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N.S. Zefirov on His 70th Anniversary

Synthesis of β-Aminophosphonates and Study of Their Acid–Base Properties and Phase Distribution in Water–Organic Solvent Systems

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Abstract—New and previously known β-aminoethylphosphonates were synthesized by addition of primary and secondary amines to vinylphosphonates, and their IR and NMR spectra were examined. Diethyl 2-diethyl-aminoethylphosphonate and diethyl 2-morpholinoethylphosphonate were found to be stronger bases than the corresponding aminomethylphosphonates, but all these are weaker bases than their precursors, nonphosphorylated amines. Distribution constants of β-aminophosphonates between water and some organic solvents were determined and compared with those of their α-amino homologs.

In the series of our preceding publications we described methods of synthesis and acid–base properties of a large number of α-aminophosphoryl compounds [1] which can be regarded as phosphorus-containing analogs of natural amino acids. In the recent years, these compounds attract attention of researchers working in the fields of not only fine organic synthesis and chemistry of biologically active substances but also related sciences, such as biochemistry, pharmacology, medicine, agricultural chemistry, etc. [2, 3]. Apart from high efficiency as bioactive substances, α-aminophosphoryl compounds were shown to be capable of forming complexes with various species, including metal ions, organic and inorganic acids, etc. [4, 5]. In particular, we studied α-aminophosphonates as extractants which ensured selective separation of noble metal ions from concomitant elements [6]. Variation of substituents at the phosphorus, α-carbon, and nitrogen atoms over a wide range showed that the most selective extractants were those aminophosphoryl reagents which contained more than 20 carbon atoms; in this case, the optimal hydrophilic–lipophilic balance was achieved. It should be emphasized specially that the above information was deduced by analysis of correlations between the number of carbon atoms in the extractant molecules and their distribution constants in water–organic sol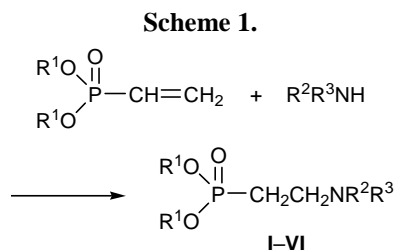vent systems [7]. Therefore, the latter parameter is necessary to elucidate the structure–property relations with a view to effect subsequent purposeful synthesis of extractants, bioactive, and other potentially useful substances possessing an optimal combination of the desired characteristics.

The present article opens a series of publications on the synthesis and study of extracting, membrane-transfer, and ionophoric properties of a new class of phosphorus-and-nitrogen-containing complexing agents, β-aminophosphoryl compounds. Here, we report on the synthesis, acid–base properties, and distribution constants in two-phase aqueous–organic systems of a series of previously described and new β-aminophosphonates. When possible, the parameters under study were compared with the data for their analogs, α-aminophosphonates, and precursors, the corresponding amines. We believe that such analysis is useful for estimation of factors responsible for physiological and complexing properties of the compounds under study.

Properties of β-phosphorylated amines have been studied to a considerably lesser extent, as compared to their α-homologs. However, even relatively poor information on their complexing power [8, 9] and other practically important properties [10] suggests some specificity of their extracting, membrane-transfer, and

ionophoric abilities, which are the subjects of our studies.

The most accessible method of synthesis of β-aminoalkylphosphonates is based on the addition of primary and secondary amines to unsaturated derivatives of four-coordinate phosphorus acids [11]. We prepared β-aminoethylphosphonates by heating vinylphosphonic acid esters with butylamine, diethylamine, butyl(octyl)amine, and morpholine in the absence of a catalyst (Scheme 1).

Scheme 1.

$$R^1O\diagdown \underset{R^1O\diagup}{\overset{O}{\underset{\|}{P}}}-CH{=}CH_2 \quad + \quad R^2R^3NH$$

$$\xrightarrow{\hspace{2cm}} R^1O\diagdown \underset{R^1O\diagup}{\overset{O}{\underset{\|}{P}}}-CH_2CH_2NR^2R^3$$

I–VI

I, R^1 = Et, R^2 = H, R^3 = Bu (I); **II**, R^2 = R^3 = Et; **III**, R^2 = Bu, R^3 = $C_8H_{17}O$; **IV**, R^2R^3N = morpholino; **V**, R^1 = *i*-Pr, R^2 = R^3 = Et; **VI**, R^1 = Bu, R^2 = R^3 = Et.

Compounds **I** and **VI** were reported previously [12, 13]; however, their spectral parameters were not given. Aminophosphonates **I–VI** are liquids which can be distilled under reduced pressure and are soluble in most organic solvents. Their IR spectra lack absorption bands in the region 1640–1650 cm^{-1}, which is typical of stretching vibrations of double C=C bond; and no N–H absorption (3200–3500 cm^{-1}) was present in the IR spectra of **II–VI**. A strong band at 1260 cm^{-1} belongs to the phosphoryl group. The IR spectrum of aminophosphonate **I** contains NH absorption band at 3300 cm^{-1}. Compounds **I–VI** showed in the ^{31}P NMR spectra only one signal at δ_P 29–32 ppm, indicating formation of a single addition product. In the ^{1}H NMR spectra of **I–VI** we observed a multiplet at δ 1.8–1.9 ppm due to methylene protons in the α-position with respect to the phosphoryl group; this means that the amino group is attached to the β-carbon atom. The α-methyl-ene proton signal is split due to coupling with the phosphorus nucleus ($^2J_{PH}$ = 18.4–19.4 Hz) and

protons of the neighboring methylene group ($^3J_{HH}$ = 6.3–8.3 Hz). Protons in the PCH$_2$CH$_2$N fragment constitute *AA'* and *BB'* parts of an *AA'BB'X* spin system where *X* is the phosphorus nucleus. The ^{1}H NMR spectrum of diethyl 2-(*N*-butyl-*N*-octylamino)ethylphosphonate (**III**) is difficult to interpret: signals from protons of the two methyl groups in the butyl and octyl radicals on the nitrogen atom overlap in the region of δ 0.86 ppm, and methylene protons in the butyl and octyl groups and methyl protons in the ethoxy groups appeared at δ 1.30–1.36 ppm.

The acid–base properties of some of the synthesized β-aminophosphonates were estimated by measuring pK_{BH^+} values of the corresponding conjugate acids according to the procedure described in [1]. The results are collected in Table 1; for comparison, the data for their α-homologs and the corresponding amines in water are given. Our results are consistent with the relations between the structure and pK_{BH^+} values, which were obtained previously for α-aminophosphonates. First of all, the examined α- and β-aminophosphoryl compounds are weaker bases than the corresponding nonphosphorylated amines. β-Aminophosphonates are stronger bases than their α-analogs. As we showed previously [1], introduction of a fairly strongly electron-withdrawing phosphoryl group to the α-carbon atom considerably reduces the basicity of amines, on the average, by 4–5 log units. Naturally, the electron-withdrawing effect weakens as the phosphorus center becomes more distant from the nitrogen atom. The basicity of amines is higher by 2–3 log units than that of their β-phosphorylated derivatives. Unlike fairly representative series of α-aminophosphonates [1], the series of available β-aminophosphonates is limited; therefore, it is difficult to draw any reliable conclusions on the effect of their structure on the basicity (a more detailed analysis will be performed in our subsequent publications with a larger series of β-aminophosphoryl compounds). Here, we can note only fairly sharp reduction (by almost 3 log units) in the basicity upon replacement of diethylamino group by electron-withdrawing morpholino group.

Table 1. Basicities of amines and the corresponding α- and β-aminophosphonates in water at 298±0.2 K

Amine	pK_{BH^+}	α-Aminophosphonate	pK_{BH^+} (ΔpK)	β-Aminophosphonate	pK_{BH^+} (ΔpK)
Et$_2$NH	10.93	Et$_2$NCH$_2$P(O)(OEt)$_2$	6.61 (4.32)	Et$_2$NCH$_2$CH$_2$P(O)(OEt)$_2$	8.48 (2.45)
morpholine NH	8.36	morpholine-N–CH$_2$P(O)(OEt)$_2$	3.89 (4.47)	morpholine-N–CH$_2$CH$_2$P(O)(OEt)$_2$	5.67 (2.69)

We also determined the distribution constants P_o of four α- and β-aminophosphonates in two-phase systems water–organic solvent by two-phase acid–base potentiometric titration. As organic solvents, we used chloroform, carbon tetrachloride, xylene (a mixture of isomers), toluene, and octanol. The $\log P_o$ values were calculated by linearization of the titration curve according to Gran (by analogy to [7]). As follows from the data in Table 2, the distribution constants of β-aminophosphonate **II** in all the examined two-phase systems are lower than the corresponding values for diethyl *N,N*-diethylaminomethylphosphonate (**VII**) containing the same substituents at the phosphorus and nitrogen atoms. It should be noted that within both reaction series, α- and β-aminophosphonates, replacement of less hydrophilic diethylamino group in compounds **II** and **VII** by more hydrophilic morpholino group (compounds **IV** and **VIII**) reduces the distribution constant. A linear correlation was found between the distribution constants of α- and β-aminophosphonates having ethyl groups on the nitrogen: $\log P_\alpha = 0.34 + 1.00 \log P_\beta$; $r = 0.997$, $s = 0.06$, $n = 5$ (Table 2). Obviously, the existence of such correlation suggests a common mechanism of solvation of these compounds in the examined solvents.

At first glance, decrease in the distribution constants in going from diethyl *N,N*-diethylaminomethylphosphonate (**VII**) to diethyl (2-diethylaminoethyl)phosphonate (**II**) (on the average, by 0.34 log unit; Table 2) contradicts the relation found by us previously, according to which introduction of every methylene group into the alkoxy substituents on the phosphorus atom leads to increase in the distribution constant, on the average, by 0.5 log unit [7]. We believe that the observed distortion of the Leo–Hansch additivity principle [14] may be rationalized as follows. Introduction of one or several methylene groups into the ester fragments of α-aminophosphonates almost does not affect the electron density on the main centers. As we found in [1], the basicity of α-phosphorylated amines within a wide homologous series remains almost unchanged, for mutual effect of the acceptor phosphoryl and amino groups does not change. Therefore, the distribution constants of compounds belonging to the above series is determined by the number of carbon atoms in the molecule, i.e., by hydrophilic–lipophilic balance. The situation changes in going from α- to β-phosphorylated amines. In this case, introduction of an additional methylene unit between the phosphorus and nitrogen atoms increases the hydrophilicity due to enhanced strength of H-comcomplexes with water molecules as a result of increase

Table 2. Distribution constants ($\log P_o \pm 0.05$) of aminoethylphosphonates in water–organic solvent systems[a]

Comp. no.	Solvent				
	CHCl$_3$	CCl$_4$	xylene	toluene	octanol
II	2.03	0.21	0.08	0.18	0.65
IV	1.28				
VII	2.37	0.65	0.41	0.48	0.95
VIII	1.58				

[a] At 298 ± 0.2 K.

in the electron density on the basic centers (nitrogen and phosphoryl oxygen atoms), for their mutual acceptor effect becomes weaker. Clearly pronounced proton-acceptor properties of aminophosphonates follow, e.g., from the results of our previous calorimetric studies on reactions of α-aminophosphonates with proton-donor regents [15].

Unfortunately, the limited set of data for β-aminophosphoryl compounds, as compared to much more extensively studied α-homologs, does not allow us to draw more profound generalizations. We plan to perform a detailed study on the relations between the structure of phosphorylated amines and their practically important properties using more representative reaction series.

EXPERIMENTAL

The ^{1}H and ^{31}P NMR spectra were recorded on a Varian Unity-300 spectrometer at 300 MHz for ^{1}H and 121.42 MHz for ^{31}P, using CDCl$_3$ as solvent. The ^{1}H chemical shifts were measured relative to the residual solvent signal, and the ^{31}P chemical shifts were measured relative to 85% phosphoric acid as external reference. The pK_{BH^+} values were measured as described in [1]. The procedure for determination of distribution constants was reported in [7]. α-Aminophosphonates **VII** and **VIII** were synthesized according to the procedure described in [1].

Reaction of dialkyl vinylphosphonates with primary and secondary amines. A mixture of 19 mmol of vinylphosphonate and 19 mmol of the corresponding amine was heated at 70–100°C until disappearance from the IR spectrum of the absorption band belonging to the double bond. β-Aminoethylphosphonates **I–VI** were isolated by vacuum distillation.

Diethyl 2-(butylamino)ethylphosphonate (I). Yield 4.12 g (73.3%), bp 85–86°C (0.8 mm), $n_D^{20} = 1.4420$; published data [11]: bp 75–77°C (0.03 mm,

n_D^{20} = 1.4400. ^{1}H NMR spectrum, δ, ppm: 0.87 t [3H, **CH$_3$**(CH$_2$)$_3$N, $^3J_{HH}$ = 7.1 Hz], 1.29 t (6H, **CH$_3$**CH$_2$O, $^3J_{HH}$ = 7.1 Hz), 1.31 m [2H, N(CH$_2$)$_2$**CH$_2$**], 1.43 m (2H, NCH$_2$**CH$_2$**C), 1.94 m (2H, P**CH$_2$**CH$_2$, $^2J_{PH}$ = 18.3, $^3J_{HH}$ = 7.4 Hz), 2.56 t (2H, NCH$_2$, $^3J_{HH}$ = 7.1 Hz), 2.86 m (2H, PCH$_2$**CH$_2$**, $^3J_{HH}$ = 7.4, $^3J_{PH}$ = 7.4 Hz), 4.06 m (4H, CH$_3$**CH$_2$**O). ^{31}P NMR spectrum: δ$_P$ 31.3 ppm.

Diethyl 2-(diethylamino)ethylphosphonate (II). Yield 3.6 g (80.4%), bp 71–72°C (0.8 mm), n_D^{20} = 1.4400. ^{1}H NMR spectrum, δ, ppm: 0.95 t (3H, NCH$_2$**CH$_3$**, $^3J_{HH}$ = 7.1 Hz), 1.24 t (6H, **CH$_3$**CH$_2$O, $^3J_{HH}$ = 6.8 Hz), 1.82 m (2H, P**CH$_2$**CH$_2$, $^2J_{PH}$ = 19.4, $^3J_{HH}$ = 7.3 Hz), 2.42 q (4H, CH$_2$NCH$_2$, $^3J_{HH}$ = 7.1 Hz), 2.72 m (2H, PCH$_2$**CH$_2$**, $^3J_{PH}$ = 8.3, $^3J_{HH}$ = 7.3 Hz), 4.02 m (4H, CH$_3$**CH$_2$**O). ^{31}P NMR spectrum: δ$_P$ 31.8 ppm.

Diethyl 2-(*N*-butyl-*N*-octylamino)ethylphosphonate (III). Yield 1.96 g (25%), bp 168–170°C (0.8 mm), n_D^{20} = 1.4504. ^{1}H NMR spectrum, δ, ppm: 1.87 m (2H, P**CH$_2$**CH$_2$, $^2J_{PH}$ = 19.2, $^3J_{HH}$ = 7.3 Hz), 2.36 q (4H, CH$_2$NCH$_2$, $^3J_{HH}$ = 7.4 Hz), 2.73 m (2H, PCH$_2$**CH$_2$**, $^3J_{PH}$ = 8.3, $^3J_{HH}$ = 7.1 Hz), 4.06 m (4H, CH$_3$**CH$_2$**O). ^{31}P NMR spectrum: δ$_P$ 32.0 ppm. Found, %: C 60.98; H 11.99. C$_{17}$H$_{40}$NO$_3$P. Calculated, %: C 60.53; H 11.86.

Diethyl 2-morpholinoethylphosphonate (IV). Yield 4.69 g (80.5%), bp 97–98°C (0.8 mm), n_D^{20} = 1.4640; published data [12]: bp 137°C (1 mm), n_D^{20} = 1.4590. ^{1}H NMR spectrum, δ, ppm: 1.28 t (6H, **CH$_3$**CH$_2$O, $^3J_{HH}$ = 7.1 Hz), 1.92 m (2H, P**CH$_2$**CH$_2$, $^2J_{PH}$ = 19.4, $^3J_{HH}$ = 8.2 Hz), 2.41 t (4H, CH$_2$NCH$_2$, $^3J_{HH}$ = 4.7 Hz), 2.60 m (2H, PCH$_2$**CH$_2$**, $^3J_{PH}$ = 8.3, $^3J_{HH}$ = 8.2 Hz), 3.66 t (4H, NCH$_2$**CH$_2$**O, $^3J_{HH}$ = 4.7 Hz), 4.06 m (4H, CH$_3$**CH$_2$**O). ^{31}P NMR spectrum: δ$_P$ 29.8 ppm. Found, %: C 47.38; H 8.91; P 12.68. C$_{10}$H$_{22}$NO$_4$P. Calculated, %: C 47.81; H 8.76; P 12.35.

Diisopropyl 2-(diethylamino)ethylphosphonate (V). Yield 2.9 g (67%), bp 68–69°C (0.5 mm), n_D^{20} = 1.4414. ^{1}H NMR spectrum, δ, ppm: 0.99 t (6H, **CH$_3$**CH$_2$N, $^3J_{HH}$ = 7.2 Hz), 1.27 d [12H, (**CH$_3$**)$_2$CHO, $^3J_{HH}$ = 6.2 Hz], 1.82 m (2H, P**CH$_2$**CH$_2$, $^2J_{PH}$ = 19.3, $^3J_{HH}$ = 8.3 Hz), 2.46 q (4H, CH$_2$NCH$_2$, $^3J_{HH}$ = 7.1 Hz), 2.75 m (2H, PCH$_2$**CH$_2$**, $^3J_{PH}$ = 6.5, $^3J_{HH}$ = 8.3 Hz), 4.65 m [2H, (CH$_3$)$_2$**CH**O, $^3J_{PH}$ = 7.9, $^3J_{HH}$ = 6.2 Hz]. ^{31}P NMR spectrum: δ$_P$ 29.6 ppm. Found, %: C 54.11; H 10.69; P 11.70. C$_{12}$H$_{28}$NO$_3$P. Calculated, %: C 54.34; H 10.57; P 11.70.

Dibutyl 2-(diethylamino)ethylphosphonate (VI). Yield 1.95 g (56%), bp 91–92°C (0.7 mm), n_D^{20} = 1.4456. ^{1}H NMR spectrum, δ, ppm: 0.98 t (6H, **CH$_3$**CH$_2$N, $^3J_{HH}$ = 7.1 Hz), 1.33 t [6H, **CH$_3$**(CH$_2$)$_3$O, $^3J_{HH}$ = 7.3 Hz], 1.35 m [4H, CH$_3$**CH$_2$**(CH$_2$)$_2$O, $^3J_{HH}$ = 7.3 Hz], 1.60 m (4H, CH$_3$CH$_2$**CH$_2$**CH$_2$O, $^3J_{HH}$ = 7.3 Hz), 1.86 m (2H, P**CH$_2$**CH$_2$, $^2J_{PH}$ = 19.2, $^3J_{HH}$ = 8.2 Hz), 2.46 q (4H, CH$_2$NCH$_2$, $^3J_{HH}$ = 7.1 Hz), 2.76 m (2H, PCH$_2$**CH$_2$**, $^3J_{HH}$ = 7.0, $^3J_{HH}$ = 8.2 Hz), 3.97 m (4H, CH$_2$**CH$_2$**O). ^{31}P NMR spectrum, δ$_P$ 32.2 ppm. Found, %: C 57.21; H 10.98; P 10.36. C$_{14}$H$_{32}$NO$_3$P. Calculated %: C 57.32; H 10.92; P 10.59

REFERENCES

1. Zakharov, S.V., Nuriazdanova, G.Kh., Garifzyanov, A.R., Galkin, V.I., and Cherkasov, R.A., *Russ. J. Gen. Chem.*, 2004, vol. 74, p. 873.
2. Cherkasov, R.A. and Galkin, V.I., *Usp. Khim.*, 1998, vol. 67, p. 940.
3. *Aminophosphonic and Aminophosphinic Acids: Chemistry and Biological Activity*, Kukhar, V.P. and Hudson, H.R., Eds., New York: Wiley, 2000.
4. Garifzyanov, A.R., Shirshova, N.V., and Cherkasov, R.A., *Russ. J. Gen. Chem.*, 2005, vol. 75, p. 537.
5. Garifzyanov, A.R., Zakharov, S.V., and Cherkasov, R.A., *Russ. J. Gen. Chem.*, 2005, vol. 75, p. 1057.
6. Garifzyanov, A.R., Zakharov, S.V., Kryukov, S.V., Galkin, V.I., and Cherkasov, R.A., *Russ. J. Gen. Chem.*, 2005, vol. 75, p. 1208.
7. Garifzyanov, A.R., Nuriazdanova, G.Kh., and Cherkasov, R.A., *Russ. J. Gen. Chem.*, 2004, vol. 74, p. 1885.
8. Gumienna-Kontecka, E., Galezowska, J., Drag, M., Lataika, R., Kafarski, P., and Kozlowski, H., *Inorg. Chim. Acta*, 2004, vol. 357, p. 1632.
9. Rahman, M.S., Oliano, M., and Hii King Kuok, *Tetrahedron: Asymmetry*, 2004, vol. 15, p. 1835.
10. Gubnitskaya, E.S., Peresypkina, L.G., and Samarai, L.I., *Usp. Khim.*, 1990, vol. 59, p. 1386.
11. Pudovik, A.N. and Denisova, G.M., *Zh. Obshch. Khim.*, 1953, vol. 23, p. 263.
12. Gubnitskaya, E.S. and Peresypkina, L.G., *Zh. Obshch. Khim.*, 1989, vol. 59, p. 556.
13. Burger, A. and Sherlver, W.H., *J. Med. Pharm. Chem.*, 1961, vol. 4, p. 225.
14. Leo, A., Hansch, C., and Elkins, D., *Chem. Rev.*, 1971, vol. 71, p. 525.
15. Sagadeev, E.V., Safina, Yu.G., and Cherkasov, R.A., *Russ. J. Org. Chem.*, 2004, vol. 40, p. 940.