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Organophosphorus Complexones

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Organophosphorus complexones represent a new class of multidentate reagents. The paper gives a broad survey of methods for the preparation of aminoalkylphosphonic acids, which include the organophosphorus complexones, and their complexing and biological properties are described. The specific characteristics of these complexones are revealed with respect both to certain elements—beryllium, the rare-earth metals, heavy elements, etc.—and with respect to extending the pH range of complex formation. The mode of reaction of organophosphorus complexones is discussed. The bibliography contains two hundred references.

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I. INTRODUCTION

An examination of research on complexones[1] leads to the conclusion that the most important tasks of coordination chemistry in general and the chemistry of complexones in particular are problems of the stability of chelates and the selectivity of chelation.

At one time the synthesis and application of derivatives of iminodiacetic, ethylenediaminetetra-acetic (EDTA), cyclohex-1,2-ylenediaminetetra-acetic (CHDATA), diethylenetriaminepenta-acetic (DETAPA), and certain other acids solved the problem of producing a universal complexone that was highly effective for most cations over a definite pH range. Their multidentate character and configurational mobility, enabling them to assume various conformations corresponding to the structural peculiarities of the cations, make these complexones highly effective for many cations. Thus great stability of the chelates was to a considerable extent achieved, but the problems of selectivity of chelation and also those of complex formation in strongly acid and strongly alkaline media still remained unsolved. The necessity thus arose of seeking new complexing reagents.

The production of highly specific reagents is difficult, since such substances should selectively chelate cations which are very closely similar to one another in physical and chemical properties, dimensions, spatial configuration, and tendency to complex formation.

Selective multidentate complexones can probably be prepared in several ways, e.g. by building up a multidentate reagent having maximum geometrical correspondence between the internal ligand profile and the cation, by introducing into the complexone molecule electron-donor atoms and groups which interact specifically with particular cations, or by building up a multidentate reagent able to satisfy the geometrical and donor–acceptor coordination requirements of the ions of one metal while, as completely as possible, not satisfying those of the ions of all other metals. To solve these problems, it is necessary to study the influence of the structural features and the nature of complexones on complex formation and on the selective character of their action. Although consideration of these questions is at present only qualitative, it is to be hoped that the accumulation of data in this field will reveal some quantitative relations.

The chemistry of organophosphorus complexones is one of the new lines of complexone research which will lead to a solution of the above problems. We include in this group those complexones in which carboxyls have been partly or completely replaced by organophosphorus acidic groupings. Whereas the complexing properties of many organophosphorus compounds, mainly extractants (phosphates, phosphonates, and phosphines and their oxides), have been widely investigated[2-8], very little work has yet been done on organophosphorus complexones. The present review systematises published information on their synthesis and properties.

Organophosphorus complexones possess several specific properties which distinguish them fundamentally from their carboxylic analogues and enable several aspects of the selectivity of chelation to be settled. The development of organophosphorus complexones became possible only after methods had been worked out for the synthesis of aminoalkylphosphonic acids, to which group these complexones belong.

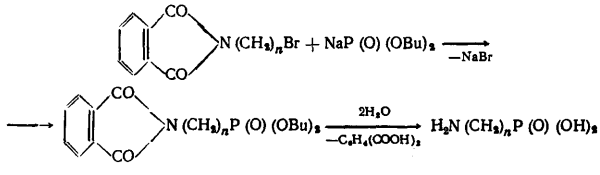
II. METHODS OF SYNTHESIS

The methods available for the preparation of aminoalkylphosphonic acids can be divided into three main groups.

1. Phosphorylation of Substituted Amines

This division comprises methods for the synthesis of aminoalkylphosphonic acids based on the introduction of a phosphonic grouping into an organic amine. The various modifications of these methods usually include either an Arbuzov rearrangement or a Michaelis–Becker reaction. The phosphorylating agents used include sodium dialkyl phosphites, trialkyl phosphites, alkylphosphonous esters, and phosphorus trichloride. In order to prevent side-reactions, the amino-group in the amines is usually blocked by easily removable protective groups.

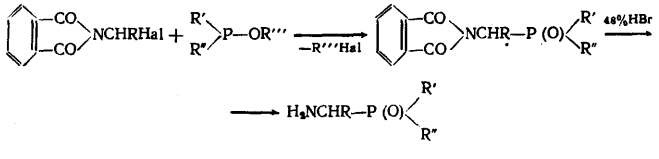
Rumpf and Chavane[9] obtained aminoalkylphosphonic acids by the action of sodium dibutyl phosphite on bromoalkylphthalimides followed by hydrolysis of the resulting phthalimidoalkylphosphonic esters:



where n = 1, 2, 4, 5, 10.

Kosolapoff[10] obtained 2-aminoethylphosphonic acid by the reaction between bromoethylphthalimide and triethyl phosphite.

This method has since been used[11] for the synthesis of α-amino-s-alkylphosphinic acids and α-aminoalkylphosphine oxides. Alkyl- and aryl-phosphonous and -phosphinous esters were subjected to Michaelis–Arbuzov condensation with N-bromomethyl- and N-1-chloroethyl-phthalimides:



where R = H, CH_3; R′ = CH_3, C_2H_5; R″ = C_6H_5, OAlk (OH after hydrolysis); and R‴ = Alk.

ω-Aminoalkylphosphonic esters are formed also by the reaction of bromoalkylamine hydrobromides with sodium dialkyl phosphites (in the proportions 1 : 2 to neutralise the hydrobromic acid liberated[12]):

$$H_2N(CH_2)_nBr\cdot HBr + 2NaP(O)(OR)_2 \rightarrow H_2N(CH_2)_nP(O)(OR)_2 + HP(O)(OR)_2 + NaBr.$$

Owing to the insolubility of hydrobromides in inert anhydrous solvents, however, the yields of the final products are low.

Phosphorus trichloride reacts with alkoxymethylamines to give derivatives of aminomethylphosphonic acid[13-15]†. Thus by adding hydroxymethylamides of aliphatic acids to excess of phosphorus trichloride, Engelmann and Pikl[17,18] obtained the corresponding substituted alkyl phosphorodichloridites $R.CONR'.CH_2.O.PCl_2$, which then isomerised into the substituted aminomethylphosphonic dichlorides. Hydrolysis of the latter readily yielded substituted aminomethylphosphonic acids $R'.NH.CH_2.PO(OH)_2$.

Taking the reaction of substituted alkoxymethylamines with phosphorus trichloride as example, Kreuzkamp and Genser showed[19] that this reaction takes place in two stages, with the formation of trialkyl phosphites and chloromethyldialkylamines as intermediate products:

$$PCl_3 + (C_2H_5)_2NCH_2OC_2H_5 \rightarrow (C_2H_5O)_3P + (C_2H_5)_2NCH_2Cl$$
$$(C_2H_5O)_3P + (C_2H_5)_2NH_2Cl \rightarrow (C_2H_5)_2NCH_2PO(OC_2H_5)_2 + C_2H_5Cl.$$

The facility of the first stage is, perhaps, due to the formation of a resonance-stabilised carbonium–immonium cation and an alkoxide anion:

$$R_2NCH_2OR' \rightarrow [R_2\ddot{N}-\overset{+}{C}H_2 \leftrightarrow R_2\overset{+}{N}=CH_2] + R'O^-.$$

In spite of the ease of the synthesis, however, this reaction has not become widely used, since its application is restricted to derivatives of aminomethylphosphonic acid.

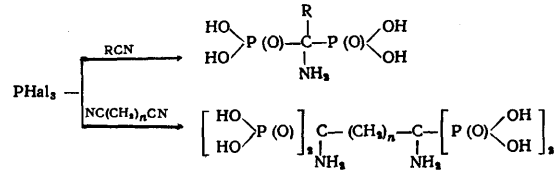
Ivanov and his coworkers have recently shown[20,21] that a similar mechanism is probably involved in the reactions of triethyl phosphite with alkoxymethylamines and with diethylaminoacetonitrile, which also yield diethylaminomethylphosphonic esters:

$$\left.\begin{matrix} R'_2NCH_2OR \\ R'_2NCH_2CN \end{matrix}\right| \xrightarrow[CH_3COOH\ or\ HCl]{(C_2H_5O)_3P} R'_2NCH_2P(O)(OC_2H_5)_2.$$

In contrast to this the reaction between triethyl phosphite and acetamidoacetyl chloride gives an ester of the corresponding amino-α-ketophosphonic acid[22]:

$$RCONHCH_2COCl + (C_2H_5O)_3P \rightarrow RCONHCH_2COP(O)(OC_2H_5)_2.$$

With nitriles and dinitriles phosphorus trihalides undergo a different type of reaction[23,24], yielding in the presence of organic (acetic) and inorganic (phosphorous) acids, on subsequent hydrolysis, the corresponding aminoalkylenepolyphosphonic acids:



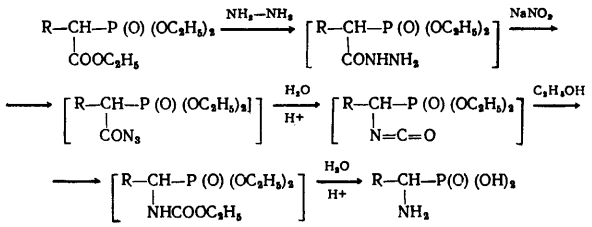
where R = Alk, Ar.

† With white phosphorus alkoxymethylamines give trisaminomethylphosphine oxide, accompanied by aminomethylphosphonic and bisaminomethylphosphinic acids as side-products[16].

2. Amination of Substituted Phosphonic Acids

In most cases classical methods of introducing an amino-group are used for the amination of substances containing a phosphonic group.

Thus by the reaction of α-ethoxycarbonylalkylphosphonic esters with hydrazine Chambers and Isbell[25] obtained the corresponding hydrazides, which after treatment with sodium nitrite and ethanol, followed by hydrolysis with concentrated hydrochloric acid, were converted into α-aminoalkylphosphonic acids in yields of 55–80%. Although the intermediate compounds in this synthesis were not isolated, there is no doubt that the process is a Curtius reaction:



where R = H, CH_3, $CH_2C_6H_5$.

Hydrazoic acid can also be used to convert carboxyalkylphosphonic into aminoalkylphosphonic acids[26]:

$$HOOC(CH_2)_nP(O)(OH)_2 + HN_3 \rightarrow H_2N(CH_2)_nP(O)(OH)_2 + N_2 + CO_2$$

as well as Hofmann decomposition of the amide[27]:

$$(C_2H_5O)_2P(O)(CH_2)_nCOOC_2H_5 \rightarrow (C_2H_5O)_2P(O)(CH_2)_nCONH_2 \xrightarrow{Br_2,KOH,H_2O}$$

$$\rightarrow (C_2H_5O)_2P(O)(CH_2)_nCH_2NH_2 \xrightarrow[H_2O]{H^+} (HO)_2P(O)(CH_2)_nCH_2NH_2,$$

Reaction of α-ketophosphonic acids with mono- and dinitrophenylhydrazines gives the corresponding phenylhydrazones, which can be converted by catalytic hydrogenation into the aminoalkylphosphonic esters[10,28]. Kosolapoff used this method to prepare α-aminobenzylphosphonic acid $C_6H_5.CH(NH_2).PO(OH)_2$.

The addition of amines at a double bond present in a phosphonic acid was described by Pudovik[29] as a case of phosphonoethylation. The reaction is usually conducted in the presence of an alkali metal or an alkali-metal alkoxide[30–33].

The above methods for obtaining aminoalkylphosphonic acids are employed comparatively rarely, since they involve the use of starting materials which are not readily available and are specific for each particular compound, and the more complicated polyaminepolyphosphonic acids cannot be obtained by these reactions. A method which eliminates to some extent these disadvantages is based on the replacement by an amino-group of the halogen in a halogenoalkylphosphonic acid.

Comparison of the kinetics of the replacement of halogen by an amino-group in methyl chloride[34] and in chloromethylphosphonic acid[35] led two of the present Reviewers to the conclusion that the phosphonic group in the latter compound has a deactivating effect on the chlorine atom. In fact, the conversion of iodo- or chloro-methylphosphonic acid into aminomethylphosphonic acid necessitates heating with concentrated ammonia in a sealed tube at 100–120°C,[36,37] and the reaction of 3-bromopropylphosphonic acid with concentrated ammonia to form 3-aminopropylphosphonic acid lasts for 2–3 weeks[10]; the yields of amino-acids are low (around 20–25%). Still more severe conditions (150–160°C) are required to replace halogen by an amino-group in arylhalogenoalkylphosphinic acids[38].

Halogen present *ortho* to the phosphonic group in an aromatic ring is replaced by an amino-group on treatment with concentrated ammonia under the conditions of the Ullmann reaction, i.e. in the presence of freshly prepared copper(I) oxide[39,40].

Primary and secondary amines react more readily than does ammonia: in strongly alkaline aqueous solution the halogen in chloromethylphosphonic acid is replaced in yields of ~ 50% at only 90–100°C. In many cases, however, mixtures of amines phosphorylated to different extents are formed, and it is frequently difficult to separate them.

In 1949 Schwarzenbach et al. synthesised dihydroxyphosphinylmethyliminodiacetic acid $(HO)_2PO.CH_2.N(CH_2COOH)_2$ and its *N*-methylbetaine $^-OPO(OH).CH_2\overset{+}{N}(CH_3)(CH_2COOH)_2$ by condensing chloromethylphosphonic acid with iminodiacetic and *N*-methyliminodiacetic acids respectively[41].

This acid has been obtained also by condensing aminomethylphosphonic acid with chloroacetic acid[42]. An analogous reaction using chloroacetic acid has been described recently for the preparation of bisdihydroxyphosphinylmethylethylenediaminediacetic acid[43].

Bersworth, Westerback and Martell, and other workers have extended to polyamines the substitution of halogen in a halogenoalkylphosphonic acid by an amino-group. Reaction of the simplest polyamine, ethylenediamine, can in principle be represented by the scheme

$$H_2NCH_2CH_2NH_2 + (n+m)\,ClCH_2PO_3^{2-} + (n+m)\,OH^- \rightarrow$$

$$\rightarrow (^{2-}O_3PCH_2)_mNH_{2-m}CH_2CH_2NH_{2-n}(CH_2PO_3^{2-})_n + (n+m)\,Cl^- + (n+m)\,H_2O$$

where n and m have the values 0, 1, 2.

It has been mentioned above that this reaction is usually accomplished by heating an aqueous solution of a mixture of ethylenediamine and chloromethylphosphonic acid at 90–100°C for several days, the pH of the medium being kept within the range 10–11 by the continual addition of aqueous alkali or sodium carbonate[44–49]. Depending on the proportions of the reactants and the reaction conditions, the product may be predominantly mono-, di-, tri-, or tetra-phosphonic acid. The polyaminepolyphosphonic acids are isolated and purified via their lead salts or by means of ion-exchange resins. Most of the acids have been isolated and identified as their sodium or potassium salts[46–49]. However, it is probably not possible to obtain individual acids in the pure form.

The reaction of chloromethylphosphonic acid with ethylenediamine has been studied in greatest detail by Uhlig and Achilles[50], who have shown that copper(II) salts have a substantial catalytic effect on the reaction. In their presence the duration of the reaction is greatly shortened (from 90–100 to 2–8 h), and preferential formation of the triphosphonic acid can be achieved. These workers isolated and identified ethylenediamine-mono-, -bis-, -tris-, and -tetrakis-methylphosphonic acids.

Besides ethylenediamine, the method has been applied also to alkylenediamines containing 2–6 carbon atoms in the chain[44,47,48,50]; to *N*-alkylated and *NN'*-dialkyl(aralkyl)-ated alkylenepolyamines of the type $RNH.A.[NH.A]_n.NHR$, where R = H, C_2H_5, C_4H_9, $C_{18}H_{37}$, $CH_2C_6H_5$, A = CH_2CH_2, $CH_2CH_2CH_2$, $CH(CH_3).CH_2$, and n = 0–4[45,51]; to alkylenediaminediacetic acids of the type $HOOC.CH_2.NH.[CH_2]_n.NH.CH_2.COOH$, where n = 2–6;[46] and to alicyclic diamines[49], aromatic amines[52], and mono-, bis-, and poly-hydroxyalkylamines[53–56].

Esters and amides of other chloroalkylphosphonic[57,58] and bischloromethylphosphinic[59] acids also exchange their chlorine for an amino-group.

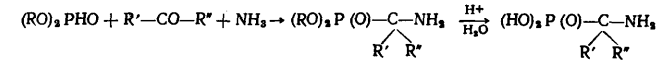
It has been claimed in a patent[60] that the use of chloromethylphosphonous acid $ClCH_2P(OH)_2$ instead of chloro-

methylphosphonic acid yields alkylenediaminetetrakismethylphosphonous acids $[(HO)_2PCH_2]_2N[CH_2]_nN[CH_2P(OH)_2]_2$.

In most cases it is not possible from patent information to assess the purity of the products, but the wide possibilities of applying this method to the phosphorylation of various polyamines indicate that it is extremely promising.

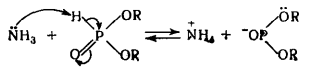
3. Condensation of Dialkyl Phosphites and their Analogues with Amines and Aldehydes or Ketones

In 1952 Kabachnik and Medved' [61,62] suggested a new method for synthesising α-aminoalkylphosphonic acids, which was based on the condensation of dialkyl phosphites with ammonia and a carbonyl compound. The resulting aminoalkylphosphonic esters were saponified to the free acids:

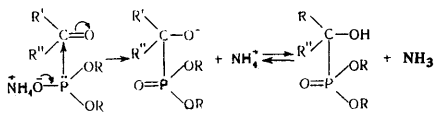


A little later Fields reported [63] the preparation of esters of substituted α-aminoalkylphosphonic acids by the action of dialkyl phosphites on primary or secondary amines and aldehydes. He was unable to obtain the free acids by saponifying the esters. Although the mechanism of this reaction was not investigated, several suggestions have been made concerning its course.

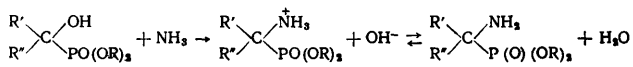
According to Kabachnik and Medved' [64] the first stage in the reaction might be ionisation of the dialkyl phosphite under the influence of ammonia, with migration of the reactive centre and formation of a phosphite anion containing a tervalent phosphorus atom‡:



followed by addition of the phosphite anion to the carbonyl compound:



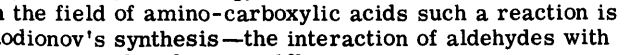
after which the hydroxy-group is replaced by amino:



To verify this hypothesis, diethyl α-hydroxybenzylphosphonate, obtained by the condensation of diethyl phosphite with benzaldehyde in the presence of a basic catalyst under the conditions of Abramov's reaction [65], was converted by heating with alcoholic ammonia into diethyl α-aminobenzylphosphonate [66].

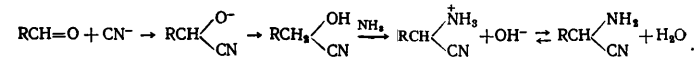
Another possibility, suggested by Fields [63], consists in the formation of an aminomethanol derivative R_2NCH_2OH as intermediate. Hellmann and Opitz [67] also regard this reaction as a typical α-aminoalkylation.

The first interpretation of the reaction mechanism is supported by its analogy with several well know reactions. In the field of amino-carboxylic acids such a reaction is Rodionov's synthesis—the interaction of aldehydes with ammonia and malonic acid [68]

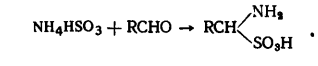


In many reactions dialkyl phosphites resemble malonic and acetoacetic esters [69]. Since, however, hydrogen attached to the phosphorus atom plays the part of the reactive methylenic hydrogen, α-amino-phosphonic acids are formed in the present case, in contrast to Rodionov's synthesis (where β-amino-carboxylic acids are formed).

Another closely analogous reaction is Zelinskii's—the formation of amino-nitriles by the action of ammonium cyanide on aldehydes [70]—where the nucleophilic cyano-group is added to the carbonyl group to form a hydroxy-nitrile, which is converted into an amino-nitrile by the action of ammonia§:



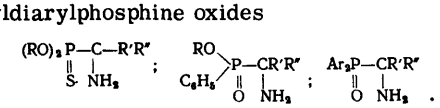
Ammonium hydrogen sulphite also adds to aldehydes with the formation of α-amino-sulphonic acids [72,73]:



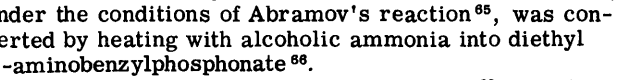
Finally, these reactions resemble the Mannich reaction, the mechanism of which has been vigorously discussed during recent years [67,74,75]. Thus phosphine, organic phosphines, and organic diphosphines react with formaldehyde and amines or with hydroxymethyl derivatives of amines under the conditions of the Mannich reaction to give the corresponding polyaminomethyl-phosphines and -diphosphines [76-79].

A common property of dialkyl phosphites, malonic ester, hydrocyanic acid, and sulphurous acid is their ability to give two series of derivatives. From this it might be supposed that the formation of amino-derivatives of the type $R.CHX.NH_2$ by the action of carbonyl compounds and ammonia is characteristic of all compounds HX which are weak acids and capable of reacting in two ways.

The above reaction was subsequently extended by the same workers to dialkyl thiophosphites [80], diaryl phosphites [81], arylphosphonous esters [64], and diarylphosphine oxides [82], compounds capable of diad tautomerism. The respective products were α-aminoalkylphosphonothioic esters, α-aminoalkylphenylphosphinic esters, and α-aminoalkyldiarylphosphine oxides



This method has been developed by Moedritzer and Irani [83], who use phosphorous acid as the phosphorus component. In syntheses with formaldehyde, ammonia, and various amines in strongly acid medium they obtained good yields of a series of α-aminoalkyl-phosphonic and -polyphosphonic acids:



Advantages of this reaction are the absence of a stage in which esters are saponified and the ease with which the products can be isolated.

Just like the phosphorus component, the amine and carbonyl components can also be varied. Hence the condensation of amines and carbonyl compounds with phosphorus compounds can be regarded as the most general method for the synthesis of α-aminoalkylphosphonic acids.

Formaldehyde has been used as the carbonyl component, usually as paraformaldehyde [31,84-86] or 40% aqueous formalin [87-93]. Use has been made also of aliphatic [62,66,95,96], alicyclic [62,95], aromatic [61,63], and heterocyclic [97] aldehydes and ketones. Aliphatic ketones react most readily;

‡ It is probable that complete transfer of the proton does not occur here, but a strong hydrogen bond is formed, which promotes transfer of the proton in the second stage.

§ It is known that hydroxy-nitriles can be converted into amino-nitriles by the action of ammonia [71].

alicyclic and alkyl aryl ketones react with greater difficulty. Purely aromatic ketones (e.g. benzophenone) and aliphatic aldehydes give only low yields of amino-phosphonic esters[95,96].

The range of application of amines—ammonia[61,62,64,66,76,95,97], primary and secondary aliphatic amines[31,63,85,93,94,98], nitrogen heterocycles[31,90], and mono- and bis-hydroxyalkylamines[88]—is also immense.

The interaction of dialkyl phosphites and carbonyl compounds with polyamines yields polyaminebisalkylphosphonic acids, which possess several interesting properties (see Section III). The reaction has been studied on alkylene-diamines[84,89,99,100] and -polyamines containing heteroatoms in a chain of methylene groups[100-102]:

$$2\,(RO)_2PHO + 2\,R'COR'' + H_2NCH_2[CH_2{-}A{-}CH_2]_nCH_2NH_2 \xrightarrow[-H_2O]{}$$
$$\rightarrow (RO)_2P(O)C(R'R'')NHCH_2[CH_2{-}A{-}CH_2]_nCH_2NHC(R'R'')P(O)(OR)_2 \xrightarrow[H_2O]{H^+}$$
$$\rightarrow (HO)_2P(O)C(R'R'')NHCH_2[CH_2{-}A{-}CH_2]_nCH_2NHC(R'R'')P(O)(OH)_2$$

where R = CH_3, C_2H_5, C_4H_9, $CH_2C_6H_5$; R′ and R″ = H, CH_3, C_2H_5, C_6H_5; n = 0, 1; and A = CH_2, O, S, NH.

The present Reviewers and their coworkers have shown that alkylenediaminebisalkylphosphonic esters can be obtained in yields of around 70–80%. The optimum reaction conditions are stoichiometric proportions of the reactants, simultaneous addition of phosphorus and carbonyl components to the polyamine (to avoid side-reactions), and a definite reaction temperature (60°C).[100,103] Hydrolysis of the esters with hydrochloric acid results in several cases in the formation of dihydrochlorides of the acids of general formula

$$[(HO)_2P(O)C(R'R'')NHCH_2CH_2{-}A{-}CH_2CH_2NHC(R'R'')P(O)(OH)_2].2HCl.$$

These are converted into the free acids by treatment with silver oxide or an organic α-oxide[100,101].

It is noteworthy that the condensation of dialkyl phosphites and carbonyl compounds with alkylenediamines yields only diphosphonic acids, in contrast to the reaction of chloromethylphosphonic acid with alkylenediamines (see subsection 2), where mixtures are always obtained of di-, tri-, and tetra-phosphonic acids, the separation of which involves great difficulties.

Apart from the fact that alkylenediaminebisalkylphosphonic acids have been especially interesting complexones of the aminoalkylphosphonic class, the presence of secondary amino-groups enables them to be used to obtain more complicated complexing agents of the phosphonic–carboxylic type. Thus by carboxymethylating ethylenediaminebismethylphosphonic acid we obtained bis-dihydroxylphosphinylmethylethylenediaminediacetic acid[84]:

$$(HO)_2PCH_2NHCH_2CH_2NHCH_2P(O)(OH)_2 \xrightarrow[\text{then HCl}]{NaCN,\ CH_2O,\ NaOH}$$
$$\rightarrow (HO)_2P(O)CH_2\diagdown\!\!\diagup N(CH_2CH_2N\diagup\!\!\diagdown CH_2P(O)(OH)_2)\diagdown\!\!\diagup CH_2COOH$$

Carboxymethylation of diethylenetriamine-*NN*″-bisisopropylphosphonic acid yields *NN*″-bis-(1-dihydroxyphosphinyl-1-methylethyl)diethylenetriamine-*N*′-acetic acid[104]:

$$(HO)_2P(O)C(CH_3)_2NHCH_2CH_2NHCH_2CH_2NHC(CH_3)_2P(O)(OH)_2 \xrightarrow{ClCH_2COOH}$$
$$\rightarrow (HO)_2P(O)C(CH_3)_2NHCH_2CH_2N(CH_2COOH)CH_2CH_2NHC(CH_3)_2P(O)(OH)_2.$$

A related method is based on the addition of dialkyl (or diaryl) phosphites to Schiff bases, the latter obtained from carbonyl compounds and amines:

$$R{-}CO{-}R' + H_2NR'' \xrightarrow[-H_2O]{} R'R\,C{=}NR'' \xrightarrow{(R'''O)_2PHO} (R'''O)_2P(O)C(RR'){-}NHR''.$$

This method permits prior removal of water in the condensation, facilitating in some cases the isolation of the aminoalkylphosphonic esters. This procedure, suggested by Pudovik[105-107], has been applied mainly to aromatic carbonyl compounds and amines, because of the ease with which the corresponding Schiff bases can be obtained[108-112]. Kennedy and Ficken[113] employed this method for synthesising α-aminoalkylphosphonate polymers of the two types

$$\vdots\ \vdots$$
$$(CH_2CHCH_2O)_2P(O)CH(CH_3)NHC_6H_5 \text{ and } (C_6H_5O)_2P(O)CH(CH_3)NHCH_2C_6H_4CHCH_2.$$
$$\vdots\ \vdots$$

The hydrolysis of the aminoalkylphosphonic esters obtained in this way has not been described, and only when hypophosphorous acid was used were the free acids obtained[114,115]:

$$RN{=}CHAr + H{-}P(H){=}O{-}OH \rightarrow HO{-}P(H){=}O{-}CH(Ar)NHR.$$

The interaction of phosphorous and hypophosphorous esters with alkoxyalkylamines or substituted methylenediamines yields respectively substituted aminoalkylphosphonic[91] and bisaminoalkylphosphinic[116] esters:

$$HP(O)(OR)_2 \xrightarrow{H_2NCH_2X} (C_2H_5)_2NCH_2P(O)(OR)_2$$
$$H_2P(O)OR \xrightarrow{H_2NCH_2X} [(C_2H_5)_2NCH_2]_2P(O)OR$$

where X = $N(C_2H_5)_2$, OCH_3, OC_2H_5. In the case of the lower ($< C_6$) hypophosphorous esters, a mixture of esters of the above two types is usually obtained.

Evdakov and his coworkers have shown that α-aminoalkylphosphonic esters can be formed also by the interaction of dialkyl *NN*-dialkylphosphoramidites with aliphatic and aromatic aldehydes and alicyclic ketones[117,118]:

$$(RO)_2PN(C_2H_5)_2 + R'COR'' \rightarrow (RO)_2P(O)C(R'R'')N(C_2H_5)_2.$$

A detailed study of this reaction has been made by Hudson et al.[119], who have extended it to arylamides of diphenylphosphinous acid:

$$R_2PNHPh + PhCHO \rightleftharpoons R_2P{-}\overset{+}{N}HPh\ (O{-}CHPh)$$
$$\rightleftharpoons R_2\overset{+}{P}H{-}NPh\ (O{-}CHPh) \rightarrow R_2PO{-}CH(Ph){-}NHPh$$
$$R_2PHO + PhCH{=}NPh \qquad R_2PO^- + Ph\overset{+}{N}H{=}CHPh$$
$$\rightarrow R_2P(O)CH(Ph)NHPh$$

III. COMPLEXING PROPERTIES

The first paper on the complexing properties of aminoalkylphosphonic acids was published in 1949 by Schwarzenbach et al.[41]. Seven years later communications appeared by Martell and his coworkers[47,120] on the potentiometric titration of these acids with metals, followed somewhat later by our own papers[84,99]. However, this early work did not reveal those interesting properties of aminoalkylphosphonic and especially polyaminepolyphosphonic acids which placed them among the most interesting and important of complexones. The most detailed studies of the complexing properties of phosphorylated polyamines have been made during recent years in the laboratories of the present Reviewers in the Institute of Organoelementary Compounds of the USSR Academy of Sciences and the Institute of Chemical Reagents and High-purity Chemicals.

Structural examination of organophosphorus complexones shows that they possess potentialities for complex formation similar to those of their carboxylic prototypes. These substances have the donor functions of the amine nitrogen atoms and the oxygen atoms of the phosphonic group, a tendency to form chelate rings, and the ability to adopt various conformations according to the configurational requirements of metal ions.

Tables 1 and 2 give the stability constants of the complexes for all the phosphorylated polyamines which have been studied up to the present, and also for comparison the stability constants of complexes of certain amino-carboxylic complexones. These data show that amino-alkylphosphonic acids are highly efficient complexing agents, in several cases not inferior to carboxylic complexones. However, in spite of the above similar prerequisites for complex formation, aminoalkylphosphonic acids possess a number of special features.

The specific character of the behaviour of organophosphorus complexones is primarily due to their increased number of donor atoms. The peculiarities of the stereochemistry of the PO_3 group also play an important part. Organophosphorus complexones differ from their carboxylic analogues in exhibiting—(1) preferential complex formation with cations of small atomic radius (beryllium, germanium, iron) and also with cations of large radius, such as the rare-earth elements, (2) diminished complex formation with the alkaline-earth metals, (3) an unusual stability sequence with transition metals, (4) the ability to form stable complexes in the acid pH range, and (5) the ability to form homo- and hetero-dinuclear complexes.

Henceforward in the text we have adopted for convenience the abbreviations for the names of the complexones listed in Table 3.

Table 1. Logarithms of stability constants for complexes of alkaline-earth and transition metals (for abbreviations for complexones see Table 3).

No.	Complexone	Mg^{2+}	Ca^{2+}	Sr^{2+}	Mn^{2+}	Co^{2+}	Ni^{2+}	Cu^{2+}	Zn^{2+}	Cd^{2+}	Pb^{2+}	Fe^{2+}	Ref.
1	EDAMP				2.20	3.20	4.40			2.7			129
					5.16	7.95	9.62	>14		7.60			
2	EDBMP	—	—	—	3.63	3.84	4.71	8.72	5.02			>8	125
3	EDABIP	<2	<2	<1	7.55	10.80	12.02	18.58	12.04		8.2	>10	125
		<2	<2	<1	8.00	11.19	11.23	20.35	13.38		16.0*	>15	
4	PMDABIP	<2	<2	<1	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	100
5	DETABIP	<1	<1	<1	3.43	4.45	4.98	9.55	5.40	4.65	6.30		100
		<1	<1	<1	9.82	13.86	14.36	19.85	15.60	13.34	17.68		
6	TBEAIP	—	—	—	3.11	2.74	—	5.96	3.75	—	5.40		100
		<3	<3	<3	8.57	10.71	11.39	15.90	12.86	12.70	14.39		
7	OBEAIP	—	—	—	—	—	—	6.30	3.76	4.96	5.65		100
		3.65	5.61	3.97	7.45	9.02	8.84	16.18	11.17	12.04	11.68		
8	EDTMP	5.0	4.95	—	6.99	8.51	9.12	11.14	9.90	8.81		—	126
		8.63	9.33		12.70	15.49	15.30	18.95	17.05	13.88			
			—		—			—				13.2	48
			5.74		9.40			16.09				19.6	
9	CHDATMP	6.41	5.49	3.72	8.42	3.3**	3.93**	9.73	9.12	8.06	7.99	23.3**	49
10	DETAPMP	3.94	4.04	—	5.34	7.35		11.60	8.44	6.36			126
		6.40	7.11		11.15	15.73		19.47	16.45	13.37			
11	PMADA	1.96	2.43	1.63									41
		6.28	7.18	5.59									
		6.00	7.1	5.40	8.0				9.0	8.5			120
12	PEADA	2.14	2.05	1.59									41
		6.33	5.44	4.10									
13	PMAAP				—			7.2					48
			4.88		7.24			13.0				16.3	
14	BPMAA				—			5.44					48
			6.17		7.0			12.53				14.65	
15	BPMEDDA	—	—	3.44	7.0	—	9.49	9.4				>12	125
		8.11	7.91	6.89	13.63	16.03	15.23	18.5	16.85*			>15	124
			8.89***	8.31***									
16	EDDA	3.9				11.2	13.5	16.2	11.1	8.8			199
17	EDTA	2.28	3.51	2.30	0.47	3.09	5.20	5.58	3.28	3.3	5.02		199
		8.69	10.59	8.63	14.04	16.31	18.62	18.80	16.50	16.46	18.04	25.1	
18	NTA	5.41	6.41	4.98	7.44	10.61	11.26	12.68	10.45	9.8		15.9	199

The first line gives values of $\lg K_{st}$ for the hydrogen complexes (MH_2L for acids Nos.2–8 and 15, MH_3L for No.10, and MHL for Nos.11–14 and 17); the lower line gives $\lg K_{st}$ for the normal complexes ML.

* Polarographic data

** Spectrophotometric data

*** Data from ion-exchange chromatography

In the remaining cases, potentiometric data.

1. Acid Dissociation

Among the aminoalkylphosphonic acids which have been investigated, two main groups of substances can be separated, which give metal complexes comparable in stability with—and in some cases even surpassing—the corresponding complexes of amino-carboxylic acids. These groups comprise (1) alkylenepolyaminebis(tris, tetrakis, and pentakis)-alkylphosphonic acids and (2) mixed alkylenepolyaminepoly-alkylphosphonic–polyacetic acids.

From a study of the titration of aminoalkylphosphonic acids with dilute acids and alkalis, Chavane[121] and Schwarzenbach[41] showed that these substances had a betaine structure. This has since been confirmed by

Table 2. Logarithms of stability constants for complexes of the rare-earth metals (for abbreviations for complexones see Table 3.).

Complexone	La^{3+}	Ce^{3+}	Pr^{3+}	Nd^{3+}	Sm^{3+}	Eu^{3+}	Gd^{3+}	Tb^{3+}	Dy^{3+}	Ho^{3+}	Er^{3+}	Tm^{3+}	Yb^{3+}	Lu^{3+}	Y^{3+}	Ce^{4+}	Ref.
EDBMP	7.49		7.84*	8.31	8.43	8.15*	8.31	8.45	8.79*	8.84	8.92	8.99*	9.44		8.79		125.150
	ppt.		ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.	ppt.		oc		
EDABIP	5.37		5.79	5.81	6.20	6.18	6	6.40	6.20	6.88	—	—	—	7.66	6.47		125.150
	10.13		10.13	11.59	12.56	12.44	12.27	12.18	12.89	12.11*	13.39	13.34	13.92*	13.37*	12.86*		
PMDABIP	4.44			4.96	5.49		5.49		5.49					6.90		8.72	100
	ppt.			ppt.	ppt.		ppt.		ppt.					ppt.		ppt.	
DETABIP	5.50			5.96	6.50												100
	9.89			12.01	14.01												
TBEAIP	4.83			5.75	5.92		5.92		5.92					6.46		8.40	100
	10.01			10.91	11.80		11.80		11.80					13.03		17.04	
OBEAIP	5.38			5.71	6.01		6.01		6.01					7.11		9.45	100
	11.06			11.04	12.02		13.37		12.04					13.36		17.62	
EDTMP	12.13			13.05	13.68		13.12			13.17		12.88					126
	20.15			21.47	22.39		21.80			21.85		21.41					
BPMEDDA	8.43		9.22	9.45	9.20	9.64*	9.22						9.20	9.20	10.36		125.150
	15.60		16.51	17.56	17.12*	17.80*	17.35	19.10*	17.45	19.02*	20.12*	20.96*	17.65	17.68	18.52*		
		18.51***													24.03***		124
EDDA	7.04		7.84	8.06	8.28	8.38	8.13	8.18	8.31	8.42	8.59	8.75	8.93	9.09	7.78		199
EDTA	3.28			4.39													
	15.50		16.40	16.61	17.14	17.35	17.37	17.93	18.30	18.67	18.85	19.32	19.51	19.83	18.09		199
DETAPA	19.48	20.15	21.17	21.6	22.34	22.39	22.46	22.71	22.82	22.78	22.74	22.72	22.62	22.44	22.05		200

DETAPA = diethylenetriaminepenta-acetic acid

* ** *** As in Table 1.

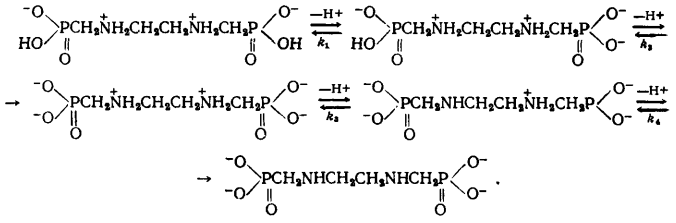
Table 3. Complexones and their abbreviations.

No.	Acid	Formula	Abbreviation
1	Ethylenediaminemethylphosphonic	$H_2NCH_2CH_2NHCH_2P(O)(OH)_2$	EDAMP
2	Ethylenediaminebismethylphosphonic	$(HO)_2P(O)CH_2NHCH_2CH_2NHCH_2P(O)(OH)_2$	EDBMP
3	Ethylenediaminebisisopropylphosphonic*	$(HO)_2P(O)C(CH_3)_2NHCH_2CH_2NHC(CH_3)_2P(O)(OH)_2$	EDABIP
4	Pentamethylenediaminebisisopropylphosphonic	$(HO)_2P(O)C(CH_3)_2NH(CH_2)_5NHC(CH_3)_2P(O)(OH)_2$	PMDABIP
5	Diethylenetriamine-*NN''*-bisisopropylphosphonic	$(HO)_2P(O)C(CH_3)_2NHCH_2CH_2NHCH_2CH_2NHC(CH_3)_2P(O)(OH)_2$	DETABIP
6	Thiabisethylamineisopropylphosphonic	$(HO)_2P(O)C(CH_3)_2NHCH_2CH_2SCH_2CH_2NHC(CH_3)_2P(O)(OH)_2$	TBEAIP
7	Oxabisethylamineisopropylphosphonic	$(HO)_2P(O)C(CH_3)_2NHCH_2CH_2OCH_2CH_2NHC(CH_3)_2P(O)(OH)_2$	OBEAIP
8	Ethylenediaminetetrakismethylphosphonic	$[(HO)_2P(O)CH_2]_2NCH_2CH_2N[CH_2P(O)(OH)_2]_2$	EDTMP
9	Cyclohex-1,2-ylenediaminetetrakismethylphosphonic	$C_6H_{10}\{N[CH_2P(O)(OH)_2]_2\}_2$	CHDATMP
10	Diethylenetriaminepentakismethylphosphonic	$[(HO)_2P(O)CH_2]_2NCH_2CH_2NCH_2CH_2N[CH_2P(O)(OH)_2]_2$ (with $CH_2P(O)(OH)_2$ on the central N)	DETAPMP
11	Dihydroxyphosphinylmethylaminediacetic	$(HO)_2P(O)CH_2N(CH_2COOH)_2$	PMADA
12	Dihydroxyphosphinylethylaminediacetic	$(HO)_2P(O)CH_2CH_2N(CH_2COOH)_2$	PEADA
13	Dihydroxyphosphinylmethylamine-*N*-acetic-*N*-propionic	$(HO)_2P(O)CH_2N(CH_2COOH)(CH_2CH_2COOH)$	PMAAP
14	Bisdihydroxyphosphinylmethylaminoacetic	$[(HO)_2P(O)CH_2]_2NCH_2COOH$	BPMAA
15	Bisdihydroxyphosphinylmethylethylenediamine-*NN'*-diacetic	$(HO)_2P(O)CH_2N(HOOCCH_2)CH_2CH_2N(CH_2P(O)(OH)_2)(CH_2COOH)$	BPMEDDA
16	Ethylenediaminediacetic	$HOOCCH_2NHCH_2CH_2NHCH_2COOH$	EDDA
17	Ethylenediaminetetraacetic	$(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$	EDTA
18	Nitrilotriacetic	$(HOOCCH_2)_3N$	NTA

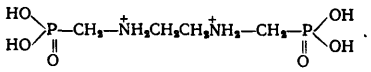
* "Phosphicin" = disodium salt of EDABIP.

results for the infrared spectra[86] and by X-ray examination[122]. Recently Burpitt and Goodlett have shown[123] by means of nuclear magnetic resonance (n.m.r.) that several dimethyl esters of substituted α-aminoalkylphosphonic acids are also internal salts.

For the initial member in the first group of organophosphorus complexones—ethylenediaminebismethylphosphonic acid (EDBMP)[84,101]—the possible stages of dissociation can be represented, according to our results, by the equations



An analogous scheme of dissociation is probably applicable in the remaining cases. In strongly acid media the original betaine is able to take up two protons to form the doubly charged cation



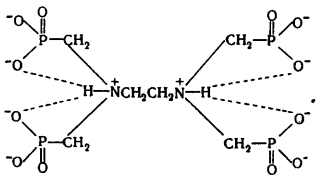
Comparison of the dissociation constants of aminoalkylphosphonic acids of the first group (Table 4) and of analogous carboxylic acids reveals a difference in the properties of these substances. For example, aminoalkylphosphonic acids have values of the latter two dissociation constants,

Table 4. Negative logarithms of dissociation constants of complexones.

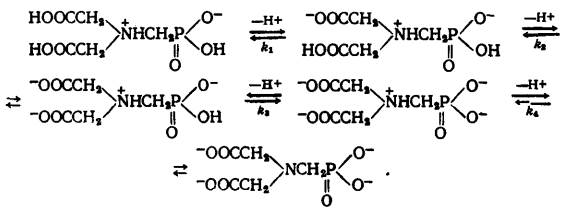
Complexone	pK_1	pK_2	pK_3	pK_4	pK_5	pK_6	pK_7	pK_8	pK_9	pK_{10}	Ref.
EDAMP	4.85	7.36	10.25								119
EDBMP	4.61	5.72	8.02	10.47							125
EDABIP	4.95	6.00	8.55	11.68							125
PMDABIP	5.77	6.13	11	11							100
DETABIP	5.39	6.55	10.40	11.20							100
TBEAIP	5.51	6.34	10.38	11.48							100
OBEAIP	5.15	6.40	10.56	11.48							100
EDTMP	1.46	2.72	5.05	6.18	6.63	7.43	9.22	10.60			48
	1	1.5	3.02	5.22	6.40	7.85	9.82	11.00			50
	—	—	3.0	5.23	6.54	8.08	10.18	12.10			126
CHDATMP	2.40	3.70	5.32	6.46	6.97	7.69	9.39	10.89			
DETAPMP	—	—	2.8	4.45	5.50	6.38	7.17	8.15	10.10	12.0	126
PMADA	2.00	2.25	5.57	10.76							41
PEADA	1.95	2.45	6.54	10.46							41
PMAAP	2.72	3.48	5.59	10.41							48
BPMAA	1.73	2.00	5.01	6.37	10.80						48
BPMEDDA	1.5	2.30	4.65	6.16	8.36	10.3					125
	2.0	2.68	5.66	6.12	8.34	10.7					124
EDDA	6.42	9.46									199
EDTA	2.00	2.67	6.16	10.26							199
NTA	1.89	2.49	9.73								199

corresponding to elimination of the betaine protons, which are unusually large but differ relatively little from one another. This is observed especially clearly in the diphosphonic acids as the methylene chain linking the aminoalkylphosphonic groups becomes longer, when the difference in the latter two dissociation constants decreases to factors of $10^{1-0.5}$, which can be explained by the weakening of the inductive effect exerted by one $^+NH_2.C.PO_2^{2-}$ group on the other[101]. Introduction of a heteroatom—nitrogen, oxygen, or sulphur—into the methylene chain has no significant effect on the dissociation constants of the corresponding acids[100].

In the case of tri-, tetra-, and penta-phosphonic acids the decrease in repulsion between the two positively charged nitrogen atoms is probably due partly to the high charge on the anion and partly to electrostatic bonding (a weak hydrogen bond) of the betaine protons to the negatively charged oxygens of the phosphonic groups[48]:



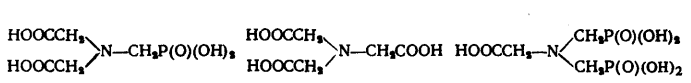
The dissociation constants of the mixed polyamine-polyphosphonic-polyacetic acids are given in Table 4. In view of the difference in basicity between carboxyl and phosphonic acid groups, it may be supposed that in this case the betaine structure is produced at the expense of the hydrogens of the latter groups. Further assignment of the individual dissociation constants of these acids to the successive elimination of carboxylic, the second phosphonic, and then the betaine protons enables the following dissociation scheme to be put forward[41,120,124,125]



2. Effect of Increase in Multidentate Character

It might have been expected that successive replacement of one, two, . . . , and finally all the carboxymethyl groups in polyamino-polycarboxylic acids by dihydroxyphosphinylalkyl groups would be accompanied by a corresponding regular change in the complexing properties of these substances. However, this is not observed.

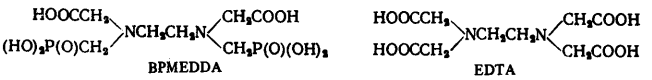
Whereas dihydroxyphosphinylmethylamine-*NN*-diacetic acid (PMADA) gives more stable complexes, both with alkaline-earth metals and with transition-metal ions, than does nitrilotriacetic acid (NTA)[41,120], bisdihydroxyphosphinylmethylaminoacetic acid (BPMAA) gives less stable complexes than does nitrilotriacetic acid throughout a comparable series of metals[48].



PMADA NTA BPMAA

Bisdihydroxyphosphinylmethylethylenediaminediacetic acid (BPMEDDA) forms with copper(II) and the rare-earth elements more stable complexes than does ethylenediaminetetra-acetic acid (EDTA)[124,125], while ethylenediaminetetrakismethylphosphonic acid (EDTMP)[48,126] and cyclohex-1,2-ylenediaminetetrakismethylphosphonic acid (CHDATMP)[49]¶ exhibit weaker complexing powers than do their carboxylic analogues—EDTA and CHDATA.

¶ The stability constants of the metal complexes of CHDATMP seem too low, since they have probably been calculated without regard to the hydrogen complexes [see subsection 3, below].



BPMEDDA EDTA

$[(HO)_2P(O)CH_2]_2NCH_2CH_2N[CH_2P(O)(OH)_2]_2$ EDTMP

$C_6H_{10}\{N[CH_2P(O)(OH)_2]_2\}_2$ CHDATA

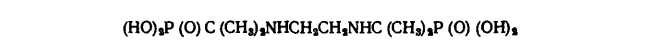
Moreover, the increase in the number of dihydroxyphosphinyl groups on passing from EDTMP to DETAPMP (diethylenetriaminepentakismethylphosphonic acid)



DETAPMP

somewhat diminishes the stability of the complexes formed with alkaline-earth and transition metals, only those with the rare-earth elements constituting an exception[126].

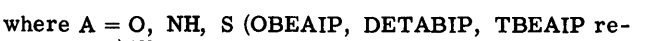
The opposite situation is found with polyaminediphosphonic acids: for example, ethylenediaminebisisopropylphosphonic acid (EDABIP)



EDABIP

not only surpasses in efficiency of complex formation its corresponding ethylenediaminediacetic acid (EDDA), but with copper(II) even surpasses EDTA[125].

Thus the replacement of one carboxymethyl by a dihydroxylphosphinylalkyl group increases the complexing power of the compound, whereas the attachment of more than one of the latter groups to the same nitrogen atom diminishes the efficiency of complex formation. Martell and his coworkers[48] attribute this to the fact that, from steric considerations, two dihydroxyphosphinyl groups attached to one nitrogen atom cannot both take part in coordination, while their high negative charge still more impedes complex formation with cations bearing a low charge (2+). Therefore the conditions are more favourable to cations bearing a high charge. It is possible on the basis of this hypothesis to explain the high stability constants of the complexes formed by iron(III) with the compounds EDTMP, CHDATMP, and EDABIP[48,49,125] and by the rare-earth elements(III) with all the aminoalkylphosphonic acids investigated[124-127], and also the enhanced stability, even in comparison with trebly charged rare-earth elements, of the complexes of cerium(IV) with the compounds

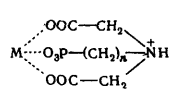


where A = O, NH, S (OBEAIP, DETABIP, TBEAIP respectively)[100].

3. Hydrogen Complexes

A characteristic feature of organophosphorus complexones is their ability to form, besides the normal complexes, stable complexes with metal ions in the pH range preceding the dissociation of the betaine protons. These are termed "hydrogen" or "acid" complexes.

The existence of such complexes was established by Schwarzenbach et al.[41] for the complexes of aminoalkylphosphonic-diacetic acids with alkaline-earth metal ions. These workers attributed to the complexes the structure



and made special mention of the absence of a metal-nitrogen bond in such a complex.

It has since been shown[48,100,125,126] that all polyamine-polyphosphonic acids form in the acid pH range very stable hydrogen complexes with ions of transition metals and rare-earth elements, as well as with bismuth (III), arsenic(III), antimony(III), titanium(IV), tin(IV), and molybdenum(VI) (polarographic data)[128]. Even pentamethylenediaminebis-isopropylphosphonic acid (PMDABIP, A = CH_2), which is a weak complexing agent owing to the great distance between the 1-dihydroxyphosphinyl-1-methylethylamino-groups, nevertheless in the acid pH range gives complexes with rare-earth elements having stability constants[100] of the order of 10^5–10^8.

It is especially noteworthy that in several cases the acid complexes of phosphorylated polyamines are comparable in stability with the normal complexes of amino-carboxylic analogues. Thus rare-earth elements form with EDABIP acid complexes of the same order of stability as the normal complexes they form with EDDA.

Further, unlike the complexes of amino-polycarboxylic acids, the normal complexes of EDTMP and DETAPMP (ML) and their mono-, di-, and tri-protonated complexes (MHL, MH_2L, and MH_3L) are closely similar in stability[126].

Elements having a coordination number of 8 (rare-earth elements, thorium) form stable hydrogen complexes having the composition $M(H_2L)_2$.[125]

The hydrogen complexes formed by beryllium with aminepolyphosphonic acids will be discussed below.

4. Dependence of Stability of Complexes on Position of Metal in Periodic Table

(*a*) Alkaline-earth metal complexes. Amino-alkyl-mono- and -di-phosphonic acids form relatively unstable complexes with alkaline-earth metals, their stability constants not usually exceeding 100.[100,125] With acids containing four or five dihydroxyphosphinyl groups (EDTMP, CHDATMP, DETAPMP), however, the stability constants increase to $10^3(Sr^{2+})$–$10^8(Mg^{2+},Ca^{2+})$.[48,49,126]

The introduction of carboxymethyl groups tends to promote complex formation with alkaline-earth metals, and the complexes of mixed aminoalkylphosphonic–acetic acids with these metals are only slightly less stable than those of the corresponding carboxylic analogues[41,48,100,120,124,125].

(*b*) Transition-metal complexes. The introduction of one dihydroxyphosphinylmethyl group into the ethylenediamine (EDA) molecule—giving ethylenediamine-methylphosphonic acid $NH_2CH_2CH_2NHCH_2PO(OH)_2$ (EDAMP)[129]—increases the complexing power towards transition metals, but not so much (Table 5) as might have been expected from the probable closing of two chelate rings.

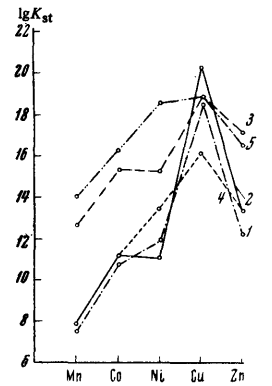
With metal ions whose 3*d*-level is almost complete, aminepolyphosphonic acids form complexes comparable in stability with those of the corresponding aminepolyacetic acids. Irving and Williams[130] established experimentally the sequence

$$Mn<Fe<Co<Ni<Cu>Zn$$

confirmed by Yatsimirskii[131] on the basis of crystal-field theory, for the stability of complexes formed by bivalent transition metals with polyamines and most of the analogues of EDTA. Although, as the accompanying diagram shows, the general variation in stability of the complexes is about the same for these compounds and for phosphorylated derivatives of polyamines, different curves are obtained in the two cases for the variation in the logarithm of the stability constant of the complex with the atomic number of the transition metal. With the phosphorylated derivatives of polyamines the nickel complexes are usually less stable than those of cobalt and zinc, differing in stability constants in the latter case always by factors of 10^2–10^3.

Table 5. Logarithms of stability constants of transition-metal complexes (metal : ligand ratio = 1 : 1).

Metal	EDAMP	EDA
Mn^{2+}	5.16	2.63
Co^{2+}	7.95	5.89
Ni^{2+}	9.62	7.66
Cu^{2+}	~14	10.66
Cd^{2+}	7.60	5.47



Graphical dependence of logarithm of stability constant for transition-metal complexes on the atomic number of the element for the complexones:
1) EDBMP; *2*) EDABIP; *3*) EDTMP; *4*) EDDA; *5*)EDTA.

An especially noteworthy feature is the considerably greater difference than usual between the stability constants of corresponding complexonates of copper and of other transition metals. The stability constants of the copper complexes of the alkylenepolyaminebisalkylphosphonic acids EDABIP, OBEAIP, and DETABIP vary between 10^{18} and 10^{20}, exceeding those of the nickel complexes by factors of 10^6–10^9,[100,125] which is quite exceptional in comparison with the complexes of polyamino-polycarboxylic acids. Whereas most transition metals form less stable complexes with the acids investigated than with EDTA, the copper(II) complex of EDABIP is more stable than the corresponding EDTA complex by a factor of 10^2.[125]

Unusual behaviour is shown by EDABIP towards iron(III). By forming a soluble complex in the pH range in which the betaine proton undergoes dissociation, iron (in fivefold excess) is not precipitated even in the presence of ten equivalents of alkali. The solution changes colour from pale yellow to wine red, gradually passing into a colloidal sol, and then into a gel[125]. This can probably be explained

by the formation in solution of a polycyclic chelate compound of polymeric type, in which cross-linkage occurs through hydroxide ions.

Stable complexes with iron(III) are formed also by EDTMP [48] and CHDATMP. [49] The extraordinarily high stability of the iron(III) complex of the latter acid in comparison with the complexes formed by other metals enabled Banks and Yerick to titrate iron in the presence of a large variety of cations (alkaline-earth metals, Al^{3+}, Zn^{2+}, Cd^{2+}, Hg^{2+}, Cu^{2+}, Ti^{4+}, Cr^{3+}, Be^{2+}, etc.)[49].

(*c*) Rare-earth metal complexes. The potential ability of aminoalkylphosphonic acids to increase their multidentate character by means of the oxygen atoms of the dihydroxyphosphinyl groups favours their formation of complexes with the rare-earth metals, which are known to be characterised by a high coordination capacity and a strong affinity for oxygen.

Alkylenepolyaminebisalkylphosphonic acids form complexes with rare-earth metals whose stability constants exceed by factors of 10^3–10^4 those for the corresponding complexes of EDDA [100,125,127]. In the case of EDBMP, which forms water-insoluble complexes, this difference would apparently be still larger, in view of the fact that even the acid complexes of this complexone with rare-earth metals are more stable than the normal complexes of EDDA. [125]

A still stronger complexing action on rare-earth metals was exhibited by EDTMP. Although in the acid pH range (up to five equivalents of alkali) it forms water-insoluble complexes having the composition $M_4(H_4L)_3$, the normal complexes, which are soluble in water at higher pH values, are far more stable than the corresponding complexes of EDTA, and are not inferior in stability to the complexes of diethylenetriaminepenta-acetic acid (DETAPA), which is regarded as the "champion" for complex formation with rare-earth metals [126]. It has been shown also that, in the presence of excess of a rare-earth element, EDTMP forms in the alkaline range soluble polynuclear complexes in which the proportions of metal to complexone are 2 : 1, whereas DETAPMP forms 3 : 1 complexes [126].

Note must be taken also of the masking power for the rare-earth metals exhibited by all the organophosphorus complexones studied [132].

(*d*) Beryllium(II) complexes. Complex formation with beryllium is especially interesting. It has been established that beryllium forms stable complexes with organophosphorus complexones, and this is most specific of the latter, distinguishing them fundamentally from their carboxylic analogues.

Potentiometric titration of mixtures of beryllium(II) and EDABIP (H_4L) in various proportions shows that, in the range preceding titration of the betaine hydrogens, homodinuclear complexes Be_2H_2L and intermediate mononuclear complexes BeH_2L are formed in solution [133].

Neither increasing the distance between the dihydroxyphosphinylalkyl groups as in PMDABIP nor replacing the middle methylene group in the latter by oxygen (OBEAIP) or sulphur(TBEAIP) makes any fundamental change in complex formation with beryllium compared with EDABIP. [134]

When carboxymethyl groups are introduced into an organophosphorus complexone, as in BPMEDDA, complexes are formed with beryllium only after two protons have been titrated. Both this and the fact that the corresponding BeH_2L and Be_2H_2L complexes are closely similar in stability to the corresponding complexes of the above diphosphonic acids probably indicate that the carboxymethyl groups are not involved in the coordination of beryllium [134]. It is interesting that this complexone masks beryllium from precipitation by hydroxides, which constitutes the first case of the masking of beryllium by a complexone [132].

The stability constants of the beryllium complexes, calculated for the monomeric compounds, are given, together with the solubility products of the insoluble complexes, in Table 6.

Table 6. Logarithms of stability constants and solubility products K_s for beryllium(II) complexes.

Complexone	BeH_2L		Be_2H_2L	
	K_s	$\lg K_{st}$	K_s	$\lg K_{st}$
EDBMP	$(2\pm1)\cdot10^{-12}$	8.76	$(3\pm1)\cdot10^{-14}$	11.4
EDABIP	—	7.65	—	11.39
PMDABIP	—	6.15	—	11.21
OBEAIP	—	7.34	—	12.46
TBEAIP	—	7.15	—	11.97
BPMEDDA	—	7.15	$(3\pm1)\cdot10^{-12}$	11.64

In the pH range corresponding to titration of the betaine hydrogens in the free acids, hydroxo-complexes BeH_2LOH and $Be_2H_2L(OH)_2$ are formed in all the cases mentioned, no complexes containing a beryllium–nitrogen bond being produced. This is confirmed also by the identity of the titration curves for beryllium with methyl-, chloromethyl-, and aminoisopropyl-phosphonic acids [135] and the high stability constants of the beryllium complexes of polymethylenediphosphonic acids not containing nitrogen atoms in the polymethylene chain (Table 7) [136].

Table 7. Solubility product and logarithms of stability constants for beryllium(II) complexes of alkylenediphosphonic acids.

Acid	BeL		Be_2L	
	K_s	$\lg K_{st}$	K_s	$\lg K_{st}$
Methylenediphosphonic	—	8.82	—	19.15
Hexamethylenediphosphonic	$(5\pm2)\cdot10^{-13}$	6.31	$(6.6\pm4.0)\cdot10^{-19}$	15.5

The fact that not all the donor atoms of a ligand take part in complex formation makes possible the coordination of another cation. In fact the formation of bimetallic heteronuclear complexes has been established in the polarographic investigation of complicated beryllium complexonate–metal ion (Ca^{2+}, Mn^{2+}, Fe^{3+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}) systems [133]. This is confirmed also by the correlation (Table 8) between the dependence of the logarithm of the stability constant of the complex ML and that of the pH at which beryllium is precipitated from a polyheteronuclear complex on the atomic number of the second metal present in the complex. A rough calculation showed [133] that the stability constants of the polynuclear complexes exceed those of the complexes ML by factors of 10^2–10^3 (Table 8).

5. Effect of Heteroatoms on the Stability Sequence of Metal Complexes

The presence in a complexone molecule of heteroatoms—nitrogen, oxygen, sulphur—which tend to coordinate with metals, produces some selectivity with respect to certain cations. Thus for the alkaline-earth metals the relative order of stability is O > N > S, for transition metals containing almost complete *d*-orbitals it is N > S > O, and for rare-earth elements it is O > N > S.

Table 8. Logarithms of stability constants for complexes of transition metals with OBEAIP and pH for hydrolysis of beryllium from the corresponding polynuclear complexes.

Complex	M^{2+}	$\lg K_{st}$ ML	pH of hydrolysis
Be^{2+}	—	—	6.3
$BeH_2L(OH)_2$	—	—	8.3
$BeML(OH)_2$	Ca	5.1	8.2—8.3
	Mn	10.19	8.1—8.2
	Fe	10.90	7.9—8.1
	Co	11.44	7.7—7.9
	Ni	13.13	7.5—7.7
	Cu	18.33	6.4—6.6
	Zn	13.11	7.4—7.6

Complex formation by the phosphonic analogues of such complexones has been investigated on alkylenepolyaminebisisopropylphosphonic acids containing oxygen, a secondary amino-group, and sulphur as heteroatom (OBEAIP, DETABIP, and TBEAIP), and also on PMDABIP), in which a methylene group which is definitely incapable of complex formation acts as a quasi-heteroatom [100]. With the phosphorylated derivatives of polyamines as well, the heteroatoms were shown to coordinate to metal ions, but their effect is not so great as, and the stability sequence of the complexonates is somewhat different from, those with the polyamino-polycarboxylic acids: for the alkaline-earth metals the order is O > S > N, for the transition metals N > S > O, and for the rare-earth metals it is N > O > S. In the case of DETABIP (nitrogen as heteroatom) a large difference has also been established in the stability of the complexes from element to element in the rare-earth metals, and hydrogen complexes of more than one type are formed by the elements from gadolinium onwards.

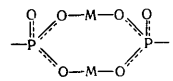
6. Structure of the Complexes

There are still very few studies of the mechanism of coordination of metal ions by phosphorylated polyamine derivatives, the reasons for the specific character of their action, the role of the phosphonic group in complex formation, and other problems.

The structure of complexes of aminepolyphosphonic acids in which coordination of the metal by nitrogen atoms is absent (hydrogen complexes, beryllium complexes, etc.) can be explained by two alternative hypotheses—(1) formation of a four-membered ring



in which the metal ion is coordinated by two of the three oxygen atoms of the phosphonate group, and (2) formation of an eight-membered ring



in which two metal ions are coordinated with four oxygen atoms of two phosphonate groups. Let us examine these postulates in greater detail, noting that neither structure is to be regarded as universally applicable to all metal ions.

1. Four-membered rings were once regarded as unstable and of rare occurrence in the chemistry of complex compounds. However, recent investigations have shown [141-145] that such rings can be formed with metal ions not only by sulphonate, carbonate, and dithiocarbonate groups but also by nitrate, trifluoroacetate, and triazen groups. It has been concluded from these investigations that polyatomic ligands in which two chemically equivalent atoms are situated closer together than are a pair of mutually independent atoms exhibit a tendency to operate through both equivalent atoms, in such a way that the middle position of this pair is located approximately at a vertex of one of the usual coordination polyhedra (octahedron or tetrahedron) [146].

In relation to phosphonate groupings this situation could be interpreted in terms of coordination of the metal ion by two oxygen atoms in each phosphonate group, in such a way that the ligand field would have a roughly tetragonal (octahedral or tetrahedral) configuration; the oxygen atoms, however, do not lie at vertices of the corresponding polyhedron, but form a new distorted polyhedron in which the coordination number of the metal is higher than usual. It is quite difficult to say anything *a priori* concerning the possible spatial configurations which are produced in this case, probably a dodecahedron or distorted antiprism type of configuration. However, it is not excluded that in certain cases the two oxygen atoms of the phosphonate group will occupy two coordination sites in the usual way [147-149].

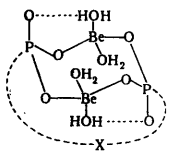
The suggested mechanism [150] provides an explanation not only for the existence and stability of the hydrogen complexes but also for several other features of complex formation by organophosphorus complexones. It suggests that, in normal complexes in which hydrogen atoms are involved in coordination, structures can be produced in several cases having additional four-membered rings, together with the usual structures in which only one oxygen atom of each phosphonate group takes part in coordination, similarly to carboxyl oxygen [151-154]. It is possible that the enhanced stability of complexes formed by phosphorylated polyamines with copper(II), lead(II), and the rare-earth metals is due to the formation of such structures strengthened by additional rings.

A very likely possibility is the formation of complexes, whose structure contains four-membered rings the phosphonate oxygens of which lie at the corners of polyhedra, with metals having a large covalent radius, e.g. uranyl UO_2^{2+} and zirconium(IV). [155,156] In fact it has recently been observed that phosphorylated polyamines exhibit special affinity for uranium in particular [157].

2. The hypothesis of eight-membered bridging rings of the type indicated above has been used by Block and his coworkers to explain the structure of the polymeric tetrahedral complexes formed by Co^{2+}, Zn^{2+}, Be^{2+}, and Cr^{3+} with dimethyl-, diphenyl-, and methylphenyl-phosphinic acids R_2POOH. [158-160] The probable existence of such structures has been confirmed by infrared spectroscopy [161-163]

and X-ray examination[164] for compounds such as the polymeric $\{[R_2PO_2]_nCo\}_n$ and the dimeric $[(C_6H_5)_2PO_2]_2 \cdot [Co(CH_3COCHCOCH_3)_2]$ [sic†].

Kabachnik et al. have suggested this type of structure for the beryllium complexes of alkylenepolyphosphonic and alkylenepolyaminebisalkylphosphonic acids[134,136]. The improved stability of such complexes in acid medium is attributed to stabilisation of the molecule as a whole by internal hydrogen bonds formed by coordinated water molecules and the phosphonate oxygen atoms in a similar manner to that suggested for phosphate complexes[165] and ammines of metal acetates[166,167]. Thus the complex Be_2H_2L (where H_4L = EDABIP, OBEAIP, TBEAIP) is probably built up in such a way that each beryllium ion is coordinated by two oxygen atoms from different phosphonate groups, while the hydrogen bonds form two additional six-membered rings:



Calculations show that the stabilising hydrogen bond should be strong, the O...O distance being around 2.5–2.6 Å.

The above discussion shows that investigation of the efficient and highly selective group of organophosphorus complexones is still far from complete. A series of questions should be studied. Thus the mechanism of complex formation by the phosphonate group and the nature of the selectivity of its action remain obscure. More complete data must be obtained on the dependence of the complexing power of aminepolyphosphonic acids on the position of a metal ion in the Periodic System, and the reasons for the departure from the order of the Irving–Williams series explained.

However, several practical applications are already being planned for this group of complexones. Because of their selective action, phosphorylated polyamines can be successfully used for the fractional determination of cations present in difficultly separable combinations. The great difference in stability of complexes of polyaminepolyphosphonic acids with transition metals and with rare-earth metals, and also the formation with the rare earths of soluble and insoluble complexes exhibiting a quite large difference in stability constants, not only enable the rare-earth elements to be separated from transition metals but also hold out the promise of separating pairs of rare earths lying close together. Complex formation by aminoalkylphosphonic acids in acid medium opens up wide possibilities in work with readily hydrolysable salts. The high stability constants of the complexes formed by several of the above complexones with copper(II) and iron(III) make them promising both for the treatment of copper and iron chloroses of plants in agriculture and for cleaning and passivating surfaces in power engineering equipment[168].

Monoesters of α-anilinobenzylphosphonic acid can be used for the extraction of metals from aqueous solutions[169]. Patents have been taken out for the use of aminoalkylphosphonic and aminoalkylphosphonous acids to soften water[23,24], to prevent the decomposition of peroxy-compounds (by combining with copper(II) ions, which catalyse the oxidation), to remove rust marks from metal structures[24], for the chelation of rare-earth and heavy metals[35,36], to prevent the precipitation of aluminium hydroxide during the etching of aluminium and its alloys[170], as nematocides and soil fungicides[60], as additives to lubricating oils[45,94], etc.

IV. BIOLOGICAL PROPERTIES

Until recently information on the biological properties of aminoalkylphosphonic acids was confined to a few disconnected publications concerned with the search for bacteriostatic preparations.

Although aminoalkylphosphonic acids can be regarded as phosphorus analogues of amino-carboxylic acids, which form part of vegetable and animal organisms, for a long time nothing was known of their occurrence in Nature. It was only in 1959 that Horiguchi and Kandatsu were able[171-172] to isolate from *Rumen protozoa* 2-aminoethylphosphonic acid $NH_2CH_2CH_2PO_3H_2$, which was given the name ciliatin‡. This was the first example of the occurrence in biological materials of a compound containing a carbon-phosphorus bond. Ciliatin and its ester with glycerol have since been detected also in bacteria of the type *Tetrahymena*[173-175], in the sea-anemone *Anthopleura elegantissima*[176], and in *Metridium dianthus*[177]. The crystal structure of ciliatin has been elucidated by Okaya[122] by X-ray structural analysis. A mechanism for the production of ciliatin in biological systems has been suggested recently by Segal[178].

In the course of the investigation of aminoarylphosphonic acids as possible analogues of sulphonamide preparations it was found that phosphanilic (*p*-aminophenylphosphonic) acid and some of its analogues possess bactericidal properties[179-184], while aminomethylphosphonic acid suppresses tobacco mosaic virus[185]. This last compound and several other aminoalkylphosphonic acids can retard the growth of the silkworm and the chick embryo, although they are not natural metabolites of these organisms[185]. It has been found also that in protein synthesis aminomethylphosphonic acid diminishes the inclusion of methionine[186]. No fundamental practical advance was made on these lines of investigation.

A systematic study of the biological properties of aminoalkylphosphonic acids was undertaken in connection with the synthesis of polyaminepolyalkylphosphonic acids and the elucidation of the specific character of their complexing properties, when possibilities were opened up for using substances of this type to treat metal poisoning in humans. Broad biological investigations of organophosphorus complexones are being conducted at the present time in the Institute of Industrial Hygiene and Occupational Diseases of the USSR Academy of Medical Sciences by one of the present Reviewers and his collaborators. It has been found[187] that derivatives of 1-amino-1-methylethylphosphonic acid, applied parenterally as the sodium salts, are tolerated in large doses by animals (mice, rats, guinea-pigs, and rabbits). Thus LD_{min} of sodium ethylenediaminebisisopropylphosphonate (the corresponding medicinal preparation is "phosphicin") is 6 g kg^{-1} for rats and mice. The absence of hypocalcaemia among the animals' symptoms, as a consequence of the low stability constant of the calcium complex, has enabled the sodium salts of these acids to be used even in large doses. Prolonged repeated injections of phosphicin did not affect the increase in weight of animals, the threshold of nervomuscular excitability to electrical stimuli, or the blood pressure, nor did they disturb the functioning of the

† The reference quoted deals with such polymeric compounds of chromium(III) which contain a $(CrOPO)_2$ bridge structure (Ed. of Translation).

‡ This name does not appear to be used in the reports in English on this material (Ed. of Translation).

kidneys or the ability of the liver to render noxious substances harmless. In animals no changes were observed in the peripheral blood. Phosphicin did not change the activity of hydrolases acting on ester bonds (EC.3. 1,.

Experiments with ^{14}C-phosphicin showed that the preparation was completely eliminated two days after parenteral introduction. After one day the urine shows its maximum activity, but a considerable proportion of the preparation is eliminated by the intestines. After ^{14}C-phosphicin has been introduced *per os*, a larger proportion of it is excreted by the intestines [188]. The effect of phosphicin on the metabolism of calcium has been examined in detail. Experiments with ^{45}Ca showed that no danger of hypocalcaemia arose on the introduction of phosphicin [188]. This distinguishes phosphicin fundamentally from polyaminepolyacetic acids, which cannot be applied as their sodium salts owing to the hypocalcaemia which they produce [189]. The relative instability of the calcium complexonates is an important property of polyaminediphosphonic acids, since, as a consequence of the high concentration of calcium in the blood, this cation competes, for a position in the complex, with any metal introduced into the organism.

The effectiveness of amino-polycarboxylic acids in the organism is determined not only by the stability of the complexonate of the metal to be eliminated but also by the ability of this metal to displace calcium from the complex. The position of equilibrium in the process of complex formation in the organism therefore depends on the relative stability constants of the complexonates of the metal and of calcium. This situation is of no fundamental significance with polyaminediphosphonic acids because of the relative instability of their calcium complexes, which has been the chief condition for the use of organophosphorus complexones in biology and medicine.

Experimental investigations have shown the usefulness of employing phosphicin to accelerate the elimination of lead from the organism [190]. It is found that lead is excreted not only by the kidneys but also to a considerable extent by the intestines, which has allowed this preparation to be applied more widely not only in the wards but perhaps also under outpatient conditions for medicinal and prophylactic purposes.

The ability of aminepolyphosphonic acids to form stable complexes with copper increases the elimination of this metal from the organism, and opens up the possibility of using them in the treatment of hepatocerebral dystrophy [191].

The formation of stable water-soluble complexes with beryllium has suggested the use of organophosphorus complexones to accelerate the elimination of this element from the organism [191-193]. Whereas amino-polycarboxylic acids have no effect on the course of acute poisoning by salts of beryllium or on its elimination from the organism, aminepolyphosphonic acids—in particular phosphicin, diethylenetriamine-*NN*″-bisisopropylphosphonic acid, and oxabisethylaminoisopropylphosphonic acid—protect animals from death on introduction of absolute lethal doses of beryllium chloride. The animals do not develop the dystrophic and necrobiotic changes in the internal organs which are characteristic of beryllium poisoning [192]. The protective effect of the complexones is explained by the formation in the organism of a non-toxic water-soluble beryllium complex which is rapidly eliminated from the organism. Experiments with $^{7}BeCl_2$ have shown that the increased excretion of beryllium from the organism results in a decrease in its content in the bones, liver, kidneys, spleen, and lungs [191-193]. The thoroughness of the eliminating effect of organophosphorus complexones is indicated also by the normalisation of the metabolic disturbances caused by beryllium. Thus phosphorylated polyamines reactivate in considerable measure the orthophosphate monoester phosphohydrolase (EC. 3.1.3.1.), and bilirubinaemia is diminished [191]. The action of phosphicin is strengthened by the simultaneous introduction of sodium nitrate, pyridoxin, and glucuronic acid [192]. The effectiveness of organophosphorus complexones in eliminating beryllium from the organism makes them promising as drugs and preventives in beryllosis, one of the most serious occupational diseases.

There are indications that diethylenetriaminepentakismethylphosphonic acid may be effective in relation to uranium [157].

The partial replacement by phosphonate groups of the carboxylate groups in a complexone molecule has been shown to improve the effectiveness of the compound obtained. Thus the introduction of bisdihydroxyphosphinylmethylethylenediaminediacetic acid into animals causes enhanced elimination of yttrium-91 and cerium-144. However, the use of compounds in which carboxylate groups have been completely replaced by phosphonate groups led to a greater accumulation of these radioactive elements in the organism than did the amino-polycarboxylic acids [194].

Data on the influence of complexing compounds on the elimination of trace elements from the organism and on the state of biocomplexes are of both theoretical and practical interest [195-198]. The possibility of complexones, including organophosphorus complexones, acting in this way is due to the high stability constants of the complexonates of copper, iron, cobalt, zinc, etc. Aminepolyphosphonic acids, when introduced into the organism, combine with trace elements and thus enter into competition with the biocomplexes of the organism, the result of this interaction depending on the strength of bonding of the trace elements with the biocomplexes. If a complexone acts on a metal whose link in the biocomplex is labile, as occurs in glycylglycinehydrolase (EC.3.4.3.1), the metal may be removed and the functions of the enzyme disturbed. In the case of the true metal enzymes, such as cytochrome $C-O_2$ oxidoreductase (EC. 1.9.3.1), and cytochrome C, the complex does not break down, as is indicated by the preservation of the haem structure [191].

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