**28**)	(**29**)	(**30**)
Log K_1	10.28	10.22	10.39	10.58	10.27
Log K_2	9.52	9.59	9.77	9.72	9.72
Log K_3	8.84	8.94	9.28	9.35	9.27
Log K_4	6.54	8.05	8.61	8.70	8.72
Log K_5	3.80	4.75	6.68	7.93	8.24
Log K_6	2.51	3.37	4.44	5.10	6.58
Log K_7		2.45	3.31	3.88	4.54
Log K_8			2.93	2.94	3.50
Log K_9				2.74	2.71
Log K_{10}					1.5
Log β [a]	41.4	47.3	55.4	60.9	65.1

[a] Log $\beta = \Sigma \log K_i$.

ones with even numbers while those with odd numbers of nitrogens will present the same behaviour as open-chain ones with even numbers of nitrogens.

If the overall basicity of both families of compounds, dimethylated open-chain polyamines and polyazacycloalkanes of the [3k]aneN_k series, are plotted against the number of nitrogens in each compound, two almost parallel straight lines are obtained with the line for the open-chain polyamines above the other one (Fig. 7).

These last two groups of compounds may serve to illustrate the application of multinuclear NMR to elucidate protonation patterns, namely, to identify which are the major prototopic isomers at each protonation step. In this sense, it should be noted the interesting approaches that several groups have performed to the determination of protonation constants and/or protonation trends of polyamines [77–84].

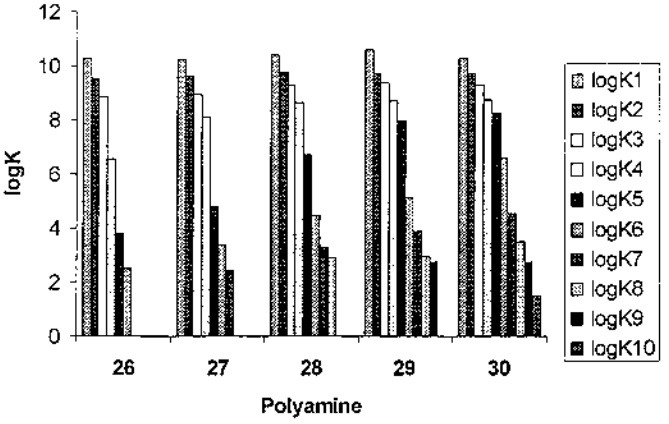


Fig. 6. Bar diagram of the logarithms of the stepwise protonation constants (log K) of methylated polyamines (**26**–**30**).

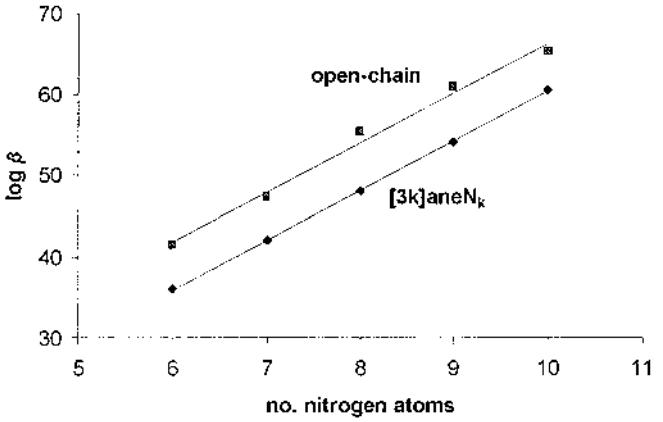


Fig. 7. Representation of the cumulative basicity constants of open-chain terminally methylated polyamines and of macrocyclic counterparts of the [3*k*]aneN$_k$ series vs. the number of nitrogen atoms in the different molecules.

It is well known that upon protonation the ^{1}H and ^{13}C signals shifting most are, respectively, those placed in α and β positions with respect to the nitrogen bearing the process [85]. In most cases, the variations of these chemical shifts can help to deduce the protonation order of polyamines. This analysis is particularly useful when either the nitrogen atoms are of different kind or their chemical environments are different as in the examples proposed here. For instance, in the dibenzylated polyamines the quaternary carbon atoms of the aromatic moieties (CB1) (see ligand drawing) are placed in the β position with respect to nitrogen atoms labeled as N1. In the same way, benzylic hydrogen atoms are the only ones in the α position with respect to such nitrogens. Therefore, the variation of the ^{13}C and ^{1}H chemical shifts of these nuclei may serve as a probe for the protonation of nitrogen atoms N1.

For α,ω-dimethylated polyamines the methyl groups at the ends of the chain or the carbon atoms (C1) next to them are highly valuable in the analysis, since clearly present are the differentiated ^{1}H and ^{13}C signals.

In Fig. 8 the variation of the chemical shifts of the ^{1}H signals of hydrogens HBn and of the ^{13}C signals of the carbon atoms CB1 of the compounds (**23**, **25**) are plotted as a function of pH. For (**23**) and (**25**), marked downfield shifts of the ^{1}H resonance of hydrogens H1 and upfield shifts of the ^{13}C signal CB1 are observed above pH 6 and 7, respectively. Below these pH values no significant shifts are observed for both ligands. These data may be interpreted considering that the two out of the first three protons attaching (**23**) and (**25**) are predominantly located at the benzylic nitrogens N1. The same type of analysis can be extended for most polyamines.

The ^{13}C-NMR spectra of polyamines (**26**–**30**) are particularly significant to interpret their protonation behavior. In Fig. 9, for instance, the ^{13}C-NMR spectra of (**26**) are shown and it can be seen that at pH 2.0, where the fully protonated $[H_6L]^{6+}$ polyamine prevails, just three signals integrating roughly 1:1:4 are ob-

served which can be assigned to the methyl carbons (C1), the carbon atoms in β position with respect to the methyl groups and to all other carbon atoms which, at this pH, are magnetically equivalent. When the pH is raised to 8 at which the triprotonated $[H_3L]^{3+}$ species predominates, the number of non-equivalent carbon atoms is half of the overall number of carbons in the molecule indicating a two-fold time averaged symmetry. If the pH is increased further, although shifted downfield, the carbon atoms recover their magnetic equivalence until at very high pH just three signals again appear.

The analysis of the ^{13}C-NMR signals for these compounds allows one to conclude that terminal nitrogens are the first ones being protonated, which probably can be attributed to a better disposition of these nitrogens for solvation with the aqueous solvent.

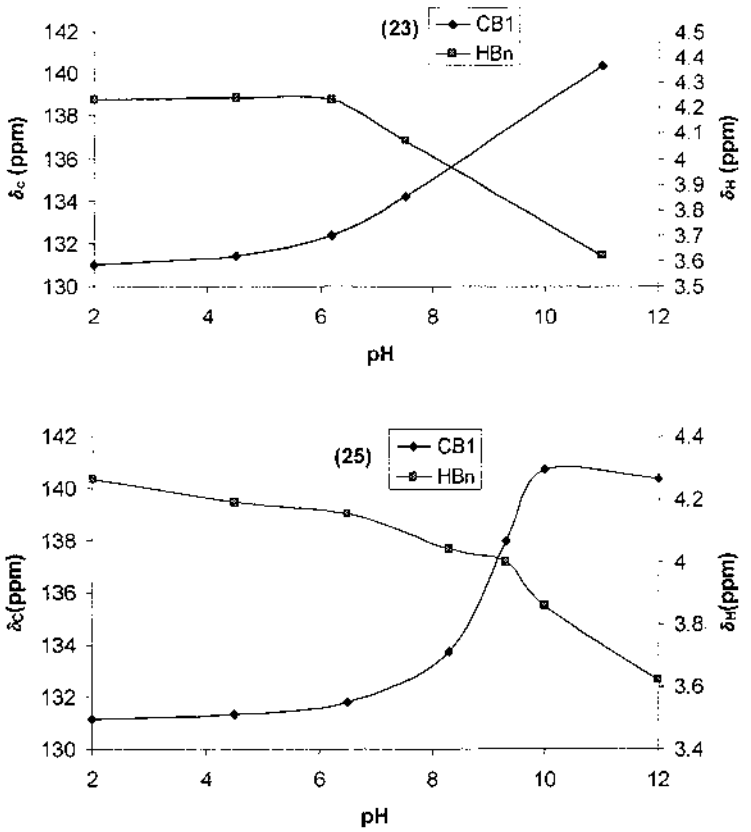


Fig. 8. Variation of the chemical shifts of hydrogens HBn and of carbon atoms CB1 with the pH for compounds (**23**) and (**25**).

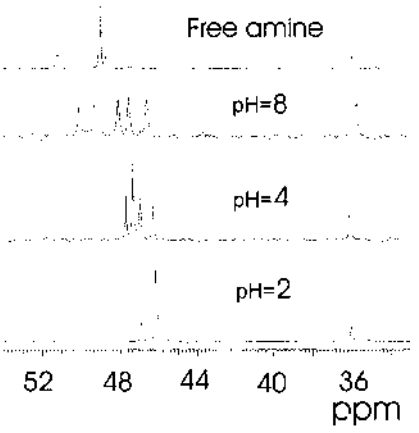


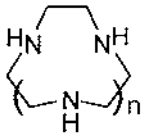
Fig. 9. ^{13}C-NMR spectra of (**26**) at different pH values.

4. Macrocyclic polyamines (polyazacycloalkanes)

This section deals with polyamines having a cyclic structure. Such molecules are commonly referred to as macrocycles. Their proton transfer properties are strictly connected with the number of amino groups in the molecular skeleton, the type of amino groups (secondary, tertiary), the presence of different donor atoms, the length of the spacers connecting the amino groups and their nature (aliphatic, aromatic), the rigidity and the overall structure of the molecule. All these aspects will be considered in this section.

4.1. Unsubstituted polyazacycloalkanes

Similarly to acyclic polyamines, polyazacycloalkanes give rise to multiple protonation equilibria in aqueous solution. Due to their cyclic skeleton, however, polyazacycloalkanes produce, in the successive protonation steps, a closer gathering of positive charge than their acyclic analogues. This rises the electrostatic repulsion between the ammonium groups in the molecule affecting the stability of the protonated forms.



n = 0	[6]aneN$_2$ (piperazine)	(**31**)
n = 1	[9]aneN$_3$	(**32**)
n = 2	[12]aneN$_4$	(**33**)
n = 3	[15]aneN$_5$	(**34**)
n = 4	[18]aneN$_6$	(**35**)
n = 5	[21]aneN$_7$	(**36**)
n = 6	[24]aneN$_8$	(**37**)
n = 7	[27]aneN$_9$	(**38**)
n = 8	[30]aneN$_{10}$	(**39**)
n = 9	[33]aneN$_{11}$	(**40**)
n = 10	[36]aneN$_{12}$	(**41**)

An instructive example of increasing protonation is offered by the series $[3k]aneN_k$ ($k = 2$–12) of polyazacycloalkanes in which secondary amino groups are connected by ethylenic chains. This series spans from the small $[6]aneN_2$ (**31**) (piperazine) up to the very large $[36]aneN_{12}$ (**41**) which forms, in its fully protonated form, the dodecacharged $H_{12}(\mathbf{41})^{12+}$ cation.

The protonation constants of (**31**–**41**), determined by potentiometric titration in aqueous solution at 298 K [9,86–93], are listed in Table 8.

If the logarithms of the overall basicity constants of (**33**–**41**) are plotted versus the number of amino groups in each macrocycle, an excellent linear correlation is obtained (Fig. 10), evidencing a mean contribution to the overall basicity of 6.2 logarithmic units per nitrogen atom.

As expected, the overall basicities of these cyclic polyamines are lower than those of their acyclic counterparts (see unsubtituted open chain polyamines). Nevertheless, the parallelism between the straight line in Fig. 10 and the analogous straight line obtained for the acyclic ligands (Fig. 7) suggests similar protonation patterns. Actually the protonation behavior of these polyazacycloalkanes with odd numbers of nitrogen atoms follows the pattern of the acyclic counterparts with even numbers of nitrogen, while polyazacycloalkanes with even numbers of nitrogens follow the protonation pattern of their acyclic related molecules with odd numbers of nitrogens. $[3k]aneN_k$ molecules with an even k number of nitrogen atoms can take up $k/2$ protons without great repulsion between positive charges (Fig. 11), while

Table 8
Logarithms of protonation constants potentiometrically determined at 298 K for $[3k]aneN_k$ ($k = 2$–12) polyazacycloalkanes (**31**–**41**) where $I = 0.15$ mol dm^{-3} unless otherwise noted

	(**31**)[a]	(**32**)	(**33**)	(**34**)[b]	(**35**)	(**36**)	(**37**)	(**38**)	(**39**)	(**40**)	(**41**)
Log K_1	9.71	12.6	10.38	10.85	10.15	9.76	9.65	9.59	9.85	9.79	9.75
Log K_2	5.59	7.55	9.71	9.65	9.48	9.28	9.33	9.40	9.44	9.48	9.65
Log K_3		2.53	2.05	6.00	8.89	8.63	8.76	8.77	8.95	9.02	8.88
Log K_4			<1	1.74	4.27	6.42	7.87	8.27	8.56	8.64	8.96
Log K_5				1.16	2.21	3.73	4.55	6.37	7.79	8.06	8.12
Log K_6					1.0	2.13	3.42	4.22	5.24	6.44	7.82
Log K_7						2.0	2.71	3.24	3.84	4.49	5.66
Log K_8							1.95	2.31	3.02	3.58	4.27
Log K_9								1.8	1.97	2.76	3.58
Log K_{10}									1.8	2.26	2.62
Log K_{11}										1.7	2.3
Log K_{12}											1.0
Log β[c]	15.3	22.68	22.1[d]	29.4	36.0	42.0	48.24	54.0	60.5	66.2	72.6
Ref.	[9]	[86]	[87]	[88]	[89]	[90]	[90]	[91]	[92]	[93]	[93]

[a] $I = 0.1$ mol dm^{-3}.
[b] $I = 0.2$ mol dm^{-3}.
[c] Log $\beta = \Sigma \log K_i$.
[d] Log K_4 is not considered for the overall basicity.

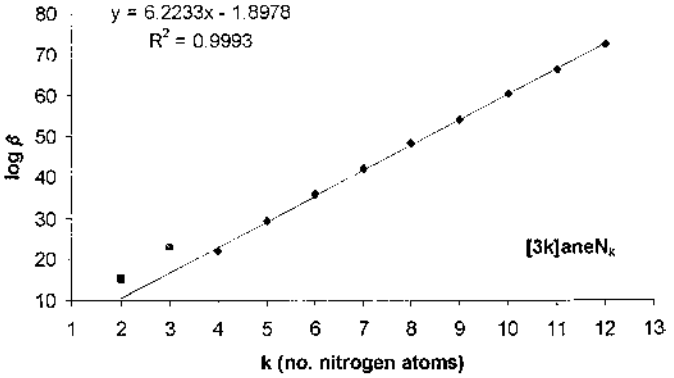


Fig. 10. Overall basicity of $[3k]aneN_k$ polyazacycloalkanes. Log $\beta = \Sigma \log K_i$.

further protons will be bound by nitrogen atoms located between charged ammonium groups, giving rise to strong electrostatic repulsion. As a consequence, there is an evident gap between the protonation constants of the first and the second half of nitrogen atoms (Table 8). On the other hand, when the k number of nitrogens in the macrocycle is odd, only $(k-1)/2$ protons can be bound without great electrostatic repulsion (Fig. 11). The successive proton will bind a nitrogen atom next to one ammonium group and the following $(k-1)/2$ protons will be placed next to two ammonium groups. Accordingly, $[3k]aneN_k$ molecules with odd k numbers of nitrogens are characterized by two groups of $(k-1)/2$ protonation constants separated by an intermediate constant (Table 8).

The presence of longer chains connecting the amino groups in polyazacycloalkanes produces a noticeable increase in basicity, due to a lower electrostatic repulsion between positive charges in the polyprotonated species. This behavior is more evident in the last protonation steps, which take particular advantage from long separation between amino groups, than in the first ones. This produces attenuation, or disappearance, of the grouping effect described previously, although, at least for the most symmetrical ligands, such protonation patterns controlled by electrostatic repulsion should be maintained. Examples are given by the stepwise basicity constants reported in Table 9 for the macrocycles $[4k]aneN_k$ ($k = 3$, 4, 6, 8) in which all nitrogens are separated by propylenic chains [94–96].

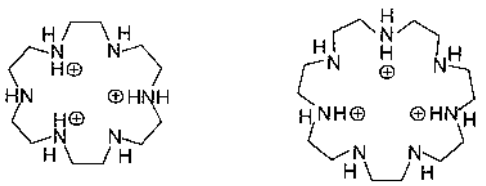
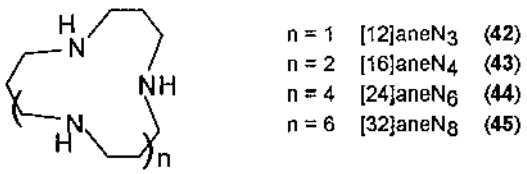


Fig. 11. Localizations of H^+ ions in $H_3(\mathbf{35})^{3+}$ and $H_3(\mathbf{36})^{3+}$ producing the minimum electrostatic repulsion.

Table 9
Logarithms of protonation constants potentiometrically determined at 298 K for [4*k*]aneN$_k$ (*k* = 3, 4, 6, 8) polyazacycloalkanes where $I = 0.1$ mol dm^{-3} unless otherwise noted

	(**42**)	(**43**)[a]	(**44**)	(**45**)
Log K_1	12.60	10.85	10.45	10.70
Log K_2	7.57	9.80	10.35	10.45
Log K_3	2.41	7.21	9.05	9.65
Log K_4		5.69	7.90	9.00
Log K_5			7.15	8.05
Log K_6			6.60	7.50
Log K_7				6.95
Log K_8				6.45
Log β[b]	22.58	33.55	51.50	68.75
Ref.	[94]	[95]	[96]	[96]

[a] $I = 0.5$ mol dm^{-3}.
[b] Log $\beta = \Sigma$ log K_i.



Also in the case of [4*k*]aneN$_k$ polyazacycloalkanes (**42**–**45**) there is an excellent linear correlation between the overall basicities and the number of amino groups in the molecules (Fig. 12). For these compounds the mean contribution to the overall basicity is 9.1 logarithmic units per nitrogen atom.

The polyazacycloalkanes already presented in this section consist of several amino groups symmetrically arranged around the cavity defined by the molecular

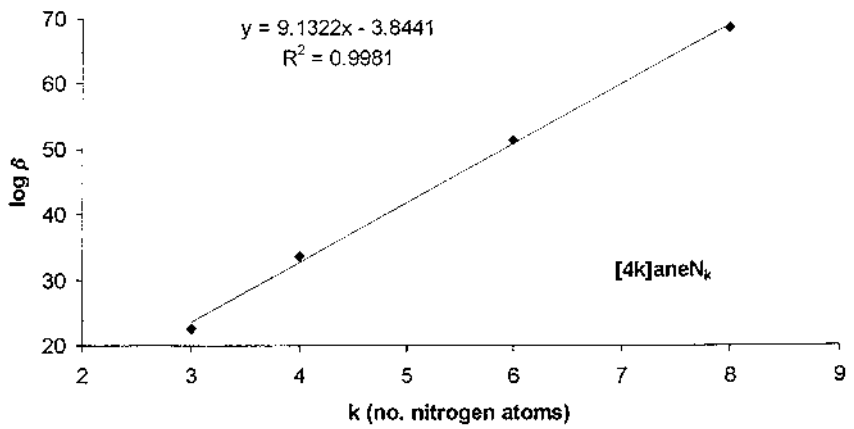


Fig. 12. Overall basicity of [4*k*]aneN$_k$ polyazacycloalkanes. Log $\beta = \Sigma$ log K_i.

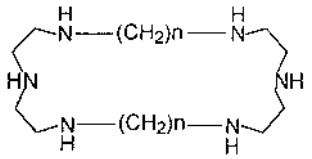
Table 10
Logarithms of protonation constants potentiometrically determined at 298 K polyazacycloalkanes (**46**–**50**) where $I = 0.1$ mol dm^{-3} unless otherwise noted

	(**46**)[a]	(**47**)[a]	(**48**)	(**49**)	(**50**)
Log K_1	10.64	10.73	[b]	10.70	[b]
Log K_2	10.12	10.31	[b]	10.70	[b]
Log K_3	9.37	9.93	9.60	9.85	10.10
Log K_4	8.86	9.47	9.25	9.60	9.60
Log K_5	3.44	3.82	4.15	7.90	7.95
Log K_6	3.42	3.57	3.55	7.30	7.30
Ref.	[99]	[99]	[98]	[97,98]	[97,98]

[a] $I = 0.5$ mol dm^{-3}.
[b] Values not determined since the unprotonated form of the compound is not soluble in water.

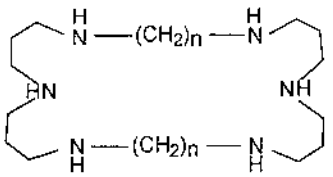
architecture. Conversely, the hexaazacycloalkanes (**46**–**50**) present two triaminic subunits held together by long aliphatic chains.

These molecules are quite interesting, from a proton binding point of view, since they represent for protons what ditopic ligands are for metal ion coordination. Their proton transfer properties (Table 10) reveal that the two triaminic subunits behave as almost independent entities towards protonation. Namely, protons occupy alternatively the two triaminic subunits giving rise to similar values of the equilibrium constants for the same protonation step in each subunit.



n = 4 (**46**)
n = 6 (**47**)
n = 9 (**48**)

The first four constants of (**46**–**48**) are grouped and separated from the fourth one by more than 5 logarithmic units. This grouping can be rationalized considering that an efficient minimization of electrostatic repulsion between positive charges in the tetraprotonated species is possible via localization of the four acidic protons in alternated position, separated by unprotonated nitrogen atoms or aliphatic chains. The much lower affinity of the molecules for the fifth and sixth protons is due to the fact that these protonation reactions occur at the central nitrogens of each end of the macrocycle. Consequently, in the penta- and in the hexaprotonated species three protonated nitrogen atoms are contiguous, leading, of course, to increased electrostatic repulsion.



n = 7 (**49**)
n = 10 (**50**)

This repulsion is lower for the penta- and the hexaprotonated forms of (**49**) and (**50**) where the nitrogen atoms in the triaminic subunits are separated by longer propylenic chains, determining a considerable increase of the last two protonation constants and a consequent attenuation of the grouping effect.

As shown in Fig. 10, the triazacycloalkane [9]aneN_3 (**32**) does not follow the linear correlation between overall basicity and number of nitrogen atoms in the molecule presented by [3*k*]aneN_k macrocycles containing four or more ($k = 4$) amino groups. This is principally due to the very high basicity of (**32**) at the first protonation step. The protonation properties of (**32**) have been studied by several authors, who reported values of the first protonation constant ranging from $\log K = 10.4$ to 11.3 at 298 K [100–107], although a NMR investigation of this protonation equilibrium gave a significantly higher value ($\log K = 12.6$) [104]. Recently, an accurate pH-metric investigation confirmed the last value (Table 8) [86].

A very high basicity at the first protonation step is characteristic of triazacycloalkanes [100–109], which show at this stage higher affinity for protons than the acyclic analogues, while acyclic triamines are much more basic than cyclic ones in the following steps. In this sense triazacycloalkanes are much representative of the effect of ring closure on the proton binding properties of polyamines. Such features can be explained by considering an inside orientation of the lone pairs of nitrogens, promoted by the cyclic structure, stabilizing the monoprotonated forms of these molecules by the formation of intramolecular hydrogen bond networks involving all three amino groups, as observed in the crystal structure of the H(51)ClO_4 ((**51**)=*N*,*N*′,*N*″-trimethyl-(**32**)) salt [110] (Fig. 13). In this compound, the acidic proton is bound to one nitrogen atoms of the cyclic triamine and interacts with the other amino groups via in-ring hydrogen bonds. The second protonation destroys such a stable arrangement forming a diprotonated species in which two positive charges are constrained to occupy neighboring amino groups. Hence, the second protonation is favored by a non-cyclic structure of the molecule.

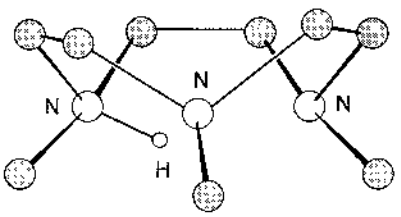


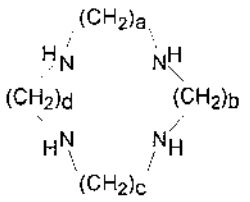
Fig. 13. View of the H(**51**)$^+$ cation showing the proton binding [110].

Table 11
Thermodynamic quantities of stepwise protonation of tetraazamacrocycles in aqueous solution at 298 K in 0.5 mol dm^{-3} KNO_3[a]

	(52)	(53)	(54)	(55)	(56)	(57)
Log K_1	11.58	11.08	11.04	10.85	10.73	11.20
Log K_2	10.62	10.38	10.47	9.80	9.85	10.13
Log K_3	1.61	5.28	3.98	7.21	6.83	7.96
Log K_4	2.41	3.60	3.41	5.69	3.96	6.30
Log β[b]	26.22	30.34	28.90	33.55	31.37	35.59
$-\Delta H_1^\circ$	51.5	45.2	46.4	41.8	46.4	43.5
$-\Delta H_2^\circ$	53.4	51.5	51.5	44.8	47.7	46.4
$-\Delta H_3^\circ$	11.7	30.2	27.2	43.1	42.7	45.6
$-\Delta H_4^\circ$	32.2	32.3	30.5	44.4	33.5	45.6
$T\Delta S_1^\circ$	14.6	18.0	16.7	20.1	14.6	20.5
$T\Delta S_2^\circ$	7.2	7.8	8.4	11.3	8.4	11.3
$T\Delta S_3^\circ$	−2.5	−0.1	−4.6	−1.7	−3.8	0.0
$T\Delta S_4^\circ$	−18.7	−11.7	−10.9	−11.7	−10.9	−9.6
Ref.	[111,112]	[111,112]	[114]	[95,115]	[114]	[114]

[a] Enthalpy and entropy changes in kJ mol^{-1}.
[b] Log $\beta = \Sigma \log K_i$.

Similar in-ring hydrogen bond networks have been invoked also to explain the particular protonation behavior of cyclam (**52**) [111,112]. The thermodynamic quantities for the stepwise protonation of several tetraazacycloalkanes (**52**–**57**) [91,111–115] are listed in Table 11.



a, b, c, d	
2, 3, 2, 3	(**52**)
2, 3, 3, 3	(**53**)
2, 3, 2, 4	(**54**)
3, 3, 3, 3	(**55**)
3, 2, 3, 4	(**56**)
3, 3, 3, 4	(**57**)

As discussed previously, these polyamines exhibit high basicities in the first two steps of protonation and lower basicities in the last two steps. The separation between the second and the third protonation constants of (**52**) is considerably greater than for any other molecule among (**53**–**57**), the third protonation constant of (**52**) being even smaller than the fourth one. To explain this apparently anomalous behavior of (**52**) it was proposed [111] that the first two protons might be involved in a diagonal hydrogen bonding, across the macrocycle, between two opposite nitrogens, possibly via a bridging water molecule [117].

Later, the molecular structure of the $H_2(\mathbf{52})^{2+}$ cation (Fig. 14) in $H_2(\mathbf{52})(ClO_4)_2$, where no bridging water molecules were present, showed that, at least in the solid state, the two acidic protons are bound effectively to two opposite nitrogen atoms, but each one of them forms an intramolecular hydrogen bonds with the contiguous amino group connected by the propylenic chain [118].

Microcalorimetric measurements showed that the higher values of the first two

protonation constants of (**52**) are determined by particularly favorable enthalpic contributions, while a considerably less favorable contribution accompanies the formation of the triprotonated form [112]. Most likely, due to the cyclic nature of the polyamine, the intramolecular hydrogen bonds are retained in solution accounting for the high stability of the diprotonated species. In the successive protonations steps such a system of hydrogen bonds is broken and the macrocycle turns its ammonium groups outward the cavity, in order to minimize the electrostatic repulsion between the positive charges, as shown by the molecular structure of $H_4(\mathbf{52})^{4+}$ (Fig. 14) in $H_4(\mathbf{52})CuCl_6$ [119]. Since the third protonation constant is even smaller than the fourth one and considering the modest enthalpic contribution measured for the addition of the third proton, it is reasonable to assume that the interconversion of the molecules from *in* to *out* nitrogen configurations occurs at the third protonation step.

In the case of larger tetraazacycloalkanes the flexibility of the molecular skeleton increases; the equilibria between *in* and *out* configurations of the amino groups are not connected with a particular protonation step and, consequently, the protonation behavior becomes similar to that of the corresponding acyclic tetraamines [114].

When macrocyclic polyamines undergo extensive protonation, the molecular framework tends to expand in order to minimize the electrostatic repulsion, the acquisition of *out* configuration by the ammonium groups providing an additional expansion of the molecular cavity. Nevertheless, the overall conformation of the polyammonium macrocyclic molecules in solution is not merely controlled by

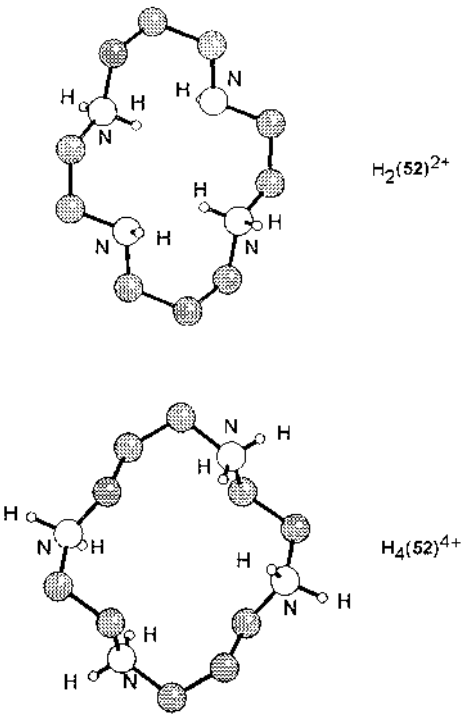


Fig. 14. Views of the diprotonated [118] and tetraprotonated [119] forms of cyclam (**52**).

Table 12
Logarithms of the protonation constants (298 K) of polyazacycloalkanes and of their nitrogen methylated derivatives

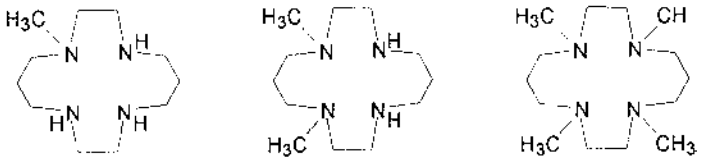
	Log K_1	Log K_2	Log K_3	Log K_4	I (mol dm^{-3})	Ref.
(**31**)	9.71	5.59			0.1	[9]
Me(**31**)	8.98	4.83			0.1	[129]
Me_2(**31**)	8.13	4.18			0.1	[130]
(**32**)	12.6	7.55	2.53		0.1	[86]
Me_3(**32**)	11.7	5.1	~0.4			[131]
(**33**)	10.6	9.49	1.6	0.8	0.15	[87]
Me_4(**33**)	10.07	8.95			0.1	[132]
(**52**)	11.58	10.62	1.61	2.41	0.5	[111]
Me(**52**)	11.40	10.35	2.8	2.3	0.5	[133]
Me_2(**52**)	10.90	9.90	3.05	2.3	0.5	[133]
Me_4(**52**)	10.10	9.35	3.45	2.7	0.5	[133]

intramolecular forces, but it is also determined by the nature of the medium and in particular by the presence of anionic species which may form stable adducts with polyammonium cations. This phenomenon which is known as 'anion coordination' [120] can influence the protonation binding properties of all kinds of amines, although it is particularly evident for macrocyclic and macropolycyclic polyamines and highly charged anions. For this reason prudent evaluations are necessary when comparisons between equilibrium data obtained in different ionic media are drawn.

Several examples of different molecular conformations and mixed or intermediate *in–out* nitrogen configurations can be found in the literature for polyammonium cations deriving from [3*k*]aneN_k polyazacycloalkanes [121–128].

4.2. Nitrogen methylated polyazacycloalkanes

Nitrogen methylation in polyazacycloalkanes gives rise to the conversion of secondary into tertiary amino groups. As discussed already, tertiary amines are less basic than secondary ones in aqueous solution and, hence, one could predict that in the stepwise protonation of a polyazacycloalkane containing both secondary and tertiary amino groups the former will be protonated before the latter, or, in a more correct form, that protons will be localized on, or shared by, the different amino groups accordingly to their relative basicities. Moreover, we must take into account the existence of a statistical effect which favors protonation of the largest set of identical amino groups. From the second protonation step, however, the electrostatic repulsion between positive charges starts being crucial in determining the protonation sites. Nevertheless, in most cases the macroscopic effect of nitrogen methylation in polyazacycloalkanes is manifested as a general trend of decreasing basicity [129–137]. This is clearly illustrated by the protonation constants of the di-, tri- and tetraazacycloalkanes (**31**), Me(**31**), Me_2(**31**), (**32**), Me_3(**32**), (**33**) and Me_4(**33**) in Table 12 [9,86,87,129–132].

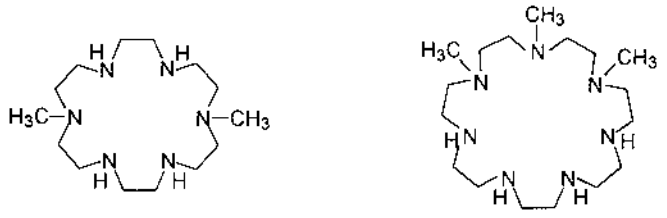


Me(**52**) Me_2(**52**) Me_4(**52**)

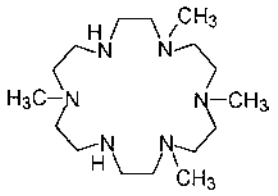
The same trend is also observed for the first two protonation equilibria of (**52**), Me(**52**), Me_2(**52**) and Me_4(**52**) (Table 12) [111,133], although a different situation, ascribable to steric effects brought about by nitrogen methylation, is observed for the third and the fourth protonation steps. First of all the singular behavior of (**52**), having the third protonation constant smaller than the fourth one, is no longer found in its Me(**52**), Me_2(**52**) and Me_4(**52**) derivatives, indicating that nitrogen methylation prevents the formation of the particularly stable hydrogen bonded structure observed for H_2(**52**)$^{2+}$ (see previous section). In addition it has been proposed that nitrogen methylation favors the *out* conformation of the ammonium groups, leading to strong hydration of the otherwise poorly solvated tertiary amino groups, to justify the enthalpically driven increase of basicity in the last two steps of protonation [112].

Owing to the different contributions determining the proton binding properties of polyazacycloalkanes, in particular for nitrogen methylated molecules which contains both secondary and tertiary amino groups, it is not possible, in general, to get clear information on the protonation patterns from the protonation constants.

As discussed before, NMR spectroscopy, coupled with the equilibrium data, can furnish an accurate analysis of protonation processes at the molecular level. It has been shown that ^{1}H- and ^{13}C-NMR spectroscopy is of great use, especially in the study of nitrogen methylated polyazacycloalkanes [136–138]. For instance, while this technique is almost insensitive in the analysis of protonation patterns of [3*k*]aneN_k polyazacycloalkanes, since all carbon and hydrogen atoms remain magnetically equivalent independent of pH, the insertion of methyl groups removes the magnetic equivalence and the pH-dependence of ^{1}H and ^{13}C spectra becomes a probe to recognize the protonation sites [136].



Me_2(**35**) Me_3(**36**)



Me_4(**35**)

This is clearly illustrated by Me_2(**35**), Me_4(**35**) and Me_3(**36**), nitrogen methylated derivatives of (**35**) and (**36**) [136,137]. The protonation constants of these molecules are reported in Table 13. As expected nitrogen methylation produces a significant basicity decrease at each protonation steps (compare log K values in Table 13 with those for (**35**) and (**36**) in Table 8). For this reason the methylated hexaazacycloalkanes Me_2(**35**), Me_4(**35**) and the methylated heptaazacycloalkane Me_3(**36**) are able to bind, at most, four and five protons, respectively, in the same pH range where the unmethylated (**35**) and (**36**) form the fully protonated species.

^{1}H and ^{13}C spectra of Me_2(**35**) at different pH values [137] showed that the first two protons bind the molecule involving all the nitrogen atoms independent of their secondary or tertiary nature. On the other hand, in the triprotonated form the protons are localized on two secondary and one tertiary amino groups in alternated positions, while in the tetraprotonated species the protons bind to the four secondary nitrogens, in agreement with simple electrostatic considerations and the lower basicity of tertiary amino groups.

Table 13
Logarithms of the stepwise protonation constants of Me_2(**35**), Me_4(**35**) and Me_3(**36**) determined in $NaClO_4$ 0.15 mol dm^{-3} at 298 K

	Me_2(**35**)	Me_4(**35**)	Me_3(**36**)
Log K_1	9.78	9.75	9.27
Log K_2	9.09	9.11	8.95
Log K_3	7.76	7.53	7.97
Log K_4	3.84	2.59	5.42
Log K_5			2.98
Log K_5			1.78
Ref.	[137]	[136]	[137]

In the case of Me_4(**35**) [136] the first protonation step involves all three contiguous methylated nitrogens, evidencing that this is the most basic portion of the molecule, and not the secondary nitrogens as might have been expected. In the diprotonated and triprotonated forms the secondary amino groups, respectively, share one or two protons, while the other proton remains localized on the middle methylated nitrogen of this molecular portion. In the tetraprotonated form the disposition of the ammonium groups is similar to that observed for Me_2(**35**), the four protons being localized on the secondary amino groups and the neighboring couple of tertiary nitrogens.

The first two protonation steps of Me_3(**36**) take place in a narrow pH range and consequently they are not distinguishable from a NMR point of view [137]. In the diprotonated form one proton is localized on the middle tertiary nitrogen of the contiguous methylated amino groups, while all secondary nitrogens share the other proton. In the successive two protonation steps one proton remains localized on the methylated nitrogen and the others bind again to the secondary amino groups. Finally in the pentaprotonated species the secondary amino groups share three protons and the tertiary amino groups share two protons.

This examples demonstrate that in absence of appropriate experimental information it is generally not possible to make reliable forecasts about the location of the first protons binding the molecules; however, for more charged species the electrostatic forces become predominant controlling at large extent the protonation patterns.

4.3. Oxa- and thia-polyazacycloalkanes

In the last few years a variety of mixed donor macrocycles have been synthesized. Most of the attention was devoted to oxa-aza and thio-aza macrocycles, containing usually up to six donors, but, more recently, several oxa-aza macrocycles with a larger number of donors have also been considered. Although the proton binding properties of such molecules have been studied with the only purpose of getting information about their coordinating ability toward other chemical species [96,132,139–176], protonation of oxa- and thia-polyazacycloalkanes displays some interesting features which deserve to be presented.

Oxygen and sulfur atoms have different electronic characteristics with respect to amino groups. Obviously, ethereal O and S cannot bind acidic protons, if not under particular conditions; they have different inductive effects on the adjacent aliphatic chains with respect to nitrogen and finally, they have a far lower tendency to form hydrogen bonds and are less solvated in aqueous solution than amino groups. Considering these features, the introduction of O or S in the macrocyclic framework may influence deeply the basicity of these molecules.

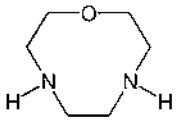
The lower stabilization via intramolecular hydrogen bonds formation brought about by O and S in the mono and/or polyprotonated species gives rise to a

Table 14
Logarithms of the protonation constants of ligands (**32**), (**58**–**62**) determined at 298 K

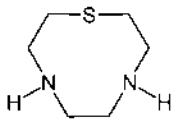
	Log K_1	Log K_2	Log K_3	Ref.
(**32**)[a]	12.6	7.55	2.53	[86]
(**58**)[b]	9.59	5.32		[140]
(**59**)[b]	9.67	3.98		[162]
(**60**)[b]	9.89	9.06	4.27	[177]
(**61**)[c]	9.89	9.14		[178]
(**62**)[c]	9.68	8.82		[179]

[a] $I = 0.15$ mol dm^{-3}.
[b] $I = 0.1$ mol dm^{-3}.
[c] $I = 0.5$ mol dm^{-3}.

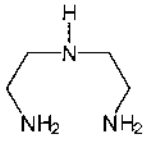
consequent basicity decrease with respect to the corresponding unsubstituted polyazacycloalkanes. Such an effect has been principally reported for macrocycles containing three or four donor atoms [139–141,145,153,154,162–164,167].



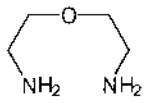
(**58**)



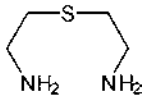
(**59**)



(**60**)



(**61**)



(**62**)

An instructive example of this effect is offered by the nine-membered macrocycles [9]aneN_2O (**58**) [139–141,162] and [9]aneN_2S (**59**) [141,162]. Table 14 reports the protonation constants of these N_2X-donors (X = N, O, S) macrocycles and of their acyclic analogues (**60**–**62**). It should be noted that for all the acyclic amines the first and the second protonation constants do not vary much as one changes the central donor atom from nitrogen to sulfur or oxygen. This suggests that the different central donor atoms do not exert any electronic effect, which markedly changes the basicity of the neighboring nitrogen donor atoms. Therefore, it can be concluded that the marked differences in the protonation constants of macrocycles as we change X from nitrogen to sulfur or oxygen do not reflect electronic, i.e. inductive, effects, but are due to differences in the hydrogen bonding ability of X. Thus, when

Table 15
Logarithms of the stepwise protonation constants of macrocycles (**33**), (**63**–**68**), determined at 298 K where $I = 0.1$ mol dm^{-3}

	Log K_1	Log K_2	Log K_3	Log K_4	Ref.
(**33**)	10.38	9.71	2.05	<1	[83]
(**63**)	10.18	8.56	1.43		[141]
(**64**)	8.43	5.77			[141]
(**65**)	9.53	7.65			[142,143]
(**66**)	11.02	9.96	1.96		[144]
(**67**)	10.35	8.64	2.78		[141]
(**68**)	10.36	6.62			[141]

X = N, the log K_1 and log K_2 values are at their highest and become progressively lower as we exchange N for O or S [139,162]. This is exactly as would be expected if the donor atoms in the macrocycle were involved in a cooperative stabilization of the attached proton by hydrogen bonding to the proton, since the expected hydrogen bonding ability of the different groups would be N > O > S.

Table 14 also shows that the second protonation constants for the cyclic molecules are lower than those of the linear analogues. The by far smaller log K_1 − log K_2 value presented by the acyclic polyamines (**60**–**62**) can be explained in terms of the electrostatic repulsion between two closely neighboring ammonium groups, i.e. between the incoming protons and those already bound to the neighboring nitrogen atoms. This effect decreases with the distance between the two nitrogen atoms, as shown by the lower value of the second protonation constant found for [10]aneN_2O (log $K_1 = 10.09$, log $K_2 = 6.31$) [139], where the two nitrogen atoms are separated by a propylenic chain.

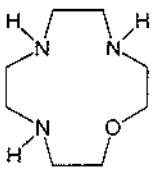
Similar effects have been also found in four donors oxa-aza and thia-aza macrocycles [141,145,153,154,163,165,167]. For these ligands, other factors, such as

Table 16
Logarithms of the protonation constants of macrocycles (**52**), (**69**–**77**) determined at 298 K

	Log K_1	Log K_2	Log K_3	Log K_4	Ref.
(**52**)[a]	11.58	10.62	1.61	2.41	[111]
(**69**)[b]	9.66	8.24	2.53		[166]
(**70**)[b]	9.71	6.60			[166]
(**71**)[b]	9.41	5.69			[166]
(**72**)[b]	9.78	8.16			[166]
(**73**)[b]	8.75				[166]
(**74**)[a]	9.13	5.04			[164]
(**75**)[a]	9.24	6.26			[164]
(**76**)[a]	10.49	7.74			[164]
(**77**)[a]	9.95	9.09			[164]

[a] $I = 0.5$ mol dm^{-3}.
[b] $I = 0.1$ mol dm^{-3}.

the number of nitrogen atoms and their relative disposition within the macrocyclic framework must be considered in the analysis of their protonation behavior. Table 15 reports the protonation constants of the 12- and 13-membered macrocycles [12]ane$N_{(4-y)}O_y$ ($y = 0$, 1, 2) [141–144,153,154] and [13]ane$N_{(4-y)}O_y$ ($y = 0$, 1, 2) [141,145], while Table 16 shows the protonation constants of the macrocycles of the series [14]ane$N_{(4-y)}S_y$ ($y = 0$, 1, 2, 3) as well as of other N_2S_2 macrocycles [163,164,166,167]. These data outline two general features: (i) replacement of nitrogens by O or S donors leads to a fall-off of the basicity constants; (ii) the values of the protonation constants, in particular log K_2, are significantly affected by the relative position of nitrogens within the macrocyclic framework.



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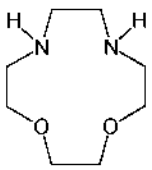

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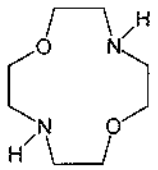

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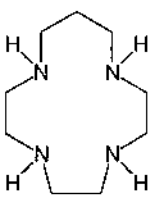

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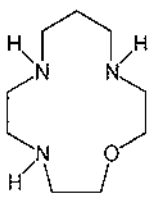

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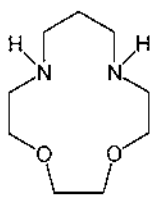
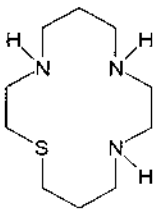


(68)

As far as point (i) is concerned, we note that the stepwise protonation constants of these macrocycles clearly show a fall-off in log K as nitrogens are replaced by oxygen or sulfur atoms. For example, considering the 12-membered macrocycles (**33**) [87], (**63**) and (**64**), log $K_1 = 10.38$ for the tetramine (**33**), 10.18 for the monooxa analogous (**33**) and 8.43 for the dioxa derivative (**64**) [146]. A similar trend is also observed for the second protonation constant, which decreases from the values of log $K_2 = 9.71$ for (**63**) to log $K_2 = 5.77$ for (**64**). Such a behavior cannot be explained only in terms of statistical effects, but can be related to the poorer hydrogen bonding ability of oxygen and sulfur [145,153], which leads to a weakening of the cooperative binding of the bound protons by the donor atoms, as reported above for macrocycles containing three donors. However, conformational effects must be taken into account.



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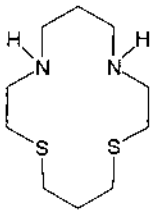

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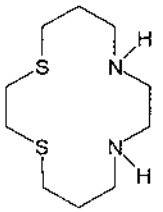

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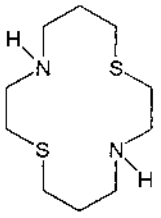

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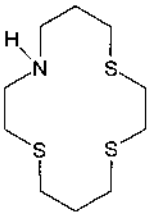


(73)

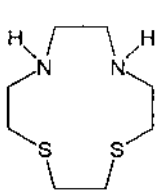
Rorabacher and coworkers analyzed the protonation behavior of the thio-aza macrocycles (**69**–**73**) [166], which are characterized by a first basicity constant markedly lower than that of [14]aneN_4 (**52**). As previously reported, it was firstly proposed that the large values of the two first protonation constants of (**52**) is due to the formation of strong hydrogen bonds between two opposite (or *trans*) nitrogen atoms [116]. If this proposal has merit, one might expect a similarly large log K_1value for the ligands (**69**) and (**72**), since each of them has the possibility of forming one internal *trans* hydrogen bond. However, both of the latter ligands have log K_1 values that are significantly smaller than the value reported for (**52**). On the other hand, in the crystal structure for the perchlorate salt of H_2(**52**)$^{2+}$ (Fig. 14), there is an indication that hydrogen bonding occurs between the protonated nitrogen donor and the nitrogen to which it is linked via a propylenic bridge [118]. This may suggest that log K_1 should be larger for (**70**) than for (**71**), which is also not observed. In fact, all three molecules containing the N_2S_2 donor set exhibit essentially the same value of log K_1, suggesting that the magnitude of log K_1 cannot be easily attributed to a specific type of internal hydrogen bond within the macrocyclic framework.

An almost linear increase of log K_1 as y increases from 0 to 3 for 14-membered macrocycles having the $N_{(4-y)}S_y$ donor set is observed (Table 16). A similar trend is also observed for log K_2. The regular trends in log K values was attributed to a general transition in the preferred conformations for the molecules from an all-*out* conformation for [14]aneS_4 to an all-*in* conformation for (**52**) [166].

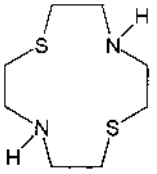
Table 17
Logarithms of the protonation constants of macrocycles (**78**–**80**), determined by potentiometric measurements at 298 K)

	(**78**)[a]	(**79**)[b]	(**80**)[b]
Log K_1	9.65	9.66	9.69
Log K_2	8.92	8.78	8.98
Log K_3	8.30	8.23	8.43
Log K_4	7.64	7.40	7.81
Log K_5	3.81	3.99	6.13
Log K_6	3.26	3.18	3.99
Log K_7			2.81

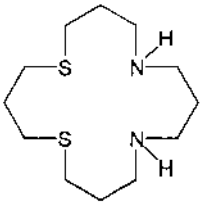
[a] $I = 0.1$ mol dm^{-3}, from Ref. [171].
[b] $I = 0.15$ mol dm^{-3}, from Ref. [173].



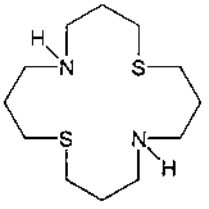
(**74**)



(**75**)



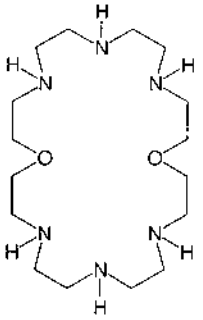
(**76**)



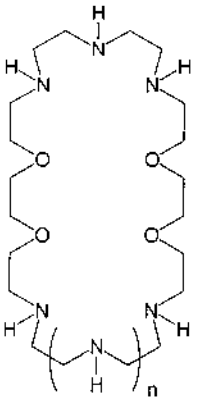
(**77**)

Considering the second point (ii), the relative position of the nitrogen donor atoms significantly affects the magnitude of log K_2, both for oxa-aza and thia-aza macrocycles, as shown clearly by comparing the log K_2 values for the couples of macrocycles (**64**–**65**) [141–143], (**74**–**75**) and (**76**–**77**) [163,164]. The diaza molecules (**65**), (**75**) and (**77**) exhibit higher second protonation constants than (**64**), (**74**), and (**76**), respectively. This observation can be principally explained in terms of electrostatic repulsion, since in (**64**), (**74**) and (**76**) protons are forced to bind adjacent nitrogens [164]. Electrostatic factors can also explain the very different log K_2 values for the 14-membered N_2S_2 molecules (**70**), (**71**) and (**72**), whose protonation constants increase with increasing distance between nitrogen atoms [166].

The lower hydrogen bonding ability of oxygen and sulfur as well as the presence of $(-CH_2)_n$–X–(CH_2-) (X = O, S) chains, which can acts as spacers between nitrogen atoms, leads to the most evident differences in the protonation constants of oxa-aza and thia-aza macrocycles with respect to the corresponding unsubstituted polyaza counterparts. However, several other factors, such as statistical effects, inductive effects due to the alkyl chains connecting the donors [132,141,145,163,164,166], methylation of the nitrogens [139,147,149–153,165,168,169], or reinforcement of the alkyl bridges linking nitrogens [155,156] affect the basicity properties of these molecules. These effects have already been discussed in the preceding sections and will not be analyzed here.



(78)

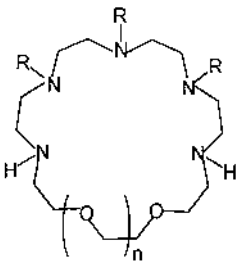


n = 1, (79)

n = 2, (80)

Let us now consider the proton binding properties of mixed donor macrocycles containing a large number of donor atoms within the macrocyclic framework. Compounds (**78**) [170–172], (**79**) and (**80**) [173] are composed by two polyaza moieties separated by two mono-oxa (**78**) or dioxa (**79**, **80**) chains. Table 17 shows the protonation constants for these macrocycles. As far as (**78**) and (**79**) are concerned, the log K values are very similar for each protonation step [171,173]. The first four basicity constants range between 9.66 and 7.40 logarithmic units, while the fifth and the sixth ones are less than 4 logarithmic units. This behavior is quite similar to that previously observed for the ditopic molecules (**46**–**50**) and can be interpreted by analogous considerations on minimization of electrostatic repulsion and protonation patterns.

Similar considerations also apply for the proton binding properties of (**80**).



n = 1, R = H, (81)

n = 1, R = CH_3, (82)

n = 2, R = CH_3, (83)

Table 18
Logarithms of the protonation constants of macrocycles (**81**–**83**), determined at 298 K, $I = 0.15$ mol dm^{-3} $NaClO_4$

	(**81**)[a]	(**82**)[b]	(**83**)[b]
Log K_1	9.57	9.31	9.32
Log K_2	8.87	8.58	8.59
Log K_3	7.70	7.50	7.57
Log K_4	3.41	2.48	2.78

[a] From Ref. [175].
[b] From Ref. [176].

Molecules (**81**–**83**) display two different binding sites (one N_5 and one O_2 or O_3 subunits), located at opposite side of the same macrocycle, and can be considered compartmental molecules [175,176]. Table 18 shows the basicity constants of the three molecules. (**81**) is less basic in each step of protonation than the dimensionally analogous polyazacycloalkane [21]aneN_7 (**36**) (Table 8), in which all the donors are secondary nitrogen atoms. A statistical effect can explain reasonably the slight difference in the first basicity constant (ca. 0.2 logarithmic units) but does not justify completely the more remarkable drop in the successive three protonation steps. Indeed, with respect to polycharged species of (**81**), in the equally polyprotonated forms of (**36**) the protons can be localized enough far away to achieve a better minimization of the electrostatic repulsion between positive charges.

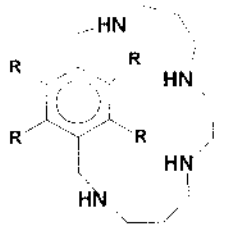
The higher basicity exhibited by (**81**) (ca. 0.2–0.3 logarithmic units in each step of protonation) with respect to (**82**) and (**83**) can be explained taking into account the presence of three tertiary nitrogens in the latter macrocycles [176]. Also of interest is the sharp decrease in basicity between the third and fourth stepwise constants of these oxa-azamacrocycles: in the case of (**82**), the difference between the first and the third protonation constants is only 1.81 logarithm units, while that between the third and the fourth ones is 5.02. Similar values can be calculated for (**53**). As previously reported, this behavior can be rationalized considering the minimization of electrostatic repulsion between positive charges. In (**82**) the first three protons can occupy alternate positions in the macrocycle, separated by an unprotonated amino group, while in the tetraprotonated molecule two or more protonated nitrogens are contiguous.

These examples seem to indicate that in large oxa-aza macrocycles electrostatic effects play the most important role in determining the protonation behavior of such polyamines.

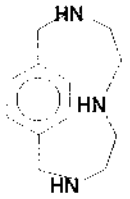
4.4. Polyazacyclophanes

Cyclophanes are cyclic compounds including one or more aromatic moieties as an integral part of their structures. Among them, polyazacyclophanes have received much attention in the last years since, very often, they are water-soluble and, on the other hand, they have the possibility to coordinate substrates including them in hydrophobic cavities enhancing particular reactivities in the bound species. The coordinated substrates can be either metal ions if the nitrogens are deprotonated or anionic or polar guests if the nitrogen atoms are partly or totally protonated.

The acid–base behaviour of these compounds depends on the general features already discussed in this review, but also on interactions with the π-clouds of the aromatic moieties and on the hydrophobic conditions these units may generate. In this review some recent examples will be provided to clarify these aspects. Examples will concern 1:1 and 2:2 polyazacyclophanes; 1:1 macrocycles are those with one aromatic unit and one polyamine chain and 2:2 those with two of each such fragments.



R = H (84)
R = CH_3 (90)



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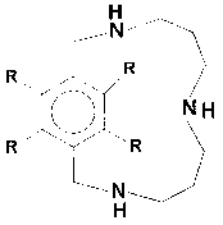
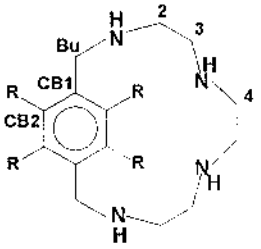
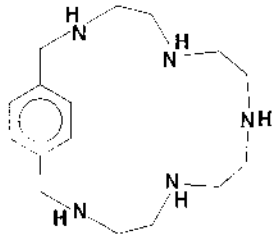


R = H (86)
R = CH_3 (87)



R = H (88)
R = CH_3 (89)



R = H (91)

Concerning 1:1 polyazacyclophanes, the simplest ones are probably those with a polyamine chain and a benzene ring as a spacer. In spite of this simplicity it was not until 1993 when one of such molecules was fully characterized and their acid–base behavior established [180]. The compound was named 2,6,9,13-tetraaza[14] paracyclophane (**84**) following the nomenclature proposed by Diederich for such molecules [181]. After this synthesis the series of related compounds (**85**)–**91**) with different hydrocarbon chains and benzene or 1,2,4,5-tetramethylbenzene spacers was prepared and their protonation behavior investigated by potentiometry, microcalorimetry and NMR [182,183]. On the other hand, in compounds with aromatic units the pH dependence of their UV–vis and fluorescence emission may be also be used to calculate the basicity constants [184].

In Table 19a the stepwise basicity constants for all these compounds are presented and in Table 19b, c the stepwise enthalpy of some relevant examples are presented [182,183].

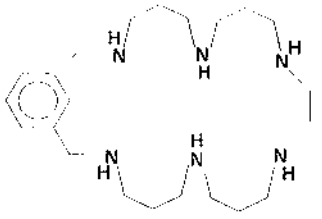
First of all, as can be seen in Fig. 15, the overall basicity of all these compounds except for (**91**) steadily increases with the atomicity of the molecules and a straight line is obtained when plotting the overall basicity constants versus the number of atoms in the polyamine chain bridging the aromatic spacer. When the compounds with the same polyamine chains are compared (couples (**84**–**90**), (**86**–**87**) and (**88**–**89**)), it can be noted that their stepwise basicity constants are rather similar. Therefore, possible solvation effects originated by methylation of the aromatic moiety do not seem to significantly affect the basicity of the compounds.

The trends in the stepwise basicity constants follow the general criteria of minimum electrostatic repulsion between same sign charges generally observed in the protonation of polyamines. In this sense, tetraazaparacyclophanes (**88**) and (**89**) with only ethylenic chains show two relatively large basicity constants, one interme-

diate and one much lower constant for the last protonation step due to the necessary entry of this proton on a nitrogen between already protonated amino groups. (**84**) and (**90**), with a symmetrical array of two propylenic and one ethylenic chain in the polyamine bridge show, however, much larger constants in the third and four protonation steps due to the presence of the larger propylenic chains. Triazaparacyclophanes (**86**) and (**87**) display high basicity in all their three protonation steps due to the same reasoning.

These tendencies are also reflected by the thermodynamic terms associated with the protonation steps of these compounds (Table 19b, c). (**86**) and (**87**) with all propylenic chains display large favorable enthalpic contribution in all their three protonation steps. (**84**) and (**90**) display large enthalpic terms for their three protonation steps and intermediate ones for their fourth protonation step which should occur on nitrogen atoms between ammonium groups separated by an ethylenic and a propylenic chain. (**88**) and (**89**) display lower enthalpic contributions for all their protonation steps and particularly for the last one due to the greater electrostatic repulsion that occur when a proton binds a nitrogen separated from the next ammonium sites just by ethylenic fragments.

These compounds are particularly prone for NMR analysis of their protonation pattern since they have clearly differentiated protonation sites. Quaternary carbon atoms (CB1) in the aromatic units are placed just in the β position to the benzylic nitrogens (N1) and, therefore, the variations of their ^{13}C-NMR chemical shifts with pH will be reflecting their actual protonation states. Analogously, the chemical shifts of the ^{1}H signals of the benzylic protons (HBn) will only be influenced significantly by the protonation of such nitrogen atoms. As an example, the variations with the pH of such ^{1}H- and ^{13}C-NMR spectra of cyclophanes (**88**) are shown in Fig. 16. Analysis of those spectroscopic data allows one to conclude that benzylic nitrogens are involved in the first protonation steps of the macrocycles. In the case of (**88**) this agrees with the low enthalpy and high entropy terms associated with its first protonation (Table 19b, c) which can probably be ascribed to a high hydrophobicity of the protonation site.



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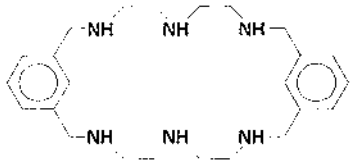

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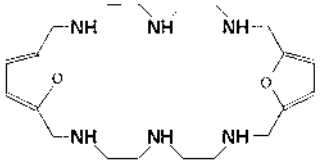

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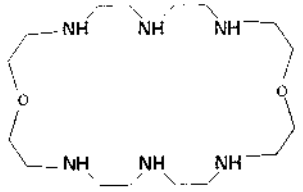


(95)

Table 19
Protonation constants of polyazacyclophanes (**84**–**91**) ($I = 0.15$ mol dm^{-3}, $T = 298$ K [183]), and enthalpy and entropy terms (kJ mol^{-1}) for the successive protonations (**84**), (**86**–**90**) taken from Ref. [183]

	(**84**)	(**85**)	(**86**)	(**87**)	(**88**)	(**89**)	(**90**)	(**91**)
(a) Protonation constants								
Log K_1	9.93	9.42	10.13	9.96	9.39	9.44	10.54	10.68
Log K_2	9.09	7.31	8.34	8.59	8.45	8.67	9.23	9.29
Log K_3	7.44	3.26	6.82	7.04	5.38	5.64	7.44	8.66
Log K_4	3.61				2.51	2.51	3.59	7.23
Log K_5								3.83
Log β[a]	30.1	20.0	25.3	25.6	25.7	26.3	30.8	39.7
(b) Enthalpy terms (kJ mol^{-1})								
$-\Delta H_1^\circ$	40.0		41.0	40.2	34.4	38.5	43.3	
$-\Delta H_2^\circ$	45.6		43.6	43.5	40.6	39.3	46.1	
$-\Delta H_3^\circ$	44.8		43.1	43.1	36.4	38.1	46.1	
$-\Delta H_4^\circ$	29.3				17.2	16.3	28.0	
(c) Entropy terms (kJ mol^{-1})								
$T\Delta S_1^\circ$	16.7		16.7	16.7	19.7	14.6	16.7	
$T\Delta S_2^\circ$	6.3		4.2	6.3	7.1	10.0	6.7	
$T\Delta S_3^\circ$	−2.5		−4.6	−2.9	−5.9	−5.4	−4.2	
$T\Delta S_4^\circ$	−8.8				−2.1	−2.1	−7.5	

[a] Log $\beta = \Sigma$ log K_i.

Also of interest is that the greater the size of the 1:1 cyclophane and the longer the hydrocarbon fragments in the chain, the shorter its difference in basicity with related open-chain polyamines. This, which is due to the greater conformational freedom of the larger molecules, is clearly reflected in the acid–base chemistry of compound (**92**) [185,186]. The protonation constants of this macrocycle (Table 20) containing a symmetric array of four propylenic and one

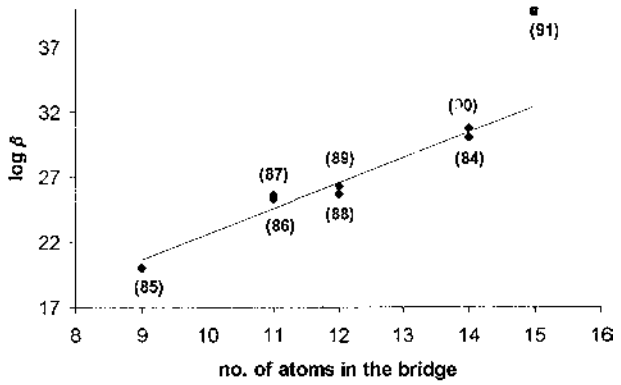


Fig. 15. Representation of the overall basicities (log $\beta = \Sigma$ log K_i) of cyclophanes (**84**–**91**) vs. the number of atoms in the bridge.

Table 20
Stepwise protonation constants of (**92**) where $I = 0.15$ mol dm^{-3} and $T = 298$ K [185,186]

	(92)
Log K_1	10.78
Log K_2	10.08
Log K_3	9.00
Log K_4	7.93
Log K_5	7.30
Log K_6	5.24
Log β[a]	50.3

[a] Log $\beta = \Sigma$ log K_i.

ethylenic hydrocarbon chains in the bridge are very close to those of the related open-chain hexaamine (**19**), denoting the smaller effects of the hydrophobic units due to the higher conformational freedom of the bridge. NMR studies on the protonation of this polyamine also denote the random characteristics of its first protonation steps [72].

Martell and co-workers have studied the protonation behavior as well as the anion and cation coordination capabilities of several 2:2 cyclophanes containing diethylene triamine bridges linked to spacers like 1,3-phenylene or 1,3-furan. (**93**–**94**) [187–189]. In such reports the chemistry of these ligands was usually compared with that of the well-known receptor 1,13-dioxa-4,7,10,16,19.22-hexaaza-tetracosane (**95**), known as bisdien [190]. In Table 21 the constants for all these receptors and the experimental conditions used in the determination are reported.

The basicity constants of these compounds follow the sequence (**94**) > (**93**) > (**95**). This tendency was explained considering that the aromatic and furan units present larger electron-withdrawing effects than the ether linkage in (**94**) and cause greater

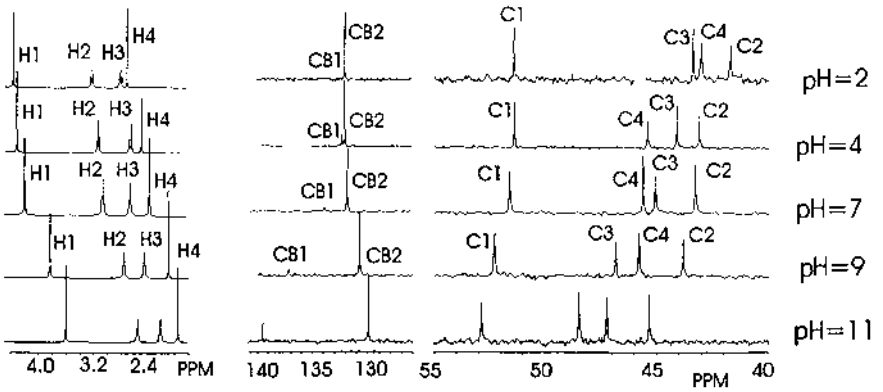


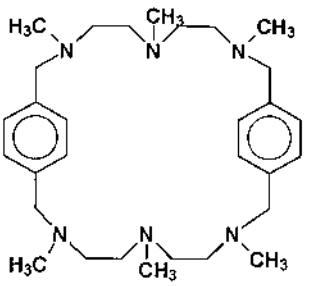
Fig. 16. Variation with the pH of ^{1}H- and ^{13}C-NMR spectra of (**88**).

Table 21
Stepwise protonation constants of cyclophanes (**93**–**95**) where $I = 0.1$ mol dm^{-3} and $T = 298$ K

	(**93**)	(**94**)	(**95**)
Log K_1	9.51	9.44	9.62
Log K_2	8.77	8.68	8.89
Log K_3	7.97	7.63	8.29
Log K_4	7.09	6.46	7.62
Log K_5	3.79	3.84	3.82
Log K_6	3.27	3.18	3.30
Log β [a]	40.4	39.2	41.5
Ref.	[188]	[189]	[190]

[a] Log $\beta = \Sigma \log K_i$.

detrimental effects on the basicity of the adjacent nitrogen atoms. Also in these compounds the criterion of minimum electrostatic repulsion operates since all them present a group of four relatively large constants and another one of two much lower constants.



(**96**)

Table 22
Stepwise constant and enthalpy and entropy terms (kJ mol^{-1}) for the protonation steps of cyclophane (**96**) where $I = 0.15$ mol dm^{-3} and $T = 298$ K [191]

Reaction	Log K	$-\Delta H°$	$T\Delta S°$
$H + L = HL$ [a]	8.93	26.4	24.5
$H + HL = H_2L$	8.22	28.4	18.5
$H + H_2L = H_3L$	7.35	42.5	−0.6
$H + H_3L = H_4L$	6.44	49.1	−12.3
$H + H_4L = H_5L$	1.5		

[a] Charges omitted.

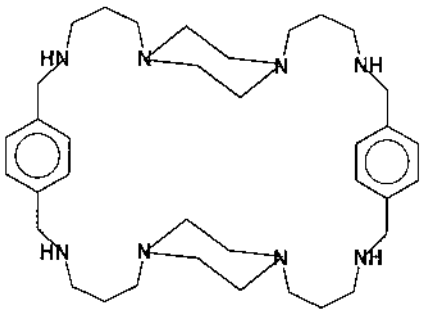
(**96**) represents another interesting 2:2 azacyclophane to analyze since it has all tertiary nitrogen atoms in its bridges (Table 22) [191].

This macrocycle behaves as a pentaprotic base in aqueous solution in the pH range 2–11. The first four basicity constants being much higher than the last one due to the fact that in $[H_4(\mathbf{96})]^{4+}$ the protons can attach alternate positions in the macrocycle. This has been confirmed by NMR studies in aqueous solution and by the crystal structure of $[H_4(\mathbf{96})](ClO_4)_4$ in which such a disposition of the charged sites is also observed.

As indicated previously in different cases, the lower magnitude of the stability constants with respect to the dimensionally analogous macrocycle (**93**), can be ascribed to the methylation of the amino groups. The enthalpy terms of the first two protonation steps are similar to each other and far lower than those for the third and four protonation steps. The increment in enthalpy observed can not be explained just by the increase in charge in the macrocycle, and the intramolecular hydrogen bonding observed in the crystal structure of $[H_4(\mathbf{96})](ClO_4)_4$ has to be somehow preserved in solution and should also contribute to the high exothermicity of the third and four protonation steps.

The entropic terms are favorable for the two first protonation steps, negligible in the third one and weakly unfavorable in the fourth one. These features can be explained considering the increasing organization of the solvent produced as the macrocycle becomes charged which leads to a decrease in translational entropy.

To conclude the section on azacyclophanes we will consider several examples of 2:2 cyclophanes containing reinforcing piperazine rings in their bridges.



(97)

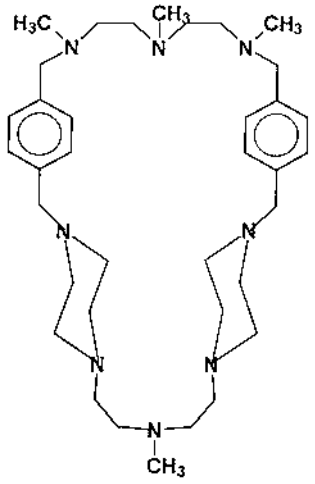
The basicity constants for compound (**97**) (Table 23) [192], made up of two *N*,*N*′-bis(propylamine)piperazine bridges linked by *p*-phenylene spacers, shows a classical distribution for a ditopic receptor with completely independent sites.

Indeed, the values of these constants are organized up to the sixth one, in groups of two having similar values. While the difference between the first and second basicity constants is 0.20 logarithmic units that between the second and third one is 1.09 logarithmic units. The difference between the third and fourth one is again much reduced ($\Delta \log K = 0.50$) and that between the K_4 and K_5 larger ($\Delta \log K = 1.37$). This trend suggests that protons bind (**97**) nitrogens in alternate sides and, therefore, the values of consecutive odd and even constants are close to each other since the electrostatic repulsions should be similar; the differences in these constants can be fully ascribed to statistical effects. The larger differences in the basicity of the different groups clearly reveal the existence of shorter-range electrostatic interactions at these protonation steps. The great drop in basicity observed between the sixth and seventh constant can be explained taking into account that the seventh proton would be attached to a nitrogen of an already monoprotonated piperazine ring. ^{1}H- and ^{13}C-NMR studies agree fully with the preceding discussion confirming the ditopic characteristics of the ligand. Also of interest in this compound is the morphology of the ^{1}H signals of the piperazine ring. These protons appear at basic pH as a very large singlet almost embedded in the base line of the spectrum while at acidic pH appear as a double doublet, indicating that the chair–chair conformational exchange of the piperazine ring is favored by the protonation of the rings DNMR studies performed on (**97**) and related compounds have confirmed this aspect.

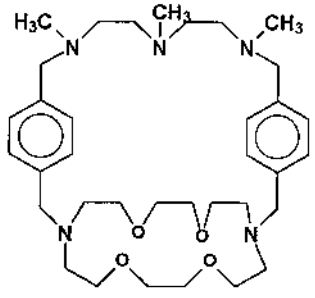
As indicated by these studies protons would bind the secondary benzylic nitrogen atoms in first place while tertiary piperazinic nitrogens would be protonated in second place. The enthalpy and entropy terms shown in Table 22 reflect the type of sites bearing protonation. In this sense, a marked diminution in exothermicity and an increase in entropy are observed at the fifth stage in which protonation of the piperazinic rings occurs.

Table 23
Stepwise protonation constants for macrocycles (**97**–**99**) at 298 K

	(**97**)	(**98**)	(**99**)
Log K_1	9.97	9.81	8.96
Log K_2	9.67	8.67	8.26
Log K_3	8.58	7.84	6.95
Log K_4	8.08	6.65	5.81
Log K_5	6.71	6.11	1.7
Log K_6	6.24	2.78	
Log K_7	3.13		
I (mol dm^{-3})	0.15	0.15	0.10
Ref.	[192]	[193]	[194]



(98)



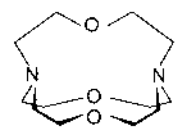
(99)

(**98**) is a 2:2 *p*-cyclophane bearing two different bridges [193], one of them made up by three methylated tertiary nitrogens, and the other one by two piperazine units and a methylated nitrogen distributed symmetrically [40]. The protonation constants of (**98**) (Table 23) show this compound takes up six protons in aqueous solution above pH 2. The first four constants range between 9.81 and 6.11 while the last one is far lower (2.78). The protonation mechanism determined by NMR show that in the pentaprotonated species, four protons are located in the benzylic nitrogen and the fifth one in the methylated central nitrogen of the bridge containing the piperazine rings. Another cyclophane based on a similar construction is (**99**), which adds to the trimethylated bridge a double bridge composed by the oxaazamacrocycle 1,10-dioxa-4,7,13,16-cyclooctadecane. In its tetrapronated

form protons both methylated benzylic nitrogens and the bridgehead nitrogen atoms of the oxazamacrocyclic portion are binding [194].

5. Macropolycyclic polyamines

5.1. Cryptands



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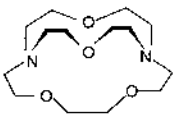

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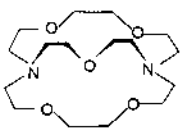

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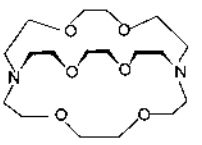

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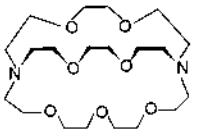

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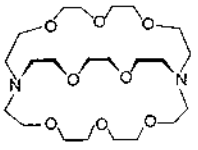

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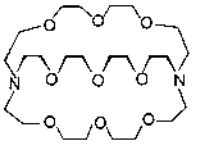

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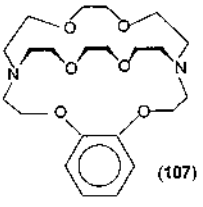

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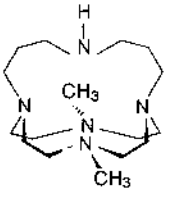

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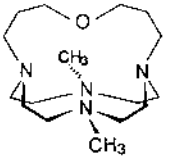

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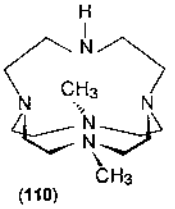

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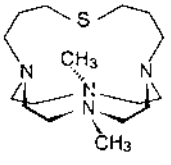

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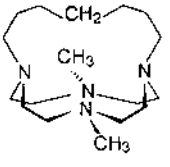

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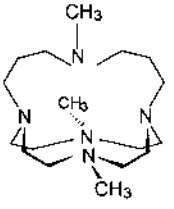

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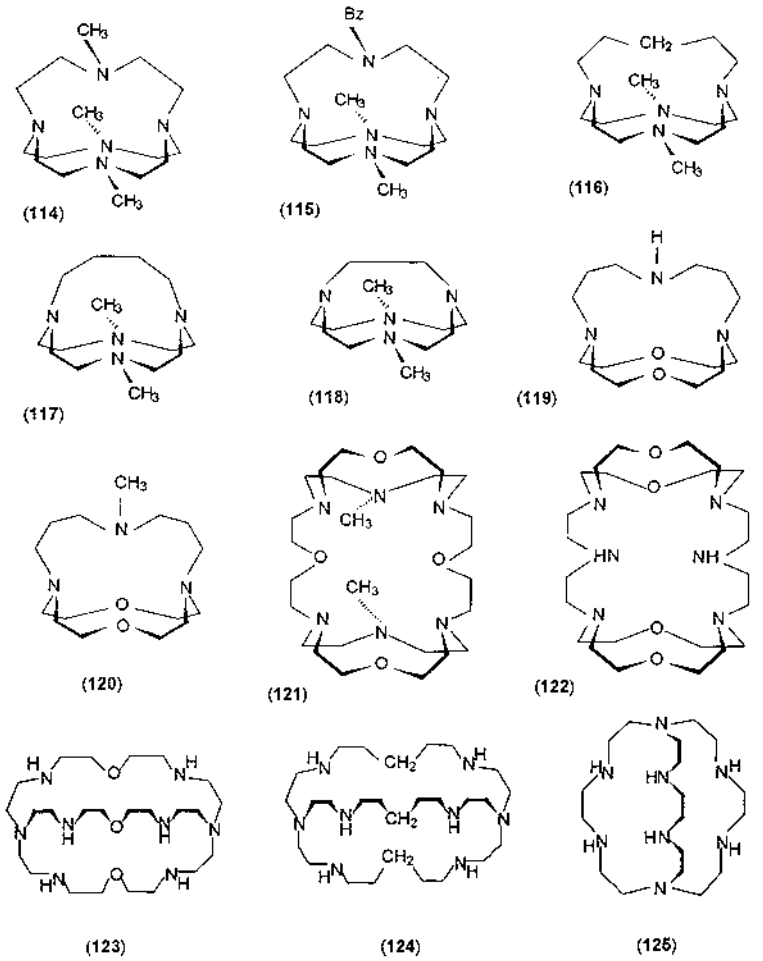


Proton transfer is usually very fast, but can be considerably affected by structural factors, slow proton transfer has been found in *N*-alkylated derivatives of 1,8-diaminonaphthalene [195,196] where the proton is held by a tight hydrogen bond and even slower rate of protonation/deprotonation can be found when the proton is bound in an intramolecular cavity [197]. Such a case is also the smallest [1.1.1] macrobicyclic cryptand 4,10,15-trioxa-1,7-diaza-bicyclo[5.5.5]heptadecane (**100**) whose kinetics and thermodynamics of protonation has been studied by Smith et al. [198] by ^{1}H- and ^{13}C-NMR.

(**100**) behaves as a diprotic base; the two protons can be bound either outside or inside the molecular cavity, five forms have been identified, io^{+}, $o^{+}o^{+}$, $i^{+}i$, $i^{+}o^{+}$, $i^{+}i^{+}$ where symbols i or o have been used to indicate the inside or outside configurations of the free amines and their protonated forms. The $i \rightarrow o$ interconversion has been investigated and although two processes could be invoked the nitrogen inversion seems to be the most important.

The log K_1 and log K_2 values for the externally protonated species io^+ and o^+o^+ are 7.1 ± 0.2 and $\cong 1$, respectively, and for the internally protonated species i^+i and i^+i^+ are ≥ 17.8 and $\cong 8$, respectively [198]. The rates of proton transfer into and out of the cavity are very slow. The internally monoprotonated species i^+i cannot be deprotonated unless the cryptand is destroyed. Even in the case of the diprotonated specie i^+i^+ one proton can be removed by base only in drastic conditions. In conclusion cryptand (**100**) is a thermodynamically very strong and kinetically extremely slow base.

A slight increase of the cavity size by adding a $-CH_2-CH_2-O-$ unit into one molecular branch produces a remarkable variation of the basicity behavior. Cryptand [2.1.1] 1,10-diaza-4,7,13,18-tetraoxabicyclo[8.5.5]eicosane (**101**), has been reported [199] to behave as a diprotic base in aqueous solution: log $K_1 = 10.64$, log $K_2 = 7.85$, ($I = 0.05$ mol dm^{-3}, $N(CH_3)_4Br$), compound (**101**) is less basic than (**100**) by 7–8 log units, furthermore compound (**101**) reacts much faster than (**100**) although still several orders of magnitude lower than those expected for a diffusion-controlled reaction [193]. Crystal studies on (**101**)·2$HClO_4$ salt [200] show that the diprotonated species $[H_2(101)]^{2+}$ adopts the i^+i^+ state with hydrogen atoms bound to both bridgehead nitrogens and forming three hydrogen bonds with the lone pairs on the closest O atoms. More recently, a substantially identical structure has been found for the (**101**)·2HCl [201]. In Fig. 17 is reported the crystal structure of the diprotonated cage $[H_2(\mathbf{101})]^{2+}$, taken from Ref. [200].

In Table 24 the thermodynamic quantities relative to cryptands (**100**), (**101**), 1,10-diaza-4,7,13,16,21-tetraoxabicyclo[8,8,5]tricosane (**102**), 1,10-diaza-4,7,13,16,-21,24-hexaoxabicyclo[8,8,8]hexacosane (**103**), 1,13-diaza-4,7,10,16,19,24,27-heptaoxabicyclo[11,8,8]nonacosane (**104**), 1,13-diaza-4,7,10,16,19,22,27,30-octaoxabicyclo[11,11,8]dotriacontane(**105**), 1,13-diaza-4,7,10,16,19,22,27,30,33-nonaoxabicyclo-[11,11,11]pentatriacontane (**106**), and 1,13-diaza-5,6-benzo-4,7,10,16,19,22,27,30,33-nonaoxabicyclo[11,11,11]-pentatriacontane (**107**) are reported.

The highest values of the protonation constants are always observed for the smallest cryptand, with increasing cavity size, the basicity strength decreases. Buschmann et al. [202] conclude that these results indicate that the other donor atoms are involved

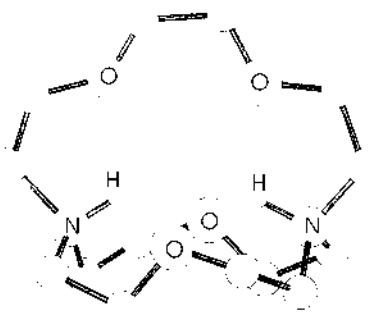
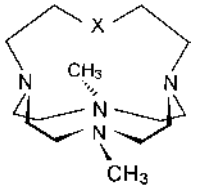


Fig. 17. Drawing of the diprotonated cation $[H_2(\mathbf{101})]^{2+}$. The atomic coordinates have been taken from Ref. [200].

in the formation of the monoprotonated species and the proton is located inside the cavities. The same authors [202] state that because the second protonation constants are similar, the second proton should be located outside the cavity. The insertion of one benzo group in compound (**107**) slightly reduces the basicity, in comparison with the unsubstituted compound (**103**), in both protonation steps [202]. The analysis of the $\Delta H°$ and $T\Delta S°$ contributions indicates that the addition of the first proton is more exothermic for compound (**107**) than for compound (**103**). This favorable exothermicity is more than compensated by an unfavorable entropic term (see Table 24). These results indicate that compound (**107**) is less hydrated than (**103**) [202].

5.2. Aza-cages

Another series of macrobicyclic cages having only or mainly nitrogen atoms as donors is represented in Scheme 1.



Scheme 1.

The first compound of these series: 12,17-dimethyl-1,5,9,12,17-pentaazabicyclo[7.5.5]nonadecane (**108**) behaves as a triprotic base in aqueous solution ($I = 0.5$ mol dm^{-3}) [203]. It is a very weak base in the third protonation step, $\log K_3 < 2$ and a moderate base in the second one ($\log K_2 = 8.41$), as the first proton cannot be removed even in strongly alkaline solution. ^{1}H- and ^{13}C-NMR studies indicate a fast proton exchange on the NMR time-scale for $H(\mathbf{108})^+$. This behavior is different from the first studied proton sponges, displaying sluggish proton transfer

Table 24
Logarithms of the equilibrium constants, $\Delta H°$ and $T\Delta S°$ values (kJ mol^{-1}) for the protonation of cryptands where $I = 0.05$ mol dm^{-3} Me_4NBr at 298 K

Cryptand	Log K_1	Log K_2	$-\Delta H_1°$	$-\Delta H_2°$	$T\Delta S_1°$	$T\Delta S_2°$	Ref.
(**101**)	10.64	7.85	–	–	–	–	[199]
(**101**)	10.99[a]	7.94	49.3	31.3	13.9	14.7	[206]
(**102**)	10.53	7.50	–	–	–	–	[199]
(**102**)	10.49[a]	7.40	56.6	22.2	4.0	19.8	[202]
(**103**)	9.60	7.28	–	–	–	–	[199]
(**103**)	10.03[a]	7.48	51.9	29.9	6.6	13.1	[202]
(**104**)	8.50	7.33	–	–	–	–	[199]
(**105**)	8.16	7.31	–	–	–	–	[202]
(**106**)	7.70	6.96	–	–	–	–	[199]
(**107**)	9.32[a]	6.15	59.0	22.2	−4.7	13.1	[202]

[a] Average of two values, see Ref. [202].

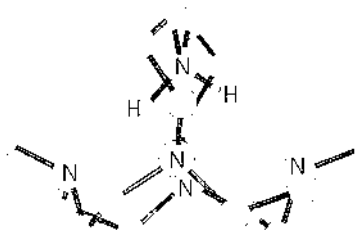


Fig. 18. Drawing of the cation $[H(\mathbf{108})]^+$. The atomic coordinates have been taken from Ref. [204].

processes, allowed to define (**108**) as a 'fast proton sponge' [203]. The crystal structure of the monoprotonated salt of (**108**) indicates that the five nitrogen are coplanar and in *endo* configuration [204]. As expected, the X-ray analysis confirms that protonation occurs on the secondary amino group. Each hydrogen atom of the apical NH_2^+ group interacts with three other nitrogen atoms, the N···H distances ranging from 2.04 to 2.70 Å (Fig. 18).

This arrangement makes the overall structure very stable from thermodynamic point of view and the hydrogen atoms of the NH_2^+ group rapidly exchangeable. This feature, fast exchange of the first bound proton, is typical of all series of these compounds. Replacing the –NH– group with the –O–, the cage 12,17-dimethyl-5-oxa-1,9,12,17-tetra-azabicyclo[7.5.5]nonadecane (**109**) is obtained which behaves as fast proton sponge in the first protonation step ($\log K_1 > 13.5$) [205] and as a relatively strong base in the second protonation step: $\log K_2 = 11.21$. The crystal structure of the diprotonated species $[H_2(\mathbf{109})]^{2+}$ shows that protonation occurs on the $N–CH_3$ groups. Each hydrogen atom of the $–NH(CH_3)–^+$ moieties interacts with the oxygen atom in the apical position, and with both bridgehead nitrogen atoms. Again, it is a particular hydrogen bond arrangement that makes the overall molecular structure very stable from a thermodynamic point of view. Slight changes in the molecular framework may have marked influence on the basicity behavior. Indeed, compound (**110**) 4,10-dimethyl-1,4,7,10,15-pentaaza-bicyclo[5.5.5]-

Table 25
Logarithms of the equilibrium constants for the stepwise protonation of aza-cages at 298 K

Apical group (X in Scheme 1)	Cage	Log K_1	Log K_2	Log K_3	I (mol dm^{-3})	Ref.
$–CH_2–NH–CH_2–$	(**108**)	>14	8.41	–	0.5	[203]
$–CH_2–O–CH_2–$	(**109**)	>14	11.21	<2	0.15	[205]
$–CH_2–S–CH_2–$	(**111**)	11.91	8.78	–	0.15	[207]
$–CH_2–CH_2–CH_2–$	(**112**)	12.00	7.86	–	0.15	[208]
$–CH_2–C(CH_3)–CH_2–$	(**113**)	11.83	9.53	3.43	0.15	[209]
–NH–	(**110**)	12.48	9.05	–	0.15	[206]
$–N(CH_3)–$	(**114**)	11.8	10.00	–	0.15	[210]
–N(Bz)–	(**115**)	11.8	8.3	–	0.15	[211]
$–CH_2–$	(**116**)	11.55	6.94	–	0.15	[212]
None	(**117**)	>14	7.8	–	0.15	[213]

heptadecane does not behave as a *proton sponge* [206] even though it is a strong base in the first protonation step: $\log K_1 = 12.48$ a moderate base in the second protonation step ($\log K_2 = 9.05$) and a very weak base in the third step: $\log K_3 < 1$ [206]. Replacing the –NH– in (**108**) with a bulkier –N(CH_3)– group yields the cage (**113**) (see Table 25 where protonation constants of the azacages of the series have been collected) which is a much weaker base [209] than (**108**). The crystal structure of $[H(\mathbf{113})]^+$ shows that protonation occurs in the apical tertiary nitrogen [209] (Fig. 19) repulsions between methyl groups weaken the hydrogen bond network with respect to that found for the related species $[H(\mathbf{108})]^+$ thus lowering the thermodynamic stability of the monoprotonated species. The protonation behavior of cages (**112**), (**116**) and (**117**), where no donor atoms are present in the bridging unit, is a clear indication of the key role played by the molecular topology [214].

All these cages are significantly stronger bases than the monocyclic macrocycle 1,4,8,11-tetramethyl-1,4,8,11-tetraazacyclotetradecane ($\log K_1 = 9.70$) [215] having only tertiary nitrogens. Remarkable is the behavior of (**117**), which behaves as a *proton sponge* in the first protonation step (Table 25). X-ray analysis on the $[H(\mathbf{117})]^+$ cation shows that protonation in the solid state occurs on the bridgehead nitrogen (Fig. 20) and that all nitrogen atoms are in *endo* configuration [213]. Further shortening of the bridging unit yields the cage 4,10-dimethyl-1,4,7,10-tetraazabicyclo[5.5.2]tetradecane (**118**) which behaves as a triprotic base in aqueous solution [216]: $\log K_1 > 13$, $\log K_2 = 5.95$ and $\log K_3 < 2$. Few direct calorimetric heats of protonation are available: $\Delta H_1^\circ = -54.4$, $\Delta H_2^\circ = -42.7$, $\Delta H_3^\circ = -13.0$ kJ mol^{-1} for (**113**) [202] and $\Delta H_1^\circ = -55.6$, $\Delta H_2^\circ = -48.1$ kJ mol^{-1} for (**111**) [207], respectively. However high exothermic contributions in the first protonation step indicates a strong interaction between proton and nitrogen atoms. As a general trend in the second protonation step the basicity is much reduced, the molecular rigidity forces two positive charges close to each other and thus the system is destabilized. Crystal structure of the diprotonated species $[H_2(\mathbf{109})]^{2+}$ and $[H_2(\mathbf{116})]^{2+}$ have been reported in Refs. [205,212], respectively. As expected in the third protonation step these cages are weak bases, only in the case of (**113**) has the third basicity constant been determined accurately. Three charges experience strong repulsion each other and the triprotonated species, in aqueous solution, is present at very low pH. In the solid state triprotonated salts are common for all cages, in the case of (**118**) the crystal structure of the triprotonated species $[H_3(\mathbf{118})]^{3+}$ has been determined [216]. In conclusion we can say that all these cages behave as a strong base in the first protonation step, in a few cases the basicity constant cannot be directly measured because it is too high, in any case the proton transfer reactions are fast, at least on the NMR time scale. The basicity is reduced in the second protonation step and became too low in the third protonation step to be measured in aqueous solution. Although four to five protonation sites are present, even in the solid state at maximum, three are occupied, the triprotonated salt being the most common. Another important feature, common to all aza-cages so far investigated, is the fastness of the proton transfer reaction in contrast with that found for cryptands.

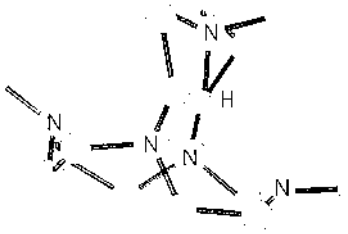


Fig. 19. Drawing of the cation $[H(\mathbf{113})]^+$. The atomic coordinates have been taken from Ref. [209].

5.3. Oxa-aza-cages

Compound 12,17-dioxa-1,5,9-triazabicyclo[7.5.5]nonadecane (**119**) which can be considered a hybrid between aza-cages and cryptands has been investigated from a basicity point of view [217]. It behaves as a very strong base in the first protonation step ($\log K_1 > 13$, $I = 0.15$ mol dm^{-3}), as a weak base in the second protonation step ($\log K_2 = 6.20$) and as a very weak base in the last protonation step: $\log K_3 < 2$ [217]. The cage 10-methyl-4,15-dioxa-1,7,10-triaza[5.5.5]cyclo-heptadecane (**120**) can be formally derived from the [1,1,1]cryptand (**100**) by replacing one oxygen atom with one methylated nitrogen. It behaves as a diprotic base in aqueous solution: $\log K_1 = 11.46$ ($I = 0.15$ mol dm^{-3}), $\log K_2 = 5.40$ [218]. The sharp decrease in basicity has been ascribed to a strong repulsion between the two positive charges forced by the molecular topology to stay close to each other. Compound 27,32 - dimethyl - 4,10,16,22 - tetraoxa - 1,7,13,19,27,32 - hexa - azatricyclo[17.5.5.5^{7,13}]tetratriacontane (**121**), which posseses two identical binding subunits, behaves, at most, as a pentaprotic base: $\log K_1 = 11.1$ ($I = 0.15$); $\log K_2 = 10.9$; $\log K_3 = 4.7$; $\log K_4 = 2.8$, and $\log K_5 = 2.5$ [218]. The first two protonation constants are rather similar to each other and a little smaller than the first basicity constant of (**120**). The molecular topology of (**121**), with two identical subunits, separated by a rather long $(-CH_2-CH_2)_2-O$ chain, has been invoked to explain such a proton transfer behavior. The two protons localize in different subunits, having a similar chemical environment and feel each other very little. Crystal structures of $[H(\mathbf{120})]^+$ and $[H_2(\mathbf{121})]^{2+}$ protonated species confirm the cage and cylindrical molecular shape of (**120**) and (**121**), respectively. An overall molecular cylindrical shape is presented also by the macrotricycle 10,22,28,32-tetraoxa-1,4,7,13,16,18-hexaazatricyclo[17.5.5.5^{7,13}]tetratriacontane (**122**). Its basicity behavior in aqueous solution has been investigated by potentiometric and NMR techniques [219]. Compound (**122**) behaves as a hexaprotic base: $\log K_1 = 10.27$, $\log K_2 = 9.52$, $\log K_3 = 7.12$, $\log K_4 = 4.62$, $\log K_5 = 2.80$, $\log K_6 = 2.27$ in $NaClO_4$ ($I = 0.15$ mol dm^{-3}).

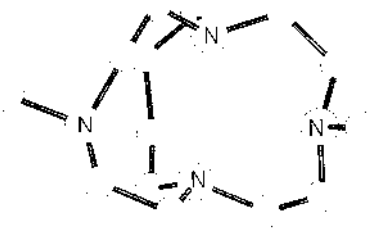
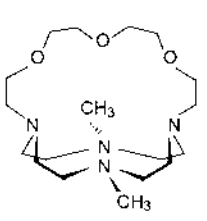


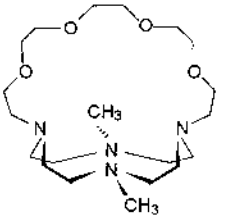
Fig. 20. Drawing of the cation $[H(\mathbf{117})]^+$. The atomic coordinates have been taken from Ref. [213].

Bis-tren 7,19,30-trioxa-1,4,10,13,16,22,27,33-octaazabicyclo-[11.11.11]-pentatriacontane (**123**) is a macropolycyclic compound containing two binding subunits able to form dinuclear complexes [220]. The protonation constants were found to be dependent on the nature of the supporting electrolyte due to the binding of anions to the protonated macrocycle. Values of $\log K_1 = 9.99$, $\log K_2 = 9.02$, $\log K_3 = 7.98$, $\log K_4 = 7.20$, $\log K_5 = 6.40$, and $\log K_6 = 5.67$ have been found at 298 K ($I = 0.1$ mol dm^{-3}, $NaClO_4$) [220]. It is interesting to compare the basicity constants of (**123**) with its polyaminic subunit 2,2′,2″-triaminotriethylamine (tren). The values of the basicity constants of O-bistren are significantly lower than those of tren itself: $\log K_1 = 10.12$, $\log K_2 = 9.41$, $\log K_3 = 8.47$. This effect has been ascribed to a greater mutual coulombic repulsion in the macrocyclic molecule and to the presence of oxygen atoms [220]. Indeed the related cage C-bistren 1,4,10,13,16,22,27,33-octaazabicyclo[11.11.11]-pentatriacontane (**124**) where the oxygen donor atoms of (**123**) are replaced by $-CH_2-$ groups is more basic than (**123**) in each protonation step: $\log K_1 = 10.35$, $\log K_2 = 9.88$, $\log K_3 = 8.87$, $\log K_4 = 8.38$, $\log K_5 = 8.14$ and $\log K_6 = 7.72$ at 298 K ($I = 0.1$ mol dm^{-3}, $NaClO_4$) [221]. The lower basicities of the nitrogens in (**123**) are considered due to the electron-withdrawing ether oxygens in the bridges between the tren moieties [220,221].

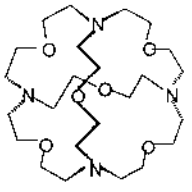
Recently the proton binding characteristics of the octaazacryptand 1,4,7,10,13,16,21,24-octaazabicyclo[8,8,8]hexacosane (**125**) has been studied [222]. It behaves as an hexaprotic base in the experimental conditions used ($I = 0.1$ mol dm^{-3}, KNO_3, 298 K), $\log K_1 = 11.2$, $\log K_2 = 9.4$, $\log K_3 = 7.6$, $\log K_4 = 5.78$, and $\log(K_5 \cdot K_6) = 4.4$, with the last value corresponding to a two-proton step. Quite unexpectedly for a large azacryptand, the ^{1}H-NMR spectra indicate that proton exchange is slow on the NMR time scale in the pH region where the two-proton step occurs. It has been proposed that this behavior is due to the disruption of an internal hydrogen bond network present in the tetraprotonated species.



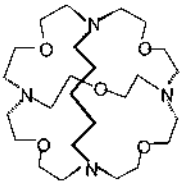
(126)



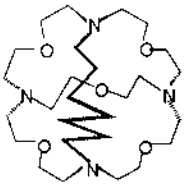
(127)



(128)



(129)



(130)

The proton transfer properties of 16,21-dimethyl-4,7,10-trioxa-1,13,16,21-tetraazabicyclo[11.5.5]tricosane (**126**) 19,24-dimethyl-4,7,10,13-tetraoxa-1,16,19,24-tetraazabicyclo[14.5.5]hexacosane (**127**) compounds have been studied in 0.15 mol dm^{-3} Me_4NClO_4 [223]. Both compounds show a similar basicity behavior, exhibiting a high basicity in the first protonation step and a much lower basicity in the second protonation step: $\log K_1 = 11.24$, $\Delta H_1^\circ = -50.5$ kJ mol^{-1}, $T\Delta S_1^\circ = 13.6$ kJ mol^{-1}, $\log K_2 = 8.39$, $\Delta H_2^\circ = -48.1$ kJ mol^{-1}, $T\Delta S_2^\circ = -0.2$ kJ mol^{-1} for (**126**) [223], and $\log K_1 = 11.52$, $\Delta H_1^\circ = -50.9$ kJ mol^{-1}, $T\Delta S_1^\circ = 14.8$ kJ mol^{-1}, $\log K_2 = 8.76$, $\Delta H_2^\circ = -55.2$ kJ mol^{-1}, $T\Delta S_2^\circ = -5.2$ kJ mol^{-1} for (**127**). The unusually favorable enthalpic contributions in the first step of protonation, for compounds having only tertiary nitrogens has been ascribed to the influence of the molecular topology which allows strong interaction between nitrogen atoms and added protons. Because of the electrostatic repulsions, the third proton cannot be appreciably bound, at least in the usual aqueous experimental conditions. The crystal structure of the $[H_2(\mathbf{127})]^{2+}$ cation has been carried out [223] and compared with that found for compound 4,10,16,22-27,32-hexaoxa-1,7,13,19-tetraazatricyclotetratriacontane (**128**) [224] (Fig. 21).

Spherical oxa-aza macrotricycles (**128**), 4,10,16,22,27-pentaoxa-1,7,13,19-tetraazatricyclotetratriacontane (**129**) and 4,10,16,22,33-pentaoxa-tetraaza-1,7,13,19-tricyclopentatriacontane (**130**) have been synthesized to bind NH_4^+ cation [225,226]. Their proton transfer properties have been studied in aqueous solution [227]. In all cases, compounds (**128**), (**129**) and (**130**) behave as tetraprotic bases: $\log K_1 = 10.57$, $\log K_2 = 8.01$, $\log K_3 = 6.73$, $\log K_4 = 4.06$ for (**128**), $\log K_1 = 10.9$, $\log K_2 = 9.65$, $\log K_3 = 5.25$, $\log K_4 = 2.0$ for (**129**), and $\log K_1 = 10.4$, $\log K_2 = 8.3$, $\log K_3 = 6.1$, $\log K_4 = 4.1$ for (**130**).

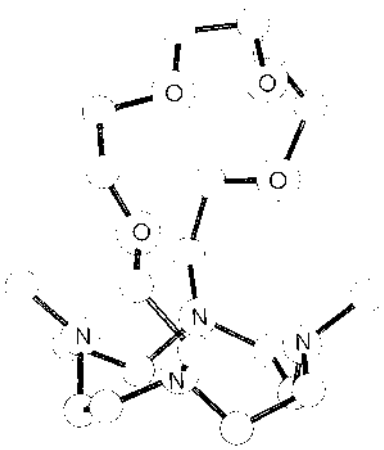


Fig. 21. Drawing of the cation $[H_2(\mathbf{127})]^{2+}$. The atomic coordinates have been taken from Ref. [223].

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