Hexacyclen Complexes of Inorganic Anions: Bonding Forces, Structure, and Selectivity

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Abstract: Complexes of protonated hexacyclen ($C_{12}H_{30}N_6$) with NO_3^-, Cl^-, ClO_4^-, and Br^- are found by conductometry and pH potentiometry to have the compositions H_4LX^{3+} (where L = hexacyclen, X = anion). Formation constants with these anions at 25 °C are determined by pH potentiometry. ΔH and ΔS for the NO_3^- and Cl^- complexes as well as the acid dissociation of H_4L^{4+} are derived from the temperature-dependent equilibrium constants. The results indicate that although the NO_3^- complex is more stable the Cl^- apparently forms stronger bonds to H_4L^{4+}. Bonding in these complexes is discussed in terms of ionic H bonding and solvent ordering effects. X-ray crystallographic study of $H_4L(NO_3)_2Cl_2 \cdot 2H_2O$ supports the proposed bonding mechanism.

The selective binding of inorganic and organic anions by macrocyclic ligands is a recently reported phenomenon.[1,2] In many cases the host ligand species feature protonated amine groups of the type $(RR'R''N^+H)_y$ (where $y > 2$), and it has generally been assumed that electrostatic and ionic hydrogen-bonding interactions provide the bonding forces in these complexes. The shape and size of the macrocycle cavity are presumed to influence the bonding interactions and so to account for selectivity.

In the present work we wish to elucidate the factors which influence these complexation reactions by means of a study of the cyclic hexamine 1,4,7,10,13,16-hexaazacyclooctadecane (hexacyclen, L) complexes of nitrate, perchlorate, chloride, and bromide ions. The study utilizes pH-potentiometric and conductometric measurements designed to determine the nature, formation constants, and thermodynamic properties of the complexes. Also an X-ray crystallographic determination provides information about structure and bonding.

Experimental Methods

Materials. All chemical reagents and solutions were purified or were reagent grade.

Hexacyclen hemihydrate, $C_{12}H_{30}N_6 \cdot 0.5H_2O$, was prepared from the commercial trisulfate salt purchased from either Aldrich or Parish Chemical Co. Weighed portions of the salt were used to prepared 0.5 M solutions of the polyamine and these were treated with an equivalent amount of solid $BaCO_3$. After the resultant slurry was mixed for 2 h at 80 °C, the filtered hot solution was dried with a rotary evaporator. The waxy product purified by vacuum sublimation yielded pure white crystalline hexacyclen–hemihydrate ($L \cdot 0.5H_2O$): NMR $H_{N,S}$ 2.02 (1), $H_{C,S}$, 2.70 (4); mass spectrum, *m/e* parent peak 259. Anal. Calcd C, 53.70; H, 11.64; N, 31.68. Found: C, 53.20; H, 11.29; N, 31.54.

Hexacyclen hexahydrochloride and hexahydrogennitrate salts were prepared directly from the concentrated filtrate solution above by addition of a large excess of the appropriate acid. The product was recrystallized from a fresh portion of the 6 M acid and then air-dried. The crystals were $C_{12}H_3N_6 \cdot 6HCl \cdot 3H_2O$ ($H_6LCl_6 \cdot 3H_2O$) and $C_{12}H_{30}N_6 \cdot 6HNO_3 \cdot H_2O(H_6L(NO_3)_6 \cdot H_2O)$.

Hexacyclen dihydrochloride tetrakis(hydrogen nitrate) $(C_{12}H_{30}N_6 \cdot 2HCl \cdot 4HNO_3)$ was prepared by recrystallizing the hexahydrochloride salt from either saturated KNO_3 or concentrated nitric acid.[3] An aqueous solution of this salt was treated with 2 mol of $NaOH$/mol of salt and slow evaporation gave crystals of $C_{12}H_{30}N_6 \cdot 2HNO_3 \cdot 2HCl \cdot 2H_2O$) as determined by acidometric titration and X-ray crystallography.

pH-Potentiometric Measurements. pH measurements employed an Orion Model 801 pH meter equipped with conventional glass and calomel electrodes. For measurements at 25.0 ± 0.1 °C, a commercial pH 7.00 ± 0.02 buffer served to standardize the meter, but a 0.05 M potassium hydrogen phthalate standard was employed for temperature-dependence

work. The temperature-dependent pH value of the standard was taken from Bates.[4]

Hexacyclen hexahydrochloride and hexakis(hydrogen nitrate) solutions were analyzed by pH-potentiometric titration with 0.1 M NaOH in the presence of 0.4 M $NaNO_3$ in the analyte solution. Under these conditions two end points are discernible. The first corresponds to a = 2 (a = mol of NaOH/mol of hexacyclen) and the second to a = 3. Consequently, the difference between a = 2 and a = 3 end points yielded a direct calculation of the salt concentration with a repeatability of ±2% or less. Moreover, the concentration estimated in this way never differed appreciably from the estimate derived directly from the a = 2 endpoint.

Conductance Measurements. Measurements of the electrolytic conductance of hexacyclen solutions during titration with HCl or HNO_3 employed a Leeds and Northrup Model 4959 conductance bridge equipped with a glass dip-type conductance cell. Solutions were thermostated at 25.0 ± 0.1 °C, and ample time was allowed for thermal equilibration after each addition of acid reagent.

X-ray Crystallographic Measurements. The diffraction data on $C_{12}H_{30}N_6 \cdot 2HNO_3 \cdot 2HCl \cdot 2H_2O$ (2θ max = 150°) were collected at room temperature on a computer-controlled Syntex $P2_1$ diffractometer operated in a θ–2θ scan mode with a graphite monochromator and Cu Kα (λ 1.54178 Å) radiation. No correction for absorption was made. The crystals are monoclinic, space group $P2_1/a$ with a = 11.569 (12) Å, b = 17.186 (24) Å, c = 5.869 (7) Å, β = 94.74 (9), Z = 2 molecules/cell. The structure was solved by direct methods[5] and difference syntheses. All H atoms were located from a difference map. In the final full-matrix least-squares calculation using atomic scattering factors,[6] the heavy atoms were refined anisotropically and the H atoms isotropically to $R = \sum ||F_o - F_c|| / \sum |F_o| = 0.039$ for 1791 observed reflections. The final values for atomic coordinates are listed in Table VII.

Discussion

Stoichiometry of Aqueous Hexacyclen Anion Complexes. pH-potentiometric titrations of hexacyclen hexahydrochloride and hexakis(hydrogen nitrate) salts with NaOH in both 0.4 M NaCl and 0.4 M $NaNO_3$ media were essentially identical in the region $0 < a < 2$. pH values in this region of the titration curve conformed to those predicted for a strong diprotic acid, and we conclude that no appreciable concentrations of H_6L^{6+} or H_5L^{5+} or their complexes are present in these experiments. Furthermore the titration curves were superimposable in the region between $a = 3$ and $a = 6$. Thus neither chloride nor nitrate complexes were formed with the H_3L^{3+}, H_2L^{2+}, or HL^+ species. Because curves differed substantially in the region between $a = 2$ and $a = 3$, we concluded that the H_4L^{4+} species formed complexes with nitrate ions if not also with chloride ions. In order to confirm this conclusion, we made conductometric titrations of approximately 5 mM L solution with HCl and HNO_3 reagents. The results of

(1) Lehn, J. M. *Acc. Chem. Res.* **1978**, *11*, 49. Dietrich, B.; Fyles, D.; Fyles, T.; Lehn, J. M. *Helv. Chim. Acta* **1979**, *62*, 2763. Lehn, J. M.; Sonveaux, E.; Willard, A. J. *Am. Chem. Soc.* **1978**, *100*, 4914.

(2) Dietrich, B., Hosseini, M.; Lehn, J. M.; Sessions, R. B. *J. Am. Chem. Soc.* **1981**, *103*, 1282.

(3) Margulis, T. N., Zompa, L. J. *Acta Crystallogr., Sect. B* **1981**, *B37*, 1426.

(4) Bates, R. G. "Determination of pH Theory and Practice", 2nd ed.; Wiley: New York, 1973.

(5) Main, P.; Hull, S.; Lessinger, L.; Germain, G.; De Clercq, J.-P.; Woolfson, M. M. "A System of Computer Programs for the Automatic Solution of Crystal Structures from X-ray Diffraction Date"; Universities of York, York, England and Louvain, Louvain, Belgium, 1978.

(6) "International Tables for X-ray Crystallography"; Kynoch Press: Birmingham, England, 1959; Vol. IV, pp 73–102.
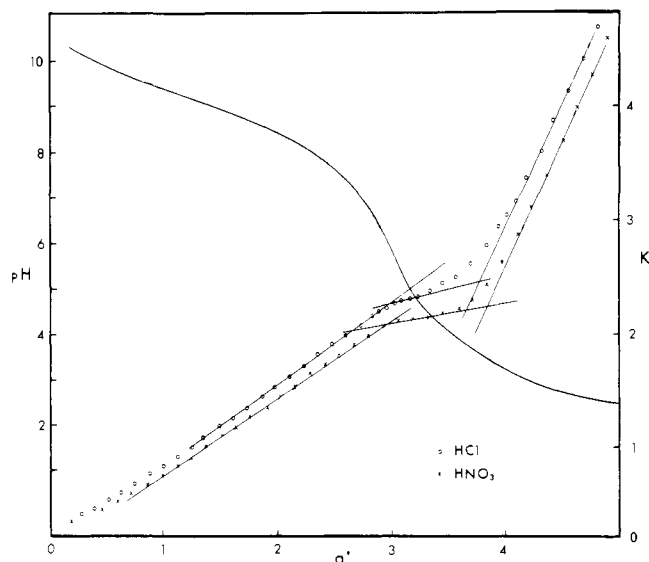
Figure 1. Conductometric and pH-potentiometric titration of hexacyclen solutions with HCl and HNO₃. The right ordinate axis indicates the species conductance of the titration solution in units of 10^{-3} Ω. At $a' = 3$, the amine is converted to H_3L^{3+}.

these experiments appear in Figure 1 along with pH-potentiometric titration data obtained with replicate portions of the same L stock solution. In these plots the abscissa function a' is defined as mol of acid/mol of L. In the region from $a' = 0$ to $a' = 3$ (which corresponds to $a = 6$ to $a = 3$ in our earlier titration of H_6LCl_6 with NaOH), the titration reaction is the stepwise protonation of L to form HL^+, H_2L^{2+}, and H_3L^{3+}. The linear increase in conductance is the result of increasing anion concentration with addition of HCl or HNO₃. Although the conductance due to the bulky L species is a small fraction of the total, this conductance is also expected to increase linearly with protonation. Since the L molecule is sufficiently large that changes in the size of the solvation sphere with changes in L ionic charge are likely to have little effect on mobility, we expect $\lambda_{H_nL^{n+}}$, the equivalent ionic conductances for the protonated L species, to be essentially constant and independent of n.

After formation of H_3L^{3+} as the dominant L species at $a' = 3$ the conductance increases only slightly with addition of HCl and remains virtually constant when HNO₃ is used as the titrant. This behavior is consistent with the titration reaction $H_3L^{3+} + H^+X^- = H_4L \cdot X^{3+}$ where acid reagent H^+X^- adds to the H_3L^{3+} species to form a complex with similar equivalent ionic conductance, i.e., $\lambda_{H_3L^{3+}} \simeq \lambda_{H_4L \cdot X^{3+}}$. As a result the conductance does not increase appreciably between $a' = 3$ and $a' = 4$. However, when strong acid in excess of $a' = 4$ is added, the conductance again rises linearly but at a steeper slope than between $a' = 0$ and $a' = 3$. The steeper slope corresponds to the expected behavior of simple addition of strong acid to water. This result precludes the presence of appreciable amounts of H_5L^{5+} and H_6L^{6+} (in confirmation of the pH-potentiometric titration data in this same region) and also appreciable amounts of their anion complexes.

The conductometric titration curves of Figure 1 also provides direct evidence of the H_4L^{4+}/anion stoichiometry in that the extrapolated intersections of the horizontal and rising portions of the curve occur at $a' = 2.95 \pm 0.05$ and $a' = 3.9 \pm 0.1$. (The uncertainties represent limits obtained from estimated extreme slopes through the data points.) These values confirm a 1:1 stoichiometry between H_4L^{4+} and both NO_3^- and Cl^-. Thus, we conclude from these experiments that the hexacyclen nitrate and chloride complexes are exlusively $(H_4LNO_3)^{3+}$ and $(H_4LCl)^{3+}$.

Formation Constants of the Complexes. Having established the stoichiometry of the complexes under study, we sought to estimate their formation constants. Numerous examples of such estimates that rely on the difference between apparent acidity constants of the complexed species in complexing and noncomplexing media have appeared in the literature. The effect of complexing H_4L^{4+}

Table I. pH Values of H_6LCl_6 Solutions[a] upon Addition of 2.5 mol of NaOH/mol of H_6LCl_6 in Various Electrolyte Media and at Differing Ionic Strengths at 25 °C

electrolyte medium[b]	ionic strength	
	0.20	0.10
NO_3^-	5.076	4.826
Cl^-	4.633	4.416
Br^-	4.320	4.127
I^-	3.856	3.745
ClO_4^-	4.095	3.928

[a] H_6LCl_6 concentrations were 4-6 mM. [b] All electrolytes added as the sodium salts

with X^- is to reduce the apparent K_{a3} value. Thus, the apparent value of K_{a3} corresponding to the acidic dissociation of H_4L^{4+} species in sodium nitrate medium, for example, could be compared to K_{a3} in some noncomplexing electrolyte medium under the same conditions of ionic strength. Both values are readily obtainable by pH-potentiometric experiments, and the data would yield formation constant values directly. This methodology relies on an ability to estimate K_{a3} in a noncomplexing electrolyte medium. But since H_4L^{4+} obviously formed complexes with most of the commonly used "passive" electrolytes, we set out to find an appropriate noncomplexing salt. This was done by estimating apparent pK_{a3} values obtained by titration of H_6LCl_6 solutions with NaOH in NaBr, NaClO₄, NaCl, and NaI electrolytes. Some of the results of these experiments appear in Table I. Among the salts employed, the lowest pK_{a3} value was always obtained in NaI media. However, the variation of pK_{a3} with iodide concentration is appreciable. This variation might be attributable to complex formation and/or activity coefficient effects. Therefore we could not immediately justify a conclusion that NaI was a noncomplexing medium for H_4L^{4+} without further analysis. Such analysis is necessarily based on an estimate of activity coefficients of H_4L^{4+} and H_3L^{3+} species as follows: The acidic dissociation constant for H_4L^{4+} is given by

$$K_{a3} = \frac{a_{H^+}a_{H_3L^{3+}}}{a_{H_4L^{4+}}} = \frac{[H^+][H_3L^{3+}]}{[H_4L^{4+}]} \frac{\gamma_H \gamma_{3+}}{\gamma_{4+}} \quad (1)$$

where γ_H, γ_{3+}, and γ_{4+} denote ionic activity coefficients of H^+, H_3L^{3+}, and H_4L^{4+}, respectively. The singly charged ion coefficient γ_H is readily estimated from an extended form of the Debye–Hückel correlation with acceptable accuracy even at ionic strengths as high as 0.3–0.4 M. However, very little activity coefficient data on highly charged polyamine species are available, and direct application of the Debye–Hückel correlation is not appropriate. Noting that the ratio γ_{3+}/γ_{4+} is required rather than individual γ values, we sought to obtain relative values of γ_{3+}/γ_{4+} as a function of ionic strength through measurements with a similar but noncomplexing polyamine. For this purpose we chose tetrakis(aminomethyl)methane (M) as a model system. Earlier work[7] indicates that the appropriate pK value (pK_{a1} in this case) is independent of the nature of the electrolyte medium for a variety of 1:1 electrolytes, and so we could safely conclude that anion complexes were not present in these experiments. Furthermore, the model system is similar in molecular dimensions to the hexacyclen ligand and appears likely to have similar solvation properties.

Model System Activity Coefficients. The acidic dissociation constant for tetraprotonated M, denoted here H_4M^{4+}, is given by eq 2. Our intent is to obtain relative values of γ_{3+}/γ_{4+} at differing

$$K_M = \frac{a_{H^+}[H_3M^{3+}]}{[H_4M^{4+}]} \frac{\gamma_{3+}}{\gamma_{4+}} \quad (2)$$

ionic strengths. We prepared solutions containing equal known (~ 10 mM) concentrations of H_4M^{4+} and H_3M^{3+} by appropriate titration and made up the ionic strength to 0.4 M with NaNO₃

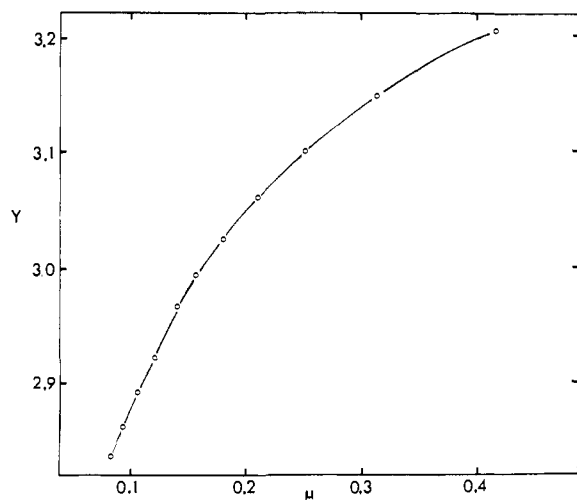(7) Zompa, L. J.; Bogucki, R. F. *J. Am. Chem. Soc.* **1966**, *88*, 5186; **1968**, *90*, 4569.

Figure 2. A plot of Y from eq 5 vs. ionic strength. Circles represent experimental data points, and the curve is the result of a least-squares polynomial fit.

and NaCl. The pH value was recorded as small volumes of water were added to a portion of the H_4M^{4+}/H_3M^{3+} solution. Repetition of these experiments with freshly prepared solutions gave highly reproducible results. In each solution, conservation relations are

$$[H_3M^{3+}] = C_M + [H^+] \tag{3}$$

$$[H_4M^{4+}] = C_M - [H^+] \tag{4}$$

Here, C_M is the analytical concentration of H_3M^{3+} or H_4M^{4+} as these are equal in this experiment. Combining eq 2, 3, and 4 we obtain

$$y \equiv pK_M + \log \gamma_{3+}/\gamma_{3+} = pH + \log \frac{C_M + 10^{-pH}/\gamma_H}{C_M - 10^{-pH}/\gamma_H} \tag{5}$$

The right-hand side of eq 5 is calculable from pH measurements and γ_H values from the Debye–Hückel correlation. A plot of y vs. ionic strength appears in Figure 2. This plot is utilized to calculate the γ_{3+}/γ_{4+} ratio at various ionic strengths relative to some arbitrary fixed ionic strength. For illustration, the ordinate, y, value in Figure 2 is 3.131 at an ionic strength of 0.290 while its value at $\mu = 0.22$ is 3.070. Following eq 5, we see the difference in y values is simply $\log (\gamma_{3+}/\gamma_{4+})_{\mu=0.29} - \log (\gamma_{3+}/\gamma_{4+})_{\mu=0.22} = 0.061$. We assume that the activity coefficient behavior of M and hexacyclen is the same. Thus we relate data obtained with hexacyclen at differing ionic strengths to a single "standard" ionic strength, which we chose arbitrarily as 0.22. All of our subsequent data will be referred to the standard, and conditional equilibrium constants at this ionic strength will be denoted by a superscript * notation.

We then sought to determine the acidic dissociation constant of H_4L^{4+} and its complexation constants with various anions and in particular to establish whether or not complexation of H_4L^{4+} occurs with I⁻.

Estimation of Acidity and Complexation Constants. In order to avoid possible air oxidation of very acidic I⁻ solutions that would be encountered in preparing H_6LI_6 samples or in direct titration of L with HI, we employed H_6LCl_6 solutions previously titrated to $a = 2.5$ and to these added varying proportions of NaI and NaCl, adjusting the ionic strength to 0.4. pH values were obtained during dilution experiments by the same methods employed with model system measurements. Thus, we obtained the pH values of H_4L^{4+}/H_3L^{3+} solutions at various Cl⁻ and I⁻ proportions and ionic strengths. These data would yield both pK_{a3} values and complexation constants as follows:

We assume first that H_4LCl^{3+} is the only complex of H_4L^{4+} in these solutions. Consequently,

$$C_L = [H_4L^{4+}] + [H_4LCl^{3+}] - [H^+] \tag{6}$$

$$C_L = [H_3L^{3+}] + [H^+] \tag{7}$$

Table II. Ionic Strength Dependence of pK_{a3} and Chloride Complex Formation Constant[a]

ionic strength	slope[b]	intercept[b]	$\log K_{Cl}^{\mu,b}$	$pK_{a3}^{\mu,b}$	$\Delta \log (\gamma_{4+}/\gamma_{3+})^c$	$\Delta \log \gamma_{Cl}^{d}$	$\Delta \log \gamma_H^{d}$	$\log K_{Cl}^{*e,g}$	$pK_{a3}^{*f,g}$
0.44	$(1.64 \pm 0.01) \times 10^5$	$(4.88 \pm 0.13) \times 10^3$	1.526 ± 0.014	3.688 ± 0.011	0.139 ± 0.008	0.080	0.027	1.74 ± 0.02	3.57 ± 0.02
0.29	$(1.89 \pm 0.02) \times 10^5$	$(3.96 \pm 0.10) \times 10^3$	1.679 ± 0.015	3.597 ± 0.010	0.061 ± 0.008	0.031	0.011	1.77 ± 0.02	3.55 ± 0.02
0.22	$(2.10 \pm 0.02) \times 10^5$	$(3.33 \pm 0.09) \times 10^3$	1.800 ± 0.016	3.523 ± 0.012	0.000 ± 0.004	0.000	0.000	1.80 ± 0.02	3.52 ± 0.02
0.15	$(2.34 \pm 0.02) \times 10^5$	$(2.72 \pm 0.07) \times 10^3$	1.934 ± 0.015	3.434 ± 0.011	-0.091 ± 0.008	-0.040	-0.016	1.80 ± 0.02	3.51 ± 0.02
0.11	$(2.53 \pm 0.02) \times 10^5$	$(2.40 \pm 0.06) \times 10^3$	2.021 ± 0.014	3.380 ± 0.010	-0.168 ± 0.008	-0.070	-0.029	1.78 ± 0.02	3.52 ± 0.02

[a] Temperature = 25.0 °C. [b] Standard error estimates in slopes and intercepts are derived from weighted least-squares regression based on ±0.004 pH measurement uncertainty. [c] Derived from interpolation or extrapolation of data plotted in Figure 2. [d] Obtained from Debye–Hückel equation. [e] Derived by adding quantities in columns 4, 6, and 7. [f] Derived by adding quantities in columns 5 and 8 and subtracting quantities in column 6. [g] Referred to $\mu = 0.22$.

Table III. Conditional Formation Constants for Hexacyclen with Various Anions[a]

ionic strength	$\log K_{NO_3}^{\mu,b}$	$\log K_{NO_3}^{-*,b}$	$\log K_{Br}^{\mu,b}$	$\log K_{Br}^{-*,b}$	$\log K_{ClO_4}^{\mu,b}$	$\log K_{ClO_4}^{-*,b}$
0.29	2.25	2.34				
0.22	2.37	2.37	1.46	1.46	1.04	1.04
0.15	2.51	2.37		1.69	1.45	1.26
0.11	2.61	2.36				1.02

[a] Temperature = 25.0 °C. [b] Referred to ionic strength 0.22 M.

Table IV. Temperature Dependence of pK_{a3} and Formation Constants for Chloride and Nitrate Complexes

temp, °C	pK_{a3}^{*a}	$\log K_{Cl}^{*a}$	$\log K_{NO_3}^{-*a}$
15	3.680 ± 0.014^b	1.763 ± 0.018^b	2.346 ± 0.018^b
25	3.345 ± 0.016	1.837 ± 0.020	2.316 ± 0.019
35	3.025 ± 0.019	1.932 ± 0.022	2.294 ± 0.022
45	2.707 ± 0.023	2.034 ± 0.026	2.318 ± 0.027
55	2.369 ± 0.023	2.210 ± 0.035	2.393 ± 0.035

[a] Referred to $\mu = 0.22$. [b] Uncertainties calculated by propagation-of-variance assuming a standard deviation of 0.004 pH units.

Table V. Enthalpies and Entropies for Acid Dissociation and Formation of the Chloride and Nitrate Complexes

reaction	ΔH^*, kcal/mol	ΔS^*, cal/mol
$H_4L^{4+} \rightleftharpoons H_3L^{3+} + H^+$	14.1 ± 0.3^b	32 ± 1^b
$H_4L^{4+} + Cl^- \rightleftharpoons H_4LCl^{3+}$	4.9 ± 0.6	24 ± 2
$H_4L^{4+} + NO_3^- \rightleftharpoons H_4LNO_3^{3+}$	-0.4 ± 0.6	12 ± 2

[a] Referred to $\mu = 0.22$. [b] Uncertainties are standard error estimates of weighted least-squares parameters.

Table VI. Enthalpies and Entropies of Dissociation for Various Tetraprotonated Amines ($H_4L^{4+} \rightleftharpoons H_3L^{3+} + H^+$)

	ΔH, kcal/ mol	ΔS, cal/ mol
triethylenetetramine (trien)[a]		
(25 °C, $\mu = 0.1$)	6.8	8
tetraethylenepentamine (tetren)[a]		
	7.9	5
N,N,N',N'-tetrakis(2-aminoethyl)- ethylenediamine (penten)[a]		
(25 °C, $\mu = 0.1$)	12.0	2
tris(3-aminopropyl)amine[a]		
(25 °C, $\mu = 0.1$)	7.3	−1
1,4,8,11-tetraazacyclotetradecane (cyclam)[b]		
(25 °C, $\mu = 0.5$)	7.7	15
1,4,8,12-tetraazacyclopentadecane[b]		
(25 °C, $\mu = 0.5$)	7.7	9.4

[a] Smith, R.; Martell, A. E. "Critical Stability Constants"; Plenum Press: New York, 1975, Vol. 2. [b] Micheloni, M.; Paoletti, P.; Vacca, A. *J. Chem. Soc., Perkin Trans. 2* 1978, 945.

Table VII. Atomic Coordinates

atom	x	y	z
N1	0.2485 (2)	0.0619 (1)	−0.2294 (4)
N2	0.2144 (2)	−0.0668 (1)	0.0850 (4)
N3	−0.0237 (2)	−0.1227 (1)	0.2396 (4)
C1	0.3469 (2)	0.0201 (2)	−0.1083 (5)
C2	0.3161 (2)	−0.0124 (2)	0.1148 (5)
C3	0.1901 (2)	−0.1039 (2)	0.3048 (4)
C4	0.0905 (2)	−0.1613 (1)	0.2817 (5)
C5	−0.1244 (2)	−0.1766 (2)	0.2557 (5)
C6	−0.2324 (2)	−0.1400 (2)	0.1407 (5)
Cl	0.02910 (5)	0.06481 (4)	0.25445 (9)
OW	0.2295 (2)	0.3091 (1)	0.1787 (4)
N4	0.4492 (2)	0.1702 (1)	0.3586 (4)
O2	0.3456 (2)	0.1763 (1)	0.3913 (4)
O3	0.4912 (2)	0.2132 (2)	0.2208 (5)
O4	0.5102 (3)	0.1218 (2)	0.4626 (6)
HC1(1)	0.370 (3)	−0.024 (2)	−0.217 (5)
HC1(2)	0.424 (3)	0.057 (2)	−0.067 (6)
HC2(1)	0.299 (2)	0.032 (1)	0.228 (5)
HC2(2)	0.377 (2)	−0.042 (2)	0.177 (5)
HC3(1)	0.174 (2)	−0.063 (2)	0.419 (5)
HC3(2)	0.263 (3)	−0.136 (2)	0.361 (5)
HC4(1)	0.091 (2)	−0.188 (2)	0.438 (5)
HC4(2)	−0.095 (3)	−0.198 (2)	0.134 (6)
HC5(1)	−0.131 (2)	−0.188 (2)	0.433 (5)
HC5(2)	−0.105 (2)	−0.227 (2)	0.179 (5)
HC6(1)	−0.222 (2)	−0.132 (1)	−0.024 (4)
HC6(2)	−0.304 (2)	−0.173 (1)	0.165 (5)
HOW(1)	0.157 (3)	0.304 (2)	0.219 (6)
HOW(2)	0.279 (4)	0.276 (3)	0.227 (8)
HN1	0.263 (3)	0.067 (2)	−0.398 (6)
HN2(1)	0.148 (3)	−0.039 (2)	0.010 (5)
HN2(2)	0.227 (3)	−0.105 (2)	0.022 (5)
HN3(1)	−0.029 (2)	−0.101 (2)	0.091 (5)
HN3(2)	−0.032 (2)	−0.083 (2)	0.339 (4)

where C_L denotes the equal analytical concentrations of both H_4L^{4+} and H_3L^{3+} species. We define K_{Cl} by

$$K_{Cl} = \frac{[H_4LCl^{3+}]}{[H_4L^{4+}][Cl^-]} \frac{\gamma_3'}{\gamma_4\gamma_{Cl}} \quad (8)$$

where γ_{Cl} is the activity coefficient of the Cl^- ion and γ_3' denotes the activity coefficient of the H_4LCl^{3+}. Combination of eq 1 and eq 6–8 yields

$$z = \frac{1}{[H^+]}\left(\frac{C_L + [H^+]}{C_L - [H^+]}\right) = \frac{1}{K_{a3}}\left(\frac{\gamma_3\gamma_H}{\gamma_4}\right)\left(1 + \frac{\gamma_4\gamma_{Cl}}{\gamma_3'}K_{Cl}[Cl^-]\right) \quad (9)$$

In order to utilize this equation, we made pH measurement of H_4L^{4+}/H_3L^{3+} solutions at different Cl^- concentrations but made up the ionic strength to a fixed value with additional NaI. A plot of z vs. $[Cl^-]$ is linear, and weighted least-squares regressions gave the results indicated in Table II at each value of the ionic strength. Since it appears reasonable that the activity coefficients are functions of the ionic strength alone and that $\gamma_3' = \gamma_3$, the slope of these plots becomes $\gamma_H\gamma_{Cl}K_{Cl}/K_{a3}$, and the intercepts are $\gamma_H\gamma_3/\gamma_4K_{a3}$ at each ionic strength. The ratio of slope to intercept values yields $K_{Cl}{}^\mu = K_{Cl}\gamma_{Cl}\gamma_4/\gamma_3$. Here $K_{Cl}{}^\mu$ is a conditional molar equilibrium constant for the formation of the H_4LCl^{3+} complex, as may be seen by referral to eq 8. Similarly the expression $K_{a3}{}^\mu = K_{a3}\gamma_4/\gamma_H\gamma_3$ is a conditional molar acidity constant for H_4L^{4+}, as seen from eq 1. Values for both $K_{Cl}{}^\mu$ and $K_{a3}{}^\mu$ are shown in Table II where their ionic strength dependencies are readily apparent. From these entries, the Debye–Hückel correlation for γ_H and γ_{Cl}, and Figure 2 for the γ_3/γ_4, $K_{Cl}{}^\mu$ and $K_{a3}{}^\mu$ are transformed into $K_{Cl}{}^*$ and $K_{a3}{}^*$ (conditional constants at the standard ionic

strength of 0.22), respectively, by a sequence of arithmetic operations detailed in Table II and its footnotes. We interpret the constancy of log $K_{Cl}{}^*$ and p$K_{a3}{}^*$ in columns 9 amd 10 of Table II as confirming (a) our supposition that no appreciable I^- complex of H_4L^{4+} is formed and (b) that the activity coefficient model is valid.

Next we made a similar series of experiments with varying proportions of NO_3^- and Cl^- electrolyte. Because both anions form H_4L^{4+} complexes, eq 9 takes a different form, given in eq 10. In

$$\left(\frac{1}{[H^+]}\right)\frac{(C_L + [H^+])}{(C_L - [H^+])} = \frac{\gamma_H\gamma_3}{K_{a3}\gamma_4}\left(1 + A\frac{\gamma_4\gamma_{Cl}}{\gamma_3}K_{NO_3} + \frac{\gamma_4\gamma_{Cl}}{\gamma_3}(K_{Cl} - K_{NO_3})[Cl^-]\right) \quad (10)$$

this equation A is the sum of Cl^- and NO_3^- molarities and K_{NO_3} is the formation constant for the $(H_4L\cdot NO_3^-)^{3+}$ species. Appropriate plots of the function on the left side of eq 10 vs. $[Cl^-]$ at a given ionic strength were linear and yielded slope and intercept values that in conjunction with the values of $K_{Cl}{}^\mu$ already found led to direct estimation of conditional $K_{NO_3}{}^\mu$ at each ionic strength. Similar experiments gave values for the conditional formation constants of Br^- and ClO_4^- with H_4L^{4+}, and these results appear in Table III. Each value is also shown referred to the standard $\mu = 0.22$.

The surprising ordering of complex strengths seemed not to conform to any reasonable explanation based on electrostatic bonding or ionic size. Therefore, we sought further information on the nature of the bonding in these complexes. Firstly, we wished to characterize the reactions observed here in terms of the thermodynamic functions ΔH and ΔS by means of a study of the temperature dependency of the formation constants.

Temperature Variation of Equilibrium Constants. For these measurements we made stock solutions of H_6LCl_6 (~4 mM) titrated to $a = 2.5$ with NaOH and adjusted to $\mu = 0.22$ with varying proportions of NaI, NaCl, or NaNO$_3$. pH measurements with these solutions yielded $K_{a3}{}^*$, $K_{Cl}{}^*$ and $K_{NO_3}{}^*$ estimates with
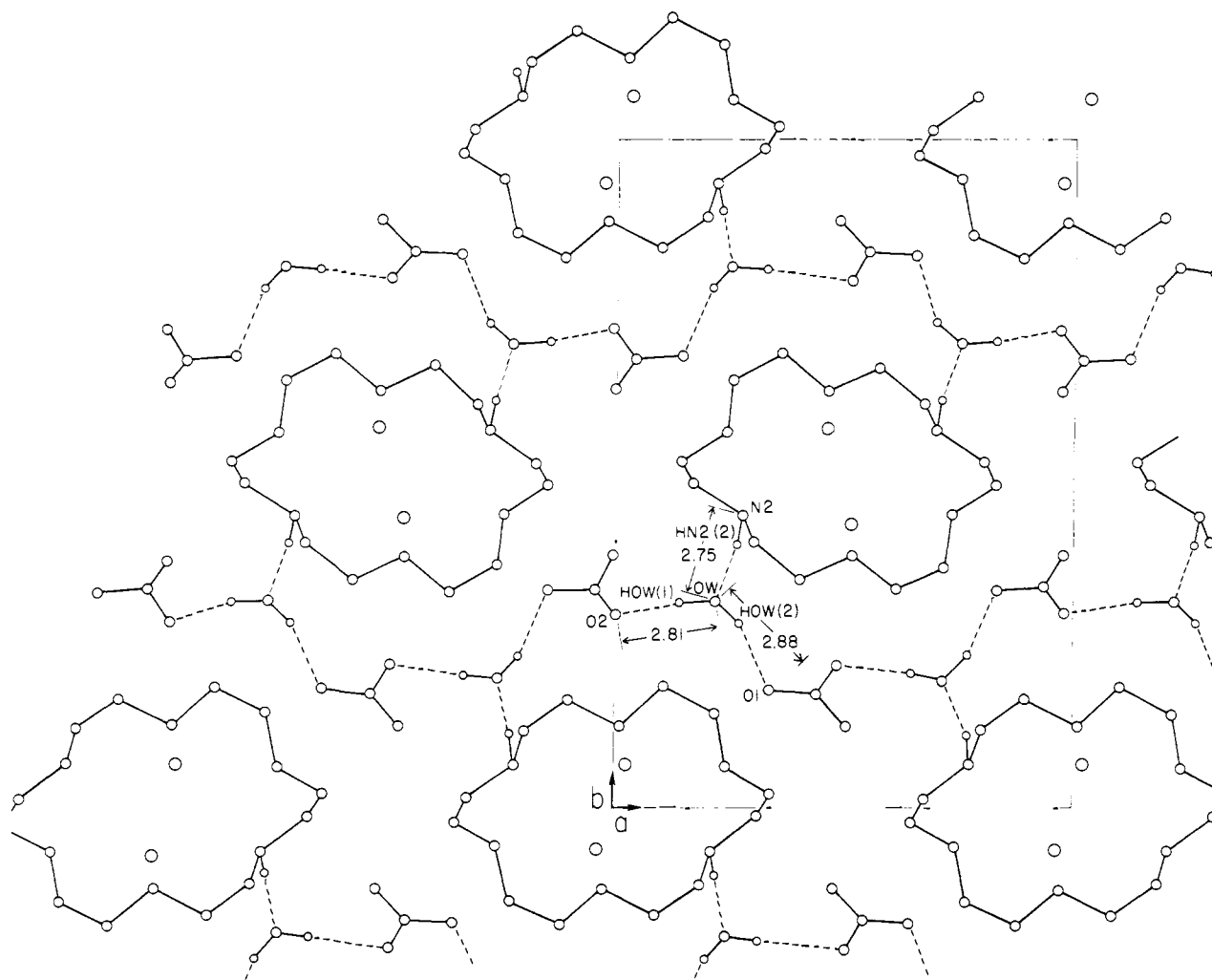
Figure 3. Crystal structure of $H_4L(NO_3)_2Cl_2 \cdot H_2O$. The view is along the crystallographic c axis.

the aid of eq 9 and 10 at 15, 25, 35, 45, and 55 °C. In our calculations we took $\gamma_x\gamma_4/\gamma_3$ as unity so that the equilibrium constants obtained were conditional constants at $\mu = 0.22$ and the resulting enthalpy and entropy values were similarly restricted. The results of our equilibrium measurements are listed in Table IV, and application of the van't Hoff equation to these data yields the ΔH^* and ΔS^* values in Table V. ΔH^* and ΔS^* values for the dissociation of H_4L^{4+} are to be compared with pertinent values for dissociation of other tetraprotonated polyamine species listed in Table VI. The most striking feature of H_4L^{4+} dissociation is the abnormally positive ΔS value, which we interpret in terms of decreased ordering of solvent molecules around H_3L^{3+} and H_3O^+ compared with H_4L^{4+}. Considering the fact that H_3O^+ is known to cause extensive solvent ordering and thus make a negative contribution to the overall ΔS value of H_4L^{4+} dissociation, the entropy difference between H_4L^{4+} and H_3L^{3+} species must be substantially greater than the 32 cal mol^{-1} K^{-1} observed, and such a large difference seems accountable only on the basis of extensive solvent interaction.

We note further that the ΔH value for the dissociation is somewhat larger and more endothermic than that observed for similar acids. This observation is at variance with a generally accepted explanation of polyammonium acid strength based on an electrostatic repulsion model whereby repulsions between proximal like-charge ammonium groups result in enhanced acid strength. If such a mechanism operates here, its effect is a minor one. Instead, we propose an explanation based both on ionic (N^+-H---) hydrogen bonding with the solvent and ion–dipole interactions. Both interactions would be weaker in the H_3L^{3+} species than in H_4L^{4+}, both by virtue of having fewer ammonium groups available for hydrogen bonding and because of smaller ionic

Table VIII. Bond Distances (Å) and Angles (Deg)^a

Ring Atoms			
N1–C1	1.479	C6′–N1–C1	113.0
C1–C2	1.499	N1–C1–C2	112.0
C2–N2	1.503	C1–C2–N2	111.7
N2–C3	1.492	C2–N2–C3	111.5
C3–C4	1.515	N2–C3–C4	113.4
C4–N3	1.481	C3–C4–N3	112.6
N3–C5	1.497	C4–N3–C5	113.6
C5–C6	1.508	N3–C5–C6	109.5
C6–N1′	1.458	C5–C6–N1′	110.4
Nitrate Ion			
N4–O2	1.234	O2–N4–O3	119.7
N4–O3	1.228	O3–N4–O4	119.7
N4–O4	1.222	O4–N4–O2	120.5

^{a} Estimated standard deviations are approximately 0.004 Å in bond distance and 0.5° in bond angles.

charge. Consequently the dissociation reaction pictured in this way would be endothermic and entropy producing. The relatively more positive ΔH value for H_4L^{4+} dissociation compared with smaller ammonium acids seems likely to reflect a cooperative effect of neighboring ammonium groups in stabilizing a bonded solvent network. Similarly, disruption of the solvent network along with decreased ion–dipole interactions between H_3L^{3+} and the solvent would provide a large positive entropy change in the dissociation reaction.

The mechanistic picture detailed above provides a useful means of interpreting H_4L^{4+} complexation of anions as well. Thus, nitrate and chloride ions may form ionic hydrogen bonds with the ammonium sites in H_4L^{4+}, which would, in turn disrupt hydrogen
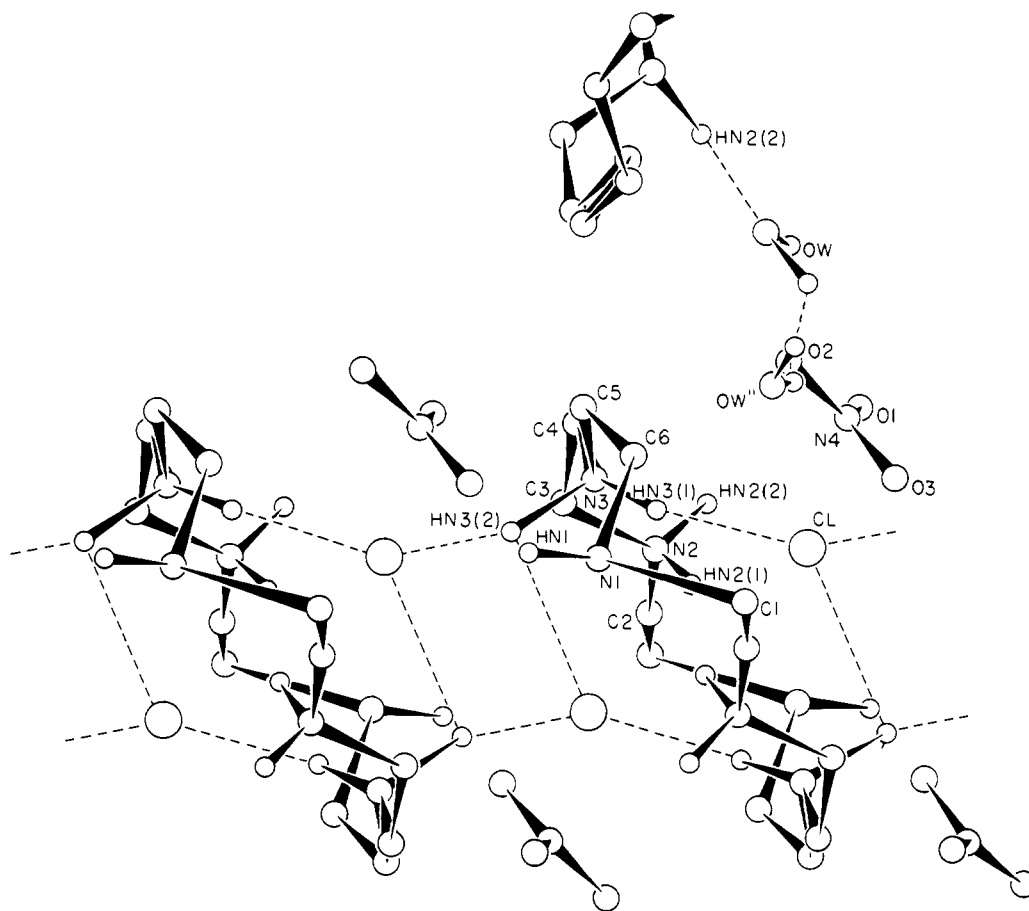
Figure 4. Crystal structure of $H_4L(NO_3)_2Cl_2 \cdot H2O$. The view is along the crystallographic a axis. The N–Cl internuclear distances indicated in the figure by dashed lines are N_3–HN3(1)–Cl 3.07 Å, N3–HN3(2)–Cl 3.14 Å, N3–HN3(2)–Cl' 3.28 Å.

bonding to the solvent. The net change in bonding between the complex and separate ions would not be large since the effect of reaction is to substitute bonding of H_4L^{4+} and anion with the solvent with H_4L^{4+}–anion bonding. The substitution results in a net positive entropy change by disruption of a highly ordered solvent network near H_4L^{4+} and by decreased long–range ion–dipole interaction of the $H_4L \cdot X^{3+}$ species compared with H_4L^{4+}.

This model also provides a rationale for comparison of the ΔH^* and ΔS^* values for chloride and nitrate complexations with H_4L^{4+}. The comparison is most readily made by considering the metathesis reaction:

$$H_4L \cdot NO_3{}^{3+} + Cl^- = H_4L \cdot Cl^{3+} + NO_3{}^-$$
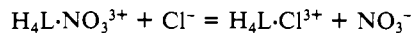
for which we calculate $\Delta H^* = +5.0$ kcal mol^{-1} and $\Delta S^* = +12.0$ cal mol^{-1} K^{-1}. These values can hardly be ascribed to differential solvation of the like-charged and similar-sized chloride and nitrate ions. Additionally, the complex species retains its 3+ charge in this reaction so that long-range ion–dipole interactions would appear to be identical for both complexes. Finally, it seems unlikely that small differences in torsional freedom in the complexes can account for the substantial enthalpic and entropic differences. These we ascribe to more effective H_4L^{4+}–Cl$^-$ bonding which results in a large decrease in solvation of the complex. This in turn gives rise to a substantially positive ΔS^* value. In other words, the chloride complex is about 4 times weaker at 25 °C than the nitrate complex. Paradoxically, the chloride complex is weaker because chloride must make a stronger bond to H_4L^{4+}, the stronger bond effectively releasing hydrogen-bonded solvent.

We sought some independent means of verifying our interpretation and so made X-ray crystallographic analyses of several hexacyclen salts containing both NO$_3^-$ and Cl$^-$. While the forces operating in the solid phase would almost certainly differ from those in solution, it seemed that strong hydrogen-bonding interactions with nitrate and particularly with chloride would provide at least a qualified confirmation of our description of the com-

plexation reactions. To this end we examined crystal structures of $H_6L(NO_3)_4Cl_2$, and the results are reported elsewhere.[3] We now report a study of crystalline hexacyclen bis(hydrogen nitrate) dihydrochloride dihydrate, $H_4L(NO_3)_2Cl_2 \cdot 2H_2O$.

Discussion of Structure

The structure of the hexacyclen bis(hydrogen nitrate) dihydrochloride monohydrate shows two differing hydrogen-bonded networks. One of these is illustrated in Figure 2, which is a projection along the crystallographic c axis. The hydrogen-bonding network is indicated by dashed lines and consists of ($>NH_2^+$) bonding to H_2O molecules, which are in turn hydrogen bonded to NO$_3^-$ ions. Figure 3 is a projection along the crystallographic a axis shows direct Cl$^-$–($>NH_2^+$) hydrogen bonding. The rather short N–Cl internuclear distances seem to indicate strong hydrogen bonding in this network, which consists of Cl$^-$ ions packed between parallel planes prescribed by the hexacyclen rings. The apparently strong and direct Cl–NH$_2^+$ hydrogen bonding which is distinguished from the H_2O-mediated hydrogen bonding of NO$_3^-$ ions seems to confirm our earlier conclusion regarding the solution properties of these complexes.