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Selective transmembrane carriers for hydroxycarboxylic acids: influence of a macrocyclic calix[4]arene platform

Maria N. Agafonova, Olga A. Mostovaya, Igor S. Antipin, Alexander I. Konovalov and Ivan I. Stoikov*

A. M. Butlerov Chemical Institute, Kazan (Volga Region) Federal University, 420008 Kazan, Russian Federation. Fax: +7 8432 92 4330; e-mail: ivan.stoikov@mail.ru

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Selective transmembrane carriers for α-hydroxy acids, acyclic α-amino phosphonates and calix[4]arenes containing α-aminophosphonate substituents at the lower rim have been synthesized; analytical HPLC has been used to monitor the selective separation of dicarboxylic, α-hydroxy and α-amino acid mixtures by membrane extraction; the attachment of α-aminophosphonate fragments to the macrocyclic calix[4]arene platform results in receptors with markedly modified efficiency and selectivity relative to those of only aminophosphonates.

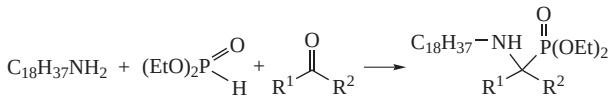
Phosphoryl compounds functionalized by oxygen- and nitrogen-containing substituents in the α- and β-positions relative to the phosphorus atom are of considerable current interest.[1–8] They can be used as improved extraction agents and carriers.[3,9–18]

Acyclic amino phosphoryl compounds with various substituents can selectively bind oxalic acid amongst a series of structurally similar dicarboxylic acids.[19] The combination of different binding sites, namely, a proton donor (NH) and two proton acceptors (P=O and a lone electron pair on the N atom) and the possibility of varying the lipophilicity and steric hindrance of the binding sites make these compounds potentially versatile receptor molecules.[20–23] Thus, it is promising to investigate the influence of a calix[4]arene macrocyclic platform on the complexation properties of α-aminophosphoryl derivatives towards a series of dicarboxylic, α-hydroxy- and α-amino acids. In this work, the complexation properties of aminophosphonates **1** and **2** with alkyl or aryl fragments towards such organic acids are compared with those of 1,3-disubstituted calix[4]arenes **3** and **4** containing similar α-aminophosphonate groups at the lower rim.

Acyclic α-aminophosphonates **1** and **2** were synthesized by the Kabachnik–Fields reaction (Scheme 1).†

Transport through lipophilic liquid membranes induced by compounds **1** and **2** was studied for dicarboxylic and α-substituted carboxylic acids. To estimate the influence of the carboxylate function, as distinct from that of the carboxylic acid unit, the membrane extraction of sodium acetate was studied.‡

Table 1 summarizes the fluxes of substrates **5**–**13**. A comparison of the mass transfer data with that for control experiments without carrier showed that the introduction of carriers **1** and **2** into the membrane phase leads to a 10–1000 fold-increase in the flux. The highest enhancement of the transport rate was observed for oxalic acid in both cases. The mass transfer flux of sodium acetate was insignificantly influenced by the test receptor. The



1 $R^1 = R^2 = Me$
2 $R^1 = Ph$, $R^2 = H$

Scheme 1

Table 1 Mass transfer flux (j_i/kmol m^{-2} s^{-1}) of substrates **5**–**13** through a liquid-impregnated membrane (25 °C).

Substrate	pK_a	j_0^a	j_1^b	j_2^b	j_3^b	j_4^b
Sodium acetate **5**	—	1.3×10^{-11}	1.8×10^{-11}	2.0×10^{-11}	1.4×10^{-11}	1.5×10^{-11}
Oxalic acid **6**	1.25	5.0×10^{-12}	3.3×10^{-9}	6.6×10^{-9}	1.6×10^{-10}	5.2×10^{-12}
Aspartic acid **7**	1.99	5.7×10^{-12}	2.5×10^{-11}	4.6×10^{-11}	2.3×10^{-11}	4.0×10^{-10}
Glutamic acid **8**	2.10	2.8×10^{-12}	3.8×10^{-11}	4.2×10^{-11}	3.0×10^{-12}	2.9×10^{-12}
Malonic acid **9**	2.85	2.9×10^{-11}	1.4×10^{-8}	1.3×10^{-8}	3.6×10^{-10}	6.1×10^{-11}
Tartaric acid **10**	3.03	4.4×10^{-11}	1.9×10^{-9}	2.4×10^{-9}	5.8×10^{-9}	4.2×10^{-10}
Mandelic acid **11**	3.37	1.5×10^{-9}	4.4×10^{-8}	3.5×10^{-8}	1.5×10^{-8}	1.7×10^{-9}
Glycolic acid **12**	3.83	9.4×10^{-12}	5.6×10^{-10}	5.5×10^{-10}	4.5×10^{-10}	1.5×10^{-10}
Succinic acid **13**	4.21	1.3×10^{-11}	3.9×10^{-9}	3.8×10^{-9}	2.9×10^{-10}	1.6×10^{-9}

[a] Mass transfer flux through a liquid-impregnated membrane without carrier. [b] Fluxes j_1–j_4 relate to carriers **1**–**4**, respectively.

† *Synthesis of α-amino phosphonates* **1** *and* **2** *(general procedure).* A mixture of octadecylamine (3.7 mmol) and an appropriate carbonyl compound (3.7 mmol) in acetone (15 ml) for **1** or toluene (15 ml) for **2** was refluxed with stirring for 1 h. Then, diethyl phosphite (4.7 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. The reaction mixture was stirred for 6 h at 80 °C. The reaction progress was monitored by ^{31}P NMR spectroscopy. The solvent was evaporated *in vacuo*. The residue was dissolved in hexane. The excess hydrophosphoryl compound was extracted with water. The organic phase was separated and dried with molecular sieves 3 Å. The molecular sieves were filtered off, and the solvent was evaporated.

For **1**: yield, 1.07 g (65%); mp 32 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 32.09. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.87 (t, 3H, *Me*$C_{17}H_{34}$, $^3J_{HH}$ 6.1 Hz), 1.25 (br. s, 32H, $MeC_{16}H_{32}$), 1.27 (d, 6H, $PCMe_2$, $^3J_{PH}$ 15.1 Hz), 1.31 (t, 6H, $POCH_2Me$, $^3J_{HH}$ 7.3 Hz), 2.69 (t, 2H, $NHCH_2CH_2$, $^3J_{HH}$ 7.3 Hz), 4.13 (m, 4H, $POCH_2$). IR (KBr, ν/cm^{-1}): 961 (*P–O–*C), 1028 (P–*O–C*), 1164 (P–O–Et), 1230 (P=O), 3100–3400 (OH, NH). Found (%): C, 68.16; H, 11.26; N, 3.06. Calc. for $C_{25}H_{54}NO_3P$ (%): C, 67.07; H, 12.16; N, 3.13.

For **2**: yield, 0.65 g (35%); mp 28 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 24.29. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.91 (t, 3H, *Me*$C_{17}H_{34}$, $^3J_{HH}$ 6.5 Hz), 1.18 (t, 3H, $POCH_2Me$, $^3J_{HH}$ 7.1 Hz), 1.25 (br. s, 32H, $MeC_{16}H_{32}$), 1.31 (t, 3H, $POCH_2Me$, $^3J_{HH}$ 7.1 Hz), 1.48 (m, 2H, CH_2CH_2NH), 2.03 (br. s, PC*H*Ph), 2.43–2.62 (m, 2H, $NHCH_2CH_2$), 3.82–4.14 (m, 4H, $POCH_2$), 7.31–7.47 (m, 5H, Ph). IR (KBr, ν/cm^{-1}): 966 (*P–O–*C), 1030 (P–*O–C*), 1164 (P–O–Et), 1244 (P=O), 3200–3400 (OH, NH). Found (%): C, 70.58; H, 10.16; N, 2.86; P, 6.60. Calc. for $C_{29}H_{54}NO_3P$ (%): C, 70.26; H, 10.98; N, 2.83; P, 6.25.

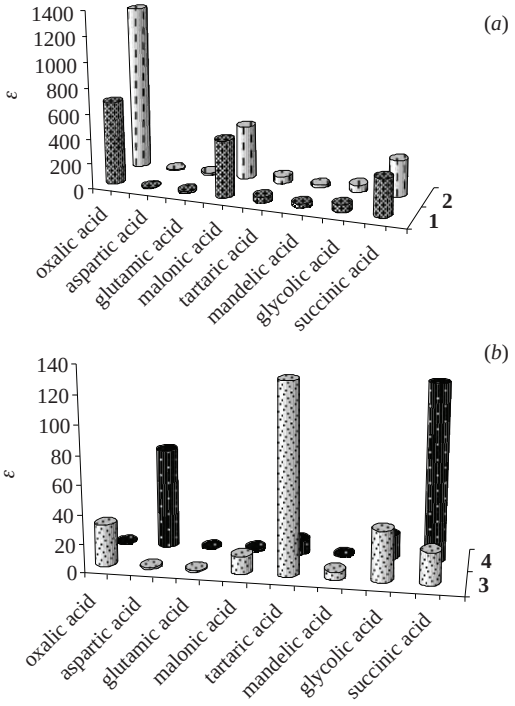
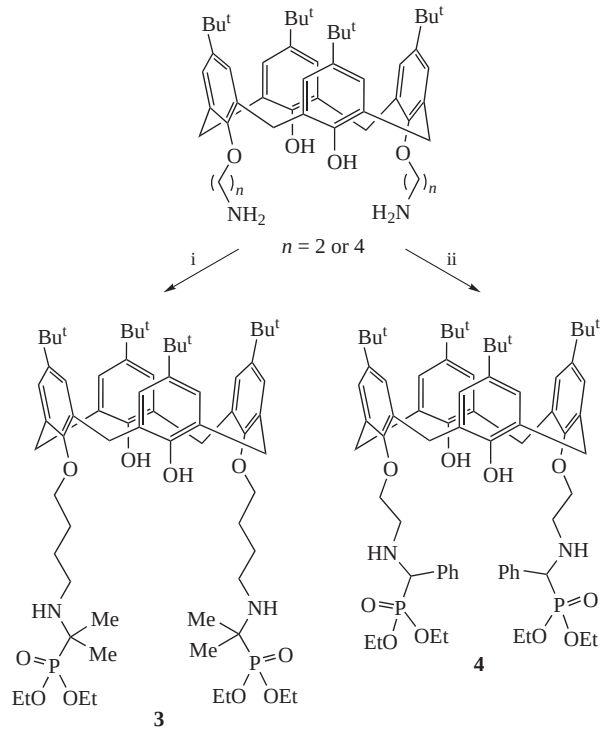


Figure 1 Transport enhancement coefficients ($\varepsilon = j_i/j_0$) for organic substrates **6**–**13** through a liquid-impregnated membrane containing carriers (*a*) **1**, **2** and (*b*) **3**, **4**.



Scheme 2 *Reagents and conditions*: i, acetone, diethyl phosphite, *p*-toluenesulfonic acid, 56 °C; ii, benzene, benzaldehyde, diethyl phosphite, *p*-toluenesolfonic acid, 80 °C.

results testify that the interaction energy of the carboxylate group with the α-aminophosphonate fragment is insufficient for the transport of highly hydrophilic carboxylate anions across a lipophilic membrane.

Compounds **1** and **2** and dicarboxylic acids exhibit a clear correlation between the flux enhancement and the acid strength [Table 1, Figure 1(*a*)]. Note that, although aminophosphonate **2** with an aryl fragment at the α-carbon atom is the most effective carrier for oxalic acid,[19] both compounds **1** and **2** demonstrated relatively high efficiency and selectivity for oxalic acid transport.

To modify this selectivity by the preorganisation of binding sites, we used macrocyclic *p-tert*-butylcalix[4]arene as a platform. Calixarenes are versatile molecular building blocks for the creation of three-dimensional structures with various internal cavity sizes and numbers and types of binding sites.[16,24–26]

Synthetic receptors[§] **3** and **4** were obtained from the amino alkyl derivatives of *p-tert*-butylcalix[4]arene (Scheme 2).[27] Their transport ability towards substrates **5**–**13** was very different from that of acyclic carriers **1** and **2** (Table 1, Figure 1).

For the macrocyclic receptors, a decrease in the enhanced transport coefficient ε for oxalic acid was observed. There was also a switch in selectivity for tartaric acid by compound **3**, and for succinic and aspartic acids by compound **4** [Figure 1(*b*)]. This reflects the higher degree of pre-organization of the carrier functional substituents; as a consequence, the characteristics of structural and geometric correlations between the binding sites and substrates become more important than the single factor of acid strength.

As an additional method of assessing the transport selectivity by different receptors, the concentrations of acids reaching the receiver phase from a source phase containing a mixture of tartaric, malonic and succinic acids were monitored by analytical

‡ *General method for membrane extraction*. The fluxes of the substrate transport through the liquid-impregnated membranes were measured in a thermostated vertical diffusion glass cell with a movable cylinder. Porous Millipore Type FA Teflon filters (thickness, 1 μm; pore size, 100 nm; porosity, 85%; the filters were reinforced with a carbon net) were used as the hydrophobic matrix of an impregnated liquid membrane. The volume ratio of the source and receiving phases was 5:1. This provided equal solution levels to eliminate the osmotic transport of an acid. The mass transport measurements were carried out under normal conditions (25 °C). A pure solvent (*o*-nitrophenyl octyl ether) or a 0.05 M solution of carrier **1**–**4** in *o*-nitrophenyl octyl ether was used as a liquid membrane. The initial concentration of substrates **5**–**13** in source phase was 0.1 mol dm^{-3}. The concentrations were determined conductometrically. The fluxes (j_i) through the membrane were calculated from the initial linear regions of the time dependence of the concentration of transported substance in the receiving phase.

§ *Synthesis of calix[4]arenes* **3** and **4** *(general procedure)*. Carbonyl compounds (2.6 mmol) were added to 1.3 mmol of an appropriate disubstituted *p-tert*-butylcalix[4]arene dissolved in 5 ml of acetone (for **3**) or benzene (for **4**). The mixture was stirred for 1 h. Then, diethyl phosphite (3.25 mmol) and a catalytic amount of *p*-toluenesulfonic acid were added. The reaction mixture was stirred for 25 h at 80 °C. The reaction progress was monitored by ^{31}P NMR spectroscopy. The solvent was evaporated *in vacuo* and the residue was dissolved in benzene. The excess hydrophosphoryl compound was extracted with water. The organic phase was separated and dried with molecular sieves 3 Å. The molecular sieves were filtered off, and the solvent was evaporated.

For **3**: yield, 0.96 g (67%); mp 58 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 31.8. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.96 (s, 18 H, Bu^t), 1.21 (t, 12 H, *Me*CH$_2$OP, $^3J_{HH}$ 4.9 Hz), 1.28 (s, 18 H, Bu^t), 1.32 (d, 12 H, Me$_2$CP, $^3J_{PH}$ 7.1 Hz), 1.75 [m, 4 H, O(CH$_2$)$_2$C*H*$_2$CH$_2$N], 2.06 [m, 4 H, OCH$_2$C*H*$_2$-(CH$_2$)$_2$N], 2.83 [t, 4 H, O(CH$_2$)$_3$C*H*$_2$N, $^3J_{HH}$ 6.8 Hz], 3.29 (d, 4 H, Ar–C*H*$_2$–Ar, $^2J_{HH}$ 12.9 Hz), 3.98 [t, 4 H, OC*H*$_2$(CH$_2$)$_3$N, $^3J_{HH}$ 6.8 Hz], 4.14 (m, 8 H, MeC*H*$_2$OP), 4.27 (d, 4 H, Ar–C*H*$_2$–Ar, $^2J_{HH}$ 12.9 Hz), 6.78 (s, 4H, H$_{Ar}$), 7.03 (s, 4 H, H$_{Ar}$), 7.42 (s, 2 H, Ar–O*H*). IR (KBr, ν/cm^{-1}): 956 (*P–O–*C), 1054 (P–*O–C*), 1163 (P–O–Et), 1240 (P=O), 3100–3400 (OH, NH). Found (%): C, 67.58; H, 10.10; N, 2.31; P, 4.92. Calc. for $C_{66}H_{104}N_2O_{10}P_2$ (%): C, 69.1; H, 9.1; N, 2.4; P, 5.4.

For **4**: yield, 0.49 g (31%); mp 74 °C. ^{31}P NMR (121.5 MHz, $CDCl_3$) δ: 23.80. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.93 (s, 18 H, Bu^t), 1.09 (t, 6 H, *Me*CH$_2$OP, $^3J_{HH}$ 7.1 Hz), 1.17 (t, 6 H, *Me*CH$_2$OP, $^3J_{HH}$ 7.1 Hz), 1.28 (s, 18 H, Bu^t), 2.97 (t, 4 H, OCH$_2$C*H*$_2$N, $^3J_{HH}$ 6.2 Hz), 3.25 (d, 4 H, Ar–C*H*$_2$–Ar, $^2J_{HH}$ 13.2 Hz), 3.79–3.88 (m, 4 H, OC*H*$_2$CH$_2$N), 3.93–4.22 (m, 8 H, MeC*H*$_2$OP), 4.35 (d, 4 H, Ar–C*H*$_2$–Ar, $^2J_{HH}$ 13.2 Hz), 6.70–7.50 (m, 20 H, H$_{Ar}$, OH). IR (KBr, ν/cm^{-1}): 965 (*P–O–*C), 1027 (P–*O–C*), 1163 (P–O–Et), 1243 (P=O), 3300–3400 (OH, NH). Found (%): C, 69.71; H, 8.46; N, 2.37. Calc. for $C_{70}H_{96}N_2O_{10}P_2$ (%): C, 70.8; H, 8.2; N, 2.4.

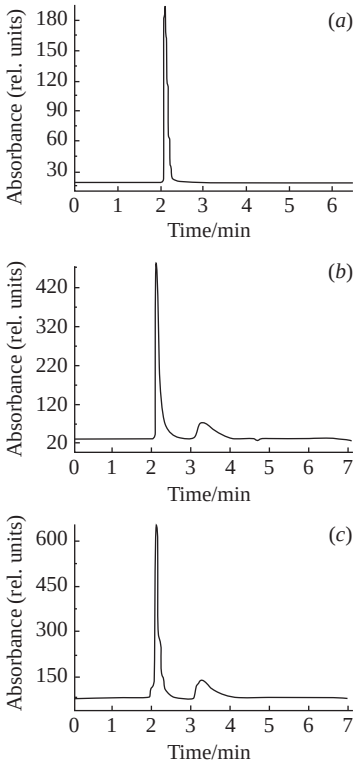


Figure 2 Chromatograms of the receiving phase for compound **3** and a mixture of tartaric, malonic and succinic acids after (*a*) 3, (*b*) 4 and (*c*) 5 h of membrane extraction. Column: Discovery RP AmideC16 (15×6 mm). Injection volume: 10 μl. Detection: 210–220 nm. Flow rate: 1.0 ml min^{-1}. Mobile phase: 25 mM buffer solution of KH_2PO_4 (pH 3).

HPLC (Figure 2). The samples of the receiving phase were taken at regular intervals of 1 h.

During the first 3 h, only the peak of tartaric acid was detected. After 4 h, succinic acid became detectable. Malonic acid was not detected. The data are consistent with results of the membrane extraction of separate species. Hence, receptor **3** can selectively transport only tartaric acid through the membrane, as it decreases ε by a factor of 6 (*cf.* succinic acid).

Thus, as a result of this kinetic study of transport through liquid-impregnated membranes, selective carriers for tartaric, succinic and oxalic acids were found. The relations established in the experiment make it possible to control the receptor abilities of 1,3-disubstituted calix[4]arenes by varying their substituents. The attachment of aminophosphonate groups to a calixarene platform switches the selectivity of complexation properties of aminophosphonate fragments.

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