N-Substituted 2-aminoethylidenediphosphonic acids as complexones

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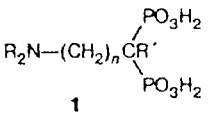
A novel complexone, 2-dimethylaminoethylidenediphosphonic acid, was synthesized. Its acid-base and complexation properties were studied by potentiometric titration in aqueous solutions (25 °C) and compared to those of 2-amino-1-hydroxyethylidenediphosphonic acid and ω-aminoalkylidenediphosphonic analogs. Parameters of efficiency and selectivity of complexation were determined. The influence of the alkylidene chain length on complexone properties in a series of ω-aminoalkylidenediphosphonic acids was analyzed.

Key words: 2-aminoethylidenediphosphonic acids, synthesis, complexation, acid-base properties; potentiometric titration.

Among aminodiphosphonic acids, ω-aminoalkylidenediphosphonic acids with geminal arrangement of phosphonic groups (**1**) are of special interest. Among the latter, efficient complexones and regulators of calcium exchange in the human organism were found.[1,2] 3-Dimethylamino-1-hydroxypropylidenephosphonic (**1a**: R = Me, R′ = OH, *n* = 2),[1] 3-amino-1-hydroxypropylidenediphosphonic (**1b**: R = H, R′ = OH, *n* = 2),[2] and 6-aminohexylidenediphosphonic (**1c**: R = R′ = H, *n* = 5)[2] acids are promising for the medical-biological practice. Data on the use of the acid with the butylidene chain (**1d**: R = Me, R′ = OH, *n* = 3) as the complexone have been published.[3]



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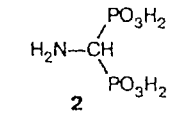
The relatively high stability of monoprotonated complexes of these compounds, the wide pH range of efficient complexation, and the sufficiently high solubility in water of the complexes formed are distinctive features of compounds of this type. These results stimulated the synthesis and study of new complexones of this class. For example, compounds of the following types were synthesized and studied in detail as complexones (acid-base properties and stability constants of the complexes): (1) aminomethylenediphosphonic acids[4–7] $R_2NCH(PO_3H_2)_2$; (2) 3-amino-1-hydroxypropylidenediphosphonic acids[8–13] $R_2NCH_2CH_2C(OH)(PO_3H_2)_2$; and (3) 4-amino-1-hydroxybutylidenediphosphonic[8] acids $R_2N(CH_2)_3C(OH)(PO_3H_2)_2$ with different substituents at the N atom. It has been shown for the complexones of the first two types that the substituents at the N atom affect slightly the stability of the complexes, but sometimes change their solubility in water.[4,5,8,9] In this work, we planned to reveal the influence of the length of the alkylidene chain on the acid-base and complexation properties of compounds of this group. We believe that if the amino group participates in the formation of chelate cycles, the properties of the complexone should depend on the stability and size of these cycles. For comparison, we chose pairs of acids of each types with amino and dimethylamino groups: aminomethylenediphosphonic (**2**) and dimethylaminomethylenediphosphonic (**3**); 2-amino-1-hydroxyethylidenediphosphonic (**4**) and 2-dimethylaminoethylidenediphosphonic (**5**); 3-amino-1-hydroxypropylidenediphosphonic (**6**) and 3-dimethylamino-1-hydroxypropylidenediphosphonic (**7**); and 4-amino-1-hydroxybutylidenediphosphonic acids (**8**).



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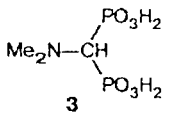

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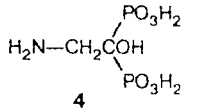

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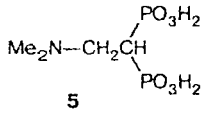

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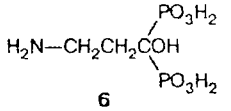

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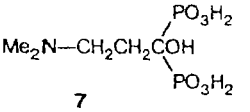

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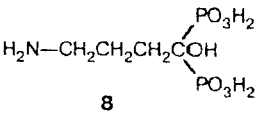

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† Deceased.

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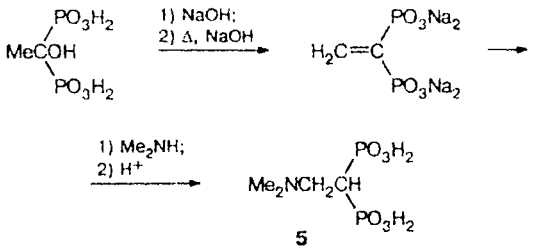
The complexones with methylene (**2**, **3**), propylidene (**6**, **7**), and butylidene (**8**) chains have been obtained and studied previously.[4—13] The complexones with the ethylidene chain (**4**, **5**), which were lacking for the comparison series, have been synthesized and studied in this work.

Acid **4** was obtained by the previously described method.[14] Acid **5** was synthesized according to the method[15] proposed for preparing substituted 2-aminoethylidenediphosphonic acids by the addition of aliphatic amines to salts of vinylidenediphosphonic acid. The starting sodium salt of vinylidenediphosphonic acid can be easily obtained by pyrolysis of the readily accessible sodium salt of 1-hydroxyethylidenediphosphonic acid.



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Acid-base properties of complexones **4** and **5** were studied by potentiometric titration at 25 °C in aqueous solutions against the background of 1 *M* KNO_3 under the same conditions* as the most studied (among the chosen series) complexone **7**. The values of stepped dissociation constants of compounds **2**, **3**, and **6**—**8** with alkylidene chains with different lengths are presented in Table 1. Acid **4** containing the aliphatic OH group is tetrahydric in aqueous solutions as hydroxy acids **6**—**8** studied previously.[8,9,11—13] For all the acids compared, the corresponding p*K* values of each step are located in approximately similar regions (somewhat different experimental conditions in different works should be taken into account). For acids **2** and **7**, the mechanism of dissociation in aqueous solutions was established by IR spectroscopy.[6,12] It has been found that both acids in solutions have the zwitterionic structure, and the betaine proton is the last to be split off. The dissociation mechanism of complexones **4** and **5** can be assumed to be the same. However, direct comparison of the p*K* values does not allow one to draw conclusions about the dissociation mechanism. Since the constants determined by potentiometric titration are macrocharacteristics of the process, they do not take into account equilibria between different tautomeric forms of a molecule and anions formed at each stage of dissociation. The presence of several tautomeric forms, which are usually stabilized due to the formation of various H-cycles, is characteristic of dissociation processes of complexones.[17]

Table 1. Negative logarithms of dissociation constants (pK_a) of complexones **2**—**8** (25 °C, μ = 1.0 (1.0 *M* KNO_3))[a]

Complexone	pK_1	pK_2	pK_3	pK_4	References
2[b]	1.7	5.59	7.33	10.47	6
3[b]	2.16	5.01	8.82	11.15	4
4	1.8	5.72	9.36	>12	[c]
5	<1	5.75	8.98	≥12	[c]
6[b]	2.55	5.83	9.9	10.8	8
7[b]	2.35	5.89	9.7	10.8	12
7	<2	5.44	9.28	11.7	13
8[b]	2.72	8.73	10.5	11.6	8

[a] For complexone **3**, according to the published data,[7] against the background of 0.2 *M* NaCl, pK_1 = 1.06, pK_2 = 4.86, pK_3 = 8.55, and pK_4 = 13.4; for complexone **7**, according to the published data,[11] thermodynamic constants pK_1 = 2.40, pK_2 = 6.10, pK_3 = 10.77, and pK_4 = 11.96.
[b] μ = 0.1 (0.1 *M* KCl).
[c] This work.

The complexation properties of ligands **4** and **5** were studied by potentiometric titration with respect to the same cation base as that for acid **7**: alkaline-earth and some transition metals (Table 2). Note that the cations of the chosen base do not displace the proton from the aliphatic OH group of complexone **4** as in the case of other ω-amino-1-hydroxyalkylidenediphosphonic acids.[1] The results of measuring the stability constants of the complexes determined at an equimolar ratio of the reagents are presented in Table 2. The stability constants of the complexes were determined from the equation

$$K_{MH_jL} = \frac{[MH_jL]}{[M][H_jL]}$$

(hereinafter the charges are omitted for simplicity).

For complexones **4** and **5**, the MH_2L, MHL, and ML complexes are significant in the pH range studied. The values of logarithms of stability constants of formation of MH_jL complexes (j = 0—2) for complexones **2**, **3**, and **6**—**8** are presented in Table 2 for comparison.

As can be seen from the data in Table 2, ligand **4** with the majority of the cations under study gives water-insoluble complexes. Among the compounds studied previously, the formation of precipitates during complexation was observed for acids **6** and **8**. All of the three ligands contain nonsubstituted amino and hydroxy groups but have alkylidene chains with different lengths.

The values characterizing the general efficiency (A) and selectivity (S) of the effect of complexones **2**—**8** were calculated by the previously described procedure[18] for two cation bases. Comparison of the data in Table 2

* Despite the fact that it is more correct to use tetraalkylammonium salts as background electrolytes, we have chosen KNO_3 to compare our results with the published data (the majority of studies of complexones was carried out against the background of KNO_3 and KCl).[1,16,17]

Table 2. Logarithms of stability constants of MH_jL complexes of complexones **3**—**8** with various metals (25 °C, μ = 1.0 (1.0 *M* KNO_3)); parameters of complexation A_1 and S_1 for the cation base of Mg^{2+}, Ca^{2+}, Mn^{2+}, Co^{2+}, Ni^{2+}, and Cu^{2+}

Complexone	Complex	Mg^{2+}	Ca^{2+}	Mn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	A_1[a]	S_1[a]	A_2[b]	S_2[b]	References
3[c]	MHL	[d]	4.56	6.71	6.09	[d]	9.49	7.19	[d]					4
	ML	[d]	4.78	7.26	7.29	[d]	11.92	9.27	[d]	—	—	8.0	4.8	4
4	MH_2L	[e]	[e]	[e]	4.1	3.1	5.7	[e]	[e]					[g]
	MHL	[e]	[e]	[e]	8.5	7.5	9.2	[e]	[e]					[g]
	ML	[e]	[e]	[e]	12.5	12.4	14.8	[e]	[e]	—	—	—	—	[g]
5	MH_2L	2.57	1.89	4.01	5.02	5.99	6.97	4.17	4.01					[g]
	MHL	5.80	5.26	8.80	8.77	9.08	11.0	8.60	9.67					[g]
	ML	6.31	5.81	9.25	9.30	9.60	12.91	10.89	10.18	8.86	3.03	9.3	4.7	[g]
6[c]	MH_2L	[d]	2.85	[d]	4.4[f]	[d]	5.8[f]	[d]	[d]					8
	MHL	[d]	5.7[f]	[d]	8.5[f]	[d]	10.9[f]	[d]	[d]					8
	ML	[d]	5.8[f]	[d]	9.9[f]	[d]	13.6[f]	[d]	[d]	—	—	9.8	5.2	8
7	MH_2L	2.55	1.87	4.30	3.87	3.25	4.84	[d]	[d]					13
	MHL	5.78	5.24	8.17	8.08	7.25	10.33	[d]	[d]					13
	ML	6.29	5.79	9.33	9.93	9.58	13.18	[d]	[d]	9.02	3.21	9.6	4.9	13
7[c]	MHL	6.32	5.57	8.09	7.89	7.52	10.76	8.90	[d]					12
	ML	6.57	5.71	8.33	9.01	8.73	12.95	10.24	[d]	8.55	2.93	9.2	4.8	12
8[c]	MH_2L	[d]	5.57	[d]	6.4[f]	[d]	7.73	[d]	[d]					8
	MHL	[d]	6.01	[d]	7.9[f]	[d]	11.31	[d]	[d]					8
	ML	[d]	6.10	[d]	8.8[f]	[d]	12.92	[d]	[d]	—	—	9.3	4.6	8

[a] Calculated in this work. [b] For the cation base of Ca^{2+}, Co^{2+}, and Cu^{2+}. [c] μ = 0.1 (0.1 *M* KCl).
[d] Complexation with this cation was not studied. [e] Water-insoluble complex. [f] Precipitation during titration. [g] This work.

shows that these parameters are approximately equal for all the ligands studied, except the A_2 value for acid **3**. It is noteworthy that the A_2 and S_2 values are approximate, because their cation base is not representative (see footnote "*b*" to Table 2).

For all the ligands under study, the stability of the magnesium complexes is higher than that of the corresponding calcium complexes, which is mentioned, in general, for the majority of aminodiphosphonic acids.[1]

The stability of the calcium complexes (ML and MHL) increases monotonically as the length of the alkylidene chain of the ligand increases: from 4.78 ($\log K_{ML}$) for ligand **3** with the methylene bridge to 6.10 for ligand **8** with the butylidene chain. This agrees well with the decrease in the induction effect of the amine substituent on phosphonic groups. However, this dependence is not retained for the complexes with Co^{2+} and Cu^{2+}. In the series of the ligands under study, complexone **4** forms the most stable ML complexes with these cations, and acid **3** forms the least stable complexes. It can be reasonably assumed that the bond between the anion of the ligand with the cation in the calcium complexes is mainly ionic due to coordination with the O atoms of the deprotonated phosphonic groups. Then the higher stability of the cobalt and copper complexes of **4** can be reasonably related to an additional coordination of the N atom of the amino group by the metal (six-membered chelate cycle in the complexes of ligand **4** and less stable five-, seven-, and eight-membered cycles in the complexes of the other ligands). However, the question about the coordination of nitrogen in similar complexes of ligand **5** with the same ethylidene fragment remains unclear. Its copper and cobalt complexes are 1.9 and 3.2 orders of magnitude less stable than those with ligand **4**. Undoubtedly, methyl substituents at the N atom (compound **5**) during its coordination with the metal should decrease the stability of the complex as compared to that for the ligand with the nonsubstituted amino group due to steric hindrances. For the pair of ligands with the propylidene chain (**6** and **7**), the replacement of the hydrogen atom of the amino group by Me decreases the values of logarithms of stability constants of the complexes with the same cation only by 0.6 and 0.9, *i.e.*, threefold lower than that for the pair of **4** and **5**. The results of the spectral study of the dissociation mechanism of ligands **4** and **5** and the structures of their complexes in aqueous solutions will be published elsewhere.

It can be seen from the data in Table 2 that the stability of the monoprotonated MHL complexes of ligands **4** and **5** is sufficiently high as in the case of the other complexones of the series under comparison. This extends the pH region of efficient complexation. It should be mentioned that the maximum difference in stability constants of the ML and MHL complexes is observed for ligand **4** ($\Delta\log K_{st}$ = 4.0—5.6 as compared

to 0.5—2.8 for the other ligands) with respect to the cations that have nitrogen affinity: Co^{2+}, Ni^{2+}, and Cu^{2+}.

Thus, as a whole, a change in the alkylidene chain length in ω-aminoalkylidenediphosphonic acids **1** beginning from $n = 1$ (ethylidene chain) virtually has no effect on the efficiency and selectivity of complexation in the studied series of cations and on the acid-base properties of the complexones. The replacement of the substituent at the N atom of the amino group (H by Me) in the ethylidene acids decreases the stability of the complexes and affects substantially their solubility. A similar phenomenon has previously been observed for the methylene[4] and propylidene[8] derivatives of this series. It is also noteworthy that the acid-base and complexation properties of the new complexone **5** virtually coincide with those of ligand **7**, which was named AMOK in medical-biological research. It can be expected that complexone **5**, like AMOK, will affect the calcium exchange in the organism.

Experimental

$^{31}P-\{^1H\}$ NMR spectra were recorded on a Bruker WP-200 SY instrument using 85% H_3PO_4 as the external standard.

2-Amino-1-hydroxyethylidenediphosphonic acid (4) was synthesized by the previously described procedure.[14]

2-Dimethylaminoethylidenediphosphonic acid (5). Tetrasodium salt of vinylidenediphosphonic acid (2.5 g) obtained by pyrolysis of tetrasodium salt of hydroxyethylidenediphosphonic acid[19] was mixed with a 30% solution (10 mL) of Me_2NH. The mixture was neutralized by conc. HCl to pH 8 and heated in a sealed glass tube at 120 °C for 12 h. The solution was filtered off and concentrated to dryness. The residue was dissolved in water (100 mL) and passed through a column filled with a UR-180 cation-exchange resin in the H^+ form. The acidic fraction was concentrated, and the residue was recrystallized from water with EtOH, recrystallized from an EtOH—H_2O mixture, and dried over P_2O_5 to obtain colorless crystals (0.77 g) with m.p. 236.5—237.5 °C. Found (%): C, 20.4; H, 5.6; N, 5.7; P, 26.6. $C_4H_{13}NO_6P_2$. Calculated (%): C, 20.6; H, 5.6; N, 6.0; P, 26.6. $^{31}P-\{^1H\}$ NMR of tetrasodium salt of acid **5** (H_2O, $C = 0.1$ mol L^{-1}), δ: 14.9 (s).

Potentiometric titration was carried out on an OP-208 pH-meter (Hungary) with an accuracy of ±0.01 pH units at 25±0.1 °C in an argon flow. The electrode pair was calibrated by standard buffer solutions with pH 1.68, 4.01, and 9.18.

Bidistilled water was used to prepare solutions. The salts used (KNO_3, $Mg(ClO_4)_2$, $Ca(NO_3)_2 \cdot 4H_2O$, $MnCl_2$, $Ni(NO_3)_2 \cdot 6H_2O$, $CoCl_2 \cdot 6H_2O$, $Cu(NO_3)_2 \cdot 2.5H_2O$, $Zn(NO_3)_2 \cdot 6H_2O$, and $Cd(NO_3)_2 \cdot 4H_2O$) (reagent and analytical purity grades) were purified by recrystallization. Concentrations of salts in solutions were monitored by trilonometric titration. Solutions of the titrant KOH (free of carbonates) were prepared from a saturated solution of KOH, and the normality of the alkali was established by indicator titration by potassium biphthalate and benzoic acid.

The concentrations of ligands **4** and **5** (C_L) were 0.005 mol L^{-1}, $C_M : C_L = 1 : 1$ in all experiments, and ionic strength $\mu = 1.0$ (1.0 *M* KNO_3). The activity coefficients for these conditions were the following: $pγ_{H^+} = 0.16$; $pγ_{OH^-} = 0.04$.[20] The volume of the titrated solution was 50 mL; at the concentration of the titrant 0.3 mol L^{-1}, the titration curve contained 30—40 points in the region of pH 2—12. The pK_a values of dissociation of acids and $\log K_{st}$ of metal complexes (under assumption of the formation of MH_jL complexes) were calculated by the known program.[21] Errors in determination of dissociation constants of acids **4** and **5** were found as a half-sum of deviations obtained when the experimental titration curve was shifted by a possible error of the pH-meter (±0.01 pH units), which was ±0.15 for pK_1 (**4**); ±0.01 for pK_2 (**4**, **5**); ±0.03 for pK_3 (**4**, **5**); and ±0.2 for pK_4 (**5**). Errors in determination of stability constants of the complexes (determined by the same procedure) were ±0.07—0.10 for the complexes of ligand **4** and ±0.02—0.05 for the complexes of ligand **5**.

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References

1. E. I. Sinyavskaya, *Koord. Khim.*, 1992, **18**, 899 [*Sov. J. Coord. Chem.*, 1992, **18** (Engl. Transl.)].
2. *Calcium Disorders*, Eds. D. Heath and S. J. Marx, Butterworth Scientific, London—Boston, 1982.
3. Ger. Offen DE 3434667, Appl. 21. Sep. 1984; *Chem. Abstrs.*, 1987, 106, 5227w.
4. G. Gross, T. Ya. Medved', B. Kostitsella, F. I. Bel'skii, and M. I. Kabachnik, *Zh. Obshch. Khim.*, 1978, **48**, 1914 [*J. Gen. Chem. USSR*, 1978, **48** (Engl. Transl.)].
5. G. Gross, B. Kostitsella, K. Shvarts, M. I. Kabachnik, F. I. Bel'skii, and Yu. M. Polikarpov, *Zh. Obshch. Khim.*, 1990, **60**, 749 [*J. Gen. Chem. USSR*, 1990, **60** (Engl. Transl.)].
6. M. N. Rusina, T. M. Balashova, B. V. Zhadanov, A. Yu. Tsitrina, and I. A. Polyakova, *Zh. Obshch. Khim.*, 1977, **47**, 1721 [*J. Gen. Chem. USSR*, 1977, **47** (Engl. Transl.)].
7. J. E. Bollinger and D. M. Roundhill, *Inorg. Chem.*, 1993, **32**, 2821.
8. M. I. Kabachnik, T. Ya. Medved', N. M. Dyatlova, Yu. M. Polikarpov, B. K. Shcherbakov, and F. I. Bel'skii, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1978, 433 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1978, **27**, 374 (Engl. Transl.)].
9. B. K. Shcherbakov, F. I. Bel'skii, A. Yu. Gukasova, Yu. M. Polikarpov, and M. I. Kabachnik, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 1780 [*Russ. Chem. Bull.*, 1998, **47**, 1732 (Engl. Transl.)].
10. T. A. Matkovskaya, L. S. Nikolaeva, E. A. Mezhonova, A. M. Evseev, and N. M. Dyatlova, *Zh. Neorg. Khim.*, 1988, **33**, 2471 [*J. Inorg. Chem. (USSR)*, 1988, **33** (Engl. Transl.)].
11. T. A. Matkovskaya, L. S. Nikolaeva, B. K. Shcherbakov, A. M. Evseev, and N. M. Dyatlova, *Zh. Neorg. Khim.*, 1987, **32**, 295 [*J. Inorg. Chem. (USSR)*, 1987, **32** (Engl. Transl.)].
12. M. I. Kabachnik, F. I. Bel'skii, M. P. Komarova, B. K. Shcherbakov, E. I. Matrosov, Yu. M. Polikarpov, N. M. Dyatlova, and T. Ya. Medved', *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1979, 1726 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1979, **28** (Engl. Transl.)].

13. B. K. Shcherbakov, F. I. Bel'skii, M. P. Komarova, Yu. M. Polikarpov, T. Ya. Medved', and M. I. Kabachnik, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1982, 560 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1982, **31** (Engl. Transl.)].
14. Ger. (East) DD 235, 068 (1986); *Chem. Abstrs.*, 1987, 106, 5628c.
15. I. S. Alfer'ev, I. L. Kotlyarevskii, N. V. Mikhalin, and V. M. Novikova, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1983, 2802 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1983, **32**, 2515 (Engl. Transl.)].
16. E. N. Rizkalla, *Rev. Inorg. Chem.*, 1983, 5, 223.
17. N. M. Dyatlova, V. Ya. Temkina, and K. I. Popov, *Kompleksony i kompleksonaty metallov* [*Metal Complexones and Complexonates*], Khimiya, Moscow, 1988, 544 pp. (in Russian).
18. M. I. Kabachnik, T. Ya. Medved', F. I. Bel'skii, and S. A. Pisareva, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1984, 844 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1984, **33**, 777 (Engl. Transl.)].
19. Monsanto Co. Brit. 1.204.967. (Cl. C07f), 09. Sep. 1970; US Appl. 636.599, 08. May 1967, 15 pp.
20. R. P. Carter, R. L. Carroll, and R. R. Irani, *Inorg. Chem.*, 1967, **6**, 939.
21. N. I. Voronezheva, Yu. V. Rudyak, N. M. Dyatlova, and A. I. Grigor'ev, *Koord. Khim.*, 1980, **6**, 991 [*Sov. J. Coord. Chem.*, 1980, **6** (Engl. Transl.)].

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