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COMPLEXES OF TRI- AND TETRAPROTONATED FORMS OF 1,4,7,10,13-PENTAAZACYCLOPENTADECANE WITH VARIOUS MONO- AND DIVALENT ANIONS IN AQUEOUS MEDIA

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Acid dissociation and anion complexation properties of 3+ and 4+ forms of 1,4,7,10,13-pentaazacyclopentadecane were investigated by pH potentiometry, conductometric titration and ^{13}C NMR experiments. The 3+ and 4+ species form complexes with a variety of mono- and divalent anions, and their complexation constants can be determined by pH potentiometric methods. However, no iodide complexes are detected and neither is a pentaprotonated species. Enthalpy and entropy changes for the acid dissociation of the 3+ ligand and for its complexation with chloride are estimated. The complexation and acid dissociation properties of the ligand are discussed in terms of internal hydrogen bonding interactions and solvation effects.

INTRODUCTION

Protonated macrocyclic polyamines form complexes with anions in aqueous solutions. Although complexation reactions of this type have been discovered only within the last decade, numerous investigations have been reported.[1–3] In most cases, the complexation reactions involve 1:1 adducts of the anion with highly protonated forms of the polyamine, although some complexes involve 2:1 adducts.[4,5] Anion complexes have been reported with tetra-, hexa- and octaprotonated macrocyclic polyamine species.[6] Bonding in these complexes has usually been explained in terms of electrostatic and ionic–hydrogen bonding interactions. Solvent release mechanisms have also been cited as driving forces in these reactions.[4,5,7]

In recent papers[8,9] we discussed the role of internal hydrogen bonding interactions between protonated and unprotonated amine sites in determining acid strengths, anion complexation and solvation properties of protonated macrocyclic polyamines. The relative number of protonated versus unprotonated sites directly influences each of these properties. We applied this analysis to the acid dissociation and anion complexation of protonated forms of 1,4,7,10,13,16-hexaazacyclooctadecane (hexacyclen) and 1,4,8,12-tetraazacyclopentadecane.

In this work, we studied the complexation behaviour of the related compound 1,4,7,10,13-pentaazacyclopentadecane, referred to subsequently as L, with Cl^-, NO_3^- and SO_4^{2-}. The structure of this macrocyclic molecule is shown in Figure 1. We determined acid dissociation constants for the tetra- and triprotonated species of L and the equilibrium constants for the complexation of these species of L with the various anions. An analysis of the values of these equilibrium constants provides further evidence that internal hydrogen bond interactions and solvation effects play an important role in the complexation behaviour of protonated macrocyclic polyamines.

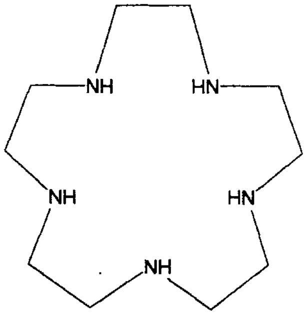

Figure 1. 1,4,7,10,13-Pentaazacyclopentadecane = L

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EXPERIMENTAL

Materials. All chemicals were of reagent grade. We tested KI, KCl, K_2SO_4 and KNO_3 solutions for the presence of trace acidic or basic impurities by a procedure in which the pH of a nitrogen-purged solution (at an ionic strength of 0·5 M) of each salt was monitored during addition of small amounts of HCl or NaOH. The concentration of acid/base impurities was always less than 0·01 mF.

1,4,7,10,13-Pentaazacyclopentadecane (H_5LCl_5) samples were obtained from Parish Chemical as the pentahydrochloride salt and were used without further purification. Alkametric titration of salt samples gave two end-points, at $a = 2$ and 3 mol KOH/mol L. The experimental ratio of end-point volumes was 1·50 with an uncertainty of less than 0·5%. L–buffer mixtures were prepared by addition of suitable amounts of KOH to portions of the pentahydrochloride stock solutions.

pH potentiometric measurements. All pH measurements employed a Beckman Model 71 pH meter equipped with conventional glass and calomel reference electrodes. The meter was standardized with solutions ranging from 1·00 to 20·0 mF HCl depending on the pH range of measurements to be made. The ionic strength was adjusted with KCl.

Because we wished to interpret the pH data as $pH = -\log[H^+]$, we made a variety of calibration experiments which have been described in detail elsewhere.[9] For the present work we extended the range of those calibration experiments to include the most acidic solutions that we would encounter (pH 1·7). These experiments included measurements made at fixed background electrolyte concentration and composition with various values of pH and also measurements made with varying electrolyte composition at fixed pH. These calibration experiments were designed to simulate the range of conditions in our experiments with L buffers. The results of these experiments indicated a linear pH response. The root mean square of the apparently random fluctuations in pH was always less than ±0·002.

Particular care was taken to insure thermal and chemical equilibrium. Electrodes were immersed in the solutions for at least 30 min before each titration and for at least 10 min before each pH measurement.

^{13}C NMR measurements. ^{13}C proton decoupled NMR spectra were obtained with a JEOL FX-90Q nuclear magnetic resonance spectrometer. The initial concentration of H_5LCl_5 in each sample solution was 0·02 F with ionic strength made up to 0·5 M with either KI or KCl. The concentration of each solution in D_2O was 10% (v/v). L mixtures were titrated with 0·60 F KOH, also 10% (v/v) in D_2O, in a 10 mm sample tube maintained near 30 °C. Data acquisition typically consisted of 1200 scans with a sweep width of 5000 Hz (*ca* 200 ppm). The spectrometer was calibrated before each experiment by measuring the single carbon resonance for portions of a stock solution containing DMSO-d_6 in 10% (v/v) D_2O in the same sample tube that would later be used for the experimental titration. This resonance line was set to 39·5 ppm (relative to tetramethylsilane) and was used as an external reference.

Conductance measurements. The electrolytic conductance of L solutions during titration with H_2SO_4 at 25·0 ± 0·1 °C was measured with a Leeds and Northrup Model 4959 conductance bridge equipped with a glass dip-type conductance cell.

pH POTENTIOMETRIC METHODOLOGY

We estimate complexation constants for protonated L species by means of potentiometric pH versus composition data obtained from experiments in which L buffer mixtures are titrated with complexing salts KCl, KNO_3 and K_2SO_4. Analysis of the experimental data relies on a non-linear regression procedure which minimizes the χ^2 statistic defined by

$$\chi^2 = \sum\left[\frac{\mathrm{pH(obs)} - \mathrm{pH(calc)}}{\sigma}\right]^2$$

where pH(obs) represents the observed pH value and pH(calc), the calculated pH value, is derived from the solution composition data by means of a set of model equations consisting of equilibrium constant expressions and mass and charge balance equations. The equilibrium constants (pK values and complexation constants) are treated as adjustable parameters. The uncertainty in each pH measurement, σ was obtained from independent calibration experiments. We set $\sigma = 0{\cdot}002$ in all our calculations, except for data at 55 °C where $\sigma = 0{\cdot}003$. Our calibration experiments at 55 °C showed that this larger uncertainty is appropriate.

The Levenberg–Marquardt[10-12] algorithm provides a systematic means of varying the adjustable parameters to obtain the best fit of the observed data to the model. Note that in order to formulate the model, it is necessary to know which species are present in the solution and which equilibrium expressions are required to provide the relationships among the concentrations of these species. A detailed discussion of this procedure appears elsewhere.[8,9]

Experiments designed to determine complexation and acidity constants for highly protonated L species require the analysis of two pH vs composition data sets: one from a mixture buffered to a pH near 6 and a second with a pH near 1·7. The values of the acid dissociation constants (pK) for H_5L^{5+} given in the literature are 1·16, 1·74, 6·00, 9·65 and 10·85 (at 25 °C and at an ionic strength of 0·2 M).[13] At pH 6 and ionic strengths between 0·12 and 0·50 M, the values of acidity constants imply that the concentrations of L, HL^+, H_4L^{4+} and H_5L^5 are all negligible and so can be set equal to zero in the model equations. At pH 1·7, although the concentrations of L and HL^+ are negligible, we would expect appreciable concentrations of H_4L^{4+} and H_5L^{5+}. However, in studies of the complexation of hexacyclen with anions, the pentaprotonated species was not detected. It seems unlikely that the fully protonated pentaaza species, H_5L^{5+}, would form under conditions similar to those where the 5+ form of the presumably more basic hexaaza compound did not. Assessments of which of the L species should be included in the model describing complexation behaviour were investigated by the experiments described in the following section.

ACIDIC DISSOCIATION AND ANION COMPLEXATION BEHAVIOUR OF H_5LCl_5

pH potentiometric titrations

In order to obtain information about the protonated L species in L mixtures with pH values between about 1·7 and 6 and with an essentially constant concentration of Cl^-, the complexing agent, we performed pH potentiometric titrations of 0·01 F H_5LCl_5 solutions containing 0·50 F KCl with a 0·20 F KOH solution containing 0·5 F KCl. pH vs volume of titrant data were analyzed using a modification of a non-linear regression algorithm used in previous work.[14] This algorithm analyzes data obtained during titration of a mixture consisting of q mmol of a partially dissociated mono- or polyprotic acid and m mmol of a strong acid. Values of q and m and the pK values of the weak acid are determined by the algorithm.

We obtained pH vs volume of titrant data for the range 0–2·3 mol KOH/mol H_5LCl_5, corresponding to a pH range of about 1·7–6. The corresponding titrant volumes were between 0 and 5 ml. The program requires as input estimates of the uncertainties in pH and in the volume. These were chosen to be 0·002 and 0·01 ml, respectively. Root mean square deviations in pH and titrant volume as determined by the program were comparable to the *a priori* estimates. We interpret this result as indicating that the experimental data are adequately fitted by a model based on complete (strong acid) dissociation of H_5LCl_5 and partial dissociation of H_4L^{4+} and H_3L^{3+} species. In other words, solutions of H_5LCl_5 are accurately modeled as an equimolar mixture of a completely dissociated acid and a partially dissociated polyprotic acid. This is confirmed by the regression analysis, which found the ratio of moles of strong acid to moles of weak acid to be 1 to within the estimated error of *ca* 2%.

As an example, an analysis of one set of titration data indicated the presence of 0·375 ± 0·006 mmol of strong acid and 0·371 ± 0·003 mmol of a partially dissociated polyprotic acid with primary and secondary pK values of 1·38 ± 0·05 and 6·27 ± 0·02, respectively. The uncertainties represent standard error estimates. The molar ratio of strong acid to weak is 1·01 ± 0·02, which is consistent with the complete dissociation of pentaprotic L to form the partially dissociated H_4L^{4+} acid. We shall show later that the conditional pK values obtained from the titration data are consistent with anion complexation of both H_4L^{4+} and H_3L^{3+} species. We infer from these observations that the H_5L^{5+} species, if they are present at all, play no significant role in these solutions even at pH values as low as 1·7. We confirmed the absence of H_5L^{5+} species and obtained further information about the solution behaviour of protonated L species by means of conductometric titration experiments.

Conductometric titrations

H_5LCl_5 solutions were titrated with NaOH reagent under various conditions. Two examples are illustrated in Figure 2. The lower curve represents the titration of 0·01 F H_5LCl_5 in water and the upper curve is essentially a replicate but employs a background electrolyte of 0·1 F NaI. The apparently linear decrease in volume-corrected conductance at the start of both curves indicates the virtually complete dissociation of the H_5L^{5+} and H_4L^{4+} species under the conditions of these experiments. The presence of significant amounts of these species, implied by pK values near 1·1 and 1·7, would result in substantial curvature of the plots in the region from $a = 0$ to 2 mol NaOH/mol H_5LCl_5. Instead, the observed linear decrease of conductance in this region corresponds to replacement of free H^+ by Na^+ from the titrant.

The titration in the absence of NaI features two additional branches before the final rise after $a = 5$ mol NaOH/mol H_5LCl_5. These correspond to the reactions

$$H_3LCl^{2+} + NaOH \rightarrow H_2L^{2+} + Na^+ + Cl^- + H_2O$$

in the region from $a = 2$ to 3 mol NaOH/mol H_5LCl_5 and to the stepwise neutralisation reactions

$$H_2L^{2+} + NaOH \rightarrow HL^+ + Na^+ + H_2O$$

and

$$HL^+ + NaOH \rightarrow L + Na^+ + H_2O$$

from $a = 3$ to 5 mol NaOH/mol H_5LCl_5.

However, only a single slope is observed in the $a = 2$–5 mol NaOH/mol H_5LCl_5 region when 0·1 F NaI is present. We ascribe this behaviour to a substantially decreased extent of H_3L^{3+} complexation in the NaI medium. This is a consequence of the significant dependence of the activity coefficient of the highly charged H_3L^{3+} species on the ionic strength of the solution. At the higher ionic strength, a decreased H_3L^{3+}

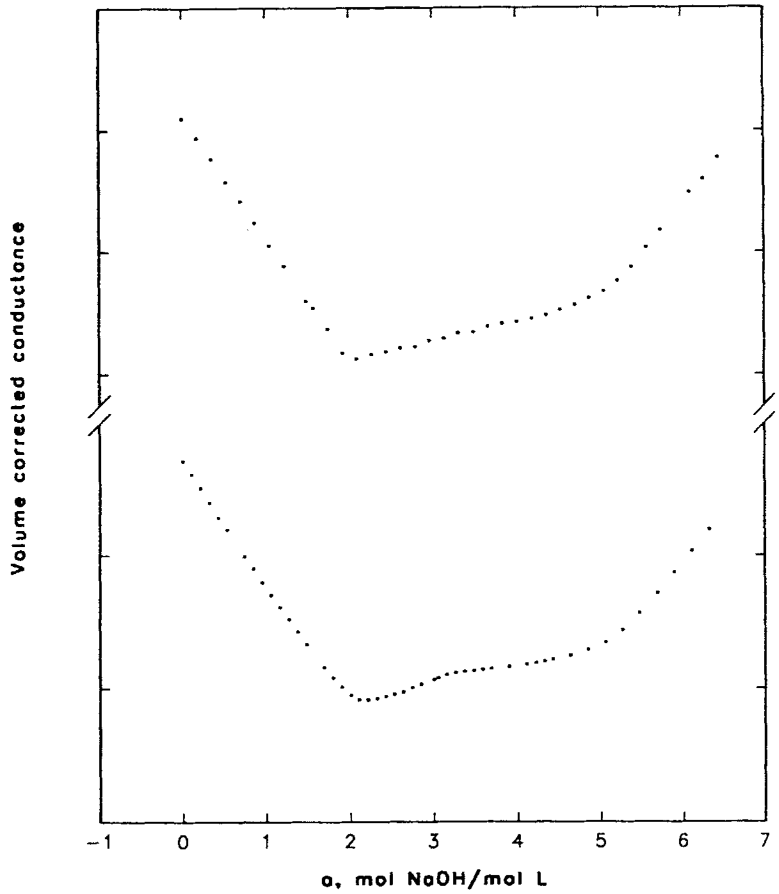

Figure 2. Conductometric titration of H_5LCl_5 solutions with NaOH. The lower curve represents electrolytic conductance vs added 0·20 F NaOH to a solution of 0·01 F H_5LCl_5 in water at 25 °C. The upper curve is a replicate titration with the analyte solution made up 0·1 F in NaI

activity coefficient results in a lower concentration of the H_3LCl^{2+} complex. Thus, the principal reactions occurring in the region from $a = 2$ to 5 mol NaOH/mol H_5LCl_5 consist of proton loss from the H_3L^{3+}, H_2L^{2+} and HL^{+} species and only one slope is observed.

^{13}C NMR spectrometric titrations

We obtained ^{13}C NMR spectra of solutions of H_5LCl_5 (initially 0·02 F and adjusted to an ionic strength of 0·5 M with KI or KCl) during the course of titrations of the solutions with 0·6 F KOH added in about ten portions. In each case the spectrum consisted only of a single resonance corresponding to the ten equivalent carbon atoms of L. The data for these titrations were essentially identical beyond $a = 3$ mol KOH/mol L where the H_2L^{2+} and L species are dominant, confirming that these L species do not undergo appreciable complexation with the chloride or iodide ions present in the titration mixtures. The spectra differ slightly in the range $a = 2$–3 mol KOH/mol H_5LCl_5, reflecting differing extents of H_3L^{3+} complexation in the 0·1 F Cl^-, 0·4 F I^- medium compared with the 0·5 F chloride solution. The chemical shift data from the two electrolyte media differ by up to about 0·2 ppm under the more acidic conditions from $a = 0$ to 2 mol KOH/mol H_5LCl_5, resulting from enhanced H_3LCl^{2+} and H_4LCl^{3+} formation at higher Cl^- concentrations.

The chemical shift vs composition data were analyzed as follows: (1) solution composition data and equilibrium constant values from pH potentiometric experiments provided estimates of the various L species concentrations in each of the KOH–H_5LCl_5 mixtures; (2) the observed chemical shifts were interpreted as the concentration-weighted average of the intrinsic chemical shifts of the various L species, H_nL^{n+}, $n =$

0–4, and chloride complexes H_3LCl^{2+} and H_4LCl^{3+}; (3) optimum values of the intrinsic chemical shifts were obtained by an iterative best-fit procedure. The intrinsic chemical shifts were 47·1, 46·7, 46·0, 45·4 and 41·0 ppm, respectively, for the five L species, and 45·3 and 44·3 ppm for H_3LCl^{2+} and H_4LCl^{3+}, respectively.

The chemical shift data are difficult to interpret since they reflect average electronic interactions, solvation changes and conformational changes within the molecule. We focus on the fact that the approximately 20 ^{13}C NMR chemical shifts could be accurately described to better than the estimated 0.02 ppm precision of measurement by a model including only protonated L species up to 4+ and chloride complexes of the 3+ and 4+ species. The presence of iodide complexes or H_5L^{5+} species would probably result in a poor fit of the data to the model. Thus, the ^{13}C NMR results provide further support for our model of the solution equilibria in the high ionic strength media employed in pH potentiometric experiments.

RESULTS

Complexation constants and acid dissociation constants at various temperatures and ionic strengths obtained from our studies of pH potentiometric titrations appear in Tables 1 and 2. In these tables, a subscripted number indicates the charge of the species and a subscripted anion name refers to the complex of that anion with L. Thus, pK_4 refers to the acid dissociation of the 4+ L species and K_{4Cl} refers to the chloride complexation constant with that species.

We give in the last column of Table 1 values of χ^2, the goodness-of-fit statistic, and the number of degrees of freedom in each non-linear regression analysis. The

Table 2. Acidity constants of tri- and tetraprotonated L species at various temperatures and ionic strengths.

I (M)	t (°C)	pK_4	pK_3
0·50	25·0	0·33 ± 0·04[a] (4)[b]	6·045 ± 0·005[a] (5)[b]
0·37	25·0		5·984 ± 0·004 (2)
0·25	25·0		5·896 ± 0·025 (2)
0·12	25·0		5·763 ± 0·006 (2)
0·50	16·7		6·207
0·50	36·2		5·786 ± 0·006 (2)
0·50	46·1		5·564
0·50	55·2		5·368

[a] Uncertainties represent standard deviations obtained from independent determinations.

[b] Numbers in parentheses indicate the number of independent pK estimates. Experiments employed two or three different stock buffers of H_4L^{4+}–H_3L^{3+} or H_3L^{3+}–H_2L^{2+}.

Table 1. Complexation constants of tri- and tetraprotonated L species with some mono- and divalent anions at various temperatures and ionic strengths

X	I(M)	t(°C)	K_{H_3LX}	K_{H_4LX}[a]	$K_{H_4LX_2}$	χ^2/d.f.[b]
Cl^-	0·50	25·0	1·11 ± 0·03	28 ± 9		9·7/11
	0·37	25·0	1·30 ± 0·05			0·7/5
	0·25	25·0	1·59 ± 0·07			0·2/5
	0·12	25·0	1·91 ± 0·11			0·5/5
	0·50	16·7	0·96 ± 0·03			1·3/5
	0·50	36·2	1·34 ± 0·03			0·3/6
	0·50	36·2	1·25 ± 0·04			0·4/5
	0·50	46·1	1·55 ± 0·04			6·4/5
	0·50	55·2	1·75 ± 0·05			7·1/5
NO_3^-	0·50	25·0	0·9 ± 0·1	7·0 ± 1·3		1·1/9[a]
SO_4^{2-}	0·50	25·0	32·0 ± 0·3	8·8(±0·4) × 10³	6·2(±0·2) × 10⁵	9·3/18[a]
	0·50	25·0	32·0 ± 0·3	7·7(±0·3) × 10³	5·3(±0·2) × 10⁵	17/11[a]
	0·37	25·0	39·0 ± 0·5			15/7
	0·12	25·0	173 ± 2			2·1/8
IO_3^-	0·25	25·0	13·1 ± 0·2			0·4/9
$C_2O_4^-$ (oxalate)	0·50	25·0	33·7 ± 0·3			9·5/9
$C_4O_4^{2-}$ (squarate)	0·50	25·0	18·0 ± 0·2			0·3/9

[a] Entries which include values for H_4L^{4+} complexes derive from simultaneous analysis of data from H_4L^{4+}–H_3L^{3+} and H_3L^{3+}–H_2L^{2+} buffer mixtures. Other entries which list only H_3L^{3+} complexation constants are obtained from data with only H_3L^{3+}–H_2L^{2+} buffers.

[b] χ^2/d.f. entries indicate values of χ^2, the goodness-of-fit statistic, and the number of degrees of freedom, i.e. number of data points minus number of adjustable parameters.

value of χ^2 is generally comparable to or less than the number of degrees of freedom, indicating that the pH potentiometric data are accurately described by the chemical model equations using the *a priori* estimate of ±0·002 for the uncertainty in pH.

The complexation constants in Table 1 reflect the results of two types of experiments. (1) A single H_3L^{3+}–H_2L^{2+} buffer mixture was titrated with a solution of the complexing anion. This type of experiment gave anion complexation and acid dissociation constants for H_3L^{3+} only. The second entry in Table 1 is an example of this type. (2) Both H_3L^{3+}–H_2L^{3+} and H_4L^{4+}–H_3L^{3+} buffers were used to obtain complexation and acid dissociation constants for H_4L^{4+} and H_3L^{3+}. For this type of experiment we could either analyze the data simultaneously or, in a two-step process, first find best-fit values for the H_3L^{3+} complexation constant and pK_3 and then use these values as fixed input parameters in the analysis of the pH vs composition data pertinent to the H_4L^{4+}–H_3L^{3+} buffer. The two procedures gave essentially identical complexation constant and pK values. The complexation constants and their standard error estimates listed in Table 1 were obtained from the simultaneous analysis of the two-buffer data.

The complexation constant data in Table 1 are conditional constants in the sense that their calculated values are based on two assumptions: ionic activity coefficients are all taken as unity and none of the protonated L species form complexes with iodide ions. The second assumption was tested using methods described previously.[9] The shift in K_{3Cl} from 1·91 ± 0·11 at an ionic strength of 0·12 M to 1·11 ± 0·03 at an ionic strength of 0·50 M could be completely explained by the differences in the ionic activity coefficients at the two ionic strengths. A similar examination of pK_3 values listed in Table 2 shows that the change in pK values as a function of ionic strength can be explained by activity coefficient effects alone. These results, indicating the absence of H_3L^{3+} or H_2L^{2+} complexes with iodide ions, are in accord with earlier findings based on conductometric and ^{13}C NMR experiments.

We were unable to analyze the variation in pK_4 as a function of ionic strength because its value is so small (0·33 ± 0·04 at an ionic strength of 0·50 M). This already small value decreases markedly with decreasing ionic strength. The accompanying loss of precision precludes a meaningful analysis. Although it is possible that an iodide complex of H_4L^{4+} exists in these solutions, our earlier conductometric titration results allow the existence of an extremely weak complex only. (Recall that even the presence of 0·1 M iodide resulted in no detectable curvature in the $a = 0$–2 mol NaOH/molH_5LCl_5 region.) Hence we shall assume that iodide complexes, if they exist at all, do not play a significant role in the present experiments.

Using the pK values and chloride complexation constants for H_4L^{4+} and H_3L^{3+} listed in Tables 1 and 2, we can re-evaluate the pH potentiometric titration data cited earlier. We found conditional acidity constants for 4+ and 3+ L species to be 1·38 ± 0·05 and 6·27 ± 0·02, respectively. These constants were obtained from alkametric titrations of 0·01 F H_5LCl_5 solutions in 0·5 F KCl media at 25 °C. Using the data in Tables 1 and 2 we calculate conditional acidity constants $pK'_4 = 1·34$ and $pK'_3 = 6·25$ in 0·50 F KCl, and find excellent agreement with those obtained from the alkametric titration experiments. The agreement seems significant since the constants in Tables 1 and 2 refer to experiments in which the chloride ion concentration varied from *ca* 0·01 to *ca* 0·2 M, while the titrations with base employed a much higher chloride concentration.

We wish to characterise the acid dissociation and complexation reactions of H_4L^{4+} and H_3L^{3+} species in terms of bonding and solvation properties. We rely on ΔH and ΔS data for this information. In general, direct calorimetric methods are useful in such determinations. However, these methods are not readily applicable to the complex equilibrium mixtures studied here. Instead, we employ a van't Hoff analysis of the temperature dependent equilibrium constants of Tables 1 and 2.

This approach for estimating ΔH and ΔS depends the accuracy of the equilibrium constant data. Thus, we took particular care to make multiple determinations of these values and employed numerous different stock

Table 3. Chloride complexation and acidic dissociation enthalpies and entropies for H_3L^{3+} and triprotonated 1,4,8,12-tetraazacyclopentadecane at ionic strength 0·5 M

Reaction[a]	ΔH (kJ mol^{-1})	ΔS (J mol^{-1} K^{-1})
$H_3L^{3+} \rightarrow H_2L^{2+} + H^+$	+41 ± 0·8[b]	+21 ± 2·5
$H_3L^{3+} + Cl^- \rightarrow H_3LCl^{2+}$	+12 ± 0·8	+42 ± 2·5
$H_3T^{3+} \rightarrow H_2T^{2+} + H^+$	+31 ± 0·8	+4 ± 2
$H_3T^{3+} + Cl^+ \rightarrow H_3TCl^{2+}$	+8·4 ± 0·8	+25 ± 3

[b] Uncertainties represent standard errors based on the scatter of points about van't Hoff lines.

solutions prepared from different batches of H_5LCl_5 in order to account for uncertainties in solution composition. The results of some of these replicate experiments are given in Tables 1 and 2.

Calculated values of ΔH and ΔS for H_3L^{3+} acid dissociation and complexation reactions along with corresponding values for 1,4,8,12-tetraazacyclopentadecane are given in Table 3. The uncertainties in these values are standard error estimates obtained from the apparently random scatter of experimental points about the regression lines. We made additional calculations using the method of weighted least squares to obtain alternative estimates of ΔH and ΔS and their uncertainties. This method relies on the uncertainty (standard error) in each experimental point to estimate standard errors in the slope and intercept and hence in ΔH and ΔS. Values of ΔH and ΔS found by weighted regression were essentially identical with those found using the ordinary regression method. However, the error estimates obtained using weighted least squares were uniformly smaller and were therefore discarded. Hence the uncertainties listed in Table 3 represent conservative estimates.

DISCUSSION

We begin with a comparison of the acid dissociation behaviour of H_3L^{3+} with that of hexacyclen (H_3Hx^{3+}) and the triprotonated forms of 1,4,8,12-tetraazacyclopentadecane (H_3T^{3+}). The H_3T^{3+} structure contains three protonated and one unprotonated amine nitrogens so that only one pairwise interaction between NH_2^+ and NH sites is possible. The loss of a proton from this ion results in a species capable of two pairwise interactions between protonated and unprotonated amine sites. Assuming that these internal interactions stabilize the ion, we would expect a negative contribution to ΔG for the proton-loss reaction.

The behaviour of H_3L^{3+} is different. Both the H_3L^{3+} and H_2L^{2+} species are capable of two pairwise interactions between protonated and unprotonated amine sites. Consequently, there is no net change in the number of internal stabilisation interactions upon proton loss from H_3L^{3+}. Finally, proton loss from the protonated cyclic hexamine H_3Hx^{3+} results in a net loss of one stabilizing interaction. The values of p*K* for H_3T^{3+} and H_3L^{3+} are 5·229 and 6·045 at ionic strength 0·5 M at 25 °C, while p*K* = 8·7 for H_3Hx^{3+} at ionic strength 0·2 M at 25 C.[15]

The relative magnitudes of these p*K* values are consistent with decreased internal stabilization in the dissociations of H_3T^{3+}, H_3L^{3+} and H_3Hx^{3+}. However, the additional stabilization interaction in the dissociation of H_3T^{3+} as compared with H_3L^{3+} results in a significantly smaller increase in acidity than does the additional interaction in the dissociation of H_3L^{3+} as compared with H_3Hx^{3+}. The internal NH–H$^+$–N interactions in H_3T^{3+} seem to be less effective than those in H_3L^{3+} or H_3Hx^{3+}. This may be a result of greater N—N distances in H_3T^{3+} whose structure consists of three propylene bridges compared with ethylene bridges in H_3L^{3+} and H_3Hx^{3+}.

1,4,7,10-Tetraazacyclododecane is structurally similar to the ethylene-bridged compounds. Although no precise p*K* values for the triprotonated form of this compound have been reported, its value has been estimated as 1·5–2·0 at an ionic strength of 0·2 M and 25 °C.[16,17] These conditions differ from those employed here, and the approximate p*K* value may be influenced by anion complexation. Nevertheless, the value seems consistent with H_3L^{3+} and H_3Hx^{3+} acidity constants. The dissociation of 1,4,7,10-tetraazacyclododecane results in a gain of one more internal stabilization interaction than does the dissociation of H_3L^{3+} and its p*K* is *ca* 3 units smaller. We note that each of the three acid dissociation products, the diprotonated amine species, is capable of two internal interactions,thus stabilizing both bound protons. This in turn implies similar solvation properties for the ammonium ions, thus allowing simple comparisons to be made.

The analysis of ΔH and ΔS for the acid dissociation reactions is complicated by the fact that the internal stablizations contribute to both ΔH and ΔS in a variety of ways. It is likely that ΔH and ΔS are influenced by restructuring of both the inner and secondary solvation spheres and also by internal strains and the concomitant loss of torsional degrees of freedom. Further, the internal strains and possible loss of torsional degrees of freedom associated with internal interactions may also influence ΔH and ΔS.

Both ΔH and ΔS are larger for the dissociation of H_3L^{3+} than for the dissociation of H_3T^{3+} (41 and 31 kJ mol^{-1} and 21 and 4·2 J mol^{-1}K^{-1}, respectively). These results can be understood by considering the proton exchange reaction

$$H_3L^{3+} + H_2T^{2+} \rightarrow H_2L^{2+} + H_3T^{3+}$$

in which there is a net loss of one internal interaction. For this reaction, $\Delta H = 10\ \text{kJ mol}^{-1}$ and $\Delta S = 17\ \text{J mol}^{-1}\text{K}^{-1}$. The positive ΔH results from a net loss in bonding interactions. We believe that the positive value of ΔS indicates a net release of solvent. Assuming that H_2T^{2+} and H_2L^{2+} have similar solvation spheres leads to the conclusion that H_3L^{3+} solvation is more extensive than that of H_3T^{3+}.

We therefore propose the following model for the internal stabilization interactions. A solvated ammonium group with strong inner sphere solvation interacts with a nearby amine nitrogen. The net effect is a bonding enhancement (negative ΔH) replacing NH_2^+–H_2O interactions with stronger ammonium–amine interactions. At the same time the inner solvation sphere is loosened or released. Finally, the stabilised ion interacts with the solvent to form a large outer sphere consisting of loosely bound water. The net effect is an increase in the number of interactive solvent molecules and a negative ΔS.

With this picture in mind we turn to a discussion of the complexation of H_3L^{3+} with anions. In previous work[8] we described monoanion complexation of protonated macrocyclic polyamines in terms of the availability of an unstabilized ammonium site. Thus, chloride ions, for example, form no detectable complexes with H_3Hx^{3+} since all three protons in H_3Hx^{3+} may be stabilized by pairwise interactions between the six amine sites. A chloride complex was detected with H_3T^{3+} since two unstabilized ammonium sites are available. The same reasoning rationalizes the existence of the chloride complex of H_3L^{3+} found in this work.

We have associated the strength of the anion complexes with a solvent expulsion mechanism. Recall that H_3L^{3+} appeared to be more extensively solvated than H_3T^{3+}. The enthalpy and entropy changes for the metathesis reaction

$$H_3TCl^{2+} + H_3L^{3+} \rightarrow H_3T^{3+} + H_3LCl^{2+}$$

are $3{\cdot}8\ \mathrm{kJ\,mol^{-1}}$ and $17{\cdot}0\ \mathrm{J\,mol^{-1}\,K^{-1}}$, respectively. If the 2+ anion complexes are solvated to a similar extent, the positive values of ΔH and ΔS imply a release of solvent in transferring from H_3L^{3+} to H_3T^{3+}. A more highly solvated H_3L^{3+} species implies, in turn, that H_3L^{3+} complexes with anions should be stronger than corresponding complexes with H_3T^{3+}, and this is observed. In fact, all of the H_3L^{3+} anion complexes observed here are stronger than corresponding H_3T^{3+} complexes by a factor of 2–4.

It is difficult to discuss the acid dissociation properties of H_4L^{4+} because the relevant data for related compounds are not available. However, we can make two sets of observations.

First, H_4L^{4+} is a significantly stronger acid than H_4Hx^{4+}. The pK values at 25 °C are $0{\cdot}33$ at an ionic strength of $0{\cdot}5$ M and $3{\cdot}52$ at an ionic strength of $0{\cdot}22$ M,[7] respectively. Both acids gain one internal stabilizing interaction on dissociation. The difference in acid strength might result from the difference in the charge repulsion of three localized ammonium groups situated on the 15-membered H_4L^{4+} ring compared with the repulsion due to only two such groups on the larger H_4Hx^{4+} ring. However, H_4T^{4+} has four ammonium groups also distributed around a 15-membered ring and its pK_4 value is $3{\cdot}65$ at an ionic strength $0{\cdot}5$ M.[8] Hence it seems more likely that the high acidity of H_4L^{4+} is related to the structure and extent of its solvation sphere.

Second, the H_4L^{4+} complexes with anions are much stronger than corresponding H_4T^{4+} complexes but are weaker than H_4Hx^{4+} complexes. The H_4Hx^{4+} species is very extensively solvated, as indicated by the values ΔH and ΔS for its acid dissociation, $58{\cdot}6\ \mathrm{kJ\,mol^{-1}}$ and $134{\cdot}0\ \mathrm{J\,mol^{-1}\,K^{-1}}$, respectively. Corresponding values for H_4T^{4+} are $36{\cdot}0\ \mathrm{kJ\,mol^{-1}}$ and $50{\cdot}2\ \mathrm{J\,mol^{-1}\,K^{-1}}$. The more endothermic and entropy-producing acid dissociation of H_4Hx^{4+} corresponds to the breakdown of an extensive secondary solvent network. It seems reasonable to assume that the solvent structure around H_4L^{4+} is intermediate between those of H_4T^{4+} and H_4Hx^{4+}, accounting for the anion complexation properties.

We conclude by noting that although our interpretations must be regarded as speculative, they do appear to provide an explanatory framework for the experimental results.

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