

complex), 94111-48-5; 6, 94111-53-2; 7, 94111-54-3; 8, 94111-55-4; 9, 94111-56-5; 10, 94111-57-6; 11, 94111-58-7; 12a, 94160-66-4; *cis*-12a, 94111-52-1; 13, 94111-59-8; 13 (diacid chloride), 94111-73-6; 14, 94111-60-1; 15, 94111-61-2; 16, 94136-31-9; 16 (dibutyl ester), 94111-72-5; 17, 94111-62-3; 18, 94111-63-4; 19, 94111-64-5; 20, 94111-65-6; 21, 94111-66-7; 22, 94111-67-8; 23, 94111-68-9; 24, 94111-69-0; 25, 94111-70-3; *o*-O<sub>2</sub>NC<sub>6</sub>H<sub>4</sub>CHO, 552-89-6; *p*-*t*-BuC<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, 98-73-7; *p*-*t*-BuC<sub>6</sub>H<sub>4</sub>COCl, 1710-98-1; *m*-MeC<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, 99-04-7; *m*-BrCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>CO<sub>2</sub>H, 6515-58-8; *m*-BrCH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>COCl, 54267-06-0; 1,3,5-C<sub>6</sub>H<sub>3</sub>(COCl)<sub>3</sub>, 4422-95-1; Im(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub>, 5036-48-6; Im(CH<sub>2</sub>)<sub>3</sub>CO<sub>2</sub>H, 72338-58-0; Im(CH<sub>2</sub>)<sub>3</sub>COCl, 66188-79-2; Im(CH<sub>2</sub>)<sub>2</sub>CO<sub>2</sub>H, 18999-45-6;

Im(CH<sub>2</sub>)<sub>2</sub>COCl, 94111-74-7; CH<sub>2</sub>(COCl)<sub>2</sub>, 1663-67-8; *t*-BuNH<sub>2</sub>, 75-64-9; 3,5-Me<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CO<sub>2</sub>H, 499-06-9; 3,5-(BrCH<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>CO<sub>2</sub>H, 94111-75-8; 3,5-(BrCH<sub>2</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>COCl, 94111-76-9; *t*-BocNH(CH<sub>2</sub>)<sub>3</sub>CO<sub>2</sub>H, 57294-38-9; BrCH<sub>2</sub>CO<sub>2</sub>Et, 105-36-2; CH<sub>2</sub>(CO<sub>2</sub>SiMe<sub>3</sub>)<sub>2</sub>, 18457-04-0; 5,5'-bis(ethoxycarbonyl)-4,4'-diethyl-3,3'-dimethyl-2,2'-dipyrrylmethane, 6305-93-7; *trans*-5-[*o*-(*p*-*tert*-butylbenzamido)phenyl]-15-[*o*-(*γ*-*tert*-butoxycarbonylamino)butyramido]phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, 94111-77-0; *trans*-5-[*o*-(*p*-*tert*-butylbenzamido)phenyl]-15-[*o*-(*γ*-aminobutyramido)phenyl]-2,8,12,18-tetraethyl-3,7,13,17-tetramethylporphyrin, 94111-78-1; 2-methyl dipicolinate, 7170-36-7; 2-methyl dipicolinic monochloride, 94111-79-2.

## Hexacyclen Complexes of Anions. 2. Bonding Forces, Structures, and Selectivity

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**Abstract:** Anion binding properties of hexacyclen (C<sub>12</sub>H<sub>30</sub>N<sub>6</sub>) with C<sub>6</sub>H<sub>5</sub>SO<sub>3</sub><sup>-</sup>, CF<sub>3</sub>CO<sub>2</sub><sup>-</sup>, ClO<sub>4</sub><sup>-</sup>, and IO<sub>3</sub><sup>-</sup> are studied by pH potentiometry and <sup>13</sup>C NMR. In each case tetraprotonated hexacyclen, H<sub>4</sub>L<sup>4+</sup>, is the sole complexing macrocycle species. Each anion forms a 1:1 complex with H<sub>4</sub>L<sup>4+</sup>, but a novel 1:2 stoichiometry is detected with IO<sub>3</sub><sup>-</sup>. Temperature-dependent binding constants are derived for each complexation in the range from 15 to 55 °C. van't Hoff analyses provide estimates of enthalpy and entropy changes for each reaction. These data are interpreted in terms of solvent ordering by the H<sub>4</sub>L<sup>4+</sup> species as providing the driving force in these reactions, while anion steric properties seem not to play an important role.

1,4,7,10,13,16-Hexaazacyclooctadecane, to be referred to as hexacyclen, L, is a macrocyclic polyamine capable of complexing anions in aqueous solution (Figure 1). Although complexation reactions of this type have been discovered only recently, several investigations<sup>1-3</sup> have been reported already. In most cases it appears that highly protonated forms of the polyamines participate in the complexation reactions and involve 1:1 anion-to-macrocycle stoichiometries. Some studies report anion complexation by tetra-, hexa-, and octa-protonated macrocyclic polyamines.<sup>4</sup> Some of us<sup>5</sup> describe exclusive 1:1 stoichiometries in tetraprotonated hexacyclen, H<sub>4</sub>L<sup>4+</sup>, with nitrate, chloride, perchlorate, and bromide ions but find no detectable complexation between these anions and other protonated hexacyclen species.

It has generally been assumed that electrostatic and ionic-hydrogen bonding interactions provide the bonding forces in anion complexes of protonated macrocyclic polyamines while the size and shape of the macrocycle cavity account for bonding selectivity. In ref 5, however, we suggest that solvent release is an important driving force in these reactions. This inference is based on the thermodynamic parameters  $\Delta H$  and  $\Delta S$  for the H<sub>4</sub>L<sup>4+</sup> complexation reactions of chloride and nitrate ions as well as an X-ray crystallographic analysis of a number of hexacyclen salts, including the tetrahydrochloride, tetrakis(hydrogen nitrate), and di(hydrogen nitrate) dihydrochloride.

Our present purpose is to obtain further information on the thermodynamic properties of hexacyclen complexation of anions in order to elucidate the solvent's role in these reactions. In order to obtain the experimental data necessary to this investigation we

employ a pH potentiometric method to estimate the temperature-dependent formation constants of H<sub>4</sub>L<sup>4+</sup> with trifluoroacetate, benzenesulfonate, perchlorate, and iodate anions. In the course of this work we also determined a novel stoichiometry between H<sub>4</sub>L<sup>4+</sup> and iodate anions which features both 1:1 and 1:2 H<sub>4</sub>L<sup>4+</sup>:iodate complexes. We begin with a description of experimental methods.

### Experimental Section

**Materials.** All chemicals were reagent grade. Sodium benzenesulfonate was found to contain trace quantities of weakly acidic impurities and was purified by repeated crystallization from 1:1 ethanol/water mixtures. The vacuum-dried product yielded essentially neutral aqueous solutions even at concentrations of 0.4 F. pH potentiometric measurements made with these solutions during addition of small amounts of HCl or NaOH indicated the absence of acidic or basic impurities even at the 0.05 mF level. Commercial sodium perchlorate, trifluoroacetate, and iodide-free sodium iodate were similarly tested and found to be free of interfering acidic or basic impurities.

Hexacyclen hexahydrochloride and hexakis(hydrogen nitrate) salts were prepared as follows: Weighed portions of the commercial tris(dihydrogen sulfate) salt from Parish Chemical Co. were dissolved in water (~0.5 F) and treated with an equivalent amount of BaCO<sub>3</sub>. After being mixed for 2 h at 80 °C, the filtered hot solution was concentrated with a rotary evaporator and treated with a large excess of mineral acid. The product was recrystallized from a fresh portion of the 6 F acid and air dried. Crystalline samples of C<sub>12</sub>H<sub>30</sub>N<sub>6</sub>·6HCl·3H<sub>2</sub>O (H<sub>6</sub>LCl<sub>6</sub>·3H<sub>2</sub>O) and C<sub>12</sub>H<sub>30</sub>N<sub>6</sub>·6HNO<sub>3</sub>·H<sub>2</sub>O (H<sub>6</sub>L(NO<sub>3</sub>)<sub>6</sub>·H<sub>2</sub>O) were obtained. Solutions were prepared directly from these samples and analyzed by pH potentiometric titration with 0.1 F NaOH in the presence of 0.4 F NaNO<sub>3</sub>. Under these conditions both  $a = 2$  and  $a = 3$  (mol of NaOH/mol of hexacyclen) end points are discernible and these end points provided a direct estimate of hexacyclen concentration.  $a = 2.5$  hexacyclen solutions were prepared by addition of NaOH solutions to the analyzed stock. Because microbial growth appeared in these solutions after a few days, the solutions were used immediately or were preserved by adding a droplet of chloroform and refrigerating. This preservation practice had no discernible effect on the pH value.

Tetrakis(aminomethyl)methane was prepared by previously described methods.<sup>6</sup> Purified samples of the tetrahydrochloride were employed to

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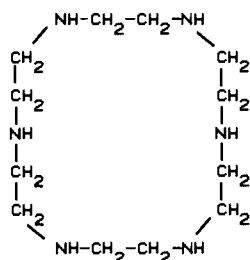
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**Table I.** Conditional Formation Constants and Their Uncertainties for  $H_4L^{4+}$  Complexes of Chloride, Perchlorate, Benzenesulfonate, and Trifluoroacetate Anions at Various Temperatures

anion	<i>t</i> , °C	slope <sup>a</sup>	intercept <sup>a</sup>	$K_{Cl}^{0.22}$ <sup>b</sup>	$K_{Cl}^{\mu}$ <sup>c</sup>	$K_X^{\mu}$ <sup>d</sup>	$K_X^{0.22}$ <sup>e</sup>
$ClO_4^-$ , $\mu = 0.235$	15	$1.99 (\pm 0.04) \times 10^5$	$2.44 (\pm 0.06) \times 10^4$	$52 \pm 2$	$45 \pm 2$	$12.5 \pm 1.0$	$13.0 \pm 1.0$
	25	$1.36 (\pm 0.02) \times 10^5$	$8.2 (\pm 0.3) \times 10^3$	$69 \pm 4$	$59 \pm 3$	$8.8 \pm 0.8$	$9.1 \pm 0.8$
	35	$8.9 (\pm 0.1) \times 10^4$	$3.9 (\pm 0.2) \times 10^3$	$90 \pm 5$	$76 \pm 4$	$8.4 \pm 0.9$	$8.7 \pm 0.9$
	45	$6.38 (\pm 0.08) \times 10^4$	$1.9 (\pm 0.1) \times 10^3$	$115 \pm 6$	$98 \pm 5$	$7.1 \pm 0.8$	$7.4 \pm 0.8$
	55	$4.01 (\pm 0.05) \times 10^4$	$9.3 (\pm 0.6) \times 10^2$	$144 \pm 7$	$123 \pm 6$	$7.2 \pm 0.8$	$7.5 \pm 0.8$
$F_3CCO_2^-$ , $\mu = 0.271$	15	$1.66 (\pm 0.02) \times 10^5$	$1.10 (\pm 0.02) \times 10^4$	$52 \pm 2$	$37 \pm 2$	$4.6 \pm 0.5$	$5.2 \pm 0.5$
	25	$9.38 (\pm 0.09) \times 10^4$	$6.33 (\pm 0.10) \times 10^3$	$69 \pm 4$	$55 \pm 3$	$7.3 \pm 0.8$	$8.2 \pm 0.8$
	35	$5.90 (\pm 0.05) \times 10^4$	$3.83 (\pm 0.07) \times 10^3$	$90 \pm 5$	$66 \pm 4$	$9.9 \pm 1.0$	$11.0 \pm 1.1$
	45	$3.78 (\pm 0.01) \times 10^4$	$2.54 (\pm 0.01) \times 10^3$	$115 \pm 6$	$85 \pm 4$	$14.0 \pm 1.0$	$16.0 \pm 1.2$
	55	$2.55 (\pm 0.03) \times 10^4$	$1.75 (\pm 0.03) \times 10^3$	$144 \pm 7$	$107 \pm 5$	$19.0 \pm 2.0$	$21.0 \pm 2.0$
benzene- sulfonate, $\mu = 0.253$	15	$1.77 (\pm 0.01) \times 10^5$	$6.17 (\pm 0.10) \times 10^3$	$52 \pm 2$	$46 \pm 2$	$2.1 \pm 0.2$	$2.3 \pm 0.2$
	25	$1.13 (\pm 0.01) \times 10^5$	$3.80 (\pm 0.06) \times 10^3$	$69 \pm 4$	$55 \pm 3$	$3.0 \pm 0.2$	$3.2 \pm 0.2$
	35	$7.06 (\pm 0.05) \times 10^4$	$2.31 (\pm 0.04) \times 10^3$	$90 \pm 5$	$71 \pm 4$	$4.6 \pm 0.4$	$5.0 \pm 0.4$
	45	$4.51 (\pm 0.03) \times 10^4$	$1.38 (\pm 0.02) \times 10^3$	$115 \pm 6$	$91 \pm 5$	$6.3 \pm 0.5$	$6.8 \pm 0.5$
	55	$2.94 (\pm 0.02) \times 10^4$	$8.78 (\pm 0.15) \times 10^2$	$144 \pm 7$	$114 \pm 6$	$8.5 \pm 0.9$	$9.2 \pm 1.0$

<sup>a</sup> Derived from weighted least-squares regression of *Y* on  $F_{Cl}$  (eq 7). Uncertainties represent standard error estimates propagated from  $\pm 0.004$  pH.

<sup>b</sup> Derived from  $\Delta H^*$  and  $\Delta S^*$  (ref 5). Uncertainties represent standard error estimates derived from root mean square scatter of points about  $\log K_{Cl}^{0.22}$  vs.  $1/T$  plots. <sup>c</sup>  $K_{Cl}^{\mu} = K_{Cl}^{0.22}(\gamma_4\gamma_{Cl}/\gamma_3)^{\mu}/\gamma_4\gamma_{Cl}/\gamma_3^{0.22}$ . Uncertainties are standard error estimates of  $K_{Cl}^{0.22}$  propagated to  $K_{Cl}^{\mu}$ . <sup>d</sup>  $K_X^{\mu} = [K_{Cl}^{\mu} - (S/I)]/[A(S/I) + 1]$  where *S* = slope and *I* = intercept (eq 7). Uncertainties are derived from standard errors in  $K_{Cl}^{\mu}$ , *S*, and *I*. <sup>e</sup>  $K_X^{0.22} = K_X^{\mu}(\gamma_4\gamma_X/\gamma_3)^{0.22}/\gamma_4\gamma_X/\gamma_3^{\mu}$ .

**Figure 1.** 1,4,7,10,13,16-Hexaazacyclooctadecane (hexacyclen).

prepare solutions which were analyzed by pH potentiometric titration.

pH measurements employed an Orion Model 801 pH meter. Although conventional glass and calomel electrodes were usually used, a silver, silver chloride electrode made up with saturated NaCl served as reference in measurements with perchlorate solutions. A 0.05 *m* potassium hydrogen phthalate (KHP) solution was used to standardize the meter at each measurement temperature. The temperature-dependent pH value of the standard was taken from Bates.<sup>7</sup> We also wished to interpret the pH meter readings in terms of hydrogen ion concentrations, and in order to do so we made the following additional measurements.

At each temperature, the KHP standardized meter measured the pH value of a 1.00 *mF* HCl solution in 0.20 *F* electrolyte ( $NaClO_4$ ,  $NaO_3SC_6H_5$ ,  $NaIO_3$ , or  $NaO_2CCF_3$ ). The measured value was compared with one calculated from the known hydrogen ion concentration and an estimate of the hydrogen ion activity coefficient obtained from the Debye-Hückel equation taking  $a = 0.9$  nm and employing the temperature-dependent *A* and *B* coefficients of Robinson and Stokes.<sup>8</sup> As an example, the pH of a solution containing 1.00 *mF* HCl in 0.20 *F*  $NaIO_3$  was measured as 3.099 at 25 °C. This value is to be compared with the calculated estimate of 3.098. We interpret the essential agreement of these values as indicating the validity of pH-derived hydrogen ion concentration values under conditions of these experiments. Measured pH values always agreed with the calculated estimates to within  $\pm 0.004$  pH.

<sup>13</sup>C NMR spectra were obtained with a Bruker HX-270 spectrometer operating at 67.89 MHz for <sup>13</sup>C detection. Typical spectra employed 4K transients. Sample solutions were contained in 1-cm tubes thermostated at  $30 \pm 2$  °C.

### Methodology

A pH potentiometric method is employed to estimate complexation constants of  $H_4L^{4+}$  with anions. The method relies on a competition between chloride, which has a known  $H_4L^{4+}$  complexation constant, and a second anion whose complexation constant is to be determined. We prepare a series of solutions containing identical concentrations of hexacyclen ( $\sim 4$  *mF*) previously titrated to  $a = 2.5$  mol of NaOH/mol of

$H_4LCl_6$ . The only important forms of hexacyclen in these solutions are the tetra- and triprotonated species and their possible anion complexes.<sup>5</sup> The solutions are made up to essentially equal ionic strengths with differing proportions of NaCl and the sodium salt of the anion under study. The chloride ion concentration in these solutions ranges from about 0.2 down to 0.02 *F* while the concentration of the second anion increases from zero to about 0.2 *F*. We employed a differential method in these experiments for a number of reasons. First, we note that the ionic activity coefficients of  $H_3L^{3+}$  and  $H_4L^{4+}$  and  $H_4LX^{3+}$  complexes are highly sensitive to the ionic strength so that it seemed prudent to carry out the experiments under conditions of constant ionic strength wherever possible. In order to employ a direct method where only a single complexing anion is present, a second noncomplexing anion is required to make up the ionic strength. At the present time only iodide has been shown not to complex  $H_4L^{4+}$ , but the problem of air oxidation and chemical reaction in these solutions precluded its use. Consequently, we employed NaCl to make up the ionic strength in these solutions in spite of the fact that uncertainties in  $H_4L(Cl)^{3+}$  formation constants would constitute error sources in the present experiments. In an effort to minimize this source of error, we would later employ "smoothed" values of  $H_4L(Cl)^{3+}$  complexation constants in our calculations. These values were derived from  $\Delta H^*$  and  $\Delta S^*$  data,<sup>5</sup> the enthalpy and entropy changes at ionic strength 0.22, respectively, for chloride complexation with  $H_4L^{4+}$ . These thermodynamic parameters represent the results of a least-squares van't Hoff analysis of complexation constant data obtained at five temperatures between 15 and 55 °C and represent about ten separate  $H_4L(Cl)^{3+}$  formation constant determinations each of which derives from about 6–8 pH measurements. Calculated  $H_4L(Cl)^{3+}$  complexation constants and their uncertainties, which were derived by propagation-of-variance methods based on the root mean square scatter of points about the least-squares van't Hoff line, appear in Table I under the heading  $K_{Cl}^{0.22}$ . These values along with pH vs. composition data obtained with  $H_4L^{4+}$ ,  $H_3L^{3+}$  buffers in NaCl, NaX mixtures allow estimation of  $H_4L(X)^{3+}$  complexation constants by the calculational methods described below.

### Calculations

Mass balance and equilibrium constant expressions relevant to these experiments are

$$C_L = [H_4L^{4+}] + [H_4L(Cl)^{3+}] + [H_4L(X)^{3+}] + [H^+] \quad (1)$$

$$C_L = [H_3L^{3+}] - [H^+] \quad (2)$$

$$K_3 \frac{\gamma_{H_4L}}{\gamma_H \gamma_{H_3L}} = K_3^{\mu} = \frac{[H^+][H_3L^{3+}]}{[H_4L^{4+}]} \quad (3)$$

$$K_{Cl} \frac{\gamma_{H_4L} \gamma_{Cl}}{\gamma_{H_4L} \gamma_{Cl}} = K_{Cl}^{\mu} = \frac{[H_4L(Cl)^{3+}]}{[H_4L^{4+}][Cl^-]} \quad (4)$$

$$K_X \frac{\gamma_{H_4L} \gamma_X}{\gamma_{H_4L} \gamma_X} = K_X^{\mu} = \frac{[H_4L(X)^{3+}]}{[H_4L^{4+}][X^-]} \quad (5)$$

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

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

In these equations,  $C_L$  represents the common analytical concentrations of  $H_3L^{3+}$  and  $H_4L^{4+}$  present in a solution containing 2  $C_L$  F hexacyclen hexahydrochloride titrated to  $a = 2.5$  (mol of NaOH/mol of  $H_6LCl_6$ ). Subscripted  $\gamma$  symbols refer to ionic activity coefficients of the various solution species. For example,  $\gamma_H$  signifies the  $H^+$  activity coefficient. Superscripted equilibrium constants represent conditional constants at a certain ionic strength. Thus,  $K_3^{\mu}$  represents the apparent value of the third acidic dissociation constant of the acid  $H_6L^{6+}$  in a noncomplexing medium of ionic strength  $\mu$ . Combination of eq 1–5 yields

$$Y \equiv \frac{1}{[H^+]} \left\{ \frac{C_L - [H^+]}{C_L + [H^+]} \right\} = \frac{1}{K_3^{\mu}} (1 + K_{Cl}^{\mu}[Cl^-] + K_X^{\mu}[X^-]) \quad (6)$$

In order to utilize this equation we make the simplifying assumption that the species concentrations of  $Cl^-$  and  $X^-$ , present in large excess compared with  $H_4L^{4+}$ , are essentially equal to their analytical concentrations. Additionally, we have carried out these experiments in such a way as to assure a constant sum of  $Cl^-$  and  $X^-$  concentrations, i.e., essentially constant ionic strength. Incorporating these factors into eq 6 yields

$$Y = \frac{1}{[H^+]} \left\{ \frac{C_L - [H^+]}{C_L + [H^+]} \right\} = \frac{1}{K_3^{\mu}} \{1 + AK_X^{\mu} + (K_{Cl}^{\mu} - K_X^{\mu})F_{Cl}\} \quad (7)$$

where the symbol  $A$  denotes the constant sum of  $Cl^-$  and  $X^-$  analytical concentrations and  $F_{Cl}$  is the analytical concentration of  $Cl^-$  in the measurement solution. Values of  $Y$  are derived from the measured pH values interpreted as  $pH = -\log \gamma_H[H^+]$  and the known value of  $C_L$ . Plots of  $Y$  vs.  $F_{Cl}$  were linear with  $ClO_4^-$ ,  $F_3CCO_2^-$ , and  $C_6H_5SO_3^-$  solutions at all measurement temperatures. However, data obtained with  $IO_3^-$  solutions always yielded curved  $Y$  vs.  $F_{Cl}$  plots, and these will be discussed later. For the present time we confine the discussion to the former three anion species.

Slopes and intercepts of  $Y$  vs.  $F_{Cl}$  plots and their uncertainties were extracted from the data by means of a weighted least-squares regression. Weighing factors were taken as  $1/\sigma_y^2$  where  $\sigma_y$ , the statistical uncertainty of each  $Y$  value, was derived by propagation-of-variance methods based on an estimate of  $\pm 0.004$  pH uncertainty. The results of these calculations appear in Table I. We now seek to interpret these data according to eq 7 to yield  $K_X^{\mu}$  values and their uncertainties. In order to do so we require estimates of  $K_{Cl}^{\mu}$  and its uncertainty at each temperature and ionic strength. As a starting point we employ the  $K_{Cl}^{0.22}$  values in Table I which are derived from least-squares analysis of van't Hoff plots of temperature-dependent equilibrium constants as described earlier. These values which refer to an ionic strength of 0.22 require adjustment to account for the somewhat different ionic strengths employed in the present experiments. In order to make this adjustment we refer to eq 4 and derive

$$K_{Cl} = \left\{ \frac{\gamma_{H_4L(Cl)}^{\mu}}{\gamma_{H_4L}^{\mu} \gamma_{Cl}^{\mu}} \right\} K_{Cl}^{\mu} = \left\{ \frac{\gamma_{H_4L(Cl)}^{0.22}}{\gamma_{H_4L}^{0.22} \gamma_{Cl}^{0.22}} \right\} K_{Cl}^{0.22} \quad (8)$$

In this equation superscripted designations of 0.22 denote activity coefficient or formation constant values at ionic strength 0.22 while  $\mu$  superscripts denote their values at some other ionic strength. It is evident from this equation that  $K_{Cl}^{\mu}$  values are derivable from  $K_{Cl}^{0.22}$  provided that the relative values of activity coefficients at ionic strength  $\mu$  and ionic strength 0.22 are available. Thus, we require the ratio of the activity coefficient function  $\gamma_{H_4L(Cl)}/\gamma_{H_4L}\gamma_{Cl}$  at ionic strength  $\mu$  compared to its value at ionic strength 0.22. In order to do so we employ the Debye–Hückel equation to estimate relative values of the monovalent chloride ion activity coefficient at different ionic strengths. This procedure seemed inappropriate to estimating relative activity coefficient values for the highly charged  $H_4L^{4+}$  and  $H_4L(Cl)^{3+}$  species, however. In order to obtain these values we resort to a procedure detailed in ref 5 which relies on an empirical activity coefficient correlation obtained with a chemical model polyamine, tetrakis(amino-

methyl)methane, referred to in the earlier work as M. This model compound has been found not to complex  $Cl^-$  or  $NO_3^-$  ions, and a series of pH vs. composition measurements with  $H_4M^{4+}/H_3M^{3+}$  buffers at various concentrations of NaCl and  $NaNO_3$  allowed estimation of  $\gamma_{H_4M}/\gamma_{H_3M}$  dependence on the ionic strength. A brief description is given below.

We prepared solutions containing equal known concentrations of  $H_4M^{4+}$  and  $H_3M^{3+}$  and made up the ionic strength to about 0.4 M with  $NaNO_3$  or NaCl. The pH value was recorded as small volumes of water were added to the mixture. These measurements provided an empirical activity coefficient correlation as follows.

In each solution conservation relations are

$$[H_4M^{4+}] = C_M - [H^+] \quad (9a)$$

$$[H_3M^{3+}] = C_M + [H^+] \quad (9b)$$

where  $C_M$  is the common analytical concentration of  $H_4M^{4+}$  and  $H_3M^{3+}$ . Species concentrations of  $H_4M^{4+}$  and  $H_3M^{3+}$  are related to the pH by

$$K_{M1} = \frac{a_H a_{H_3M}}{a_{H_4M}} = \frac{a_H [H_3M^{3+}] \gamma_{H_3M}}{[H_4M^{4+}] \gamma_{H_4M}} \quad (10)$$

where  $K_{M1}$  is the first acidic dissociation constant of the acid  $H_4M^{4+}$ . Combining eq 9a, 9b, and 10 we obtain

$$g \equiv pK_{M1} - \log (\gamma_{H_4M}/\gamma_{H_3M}) = pH - \log \left\{ \frac{C_M + 10^{-pH}/\gamma_H}{C_M - 10^{-pH}/\gamma_H} \right\} \quad (11)$$

The right-hand side of eq 11 is calculable from the measured pH values and  $\gamma_H$  estimates from the Debye–Hückel equation. A least-squares polynomial fit of  $g$  values vs.  $\mu^{1/2}$  yields an empirical correlation of  $pK_{M1} - \log (\gamma_{H_4M}/\gamma_{H_3M})$  vs. the ionic strength. Finally, we compare the correlation to the value of  $g$  at an ionic strength of 0.22 to obtain

$$\log (\gamma_{H_4M}^{\mu}/\gamma_{H_3M}^{\mu}) - \log (\gamma_{H_4M}^{0.22}/\gamma_{H_3M}^{0.22}) = 0.962 - 3.46\mu^{1/2} + 3.75\mu - 1.59\mu^{3/2} \quad (12)$$

This equation compares the ratio of 4+ and 3+ M species activity coefficients at an ionic strength  $\mu$  between 0.09 and 0.44 to the value of the activity coefficient ratio at an ionic strength of 0.22, arbitrarily chosen as a standard. The root mean square scatter of eight points about the regression curve was  $\pm 0.001$  log. We will assume that the ionic strength dependence of 4+ and 3+ hexacyclen species activity coefficients ( $\gamma_{H_4L}/\gamma_{H_4L(Cl)}$ ), ( $\gamma_{H_4L}/\gamma_{H_4L(X)}$ ), and ( $\gamma_{H_4L}/\gamma_{H_3L}$ ) is the same as that of ( $\gamma_{H_4M}/\gamma_{H_3M}$ ). Results obtained in ref 5 seem to verify this assumption at least at the precision level of the experimental data. One further complication remains before applying eq 12 to the present analysis, and this results from the fact that the equation refers only to experiments made at 25 °C. While it appeared unlikely that the relative activity coefficient ratio at similar but differing ionic strengths would vary substantially with temperature, we sought some further confirmation of this hypothesis. In this connection we made calculations employing the Debye–Hückel equation with temperature-dependent  $A$  and  $B$  coefficients and taking  $a = 1.0$  nm for both 4+ and 3+ species. Admittedly, activity coefficient ratios for these highly charged species are not likely to describe  $H_4L^{4+}$  and  $H_3L^{3+}$  experimental behavior very accurately but should nevertheless provide a rough estimate of the temperature variability. Thus, we calculated values of  $\log (\gamma_4/\gamma_3)_{\mu=0.27} - \log (\gamma_4/\gamma_3)_{\mu=0.22}$  at several temperatures between 15 and 55 °C which values represent the extreme temperature conditions of our experiments while the ionic strength of 0.27 corresponds to the most concentrated solutions in the present series of experiments. The results of these calculations indicate that the relative activity coefficient ratio,  $\log (\gamma_4/\gamma_3)_{\mu=0.27} - \log (\gamma_4/\gamma_3)_{\mu=0.22}$ , is essentially temperature independent, its value varying by only 0.001 log between the temperature extremes. We interpret this behavior as indicating that temperature variation of relative activity

**Table II.** Enthalpies and Entropies for Acid Dissociation and Formation of  $H_4L^{4+}$  Complexes with Various Anions

reaction	$\Delta H^*,^a$ kcal/mol	$\Delta S^*,^a$ cal/mol K
$H_4L^{4+} = H_3L^{3+} + H^+$	$14.1 \pm 0.3^b$	$32 \pm 1^c$
$H_4L^{4+} + C_6H_5OSO_2^- = H_4L\cdot OSO_2C_6H_5^{3+}$	$6.6 \pm 0.2$	$24.6 \pm 0.7$
$H_4L^{4+} + CF_3CO_2^- = H_4L\cdot O_2CCF_3^{3+}$	$6.5 \pm 0.2$	$25.9 \pm 0.6$
$H_4L^{4+} + Cl^- = H_4L\cdot Cl^{3+}$	$4.9 \pm 0.6$	$24 \pm 2^c$
$H_4L^{4+} + ClO_4^- = H_4L\cdot ClO_4^{3+}$	$-2.5 \pm 0.7$	$-3.8 \pm 2.1$
$H_4L^{4+} + NO_3^- = H_4L\cdot NO_3^{3+}$	$-0.4 \pm 0.6$	$12 \pm 2^c$

<sup>a</sup> Referred to  $\mu = 0.22$ . <sup>b</sup> Uncertainties are standard error estimates derived from least-squares van't Hoff plots. <sup>c</sup> Reference 5.

coefficient ratios in eq 12 may be safely ignored, and we employed this equation as an empirical activity coefficient correlation at each measurement temperature. In addition we require relative activity coefficient values for singly charged  $Cl^-$  and  $X^-$  ions and obtain these from the Debye-Hückel correlation employing the temperature-dependent  $A$  and  $B$  coefficients cited above. In these calculations we take  $a$  as 0.5 nm for  $F_3CCO_2^-$  and  $C_6H_5SO_3^-$  and 0.3 nm for  $Cl^-$ ,  $ClO_4^-$ , and  $IO_3^-$  ions.

Relative activity coefficients of the 4+, 3+, and  $Cl^-$  ions derived above along with  $K_{Cl}^{0.22}$  values allow estimation of  $K_{Cl}^{\mu}$  at the various ionic strengths and temperatures indicated in Table I. Finally,  $K_{Cl}^{\mu}$ , slope, and intercepts of  $Y$  vs.  $F_{Cl}$  plots allow calculation of  $K_X^{\mu}$  at each measurement temperature. Standard error estimates of  $K_X^{\mu}$  were derived by propagation-of-variance methods. In these calculations we neglected the additional variances introduced by the small ionic strength adjustments. Finally,  $K_X^{\mu}$  values were adjusted to  $\mu = 0.22$  for the sake of comparison with earlier results, and we note the apparently good agreement between the  $ClO_4^-$  complexation constant reported here ( $K_{ClO_4}^{0.22} = 9.1 \pm 0.8$ ) and previously determined values of 11.0 and 10.5 ( $\log K_{ClO_4}^{0.22} = 1.04, 1.02$ ).<sup>5</sup>

Temperature-dependent  $K_X^{0.22}$  values derived in Table I allowed calculation of  $\Delta H^*$  and  $\Delta S^*$  and complexation enthalpy and entropy changes, respectively, at ionic strength 0.22. van't Hoff plots appeared linear and points were randomly scattered about the least-squares lines. Slope and intercepts and their uncertainties yielded  $\Delta H^*$  and  $\Delta S^*$  along with standard error estimates. The results of these calculations are compared to  $\Delta H^*$  and  $\Delta S^*$  for other hexacyclen reactions in Table II. We defer discussion of these data and now describe an analysis of pH vs. composition data obtained with hexacyclen, iodate mixtures.

### Hexacyclen Complexes with Iodate

We have mentioned earlier that plots of  $Y$  vs.  $F_{Cl}$  derived from pH potentiometric data with iodate mixtures were always non-linear. In order to check our experimental methods and materials we prepared a second series of chloride, iodate mixtures from fresh chemical stocks. Measurements with these solutions at 25 °C yielded results essentially identical with the earlier ones. We concluded that the model eq 1–5 do not adequately describe equilibria in these solutions and therefore allowed for the possibility of additional hexacyclen, anion complex stoichiometries. We hypothesized  $H_3L(IO_3)_2^{2+}$ ,  $H_4L(IO_3)_2^{2+}$ , and  $H_4L(IO_3)(Cl)^{2+}$  complexes based on the following considerations.

Qualitative examination of  $Y$  vs.  $[IO_3^-]$  plots seemed to suggest formation of a ternary  $H_4L(IO_3)_2^{2+}$  complex in addition to the expected binary  $H_4L(IO_3)^{3+}$  complex. We envision formation of the 1:2 complex via a stepwise process in which an  $IO_3^-$  ion is added to the  $H_4L(IO_3)^{3+}$  species. In the same solution are present  $H_4L(Cl)^{3+}$  and  $H_3L^{3+}$  species. These 3+ hexacyclen species do not appear qualitatively different from the  $H_4L(IO_3)^{3+}$  complex, and so we could not a priori exclude their complexation with  $IO_3^-$  ions. In fact, an electrostatic bonding model for these complexes seems to suggest that  $IO_3^-$  complexation is equally feasible with each of the 3+ hexacyclen species. While it might be argued that the presence of  $Cl^-$  in the supposed hexacyclen "cavity" might prevent further complexation with  $IO_3^-$ , such reasoning can hardly be applied to  $IO_3^-$  complexation with  $H_3L^{3+}$ . As a consequence of these considerations it seemed worthwhile to elucidate hexacyclen,  $IO_3^-$  complexation equilibria because such analysis would provide new information about bonding and steric factors in these macrocycle, anion complexes.

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### $H_3L^{3+}$ Complexation

We sought to investigate the possibility of  $H_3L(IO_3)_2^{2+}$  formation by a pH potentiometric titration method. Presumably formation of such a complex would be reflected in the acidimetric titration curve beyond  $a = 3$  mol of NaOH/mol of  $H_6L$ . Complexation of the  $H_3L^{3+}$  species by  $IO_3^-$  would result in increased pH values in the region between  $a = 3$  and  $a = 4$  where the dominant hexacyclen species are  $H_3L^{3+}$  and  $H_2L^{2+}$ . We found that addition of  $IO_3^-$  to strongly acid hexacyclen solutions prepared directly from  $H_6LCl_6$  samples decomposed immediately with apparent formation of elemental iodine. However,  $H_6LCl_6$  solutions previously titrated to  $a = 2$  were stable to  $IO_3^-$  addition and remained clear and colorless with constant pH readings for indefinite periods. Upon titration of these solutions beyond  $a = 3$ , however, decomposition of the more basic solution was again noted with formation of iodine. The chemical reactions responsible for this behavior precluded any direct determination of possible  $H_3L^{3+}$  complexation. These experiments did confirm, however, that our earlier measurements with  $a = 2.5$  hexacyclen, iodate solutions represent true equilibria. The decomposition reactions occur only in strongly acidic (pH < 2) solutions and in basic (pH > 9) solutions. As a consequence of these factors any information regarding possible  $H_3L^{3+}$  complexation of iodate would necessarily derive from an analysis of equilibrium data in the appropriate pH range. In fact we were able to reject  $H_3L^{3+}$  complexation as a complicating factor in these experiments based on the data analysis that followed, and for the sake of simplicity we will delete an  $H_3L(IO_3)_2^{2+}$  complex from the model equilibrium equations below.

The supposed  $H_4L(IO_3)_2^{2+}$  and  $H_4L(Cl)(IO_3)^{2+}$  complexes enter mass balance and equilibrium equations relating to  $a = 2.5$  mol of NaOH/mol of  $H_6LCl_6$  hexacyclen buffers in mixed  $Cl^-$ ,  $IO_3^-$  solutions.

$$C_L = [H_4L^{4+}] + [H_4L(Cl)^{3+}] + [H_4L(IO_3)^{3+}] + [H_4L(Cl)(IO_3)^{2+}] + [H^+] \quad (13)$$

$$C_L = [H_3L^{3+}] - [H^+] \quad (14)$$

$$K_{1,IO_3}^{\mu} = K_{1,IO_3} \left\{ \frac{\gamma_4 \gamma_{IO_3}}{\gamma_3} \right\} = \frac{[H_4L(IO_3)^{3+}]}{[H_4L^{4+}][IO_3^-]} \quad (15)$$

$$K_{2,IO_3}^{\mu} = K_{2,IO_3} \left\{ \frac{\gamma_3 \gamma_{IO_3}}{\gamma_2} \right\} = \frac{[H_4L(IO_3)_2^{2+}]}{[H_4L(IO_3)^{3+}][IO_3^-]} \quad (16)$$

$$K_{Cl,IO_3}^{\mu} = K_{Cl,IO_3} \left\{ \frac{\gamma_3 \gamma_{IO_3}}{\gamma_2} \right\} = \frac{[H_4L(Cl)(IO_3)^{2+}]}{[H_4L(Cl)^{3+}][IO_3^-]} \quad (17)$$

In these equations  $\gamma_2$ ,  $\gamma_3$ , and  $\gamma_4$  refer to ionic activity coefficients of 2+, 3+, and 4+ hexacyclen species, respectively. We will assume that hexacyclen species activity coefficients depend only on charge type, and  $\gamma_2$ , for example, represents a common activity coefficient value for both  $H_4L(IO_3)_2^{2+}$  and  $H_4L(Cl)(IO_3)^{2+}$  species. Equilibrium expressions (eq 16 and 17) are stepwise formation constants for ternary hexacyclen complexes formed by  $IO_3^-$  addition to binary  $H_4L(IO_3)^{3+}$  and  $H_4L(Cl)^{3+}$  species. Combination of eq 3–5 and 13–17 yields

$$Z \equiv \frac{K_{a3}^{\mu} Y - K_{Cl}^{\mu} [Cl^-] - 1}{[IO_3^-]} = \frac{K_{IO_3}^{\mu} \{ K_{2,IO_3}^{\mu} - K_{Cl,IO_3}^{\mu} [IO_3^-] + K_{IO_3}^{\mu} \{ K_{Cl,IO_3}^{\mu} A + 1 \} \}}{[IO_3^-]} \quad (18)$$

with  $Y$  defined by eq 6 and  $A$  denoting the constant sum of  $IO_3^-$  and  $Cl^-$  concentrations in our measurement solutions.

In order to apply this equation to pH vs. composition data for  $H_4L^{4+}$ ,  $H_3L^{3+}$  buffers in an iodate, chloride mixture we first made the simplifying assumption that concentrations of these anions could be taken as their analytical concentrations. Next, we required estimates of  $K_{Cl}^{\mu}$  and  $K_{2,IO_3}^{\mu}$  at each measurement temperature.

**Table III.** Slopes and Intercepts and Their Ratios for  $Z^a$  vs.  $[\text{IO}_3^-]$  Plots<sup>b</sup> at Various Temperatures

$T, ^\circ\text{C}$	slope	intercept	$R$
15	$7.77 (\pm 0.18) \times 10^3$	$5.47 (\pm 0.18) \times 10^2$	$14.1 \pm 0.9$
25	$7.26 (\pm 0.19) \times 10^3$	$6.02 (\pm 0.20) \times 10^2$	$12.1 \pm 0.7$
25	$6.88 (\pm 0.17) \times 10^3$	$5.75 (\pm 0.20) \times 10^2$	$12.0 \pm 0.7$
35	$7.14 (\pm 0.18) \times 10^3$	$6.04 (\pm 0.20) \times 10^2$	$11.8 \pm 0.7$
45	$6.07 (\pm 0.17) \times 10^3$	$6.57 (\pm 0.20) \times 10^2$	$9.2 \pm 0.6$
55	$6.29 (\pm 0.19) \times 10^3$	$7.25 (\pm 0.22) \times 10^2$	$8.7 \pm 0.5$

<sup>a</sup>  $Z$  defined by eq 18. <sup>b</sup> Solutions prepared from  $\text{H}_6\text{LCl}_6$  titrated to  $a = 2.5$  and containing varying proportions of  $\text{NaCl}$  and  $\text{NaIO}_3$  at  $\mu = 0.234$ . <sup>c</sup> Uncertainties are standard error estimates from weighted least-squares regression.

$K_{\text{Cl}}^{\mu}$  values were determined as described earlier.  $K_{\text{a}_3}^{\mu}$  estimates were obtained from the current experimental data in an effort to minimize systematic errors in the results. The necessary data were obtained by including a solution containing  $\text{Cl}^-$  as the only anion in each series of  $\text{H}_4\text{L}^{4+}$ ,  $\text{H}_3\text{L}^{3+}$  buffers and prepared from the same buffer and  $\text{Cl}^-$  stock solutions to be employed later. The measured pH value along with  $\gamma_{\text{H}}$  estimated from the Debye-Hückel equation allowed calculation of  $Y$  in the  $\text{Cl}^-$  only solution, and this value along with  $K_{\text{Cl}}^{\mu}$  and  $[\text{Cl}^-]$  provided a value of  $K_{\text{a}_3}^{\mu}$  since  $K_{\text{a}_3}^{\mu}Y - K_{\text{Cl}}^{\mu}[\text{Cl}^-] - 1 = 0$  when  $[\text{IO}_3^-] = 0$ . The value of  $K_{\text{a}_3}^{\mu}$ , thus determined, along with pH vs. composition data corresponding to about six to ten solutions, allowed  $Z$  vs.  $[\text{IO}_3^-]$  plots to be prepared and analyzed by a weighted least-squares regression. Weighting factors were derived from the estimated  $\pm 0.004$  uncertainty in each pH reading. The plots were linear with apparently random scatter of points about the regression line. Derived slope and intercept values and their uncertainties at each measurement temperature appear in Table III. Before continuing we note that the two entries at  $25^\circ\text{C}$ , obtained from measurements with different chemical batches, are in apparent agreement which we interpret as validating our experimental procedures. Furthermore, the observed linearity of  $Z$  vs.  $[\text{IO}_3^-]$  indicates that  $\text{H}_3\text{L}^{3+}$  complexation plays no appreciable role in these experiments. We infer this conclusion from the fact that any appreciable  $\text{H}_3\text{L}^{3+}$  complexation not accounted for by the model equations used to derive eq 18 results in curved  $Z$  vs.  $[\text{IO}_3^-]$  plots which were not observed.

We wish to interpret the slope and intercept values of Table III in terms of complexation constants via eq 18. However, inspection of this equation indicates that the data obtained thus far are not adequate to determine the complexation stoichiometry. That is, the slope and intercept values of  $Z$  vs.  $[\text{IO}_3^-]$  plots obtained at constant ionic strength do not uniquely determine the values of the equilibrium constants nor do they distinguish between  $\text{H}_4\text{L} \cdot (\text{IO}_3)_2^{2+}$  and  $\text{H}_4\text{L}(\text{Cl})(\text{IO}_3)_2^{2+}$  complexes. Consequently, it was necessary to make experiments under conditions of different ionic strength (and  $A$  values) to assign the stoichiometry and formation constants of the complexes.

#### Composition and Stoichiometry of Ternary Hexacyclen, Iodate Complexes

We now seek to distinguish between two possible ternary  $\text{H}_4\text{L}^{4+}$  complexes,  $\text{H}_4\text{L}(\text{IO}_3)_2^{2+}$  and  $\text{H}_4\text{L}(\text{Cl})(\text{IO}_3)_2^{2+}$ , and focus on the ratio of slope-to-intercept values of  $Z$  vs.  $[\text{IO}_3^-]$  plots as defined by eq 18. This ratio,  $R$ , is related to equilibrium constant values by eq 19a. In principle, the two equilibrium constant values

$$\frac{1}{R} = \frac{AK_{\text{Cl},\text{IO}_3}^{\mu} + 1}{K_{2,\text{IO}_3}^{\mu} - K_{\text{Cl},\text{IO}_3}^{\mu}} \quad (19a)$$

determining  $R$  may be determined independently by comparison of  $R$  vs.  $A$ . However, such analysis is complicated by variation of conditional equilibrium constants  $K_{\text{Cl},\text{IO}_3}^{\mu}$  and  $K_{2,\text{IO}_3}^{\mu}$ , whose values depend on the ionic strength. That is, experiments meant to determine  $R$  at differing values of  $A$  involve measurements at different ionic strengths which, in turn, alter the activity coefficient term  $\gamma_3\gamma_{\text{IO}_3}/\gamma_2$  implicit in both  $K_{\text{Cl},\text{IO}_3}^{\mu}$  and  $K_{2,\text{IO}_3}^{\mu}$ . Equation 19b takes account of this variation by relating the conditional equilibrium constants at ionic strength  $\mu$  to their values at some fixed

ionic strength again chosen arbitrarily as 0.22.

$$R^{-1} \left\{ \frac{\gamma_2}{\gamma_3\gamma_{\text{IO}_3}} \right\}^{0.22} \left\{ \frac{\gamma_3\gamma_{\text{IO}_3}}{\gamma_2} \right\}^{\mu} = A \left\{ \frac{\gamma_2}{\gamma_3\gamma_{\text{IO}_3}} \right\}^{0.22} \left\{ \frac{\gamma_3\gamma_{\text{IO}_3}}{\gamma_2} \right\}^{\mu} \left\{ \frac{K_{\text{X},\text{IO}_3}^{0.22}}{K_{2,\text{IO}_3}^{0.22} - K_{\text{Cl},\text{IO}_3}^{0.22}} \right\} + \left\{ \frac{1}{K_{2,\text{IO}_3}^{0.22} - K_{\text{Cl},\text{IO}_3}^{0.22}} \right\} \quad (19b)$$

From eq 19 it is evident that analysis of  $R$  vs.  $A$  data relies on relating activity coefficient values at various ionic strengths to those at  $\mu = 0.22$ . For this purpose the Debye-Hückel correlation would suffice to give reasonable accurate coefficient values for the singly charged iodate species up to ionic strengths of 0.3 or 0.4. However, it seemed unlikely that reliable estimates would be obtained for the 2+ and 3+ hexacyclen complexes. Therefore, we adopted the procedure employed previously to model activity coefficient behavior for the  $\text{H}_4\text{L}^{4+}$  and  $\text{H}_3\text{L}^{3+}$  hexacyclen species. Namely, we chose tetrakis(aminomethyl)methane,  $\text{M}$ , as a chemical model to determine ionic strength dependence of the ratio  $\gamma_3/\gamma_2$  for hexacyclen complexes. This model system seems to have successfully mimicked activity coefficient behavior of 3+ and 4+ hexacyclen species and seemed suitable to the present application.

#### Model System Activity Coefficients

The acidic dissociation constant for triprotonated  $\text{M}$  denoted by  $\text{H}_3\text{M}^{3+}$  is given by eq 20. Our intent is to obtain relative values

$$K_{2\text{M}} = \left\{ \frac{a_{\text{H}}[\text{H}_2\text{M}^{2+}]\gamma_2}{[\text{H}_3\text{M}^{3+}]\gamma_3} \right\} \quad (20)$$

of  $\gamma_2/\gamma_3$  at differing ionic strengths. We prepared solutions containing equal known ( $\sim 2$  mF) concentrations of  $\text{H}_3\text{M}^{3+}$  and  $\text{H}_2\text{M}^{2+}$  and made up the ionic strength to 0.44 with  $\text{NaCl}$ . The pH values were obtained as small volumes of water were added to a portion of the  $\text{H}_3\text{M}^{3+}/\text{H}_2\text{M}^{2+}$  buffer. Repetition of these experiments gave results reproducible to better than  $\pm 0.004$  pH. Obtained in this way, pH vs. ionic strength data, along with relevant mass balance equations, yielded an empirical correlation between  $\log(\gamma_2/\gamma_3)^{\mu} - \log(\gamma_2/\gamma_3)^{0.22}$  and the ionic strength. Equation 21 represents a least-squares polynomial fit of the appropriately manipulated data and provides the desired relationship between relative  $\gamma_2/\gamma_3$  values at differing ionic strengths. The

$$\log(\gamma_2/\gamma_3)^{\mu} - \log(\gamma_2/\gamma_3)^{0.22} = -0.924 + 4.11\mu^{1/2} - 6.11\mu + 3.31\mu^{3/2} \quad (21)$$

root mean square scatter of points about the virial equation is  $\pm 0.001$  log over the ionic strength range from 0.15 to 0.44. We will assume that the activity coefficient behavior of 2+ and 3+ hexacyclen species and corresponding  $\text{M}$  species is the same in this range of ionic strengths.

In order to utilize eq 19b and 21 we obtained pH vs. composition data of  $\text{H}_4\text{L}^{4+}$ ,  $\text{H}_3\text{L}^{3+}$  buffers at differing ionic strengths and different proportions of  $\text{Cl}^-$  and  $\text{IO}_3^-$ . Solutions containing  $\sim 4$  mF hexacyclen titrated to  $a = 2.5$  and up to 0.2 F  $\text{KIO}_3$  were made up to  $\mu = 0.44$  with  $\text{NaCl}$ . The pH was monitored during addition of small portions of water with ample time allowed for equilibration after each dilution. The resultant pH vs.  $[\text{IO}_3^-]$  data at each ionic strength yielded a  $Z$  vs.  $[\text{IO}_3^-]$  plot to be analyzed by a weighted least-squares regression described above. Each calculation required an estimate of  $K_{\text{Cl}}^{\mu}$  at the appropriate ionic strength. These values, along with derived  $Z$  vs.  $[\text{IO}_3^-]$  slopes and intercepts, their ratios, and uncertainties are summarized in Table IV. Slope to intercept ratios and  $A$  values are manipulated by the arithmetic operations detailed in the table to provide data for analysis via eq 19b. We find that a plot of the values in column 8 of Table IV vs. corresponding values in column 7 results in a slope indistinguishable from zero and conclude that  $K_{\text{Cl},\text{IO}_3}^{0.22}$  is essentially zero. Consequently, these experiments at varying ionic strengths imply that

Table IV. Slopes, Intercepts, Their Ratios, and Uncertainties for Z vs.  $[\text{IO}_3^-]$  Plots at Various Ionic Strengths in NaCl, NaIO<sub>3</sub> at 25 °C

$\frac{A^a}{[\text{IO}_3^-] + [\text{Cl}^-]}$	$K_{\text{Cl}}^b$	slope <sup>c</sup>	intercept <sup>c</sup>	$R^d = \text{slope}/\text{intercept}$	$(\gamma_2/\gamma_3\gamma_{\text{IO}_3})^{0.22}$	$A(\gamma_2/\gamma_3\gamma_{\text{IO}_3})^{0.22}$	$R^{-1}(\gamma_2/\gamma_3\gamma_{\text{IO}_3})^{0.22}$	$K_{\text{IO}_3}^{0.22, h}$	$K_{2, \text{IO}_3}^{0.22, i}$
0.435	46.4	$3.4 (\pm 0.1) \times 10^3$	$3.8 (\pm 0.2) \times 10^2$	$9.0 \pm 0.7$	0.743	0.323	$0.082 \pm 0.006$	$5.8 \pm (0.3) \times 10^2$	$12.1 \pm 0.9$
0.368	50.5	$4.4 (\pm 0.1) \times 10^3$	$4.2 (\pm 0.2) \times 10^2$	$1.5 \pm 0.8$	0.813	0.299	$0.077 \pm 0.006$	$5.8 \pm (0.3) \times 10^2$	$13.0 \pm 1.0$
0.319	54.9	$5.1 (\pm 0.2) \times 10^3$	$4.6 (\pm 0.2) \times 10^2$	$11.0 \pm 1.0$	0.859	0.274	$0.078 \pm 0.006$	$5.8 \pm (0.3) \times 10^2$	$12.8 \pm 1.0$
0.252	63.6	$6.6 (\pm 0.3) \times 10^3$	$5.4 (\pm 0.2) \times 10^2$	$12.2 \pm 1.0$	0.948	0.239	$0.078 \pm 0.007$	$5.9 \pm (0.2) \times 10^2$	$12.8 \pm 1.0$
0.199	74.4	$8.7 (\pm 0.5) \times 10^3$	$6.4 (\pm 0.3) \times 10^2$	$13.6 \pm 1.5$	1.047	0.208	$0.077 \pm 0.008$	$6.0 \pm (0.3) \times 10^2$	$13.0 \pm 1.3$

<sup>a</sup> Ionic strength values are about 5% larger than  $A$ . <sup>b</sup> Smoothed 25 °C value of  $\text{H}_4\text{L}\cdot\text{Cl}^{3+}$  formation constants adjusted to ionic strength  $\mu$  via eq 12 for  $\gamma_4/\gamma_3$  and the Debye-Hückel correlation for  $K_{\text{Cl}}$ . <sup>c</sup> Slopes, intercepts, and their uncertainties are derived from weighted least-squares regression based on  $\pm 0.004$  pH uncertainty. <sup>d</sup> Uncertainties are propagated from slope and intercept standard errors. <sup>e</sup> Values derived from eq 21 for  $\gamma_2/\gamma_3$  and the Debye-Hückel correlation. <sup>f</sup> Values represent the products of entries in columns 1 and 6. <sup>g</sup> Values represent the ratios of entries in column 6 to column 5. <sup>h</sup>  $K_{\text{IO}_3}^{0.22} = \text{intercept} \times (\gamma_4\gamma_{\text{IO}_3}/\gamma_3)^{0.22} \times (\gamma_3/\gamma_4\gamma_{\text{IO}_3})^{\mu}$ . <sup>i</sup>  $K_{2, \text{IO}_3}^{0.22}$  is the reciprocal of the entry in column 8.

Table V. Stepwise  $\text{H}_4\text{L}^{4+}$  Complexation Constants with  $\text{IO}_3^-$  at Various Temperatures

$T$	$K_{\text{IO}_3}^{0.22, 34}$	$K_{\text{IO}_3}^{0.22}$	$K_{2, \text{IO}_3}^{0.22, 34}$	$K_{2, \text{IO}_3}^{0.22}$
15	$5.47 (\pm 0.13) \times 10^2$	$5.7 \pm 0.2 \times 10^2$	$14.2 \pm 0.9$	$14.6 \pm 0.9$
25	$6.02 (\pm 0.20) \times 10^2$	$6.3 \pm 0.2 \times 10^2$	$12.1 \pm 0.7$	$12.4 \pm 0.7$
25	$5.75 (\pm 0.20) \times 10^2$	$6.0 \pm 0.2 \times 10^2$	$12.0 \pm 0.7$	$12.2 \pm 0.7$
35	$6.04 (\pm 0.20) \times 10^2$	$6.3 \pm 0.2 \times 10^2$	$11.8 \pm 0.7$	$12.0 \pm 0.7$
45	$6.57 (\pm 0.20) \times 10^2$	$6.9 \pm 0.2 \times 10^2$	$9.2 \pm 0.6$	$9.4 \pm 0.6$
55	$7.27 (\pm 0.22) \times 10^2$	$7.6 \pm 0.2 \times 10^2$	$8.7 \pm 0.5$	$8.9 \pm 0.5$

Table VI.  $\Delta H^*$  and  $\Delta S^*$  and Their Uncertainties<sup>b</sup> for Stepwise Binary and Ternary  $\text{H}_4\text{L}^{4+}$  Complexes of  $\text{IO}_3^-$ 

reaction	$\Delta H^*$ , kcal mol <sup>-1</sup>	$\Delta S^*$ , cal mol <sup>-1</sup> K <sup>-1</sup>
$\text{H}_4\text{L}^{4+} + \text{IO}_3^- = \text{H}_4\text{L}(\text{IO}_3)^{3+}$	$+1.3 \pm 0.1$	$+17.1 \pm 0.5$
$\text{H}_4\text{L}(\text{IO}_3)^{3+} + \text{IO}_3^- = \text{H}_4\text{L}(\text{IO}_3)_2^{2+}$	$-2.3 \pm 0.3$	$-2.8 \pm 1.1$

<sup>a</sup> Referred to an ionic strength of 0.22. <sup>b</sup> Uncertainties are standard error estimates derived by propagation-of-variance methods from regressions of  $\ln K$  vs.  $1/T$  and employing data in Table V.

ternary  $\text{H}_4\text{L}^{4+}$ ,  $\text{IO}_3^-$  complexes are comprised only by an  $\text{H}_4\text{L}(\text{IO}_3)_2^{2+}$  species.

Slopes and intercepts of Z vs.  $[\text{IO}_3^-]$  plots in Table IV may now be interpreted in terms of equilibrium constants as indicated in the last two columns of the table. We interpret the consistency of these values as confirming our conclusions regarding the absence of  $\text{H}_4\text{L}(\text{Cl})\text{IO}_3^{2+}$  complexes in these solutions.

Finally, the results of our temperature-dependent hexacyclen, iodate studies are interpreted in terms of complexation constants in Table V. We note the essential agreement of  $K_{\text{IO}_3}^{0.22}$  values determined in the variable ionic strength experiments at 25 °C ( $5.8 \times 10^2$  to  $6.0 \times 10^2$ ) compared with independently derived 25 °C values of  $6.3 (\pm 0.2) \times 10^2$  and  $6.0 (\pm 0.2) \times 10^2$ .  $K_{2, \text{IO}_3}^{0.22}$  values from the different experimental series show similar agreement. Values ranged between 12.1 and 13.0 in variable ionic strength experiments while  $K_{2, \text{IO}_3}^{0.22}$  values at 25 °C derived from measurements at  $\mu = 0.234$  were  $12.4 \pm 0.7$  and  $12.2 \pm 0.7$ .

Temperature-dependent  $K_{\text{IO}_3}^{0.22}$  and  $K_{2, \text{IO}_3}^{0.22}$  data served to estimate enthalpy and entropy changes for the stepwise complexation via a van't Hoff analysis. The results of these calculations along with standard error estimates derived from the regression analysis appear in Table VI.

### <sup>13</sup>C NMR Measurements

Before proceeding to interpret the results above, we sought some further information regarding the nature of hexacyclen complexation equilibria. In particular we wished to confirm the general picture of an acid/base equilibrium involving  $\text{H}_4\text{L}^{4+}$  and  $\text{H}_3\text{L}^{3+}$  which is perturbed by anion complexation and additionally to investigate the unusual slow pH response we have noted in all our pH potentiometric measurements. Thus, we determined proton-decoupled <sup>13</sup>C NMR spectra with a series of partially titrated 0.02 F hexacyclen solutions in 5% D<sub>2</sub>O/H<sub>2</sub>O. Sample solutions with similar ionic strengths contained 0.20 F Cl<sup>-</sup> as the only complexing anion. The spectra consist of two resonance lines for each of five solutions with  $1.5 \leq a \leq 2.6$  mol of NaOH/mol of  $\text{H}_6\text{L}^{6+}$ . The pH-independent signal at  $47.15 \pm 0.02$  ppm downfield of Me<sub>4</sub>Si is the major feature of the spectrum, and we assign this resonance to 12 equivalent carbon atoms in  $\text{H}_4\text{L}(\text{Cl})^{3+}$ . A second less intense resonance appears at 45.23 ppm at  $a = 1.5$  and is displaced downfield toward the major peak with increasing pH. We assign this resonance to 12 equivalent carbon atoms in the rapidly exchanging  $\text{H}_4\text{L}^{4+}$ ,  $\text{H}_3\text{L}^{3+}$  equilibrium mixture. We wish to obtain intrinsic chemical shifts for each of these species, and these values are derived below.

The observed chemical shift,  $\delta_{\text{obsd}}$ , due to two rapidly exchanging species  $\text{H}_4\text{L}^{4+}$  and  $\text{H}_3\text{L}^{3+}$ , is the concentration weighted average of the intrinsic chemical shift for each of the species which we denote by  $\delta_4$  and  $\delta_3$ , respectively.

$$[\text{H}_4\text{L}^{4+}]\delta_4 + [\text{H}_3\text{L}^{3+}]\delta_3 = \delta_{\text{obsd}}([\text{H}_4\text{L}^{4+}] + [\text{H}_3\text{L}^{3+}]) \quad (22)$$

Combining this equation with eq 3 yields

$$\delta_{\text{obsd}} \left\{ 1 + \frac{[\text{H}^+]}{K_3^*} \right\} = \delta_3 + \delta_4 \frac{[\text{H}^+]}{K_4^*} \quad (23)$$

Solution composition data, along with known values of  $K_3^*$  and  $K_4^*$ , allow estimation of  $[\text{H}^+]$  in each measurement solution, and these values along with corresponding  $\delta_{\text{obsd}}$  data yield estimates of  $\delta_3$  and  $\delta_4$  by means of regression analysis in accord with eq 23. These calculations yield  $\delta_4 = 45.25 \pm 0.05$  ppm and  $\delta_3 = 46.40 \pm 0.05$  ppm where the uncertainties represent standard error estimates derived from estimated  $\pm 0.03$  ppm uncertainties in  $\delta_{\text{obsd}}$  values.

A second series of measurements replaced  $\text{Cl}^-$  as the complexing anion with  $\text{NO}_3^-$ . Again the major feature of the spectra was a single pH-independent resonance, this time appearing at  $47.67 \pm 0.03$  ppm downfield of  $\text{Me}_2\text{Si}$ , which we assign to 12 equivalent carbon atoms in  $\text{H}_4\text{L}(\text{NO}_3)^{3+}$ . A second resonance corresponding to  $\text{H}_4\text{L}^{4+}$ ,  $\text{H}_3\text{L}^{3+}$  could be distinguished only as a shoulder at higher  $\alpha$  values. Apparently the concentration of  $\text{H}_4\text{L}^{4+}$  and  $\text{H}_3\text{L}^{3+}$  at lower pH values is too low to provide a clearly detectable signal in the more strongly complexing  $\text{NO}_3^-$  medium under the conditions of these experiments. Nevertheless, these spectra seem to conform to the pattern of those obtained with  $\text{Cl}^-$  which indicate a rapidly exchanging  $\text{H}_4\text{L}^{4+}$ ,  $\text{H}_3\text{L}^{3+}$  equilibrium mixture which is in very slow exchange equilibrium with an  $\text{H}_4\text{L}(\text{X})^{3+}$  complex. The essential linearity of the plot described by eq 23 confirms an earlier assumption that no complicating  $\text{H}_3\text{L}^{3+}$  species is present even at  $\text{H}^+$  concentrations as high as 0.012 M. Additionally, the single resonance line observed for  $\text{H}_4\text{L}(\text{Cl})^{3+}$  and  $\text{H}_4\text{L}(\text{NO}_3)^{3+}$  confirms the existence of only a single complex species and furthermore that no drastic conformational change or conformational "freezing" occurs upon  $\text{H}_4\text{L}^{4+}$  complexation or in proton exchange with  $\text{H}_3\text{L}^{3+}$  since these would presumably be reflected in marked displacements of the chemical shift or in line splitting.

These observations will be useful in our discussion of the thermodynamic data which follows.

### Discussion

We begin to interpret the present results by noting the unusually positive entropy change ( $+32 \text{ cal mol}^{-1} \text{ K}^{-1}$ ) accompanying  $\text{H}_4\text{L}^{4+}$  acidic dissociation. This value is to be compared to  $\Delta S$  values for acid dissociation of  $+5 \text{ cal mol}^{-1} \text{ K}^{-1}$  for tetraprotonated tetraethylenepentamine (tetren,  $\text{H}_2\text{NC}_2\text{H}_4(\text{NHC}_2\text{H}_4)_3\text{NH}_2$ )<sup>9</sup> and  $+15 \text{ cal mol}^{-1} \text{ K}^{-1}$  for tetraprotonated 1,4,8,11-tetraazacyclotetradecane (cyclam).<sup>10</sup> We associate the large positive entropy change accompanying hexacyclen  $\text{H}_4\text{L}^{4+}$  dissociation with substantially decreased ordering of solvent molecules around  $\text{H}_3\text{L}^{3+}$  and  $\text{H}_3\text{O}^+$  compared with  $\text{H}_4\text{L}^{4+}$ . Considering the fact that  $\text{H}_3\text{O}^+$  is known to cause extensive solvent ordering, which provides a negative contribution to  $\Delta S$  for the overall process of  $\text{H}_4\text{L}^{4+}$  dissociation, the entropy difference between  $\text{H}_4\text{L}^{4+}$  and  $\text{H}_3\text{L}^{3+}$  must be much larger than  $32 \text{ cal mol}^{-1} \text{ K}^{-1}$ . An entropy difference of this magnitude does not seem accountable in terms of internal degrees of freedom of  $\text{H}_3\text{L}^{3+}$  compared with  $\text{H}_4\text{L}^{4+}$  nor does it seem likely that this difference reflects an unusually weak solvent interaction of the  $\text{H}_3\text{L}^{3+}$  species. Instead, we propose the existence of a highly ordered solvent network around the  $\text{H}_4\text{L}^{4+}$  species which is substantially disrupted by acidic dissociation. This supposition seems also to be supported by an unusually positive  $\Delta H$  value for  $\text{H}_4\text{L}^{4+}$  acidic dissociation of  $+14.1 \text{ kcal mol}^{-1}$ . This value is to be compared to corresponding values of  $+7.9$  and  $+7.7 \text{ kcal mol}^{-1}$  for dissociation of tetraprotonated forms of tetren and cyclam. Thus, an extensive solvent network surrounding  $\text{H}_4\text{L}^{4+}$ , presumably formed through ( $>\text{HN}^+-\text{H}\cdots$ ) and ( $>\text{NH}\cdots$ ) bonding as well as cooperative interactions between bound solvent molecules, is disrupted through dissociation of  $\text{H}_4\text{L}^{4+}$  with concomitant loss in bonding. Decreased bonding interactions would

then be reflected as an endothermic contribution to  $\Delta H$  and account for the observed value. Furthermore, the bonding loss implied by  $\Delta H$  seems to preclude the possibility of some unusual property of  $\text{H}_3\text{L}^{3+}$  as accounting for the very positive  $\Delta S$  value. We make this inference by the following argument.

Suppose indeed that  $\Delta S^*$  reflects an unusually small interaction of  $\text{H}_3\text{L}^{3+}$  with the solvent compared with other triprotonated polyamine species. Such behavior would presumably result from unusually strong internal ( $\text{N}-\text{H}-\text{N}^+$ ) interactions in the triprotonated  $\text{N}_6$  ring system in place of solvent bonding. However, such interactions would provide a negative contribution to  $\Delta H$  for the dissociation reaction and seem unlikely to allow for the observed  $\Delta H$  value which is more positive by 6 or 7  $\text{kcal mol}^{-1}$  than that observed for related reactions. Consequently, we reject the hypothesis of unusual interactions of  $\text{H}_3\text{L}^{3+}$  as accounting for properties of  $\text{H}_4\text{L}^{4+}$  dissociation.

Finally, we note the  $^{13}\text{C}$  NMR data pertaining to  $\text{H}_4\text{L}^{4+}$  and  $\text{H}_3\text{L}^{3+}$ . The single resonance observed for these rapidly exchanging equilibrium species as well as the rather small chemical shift displacement due to  $\text{H}_3\text{L}^{3+}$  protonation ( $\delta_4 = 45.25$  ppm,  $\delta_3 = 46.40$  ppm) seems to preclude any substantial difference of conformation or internal constraint in these species. Instead, the  $^{13}\text{C}$  resonance data are readily accounted for by solvation differences. Thus, while an  $\text{H}_4\text{L}^{4+}$  solvent network provides a useful means of interpreting anion complexation reactions, detailed below, formation of such a network has a relatively minor effect on carbon atoms in the macrocycle skeleton.

Thermodynamic data in Tables II and VI seem to suggest three distinct classes of  $\text{H}_4\text{L}^{4+}$ , anion complexes. The first of these is comprised by  $\text{Cl}^-$ ,  $\text{F}_3\text{CCO}_2^-$ , and  $\text{C}_6\text{H}_5\text{SO}_3^-$  complexations which feature large positive  $\Delta S^*$  values of  $+24$ ,  $+26$ , and  $+25 \text{ cal mol}^{-1} \text{ K}^{-1}$ , respectively, and whose formation is substantially endothermic with  $\Delta H^* = +4.9$ ,  $+6.5$ , and  $+6.6 \text{ kcal mol}^{-1}$ . Thus, these reactions are entropy driven but feature a substantial loss in bonding interactions. A second, different class of complexations is represented by  $\text{NO}_3^-$  and 1:1  $\text{IO}_3^-$  reactions with  $\text{H}_4\text{L}^{4+}$  which are characterized by smaller positive  $\Delta S^*$  values of  $+12$  and  $+17 \text{ cal mol}^{-1} \text{ K}^{-1}$  with corresponding  $\Delta H^*$  values of  $-0.4$  and  $+1.3 \text{ kcal mol}^{-1}$ . These complexations, like those above, are entropy driven but proceeded with only minor changes in bonding interactions. Finally, a third class of complexation reactions which, unlike those above, are exothermic and have unfavorable  $\Delta S^*$  values seem to be represented by  $\text{H}_4\text{L}^{4+}$  reaction with  $\text{ClO}_4^-$  and ternary  $\text{H}_4\text{L}-(\text{IO}_3)_2^{2+}$  formation.  $\Delta H^*$  values of  $-2.5$  and  $-2.3 \text{ kcal mol}^{-1}$ , respectively, reflect enthalpy-driven reactions which result in net ordering of product solutions compared with reactants.

We rationalize this behavior in terms of a stepwise disruption of the  $\text{H}_4\text{L}^{4+}$  solvation sphere. In this connection we cite earlier X-ray crystallographic evidence<sup>5,11</sup> about  $\text{H}_4\text{L}(\text{NO}_3)^{3+}$  and  $\text{H}_4\text{L}(\text{Cl})^{3+}$  structures which indicate direct  $>\text{N}^+-\text{H}-\text{Cl}^-$  bonding interaction in the latter complex while  $\text{NO}_3^-$  interactions with  $\text{H}_4\text{L}^{4+}$  are mediated by a water molecule. Admittedly, the X-ray data are pertinent to solid-phase structures and do not necessarily describe the solution properties of these complexes. Nevertheless, comparison of these results with thermodynamic  $\Delta H^*$  and  $\Delta S^*$  data points to direct hydrogen bonding interactions between chloride ions and hexacyclen ammonium groups and, consequently, to release of water previously bonded to  $\text{H}_4\text{L}^{4+}$ . The similar values of  $\Delta S^*$  for  $\text{F}_3\text{CCO}_2^-$  and  $\text{C}_6\text{H}_5\text{SO}_3^-$  complexations obtained here to  $\Delta S^*$  for  $\text{Cl}^-$  complexation seem to indicate a similar interaction mechanism, namely, a close association involving substantial stripping of the  $\text{H}_4\text{L}^{4+}$  solvation sphere. We interpret the somewhat more endothermic  $\Delta H^*$  values for  $\text{F}_3\text{CCO}_2^-$  and  $\text{C}_6\text{H}_5\text{SO}_3^-$  complexation compared with  $\text{Cl}^-$  as indicating that  $>\text{N}^+-\text{H}-\text{O}_3\text{S}-\text{C}_6\text{H}_5$  and  $>^+-\text{H}-\text{O}_2\text{CCF}_3$  bonding interactions are somewhat weaker than  $>\text{N}^+-\text{H}-\text{Cl}^-$  bonding. It seems likely that a number of factors contribute to this result, including differing solvation properties of the uncomplexed anions and charge distribution on the anion species. A variety of interesting spec-

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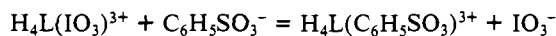
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ulations regarding bonding differences in these complexes are possible. However, it seems clear that  $H_4L^{4+}$  complexation of  $Cl^-$ ,  $C_6H_5SO_3^-$ , and  $F_3CCO_2^-$  relies on expulsion of strongly bound inner-sphere water with subsequent increase in entropy as the driving force in these reactions.

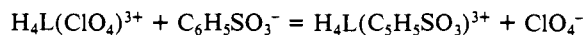
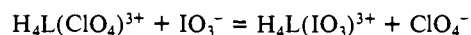
We now turn to  $NO_3^-$  and  $IO_3^-$  complexations of  $H_4L^{4+}$  and interpret bonding in these complexes in terms of a previously proposed water-mediated complex. That is, we assign to these complexes structures in which the inner  $H_4L^{4+}$  solvation sphere is left at least partially intact and note that this situation seems to result in optimum complex formation. The complexations are entropy driven but seem to involve little or no change in net bond strength comparing  $H_4L^{4+}$ ,  $NO_3^-$ , and  $IO_3^-$  bonding with  $H_4L^{4+}$ , water bonding. It appears that these anions do not form sufficiently strong bonds with  $>N^+-H$  groups of  $H_4L^{4+}$  to displace inner-sphere water and so their complexation reactions do not suffer from the large positive  $\Delta H^*$  contribution which we connect with displacement of inner-sphere water. This is most clearly demonstrated by examining the metathesis reaction



for which  $\Delta H^* = +5.3 \text{ kcal mol}^{-1}$  and  $\Delta S^* = +8 \text{ cal mol}^{-1} \text{ K}^{-1}$ . The fairly positive value of  $\Delta S^*$  suggests release of bound solvent from the  $H_4L(IO_3)^{3+}$  complex, but this is accompanied by a substantial loss in bonding interactions in the  $H_4L(C_6H_5SO_3)^{3+}$  complex which results from solvent release. The net effect of this solvent release is an unfavorable free energy for this reaction. Thus, because direct bonding interaction of  $C_6H_5SO_3^-$  is favored over a solvent-mediated interaction, this anion forms only weak complexes with  $H_4L^{4+}$ . In contrast,  $NO_3^-$  and  $IO_3^-$  ions, unable to penetrate the  $H_4L^{4+}$  inner-solvation sphere, rely on solvent-mediated interactions to form strong  $H_4L^{4+}$  complexes.

We continue the discussion by contrasting the entropy-driven reaction schemes characterized above with hexacyclen complexations resulting in  $H_4L(ClO_4)^{3+}$  and  $H_4L(IO_3)_2^{2+}$  products. Formation reactions of these complexes are exothermic and have small negative  $\Delta S^*$  value. It seems reasonable to characterize these species as "outer-sphere" complexes where electrostatic interactions represent the primary binding force.  $\Delta S^*$  values of  $-3.8 \pm 2.1$  and  $-2.8 \pm 1.1 \text{ cal mol}^{-1} \text{ K}^{-1}$  for  $H_4L(ClO_4)^{3+}$  and  $H_4L(IO_3)_2^{2+}$  formation, respectively, do not differ significantly from the value of  $-R \ln 2$  ( $= -1.4 \text{ cal mol}^{-1} \text{ K}^{-1}$ ) expected for an ideal bimolecular coupling reaction of the form  $A + B = AB$ , and we conclude that these complexation reactions do not result in significant solvent reorganization. Indeed, it might be expected that  $ClO_4^-$  ions, generally presumed to be nonpolarizable and poorly solvated, would not participate in strong hydrogen-bonding interactions with  $H_4L^{4+}$ . Consequently, the only  $H_4L^{4+}$  interaction with  $ClO_4^-$  would involve electrostatic attraction between the ions. That  $IO_3^-$  ions appear to have a similar interaction with  $H_4L-(IO_3)^{3+}$  is somewhat puzzling except in the light of the previous discussion of  $H_4L^{4+}$ ,  $IO_3^-$  complexation. There we ascribed bonding in  $H_4L(IO_3)^{3+}$  complex species to expulsion of outer-sphere water. The  $H_4L(IO_3)^{3+}$  complex formed in this way would presumably carry only a small solvation sphere which would allow relatively close approach of a second  $IO_3^-$  ion with consequent electrostatic binding.

The interpretation of bonding in  $H_4L(ClO_4)^{3+}$  above along with thermodynamic  $\Delta H^*$  and  $\Delta S^*$  data serve to confirm our model of other  $H_4L^{4+}$  complexations as follows. We consider the reactions below.



$\Delta H^*$  and  $\Delta S^*$  for the first of these reactions are  $+3.8 \text{ kcal mol}^{-1}$  and  $+21 \text{ cal mol}^{-1} \text{ K}^{-1}$ , respectively, while corresponding values for the second displacement reaction are  $+9.1 \text{ kcal mol}^{-1}$  and  $+28 \text{ cal mol}^{-1} \text{ K}^{-1}$ . In both reactions we associate large positive entropy changes with expulsion of part of the  $H_4L^{4+}$  solvation sphere, and this factor provides the net driving force in both reactions. Because it seems unlikely that the endothermic  $\Delta H^*$  value of  $3.8 \text{ kcal mol}^{-1}$  can be accounted for by differences in electrostatic interaction between  $IO_3^-$  and  $ClO_4^-$  with  $H_4L^{4+}$  and because  $ClO_4^-$  is known to be a poor hydrogen bond acceptor, and furthermore because  $IO_3^-$  is not particularly strongly solvated, we associate bonding loss in this complex primarily with loss of  $H_4L^{4+}-H_2O$  bonding. Thus, a loss of rather weakly bound outer-sphere water results in a large entropy increase balanced by a relatively small loss in net bonding.

Interpreted in the same way, the second anion transfer reaction suggests a solvent stripping reaction in which  $H_4L^{4+}-H_2O$  bonding suffers to a much greater extent than in the former case. This we associate with loss of more strongly bound solvent from  $H_4L^{4+}$ , i.e., inner-sphere solvation water.

We conclude the present discussion by noting that our studies seem to indicate that steric properties of the anion substrates do not play an important role in these reactions. Instead complexation selectivity seems to depend primarily on hydrogen-bonding properties and inner-sphere vs. outer-sphere binding. In this connection we note the X-ray crystallographic results of ref 5. In that study of  $H_4L(NO_3)_2Cl_2 \cdot 2H_2O$ ,  $NO_3^-$  ions were external to the  $H_4L^{4+}$  ring and  $Cl^-$  ions, while closer to the ring plane than  $NO_3^-$ , did not penetrate the cavity of  $H_4L^{4+}$ . Later studies<sup>11</sup> with other hexacyclen salts gave similar results. We conclude that the structures of the solution complexes are likely to be similar in the sense that anion substrates probably do not penetrate the hexacyclen cavity. Anion penetration would likely result in a high degree of steric specificity which we have not observed.

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**Registry No.** Hexacyclen, 296-35-5;  $C_6H_5SO_3^-$ , 3198-32-1;  $F_3CCO_2^-$ , 14477-72-6;  $ClO_4^-$ , 14797-73-0;  $IO_3^-$ , 15454-31-6.