LITERATURE CITED

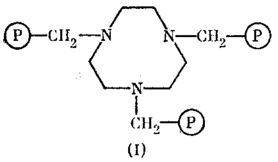
1. P. Sobota, M. Nowak, and W. Kramarz, J. Organometal. Chem., 275, 161 (1984).
2. T. Yamamoto, T. Kahara, and A. Yamamoto, Chem. Lett., 11, 1217 (1976).
3. W. F. Goure, M. E. Wright, P. D. Davis, S. S. Labadie, and J. K. Stille, J. Am. Chem. Soc., 106, 6417 (1984).
4. F. Sato, H. Iscikawa and M. Sato, Tetrahedron Lett., 21, 365 (1980).
5. S. Takahashi, T. Shibano, and N. Nagihara, Tetrahedron Lett., 26, 2451 (1967).
6. S. Takahashi, T. Shibano, and N. Nagihara, Bull. Chem. Soc., Japan, 51, 1915 (1978).
7. U. M. Dzhemilev, O. S. Vostrikova, A. G. Ibragimov, and R. M. Sultanov, Abstracts of Proceedings, IV International Symposium on Homogeneous Catalysis, Leningrad (1984), Vol. 1, p. 223.

SYNTHESIS AND COMPLEXING PROPERTIES OF 1,5,8,12-TETRAKIS(DIHYDROXYPHOSPHORYLMETHYL)-1,5,8,12-TETRAAZACYCLOTETRADECANE, A CYCLOPENDANT PHOSPHORORGANIC COMPLEXON

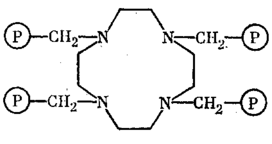
S. A. Pisareva, F. I. Bel'skii,
T. Ya. Medved', and M. I. Kabachnik

UDC 542.91:541.49.547.1'118

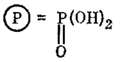
Earlier we prepared the first two representatives of cyclopendant phosphororganic complexons, viz. 1,4,7-tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclonane (I) and 1,4,7,10-tetrakis(dihydroxyphosphorylmethyl)-1,4,7,10-tetraazacyclodecane (II), having strong complexing properties and high selectivity for binding cations [1-3].



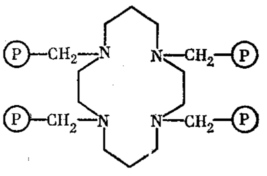
(I)



(II)



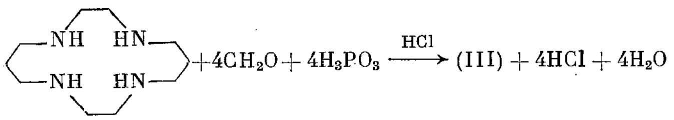
$\text{Ⓟ} = \underset{\underset{\displaystyle O}{\|}}{P}(OH)_2$



(III)

In this article we describe the synthesis of the next representative (III) of cyclopendant phosphororganic compounds, 1,5,8,12-tetrakis(dihydroxyphosphorylmethyl)-1,5,8,12-tetraazacyclotetradecane, containing in its molecule the cyclam fragment.

The synthesis of complexon (III) was realized by reacting tetraalkylenetetramine (IV) with formalin and H_3PO_3 in the presence of HCl according to the model of the Moedritzer–Irani reaction [4].



Tetraalkylenetetramine (IV) (cyclam) was prepared by a modification of method [5] by reacting 1,3-dibromopropane with ethylenediamine to the corresponding trialkylenetetramine (V), which on reaction with TsCl and EtONa is converted into tetratosyl derivative (VIa) and its disodium salt (VIb). Reaction of salt (VIb) with the tosylate of trimethyleneglycol (VII) under the conditions of [6] gives cyclic tetratosylate (VIII), which on hydrolysis is converted to cyclam (IV).

A. N. Nesmeyanov Institute of Heteroorganic Compounds, Academy of Sciences of the USSR, Moscow. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 2, pp. 413-417, February, 1987. Original article submitted July 10, 1985.

0568-5230/87/3602-0372$12.50

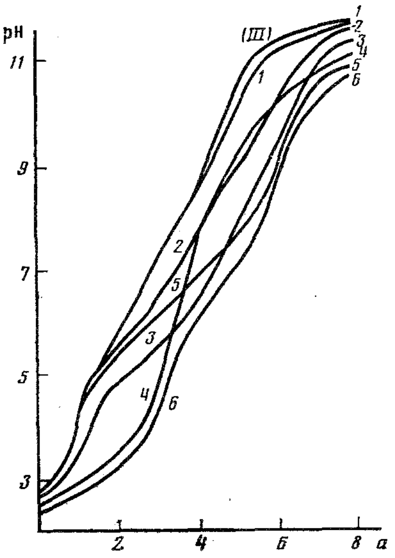
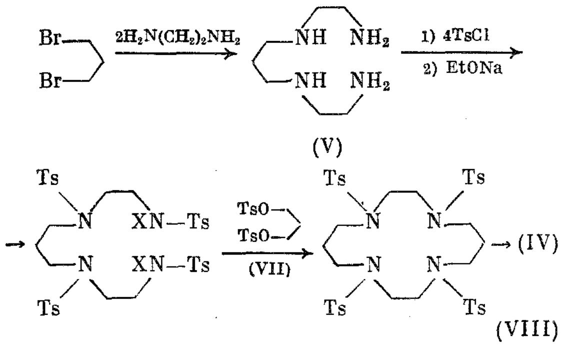


Fig. 1. Neutralization curves free of 0.002 M complexon (III) and with the presence of 0.002M cations: 1) Mg^{2+} 2) Mn^{2+} 3) Zn^{2+} 4) Eu^{3+} 5) 0^{2+} and 6) Cu^{2+}.



X = H (VIa), Na (VIb).

In the ^{31}P-{H} NMR spectrum of complexon (III) in D_2O a singlet at δ 13 ppm is found, which is evidence of the equivalence of the phosphorus atoms in the molecule. Likewise, the ^{31}P-{H} NMR spectra of complexons (I) and (II) show singlets at δ 13.0 and 13.6 ppm, respectively.

The acid-base and complexing properties of (III) were studied by means of potentiometric titration in water according to [1, 2]. Calculation of pK_a values and stability constants of the complexes was carried out with a computer program on a BÉSM-6 computer [7]. In Table 1 are listed the acid dissociation constants of complexon (III) in comparison with the pK_a values of compound (II). The errors in the determination of the constants were determined as in [2, 3], and for (III) there were for pK_2-pK_5 ± 0.02, and for pK_1 and pK_6-pK_8 ± 0.20.

Dissociation of only one proton in the first buffer region (Fig. 1) may point to realization of a betaine structure, in which three protons of PO_3H_2 groups are bound to nitrogen atoms of the ring. Thus, enlargement of the cyclic part of (III) as compared with (II) leads to a corresponding change in the dissociation mechanism.

The complexing properties of (III) were studied in relation to Mg^{2+} and the alkaline-earth elements, the transition and rare-earth elements, and Pb^{2+}. With Mg^{2+}, Ca^{2+}, Sr^{2+}, and Ba^{2+} (III) forms complexes with logarithms of stability constants (K_{st}) < 2. A sharp decrease of K_{st} (by a factor of 10^6-10^8) of the complexes of complexon (III) was found as compared with

TABLE 1. pK_a (concentration) of Complexons (III) and (II) (25°C, μ = 1.0, KNO_3)

Complexon	pK_1	pK_2	pK_3	pK_4	pK_5	pK_6	pK_7	pK_8
(III)	<2	4.96	6.27	7.67	9.16	11.8	12.8	13.5
(II)	<1	<2	4.88	5.73	7.28	8.46	11.52	12.1

TABLE 2. Logarithms of K_{st} of the Complexes MHL of Complexons (III), (II), (IX), and (X), and A and S of the Complex Formation for the Bases Mn^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+} (25°C, μ = 1.0)

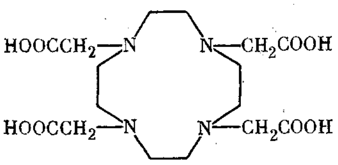
Cation	(III)				(II)	(IX)	(X)
	MH_3L	MH_2L	MHL	ML	ML	ML	ML
Mn^{2+}	5.6	8.2	10.0	10.8	16.9	17.8	11.2
Co^{2+}	7.1	10.9	13.6	15.3	20.8	18.4	15.0
Ni^{2+}	7.1	10.8	13.3	15.6	19.0	17.3	15.3
Cu^{2+}	17.4	21.6	24.7	26.6	25.4	19.0	18.6
Zn^{2+}	9.6	13.7	16.2	17.6	24.8	18.9	15.8
Cd^{2+}	9.9	13.0	15.1	16.7	22.9	19.0	15.5
Pb^{2+}	9.2	12.1	13.9	15.5	23.3	19.9	14.7
Nd^{3+} *	12.8	14.6	16.1	17.8	–	–	–
Eu^{3+} †	12.9	15.3	17.1	18.9	–	–	–
A ‡				16.9 (15.3)	21.9 (21.3)	18.6 (18.6)	14.7 (14.6)
S				5.1 (2.6)	3.8 (3.6)	1.0 (1.1)	2.4 (1.7)

*Insoluble complex in the region 5 < a < 8.

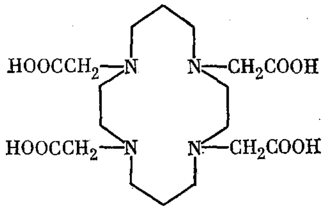
†Insoluble complex in the region 0 < a < 3.

‡In parentheses the value of A and S for the bases Mn^{2+}, Co^{2+}, Ni^{2+}, Zn^{2+}, Cd^{2+}, and Pb^{2+}.

complexon(II). An analogous decrease was found earlier [8] on switching from carboxyl containing complexon (IX) to (X).



(IX)



(X)

We should bear in mind that ethylenediaminodialkyl-phosphonic acids form complexes with logarithms of K_{st} < 2 [9] with Mg^{2+} and alkaline-earth elements. The complexing capacity of complexon (III) was determined by using the criteria suggested in [3] for the efficiency (A) and the selectivity (S) of the complex formation with a chosen series of cations in which n is the number of cations being

$$A = \overline{\lg K_j}; \qquad S = \frac{\sum_{i=1}^{n} \sum_{i=i}^{n} (|\lg K_i - \lg K_j|)}{n(n-1)}$$

compared and K_{ji} the stability constant of the complex ML of the i, j-th complexonate.

In Table 2 are listed K_{st} of the complexes, and A and S of the complexing forming complexons (III), (II), and their carboxyl containing analogs (IX) and (X).

Errors in the determination of K_{st} were determined as in [2, 3]; for (III) they were ±0.10-0.20 logarithm units.

From the data given it is clear that (III) forms less stable complexes than (II). A similar decrease in the efficiency of complex formation has also been found for carboxyl containing complexon (X) in comparison with (IX) [10].

Evidently, the cause of the lowering of the stability constants is the same in both cases and related to the size and conformation of the tetraaza ring. Preliminary study of ligand (III) from the conformation point of view* showed that within a range of 1-2 kcal/mole that ligand, showing chain flexibility, forms many conformations of similar energies. Indeed, if we compare the stability constants of complexes ML of ligand (III) with thoses of ethylenediaminodimethylphosphonic acid (EDMP), it is not difficult to see a distinct parallelism between the stability constants of these two series (with the exception of Cu^{2+}).

Cation	Mn^{2+}	Co^{2+}	Ni^{2+}	Zn^{2+}	Cd^{2+}	Cu^{2+}	Rare-earth elements
Ligand (III)	10.8	15,3	15,6	17.6	16.7	26,6	<2
EDMP	7.55	10,8	12,0	12.0	10,9	18,6	<1

But EDMP is a complexon of high flexibility!

It may be assumed that the observed lowering of the stability constants on going from (II) to (III), and correspondingly from (IX) to (X), is of entropic origin.

For complexons (I) and (II) we have found selectivity of complex formation which is connected with the size of the chelating cation. Complexon (I) forms the most stable complexes with cations with a small ionic radius (<0.8 Å), and complexon (II) with cations with a large ionic radius (>0.8 Å) [2, 3]. It can be seen for the results given that (III) forms complexes of similar stability with all cations tested (with the exception of Cu^{2+}), which differ considerably in their ionic radii. It may be thought that the size of the cyclic part of (III) is sufficiently large and sufficiently flexible in order to "adopt" cations of any ionic radius, which also determines the absence of selectivity with regard to the cations mentioned.

However, complexon (III) has a very high selectivity in complex formation with regard to the Cu^{2+} ion. The stability constant of (III) with Cu^{2+} surpasses with many orders of magnitude the stability constants (K_{st}) of the complexes with the other metals mentioned. The differences between lg K_{st} of the complexes with Cu^{2+} and Ni^{2+} is 11 for complexon (III). For polyaminopolyacetic acids (carboxyl containing complexons) that difference is not more than a factor of $10-10^2$, and only the complexon having in its molecule an azacrownpolyether fragment, 1,10-diaza-4,7,13,16-tetraoxacyclooctadecane-N,N-diacetic acid, forms with Cu^{2+} a complex that is by a factor of $10^{7.1}$ more stable than that with Ni^{2+} [11]. Amongst the phosphororganic complexons the maximal difference in log K_{st} of the complexons for Cu^{2+} and Ni^{2+}, 9.2, is shown by ethylenediamine-N,N-diisopropylphosphonic acid [9]. Thus, in this respect (III) surpasses all known complexons. Calculation of the conformation of complexon (III) by the method of the atom-atom potential function has shown that in stable conformations the four nitrogen atoms form a planar square, a conformation which is the most favorable one for complex formation with the Cu^{2+} ion. Moreover, the planar square Cu^{2+} complex may in addition be stabilized by means of extracoordination of the phosphonic group in apical positions.

On inclusion of the cations under investigation in the base, the Cu^{2+} ion (see Table 2) leads to a sharp increase in the selectivity of the complex formation of compound (III), e.g., it is a specific complexon for the copper ion.

EXPERIMENTAL

Potentiometric titrations was carried out with a OP-208 (BHP) pH meter with an accuracy of of ±0.01 pH unit at 25°C. The concentration of the titrated acid (III) was 0.002 M; the ratio of M:L was 1:1 in all the experiments. The experimental conditions and the method of calculation of the dissociation constants and the stability constants of the complexes is described

---

*Results of conformational analyses will be published separately.

in [2, 3]. $^{31}P-\{H\}$ NMR spectra were taken on a Bruker HX-90 (36.43 MHz) spectrometer from 85% H_3PO_4; IR spectra were recorded on a UR-20 instrument.

Trialkylenetetramine (V) was prepared according to [5] from 50 g of 1,3-dibromopropane, 83 g of ethylenediamine, and 67 g of KOH with a yield of 42%, bp 160-163°C/15 mm, n_D^{20} 1.4930.

The tetratosyl derivative (VIa) of the trialkylenetetramine was prepared according to [12] from 10.9 g of (V), 6.3 g of NaOH in 100 ml of water, and 51.5 g of TsCl with a yield of 52%, mp 140-143°C. Found, %: C 53.7, H 5.7, N 7.3. $C_{35}H_{44}N_4O_8O_4$. Calculated %: C 54.0, H 5.7, N 7.2.

The disodium salt (VIb) of the tetratosyl derivative of the trialkylenetetramine was prepared according to [12] with quantitative yield from 34.2 g of (VIa) and 2 g of Na in 400 ml of ethanol. There is no NH absorption band in the IR spectrum.

The ditosyl ester of trimethyleneglycol (VII) was prepared according to [12] from 38 g of trimethyleneglycol in 100 ml of pyridine and 210 g of TsCl in 225 ml of pyridine with a yield of 76%, mp 92-84°C.

Tetratosylcyclam (VIII) was prepared according to [6] from 36 g of (VIb) in 585 ml of DMF and 16.9 g of (VII) in 294 ml of DMF with a yield of 65%, mp 284-287°C.

Detosylation of tetratosylcyclam was carried out according to [12]: 21.2 g of (VIII) was hydrolyzed in 130 ml of concentrated H_2SO_4; yield 81% of (IV), mp 184-187°C.

1,5,8,12-Tetrakis(dihydroxyphosphorylmethyl)-1,5,8,12-tetraazacyclotetradecane (III). To a mixture, heated to 108°C, of 1 g of cyclic tetraalkylenetetramine (IV), 1.8 g of H_3PO_4, 4 ml of H_2O, and 4 ml of concentrated HCl was added dropwise 4.5 ml of 26.6% formaline, and the mixture was kept at 108°C for 2.5 h. The next day the precipitate was filtered off, washed with water till neutral reaction, and recrystallized from aqueous acetone. Yield 85%, mp 250-252°C (dec.). Found %: C 27.4, H 6.3, N 9.2, P 20.3. $C_{14}H_{36}N_4O_{13}P_4$. Calculated %: C 27.6, H 6.3, N 9.2, P 20.0.

CONCLUSIONS

1. We have synthesized the novel cyclopendant complexon 1,5,8,12-tetrakis(dihydroxyphosphorylmethyl)-1,5,8,12-tetraazacyclotetradecane and studied its acid-base and complexing properties.

2. The prepared compound is characterized by high selectivity of complex formation with respect to the copper (II) ion.

LITERATURE CITED

1. Yu. M. Polikarpov, B. K. Shcherbakov, F. I. Bel'skii, T. Ya. Medved', and M. I. Kabachnik, Izv. Akad. Nauk SSSR, Ser. Khim., 1669 (1982).
2. 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).
3. M. I. Kabachnik, T. Ya. Medved', F. I. Bel'skii, and S. A. Pisareva, Izv. Akad. Nauk SSSR, Ser. Khim., 844 (1984).
4. K. Moedritzer and R. Irani, J. Org. Chem., 31, 1603 (1966).
5. H. G. Hamilton and M. D. Alexander, Inorg. Chem., 5, 2060 (1966).
6. J. E. Richman, Th. J. Atkins, J. Am. Chem. Soc., 96, 2268 (1974).
7. N. I. Voronezheva, Yu. V. Rudyak, N. M. Dyatlova, and A. I. Grigor'ev, Koordinats. Khim., 6, 991 (1980).
8. H. Stetter, W. Frank, and R. Mertens, Tetrahedron, 37, 767 (1981).
9. N. M. Dyatlova, M. I. Kabachnik, T. Ya. Medved', M. V. Rudomino, and Yu. F. Belugin, Dokl. Akad. Nauk SSSR, 161, 607 (1965).
10. A. E. Martel and R. M. Smith, Critical Stability Constants, Amino Acids, Vol. 1, New York—London (1974).
11. C. A. Chang and M. E. Rowland, Inorg. Chem., 22, 3866 (1983).
12. W. Wehner and F. Vögtle, Chem. Exp. Didakt., 1, 77 (1975).