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Synthesis and Acid–Base Properties of α-Aminophosphoryl Compounds

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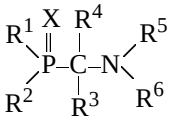
Abstract — α-Aminophosphoryl compounds of the phosphonate, phosphine oxide, and α,ω-bis(phosphine oxide) series and some of their thiophosphoryl analogs were synthesized. Potentiometric measurements of the pK_a of the conjugate acids revealed an insignificant effect of variation of substituents on the phosphorus, nitrogen, and α-carbon atoms on the basicity of the phosphorylated amines. The latter are weak bases. Organophosphorus groups decrease the basicity of the amines by almost 5 pK_a units. The role of the hydrophobic effect and intramolecular H-bonding in the obtained substances was discussed.

The enduring interest in α-aminophosphoryl compounds of researchers in organic chemistry, biochemistry, biology, medicine, and allied sciences is primarily connected with the high and diverse biological activity of these compounds [1, 2]. Being organophosphorus analogs of proteinogenic amino acids, α-aminophosphoryl compounds bind with the same enzymes and receptors, thus acting as their antagonists. Organophosphorus amino acids have been isolated from natural objects [3]. Among synthetic organophosphorus amino acids, compounds that exhibit bactericide, antibiotic, cancerostatic, and some other properties of pharmacological interest have been found [4].

Though physiological activity is the most attractive and important property of α-aminophosphoryl compounds, it by no means limits the range of their practical use. In the last years, many application fields of aminophosphoryl compounds, based on their complex-forming ability have been reported. As polyfunctional organophosphorus substances they can act as mono-, bi-, and polyfunctional ligands and have been used for design of new extractants, ion-selective electrodes, transporting agents, and other high-tech products.

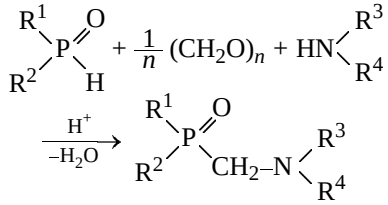
In connection with that, such a fundamental characteristic of α-aminophosphoryl compounds as their acid–base properties seems to be important. However, the information in this field is very scarse [5]. In this work we present a study of the acid–base properties of 56 α-aminophosphoryl compounds **I** with widely varied substituents at the centers of the aminophosphoryl skeleton, viz. phosphorus, α-carbon, and nitrogen.



X = O, S; R^1 = R^2 = OAlk, Alk, Ar; R^3, R^4 = H, Alk; R^5 = H, Alk; R^6 = Alk, α-pyridyl; R^5 + R^6 = $(CH_2)_5$, $(CH_2)_2O(CH_2)_2$.

The pK_a values of the conjugate acids were measured by potentiometric titration of semi-micro amounts of α-aminophosphoryl compounds in water–2-propanol mixtures (Tables 1–4).

α-Aminophosphoryl compounds of the phosphonate structure **I**–**XL** were obtained by the Kabachnik–Fields reaction in a ternary system containing hydrophosphoryl compound, Paraform, and amine, according to the following scheme.



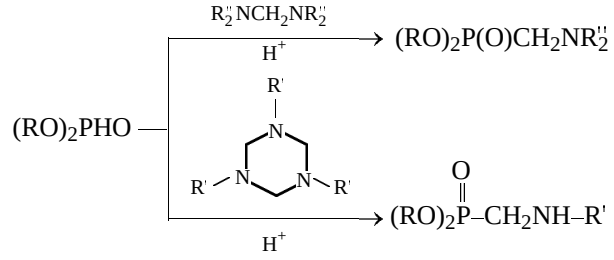
In the syntheses of compounds **LIV**–**LVI**, acetone, cyclohexanone, and 2-methylpropanal were respectively used instead of Paraform. In compound **LVI**, R^1 = R^2 = $OCH(CH_3)_3$, R^3 = H, R^4 = $CH(CH_3)_2$, R^5 = H, and R^6 = $CH(CH_3)_2$.

In some cases, the reaction of dialkyl hydrogen phosphites with geminal diamines and *symm*-hexa-

Table 1. Ionization constants (pK_a) of dialkyl α-aminomethylphosphonates **I** [$R^3 = R^4 = H$, X = O] in water–2-propanol mixtures (water contents 25, 50, and 100 vol%) at T 298 ± 0.2 K

Comp. no.	$R^1 = R^2$	R^5	R^6	2-propanol : water ratio		
				1 : 1	3 : 1	0 : 1
I	CH_3O	$(CH_2)_5$		5.54	–	–
II	CH_3O	$(CH_2)_2O(CH_2)_2$		3.27	–	–
III	C_2H_5O	$(CH_2)_5$		5.73	5.19	6.54
IV	C_2H_5O	$(CH_2)_2O(CH_2)_2$		3.30	–	3.9
V	C_2H_5O	CH_3	CH_3	–	–	6.16
VI	C_2H_5O	C_2H_5	C_2H_5	5.80	–	6.60
VII	C_2H_5O	H	C_4H_9	–	–	6.93
VIII	C_2H_5O	$(CH_3)_3C$	H	–	–	6.39
IX	C_3H_7O	CH_3	CH_3	–	–	6.15
X	C_3H_7O	C_2H_5	C_2H_5	–	–	6.66
XI	C_3H_7O	$(CH_2)_5$		5.76	–	6.56
XII	C_3H_7O	$(CH_2)_2O(CH_2)_2$		–	–	3.93
XIII	$(CH_3)_2CHO$	C_2H_5	C_2H_5	5.78	–	–
XIV	$(CH_3)_2CHO$	$(CH_2)_5$		5.67	–	–
XV	$(CH_3)_2CHO$	$(CH_2)_2O(CH_2)_2$		3.37	–	–
XVI	$(CH_3)_2CHO$	$(CH_3)_2CH$	$(CH_3)_2CH$	5.42	–	–
XVII	$(CH_3)_2CHO$	$(CH_3)_3C$	H	6.37	–	–
XVIII	$(CH_3)_2CHO$	*cyclo*-C_6H_{11}	C_4H_9	4.94	–	–
XIX	C_4H_9O	$(CH_2)_5$		5.37	4.77	–
XX	C_4H_9O	$(CH_2)_2O(CH_2)_2$		3.00	–	3.62
XXI	C_4H_9O	CH_3	CH_3	–	–	6.15
XXII	C_4H_9O	C_2H_5	C_2H_5	5.46	–	6.48
XXIII	C_4H_9O	$(CH_3)_2CH$	H	5.79	–	–
XXIV	C_4H_9O	C_4H_9	H	5.66	–	–
XXV	C_4H_9O	*iso*-C_4H_9	H	5.29	–	–
XXVI	C_4H_9O	$(CH_3)_3C$	H	6.08	–	–
XXVII	C_4H_9O	α-Pyridyl	H	4.69	–	–
XXVIII	$C_5H_{11}O$	$(CH_2)_5$		5.19	4.76	5.98
XXIX	$C_5H_{11}O$	$(CH_2)_2O(CH_2)_2$		2.84	2.52	–
XXX	$C_5H_{11}O$	C_2H_5	C_2H_5	5.40	–	–
XXXI	$C_5H_{11}O$	C_6H_{13}	H	5.81	5.34	–
XXXII	$C_5H_{11}O$	$(CH_3)_3C$	H	5.94	–	–
XXXIII	$C_5H_{11}O$	α-Pyridyl	H	4.50	4.04	–
XXXIV	*iso*-$C_5H_{11}O$	C_8H_{17}	H	5.81	5.32	–
XXXV	$C_6H_{13}O$	$(CH_2)_5$		5.05	–	–
XXXVI	$C_6H_{13}O$	$(CH_2)_2O(CH_2)_2$		2.72	–	–
XXXVII	$C_6H_{13}O$	C_2H_5	C_2H_5	5.23	–	–
XXXVIII	*cyclo*-$C_6H_{11}O$	$(CH_2)_5$		5.38	4.79	–
XXXIX	*cyclo*-$C_6H_{11}O$	$(CH_2)_2O(CH_2)_2$		3.11	–	–
XL	*cyclo*-$C_6H_{11}O$	C_2H_5	C_2H_5	5.62	–	–

hydrotriazine derivatives in a binary system by the procedure developed in [6] was used.

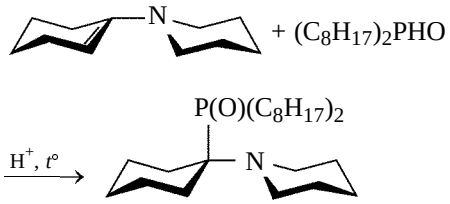


α-Aminophosphoryl compounds of the thiophosphonate structure **XLI**–**XLIII** were prepared by the Kabachnik–Fields reaction of dibutyl hydrogen thiophosphite, Paraform, and secondary amines. The reaction proceeds under more rigid conditions than with dialkyl hydrogen phosphites. All attempts to substitute the phosphoryl group in α-aminophosphoryl compounds by thiophosphoryl with the aid of Lawesson reagent [7] failed. Instead of the target product, hardly separable multicomponent mixtures were formed.

α-Aminophosphoryl compounds of the phosphine oxide structure **XLIX**–**LIV** were also obtained in a diorganylphosphinous acid–Paraform–amine ternary system largely similarly to aminophosphonates, but sometimes heating of the reaction mixture without solvent at 130–135°C in the presence of *p*-toluenesulfonic acid was needed to complete the reaction. Reaction progress was controlled by TLC and ^{31}P NMR spectroscopy.

1-(Dioctylphosphinoyl)-1-(*N*-piperidino)cyclohexane (**LIII**) was prepared by the Pudovik reaction by acid-catalyzed addition of dioctylphosphinous acid to 1-(cyclohexen-1-yl)piperidine under heating.

Our previous works [8] showed that hydrophosphoryl compounds add to enamines according to the

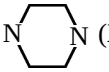


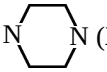
Markovnikov rule (electrophilic Pudovik reaction) to form aminophosphoryl compounds.

We are the first to synthesize α, ω-bisphosphoryl compounds **XLIV**–**XLVIII**.

$[R_2P(O)CH_2]_2Z$

XLIV–**XLVIII**

R = *n*-AmO, Z =  (**XLIV**); R = *n*-Hex,

Z =  (**XLV**); R = Ph, Z = N(Bu)CH_2CH_2N(Bu)

(**XLVI**); R = *n*-Am, Z = N(Bu)$CH_2CH(OH)CH_2$N(Bu) (**XLVII**); R = *n*-Am, Z = N(Bu)$CH_2CH_2OCH_2CH_2OCH_2 \cdot CH_2$N(Bu) (**XLVIII**).

Table 2. Ionization constants (pK_a) of α-aminothiophosphonates **XLI**–**XLIII** and pK_a^{*} [a] values of bisphosphorylated diamines **XLIV**–**XLVIII** in a 1 : 1 water–2-propanol mixture at 298 ± 0.2 K.

Comp. no.	pK_a(pK_a^{*})	Comp. no.	pK_a(pK_a^{*})
XLI	–5.22	**XLV**	(3.95)
XLII	2.67	**XLVI**	(3.35)
XLIII	5.27	**XLVII**	(4.27)
XLIV	(3.81)	**XLVIII**	(6.12)

[a] The pK_a^{*} is the first-step dissociation constant of the conjugate acid of α-aminophosphoryl compound.

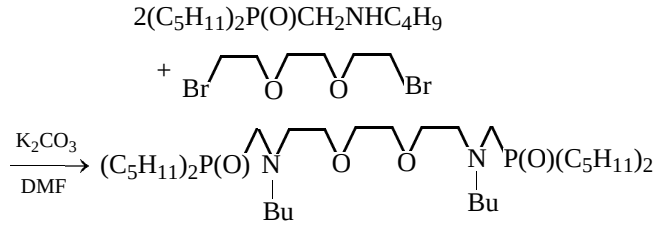
Table 3. Ionization constants (pK_a) of α-aminophosphoryl compounds **I** (X=O) in 3 : 1 and 1 : 1 2-propanol–water mixtures at 298 ± 0.2 K

Comp. no.	R^1	R^2	$R^{3,4}$	R^5	R^6	2-propanil : water ratio	
						3 : 1	1 : 1
XLIX	C_6H_{13}	C_6H_{13}	H	$(CH_2)_5$		4.96	5.19
L	C_6H_{13}	C_6H_{13}	H	$(CH_2)_2O(CH_2)_2$		3.05	3.20
LI	CH_3	4-(*cyclo*-C_6H_{11})C_6H_4	H	$(CH_2)_5$		5.10	5.45
LII	CH_3	4-(*cyclo*-C_6H_{11})C_6H_4	H	$(CH_2)_2O(CH_2)_2$		2.27	2.65
LIII	C_8H_{17}	C_8H_{17}	$(CH_2)_5$	$(CH_2)_5$		4.60	–
LIV	C_8H_{17}	C_8H_{17}	CH_3	H	C_6H_{13}	5.32	5.53
LV	C_4H_9O	C_4H_9O	$(CH_2)_5$	H	C_8H_{17}	4.67	4.98
LVI	$(CH_3)_2CHO$	$(CH_3)_2CHO$	H, *i*-Pr	H	*i*-Pr	4.52	–

Table 4. Phosphonomethylation-induced basicity decrease of amines

Amine	pK_a	α-Aminophosphonate		pK_a	ΔpK_a
		Comp. no.	X		
$(C_2H_5)_2NH$	10.62	**VI**	$(C_2H_5O)_2P(O)CH_2$	5.80	4.82
$C_6H_{13}NH_2$	10.40	**XXXI**	$(C_5H_{11}O)_2P(O)CH_2$	5.81	4.59
Piperidine	10.98	**III**	$(C_2H_5O)_2P(O)CH_2$	5.73	5.25
Morpholine	8.76	**IV**	$(C_4H_9O)_2P(O)CH_2$	3.30	5.46

Compounds **XLIV-XLVII** were obtained by the Kabachnik–Fields reaction in a 2:2:1 diorganylphosphinous acid–Paraform–diamine ternary system. Phosphorylated bisaminodiester **XLVIII**, a promising azapodand [9], was obtained by N-alkylation of diamyl(*N*-butylaminomethyl)phosphine oxide with 1,8-dibromo-3,6-dioxaoctane in the presence of anhydrous potassium carbonate in DMF.



For compounds **XLIV**–**XLVIII**, first-step pK_a values of the corresponding conjugate acids were measured.

Characteristics of all the prepared aminophosphoryl compounds are presented in Table 5.

From the resulting data we can draw some the most general rules that relate the structure and basicity of α-aminophosphoryl compounds. First of all, note that all the α-aminophosphoryl compounds under study are significantly weaker bases than their precursors, that is nonphosphorylated amines. From Table 4 it follows that the pKa values of amines and the corresponding aminophosphoryl compounds differ by 4–5 log units. Such changes in the basicity of amines, induced by their prosphorylation are readily explainable by the strong electron-acceptor effect of the phosphoryl group [10].

Note that the surrounding of the phosphorus atom only slightly affects the pK_a values. Hence, the difference in pK_a for *n*-hexyl derivatives in the **XXXV, XLIX** and **XXXVI, L** pairs is ~0.2–0.5 log units (in a 1:1 2-propanol–water mixture). This is connected with the enhancement of donor properties in going

Table 5. Characteristics of α-aminophosphoryl compounds **I**–**LVI**

Comp. no.	bp, °C (*p*, mm) or mp, °C	n_D^{20}	n_4^{20}	δ, ppm
I	84 (0.3)	1.4660	1.0839	22
II	101 (0.35), 95 (0.23)	1.4675	1.1666	18
III	96 (0.38)	1.4570	1.0436	23
IV	108–109 (0.37)	1.4572	1.1317	19
V	70–72 (0.4)	1.4303	1.0070	25
VI	66–66.5 (0.15)	1.4343	0.9865	26
VII	109–113 (0.4)	1.4372	0.9783	25
VIII	82–84 (0.33)	1.4330	1.0177	24
IX	91–92 (0.45)	1.4324	0.9982	21
X	98–98.5 (0.5)	1.4355	0.9722	24
XI	105–106 (0.5)	1.4484	0.9848	23
XII	117 (0.5)	1.4558	0.9930	23
XIII	81–82 (0.47)	1.4318	0.9644	22
XIV	99–100 (0.38)	1.4498	1.0005	23
XV	106 (0.38)	1.4516	1.0246	24
XVI	92–93 (0.3)	1.4342	0.9873	25
XVII	101–103 (0.3)	1.4346	0.9586	25
XVIII	130–133 (0.28)	1.4581	0.9775	26
XIX	112–112.5 (0.14)	1.4578	0.9834	24
XX	126 (0.23)	1.4589	1.0433	22
XXI	109–110 (0.42)	1.4322	0.9612	23
XXII	117–118(0.41)	1.4395	0.9521	23
XXIII	116–117(0.41)	1.4321	0.9508	20
XXIV	122–123(0.3)	1.4365	0.9426	19
XXV	127–127.5(0.36)	1.4370	0.9463	22
XXVI	113–116(0.32)	1.4368	0.9441	14
XXVII	163–166(0.38)	1.5042	1.0502	26
XXVIII	140–143(0.23)	1.4601	0.9816	21
XXIX	152–153 (0.34)	1.4547	1.0065	24
XXX	117–119 (0.22)	1.4416	0.9901	25
XXXI	155–158 (0.25)	1.4469	0.9756	23
XXXII	135 (0.37)	1.4393	0.9394	18
XXXIII	183–185 (0.19)	1.5017	1.0412	26
XXXIV	–	1.4457	0.9720	32
XXXV	156–158 (0.33)	1.4587	0.9527	26
XXXVI	154–155 (0.41)	1.4569	0.9584	25
XXXVII	157–158 (0.31)	1.4451	0.9291	25
XXXVIII	170–173 (0.38)	1.4894	1.0159	27
XXXIX	180–183 (0.38)	1.4912	1.0356	28
XL	162–164 (0.25)	1.4768	0.9924	27
XLI	129–131 (0.39)	1.4839	0.9868	90
XLII	140–142 (0.38)	1.4820	1.0018	88
XLIII	124–126 (0.43)	1.4682	0.9737	86
XLIV	–	1.4630	0.9844	28
XLV	61–62	–	–	42
XLVI	65	–	–	46

Table 5. (Contd.)

Comp. no.	bp, °C (*p*, mm Hg) or mp, °C	n_D^{20}	n_4^{20}	δ, ppm
XLVII	–	1,4887	–	49
XLVIII	32	–	–	43
XLIX	170–173 (0.21)	1.4788	0.9865	39
L	178–179 (0.15)	1.4572	1.0180	40
LI	67–68	–	–	42
LII	44–45	–	–	42
LIII	43	–	–	37
LIV	–	1.4725	–	53
LV	–	1.4581	0.9812	30
LVI[a]	112	–	–	24

[a] The melting point of hydrochloride from ethyl acetate; δ_P of the free aminophosphonate.

from the hexyloxy to hexyl substituent. Naturally, the increase in the electron density on nitrogen is not large, because the electronic effect of the varied groups is transmitted through the phosphinomethylene bridge.

Derivatives containing a tertiary nitrogen atom are slightly weaker bases as compared to their analogs with a secondary nitrogen atom. The differences in pK_a in the **XXII** and **XXIV**, **VI** and **VII**, and **XXX** and **XXXI** pairs (diethylamino vs. dialkylamino derivatives) are 0.2–0.4 log units.

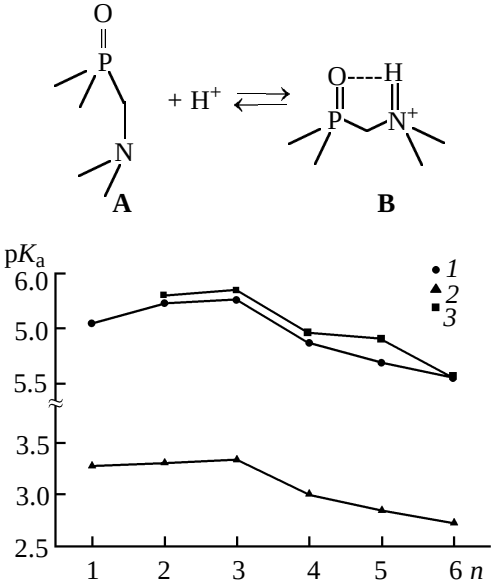
The trend in variation of the pK_a values of homologous α-aminophosphoryl compounds containing identical aminoalkyl fragments is presented in the graphic form in the figure. The trend is the same for all the homologous series studied: (1) piperidine derivatives **I, III, XI, XIX, XXVIII,** and **XXXV**; (2) morpholine derivatives **II, IV, XII, XX, XXIX,** and **XXXVI**; and (3) diethylamine derivatives **VI, X, XXII, XXX,** and **XXXVII**. Basicity decreases with increasing length of the hydrocarbon radical at the phosphoryl group. Note that dimethyl phosphonates do not obey the general rule. Probably, the noted phenomenon is associated with intramolecular hydrophobic interactions between lipophilic parts of the aminophosphoryl compound, that, together with the effect of stabilization of the protonated form of the aminophosphoryl compound by H-bonding (see below), control the acid–base properties of the whole molecule. In this case, increasing lengths of the alkyl roup at the phosphoryl center decreases pK_a, beginning with the butyl group. For example, the following pK_a values were obtained for the series of compounds of the general formula $(RO)_2P(O)CH_2N(CH_2)_5$: 5.54 (R = CH_3), 5.73 (R = C_2H_5), 5.76 (R = C_3H_7), 5.37 (R = C_4H_9), 5.19 (R = C_5H_{11}1), and 5.05 (R = C_6H_{13}).

However, in the general case, the relationship between the structure and basicity of α-aminophosphoryl compounds is rather difficult to interpret unambiguously. Note that the modern interpretation of the basicity trend in the series of aliphatic amines in solutions was given only when gas-phase basicities had become available [11].

At the same time, with the sufficiently representative set of aminophosphoryl compounds in hand, we can reveal certain structural features that affect their acid–base properties and distinguish phosphorylated amines from their nonphosphorylated analogs. First of all note that acids conjugate to aminophosphoryl compounds contain an intramolecular hydrogen bond that stabilizes the protonated form [12].

This effect to some extent compensates for the decrease in basicity, caused by the electron-acceptor effect of the phosphoryl-containing fragment. Evidently, a significant role in protonation of aminophosphoryl compounds must belong to conformational and solvation effects. In detail, the lower basicity of tertiary aminophosphonates as compared to secondary can be explained as follows.

Tertiary α-aminophosphoryl derivatives prefer a *trans* position of nitrogen with respect to phosphoryl oxygen (structure **A**) because of the dipole repulsion of the polar P–O and C–N bonds. Hence, protonation of these compounds should be accompanied by a *trans–cis* conformational transition and formation of an intramolecular hydrogen bond in H-complex **B**.



Basicity vs. number of carbon atoms in the $(R^1O)_2P(O)$ group for a series of homologous dialkyl α-aminomethylphosphonates (1 : 1 water–2-propanol).

Evidently, such transition is impossible is secondary phosphorylated amines, where nitrogen and phosphoryl oxygen are already H-bonded [12]. This fact may explain the increased basicity of these compounds.

Note that substitution of the phosphoryl group by thiophosphoryl has no significant basicity effect, even though the latter group is a slightly stronger electron acceptor [13]. The thiophosphoryl compounds under discussion have the general formula $(BuO)_2P(S)CH_2 \cdot NR_2$ [R + R = $(CH_2)_5$ (**XLI**), $(CH_2)_2O(CH_2)_2$ (**XLII**); R = C_2H_5 (**XLIII**]. However, subsitution of oxygen by sulfur definitely decreases pK_a (by 0.15–0.33 log units) for all the three pairs of compounds: **XXII** and **XLIII**, **XIX** and **XLI**, and **XX** and **LXII**. This fact can be explained in terms of the above-discussed stabilization of the protonated form of α-aminophosphoryl compound by H-bonding of phosphoryl oxygen with the proton added. This stabilization will contribute much less in thio derivatives, since the sulfur atom is known to exhibit quite a weak tendency for H-bonding.

Noteworthy is also an abnormally high basicity of homologous dialkyl *tert*-butylaminomethylphosphonates, which is higher that the respective characteristic of their diethylaminomethyl derivatives by 0.6 pK_a unit, on average. This phenomenon may be connected with the above-described *cis–trans* conformational transition, as well as with the significant positive inductive effect of the *tert*-butyl group. Steric factors, too, contribute here but evidently not so significantly, because, a considerable basicity increase is observed instead of the expected decrease.

It cannot be excluded that the structural variation noticeably affects the solvation energy of the conjugate acid that bears a positive charge, thus also contributing in the pK_a trend in the series of compounds in hand, as is observed with usual aliphatic amines [11].

It is important that the dissociation constants of homologous dialkyl (*N*-dimethylaminomethyl)phosphonates $(RO)_2P(O)CH_2N(CH_3)_2$ in water are practically the same (cf. compounds **V, IX,** and **XXI**). This fact provides further evidence for the necessity, in the general case, of accounting for the contribution of intramolecular hydrophobic interactions into ionization constants; but in the compounds under discussion these interactions are negligible because of the small size of the dimethylamino group.

Hence, the role of structural and solvation factors requires accounting (even if variations are inconsiderable) for the structure of α-aminophosphoryl compounds and conditions of measurements of their acid–base characteristics, which significantly complicates quantitative structure–properties correlations. This feature radically distinguishes this class of compounds from organic nitrogenous bases [14]. At the same time, the information on the acid-base properties of α-aminophosphoryl compounds occurs to be very important for practical applications of these compounds, for example, in a highly sensitive determination of low concentrations of metal ions [9] or their extraction from aqueous solutions of metal salts of complex composition [15]. Some our new results in this field will be presented in further publications.

EXPERIMENTAL

Potentiometric titration of α-aminophosphoryl compounds was carried out using an ESL-43-07 glass electrode and an EVL-1M3 silver chloride reference electrode, an I-130 universal pH-meter, and a U15-MLW thermostat. The ^{31}P NMR spectra were measured on a custom-made spectrometer with the working frequency 8 MHz against internal 85% phosphoric acid. The ^1H NMR spectra were obtained on a Tesla-BS-497 spectrometer (100 MHz) in $CDCl_3$ against internal TMS. Solutions were prepared with chemical grade 2-propanol, special purity grade sodium chloride, and twice distilled water. Analytical data were processes on a computer using an original program written in the VisualBasic editor.

Potentiometric titration. A solution of a sample (0.25–0.5 mmol) in 20 ml of aqueous–2-propanol NaCl (background electrolyte, ionic strength 0.05, 20 ml) was placed in a temperature-controlled cell and titrated with 0.1 or 0.05 N HCl solution containing sodium chloride to maintain constant ionic strength. The concentration of hydrogen ions in the course of titration was measured with two glass electrodes. Potentials of the indicator electrodes were taken 2–3 min after addition of a successive portion of the titrant.

Corrections for diffusion potentials (E_D) were calculated by the Lewis–Sergeant equation [16].

$$E_D = \pm \frac{RT}{F} \log \frac{U_{(+2)} + U_{(-2)}}{U_{(+1)} + U_{(-1)}} = \frac{RT}{F} \ln \frac{\lambda_{(2)}}{\lambda_{(1)}}.$$

Here R is the universal gas constant, T is the temperature, F is the Faraday constant, U_i is the mobility of particles, λ_1 and λ_2 are the equivalent electrical conductivities of solutions of a given concentration.

The pK_a values were calculated by the Gran procedure by linearization of the titration curves [17]. The choice of indicator electrodes was carried out as

follows. A batch of 10 glass electrodes was used to measure the potentials of aqueous buffer solutions with pH 1.68 and 6.86, after which two electrodes whose *E*/pH unit ratios were the closest to the theoretical value of 59.14 mV were chosen. These electrodes were handled for some days in a 0.1 N solution of HCl in aqueous 2-propanol. Calibration of glass electrodes was carried out as described in [17].

The dissociation constants of the conjugate acids (pK_a) of α-aminophosphoryl compounds were measured in 1:1 and 3:1 2-propanol–water mixtures and in water (for water-soluble compounds). The resulting data are listed in Tables 1–3. The absolute error in the pK_a measurements was ±0.03 log units.

Synthesis of α-aminophosphoryl compounds by the Kabachnik–Fields reaction in a hydrophosphoryl compound–Parform–amine ternary system *(general procedure).* A mixture of 50 mmol of phosphite, Paraform, and amine (volatile amines, such as diethylamine, isopropylamine, or *tert*-butylamine were taken in a 15–20% excess), 35 ml of benzene, and 100 mg of *p*-toluenesulfonic acid was refluxed until water no longer separated in the trap (ca. 90 min). Reaction progress was controlled by the amount of water in the trap, as well as by TLC on Silufol plates, eluent chloroform–acetone (4:1 v/v), development with iodine vapor with subsequent treatment of the chromatogram with water. After the reaction had been complete, 500 mg of sodium bicarbonate was added to the yellow reaction mixture, and the resulting solution was refluxed for 10–15 min to remove the catalyst. After cooling, the precipitate of sodium salts was filtered off through a folded filter and washed with benzene (3 × 7 ml). The filtrate was evaporated in a vacuum on a rotary evaporator, and the residue was distilled in a vacuum (0.15–0.40 mm Hg). The yields of the target aminophosphoryl compounds were 70–88%.

The yields of α-pyridylamino derivatives by the above procedure did not exceed 30%. In this case, the initially formed bis(2-pyridylamino)methane could be reacted with the starting hydrophosphoryl compound only at 125–130°C without solvent in the presence of acid catalyst.

The use of acid catalyst is not always necessary. In the latter case, the isolation procedure is facilitated, since there is no need to use sodium bicarbonate to remove the catalyst.

When the final product of the Kabachnik–Fields reaction could not be distilled in a vacuum (products with long radicals at the phosphoryl group), it was purified by column chromatography on silica gel with TLC control. Depending on the mobility of the product and admixtures, a mixture of chloroform with acetone or methanol was used.

Compounds **I**–**XL**, **XLIV**–**XLVII**, **XLIX**–**LII**, **LIV**, and **LVI** were prepared according to this procedure.

Synthesis of α-aminophosphoryl compounds by the Kabachnik–Fields reaction in a binary system *(general procedure).* This reaction proceeds in the presence of acid catalyst at elevated temperatures (110–120°C). With base catalyst (NaOEt), the reaction is very slow.

This procedure is convenient for preparing α-aminophosphoryl compounds derived from gaseous or volatile amines, such as dimethylamine, isopropylamine, a methylamine, which is connected with the sufficient difference in the boiling points of the starting amines and corresponding geminal amines and hexahydrotriazines. Under the conditions of the Kabachnik–Fields reaction, the latter remain in the reaction mixture. In their turn, these intermediate products can be easily prepared by condensation of amines with formaldehyde in water.

A solution of dialkyl hydrogen phosphite in equal volume of toluene was mixed with *gem*-diamine or *symm*-hexahydrotriazine (1:1 or 3:1, respectively), and 1 mol% of *p*-toluenesulfonic acid was added. This mixture was refluxed for 8 h. Reaction progress was controlled by TLC. After the reaction had been complete, excess catalyst was removed by refluxing with 500 mg of sodium bicarbonate. The mixture was then cooled, and the precipitate of sodium salts was filtered through a folded filter and washed with toluene (3 × 7 ml). The solvent was removed from the filtrate on a rotary evaporator, and the residue was distilled in vacuum (0.15–0.40 mm Hg). The yield of the target α-aminophosphonates by this procedure was 45–75%.

The eluent composition in TLC was varied depending of the mobility of the target product. The R_f values of the phosphites were always larger than those of the target products and varied within the range 0.85–0.95. Water-soluble hydrophilic aminophosphonates (C_1–C_3 alkyl radical in the phosphoryl group) could not be developed by iodine vapor. In this case, the chromatogram was sprayed with a 0.5% ninhydrin solution (if an NH group was present) and then kept for 5 min in an oven at 100°C. Alternatively, the chromatogram was treated with Dragendorf reagent ($KBiI_4$) without heating and then with a 5% sodium sulfite solution. Under these conditions, aminophosphoryl compounds appeared as lilac spots on a pink background (with

ninhydrin) or as orange or pink spots on a white background (with Dragendorf reagent).

***N,N'*-Bis(diamylphosphinoyl)-*N,N'*-dibutyl-2,11-diaza-5,8-dioxadodecane (XLVIII).** To a mixture of 3.8 g of freshly distilled diamyl(*N*-butylaminomethyl)-phosphine oxide, 20 ml of dimethylamine-free DMF, and 0.91 g of anhydrous finely ground potassium carbonate, a solution of 1.83 g of freshly distilled 1,8-dibromo-3,6-dioxaoctane in 5 ml DMF was added dropwise with stirring at 50–55°C over the course of 0.5 h. The resulting mixture was stirred for 2.5 h. Over this period, it was gradually heated to 70°C and then stirred on a boiling water bath for 2 h, cooled, and poured in 100 ml of water, and extracted with methylene chloride (6 × 10 ml). The combined organic extracts were washed with 15 ml of water and dried over anhydrous sodium sulfate. The solvent was removed in a vacuum to give 4.13 g (90%) of a crude product as a yellow oil. This oil crystallized on handling to form a yellowish crystalline material, mp 35–37°C, δ_P 43 ppm. According to TLC data, this material was practically free of admixtures of the starting reagents, but, if necessary, it can be purified by column chromatography, eluent chloroform–acetone (4 : 1).

1-(Dioctylphosphinoyl)-1-(*N*-piperidino)cyclohexane (LIII) was prepared by mixing of equimolar reagent amounts with a catalytic amount of *p*-toluenesulfonic acid without solvent. The reaction mixture was heated at 140°C in an inert atmosphere and then diluted with toluene, and washed with a dilute sodium bicarbonate solution and water. The organic phase was dried over magnesium sulfate. The solvent was removed in a vacuum, the residue was dissolved in a minimum of boiling hexane, and the hot solution was filtered and left for 3 days in a freezer. The crystals that formed were filtered off, washed with dry hexane, and dried in air. The α-aminophosphoryl compound was obtained as a slightly yellowish crystalline powder, mp 43–45°C, yield 58%, δ_P 37 ppm.

Synthesis of *O,O*-dibutyl (α-aminomethyl)thiophosphonates *(general procedure).* *O,O*-Dibutyl thiophosphite, 50 mmol, was mixed with equimolar amounts of Paraform and secondary amine, and 35 ml of anhydrous toluene and about 100 mg of *p*-toluenesulfonic acid were added to the mixture. Volatile amines, such as diethylamine and *tert*-butylamine, are desirable to take in a 15–20% excess. The reaction mixture was refluxed with stirring until water no longer separated in the trap (about 2 h). Reaction progress was controlled by the amount of water in the trap, as well as by TLC on Silufol UV-254 plates, eluent chloroform–acetone (4 : 1 v/v), development with iodine vapor followed by treatment with water. With sufficiently strong bases, such as diethylamine and piperidine (pK_a 10–11), the reaction was complete within this time. With weaker bases, such as morpholine, oligooxyethylene-α,ω-diamines, ethanolamine derivatives, etc. (pK_a 6–8), removal of the solvent from the reaction mixture and additional heating of the residue at 130–135°C for 3–4 h was needed with subsequent dilution of the brown residue with benzene. Sodium bicarbonate, 500 mg, was added to the resulting brown solution, and it was refluxed with stirring for 10–15 min to remove the catalyst. After cooling, the precipitate of sodium salts was filtered off through a folded filter and washed with benzene (3 × 7 ml). The combined filtrates were evaporated on a rotary evaporator to remove the solvent, and the residue was fractionated in a vacuum (0.15–0.20 mm Hg). The yield of the target α-aminothiophosphonates by this procedure was 50–60%.

***O,O*-Dibutyl-(*N*-piperidinomethyl)thiophosphonate.** ^{1}H NMR spectrum, δ, ppm: 0.8–1.05 m (6H, butyl CH_3), 1.3–1.8 m [14H, butyl $(CH_2)_2$ and piperidyl C^3H_2, C^4H_2, and C^5H_2], 3.90–4.18 m (4H, butyl CH_2O), 3.06 d (2H, P–CH_2–N, $^2J_{HP}$ 10.1 Hz), 2.35–2.65 m (4H, piperidyl CH_2N).

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