Membrane transport of dicarboxylic and α-hydroxy carboxylic acids induced by α-amino phosphonates

I. I. Stoikov,[a]★ N. A. Fitseva,[a] L. R. Akhmetzyanova,[a] L. I. Gafioullina,[a] I. S. Antipin,[a,b] V. F. Zheltukhin,[b] A. I. Devyaterikova,[b] V. A. Al´fonsov,[b] and A. I. Konovalov[a,b]

[a]*Kazan State University,*
18 ul. Kremlevskaya, 420008 Kazan, Russian Federation.
Fax: +7 (843 2) 75 5322. E-mail: istoikov@ksu.ru
[b]*A. E. Arbuzov Institute of Organic and Physical Chemistry, Kazan Research Center of the Russian Academy of Sciences,*
8 ul. Akad. Arbuzova, 420088 Kazan, Russian Federation.
Fax: +7 (843 2) 75 2253. E-mail: iantipin@ksu.ru

New α-amino phosphonates containing different alkyl and aryl substituents at the α-carbon atom were synthesized in high yields by the Kabachnik—Fields and Pudovik reactions. These compounds were studied as carriers of several α-hydroxy carboxylic and dicarboxylic acids through liquid impregnated membranes. These α-amino phosphonates studied are capable of molecular recognition of oxalic acid among structurally similar α-hydroxy carboxylic and dicarboxylic acids. The efficiency and selectivity of mass transfer of oxalic acid increase with an increase in the lipophilicity of the α-amino phosphonate.

Key words: α-amino phosphonates, membrane transport, dicarboxylic acids, α-hydroxy carboxylic acids, synthetic receptors.

Various biochemical and technological processes are based on the selective permeability of biological and synthetic membranes.[1—3] Membrane methods of concentration, purification, or separation of complex multicomponent mixtures have been developed actively during the past two decades.[3] The selective permeability of membrane and acceleration of membrane extraction in comparison with free diffusion are usually achieved by virtue of carrier molecules which selectively interact with the substance to be transported. The principles for the design of synthetic complex-forming agents are taken from biological systems, whose functioning is tightly related to their ability of molecular recognition.

Molecular recognition is determined by information inherent in the interacting components. The result of recognition is the selective binding of a substrate to a receptor to form a "supermolecule". A synthetic receptor needs to possess steric and electronic properties complementary to a substrate that is bound.[2] The study and establishment of the structure of the "carrier molecule structure—transport properties" relationship are essential.[4] It is of interest to reveal regularities relating the structure of a synthetic receptor to the membrane transport rate and substrate specificity.

We chose such organic compounds as α-hydroxy carboxylic and dicarboxylic acids as the subjects for studies. They are of theoretical and practical interest due to their biological significance.[5] For instance, successful treatment of some diseases related to defects of enzyme systems requires early selective quantitation of several dicarboxylic and α-hydroxy carboxylic acids in different biological fluids.[6] Until recently, the main success in recognition of carboxylic acids and their derivatives has been related to the creation of receptors to the carboxylate or, in the case of amino acids, carboxylate and ammonium functions.[7] The design of synthetic receptors towards molecular forms of acids is still a difficult problem because of weak intermolecular interactions. Binding and recognition of noncharged molecules are based on the involvement of hydrogen bonds and electrostatic and donor-acceptor interactions. Nitrogen-containing compounds (oligoamines, urea derivatives, guanidinium salts, tetraazonium compounds, *etc*.) found wide use for the design of synthetic receptors towards carboxylate anions and carboxylic acids.[8]

Combination of several functional groups capable of complex formation in a single molecule and variation of the lipophilicity and steric shielding of binding sites of a carrier with a substrate owing to introduction of different alkyl or aryl fragments provide an access to the synthesis of a new generation of receptors capable of recognition of organic acids. In this respect, α-aminophosphonates are most attractive, because they contain several binding sites, *viz*., one proton-donating (NH) and two proton-with-

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 7, pp. 1517—1523, July, 2004.

1066-5285/04/5307-1577

drawing sites (P=O and a lone electron pair (LEP) of the N atom),[9,10] which can form hydrogen bonds with hydroxy and carboxy groups of carboxylic acids.

Experimental

IR spectra of liquid films of compounds under study between KBr plates were recorded on a Specord M-80 spectrometer in a wave number interval of 700—3600 cm^{-1}. ^{31}P NMR spectra of α-amino phosphonates in $CDCl_3$ were obtained on a Varian-XL-300 spectrometer, and chemical shifts were determined relatively to the external standard (85% H_3PO_4). The concentration of solutions analyzed was 3—5 wt.%. The conductometric control was carried out using a WTW inoLab Cond Level 1 conductometer. Electronic spectra were recorded on a Perkin Elmer Lambda-35 spectrometer, the transmitting layer thickness being 1 cm. The following acids were used: DL-mandelic, glycolic, DL-tartaric DL-glutamic, oxalic, malonic, and succinic. All acids and sodium acetate were of "reagent grade" purity. Quantum-mechanical calculations of the conformations of α-amino phosphonates were performed by the molecular mechanics (MM+) and semiempirical PM3 methods included into the MOPAC 7.00 program package.

***O,O*-Bis(2-ethylhexyl)benzylaminomethylphosphonate (1),** d_4^{20} 1.02, n_D^{20} 1.4844, ***O,O*-bis(2-ethylhexyl)-1-benzylamino-1-methylethylphosphonate (2),** d_4^{20} 0.85, n_D^{20} 1.4823, and ***O,O*-bis(2-ethylhexyl)-1-(benzylamino)cyclopentylphosphonate (3),** d_4^{20} 0.99, n_D^{20} 1.4884, were synthesized according to a known procedure.[4]

Synthesis of α-amino phosphonates 4—8 (general procedure). A mixture of an azomethine (2.2 mmol)[11] and dialkyl phosphite (2.2 mmol) in benzene (10 mL) was refluxed with stirring for 11—20 h. The solvent was removed *in vacuo*. The completion of the reaction and purity of the reaction products were monitored by ^1H and ^{31}P NMR spectroscopy. The residue was chromatographed on a column with silica gel L 100—160 μm using a $CHCl_3$—Pr^iOH (10 : 1) mixture as the eluent.

***O,O*-Didecyl 1-(1-hydroxybutan-2-ylamino)octylphosphonate (4).** The reaction mixture was stirred for 14 h. The yield of the product as a yellow viscous liquid was 0.94 g (76%), n_D^{20} 1.4588. Found (%): C, 68.10; H, 12.18; P, 5.55. $C_{32}H_{68}NO_4P$. Calculated (%): C, 68.41; H, 12.20; P, 5.51. IR spectrum (KBr), ν/cm^{-1}: 3390 (OH); 1223 (P=O). ^{31}P NMR ($CDCl_3$), δ: 28.08, 27.83 (60 : 40).

***O,O*-Didecyl 1-(1-hydroxybutan-2-ylamino)decylphosphonate (5).** The reaction mixture was stirred for 16 h. The yield of the reaction product (yellow viscous liquid) was 0.97 g (75%), n_D^{20} 1.4540. Found (%): C, 69.01; H, 12.19; P, 5.28. $C_{34}H_{72}NO_4P$. Calculated (%): C, 69.22; H, 12.30; P, 5.28. IR (KBr), ν/cm^{-1}: 3400 (OH); 1220 (P=O). ^{31}P NMR ($CDCl_3$), δ: 30.19, 30.07 (55 : 45).

***O,O*-Dioctyl 1-(1-hydroxybutan-2-ylamino)benzylphosphonate (6).** The reaction mixture was stirred for 20 h. The yield of the product (yellow viscous liquid) was 1.01 g (95%), n_D^{20} 1.4952. Found (%): C, 66.97; H, 10.30; P, 6.45. $C_{27}H_{50}NO_4P$. Calculated (%): C, 67.05; H, 10.42; P, 6.40. IR (KBr), ν/cm^{-1}: 3400 (OH); 1250 (P=O). ^{31}P NMR ($CDCl_3$), δ: 25.1.

***O,O*-Dioctyl 1-(1-hydroxybutan-2-ylamino)-*p*-methoxybenzylphosphonate (7).** The reaction mixture was stirred for 20 h. The yield of the product (yellow viscous liquid) was 1.01 g (90%), n_D^{20} 1.4900. Found (%): C, 65.23; H, 10.41; P, 6.11. $C_{28}H_{52}NO_3P$. Calculated (%): C, 65.47; H, 10.20; P, 6.03. IR (KBr), ν/cm^{-1}: 3400 (OH); 1240 (P=O). ^{31}P NMR ($CDCl_3$), δ: 25.0.

***O,O*-Didecyl 1-(1-hydroxybutan-2-ylamino)-*o*-allyloxybenzylphosphonate (8).** The reaction mixture was stirred for 11 h. The yield of the product (yellow viscous liquid) was 0.92 g (70%), n_D^{20} 1.4833. Found (%): C, 68.61; H, 10.50; P, 5.20. $C_{34}H_{62}NO_5P$. Calculated (%): C, 68.54; H, 10.49; P, 5.20. IR (KBr), ν/cm^{-1}: 3400 (OH); 1240 (P=O). ^{31}P NMR ($CDCl_3$), δ: 25.73, 25.60 (30 : 70).

Membrane transfer. The rate of substrate transport through liquid impregnated membranes was measured in a vertical glass diffusion cell with a movable cylinder at constant temperature.[12] Porous Teflon Millipore Type FA filters (thickness 1 μm, pore size 100 nm, porosity 85%) reinforced with a capron fiber which were impregnated with a liquid phase served as hydrophobic matrices. The ratio of volumes of the source and receiving phases was 5 : 1, which provided equal levels of solutions to prevent the osmotic acid transfer. Experiments on mass transfer were carried out at 25 °C. The initial solutions of substrates in twice-distilled water were freshly prepared before experiments. A solution of an α-amino phosphonate (**1—8**) in an organic solvent or a pure solvent (*o*-nitrophenyl *n*-octyl ether) were used as the liquid phases.

Determination of the membrane transfer. The initial solution of the substrate was placed in an external vessel kept at constant temperature and twice-distilled water was placed in an internal vessel. The source and receiving solutions were magnetically stirred. The concentrations of substances were determined from electric conductivity of the solutions. The calibration curves were averaged from three runs. Experiments on membrane transfer were carried out in triplicate under identical conditions.

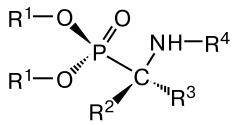
The liquid phase of the membrane was analyzed following transport by ^{31}P NMR spectroscopy, which showed that all the carriers are stable in the systems studied. The error of determination of the mass transfer flux J_i was ≤ 10%.

Determination of stoichiometry of complexes. The stoichiometry of complexes was determined by plotting curves of isomolar series. Solutions of the substrate and the synthetic receptor in methanol were prepared with a concentration of $1 \cdot 10^{-3}$ mol L^{-1}. The spectra of the initial solutions and mixtures of the initial solutions of an acid and α-amino phosphonate ratios of 4.6 : 1, 1.8 : 1, 1 : 1, 1 : 1.8, and 1 : 4.6 (v/v), respectively, were recorded at λ_{max} = 322 nm. The results were processed as described.[13]

Results and Discussion

A series of lipophilic α-aminophosphonates **1—8**, where substituents R^1 and R^4 at the phosphorus and nitrogen atoms and the number and the nature of alkyl substituents R^2 and R^3 at the α-C atom were varied, were synthesized from the corresponding dialkyl phosphites[14,15] in 62—95% yields.

Lipophilic α-amino phosphonates **1—3** were synthesized by the Kabachnik—Fields reaction[14] in 70—90% yield from the corresponding carbonyl compounds, benzylamine, and bis(2-ethylhexyl) phosphite. The Pudovik reaction[15] was chosen to synthesize α-amino



1—8

	R^1	R^2	R^3	R^4
1	$CH_2CH(Et)Bu$	H	H	CH_2Ph
2	$CH_2CH(Et)Bu$	Me	Me	CH_2Ph
3	$CH_2CH(Et)Bu$	$(CH_2)_4$		CH_2Ph
4	$C_{10}H_{21}$	H	C_7H_{15}	$CH(Et)CH_2OH$
5	$C_{10}H_{21}$	H	C_9H_{19}	$CH(Et)CH_2OH$
6	C_8H_{17}	H	Ph	$CH(Et)CH_2OH$
7	C_8H_{17}	H	4-$MeOC_6H_4$	$CH(Et)CH_2OH$
8	$C_{10}H_{21}$	H	2-CH_2=$CHCH_2OC_6H_4$	$CH(Et)CH_2OH$

phosphonates **4**—**8** from the corresponding azomethines and dioctyl and didecyl phosphites in boiling benzene without a catalyst.[15] Phosphonates **6** and **7** are formed with high stereoselectivity, and diastereomeric excess, according to the ^{1}H NMR spectroscopic data in the case of compound **6** (signals of protons of PCH were integrated), was higher than 95%, whereas in the case of compound **7** (signals of aromatic protons were integrated), it was of about 90%. Other amino phosphonates are formed stereoselectively as well, although diastereoselectivity of their formation is lower than that of phosphonates **6** and **7**. Diastereomers of compounds **4**, **5**, and **8**, unlike those of compounds **6** and **7**, are distinguishable in the ^{31}P NMR spectra and appear as two singlets in the region corresponding to the phosphonate phosphorus atom.

The membrane transport induced by α-amino phosphonates **1**—**8** was studied for several dicarboxylic and α-hydroxy carboxylic acids: glycolic **9**, tartaric **10**, mandelic **11**, oxalic **12**, malonic **13**, and succinic **14**. To estimate the influence of the carboxylate function on the mass transfer of carboxylic acids by the carriers under study, we studied the membrane extraction of sodium acetate **15**. Liquid membranes were prepared from Teflon filters impregnated with 1 *M* solutions of compounds **1**—**8** in *o*-nitrophenyl *n*-octyl ether.[9] The initial concentration of substrates **9**—**15** to be transported in the source phase was 0.1 mol L^{-1}. In the systems studied, the acid transport occurred according to the dialysis scheme, *i.e.*, under the chemical potential gradient.

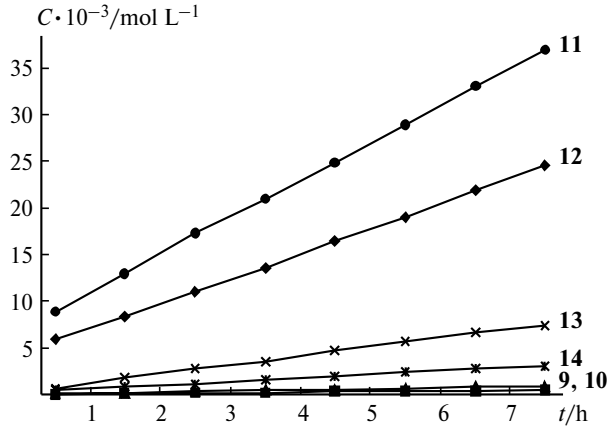


Fig. 1. Dependences of the concentrations of acids (**9**—**14**) in the acceptor phase on time (*t*) for carrier **4**. The initial linear regions are presented.

The fluxes through the membrane were calculated from the initial linear regions of the time dependence of the concentration of the transported substance in the receiving phase (Fig. 1). The flux (J_0) in the control experiment in which the membrane was represented by the pure solvent (*o*-nitrophenyl *n*-octyl ether) and the transport enhancement coefficients ($\in = J_i/J_0$) of substrates **9**—**15** through the liquid impregnated membranes are presented in Table 1. The logarithms of the distribution constant of the acids in the octanol—water two-phase system (log*P*)[9] characterize the lipophilicity of compounds **9**—**15**. As can be seen, the enhancement coefficients ∈ for acids **9**—**14** are higher than unity and, therefore, the introduction of α-amino phosphonates **1**—**8** into the membrane phase

Table 1. Flux enhancement coefficients of the mass transfer fluxes ($\in = J_i/J_0$) of organic acids **9**—**14** through the liquid impregnated membrane (25 °C)[a]

Compound	Acid	pK_a	log*P*	J_0[b]	∈							
					1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
9	Glycolic	3.83	−1.02	$9.4\cdot10^{-12}$	200[c]	110[c]	70[c]	62	77	56	26	30
10	Tartaric	3.03	−1.96	$4.4\cdot10^{-12}$	160	100	70	70	120	18	45	18
11	Mandelic	3.37	0.64	$1.5\cdot10^{-9}$	17	46	21	17	15	21	33	17
12	Oxalic	1.25	−1.88	$5.0\cdot10^{-12}$	170	1400	4400	3400	3400	2600	3400	2800
13	Malonic	2.85	−0.49	$2.8\cdot10^{-11}$	100	640	280	190	170	200	340	86
14	Succinic	4.21	−0.47	$1.3\cdot10^{-11}$	110	850	410	160	190	470	600	120
15	Sodium acetate	—	−4.24	$1.3\cdot10^{-12}$	1	1	1	1	1	1	1	1

[a] The error of determination of the mass transfer flux is ±10%. The membrane surface area $S = 9.616$ cm^2.
[b] The acid flux through the membrane containing no carrier, kmol m^{-2} s^{-1}.
[c] According to the data in Ref. 4.

increases the transfer rates of all substrates studied, except for sodium acetate. According to the mass transfer mechanism, the transport should be classified as the induced one, *i.e.*, involving a carrier molecule. The absence of an effect of the compounds studied on the flux of sodium acetate indicates that the energy of interaction of the carboxylate group with the α-amino phosphonate fragment is insufficient for transport through the lipophilic membrane of highly hydrophilic carboxylate anions.

Determination of the limiting step of the mass transfer process is important, in principle, for the analysis of the kinetic data on membrane extraction and elucidation of relationships between structures of a carrier molecule and a substrate and the rate of membrane transport and its substrate specificity. For this purpose, we studied dependences of the fluxes of the above-mentioned acids through the liquid membrane containing carriers **4**—**8** on the substrate concentration in the source phase. The typical dependence is presented in Fig. 2 for amino phosphonate **4**. The fluxes increase with an increase in the content of substrates in the source phase. This indicates that in this concentration range the extraction of the substrate from the aqueous to the organic phase is the limiting step of the process.

However, it should be noted that the rate-determining step can change with an increase in the substance concentration in the source phase and the corresponding increase in the transfer rate. This seems most probable for both lipophilic substrates and highly efficient carrier molecules where a substrate is efficiently extracted to the organic phase. For instance, the absence of changes in the flux (J^{max}) through the membrane with the increase in concentrations of mandelic and oxalic acids in the source phase as the substrate concentration is higher than 0.2 *M* (C_{sat}) indicates that re-extraction becomes the slowest step of the process (see Fig. 2). This situation is similar for other amino phosphonates under study. Therefore, the influence of structural factors on the transport was studied at the initial concentration of acids in the source phase of 0.1 mol L^{-1}.

Another important problem is the dependence of the mass transfer rate on the amino phosphonate concentration in the liquid membrane. To reveal the influence of the carrier concentration in the membrane phase on the mass transfer kinetics for compounds **4**—**8**, we studied the rates of oxalic acid transfer at its different concentrations in the source solution. The results for amino phosphate **7** are presented in Fig. 3. The mass transfer of compound **12** increases with an increase in the concentration of α-amino phosphonate in the liquid phase. In this case, a linear dependence of the acid flux on the carrier concentration is observed (Fig. 4). Thus, when the concentration of amino phosphonates in the liquid membrane reaches 1 mol L^{-1}, no influence of self-association[16] of the carrier on the flux of the substrate is observed.

Analysis of the results obtained (Fig. 5) shows that the highest flux enhancement coefficient, of all substrates

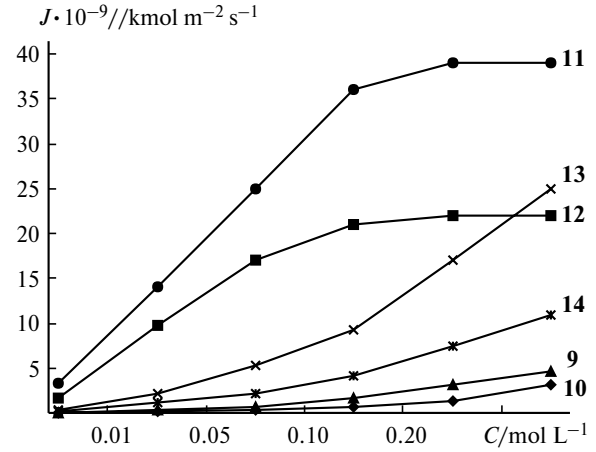


Fig. 2. Dependences of the flux parameters of several organic acids through the liquid impregnated membrane on their concentration in the feeding phase for carrier **4**.

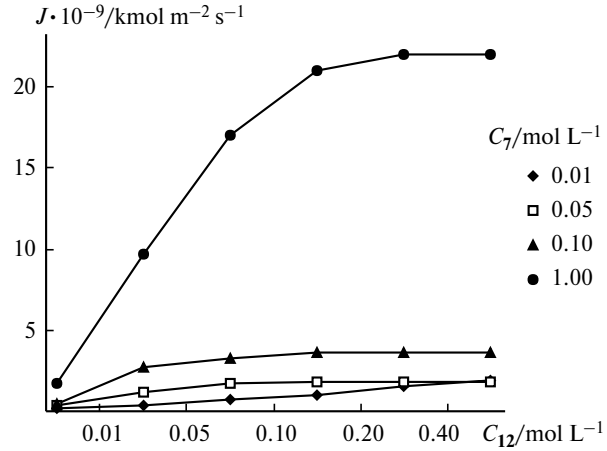


Fig. 3. Dependences of fluxes of oxalic acid on its concentration in the feeding phase at different concentrations of carrier **7** in the membrane.

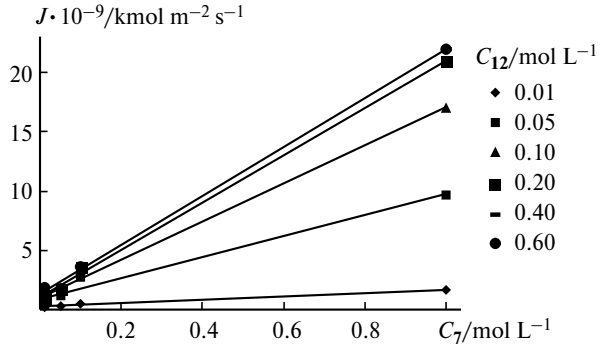


Fig. 4. Dependences of the fluxes of oxalic acid on the concentration of carrier **7** in the membrane at different concentrations of substrate **12** in the feeding phase.

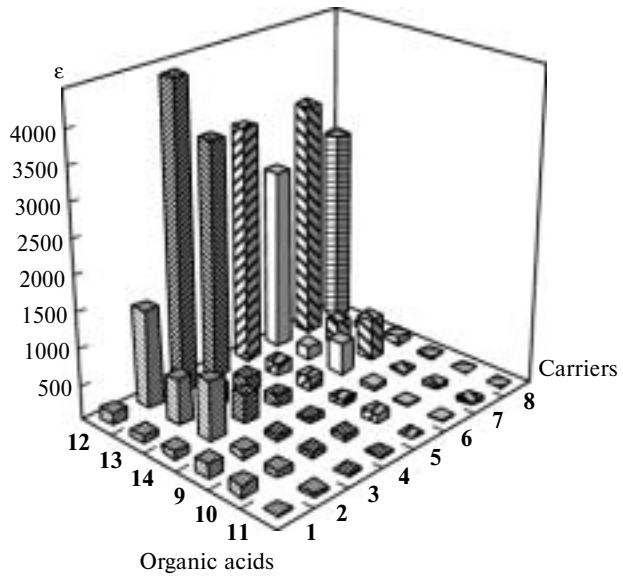


Fig. 5. Flux enhancement coefficients of several organic acids through the liquid impregnated membrane containing carriers **1**—**8**.

studied, is observed for highly hydrophilic oxalic acid and one can speak about its molecular recognition by amino phosphonates **2**—**8**, which increase the rate of its transfer through the lipophilic liquid membrane more than 1000-fold. The highest enhancement coefficient is achieved in the case of α-amino phosphonates **3**—**5** and **7**, where the increase in the flux through the membrane is more than 1000-fold compared to that in the control experiment. The lowest enhancement coefficient is observed for the most lipophilic substrate of the substrates studied, *viz.*, mandelic acid **11**, although it should be noted that no general dependence between the flux enhancement coefficients, on the one hand, and lipophilicity (log*P*)[9] and strength (pK_a)[17] of acids, on the other hand, is observed in the series of acids studied.

In the case of hydroxy carboxylic acids, a tendency for the flux enhancement with a decrease in the size of the substituent at the α-C atom of the acid is distinctly observed: **11** < **10** < **9**. This agrees with the strong influence of steric crowding of the binding sites in α-amino phosphonates **1** < **2** < **3** themselves, which has been found by us previously,[4] and exerts an unfavorable effect on the flux through the membrane. α-Amino phosphonates have two proton-withdrawing groups: the phosphoryl group P=O and the LEP of the nitrogen atom. They can interact specifically with the hydroxy and carboxy groups of α-hydroxy carboxylic acids. It was shown by IR spectroscopy, ^{1}H and ^{31}P NMR spectroscopy, and X-ray diffraction analysis[18] that complexation occurs due to the proton transfer from α-hydroxy carboxylic acid to α-amino phosphonate to form the ammonium nitrogen atom and a system of hydrogen bonds involving the phosphoryl group. Evidently, steric crowding near the coordination site prevents the efficient interaction of the substrate with both binding sites of the amino phosphonate, decreases the stability of complexes formed in the membrane phase and, as a consequence, decreases the mass transfer rate of α-hydroxy carboxylic acids.

The optimization of the structures of protonated *N*-benzyl α-amino phosphonates **1** and **3** performed by the PM3 method agrees with this statement (Fig. 6). As can be seen, the most stable conformation for α-unsubstituted derivative **1** is favorable for the interaction with α-hydroxy carboxylic acids. The distance between the phosphoryl O(1) oxygen atom and ammonium H(1) and H(2) protons is 2.8—2.9 Å. At the same time, the most favorable calculated conformation of protonated

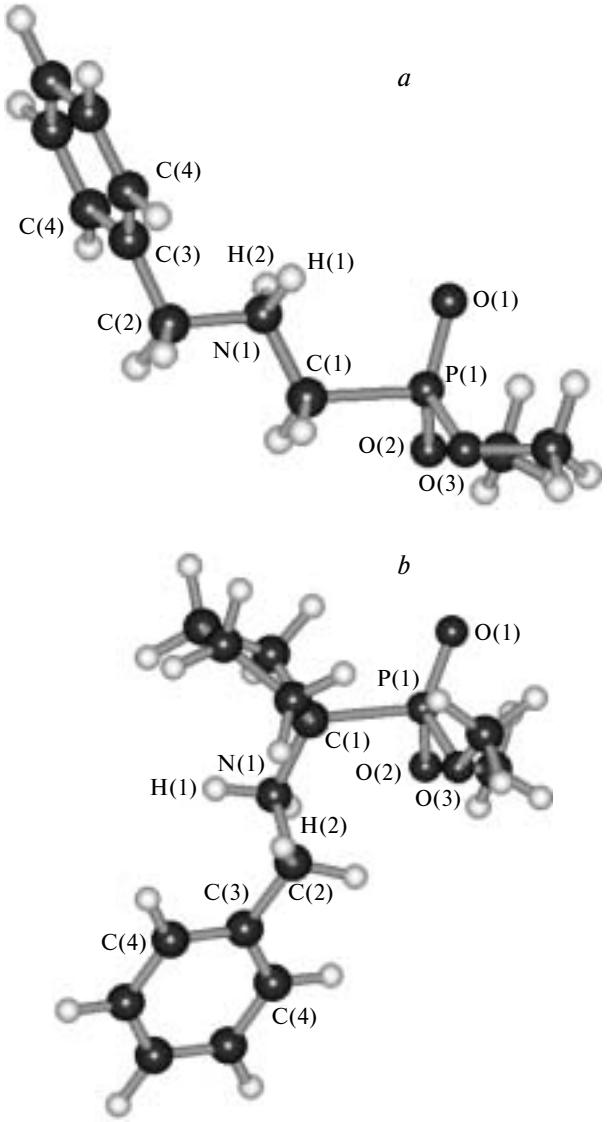


Fig. 6. Geometries of the protonated forms of α-unsubstituted amino phosphonate (*a*) and amino phosphonate with a cyclic substituent at the α-C atom (*b*) calculated by the PM3 method.

α-amino phosphonate **3** prevents the amino and phosphoryl groups to be involved simultaneously in substrate binding, because the O(1)H(1) and O(1)H(2) distances increase to 4.2—4.9 Å due to the steric effect of the cyclic substituent. As a result, the stability of the complexes and the flux through the membrane decrease.

The influence of steric factors on the transport of hydroxy carboxylic acids is observed for other series of structurally similar α-monosubstituted amino phosphonates **4**—**8**. It should be noted that carrier **8** having a substituent in the *ortho*-position of the aryl group was the least efficient, while amino phosphonates **4** and **5** with linear alkyl substituents in the α-position were the most efficient. On the whole, amino phosphonates **4**—**8** manifested no high efficiency for binding of hydroxy carboxylic acids studied, which suggests the absence of a substantial contribution of the interaction of the substrate with the hydroxy group of the substituent at the nitrogen atom of the amino phosphonate.

A quite different influence of electronic and steric effects is observed in the case of the oxalic acid transfer. The highest transport enhancement coefficient is observed for α-amino phosphonate **3** with cyclic substituents at the α-C atom, and the transfer rate decreases sharply in the series **3** > **2** ≫ **1** with a decrease in the number of alkyl substituents in the carrier. Therefore, the mutual orientation of the amino and phosphoryl groups in the carrier, unlike hydroxy carboxylic acids, is not the factor determining the stability of complexes formed in the membrane. This suggests that the phosphoryl group is not likely involved in binding of oxalic acid to amino phosphonate.

For deeper understanding of the mechanism of the membrane transfer of oxalic acid, we studied its interaction with α-amino phosphonate **7** by spectrophotometry. The complexation is accompanied by a decrease in the intensity of the absorption band of compound **7** at 283 nm and the appearance of a new band at 323 nm (Fig. 7). This band does not correspond to the absorption of the carboxylate group, because the addition of an excess of more basic triethylamine to oxalic acid does not result in the appearance of the band. Its intensity depends on the strength of the acid used, and it is absent already in the case of acetic acid. In addition, the interactions of amino phosphonates **4**—**8** with oxalic acid result in a considerable down-field shift (by 7—8 ppm) in the ^{31}P NMR spectra, which is attributed to the formation of a withdrawing ammonium group in amino phosphonate.

The 2 : 1 stoichiometry of carrier **7** with an oxalic acid complex was determined by plotting curves of isomolar series.[13,19] Job´s plot is presented in Fig. 8. Thus, oxalic acid binds two amino phosphonate molecules due to the protonation of nitrogen atoms in both molecules. Therefore, the flux enhancement of oxalic acid in the series **1** ≪ **2** < **3** can be related to the increase in the basicity of amino phosphonates. However, alkyl substituents at the α-C and nitrogen atoms were shown[20] to exert no substantial effect on their basicity. Thus, the lipophilicity of the 2 : 1 complex formed in which the hydrophilic molecule is localized inside the pseudocavity formed by two amino phosphonate molecules (Fig. 9) can be the crucial factor.

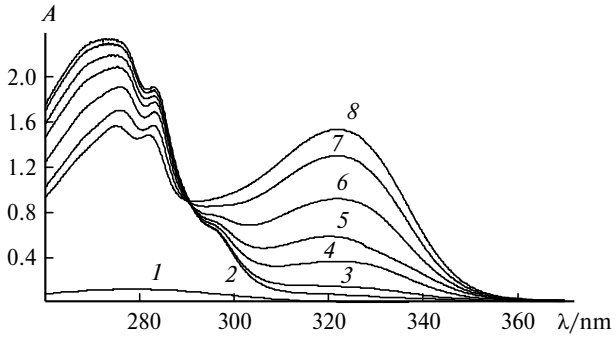


Fig. 7. Absorption spectra of compounds **7** and **12** and their mixtures in methanol: [**12**] = $2.5 \cdot 10^{-4}$ mol L^{-1} (*1*); [**7**] = $7.3 \cdot 10^{-4}$ mol L^{-1} (*2*); **12** : **7** = 1 : 100 (*3*); **12** : **7** = 1 : 33 (*4*); **12** : **7** = 1 : 20 (*5*); **12** : **7** = 1 : 10 (*6*); **12** : **7** = 1 : 3 (*7*); **12** : **7** = 1.3 : 1 (*8*).

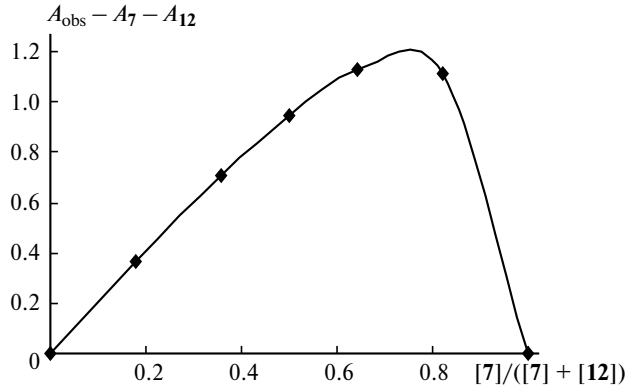


Fig. 8. Job´s plot for complexation of compounds **7** and **12**.

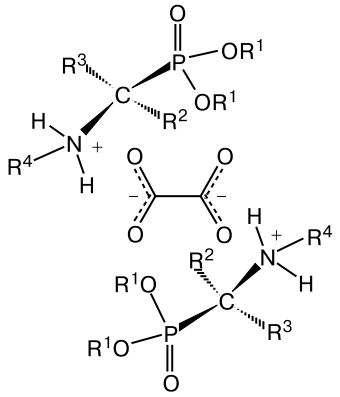


Fig. 9. Assumed structure of the complex of α-amino phosphonate with oxalic acid.

However, it is difficult to rationalize the increase in the flux of oxalic acid by almost an order of magnitude on going from carrier **1** to **2** only by changes in the lipophilicity of the carrier. In this case, the ability of amino phosphonates to form an intramolecular hydrogen bond can play an important differentiating role. Evidently, this hydrogen bond can be formed if the P(1)—O(1) and C(1)—N(1) bonds (see Fig. 5) are in the *gauche*-conformation. It is characteristic of α-unsubstituted amino phosphonate **1** (see Fig. 6, *a*). The presence of substituents at the α-C atom leads to the transition of a molecule to the *trans*-conformation (see Fig. 6, *b*). An additional stabilization of an amino phosphonate molecule due to an intramolecular hydrogen bond decreases its complex-forming ability and reactivity.[21]

Carriers **4**—**8** containing one alkyl or aryl substituent in the α-position exhibit a high selectivity toward oxalic acid. The introduction of long-chain alkyl substituents into the α-position of amino phosphonates **4** and **5** increases their lipophilicity, and they demonstrate high efficiency and selectivity of transport. This additionally demonstrates that the lipophilicity of a carrier exerts a decisive effect on the transport of oxalic acid. The behavior of α-aryl-substituted amino phosphonates **6**—**8** agrees, on the whole, with this suggestion, although a slight influence of steric effects is also observed in the case of carrier **8** having a substituent in the *ortho*-position.

Thus, the present studies showed that the α-amino phosphonates are capable of molecular recognition of oxalic acid in the series of dicarboxylic and α-hydroxy carboxylic acids with similar structures. The efficiency and selectivity of mass transfer of oxalic acid increase with an increase in the lipophilicity of α-amino phosphonate.

This work was financially supported by the Ministry of Education of the Russian Federation (Grant PD 02-1.3-95), the Russian Foundation for Basic Research (Project Nos. 02-03-32934 and 03-03-96185), and the Program "Fundamental Research and Higher Education" (BRHE, Grant REC-007).

References

1. T. Araki and H. Tsukube, *Liquid Membranes: Chemical Application*, CRC Press, Inc., Boca Raton, Florida, 1990, 213 pp.
2. T. M. Fyles and W. F. Van Straaten-Nijenhuis, *Ion Channel Models*, in *Comprehensive Supramolecular Chemistry*, Pergamon Press, Oxford, UK, 1996, 448 pp.
3. M. Mulder, *Basic Principles of Membrane Technology*, Kluwer Academic Publishers, Dodbrecht, 1995, 513 pp.
4. I. S. Antipin, I. I. Stoikov, S. A. Repeikov, and A. I. Konovalov, *Izv. Akad. Nauk, Ser. Khim.*, 1998, 1746 [*Russ. Chem. Bull.*, 1998, **47**, 1697 (Engl. Transl.)].
5. I. S. Antipin, I. I. Stoikov, A. A. Khrustalev, and A. I. Konovalov, *Izv. Akad. Nauk Ser. Khim.*, 2001, 2038 [*Russ. Chem. Bull., Int. Ed.*, 2001, **50**, 2038 (Engl. Transl.)].
6. L. Z. Kazantseva, *Lechashchii vrach* [*Doctor in Charge of the Case*], 1999, **1**, 17 (in Russian).
7. R. J. Fitzmaurice, G. M. Kyne, D. Douheret, and J. D. Kilburn, *J. Chem. Soc., Perkin Trans. 1*, 2002, 841.
8. F. P. Schmidtchen and M. Berger, *Chem. Rev.*, 1997, **97**, 2182.
9. I. I. Stoikov, S. A. Repeikov, I. S. Antipin, and A. I. Konovalov, *Heteroatom Chem.*, 2000, **11**, 518.
10. I. S. Antipin, I. I. Stoikov, and A. I. Konovalov, *Phosphorus, Sulfur and Silicon*, 1999, **147**, 347.
11. Weygand-Hilgetag, *Organisch-chemische Experimentierkunst*, Johann Ambrosius Barth Verlag, Leipzig, 1964.
12. S. Yu. Ivakhno, A. V. Afanas´ev, and G. A. Yagodin, *Itogi Nauki i Tekhniki. Neorganicheskaya Khimiya* [*Results of Science and Technique. Inorganic Chemistry*], VINITI USSR Akad. Nauk, 1984, **13**, 3 (in Russian).
13. K. Hirose, *J. Incl. Phenom. Macro.*, 2001, **39**, 193.
14. M. I. Kabachnik, T. Ya. Medved´, N. M. Dyatlova, O. G. Arkhipova, and M. V. Rudomino, *Usp. Khim.*, 1968, **37**, 1161 [*Russ. Chem. Rev.*, 1968, **38**, 503 (Engl. Transl.)].
15. R. A. Cherkasov and V. I. Galkin, *Usp. Khim.*, 1998, **67**, 940 [*Russ. Chem. Rev.*, 1998, **67**, 940 (Engl. Transl.)].
16. R. G. Islamov, M. G. Zimin, T. A. Dvoinishnikova, I. S. Pominov, and A. N. Pudovik, *Zh. Obshch. Khim.*, 1977, **47**, 1452 [*J. Gen. Chem. USSR*, 1977, **47** (Engl. Transl.)].
17. R. Dawson, D. Elliott, W. Elliot, and K. Jones, *Data for Biochemical Research*, Clarendon Press, Oxford, 1986, 544 pp.
18. I. S. Antipin, I. I. Stoikov, S. A. Repeikov, E. G. Yarkova, A. T. Gubaidullin, I. A. Litvinov, and A. I. Konovalov, *Zh. Obshch. Khim.*, 1998, **68**, 1524 [*Russ. J. Gen. Chem.*, 1998, **68** (Engl. Transl.)].
19. P. Job, *Compt. Rend.*, 1925, **180**, 928.
20. A. R. Garifzyanov, E. Yu. Mikryukova, and V. F. Toropova, *Zh. Obshch. Khim.*, 1991, **61**, 1342 [*J. Gen. Chem. USSR*, 1991, **61** (Engl. Transl.)].
21. R. D. Sayakhov, A. R. Cherkasov, A. A. Shajmardanova, V. I. Galkin, R. A. Cherkasov, P. Finocchiaro, and S. Failla, *Phosphorus, Sulfur and Silicon*, 2002, **177**, 1281.

Received October 14, 2003;
in revised form March 15, 2004