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# NMR and Potentiometric Determination of the High p*K* Values and Protonation Sequence of Dipyridino-hexaaza-28-Crown-8 and Its Interactions with Selenate, Sulfate and Nitrate Ions in Aqueous Solution

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**Abstract.** The aqueous protonation and anion-binding ($SeO_4^{2-}$, $SO_4^{2-}$, and $NO_3^-$) constants of the macrocyclic polyamine ligand, dipyridino-hexaaza-28-crown-8(L), were measured in 0.1M KCl using a potentiometric titration technique. The protonation sequence of the aza groups of L was studied in $D_2O$ from the chemical shifts of the nonlabile protons so as to find the charge distribution geometry as a function of pD. The study indicates that in 0.1M KCl fully protonated L forms stable 1 : 1 complexes with $SeO_4^{2-}$ ($\log K = 3.68$) and $SO_4^{2-}$ ($\log K = 3.55$), but not with $NO_3^-$ ($\log K < 1.5$). All of the amine p*K* values were above 6.3, thus allowing the use of the protonated form of this ligand over a wide pH range.

**Key words.** Macrocyclic polyamine, inorganic oxa-anions, equilibrium constants, protonation sequence, NMR pH-titration.

## 1. Introduction

The design of organic receptor molecules capable of the selective molecular recognition of anionic substrates is a subject of great theoretical and practical interest. Successful development of such host molecules capable of high anion selectivities and large anion binding affinities would be of interest to workers in biological [1–3], environmental [4–6], industrial [5], culinary water [4–6], and separations [7] chemistry. Highly protonated polyamine macrocycles are among the most promising candidates [8, 9] for receptors capable of strong and selective interaction with anionic species. During the past two decades, many workers have investigated the principles which govern anion coordination chemistry, in particular where protonated polyammonium macrocycles are the receptors [1–3, 8–19].

The purpose of the present study was to learn whether or not the incorporation of polyammonium binding sites, propylene bridging groups, and rigid aromatic spacers into macrocycle hosts would produce effective anion receptors as has been done in the preparation of cationic bicyclic hosts [16]. An important feature for effective anion complexation is to design the macrocycle structure so as to realize a compromise between the pH values required for full protonation of the ligand and

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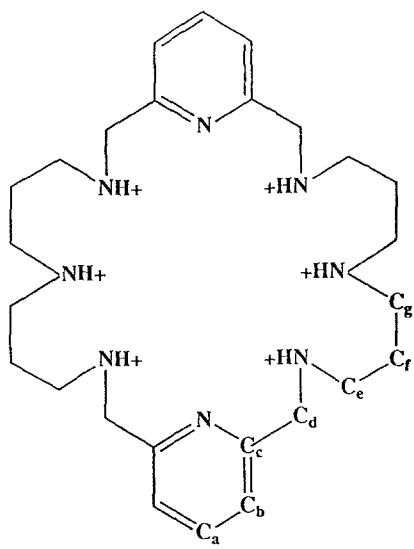
for full ionization of the anion. In this study, propylene rather than ethylene bridging groups [17] were chosen in order that all of the polyammonium binding sites would be protonated in the near neutral pH range. This feature should optimize conditions for anion-receptor interaction since a wide pH range would be available in which both fully-protonated ligand and fully-ionized anion are present. Among the spacers available to increase cavity rigidity while maintaining cavity hydrophilicity, aromatic nitrogen heterocycles are considered to be the best [18]. Increasing the rigidity of the protonated host cavity often increases selectivity for guests.

The protonation and anion binding constants were obtained using a potentiometric titration technique. The protonation sequence of L was obtained using a $^1H$ NMR pD titration procedure. The determination of the protonation sequence of this macrocycle should provide important structural information concerning its complexation with anions as a function of pH.




**Protonated dipyridino-hexaaza-28-crown-8 ($H_6L^{6+}$)**

## 2. Experimental

### 2.1. MATERIALS

The preparation of L has been described [20]. $HNO_3$, KOH and the metal salts ($Na_2SO_4$, $Na_2SeO_4$, $NaNO_3$, and NaCl) were purchased and used without further purification. Spectral grade $D_2O$ (99.7%, Merck) was used for the NMR study.

### 2.2. E.M.F. MEASUREMENTS

All semimicro potentiometric titrations were carried out in a sealed, thermostated vessel (6 mL, 25° ± 0.1°) under a $CO_2$-free nitrogen atmosphere using a semi-automatic titrator (Metrohm) or a fully-automatic potentiometric titration unit of our

own design. $CO_2$-free standard 0.1M KOH was used as the titrant. The hydrogen ion concentration was measured using an Orion–Ross double junction semimicro combination glass electrode and an Orion 701A potentiometer adjusted with standard $HNO_3$ and KOH to read E.M.F. values directly.

Standard electrode potentials, $E^0$, and $\log K_n$ values for the protonation of L were determined by titrating an $HNO_3$ solution (3–5 mL) containing fully protonated ligand with standard KOH. Log $K$ values for anion ($A^{n-}$)—L interactions in 0.1M KCl were computed from the data obtained by titrating acidified solutions (3–5 mL) containing $A^{n-}$ and L with KOH. Titrations were performed in triplicate. E.M.F. values were reproducible to within 0.3 mV.

All calculations concerning the calibration of the electronic system, the purity of the ligands, and $\log K$ values were performed using the computer program SUPERQUAD [21] which refines the parameters of an acid–base potentiometric titration. Distribution diagrams were obtained bv means of the computer program DISDI [22].

### 2.3. NMR SPECTRAL MEASUREMENTS

Solutions of L for $^1H$ and $^{13}C$ NMR pD titrations were prepared in $D_2O$ and the pD was adjusted with DCl (Sigma) or $CO_2$-free NaOD (Sigma). Several tens of milligrams of L were dissolved in 0.5 mL of $D_2O$. Appropriate amounts of concentrated DCl solution were added to ensure the quantitative presence of the hexaprotonated form of L without adding a significant excess of acid. Full protonation and the insignificant excess of acid were confirmed using pD measurements and the p$K$ values. This solution was then titrated with concentrated $CO_2$-free NaOD. After each NaOD addition, a $^1H$ NMR spectrum was recorded. The initial and final pD values were determined using the same set-up as was used in the E.M.F. measurements and with the use of the equation pD = pH + 0.4 [23]. All $^1H$ and broad-band proton-decoupled $^{13}C$ NMR spectra were recorded on a Varian Gemini 200 MHz (50 MHz) spectrometer. For the anion binding NMR study, the acidified solution of L was titrated with $Na_2SeO_4$ solution. The $^{13}C$ spectrum was taken after each aliquot titration, using $t$-butyl alcohol as an internal standard.

## 3. Results and Discussion

Log $K$ values valid in 0.1M KCl for the interaction of L with $H^+$ and of the various protonated forms of L with $SeO_4^{2-}$, $SO_4^{2-}$, and $NO_3^-$ are given in Table I. A binding stoichiometry of one anion per macrocycle was confirmed from potentiometric titration curve computer analysis in all cases and was found by $^{13}C$ NMR spectroscopy in the case of $SeO_4^{2-}$.

It is necessary to know the protonation sequence of L so that the charge distribution patterns as a function of pH can be determined. This microscopic protonation scheme can be obtained by following the NMR chemical shifts of the ligand methylenic protons as a function of pH. The protonation of a basic site of a polyamine compound in aqueous solution leads to a deshielding of the adjacent methylene protons [25]. The aliphatic proton peaks shifted 0.7–0.9 ppm upon

Table I. Conditional consecutive formation constants[a] (Log $K$) for $nH^+$—L interaction and for $H_nL^{n+}$ interactions with $SeO_4^{2-}$,[b] $SO_4^{2-}$,[c] and $NO_3^-$

| | $(H_6^{6+}L)$ | $(H_5^{5+}L)$ | $(H_4^{4+}L)$ | $(H_3^{3+}L)$ | $(H_2^{2+}L)$ | $(H^+L)$ |
|---|---|---|---|---|---|---|
| $H^+$ | 6.38 | 6.97 | 7.35 | 7.93 | 9.32 | 9.97 |
| $SeO_4^{2-}$ | 3.68 | 3.30 | 2.69 | 1.4(5) | ND | ND |
| $SO_4^{2-}$ | 3.55 | 3.30 | 2.79 | 1.5(5) | ND | ND |
| $NO_3^-$ | ND | ND | ND | ND | ND | ND |

[a]Log $K$ values are valid in 0.1M KCl. ND means 'not determined' because the limit of sensitivity for log $K$ determinations by potentiometry is less than about 1.5. Standard deviations of the log $K$ values are less than 0.010 unless indicated otherwise.

[b]p$K$a($HSeO_4^-$) value (1.26, $\mu = 0.1$) was derived from those in Reference [24] and Debye–Hückel theory.

[c]p$K$a($HSO_4^-$) = 1.55 ($\mu = 0.1$) [24].

[d]$E^0$ and p$K_w$ were determined as 400.0 ± 0.1 mV and 13.541 ± 0.002, respectively.

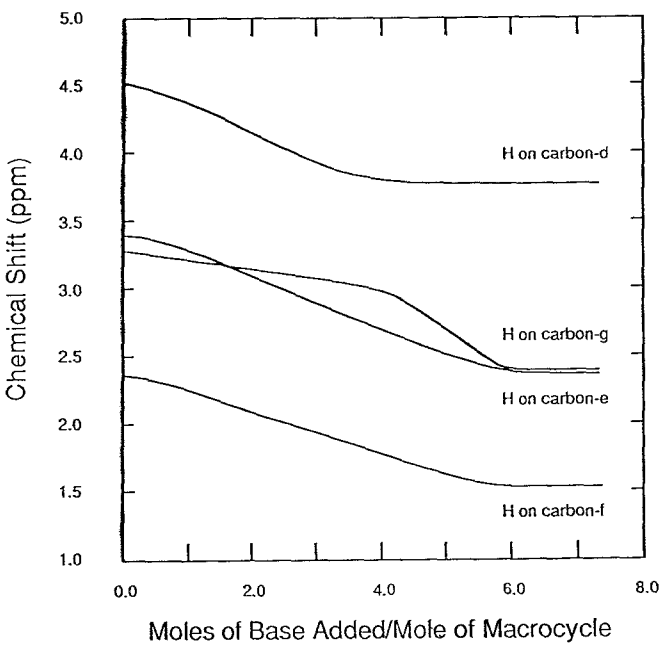



Fig. 1. Plot of chemical shift (ppm) for the indicated methylenic protons of $D_6L^{6+}$ vs. moles of NaOD added.

addition of base as shown in Figure 1. The chemical shift of the peak which corresponds to the protons attached to carbon 'd' varies in nearly linear fashion with the addition of base until four equivalents of base have been added. The chemical shift of this peak then remains reasonably constant. This result suggests that the four aza nitrogen atoms adjacent to the pyridine groups (see structure) are deprotonated first. This is confirmed by noting that the peak which corresponds to

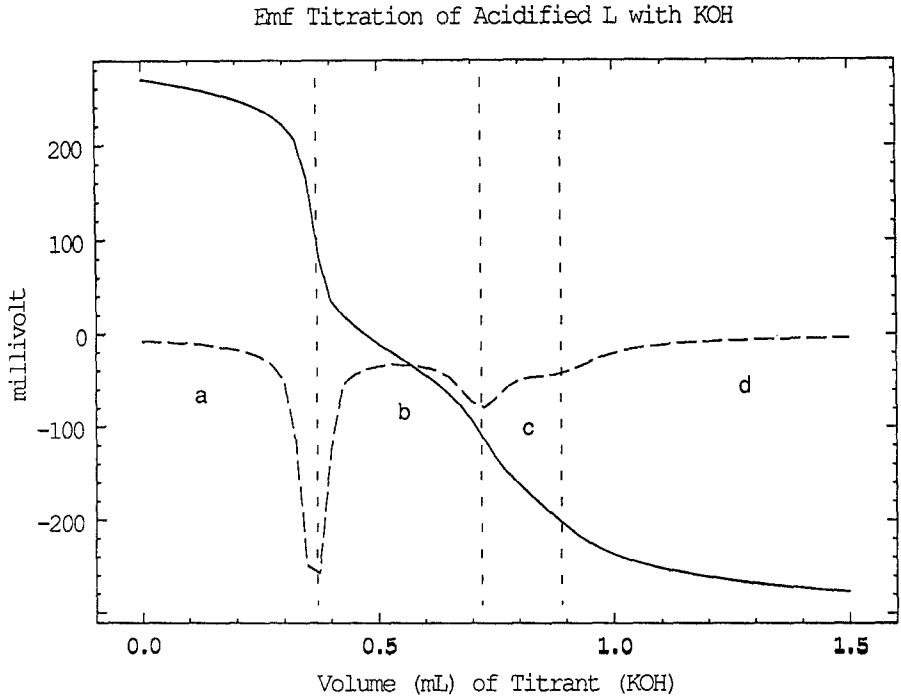



Fig. 2. Potentiometric titration curve of a solution containing 0.00161M L, 0.01602M HCl, and 0.1M KCl with 0.0881M KOH at 25°C. Dashed line is the first derivative with respect to volume.

the protons bonded to carbon 'g' shifts most rapidly in the range of 4–6 equivalents. Furthermore, the buffer regions b and c of the potentiometric titration curve in Figure 2 correspond to four and two equivalents of base, respectively. The upper buffer region c is well defined on the first derivative with respect to volume curve of the emf titration curve.

The $H_6L^{6+}$, $H_5L^{5+}$, and $H_4L^{4+}$ species form stable complexes (Table I) with the oxa-anions $SeO_4^{2-}$ and $SO_4^{2-}$ in aqueous solutions in the neutral pH range in 0.1M KCl. Complexation of $NO_3^-$ was not detected, probably because 0.1M KCl was used as the supporting electrolyte, resuting in competition between $Cl^-$ and $NO_3^-$ for the protonated ligand. Log $K$ values for the interaction of $Cl^-$ with other polyammonium cations range from 1.5 to 2.5 log $K$ units depending upon the degree of protonation of the polyamine macrocycle [16, 26]. It is apparent that log $K$ values for protonated L interactions with the divalent anions $SeO_4^{2-}$ and $SO_4^{2-}$ are much larger than those for interactions with the monovalent anions, $NO_3^-$ and $Cl^-$. The absolute log $K$ values of $H_6L^{6+}$ with $SeO_4^{2-}$ and $SO_4^{2-}$ will be at least larger than 5. These strong interactions with divalent anions indicate clearly an electrostatic component in polyammonium macrocycle–anion recognition.

The complexation of $SeO_4^{2-}$ was studied by following the changes in $^{13}C$ NMR shifts on the addition of $SeO_4^{2-}$ to a solution of the polyammonium ligand at pD $\approx$ 3. The $^{13}C$ NMR spectral shifts of the aromatic carbons were observed, while the signals of the aliphatic carbons show weak diamagnetic shifts. A 1 : 1 complexation stoichiometry for $SeO_4^{2-}$ interaction with $H_6L^{6+}$ was confirmed, although a

sharp break point was not seen because log $K$ is less than $10^5$. None of the $^{13}C$ or $^1H$ signals is split during the selenate titration. The lack of NMR signal splitting may result from the averaging of the signals due to a fast exchange mechanism of the protonation sites. However, if the interaction were an exclusive one, additional $SeO_4^{2-}$ interaction beyond the 1:1 stoichiometry would be expected. This argument suggests that the symmetry of the ligand is preserved in the anion complex indicating a possible inclusion of $SeO_4^{2-}$ in the macrocycle cavity.

In conclusion, electrostatic interactions play a major role in the anion binding strength and selectivity. High charge density in the anion receptors can be achieved by organizing the ammonium sites with propylene and pyridine spacers. Thus, rigidity is introduced by the pyridine groups and elevated p$K$ values of the propylene spacers insure full protonation of the ligand in the low pH range 1–3 [8]. The strong complexation of this cyclic polyammonium ligand with anions provides a rationale for the nature of anion complexation. Reactions of lower stability have been observed with similar acyclic polyamines [17]. The acyclic structures do not assemble a high charge density zone as do the cyclic structures. Therefore, the acyclic structures provide less of the attraction between anionic and cationic species which is necessary to overcome ionic solvation. These preliminary results also suggest that the highly protonated polyamine macrocycles should be able to bind a variety of oxo-anions and might be used as separation reagents for many metallic oxo-anions and metal complex anions.

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## References

1. M. W. Hosseini, J. M. Lehn and M. P. Mertes: *Helv. Chim. Acta* **66**, 2454 (1983).
2. E. Kimura, T. Koike and M. Kodama: *Chem. Pharm. Bull. Jpn.* **32**, 3569 (1984).
3. E. Kimura: 'Macrocyclic Polyamines as Biological Cation and Anion Complexones – An Application to Calculi Dissolution', in *Top. Curr. Chem.* **128**, 113 (1985).
4. *Drinking Water and Health*, National Research Council, National Academy of Sciences, Washington, D.C., 1977.
5. S. E. Carson and K. K. Hank: *Ultrapure Water* **4**, 47 (1987).
6. F. W. Pontius: *J. Am. Water Works Assoc.* **82**, 32 (1990).
7. *Separation and Purification: Critical Needs and Opportunities*, Report to the National Research Council by the Committee on Separation Science and Technology, C. J. King, Chairman, National Academy Press, Washington, D.C., 1987.
8. R. M. Izatt, K. Pawlak, R. L. Bruening, J. S. Bradshaw: *Chem. Rev.* **91**, 1721 (1991).
9. A. Bencini, A. Bianchi, E. G. Espana, M. Giusti, S. Maugan, M. Micheloni, P. Orioli and P. Paoletti: *Inorg. Chem.* **26**, 3902 (1987).
10. C. H. Park and H. E. Simmons: *J. Am. Chem. Soc.* **90**, 2431 (1968).
11. E. Graf and J.-M. Lehn: *J. Am. Chem. Soc.* **98**, 6403 (1976).
12. B. Dietrich, M. W. Hosseini, J.-M. Lehn and R. B. Sessions: *J. Am. Chem. Soc.* **103**, 1282 (1981).
13. F. P. Schmidtchen: *Top. Curr. Chem.* **132**, 101 (1986).
14. A. Bianchi, M. Micheloni and P. Paoletti: *Inorg. Chim. Acta* **151**, 269 (1988).
15. M. W. Hosseini and J.-M. Lehn: *Helv. Chim. Acta* **70**, 1312 (1987).
16. M. W. Hosseini and J.-M. Lehn: *Helv. Chim. Acta* **71**, 749 (1988).

17. E. Kimura, A. Sakonaka, T. Yatsunami and M. Kodama: *J. Am. Chem. Soc.* **103**, 3041 (1981).
18. M. W. Hosseini, J. Comarmond and J.-M. Lehn: *Helv. Chim. Acta* **72**, 1066 (1989).
19. F. P. Schmidtchen, A. Gleich and A. Schummer: *Pure Appl. Chem.* **61**, 1535 (1989).
20. K. E. Krakowiak, J. S. Bradshaw, W. Jiang, N. K. Dalley, G. Wu and R. M. Izatt: *J. Org. Chem.* **56**, 2675 (1991).
21. P. Gans, A. Sabatini, and A. Vacca: *J. Chem. Soc. Dalton Trans.* 1195 (1985).
22. R. Maggiore, S. Musumeci and S. Sammartano: *Talanta* **23**, 43 (1976).
23. K. Mikkelsen and S. O. Nielson: *J. Phys. Chem.* **64**, 632 (1960).
24. E. Martell and R. M. Smith: *Critical Stability Constants*, Plenum Press, New York, NY, 1982.
25. J. L. Sudmeier and C. N. Reilley: *Anal. Chem.* **36**, 1699 (1964).
26. J. Cullinane, R. I. Gelb, T. N. Margulis and L. J. Zompa: *J. Am. Chem. Soc.* **104**, 3048 (1982).