- 19. R. P. Carter, M. M. Crutchfield, and R. R. Irani, Inorg. Chem., 6, 943 (1967).
- 20. A. E. Martell and R. M. Smith, Critical Stability Constants. Amino Acids, New York, London (1974), Vol. 1.
- 21. M. Irving and R. G. P. Williams, J. Chem. Soc., 3192 (1953).
- 22. K. B. Yatsimirskii, Zh. Neorg. Khim., <u>1</u>, 2451 (1956).
- 23. L. I. Zompa, Inorg. Chem., <u>17</u>, 2531 (1978).
- 24. T. Ya. Medved', M. V. Rudomino, N. M. Dyatlova, and M. I. Kabachnik, Izv. Akad. Nauk SSSR, Ser. Khim., 1211 (1968).
- 25. R. P. Carter, R. L. Carroll, and R. R. Irani, Inorg. Chem., 6, 939 (1967).

SYNTHESIS AND ACID-BASE AND COMPLEX-FORMING PROPERTIES OF 1,4,7,10-TETRAKIS(DIHYDROXYPHOSPHORYLMETHYL)-1,4,7,10-TETRAAZACYCLODODECANE

I. M. Kabachnik, T. Ya. Medved', F. I. Bel'skii, and S. A. Pisareva UDC 542.91 + 541.49:547.1'118

Recently we synthesized the first representative of a new group of complexones the phosphorylated macrocyclic polyalkylene polyamines — viz., 1,4,7-tris(dihydroxyphosphoryl-methyl)-1,4,7-triazacyclononane, I [1], which is distinguished by its high selectivity for cations of small radius, in particular Mg^{2+} , and the unusually large stability constant for its Zn^{2+} complex.



The present work reports the synthesis and study of the next representative of this group of complexones, viz., 1,4,7,10-tetrakis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazacyclododecane, II. It was synthesized by the Moedritzer-Irani reaction from cyclic tetraethylenetetramine hydrochloride, formalin, and phosphorous acid in the presence of HC1:



The cyclic tetraethylenetetramine has been described, but without a method of synthesis [2]. This required the improvement of the intermediate steps of the synthesis of 1,4,7,10-tetrakis(p-toluenesulfonyl)-1,4,7,10-tetraazacyclododecane, and the development of a method for separating the cyclic tetraethylenetetramine.

With cyclohexylamine, complexone II gives a crystalline salt, (II) $\cdot 2C_{e}H_{11}NH_{2}$; with methyl iodide, it gives the methyl iodide (II) $\cdot MeI$.

The acid-base and complex-forming properties of II were studied by means of potentiometric titration in water.

Table 1 compares the dissociation pKa of complexones I and II.

The dissociation in the first buffer region (0 < a < 2, where a = moles of KOH per mole of acid) of two protons (Fig. 1, curve 1) permits us to propose a zwitterion structure

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 4, pp. 844-849, April, 1984. Original article submitted October 14, 1983.

TABLE 1. Concentration Dissociation Constants (pK_a) of Complexones II and I (25°; ionic strength μ = 1.0, 1.0 M KNO₃)



Fig. 1. Neutralization curves of acid II (1) by itself and in the presence of cations: (2) Mg^{2+} , (3) Sr^{2+} , (4) Ca^{2+} , (5) Cd^{2+} , (6) Co^{2+} , (7) Cu^{2+} , (8) Zn^{2+} .

for the complexone in aqueous solution. The very high pK_a values of the last two protons compel us to propose a dual (or triple) betaine structure.

The complex-forming properties of II were studied for a wide range of cations.

Titration of II with Me₄NOH solution in Me₄NCl medium in the presence of alkali metals (Li⁺, Na⁺, K⁺) showed that in the 6 < a < 8 region these metals form unstable complexes, the sequence of whose stability is Li⁺ > Na⁺ > K⁺. Numerical values of the stability constants could not be calculated because they are so small. Since K⁺ forms a complex whose log stability constant is <1, the use of KNO₃ to maintain a constant ionic strength does not introduce any significant experimental error. But since some complexation with K⁺ does occur, the pK₇ and pK₈ values for II are actually somewhat larger than those shown in Table 1.

The rare earths (Nd³⁺, Eu³⁺, Sm³⁺, Tb³⁺, Dy³⁺, Ho³⁺, Er⁺, Yb³⁺) and Th⁴⁺ form water-insoluble complexes that precipitate when KOH is added to solutions of the acid and metal nitrate. La³⁺, for which the stability constant of the complex could be calculated, forms an insoluble chelate in the 3 < a < 6 region. The other cations form water-soluble complexes. The curves for neutralization of II in the presence of some of the cations studied are shown in Fig. 1.

Table 2 gives the log stability constants for II complexes and, for comparison, for the ML complexes of I.

Previously with I [1] the formation of very stable complexes has been observed with cations of small ionic radius. Since in II the cyclic segment is of larger size than in I, we might expect a shift in maximum complexation efficiency toward cations of large ionic radius. Actually our results show that the general tendency in the complexing capability of II is to form more stable chelates with relatively large-size cations.

Cation	Ionic radius, Å*	¢	Complexone I				
		MH4L	MH3L	MH2L	MHL	ML	ML
$\begin{array}{c} Mg^{2+}\\ Ca^{2+}\\ Sr^{2+}\\ Ba^{2+}\\ Cu^{2+}\\ Co^{2+}\\ Ni^{2+}\\ Mn^{2+}\\ Zn^{2+}\\ Cd^{2+}\\ Hg^{2+} \end{array}$	0,66 0,99 1,12 1,34 0,72 0,72 0,69 0,80 0,74 0,97 1,10	2,2 - 10,6 6,8 6,6 4,6 9,2 10,3 10,7	$\begin{array}{c} 3,1\\ 3,1\\ -\\ 13,3\\ 9,2\\ 8,4\\ 7,1\\ 11,7\\ 13,5\\ 14,3\\ \end{array}$	3,2 4,7 3,8 1,9 15,6 11,8 10,7 8,8 15,1 15,3 16,7	6,0 7,7 7,2 6,1 20,7 16,5 14,7 12,9 19,9 19,9 21,1	7,3 10,3 9,8 8,8 25,4 20,8 19,0 16,9 24,8 22,9 25,1	11,0 6,4 5,3 4,4 21,3 19,7 19,4 16,6 24,9 19,7 23,0
РБ ²⁺ Fe ³⁺ La ³⁺	1,20 0,64 1,02	9,9 10,0 7.3	12,4 12,5 10,3	14,9 15,3 13,7	19,4 19,4 19,3	23,3 23,7 25,0	22,1 29,6 14,3

TABLE 2. Logarithms of Stability Constants for Complexes of II and I (25°; μ = 1.0, 1.0 M KNO₃)

*Ionic radii taken from [3].

In contrast to I, II forms a more stable complex with Ca^{2+} than with Mg^{2+} . Comparison of the last two columns of Table 2 shows that for ions of radius less than 0.7 Å, the complexes of I are more stable; ions with radius from 0.7 to 0.8 A generally form complexes of approximately the same stability, while the larger cations form more stable complexes with II.

 Cu^{2+} is an exception; it forms an especially stable complex with II, possibly by tetragonal coordination with the four N atoms. As soon as solutions of II and $Cu(NO_3)_2$ are mixed a bright blue color appears, the intensity of which is almost unchanged by the addition of KOH during the titration. This seems to be evidence that Cu^{2+} is linked to all four ring N atoms even in the acid pH region (in the 0 < a < 4 buffer region) (see Fig. 1, curve 7). The unsubstituted 1,4,7,10-tetraazacyclododecane forms aCu^{2+} complex with log stability constant of 24.8 [4].

II forms a very stable complex with La^{3+} ; it is more than 10 orders of magnitude more stable than the I complex. Conceivably this is favored by the possibility of achieving the coordination number of 8 that is characteristic of La^{3+} .

In the acid region Cd^{2+} forms more stable protonated complexes than does Zn^{2+} (cf. log K_{stab} of MH₄L-MH₂L complexes); the Zn^{2+} complex "overtakes" the Cd^{2+} complex in stability only in the neutral pH region (see Fig. 1, curves 5 and 8). In contrast to I, acid II forms a more stable complex with Hg²⁺ than with Zn^{2+} .

As follows from the pH dependence of the distribution of the ionic forms of the complexes (Figs. 2 and 3), Mg^{2+} and Ca^{2+} (as well as Sr^{2+} and Ba^{2+}) chelate in the alkaline pH region; the other cations, just as with acid I, form stable complexes already in the acid pH region (the distribution diagrams for the other cations are like those shown for Co^{2+} and La^{3+}).

It is of interest to compare the complexing capability and selectivity of I, II, and the carboxyl analog of II - 1,4,7,10-tetrakis(carboxymethyl)-1,4,7,10-tetraazocyclododecane (III) [5]. Obviously a ligand is more selective when there is a considerable difference between the stability constants of the complexes of the different cations.

As a general measure of the complexing capability of a ligand toward a given group of cations, we can take the average of the stability constants:

$$A = \overline{\log K}$$

as a measure of selectivity, the average difference for the modulus of the log K_j (ML) constants for all the cations taken in pairs, i.e.:

$$S = \frac{\sum_{i=1}^{n} \sum_{i=j}^{n} (|\log K_i - \log K_j|)}{n(n-1)}$$

where n is the number of cations being compared.



Fig. 2. pH distribution of ionic forms of Mg^{2+} and Co^{2+} complexes of acid II.

Fig. 3. pH distribution of ionic forms of Ca^{2+} and La^{3+} complexes of acid II.

TABLE 3. Efficiency (A) and Selectivity (S) of Complex Formation of Complexones I-III and EDTA

Set of cations		Complexone								
		(I)		(II)		(III)		EDTA [6]		
		A	S	A	S	Α	S	A	S	
I	Mg ²⁺ , Ca ²⁺ , Sr ²⁺ , Ba ²⁺	6,8	3,5	9,0	1,7	12,8	2,7	9,0	1,6	
II	Cu ²⁺ , Co ²⁺ , Ni ²⁺ , Mn ²⁺ , Zn ²⁺ , Cd ²⁺ , Pb ²⁺ , Hg ²⁺ , Fe ³⁺ , La ³⁺	21,1	5,0	22,7	3,2	-	-	17,5	3,6	
111 *	Cu ²⁺ , Co ²⁺ , Ni ²⁺ , Mn ²⁺ , Zn ²⁺ , Cd ²⁺ , Pb ²⁺	20,5	3,0	21,9	3,8	18,6	1,0	17,0	2,0	

*This set of cations was studied in [5].

Of course the S value for each cation depends significantly on the set of cations chosen. Table 3 is constructed accordingly.

As the results show, the distinguishing feature of II is its very highly efficient complex formation with the cations of groups II and III (of Table 3), which exceeds that of EDTA by about five orders of magnitude. The Cd^{2+} , Pb^{2+} , and La^{3+} chelates are more stable than the corresponding complexes of any other known complexones [6].

In selectivity of binding Mg^{2+} and the alkaline earths, II is inferior to I and III, but it shows the maximum selectivity for the transition metals, Cd^{2+} , and Pb^{2+} (group III of Table 3).

Since complexone II is potentially octadentate, for cations of coordination number 6, two chelate positions are unoccupied. These can be either the ring N atoms or the phosphonic groups. Because of the large number of possible conformations, II ought to be less selective than I. Indeed, with respect to all the cations studied (groups I and II of Table 3), complexone II is significantly inferior to I in selectivity, and similar to the EDTA which has low selectivity.

The phosphonic groups in II significantly decrease its complexing capability below that of its carboxyl analog III.

Thus the new complexone II shows complexing properties that distinguish it from the previously synthesized I and from its carboxyl-containing analog III. Of special interest is its ability to form very stable chelates with cations of large ionic radius, viz., Cd^{2+} , Pb^{2+} , and La^{3+} .

EXPERIMENTAL

³¹P-{¹H} NMR spectra were obtained on a Bruker HX-90H spectrometer (36.43 MHz) from 85% H₃PO₄; PMR spectra, on a Bruker WP-200 SY apparatus (200.13 MHz) from TMS internal standard.

<u>N,N¹,N²-Tri(tosyl)diethylenetriamine</u>. To a solution of 10.3 g of diethylenetriamine and 12 g of NaOH in 80 ml of water at 35° was added 57 g of p-toluenesulfonyl chloride in 150 ml of ether. The mixture was stirred for 1 h at $\sim 20^{\circ}$. The precipitate was filtered off, washed with water, and recrystallized from MeCN. There was obtained 47.5 g (85%) of product, mp 171-173° (cf. [7]).

Disodium Salt of N, N^1, N^2 -Tri(tosyl)diethylenetriamine. This was obtained according to [2] in quantitative yield from 47.5 g of N, N^1, N^2 -tri(tosyl)diethylenetriamine and 8.3 g of sodium metal in 250 ml of EtOH.

<u>N-Tosyldiethanolamine</u>. To a mixture of 57.2 g of diethanolamine and 3 g of Na_2CO_3 in 300 ml of water was added 103 g of p-toluenesulfonyl chloride in small portions over 3 h. The mixture was then heated for 1 h at 95°. The precipitate was filtered off, air-dried, and recrystallized from toluene. There was obtained 120 g (85%) of product, mp 101° (cf. [8]).

<u>0,0,N-Tri(tosyl)diethanolamine</u>. To 38.2 g of N-tosyldiethanolamine in 30 ml of pyridine was added dropwise at 10-14° a solution of 73 g of p-toluenesulfonyl chloride in 80 ml of pyridine. The mixture was transferred with intensive stirring into a flask containing water cooled to 10°. Over night a solid formed, which was separated, washed with dilute H_2SO_4 and then with water until neutral, dried in air, and recrystallized from EtOH. There was obtained 60 g (72%) of product, mp 78° (cf. [8]).

 N,N^1,N^2,N^3 -Tetra(tosy1)-1,4,7,10-tetraazacyclododecane. This was synthesized according to [2] from 19 g of 0,0,N-tri(tosy1)diethanolamine in 168 ml of DMF and 26.6 g of the disodium salt of N,N¹,N²-tri(tosy1)diethylenetriamine in 330 ml of DMF. There was obtained 20.9 g of product, mp 292° (cf. [2]).

<u>1,4,7,10-Tetraazacyclododecane Hydrochloride</u>. A mixture of 32.5 g of N,N^1,N^2,N^3 -tetra(tosy1)-1,4,7,10-tetraazacyclododecane and 125 ml of conc. H₂SO₄ was heated for 70 h at 100°. The mixture was cooled to -30° and treated in a current of inert gas with a saturated solution of alkali [sic]. The precipitate was filtered off and the filtrate was extracted with chloroform. The extract was dried with sodium sulfate. After the solvent was removed the residual syrup was treated with 20% HCl. The resulting hydrochloride was recrystallized twice from 20% HCl. There was obtained 7.2 g of product (53.3% based on amine), mp 257-260° (with decomposition) (cf. [2]).

<u>N,N¹,N²,N³-Tetrakis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazacyclododecane (II).</u> To a mixture of 3.2 g of 1,4,7,10-tetraazacyclododecane, 3.6 g of phosphorous acid, 7 ml of conc. HCl, and 7 ml of water at 110° was added 6.5 g of 37% formalin solution through a dropping funnel. The mixture was kept at that temperature for another 2.5 h, then concentrated to 1/3 the original volume. Water was added and the solution was concentrated again to remove HCl, and the operation was repeated five times. Acetone was added and a syrup separated, which crystallized at $\sim 20^{\circ}$. The solid was recrystallized from aqueous acetone. There was obtained 3.5 g (64.8%) of colorless crystals of II, mp 250-255° (with decomposition). Found: C 26.3; H 5.9; P 22.6%. C₁₂H₃₂P₄N₄O₁₂. Calculated: C 26.2; H 5.8; P 22.6%. ³¹P-(¹H) NMR spectrum in H₂O, δ , ppm: 13.6. For tetrasodium salt of II, PMR spectrum in H₂O, δ , ppm: 3.25 d (CH₂P), 3.47 s (CH₂N).

<u>Dicyclohexylamine Salt of N,N¹,N²,N³-Tetrakis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazacyclododecane (II).</u> Acid II was dissolved in cyclohexylamine. On the next day acetone was added until the mixture became turbid. A solid product separated gradually; it was washed with a large amount of acetone; mp 300° (with decomposition). Found: C 38.4; H 7.6; N 11.1%. $C_{12}H_{32}P_4N_4O_{12}$. Calculated: C 38.6; H 7.8; N 11.3%.

<u>N,N¹,N²,N³-Tetrakis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazacyclododecane Methyl</u> <u>Iodide.</u> To an aqueous solution of acid II was added a 30-fold excess of MeI at $\sim 20^{\circ}$ with stirring. The mixture was stirred for 3 h at $\sim 20^{\circ}$. On the next day the aqueous layer was separated and treated with acetone until it became turbid. The precipitate was separated and recrystallized from acetone, mp >320° (with decomposition). Found: N 7.8; P 18.0%. C₁₃H₃₅P₄N₄O₁₂I. Calculated: N 8.1; P 18.0%.

Potentiometric titration was carried out with a OP-208 pH meter (Hungary) with accuracy of ± 0.01 pH units at 25°. The experimental conditions and the calculation of the dissociation constants and the stability constants of the complexes have been described in [1]. For Ni²⁺ and La³⁺, for which the complexation equilibrium is established very slowly, point-by-point titration was used. The errors in the determination of the dissociation and stability constants were determined as the average of the deviations obtained when the experimental titration curve was shifted by the amount of the pH-meter error, which was ± 0.03 log units for pK₃-pK₆, and ± 0.05 and 0.10 for pK₇ and pK₆, respectively.

The errors in the stability constants of the complexes thus determined were ± 0.04 -0.08 log units for Mg²⁺, Ca²⁺, Sr²⁺, Ba²⁺, Co²⁺, Ni²⁺, and Mn²⁺, and ± 0.10 -0.20 log units for the other cations.

CONCLUSIONS

A new complexone, 1,4,7,10-tetrakis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazacyclododecane, has been synthesized and its acid-base and complex-forming properties have been studied. It shows a very high complexing capability and marked selectivity for cations of large ionic radius (Cd²⁺, Hg²⁺, Pb²⁺, La³⁺).

LITERATURE CITED

- M. I. Kabachnik, T. Ya. Medved', Yu. M. Polikarpov, B. K. Shcherbakov, F. I. Bel'skii,
 E. I. Matrosov, and M. P. Pasechnik, Izv. Akad. Nauk SSSR, Ser. Khim., 835 (1984).
- 2. I. E. Richman and I. G. Atkins, J. Am. Chem. Soc., 6, 2268 (1974).
- R. C. Weast, Handbook of Chemistry and Physics, 55th edn., CRC Press (1974-1975), p. F198.
- 4. M. Kodama and E. Kimura, J. Chem. Soc. Dalton Trans., 116 (1976).
- 5. H. Stetter, W. Frank, and R. Mertens, Tetrahedron, 37, 767 (1981).
- 6. A. E. Martell and R. M. Smith, Critical Stability Constants, Vol. 1, Amino Acids, Plenum Press, New York, London (1974).
- 7. H. Koyama and T. Ioschino, Bull. Chem. Soc. Jpn., 45, 481 (1972).
- 8. D. H. Peacock and U. C. Dutta, J. Chem. Soc., 1303 (1934).