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

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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.

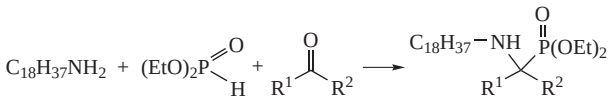
Phosphoryl compounds functionalized by oxygen- and nitrogen-containing substituents in the α- and β-positions relative to the phosphorus atom are of considerable current interest.[1–8] They can be used as improved extraction agents and carriers.[3,9–18]

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, $MeC_{17}H_{34}$, $^3J_{HH}$ 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, $MeC_{17}H_{34}$, $^3J_{HH}$ 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.