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Calix[4]arene Based α-Aminophosphonates: Novel Carriers for Zwitterionic Amino Acids Transport.

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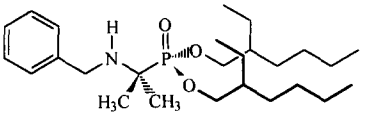
Abstract: a series of calix[4]arene based α-aminophosphonates were synthesized by the Kabachnik-Fields reaction of the calixarene-diamine (either at lower or upper rim), diethyl phosphite and a carbonyl compound (acetone or cyclohexanone). These compounds exhibited remarkable selectivity as carriers for the membrane transport of the zwitterionic form of aromatic amino acids.

Molecular recognition of biorelevant molecules constitutes an important problem in organic chemistry.[1] In particular, great attention has been drawn to the transport of amino acids and their derivatives.[2] Amino acids exist as strongly solvated zwitterions in neutral aqueous solutions and their extraction and transport through the lipophilic membranes is very difficult. Although a number of synthetic receptors binding either ammonium or carboxylate moieties has been reported,[3] only a few examples of zwitterionic amino acids transport are known.[4,5]

α-Aminophosphonates possess an array of potential binding sites for both ammonium (phosphoryl group, nitrogen lone pair) and carboxylate (N-H bond) moieties. Recently we have described the transport of amino acids through a liquid membrane supported on a polymer film induced by α-aminophosphonate **1**.[5]



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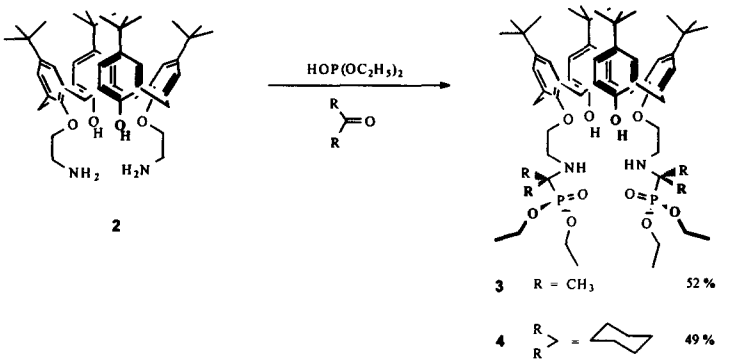
Using a chiral α-aminophosphonate as carrier the certain enantioselectivity of amino acids transport can be achieved.[6]

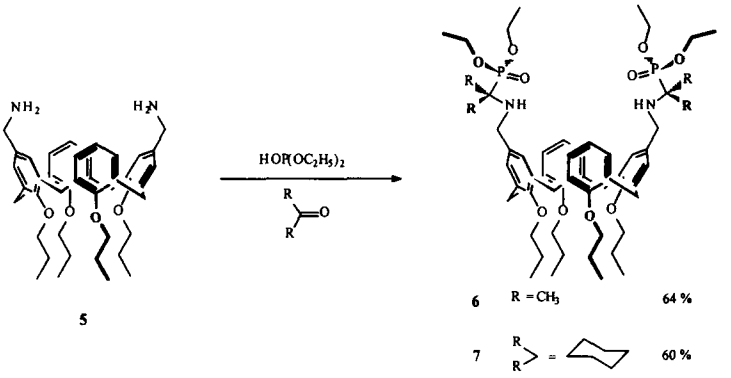
One attractive way to create new selective receptors is a functionalization of available natural or synthetic macrocycles by the suitable functional groups which are properly arranged in receptor for the achievement of effective interaction with the substrate. The calix[4]arene framework is a rigid scaffold and provides the lipophilicity to the whole molecule. 1,3-diaminocalix[4]arenes fixed in *cone* conformation were chosen as the starting platform because tweezer-like structure is likely to combine the appropriate binding mode with the lack of steric hindrance.

The synthesis of **3** and **4** was performed by the Kabachnik-Fields reaction[7] of 1,3-bis(aminoethoxy)-calix[4]arene **2**[8] with diethylphosphite and corresponding carbonyl compound (Scheme 1):



Scheme 1

Synthesis of **3**[9] was carried out in the refluxing acetone (carbonyl compound was acting also as a solvent) while synthesis of **4** was accomplished in toluene at 80 °C. Compounds **6**[9] and **7** were synthesized analogously from **5**[10] (Scheme 2). All novel receptors were isolated by column chromatography (silica gel).



Scheme 2

We examined the obtained receptors as carriers for the transport of zwitterionic amino acids through a supported liquid membrane composed of a porous polymeric support (Millipore Type FA) impregnated with 10^{-1} M carrier [11] in *o*-nitrophenyl *n*-octyl ether (NPOE)[12]. For comparison, the same experiments was performed with the α-aminophosphonate **1**, which is not anchored on a calixarene platform. The results are summarized in Table 1. Preliminary experiments have shown that **4** and **7** transport the amino acids with essentially the same rate as **3** and **6**, respectively. So the nature of the alkyl group at the aminophosphonate fragment does not play a significant role in the transport processes. Another observation is that the hydrophilicity of the amino acids is not important to the efficiency of the membrane transport. There is no dependence between the flux *J* and the values of log*P* that is a quantitative measure of hydrophilic/lipophilic properties of organic compounds. Thus, the transport of tryptophane (the most lipophilic of these amino acids) exhibits lower flux values through the organic membrane, whereas higher fluxes of hydrophilic histidine were observed.

Table 1. Initial Amino Acid Fluxes [a-d] through a Supported Liquid Membrane Measured for Different Carriers in NPOE ($J\ 10^6$ mol·cm^{-2}·h^{-1}).

Amino acid	log*P* [e]	Carrier		
		1	**3**	**6**
d,l-Phenylalanine (Phe)	-1.45	4.8	3.1	9.7
d,l-3,4-Dihydroxyphenylalanine (Dih)	-	2.9	3.0	5.7
d,l-Tyrosine (Tyr)	-2.11	1.7	2.8	4.5
d,l-Histidine (His)	-2.85	2.4	6.6	5.1
d,l-Tryptophane (Trp)	-1.16	0.66	0.63	0.24

[a] Amino acid concentration in source phase, 10^{-3} M. [b] In all runs, doubly distilled water was used as receiving phase. [c] Blank (without carrier) fluxes of the all measured amino acids were less than 10^{-7} mol·cm^{-2}·h^{-1}. [d] Estimated errors of flux measurements are ±10%. [e] Octanol / Water partition coefficient[13]; more negative value of log*P* corresponds to less lipophilic compound

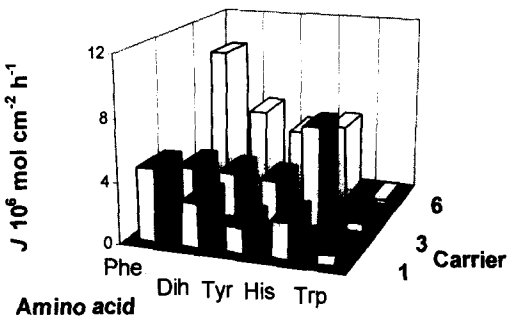


Figure 1. The comparison of amino acids fluxes

One can see (Fig.1) linear aminophosphonate **1** does not demonstrate the essential transport selectivity. The higher selectivity was established for phenylalanine relative to tryptophane (fluxes ratio is 7.3). Other amino acids are transported by **1** with practically the same rates. The attachment of aminophosphonate moieties to the lower and upper rim of the calix[4]arene lead to the different changes in the rate and selectivity of amino acid transport. Calixarene **3** (substituted in lower rim) and **1** are similar in efficiency as carriers. With the exception of histidine, the transport rates of the studied amino acids do not significantly differ. Very hydrophilic histidine shows a surprisingly high transport rate through the hydrophobic membrane. It seems likely that the interior of **3** presents a polar microenvironment complementary to the zwitterionic form of histidine. Besides carboxylate and ammonium groups, the imidazol side chain of histidine possessing protonodonor and protonoaceptor centers interacts with aminophosphonate units of **3**.

Unlike carrier **3** the molecular cavity of calixarene **6** (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, **6** transports phenylalanine 40 times faster than tryptophane (fluxes ratio for **1** - 7.3, for **3** - 4.9). This proves that (i) the molecular cavity of calixarene **6** is involved in the complexation and (ii) the three points interaction of amino acid (due to carboxylate, ammonium groups and side chain) with the carrier leads to the enhancing of transport efficiency and selectivity.

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9. Compound **3**: IR ν_{max}(in KBr)/cm^{-1} 3100-3400 (OH, NH), 1220 (P=O), 1020, 1060 (P-O-C), 960 (P-O-Et);
   ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.05 (s, 4H, ArH), 6.75 (s, 4H, ArH), 4.34 (d, J 13.2Hz, 4H, ArC$\underline{H_2}$Ar), 4.20-4.11 (m, 8H, P-O-C$\underline{H_2}$-CH_3), 4.06 (t, J 5.0Hz, 4H, O-C$\underline{H_2}$-CH_2N), 3.29 (d, J 13.2Hz, 4H, ArC$\underline{H_2}$Ar), 3.27 (t, J 5.0Hz, 4H, O-CH_2-C$\underline{H_2}$N), 1.51 (d, J_{PH} 15.4Hz, 12H, P-C(C$\underline{H_3}$)$_2$), 1.31 (t, J 7.7Hz, 12H, P-O-CH_2-C$\underline{H_3}$), 1.28 (s, 18H, t-Bu), 0.89 (s, 18H, t-Bu).
   Compound **6**: IR ν_{max}(in KBr)/cm^{-1} 3400-3200 (NH), 1240 (P=O), 1010, 1040 (P-O-C), 960 (P-O-Et);
   ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.94 (s, 4H, ArH), 6.29-6.20 (m, 6H, ArH), 4.41 (d, J 13.2Hz, 4H, ArC$\underline{H_2}$Ar), 4.23-4.15 (m, 8H, P-O-C$\underline{H_2}$-CH_3), 3.93 (t, J 8.2Hz, 4H, O-C$\underline{H_2}$-CH_2-CH_3), 3.82 (s, 4H, ArC$\underline{H_2}$N), 3.70 (t, J 8.2Hz, 4H, O-C$\underline{H_2}$-CH_2-CH_3), 3.10 (d, J 13.2Hz, 4H, ArC$\underline{H_2}$Ar), 1.98-1.80 (m, 8H, O-CH_2-C$\underline{H_2}$-CH_3), 1.37 (t, J 6.9Hz, 12H, P-O-CH_2-C$\underline{H_3}$), 1.26 (d, J_{PH} 12.6Hz, 12H, P-C(C$\underline{H_3}$)$_2$), 1.06 (t, J 7.4Hz, 6H, O-CH_2-CH_2-C$\underline{H_3}$), 0.89 (t, J 7.4Hz, 6H, O-CH_2-CH_2-C$\underline{H_3}$).
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11. All obtained receptors are hydrolytic stable. ^{31}P NMR analysis of the membrane phase after the transport experiments showed 100% recovery of the carrier.
12. The transport experiments were performed in an apparatus that consists of two concentric glass tubes (source and receiving phases volume 5-8 ml, effective membrane area 1.3 cm^2). The membrane was positioned on the bottom of inner tube. Stirring of the both phases was accomplished by a magnetic stirrer. The outer tube was double-walled for thermostating. The water bath was set at 298 K. A sipper system composed of a peristaltic pump and quartz flow cell was used to control the substrate concentration in the receiving phase by UV/VIS method.
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