Membrane extraction of organic compounds 3.* A new receptor fragment for carboxylate groups based of the calix[4]arene platform

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A new type of macrocyclic receptor able to bind organic substrates containing carboxy and carboxylate groups was designed on the basis of 1,3-disubstituted calix[4]arenes. A series of disubstitited calix[4]arenes were prepared in 60—80% yields by selective 1,3-alkylation of *p-tert*-butylcalix[4]arene. The compounds obtained were tested as carriers for DL-tartaric, glycolic, DL-amygdalic, and DL-glutamic acids through liquid membranes immobilized on a polymer matrix. The structural factors favorable for the transport of these hydrophilic substrates through lipophilic membranes were established.

Key words: calix[4]arene, alkylation, membrane transport, α-hydroxy acids, α-amino acids.

Vigorous development of the chemistry of transmembrane transport, which plays an important role in biological systems, has started rather recently. The appearance of the first synthetic receptor molecules[2] capable of selective binding of organic and inorganic substrates has given impetus to the development of a new interdisciplinary field of science, supramolecular chemistry. Together with recognition and catalysis, transport is an essential function of supramolecular systems, which belongs to fundamental processes of supramolecular chemistry.[3]

Selective permeability of membranes is provided by carrier molecules present in the liquid membrane and able to interact selectively with the compound to be transported. Carriers determine the nature of the substrates penetrating the membrane and the physicochemical characteristics of the mass transfer such as the flux, selectivity, and type of the process. Variation of the receptor architecture makes it possible to control the transport process and to analyze the influence of various structural factors on the thermodynamic and kinetic parameters of the transport.

It is clear that effective recognition of a substrate by a receptor can be attained by maximizing the area of interaction between them. This is possible in the case where a receptor can embrace a substrate from every side being linked to it by numerous noncovalent intermolecular interactions; this stipulating the substrate structure, size, and shape. Macrocyclic compounds satisfy these requirements. Indeed, they have molecular cavities of appropriate size and incorporate a lot of reactive sites; this makes possible the design of structures with a complementary arrangement of binding sites.

In the last decade, calix[4]arenes, which are the products of cyclocondensation of phenols with formaldehyde, have been extensively used for the molecular receptor design.[4—7] Calix[4]arenes possess a number of attractive properties; this fact together with rather ready availability of calix[4]arene derivatives makes them indispensable objects for the design of natural molecules and their fragments. First, calixarenes are capable of incorporating small molecules in the molecular cavities due to hydrophobic interactions giving host—guest complexes.[4,5] Second, the *meta*-cyclophane fragment of calix[4]arenes has a sufficient conformational rigidity to provide the formation of systems with a required spatial arrangement of the binding sites.[6,7]

The problem of molecular recognition of carboxylate anions and carboxylic acid derivatives presents both theoretical and practical interest due to the vast biological importance of compounds containing a carboxy group. Macrocyclic oligoamines and their derivatives (**1**, **2**) have been among the first receptors for compounds containing carboxylate groups.[8,9]

Ligands with proton-donor or proton-acceptor nitrogen-containing fragments such as urea (**3**),[10,11] thiourea (**4**),[12—14] and 2-acylaminopyridine (**5**)[15—20] fragments have shown both the substrate specificity and enantio-

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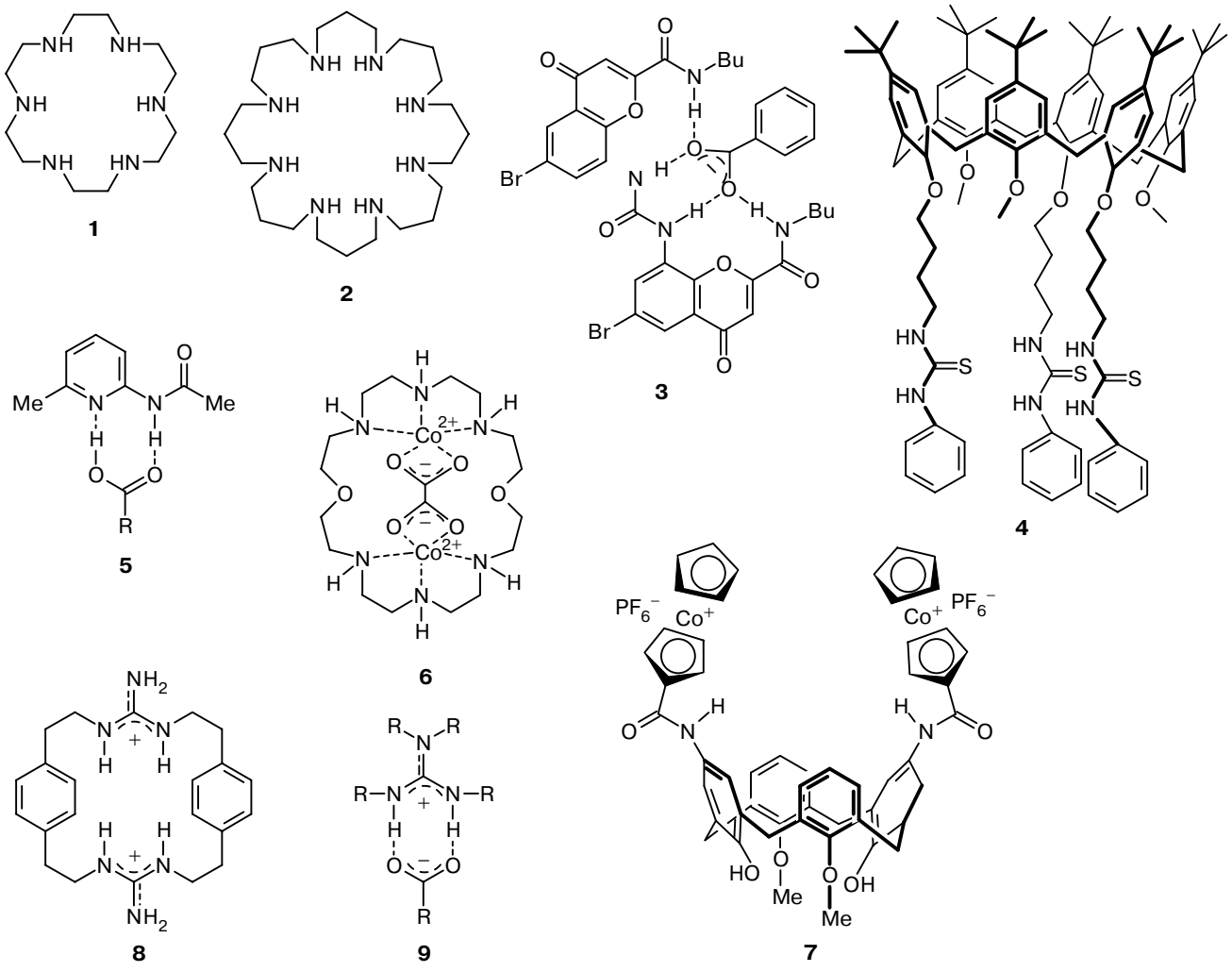


selectivity in guests binding.[10—20] Natural metalloenzymes recognize and efficiently bind anionic substrates through ternary complexation of the "protein—metal cation—anion" type; therefore, their synthetic analogs **6** and **7** are used in the selective transport of various carboxylates.[21—25] Compounds containing a guanidine fragment (**8**, **9**) showed themselves as a very effective class of receptors for carboxylate anions; this is due to the complementarity of the intermolecular interactions involved in the complex formation.[26—35]

We proposed a new type of receptors for binding substrates containing carboxy groups (Fig. 1). The two free hydroxy groups in the calix[4]arenes 1,3-disubstituted at the lower rim are arranged in such a way that they are complementary to the carboxy group and the carboxylate anion, which provided grounds to expect that these calix[4]arene derivatives would ensure efficient binding when used for the transport of α-hydroxy and α-amino acids. In this case, the substrate can be bound both through hydrogen bonding between the carboxy fragment of the acid and the calix[4]arene hydroxy groups and through the interaction of the second functional group or the side chain of the compound being transported with the calix[4]arene substituents located at the lower rim of the macrocycle.

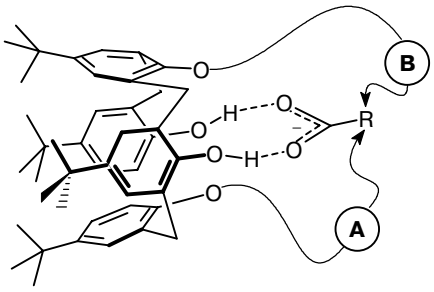


Fig. 1. Possible scheme of binding of the carboxylate function by calix[4]arenes 1,3-disubstituted at the lower rim.

Experimental

^{1}H NMR spectra were recorded on a Varian XL-300 instrument (300 MHz) using $CDCl_3$ as the solvent. High-

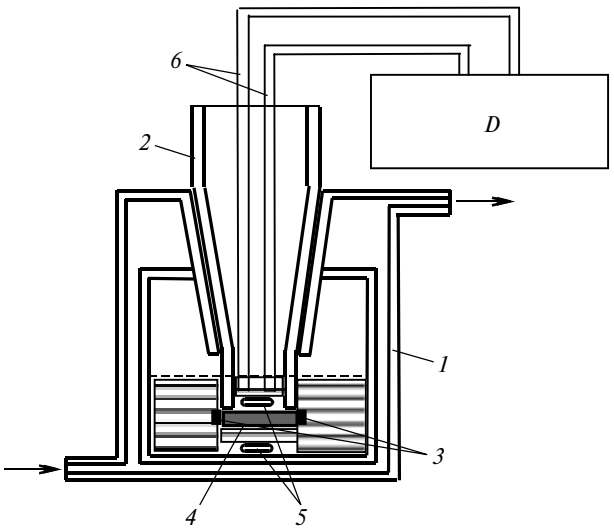


Fig. 2. Glass cell in a thermostat with a vertical movable cylinder for membrane extraction: (*1*) the external vessel maintained at a constant temperature for the source phase; (*2*) internal vessel with the receiving solution; (*3*) supporting ring; (*4*) impregnated membrane; (*5*) magnetic stirrer; (*6*) conductometric cell; *D* is conductometer.

resolution mass spectra (EI) were recorded on an MX-1310 (60 eV, 200—450 °C) instrument. Complexation of calix[4]arenes with benzoic and aminoacetic acids and tetrabutylammonium benzoate was studied by ^{1}H NMR spectroscopy at 25 °C for $8 \cdot 10^{-2}$ *M* solutions in CCl_4 containing 5% $(CD_3)_2CO$. The IR spectra of the complexes and the corresponding initial compounds were recorded in Vaseline oil on a Specord M-80 spectrometer in the 3600—600 cm^{-1} range. The electrical conductivity of solutions was measured on a Hydromat-LM 301 conductometer. The flux through liquid impregnated membranes was measured in a glass cell with a vertical movable cylinder placed in a thermostat[36] (Fig. 2). The liquid membrane was represented by a 0.05 *M* solution of the carrier (**10—18**) in *o*-nitrophenyl octyl ether (ONPOE) incorporated into pores of a Millipore Type FA Teflon filter (thickness 100 μm, pore size 1 μm, porosity 85%, reinforced by a Nylon mesh). The concentration of the transported compound in the source[37] phase was 0.1 mol L^{-1}. The substrate concentration in the receiving phase was determined by conductometry. The model calculations of complexes were done by the MM+ molecular mechanics method and by the semiempirical quantum-mechanical PM3 method included in the MOPAC 7.00 package.

Synthesis of 5,11,17,23-tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis-substituted calix[4]arenes (10—17) (general procedure). A mixture of *p*-*tert*-butylcalix[4]arene (1.54 mmol),[38] the appropriate alkyl bromide (3.24 mmol), and anhydrous K_2CO_3 (1.7 g, 13.9 mmol) in 30 mL of MeCN was refluxed with stirring for 12 h. The solvent was removed and the residue was treated with 10 mL of 5 *M* HCl and extracted with 50 mL of $CHCl_3$. The organic phase was dried with 4 Å molecular sieves. After evaporation of the solvent, the residue was recrystallized from a $CHCl_3$—MeOH mixture.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(benzyloxy)calix[4]arene (10). Yield 1.0 g (79%), m.p. 202—203 °C. ^{1}H NMR, δ: 0.96 (s, 18 H, CMe_3); 1.30 (s, 18 H, CMe_3); 3.28 (d, 4 H, Ar$\underline{CH}_{2eq}$Ar, ^2J = 13.4 Hz); 4.29 (d, 4 H, Ar$\underline{CH}_{2ax}$Ar, ^2J = 13.4 Hz); 5.11 (s, 4 H, OCH_2); 6.81 (s, 4 H, ArH); 6.96 (s, 4 H, ArH); 7.34 (s, 2 H, OH); 7.37—7.39 (m, 6 H, ArH); 7.65—7.69 (m, 4 H, ArH). Found (%): C, 83.53; H, 8.35. $C_{58}H_{68}O_4$. Calculated (%): C, 84.02; H, 8.27. Found: *m*/*z* 828.5103 $[M]^+$. $C_{58}H_{68}O_4$. Calculated: M = 828.5118.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(2-naphthylmethyloxy)calix[4]arene (11). Yield 0.85 g (59%), m.p. 206—207 °C. ^{1}H NMR, δ: 0.97 (s, 18 H, CMe_3); 1.29 (s, 18 H, CMe_3); 3.29 (d, 4 H, Ar$\underline{CH}_{2eq}$Ar, ^2J = 13.4 Hz); 4.36 (d, 4 H, Ar$\underline{CH}_{2ax}$Ar, ^2J = 13.4 Hz); 5.21 (s, 4 H, OCH_2); 6.84 (s, 4 H, ArH); 7.05 (s, 4 H, ArH); 7.30—7.35, 7.42—7.48, 7.63—7.83 (m, 14 H, ArH); 8.04 (s, 2 H, OH). Found (%): C, 84.15; H, 8.03. $C_{66}H_{72}O_4$. Calculated (%): C, 85.30; H, 7.81. Found: *m*/*z* 928.5413 $[M]^+$. $C_{66}H_{72}O_4$. Calculated: M = 928.5431.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(9-fluorenyloxy)calix[4]arene (12). Yield 0.9 g (60%), m.p. 210—211 °C. ^{1}H NMR, δ: 0.96 (s, 18 H, CMe_3); 1.26 (s, 18 H, CMe_3); 3.17 (d, 4 H, Ar$\underline{CH}_{2eq}$Ar, ^2J = 13.2 Hz); 4.24 (d, 4 H, Ar$\underline{CH}_{2ax}$Ar, ^2J = 13.2 Hz); 5.97 (s, 4 H, OCH); 6.81 (s, 4 H, ArH); 6.85 (s, 2 H, OH); 7.00 (s, 4 H, ArH); 7.12—7.18 (m, 2 H, fluorenyl); 7.40—7.46 (m, 4 H, fluorenyl); 7.68—7.70 (m, 2 H, fluorenyl). Found (%): C, 85.81; H, 7.11. $C_{70}H_{72}O_4$. Calculated (%): C, 86.03; H, 7.43. Found: *m*/*z* 976.5411 $[M]^+$. $C_{70}H_{72}O_4$. Calculated: M = 976.5431.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(3-phenylprop-2*E*-en-1-yloxy)calix[4]arene (13). Yield 0.76 g (56%), m.p. 190—191 °C. ^{1}H NMR, δ: 0.94 (s, 18 H, CMe_3); 1.30 (s, 18 H, CMe_3); 3.32 (d, 4 H, Ar$\underline{CH}_{2eq}$Ar, ^2J = 13.2 Hz); 4.37 (d, 4 H, Ar$\underline{CH}_{2ax}$Ar, ^2J = 13.2 Hz); 4.72 (d, 4 H, OCH_2, ^3J = 6.1 Hz); 6.57 (td, 2 H, $CH_2\underline{CH}$= CH—Ph, ^3J = 6.1 Hz, $^3J_{trans}$ = 15.9 Hz); 6.77 (s, 4 H, ArH); 6.84 (d, 2 H, CH_2CH=$\underline{CH}$—Ph, $^3J_{trans}$ = 15.9 Hz); 7.06 (s, 4 H, ArH); 7.20 (s, 2 H, OH); 7.24—7.30 (m, 6 H, ArH); 7.38—7.43 (m, 4 H, ArH). Found (%): C, 84.01; H, 8.35. $C_{62}H_{72}O_4$. Calculated (%): C, 84.50; H, 8.24. Found: *m*/*z* 880.5419 $[M]^+$. $C_{62}H_{72}O_4$. Calculated: M = 880.5431.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(4-nitrobenzyloxy)calix[4]arene (14). Yield 1.09 g (78%), m.p. 280 °C. ^{1}H NMR, δ: 0.96 (s, 18 H, CMe_3); 1.30 (s, 18 H, CMe_3); 3.35 (d, 4 H, Ar$\underline{CH}_{2eq}$Ar, ^2J = 13.2 Hz); 4.24 (d, 4 H, Ar$\underline{CH}_{2ax}$Ar, ^2J = 13.2 Hz); 5.17 (s, 4 H, O$\underline{CH}_2$Ar); 6.83 (s, 4 H, ArH); 7.08 (s, 4 H, ArH); 7.15 (s, 2 H, OH); 7.93, 8.17 (both d, each 4 H, $CH_2\underline{C_6H_4}NO_2$, ^3J = 8.4 Hz). Found (%): C, 75.53; H, 7.19; N, 3.01. $C_{58}H_{66}N_2O_8$. Calculated (%): C, 75.79; H, 7.24; N, 3.05. Found: *m*/*z* 918.4801 $[M]^+$. $C_{58}H_{66}N_2O_8$. Calculated: M = 918.4819.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(4-cyanobenzyloxy)calix[4]arene (15). Yield 0.92 g (68%), m.p. 246—247 °C. ^{1}H NMR, δ: 0.95 (s, 18 H, CMe_3); 1.30 (s, 18 H, CMe_3); 3.31 (d, 4 H, Ar$\underline{CH}_{2eq}$Ar, ^2J = 13.2 Hz); 4.21 (d, 4 H, Ar$\underline{CH}_{2ax}$Ar, ^2J = 13.2 Hz); 5.12 (s, 4 H, O$\underline{CH}_2$Ar); 6.80 (s, 4 H, ArH); 7.02 (s, 2 H, OH); 7.07 (s, 4 H, ArH); 7.67, 7.82 (both d, each 4 H, $CH_2\underline{C_6H_4}CN$, ^3J = 8.6 Hz). Found (%): C, 81.81; H, 7.62; N, 3.11. $C_{60}H_{66}N_2O_4$. Calculated (%): C, 81.97; H, 7.57; N, 3.19. Found: *m*/*z* 878.5001 $[M]^+$. $C_{60}H_{66}N_2O_4$. Calculated: M = 878.5023.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis[4-(ethoxycarbonyl)benzyloxy]calix[4]arene (16). Yield 0.88 g (59%), m.p. 110 °C. ^{1}H NMR, δ: 0.93 (s, 18 H, CMe_3); 1.26 (s, 18 H, CMe_3); 1.36 (t, 6 H, $OCH_2\underline{Me}$, ^3J = 7.2 Hz); 3.28 (d, 4 H, Ar$\underline{CH}_{2eq}$Ar, ^2J = 13.2 Hz); 4.25 (d, 4 H, Ar$\underline{CH}_{2ax}$Ar, ^2J = 13.2 Hz); 4.37 (q, 4 H, O$\underline{CH}_2$Me, ^3J = 7.2 Hz); 5.12 (s, 4 H, O$\underline{CH}_2$Ar); 6.78 (s, 4 H, ArH); 7.04 (s, 4 H, ArH); 7.26 (s, 2 H, OH); 7.76, 8.02 (both d, each 4 H, $CH_2\underline{C_6H_4}CO_2Et$, ^3J = 8.4 Hz). Found (%): C, 78.87;

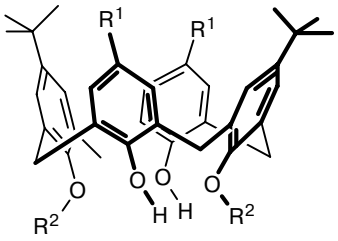
H, 7.95. $C_{64}H_{76}O_8$. Calculated (%): C, 78.98; H, 7.87. Found: *m/z* 972.5533 $[M]^+$. $C_{64}H_{76}O_8$. Calculated: M = 972.5540.

5,11,17,23-Tetra-*tert*-butyl-25,27-dihydroxy-26,28-bis(ethoxycarbonylmethyloxy)calix[4]arene (17). Yield 0.90 g (71%), m.p. 168—169 °C. ^{1}H NMR, δ: 0.99 (s, 18 H, CMe_3); 1.27 (s, 18 H, CMe_3); 1.34 (t, 6 H, $OCH_2\underline{Me}$, ^3J = 7.1 Hz); 3.33 (d, 4 H, $Ar\underline{CH}_{2eq}Ar$, ^2J = 13.1 Hz); 4.31 (q, 4 H, $O\underline{CH}_2Me$, ^3J = 7.1 Hz); 4.47 (d, 4 H, $Ar\underline{CH}_{2ax}Ar$, ^2J = 13.1 Hz); 4.73 (s, 4 H, $O\underline{CH}_2CO_2Et$); 6.82 (s, 4 H, ArH); 7.02 (s, 4 H, ArH); 7.06 (s, 2 H, OH). Found (%): C, 75.89; H, 8.23. $C_{52}H_{68}O_8$. Calculated (%): C, 76.06; H, 8.35. Found: *m/z* 820.4919 $[M]^+$. $C_{52}H_{68}O_8$. Calculated: M = 820.4914.

26,28-Bis(benzyloxy)-5,17-di-*tert*-butyl-25,27-dihydroxy-11,23-dinitrocalix[4]arene (18). 65% HNO_3 (5.6 mL, 80 mmol) was added to a solution of compound **1** (0.5 mmol) in a mixture of 50 mL $CHCl_2$ and glacial AcOH (2.9 mL, 50 mmol). The mixture was stirred for 30 min at ~20 °C and poured into 50 mL of water. The organic layer was separated, washed twice with water, and dried with 5 Å molecular sieves. After removal of the solvent, the residue was recrystallized from a 95% EtOH—CH_2Cl_2 mixture. Yield 0.25 g (63%), m.p. 294 °C. ^{1}H NMR, δ: 1.03 (s, 18 H, CMe_3); 3.45 (d, 4 H, $Ar\underline{CH}_{2eq}Ar$, ^2J = 13.4 Hz); 4.27 (d, 4 H, $Ar\underline{CH}_{2ax}Ar$, ^2J = 13.4 Hz); 5.08 (with 4 H, $O\underline{CH}_2Ar$); 6.91 (s, 4 H, ArH); 7.42—7.44 (m, 6 H, ArH); 7.58—7.62 (m, 4 H, ArH); 8.05 (s, 4 H, ArH); 8.90 (s, 2 H, OH). Found (%): C, 74.37; H, 6.35; N, 3.41. $C_{50}H_{50}N_2O_8$. Calculated (%): C, 74.42; H, 6.25; N, 3.47. Found: *m/z* 806.3582 $[M]^+$. $C_{50}H_{50}N_2O_8$. Calculated: M = 806.3567.

Results and Discussion

A series of compounds (**10—17**) were prepared in 60—80% yields by selective alkylation[7,39,40] of *p-tert*-butylcalix[4]arene by the corresponding halogen derivatives in MeCN in the presence of K_2CO_3. Compound **18** was synthesized by nitration of macrocycle **10** with nitric acid in CH_2Cl_2 in the presence of AcOH at ~20 °C.[41]



10—18

R^1 = Bu^t (**10—17**), NO_2 (**18**)
R^2 = Bn (**10**), CH_2-(2-naphthyl) (**11**), 9-fluorenyl (**12**), *trans*-CH_2—CH=CH—Ph (**13**), *p*-CH_2—C_6H_4—NO_2 (**14**), *p*-CH_2—C_6H_4—CN (**15**), *p*-CH_2—C_6H_4—COOEt (**16**), CH_2COOEt (**17**), Bn (**18**)

The structures of the compounds synthesized were supported ^{1}H NMR spectroscopy, mass spectrometry, and elemental analysis. In the ^{1}H NMR spectra of compounds **10—18**, the signals for the bridging methylene protons of the macrocycles occur as two doublets, pointing to a *cone* conformation of the calix[4]arenes.[7]

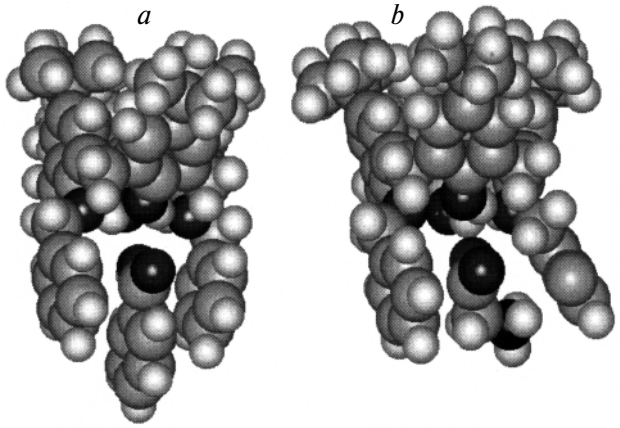


Fig. 3. Results of PM3 simulation of calixarene (**10**) complexes with benzoic (*a*) and aminoacetic (*b*) acids.

Preliminarily, molecular mechanics (MM+) and semiempirical PM3 calculations were carried out for the proposed model of binding of organic acids by 1,3-disubstituted calix[4]arenes in order to find out whether the structure shown in Fig. 1 is possible, in principle. This structure was used as the initial one in all calculations.

The results of the semiempirical PM3 simulation of complexes formed by macrocycle **10** with benzoic acid (**19**) or aminoacetic (**20**) acid are presented in Fig. 3. One can see that the calix[4]arene hydroxy groups are arranged complementarily to the carboxy fragment. The aromatic system of benzoic acid is oriented in such a way as to enable the π-stacking interaction with the benzyl substituents of calixarene. In the case of aminoacetic acid, the N—H bonds of the ammonium group are oriented toward one aromatic ring at the calix[4]arene substituent, which implies possible hydrogen bonding.[42] Thus, quantum-chemical simulation demonstrated the absence of steric restrictions for complexation and confirmed the complementary manner of interaction between the potential binding sites in the substrates and the receptors under interest.

Evidently, the possibility of complex formation due to inclusion of the guests into the calix[4]arene molecular cavity formed by the four aromatic rings also cannot be ruled out from consideration. Complexes of *p-tert*-butylcalix[4]arene with compounds of this type, for example, with benzene, toluene, and anisole, are well known and have been characterized in the solid phase.[4,5] However, in solution, the situation changes dramatically.[42,43] Only complexation of *p-tert*-butylcalix[4]arene with relatively small molecules such as acetonitrile, nitromethane, and dichloro-, bromocyano-, and dicyanomethane can be detected experimentally by ^{1}H NMR spectroscopy.[44] This appears natural recalling the size and the energy of inclusion of organic compounds into calix[4]arene cavity.

Data on the complexation energy of organic compounds with solid *p-tert*-butylcalix[4]arene[45,46] show that

the energy of transfer of aromatic hydrocarbons from the pure liquid state to a solid complex does not exceed 8 kJ mol^{-1}; thus, the formation of a solid complex is only 8 kJ mol^{-1} more favorable than solvation. In solution, this gain would be even smaller due to the entropy factor, macrocycle inversion, and the competition with solvent molecules. Thus, in the case of *p-tert*-butylcalix[4]arene, the guest—solvent interaction is slightly less pronounced than the guest—solid host one. This is not unexpected because the nonpolar aromatic cavity of calixarene and the surrounding solvent molecules interact with the guests by the same mechanism through dispersion, hydrophobic, and CH-π-interactions, and so on. Moreover, the solvent itself can also be included (wholly or partly) in the calix[4]arene molecular cavity. In view of the fact that both guest and host concentrations are several orders of magnitude lower than the solvent concentration, it becomes clear why complexes of this type fail to be detected in solution. Evidently, stronger interactions are required to bind the substrates in solution. The hydroxy groups at the lower rim are able to form hydrogen bonds both as proton donors (in the case of carboxylates) and proton acceptors (in the case of carboxy groups).

The complexing capacity of the synthesized macrocycles with respect to a number of organic acids was studied by IR and ^1H NMR spectroscopy and by membrane extraction. The crystalline complexes of receptor **10** with acid **19** and **20**, studied by IR spectroscopy, were prepared by dissolution of equimolar amounts of the guest and the host in 95% EtOH followed by solvent evaporation. Table 1 gives the assignment for a number of characteristic absorption bands in the IR spectra of benzoic (**19**) and aminoacetic (**20**) acids and their 1 : 1 complexes with **10** recorded in the range of 700—3600 cm^{-1} at 25 °C. The absorption bands corresponding to vibrations whose position and intensity remained unchanged upon complex formation are not given in the Table 1.

Table 1. Some characteristic bands in the IR spectra of complexes of carriers **10** with benzoic (**19**) and aminoacetic (**20**) acids at 25 °C*

Vibration, assignment	ν/cm^{-1}			
	19	**20**	Complex	
			10+**19**	**10**+**20**
νOH, dimer	2500—2800		—	
Compound vibrations of OH- and C=O groups in the dimer	1420, 1300		—	
νC=O	1690 vs		1700 w	
δOH	940 s		940 w	
δCH	710 s		710 w	
ν_{as} COO^-		1600 s		1600 w
ν_s COO^-		1400 s		1400 w
δ_{scis} COO^-		700		—
νNH_3^+		3160		—
νNH_3^+, a series of bands		2100—3000		—
$\delta_{ac} NH_3^+$		1630 s		1630 w
$\delta_c NH_3^+$		1525 s		1525 w

* In Vaseline oil.

It can be seen from Table 1 that the reactions of compound **10** with acids induce appreciable changes in the IR spectra. The absorption band corresponding to the stretching vibrations of the hydroxy groups in the benzoic acid dimer (2500—2800 cm^{-1}) disappears almost completely. In addition, the spectra of the complex contain no absorption bands (1420 and 1300 cm^{-1}) associated with the interaction between the OH and C=O groups in the benzoic acid dimer. All these changes, in addition to the decrease in the intensity and the shift of the absorption band of the carboxy group in the complex from 1690 to 1700 cm^{-1} indicate that the dimeric structure of the acid is destroyed upon complexation.

It is of interest that the IR spectrum of the mixture prepared by dissolution of 2 moles of phenol and 1 mole of benzoic acid in 95% EtOH with the subsequent evaporation of the solvent does not display the changes listed above, *i.e.*, the dimeric structure of the benzoic acid is retained. This difference between the reactions of 1,3-disubstituted calix[4]arene and phenol with benzoic acid may be due to the well-known macrocyclic effect (entropy factor). 1,3-Disubstituted calix[4]arene is a rigid pre-organized system with a fixed spatial arrangement of the hydroxy groups.

As shown by molecular simulation data, π-stacking interaction of the guest and host aromatic rings may serve as an additional factor stabilizing the complex of 1,3-dibenzyl-substituted calix[4]arene with benzoic acid. This assumption is in good agreement with the sharp decrease in the intensity of the absorption bands at 940 and 710 cm^{-1}, corresponding to the nonplanar deformation vibrations of the carboxyl OH group and the C—H bonds of the aromatic ring in benzoic acid complexes with compound **10**. Apparently, a decrease in the intensity of these absorption bands upon complexation is due to the position of benzoic acid between two benzyl substituents of calix[4]arene **10**. In a mixture of phenol with benzoic acid (**19**), these bands remain unchanged.

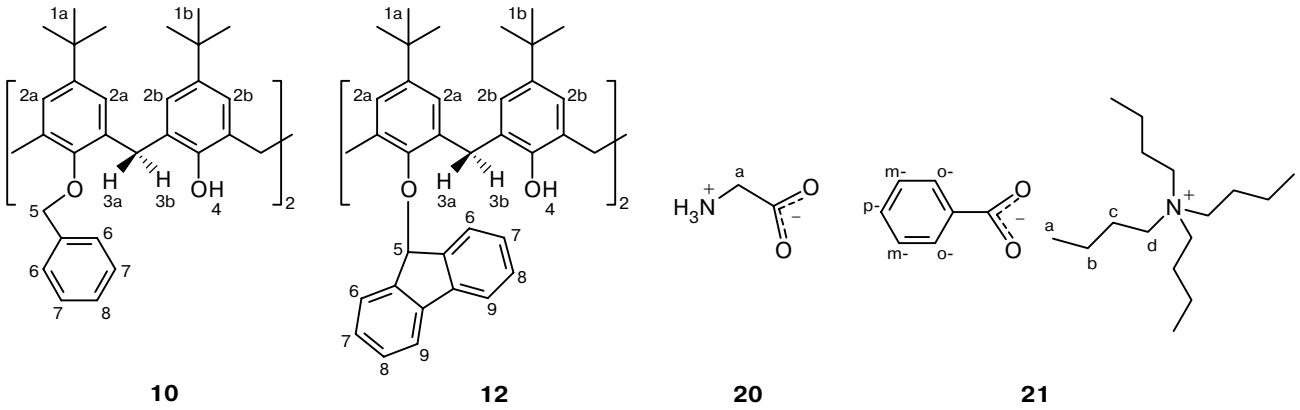
The reaction of **10** with aminoacetic acid (**20**) entails substantial changes in the IR spectra. The intensity of the bands due to the asymmetric and symmetric stretching vibrations of the carboxylate anion (1600 and 1400 cm^{-1}) sharply decreases, and the band at 700 cm^{-1} caused by the scissoring vibrations of the carboxylate anion is completely absent. This is consistent with the results of simulation according to which the carboxylate anion can potentially be linked to two hydroxy groups of calix[4]arene. The absorption bands due to vibrations of the protonated amino group also undergo pronounced changes upon complexation. Thus the stretching band at 3160 cm^{-1} and a series of bands in the region of

2100—3000 cm^{-1} virtually disappear, while the absorption bands at 1630 cm^{-1} and 1525 cm^{-1} corresponding to asymmetric and symmetric bending vibrations of the ammonium group, respectively, decrease in intensity. This may be a result of hydrogen bonding between the ammonium group and the π-system of the aromatic ring.[42]

Complexation of calixarenes **10**, **12** in solution was studied by ^{1}H NMR spectroscopy using benzoic (**19**) and aminoacetic acids (**20**) and tetrabutylammonium benzoate (**21**). The spectra of 1 : 1 mixtures of compounds **10**, **12** with **19** did not display any significant changes with respect to the spectra of individual compounds. However, the reaction with **21** induces substantial changes in the ^{1}H NMR spectra (Table 2).

Analysis of the variations of the chemical shifts for all host protons is rather complicated because the whole spatial structure of calixarene changes significantly upon complexation. Therefore, analysis of the pattern of variation of guest signals provides more information. In view of the conformational rigidity of the substrates under study, the change in the chemical shifts of the corresponding protons can be related to the complexation alone. Thus the signals of the aromatic protons of the benzoate anion undergo a downfield shift by 0.1 ppm (Fig. 4), which indicates that the protons of the benzoate anion are located in the deshielding region of aromatic substituents of calixarene. These data are in good agreement with the assumed π-stacking interaction between the aromatic fragments of the benzoate anion and calix[4]arene substituents. The signals of the hydroxy protons of calix[4]arene either undergo an upfield shift (compound **10**) or do not change, as in the case of difluorenyl-substituted calix[4]arene **12**. If the guest were located in the calixarene cavity, its protons would experience a strong upfield shift because they would get in

Table 2. ^{1}H NMR spectra of compounds **10** and **12** and their complexes with glycine (**20**) and tetrabutylammonium benzoate (**21**)*



10 **12** **20** **21**

Compound	δ_H (*J*/Hz)
10	1.27 (s, C(1a)H); 1.02 (s, C(1b)H); 7.03 (s, C(2a)H); 6.95 (s, C(2b)H); 4.31 (d, H(3a), *J* = 12.8); 3.32 (d, H(3b); *J* = 12.8); 7.93 (s, H(4)); 5.08 (s, C(5)H); 7.66—7.69 (m, C(6)H); 7.33—7.38 (m, C(7)H, C(8)H)
10+**20**	**10:** 1.28 (s, C(1a)H); 1.01 (s, C(b)H); 7.00 (s, C(2a)H); 6.88 (s, C(2b)H); 4.31 (d, H(3a), *J* = 12.9); 3.29 (d, H(3b), *J* = 12.9); 7.73 (s, H(4)); 5.08 (s, C(5)H); 7.65—7.68 (m, C(6)H); 7.34—7.36 (m, C(7)H, C(8)H); **20:** 1.95 (br.s, C(a)H)
10+**21**	**10:** 1.39 (s, C(1a)H); 1.11 (s, C(1b)H); 7.11 (s, C(2a)H); 6.99 (s, C(2b)H); 4.41 (d, H(3a), *J* = 12.9); 3.39 (d, H(3b), *J* = 12.9); 7.88 (s, H(4)); 5.18 (s, C(5)H); 7.75—7.79 (m, C(6)H); 7.43—7.47 (m, C(7)H, C(8)H); **21:** 1.01 (t, C(a)H, *J* = 7.3); 1.43 (tq, C(b)H, *J* = 7.6); 1.58—1.68 (m, C(c)H); 3.33—3.39 (m, C(d)H), 8.05—8.08 (m, C(o)H); 7.30—7.32 (m, C(m, p)H); 1.34 (s, C(1a)H); 1.11 (s, C(1b)H); 7.05 (s, C(2a)H); 6.99 (s, C(2b)H); 4.32 (d, H(3a), *J* = 13.1); 3.26 (d, H(3b), *J* = 13.1); 7.21 (s, H(4)); 6.01 (s, C(5)H); 7.13—7.19 (m, C(6)H); 7.42—7.49 (m, C(7)H, C(8)H); 7.75—7.77 (m, C(9)H)
12+**20**	**12:** 1.32 (s, C(1a)H); 1.07 (s, C(1b)H); 7.02 (s, C(2a)H); 6.94 (s, C(2b)H); 4.30 (d, H(3a), *J* = 13.2); 3.23 (d, H(3b), *J* = 13.2); 7.13 (s, H(4)); 5.99 (s, C(5)H); 7.12—7.16 (m, C(6)H); 7.42—7.47 (m, C(7), C(8)H); 7.73—7.75 (m, C(9)H); **20:** 1.88 (br.s, C(a)H)
12+**21**	**12:** 1.34 (s, C(1a)H); 1.11 (s, C(1b)H); 7.05 (s, C(2a)H); 6.99 (s, C(2b)H); 4.33 (d, H(3a), *J* = 13.1); 3.26 (d, H(3b), *J* = 13.1); 7.21 (s, H(4)); 6.01 (s, C(5)H); 7.13—7.19 (m, C(6)H); 7.42—7.49 (m, C(7)H, C(8)H); 7.75—7.78 (m, C(9)H); **21:** 0.99 (t, C(a)H, *J* = 7.3); 1.41 (tq, C(b)H, *J* = 7.2); 1.61—1.68 (m, C(c)H); 3.34—3.39 (m, C(d)H); 8.02—8.05 (m, C(o)H), 7.26—7.28 (m, C(m, p)H)
20	2.03 (s, C(a)H)
21	0.90 (t, C(a)H, *J* = 7.3); 1.33 (tq, C(b)H, *J* = 7.3); 1.51—1.61 (m, C(c)H); 3.28—3.33 (m, C(d)H); 7.90—7.93 (m, C(o)H); 7.14—7.18 (m, C(m, p)H)

* The spectra were recorded in a 5% solution of $(CD_3)_2CO$ in CCl_4; the substance concentration was $8 \cdot 10^{-2}$ mol L^{-1}.

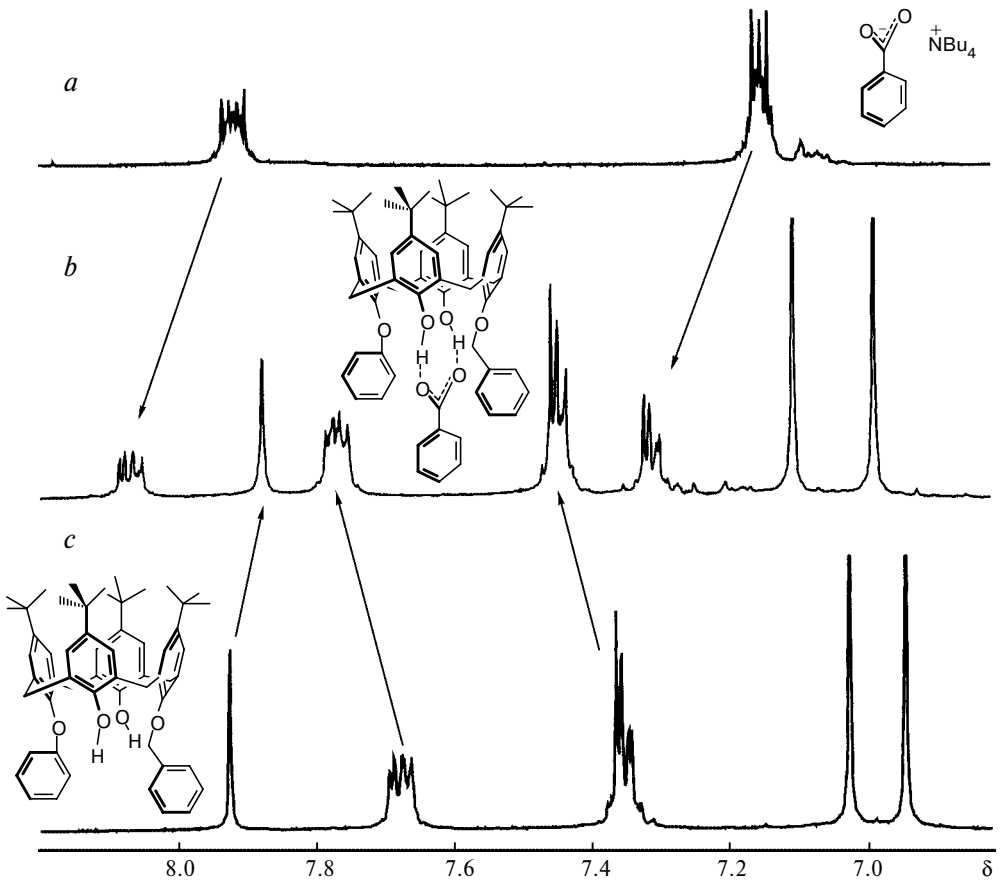


Fig. 4. Fragments of the ^{1}H NMR spectra: (*a*) tetrabutylammonium benzoate (**21**); (*b*) complex of carrier **10** with tetrabutylammonium benzoate (**21**); (*c*) carrier **10**.

the shielding area of aromatic rings. For example, in acetonitrile complexation with *p-tert*-butylcalix[4]arene, the signal of its methyl protons shifts upfield by 5.9 ppm and occurs at −3.9 ppm.[44]

Due to the size mismatch, the tetrabutylammonium cation does not form complexes with calix[4]arenes containing no negatively charged groups[42] at the lower or upper rim of the macrocycle. For this reason, it is this cation that is used as the counter-ion in investigations of the molecular recognition of anions.[23] Therefore, downfield shifts of about 0.05—0.1 ppm observed for signals of the methyl and methylene protons of the tetrabutylammonium cation can be due to the transition from a contact ion pair to a solvent-separated ion pair.

Upon complex formation of macrocycles **10** and **12** with **20** (Fig. 5), the signals of the methylene protons of glycine undergo an upfield shift by 0.08 ppm. This indicates that upon complexation, glycine molecules are arranged between the aromatic substituents of calix[4]arene, the methylene protons of glycine occurring in the shielding region of aromatic rings. The signals of calix[4]arene hydroxy protons, as in the case with the benzoate anion, undergo an upfield shift.

Further, the complex-forming properties of diaryl-substituted calix[4]arenes were studied by membrane transport. The fluxes (F) of several α-hydroxy and α-amino acids (DL-tartaric, glycolic, DL-amygdalic, and DL-glutamic acid) and sodium acetate through an impregnated liquid membrane are presented in Table 3. The Table also includes the results of a blank experiment, *i.e.*, the fluxes of the substrates under study through a membrane without a carrier.

Proceeding from the suggested model for the interaction of carboxy and carboxylate functions with 1,3-disubstituted calix[4]arenes, we analyzed the influence of the nature of substituents at the lower rim of the macrocycle on the transport efficiency. We considered the following structural factors influencing the rate of substrate mass transfer: the area and the electron-withdrawing characteristics of the substituent π-systems, acid-base properties of free phenolic groups of calixarene, and complementarity of the arrangement of the interacting binding sites.

One of the factors that might affect the transport rate is the area of the π-systems of the substituents located at the calix[4]arene lower rim. The incorporation of carriers **10**—**12**, containing phenyl, naphthyl, or fluorenyl

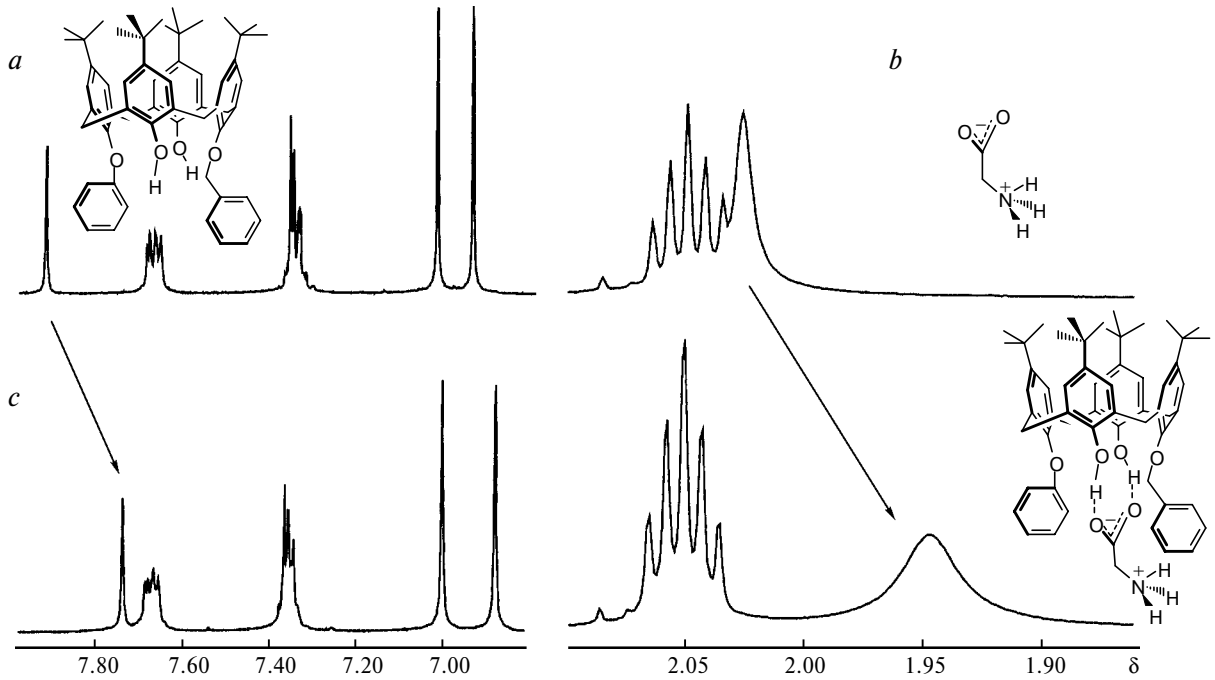


Fig. 5. Fragments of the ^{1}H NMR spectra: (*a*) carrier **10**; (*b*) aminoacetic acid (**20**); (*c*) complex of carrier **10** with acid **20**.

fragments, into the membrane phase was found to induce a relatively slight, 1.2—3.3-fold acceleration of the substrate transport with respect to the blank experiment. This behavior points to the formation of a carrier—substrate complex, whose energy does not suffice to make up for the energy expences for desolvation of the highly hydrophilic substrates in water and to transfer them to the lipophilic membrane phase. Although no clear correlation can be found between the flux and the area of the π-systems of substituents, the fact of participation of aromatic substituents in complexation (through the OH-π hydrogen bonding[42]) can be detected by comparing the fluxes observed with carrier **13**. The spatial remoteness of the aromatic fragment of the substituent from the lower rim of calix[4]arene entails reduction of the flux down to the values observed in the blank experiment for all the substrates studied because the α-hydroxy groups of the acid are no longer complementary to the aromatic ring of the substituent in the receptor. Tartaric acid is an exception, which deserves attention. In the case of this acid, unlike monobasic hydroxy acids, the flux through the membrane increases, which may imply the presence of OH-π hydrogen bonding between the second carboxy group of the tartaric

Table 3. Initial flux (F) for a number of organic acids through a liquid impregnated membrane (25 °C)[a]

Transporting agent	F[b]/mol h^{-1} m^{-2}				
	DL-Tartaric acid	Glycolic acid	DL-Amygdalic acid	DL-Glutamic acid	AcONa
10	$9\cdot10^{-8}$	$5.7\cdot10^{-7}$	$5.9\cdot10^{-5}$	$5\cdot10^{-8}$	$2.3\cdot10^{-7}$
11	$9\cdot10^{-8}$	$4.8\cdot10^{-7}$	$3.9\cdot10^{-5}$	$5\cdot10^{-8}$	$3.5\cdot10^{-7}$
12	$9\cdot10^{-8}$	$2.1\cdot10^{-7}$	$5.1\cdot10^{-5}$	$6\cdot10^{-8}$	$3.4\cdot10^{-7}$
13	$2.3\cdot10^{-7}$	$1.7\cdot10^{-7}$	$2.7\cdot10^{-5}$	$5\cdot10^{-8}$	$2.3\cdot10^{-7}$
14	$1.4\cdot10^{-7}$	$1.8\cdot10^{-7}$	$3.4\cdot10^{-5}$	$1.5\cdot10^{-7}$	$4.3\cdot10^{-7}$
15	$9\cdot10^{-8}$	$1.9\cdot10^{-7}$	$3.3\cdot10^{-5}$	$8\cdot10^{-8}$	$3.6\cdot10^{-7}$
16	$1.3\cdot10^{-7}$	$4.0\cdot10^{-7}$	$3.7\cdot10^{-5}$	$6\cdot10^{-8}$	$2.8\cdot10^{-7}$
17	$9\cdot10^{-8}$	$6.3\cdot10^{-7}$	$8.6\cdot10^{-5}$	$5.8\cdot10^{-7}$	$5.4\cdot10^{-6}$
18	$9\cdot10^{-8}$	$2.6\cdot10^{-7}$	$2.7\cdot10^{-5}$	$5\cdot10^{-8}$	$2.2\cdot10^{-7}$
[c]	$9\cdot10^{-8}$	$1.7\cdot10^{-7}$	$2.7\cdot10^{-5}$	$5\cdot10^{-8}$	$2.3\cdot10^{-7}$

[a] The error of determination of the mass transfer flux was ± 10%.
[b] The area of the membrane was $S = 9.616$ cm^2.
[c] Blank experiment

acid and the aromatic ring of the cinnamyl substituent in carrier **13**.

It is noteworthy that the increase in the acidity of free hydroxy groups in calix[4]arene **18** following the replacement of two *tert*-butyl substituents at the upper rim of the macrocycle by nitro groups resulted in almost complete loss of the ability to transport carboxyl-containing substrates through membranes. Thus, in complexation with carboxy groups, free hydroxy groups of calixarene act as proton-acceptors rather than as proton-donors. This is an important regularity, which allows one to elaborate a correct strategy for the modification of the calixarene platform aimed at the development of more effective carriers.

As regards the substrates containing the COO^- carboxylate fragment (AcONa and glutamic acid), neither carrier **10** nor its nitro derivative **18** influence the rate of membrane transport (*cf.* the blank experiment), *i.e.*, the energy of these interactions does not suffice to compensate the energy spent for desolvation (dehydration) of these highly hydrophilic compounds when they migrate from water into the organic phase.

The next type of carriers studied are calixarenes **14—16**, which contain electron-withdrawing substituents at the lower rim of the macrocycle. The introduction of these compounds into a membrane does not exert any noticeable influence on the transport of monobasic α-hydroxy acids such as glycolic and amygdalic acids, which is quite consistent with the above assumption that the OH-π hydrogen bonding contributes significantly to the hydroxy acid—carrier complexation. Obviously, upon the introduction of electron-withdrawing groups into the aromatic substituents of calix[4]arene, the strength of this bond can only decrease. The high flux values for DL-tartaric acid, as in the case of carrier **13**, can be interpreted by assuming additional interaction of hydrogen bonding type between the second functional group of the hydroxy acid and the heteroatom substituents located in the *para*-position of the benzyl fragment.

Meanwhile, in the case of substrates containing carboxylate functions such as glutamic acid and sodium acetate, the electron-withdrawing effect of substituents in the aromatic ring can be followed quite clearly. As the electron-withdrawing capacity of the carrier decreases (**16** < **15** < **14**), the flux through the membrane for these substrates increases (up to 2.5-fold), which may stem from the donor-acceptor interactions involved in complexation.

Compound **17**, in which the ethoxycarbonyl groups (COOEt) are linked to the calixarene platform through one methylene unit, proved to be the most efficient carrier. The introduction of this compound in the membrane phase accelerates the transport of the substrates under study 3- to 20-fold. The exception is tartaric acid, whose flux through the membrane with the carrier does not differ from that observed in the blank experiment to within the experimental error. In view of the low efficiency of compounds **10—12**, containing two free phenoxy groups, the acceleration of mass transfer of the hydroxy and amino acids in the presence of calix[4]arene **17** is apparently due to the formation of stronger "carrier—substrate" complexes in the membrane phase owing to the participation of both functional groups of the substrates in binding with both the hydroxy and ester fragments of the receptor. In this particular case, complementary arrangement of the interacting sites is necessary for binding.

The significance of this factor is indicated by the data obtained for carrier **16**. In this molecule, the ester fragments are essentially remote from the two free phenol groups of calix[4]arene; therefore, the substrate cannot interact simultaneously with both binding sites of the carrier for geometric reasons, while interaction with only one site is inadequate for the formation of a stable complex and transfer of the hydrophilic substrate to the lipophilic phase. As a consequence, macrocycle **16** has virtually no influence on the flux of the above-mentioned hydroxy and amino acids through the membrane.

The same reasoning, complementary positions of the interacting sites, is responsible for the absolutely opposite influence of carriers **16** and **17** on the transport of tartaric acid. Compound **16** was found to accelerate selectively the transport of tartaric acid, which seems to be due to the possible involvement of the second carboxy group of tartaric acid in binding with the ester group located in the *para*-position of the benzyl substituent.

The carrier **17** increases the flux of AcONa through a lipophilic membrane more than 20-fold. In view of the low concentration of the carrier in the membrane phase (0.05 mol L^{-1}), this result appears quite encouraging for the design of effective carriers for compounds containing carboxylate functions. The experiment on the transport of NaBr through a membrane containing **17** showed that the introduction of this calix[4]arene in a membrane does not influence the transport of NaBr. Hence, it can be stated that the transport of AcONa is mainly due to the interaction of the carrier with the acetate anion rather than with the sodium cation.

Thus, in this study, a new type of macrocyclic receptors based on 1,3-disubstituted calix[4]arenes able to bind organic substrates containing carboxy and carboxylate groups was designed and the structural factors favorable for the transport of these hydrophilic substrates through lipophilic membranes were established. The efficiency of the acid transport is facilitated by an increase in the area of the π-system of the aryl substituents, an increase in the basicity of two free phenolic groups, and by proton-donating substituents located at an appropriate distance from the macrocycle.

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