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Synthesis of Novel Mono- and Bisaminophosphoryl Compounds and Their Membrane Transport Properties for Acidic Substrates

R. A. Cherkasov, A. S. Talan, A. V. Tarasov, and A. P. Garifzyanov

Kazan State University,
ul. Kremlevskaya 18, Kazan, Tatarstan, 420008 Russia
e-mail: rafael.cherkasov@ksu.ru

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Abstract—Some novel aminophosphoryl compounds were synthesized by the Kabachnik–Fields reaction. Their membrane transport properties for mono- and polyfunctional carboxylic acids with different number of functional groups were studied to establish that the transport rate of acidic substrates through liquid impregnated membranes increases in going from mono- to diphosphoryl carriers. Additional hydrophilic groups in the substrate molecule, too, affect transport efficiency.

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Earlier we reported that α- and β-aminated phosphoryl compounds can be used as selective extractants for noble metal ions [1, 2] and as ionophores in ion-selective electrodes [3]. They are also of undoubtful interest as carriers in membrane extraction of organic and inorganic substrates [4, 5]. Research on the influence of the structure of functionalized phosphoryl carriers on the efficiency of membrane transport of proton–donor substrates [4] and phase transfer of metal ions [2, 6] established that the complexing ability of phosphoryl extractants is affected by "additional" donor functional groups. Mono- and diphosphorylated phosphine oxides have never been compared as membrane carriers for proton-donor substrates. Phosphine oxide carriers are obviously advantageous over their phosphonate analogs in being hydrolytically more stable in acidic and alkaline media.

In the present work we synthesized novel α-aminophosphine oxides of various nature and studied their membrane transport properties for proton-donor substrates. Using the Kabachnik–Fields reaction we obtained a number of amines of the phosphonate and phosphine oxide structures with various mutual arrangements of the nitrogen and phosphorus atoms, one or two phosphorus-containing groups, and, for a required hydrophilic–lypophilic balance, fairly long-chain substituents at the potential coordination centers [7]. Their formulas and the transport flows rates of organic acids are given in the table. The one-pot syntheses of compounds **I**–**V** were carried out in the three-component system formaldehyde–octylamine–dihexyl phosphinite (for **I**) or dioctyl phosphinite (for **II**). Phosphonate **III** was synthesized from bis(2-ethylhexyl)amine and dicyclohexyl hydrogen phosphite. Phosphorylated amine **II** was, in its turn, used as the amine component in the three-component Kabachnik–Fields system, along with formaldehyde and dihexylphosphinous acid to synthesize diphosphorylated amine **IV**. The synthesis of γ-aminophosphonate **V** was carried out in three stages. In the first stage we obtained diisopropyl (3-chloropropyl)phosphonate by selective substitution of bromine in 1-chloro-3-bromopropane with sodium diisopropyl phosphite by the Michaelis–Becker reaction [8]. The product was refluxed in excess butylamine to obtain the corresponding γ-(*N*-butylamino)phosphonate whose Kabachnik–Fields reaction with formaldehyde and dioctyl phosphinite gave diphosphorylated amine **V** with high yield. We developed a procedure for purification of aminophosphine oxides, according to which the latter are converted into crystalline oxalic acid salts in diethyl ether, and the oxalates are recrystallized and treated with aqueous alkali to recover the neutral form.

Our obtained aminophosphoryl carriers were investigated as carriers for membrane extraction of medium-strength organic acids with different numbers

Membrane transport flow rates of organic acids with aminophosphoryl compounds $R_2P(O)CH_2NR^1R^2$

Carrier				Flow rate×10^6 mol $min^{-1}m^2$			
Comp. no.	R	R^1	R^2	Acetic acid	Glutaric acid	Tartaric acid	Citric acid
I	Hex	Oct	H	170	79	0.026	19
II	Oct	Oct	H	190	260	2.3	95
III	*cyclo*-HexO	2-EtHex	2-EtHex	200	0.294	0.066	13
IV	Hex	Oct	$CH_2P(O)Hex_2$	460	240	18	30
V	Oct	Bu	$(CH_2)_3P(O)(OPr\text{-}i)_2$	420	330	11	23

of functional groups: acetic, glutaric, tartaric, and citric. We considered it important and interesting to choose specifically this series of acids, since the consecutive increase in the number of the hydrophilic carboxy and hydroxy groups was expected to affect strongly the ability of the acids "to employ" certain basic centers of carriers and also to form complexes with hydrogen bonds of various strength with was molecules in the feed phase.

We carried out the purposeful selection of the structure of aminophosphoryl carriers in view of the fact that, as we earlier established [4], the most effective membrane transport of acids with functionalized phosphoryl compounds containing hydroxy, alkoxy, and amino groups in various positions to the phosphorus atom is observed with the latter derivatives: Aminophosphonates provide much higher transport flow rates compared to oxygen analogs. Hydrogen bonding of transported acidic substrates is obviously much stronger with nitrogen centers than with oxygens. The second phosphoryl group in the carrier molecule, α (**IV**) or γ (**V**) to nitrogen, not only affects (decreases) the electron density on the latter [9], but also creates obvious steric hindrances to complex formation, especially with large molecules of polyfunctional acids. Thus we had a good chance to assess the efficiency and selectivity of membrane extraction and concentration of acidic substrates by selecting complementary substrate–-aminophosphoryl carrier pairs.

The low-polarity phenylcyclohexane was chosen as a membrane solvent to exclude the possibility of specific solvation of both carriers and complexes formed in the membrane phase.

It is known that weak organic and inorganic acids are extracted by the solvate mechanism, which assumes formation of H-complexes between the proton donor and the corresponding basic center of the partner [4]. In this case, the extraction efficiency will be defined by the hydration energy of the acid molecule and the energy of the forming hydrogen bond, i.e. by the strength of the arising carrier–acid associate and its hydrophilicity. It is quite probable that our studied carriers and acids, too, form such associates.

Interrelationships between the structure and transport properties of carriers are commonly not sufficiently simple, since the transport efficiency is dependent both the rate of carrier-substrate bonding and on the facility of re-extraction in the receiving phase. Moreover, polyfunctional complex-forming agents, like our studied aminophosphoryl compounds, not always employ simultaneously all their coordination centers in bonding with the transported substrate, say, by steric reasons.

Nevertheless, the results presented in the table reveal fair correlations between the structure of the complex-forming partners and the transport flow rates. This correlation is especially clear in the case of the monobasic acetic acid. Comparison of the flow rates of amines **I–V** provides unequivocal evidence showing that the nitrogen atom is the protonation center of the carrier, and the phosphoryl oxygen is not involved in bonding with the substrate. As we showed earlier [4], the efficiency of nitrogen-free phosphoryl carriers for monobasic acids is much enhanced when the electron-acceptor alkoxy substituents on phosphorus are replaced by the donor alkyl groups. In this case, the transport flow rate over the series phosphine oxide **I, II**, phosphonate **III** remains almost unchanged.

At the same time, with diphosphorylated amines, the transport flow rate of acetic acid increases sharply, implying that it is the phosphoryl group that is involved in H-complex formation with the substrate.

There are two possible reasons for the "inclusion" in bonding of an additional basic center, the oxygen atom. On the one hand, tertiary amines, such as carriers **IV** and **V**, are incapable of forming intramolecular hydrogen bonds, which, as we showed earlier [10], can seriously affect the acid–base properties of aminophosphoryl compounds. This makes additional coordination centers available for protonation, even though the structure of the resulting complexes (simultaneous H-bonding with two or three centers and complex formation with two or three acid molecules at once) is difficult to establish from the available data.

The "structure–transport efficiency" interrelationship for the dibasic glutaric acid is less unequivocal. In this case, diphosphoryl carriers, too, tend to provide a more efficient transport, but this tendency is not as well-defined as with the monobasic acid substrate. The high flow rate with phosphine oxide **II** is attributable to the involvement of both the carboxylic groups in protonation of the two basic centers of the phosphorylated amine, as may also be the case with diphosphorylated amines **IV** and **V**. In this respect quite illustrative is an almost 1.5-fold difference in the efficiency of the latter two amines: α,α-Diphosphylamine **IV** is highly sterically congested, and, therefore, the nitrogen center in it is shielded and less accessible than in its α,γ-analog **V**. The reason for the low efficiency of transport of glutaric acid with phosphine oxide **I** and, especially, phosphonate **II** can consist in an unfavorable hydrophylic-lipophilic balance of the carriers (we earlier observed such distinction when varied the length of the hydrocarbon groups on phosphorus in a membrane transport study on phosphorylated aza podands [6]). Another possible explanation of the observed phenomenon is the presence of the second hydrophilic carboxy group which is not bonded with the carrier but has a strong hydrogen bond with the medium and thus keeps the substrate in the feed phase. However, the lack of transfer with complex formation in the case of phosphonate **II** can be connected with its specific properties, for example, poor solubility in the organic membrane phase.

The effect of an "additional" hydrophilic group, which we observed earlier on transport of dicarboxylic and hydroxy acids with functionalized phosphoryl carriers [4], revealed itself to full measure in the present reaserch, too. The low transport flow rates for di- and trihydroxy acids, such as tartaric and citric, are obviously connected just with a high hydrophilicity of the H-complexes of phosphorylated amines with these substrates, since the carriers have not enough basic centers for bonding with all their proton-donor functional froups. The excess nonbound hydroxy and carboxy groups form hydrogen bonds with water molecules and thus keep the substrates in the feed phase.

Thus, the present results provide evidence for our earlier conclusion that efficient membrane transport of substrates of various nature is provided exclusively by complementary carrier-substrate interactions. Thus, in the transport of metal ions with phosphorylated aza podands [6] or in the use of aminophosphoryl compounds in ion-selective electrodes [3], of importance is for the ion size to be compatible with the size of the potential pseudo-cavity formed by the podand. Acid–base interactions of a proton donor with potential electron-donor centers of the complex-forming agent and presence or absence of "additional" hydrophilic groups in the substrate should also be taken into account in considering membrane transport of acidic substrates. Evidently, features of the hydrophylic–lipophilic balance both in the carrier and in its formed complex, too, should be taken into consideration, even though this factor is fairly difficult to evaluate explicitly. This relates to full measure to steric factors essential on the formation of complexes transferred into the membrane phase. Nevertheless, the revealed trends in variation of the transport properties of carriers as a function of their and transported substrate structure allow optimization of membrane transport processes by selection of complementary substrate–carrier pairs.

EXPERIMENTAL

Equipment and technique of the membrane transport study are described in [5]. Vladipor MFFK-4 filters, pore size 0.1 μm, impregnated with 0.1 M solutions of carriers in phenylcyclohexane were used as impregnated membranes. The initial concentration of carboxylic acids in the feed solution was 0.1 M.

Synthesis of aminophosphoryl compounds by the Kabachnik–Fields reaction (*general procedure*). A solution of 0.3 mol of dialkyl phosphinite or phosphite, 0.3 mol of Paraform, 0.3 mol of amine, and a small amount of *p*-toluenesulfonic acid in 30 ml of solvent (benzene, toluene, or *o*-xylene) was refluxed with a Dean–Stark trap until water no longer released.

A calculated quantity of Na_2CO_3 was added to remove the catalyst. The reaction mixture was washed with water, and the aqueous layer was extracted with benzene. The organic fractions were combined and dried over anhydrous magnesium sulfate. The solvent was removed in a rotary evaporator. The crystalline or oily residue was treated with a calculated quantity of oxalic acid in diethyl ether. White crystals precipitated and were recrystallized from acetone and then treated with aqueous alkali until neutral reaction. The target aminophosphoryl compound was extracted with toluene, dried over anhydrous magnesium sulfate, and the solvent was removed under a vacuum.

Dihexyl(*N*-octylaminomethyl)phosphine oxide (I). Yield 70%, mp 35°C. ^{31}P NMR spectrum (toluene): δ_P 48 ppm. IR spectrum, ν, cm^{-1}: 1159 (P=O). Calculated, %: P 8.61; N 3.90. $C_{21}H_{46}NOP$. Found, %: P 8.60; N 3.89.

Dioctyl(*N*-octylaminomethyl)phosphine oxide (II). Yield 80% mp 48°C. ^{31}P NMR spectrum (toluene): δ_P 48 ppm. IR spectrum, ν, cm^{-1}: 1161 (P=O). Calculated, %: P 7.45; N 3.37. $C_{25}H_{54}NOP$. Found, %: P 7.41; N 3.32.

Dicyclohexyl [*N*,*N*-bis(2-ethylhexyl)aminomethyl]-phosphonate (III). Yield 70%, n_D^{20} 1.4729. ^{31}P NMR spectrum (toluene): δ_P 25 ppm. IR spectrum, ν, cm^{-1}: 1246 (P=O). Found, %: P 5.54; N 2.76. $C_{29}H_{58}NO_3P$ Calculated, %: P: 6.20; N: 2.80.

Dihexyl[[*N*-octyl-*N*-(dihexylphosphinoylmethyl) amino]methyl]phosphine oxide (IV). Yield 50%, n_D^{20} 1.4729. ^{31}P NMR spectrum (toluene): δ_P 44 ppm. IR spectrum, ν, cm^{-1}: 1165 (P=O).

{[*N*-Butyl-*N*-[3-(diisopropoxyphosphinoyl)propyl]-amino]methyl}dioctylphosphine oxide (V). Yield 40%, n_D^{20} 1.4651. ^{31}P NMR spectrum (toluene), δ_P, ppm: 45, 31.

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