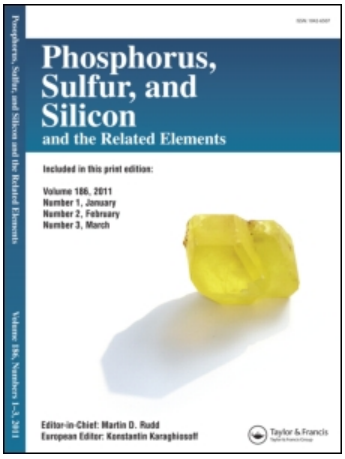

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α-Aminophosphonates: Effective Carriers for the Membrane Transport of Biorelevant Species

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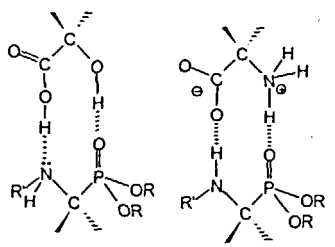
The novel lipophilic α-aminophosphonates were synthesized by the Kabachnik-Fields reaction. These compounds exhibited remarkable selectivity as carriers for the membrane transport of the biorelevant species such as α-amino and α-hydroxy acids.

Keywords: α-aminophosphonates; membrane transport; host-guest complexes

INTRODUCTION

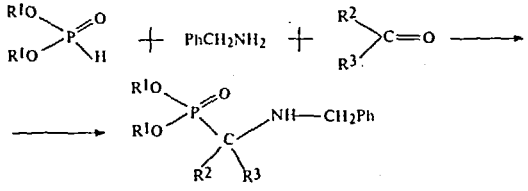
The transport of biorelevant species across membrane constitute an important process in host-guest chemistry from biomimetic, analytical and industrial points of view. Presently some information is available about the dynamics and regulation of hydroxy and amino acid transport in nature, but a detailed mechanistic and structural understanding remains inadequate. Besides the transport of such hydrophilic species is a difficult problem due to their strong solvation in water. This provides an impetus to create artificial receptors that are capable of performing hydroxy and amino acid transport. Although many artificial receptors have been reported to bind ammonium, carboxyl and carboxylate moieties, only few successful examples of membrane transport of hydroxy and zwitterionic amino acids are known [1-4].

Ammonium, carboxyl and carboxylate groups are expected to act as binding sites for hydrogen bonding and electrostatic interactions. α-Aminophosphonates as carriers also possess an array of binding sites capable to form H-bonds with ammonium, carboxyl (phosphoryl group, nitrogen lone pair) and carboxylate (N-H bond) moieties of hydroxy and amino acids.



RESULTS AND DISCUSSION

A series of the new lipophilic α-aminophosphonates were synthesized by the Kabachnik-Fields reaction in 62-95% yields.



(1) R_1 = Am, R_2, R_3 =  ; (2) R_1= 2-ethylhexyl, R_2, R_3 =  ;

(3) R_1 = Am; R_2,R_3 =  ; (4) R_1= 2-ethylhexyl, R_2,R_3 = 

(5) R_1 = 2-ethylhexyl, R_2, R_3 = Me; (6) R_1 = decyl, R_2, R_3 = Me;

(7) R_1=2-ethylhexyl, R_2=H, R_3=Me; (8) R_1=2-ethylhexyl, R_2=H, R_3=Bu;

(9) R_1=2-ethylhexyl, R_2, R_3 = H; (10) R_1 = decyl, R_2, R_3 = H.

The α-aminophosphonates **1-10** were examined as carriers for glicolic acid transport across polymer supported liquid membranes (SLM) impregnated by carrier's solution in *o*-nitrophenyl *n*-octyl ether (NPOE). Obtained results are summarized in Table 1.

TABLE 1. Initial Glycolic Acid Flux [a-c] across SLM Impregnated by **1-10**.

Carrier	1	2	3	4	5	6	7	8	9	10
$J \cdot 10^6$	2.4	3.7	4.0	4.5	7.2	9.6	11	24	13.5	30

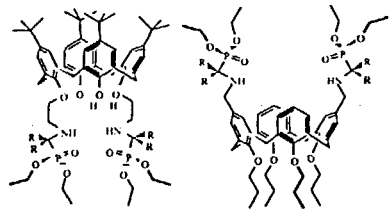
[a] J - mol·cm^{-2}·h^{-1} (25°C); [b] Glycolic acid concentration in source phase, 10^{-1} M.
[c] Blank (without carrier) flux is 6 10^{-7} mol·cm^{-2}·h^{-1}.

The comparison of fluxes with and without carrier indicates that introduction of α- aminophosphonates in membrane phase leads to increasing glicolic acid transfer across SLM. So α-aminophosphonate forms the complex with glicolic acid in membrane phase. The inspection of Table 1 leads to conclusion that two factors effect on glycolic acid flux. These are the carrier lipophilicity and steric repulsion of α-alkyl and N-benzyl substituents in α-aminophosphonate - glycolic acid complexes. The comparison of the following pairs of carriers: **1/2**, **3/4**, **5/6**, **7/8** and **9/10**, indicates the carrier possessing more larger alkyl substituents either in alkoxy groups or at α-carbon performs a more intensive transport of glycolic acid across membrane.

Also the number and nature of alkyl groups at α-carbon influence on flux across membrane. The order of carrier's efficiency is: α-unsubstituted < monosubstituted <

disubstituted. The PM3 simulation of complex structure demonstrates that in optimal conformation for complex formation one of α-substituent is close to phenyl ring. Interatomic distance is equal 2.8 A (for α-unsubstituted compounds **9**, **10**). So introduction bulky alkyl substituents in this position (it's possible only for α-disubstituted compounds) results very strong repulsion between mentioned groups and complex destabilization. As result the glycolic acid flux across SLM is decreased.

The substituents on α-carbon of α-amino and hydroxy acids can provide additional recognition sites due to electrostatic, van der Waals or hydrophobic interactions and even steric repulsion. It's well known that organic molecules (alkanes, aromatics, etc) can be incorporated into calix[4]arene's cavity with the formation stable host-guest complexes. So novel macrocyclic receptors **11**, **12** containing α-aminophosphonate fragments in lower and upper rim of calix[4]arene were synthesized.



(11) (12)

These compounds exhibited the efficiency and selectivity as carriers for the membrane transport of the zwitterionic amino acids (Table 2). In this case the lipophilicity of the amino acids is not important for the membrane transport. The flux J doesn't depend on the amino acids (see log$P$ values) as well as carrier's lipophilicity.

TABLE 2. Initial Amino Acid Fluxes across a SLM (J 10^6 mol·cm^{-2}·h^{-1})[a,b].

Amino acid	log$P$ [c]	Carrier		
		5	**11**	**12**
d,l-Phenylalanine	-1.45	4.8	3.1	9.7
d,l-3,4-Dihydroxyphenylalanine	-	2.9	3.0	5.7
d,l-Tyrosine	-2.11	1.7	2.8	4.5
d,l-Histidine	-2.85	2.4	6.6	5.1
d,l-Tryptophane	-1.16	0.66	0.63	0.24

[a] Amino acid concentration in source phase, 10^{-3} M. [b] Blank (without carrier) fluxes of the all amino acids were less than 10^{-7} mol·cm^{-2}·h^{-1}. [c] Octanol/Water partition coefficient[5]; more negative value of log$P$ corresponds to less lipophilic compound.

Linear aminophosphonate **5** does not demonstrate the essential transport selectivity. The attachment of aminophosphonate moieties to the lower and upper rim of the calix[4]arene leads to the different changes in selectivity of amino acid transport.

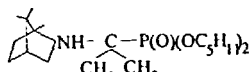
Calixarene **11** (substituted in lower rim) and **5** are similar in carrier's efficiency with the exception of histidine. Very hydrophilic histidine shows a surprisingly high transport rate through the hydrophobic membrane. It seems likely that imidazol side chain of histidine can also present the additional sites for interaction with aminophosphonate units of **11**. Unlike carrier **11** the molecular cavity of calixarene **12** (substituted in upper rim) can participate in complexation and recognize the aromatic side chains of amino acids. As a result, the selectivity of membrane transport for some amino acids is enhanced. For example, **12** transports phenylalanine 40 times faster than tryptophane (fluxes ratio for **5** - 7.3, for **11** - 4.9).

TABLE 3. Initial fluxes of some enantiomers (25°C) through SLM and coefficient of enantiomeric selectivity (K_{LD}) [a].

	d- Tartaric acid	l- Tartaric acid	d-β-Phenyl-α-alanine	l-β-Phenyl-α-alanine
J, mol/(h cm^2)	$6.7\,10^{-4}$ [b]	$1.8\,10^{-3}$ [b]	$4.7\,10^{-5}$ [c]	$6.1\,10^{-5}$ [c]
K_{LD} [d]	4.5		1.3	

[a] 1 M solution of **13** in o-xylene, [b] The concentration in source phase 1.0 M, [c] The concentration in source phase 0.1 M, [d] $K_{LD} = J_L/J_D$.

Using a chiral *O,O*-diamyl-1-methyl-1-[N-(l-bornyl)amino]ethylphosphonate **13** as carrier the certain enantioselectivity of hydroxy and amino acids transport can be achieved. In this case the steric repulsion with bulky chiral substituent in α-aminophosphonate leads to enantiomeric recognition of amino and hydroxy acids (Table 3).



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