Available online at www.sciencedirect.com
ScienceDirect
Mendeleev Commun., 2009, **19**, 163–164
Mendeleev Communications

New membrane carrier for glutamic acid based on *p-tert*-butylcalix[4]arene 1,3-disubstituted at the lower rim

Ivan I. Stoikov,* Maria N. Agafonova, Pavel L. Padnya, Evgeny N. Zaikov and Igor S. Antipin

A. M. Butlerov Chemical Institute, Kazan State University, 420008 Kazan, Russian Federation.
Fax: +7 8432 315 416; e-mail: ivan.stoikov@mail.ru

DOI: 10.1016/j.mencom.2009.05.018

Calix[4]arenes 1,3-disubstituted at the lower rim were synthesized and their receptor ability toward dicarboxylic, α-hydroxy and amino acids was investigated. A new synthetic receptor for glutamic acid based on 1,3-disubstituted calix[4]arene was suggested.

Recently, attention has been focused on modeling synthetic receptors able to specifically change and control biomacromolecule functions. Simple and synthetically available molecules able to switch reversibly various functions of proteins can be requested for modeling biological processes and developing new drug delivery systems and pharmaceutical screening. The selective binding of a protein surface is mainly based on the recognition of amino and carboxylic groups of prevailing amino acid residues by means of synthetic molecular platform.[1]

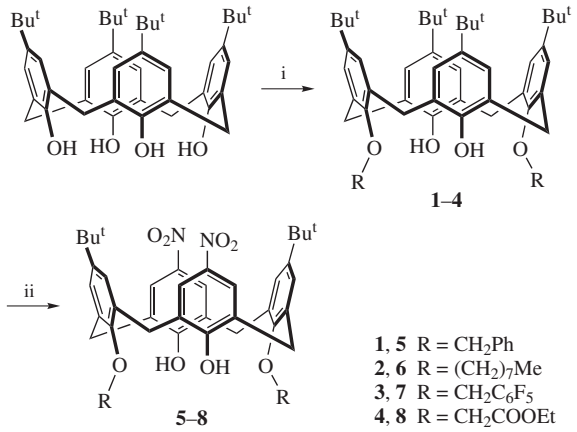
Among other synthetic receptors, calixarenes are of special interest because of their applicability to designing three-dimensional structures with various sizes of internal cavities, numbers and types of binding centers, spatial arrangements of binding groups and the ability to form asymmetric cavities and affect the balance between the hardness and flexibility of a receptor.[2,3]

Previously, it was shown[4] that di- and tetrasubstituted calix[4]arenes with various functional groups at the lower rim are able to molecular recognition of oxalic acid. The efficiency of interaction of calix[4]arene receptors with the acids depended on various factors, *i.e.* π-system area of the substituents, their structural accepting characteristics, geometrical complementarities of the binding centers, and the acid-base properties of free phenolic groups.

In this work, the molecular design of the receptor structures was performed for the recognition of biologically significant acids. For this purpose, *p-tert*-butylcalix[4]arenes **1**–**8** substituted at the lower rim were synthesized and their ability to efficient and selective transport of dicarboxylic and α-hydroxy acids through a lipophilic membrane was investigated. In addition, glutamic acid was used as a substrate to study the interaction of the compounds with amino acids. In compounds **1**–**8**, the nature of substituents at the lower rim of calixarene macrocycle and the acidity of phenolic protons were varied to affect the transport ability of the receptors toward various substrates.

Calix[4]arene derivatives **1**–**4**[5–7] disubstituted at the lower rim were synthesized with yields of 60–80% by selective alkylation[8,9] of *p-tert*-butylcalix[4]arene with appropriate alkyl halides in acetonitrile in the presence of potassium carbonate. Compounds **5**[7]–**8** were synthesized by the nitration of disubstituted calix[4]arene obtained with nitric acid in methylene chloride in the presence of acetic acid at ~20 °C.[10] The structures of compounds **6**–**8** (Scheme 1) were characterized by physical methods.†

The complexation ability of compounds **1**–**8** toward selected acids was investigated by membrane extraction.‡ The experiments on the transport of dicarboxylic, α-hydroxy- and α-amino acids through lipophilic liquid membranes induced by calixarenes **1**–**8** were performed. The fluxes (j_i) through a membrane were



Scheme 1 *Reagents and conditions*: i, see refs. 4–7; ii, 160 equiv. of 65% nitric acid, 100 equiv. of acetic acid, CH_2Cl_2, reflux.

† *General procedure of the synthesis of 5,17-di*-tert-*butyl-11,23-dinitro-25,27-disubstituted-26,28-dihydroxycalix[4]arenes* **6**–**8**. 65% Nitric acid (5.6 ml, 80 mmol) was added to 0.5 mmol of an appropriate disubstituted *p-tert*-butylcalix[4]arene dissolved in a mixture of 50 ml of CH_2Cl_2 and 2.9 ml (50 mmol) of acetic acid. The reaction mixture was stirred for 30 min at 20 °C. Then, the mixture was poured out in 50 ml of water. The organic phase was separated and dried with molecular sieves 4 Å. The solvent was evaporated to dryness, and the precipitate was recrystallized from CH_2Cl_2–ethanol.

5,17-Di-tert-*butyl-11,23-dinitro-25,27-dioctyloxy-26,28-dihydroxycalix[4]arene* **6**: yield 0.19 g (44%), yellow powder, mp 156–157 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 0.89 [t, 6H, $OCH_2(CH_2)_6Me$, $^3J_{HH}$ 6.5 Hz], 1.11 (s, 18H, CMe_3), 1.25–1.50 [m, 16H, $O(CH_2)_2CH_2(CH_2)_4Me$], 1.67 [tt, 4H, $O(CH_2)_2CH_2(CH_2)_4Me$, $^3J_{HH}$ 7.4 Hz, $^3J_{HH}$ 7.6 Hz], 2.08 [tt, 4H, $OCH_2CH_2(CH_2)_5Me$, $^3J_{HH}$ 6.8 Hz, $^3J_{HH}$ 7.6 Hz], 3.48 (d, 4H, $ArCH_{2ax}Ar$, $^2J_{HH}$ 13.2 Hz), 4.02 [t, 4H, $OCH_2(CH_2)_6Me$, $^3J_{HH}$ 6.8 Hz], 4.28 (d, 4H, $ArCH_{2eq}Ar$, $^2J_{HH}$ 13.2 Hz), 6.97 (s, 4H, H_{Ar}), 8.04 (s, 4H, H_{Ar}), 9.44 (s, 2H, OH). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 14.1, 22.6, 25.9, 29.3, 29.4, 29.9, 31.1, 31.5, 31.9, 34.2, 124.3, 126.2, 128.7, 131.3, 139.8, 148.5, 149.7, 159.6. IR (vaseline oil, ν/cm^{-1}): 3238 (OH), 1208 (COC). Found (%): C, 74.55; H, 8.56; N, 3.36. Calc. for $C_{52}H_{70}N_2O_8$ (%): C, 73.38; H, 8.29; N, 3.29.

5,17-Di-tert-*butyl-11,23-dinitro-25,27-bis(pentafluorophenyl)-26,28-dihydroxycalix[4]arene* **7**: yield 0.23 g (46%), yellow powder, mp 238–239 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 1.00 (s, 18H, CMe_3), 3.26 (d, 4H, $ArCH_{2ax}Ar$, $^2J_{HH}$ 13.2 Hz), 4.21 (d, 4H, $ArCH_{2eq}Ar$, $^2J_{HH}$ 13.2 Hz), 5.08 (s, 4H, OCH_2), 6.35 (s, 2H, OH), 6.73 (s, 4H, H_{Ar}), 7.05 (s, 4H, H_{Ar}). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 31.0, 31.1, 34.2, 64.4, 124.4, 126.5, 128.4, 130.8, 139.9, 149.1, 149.4, 159.0. IR (vaseline oil, ν/cm^{-1}): 3389 (OH), 2964 (CH), 1261 (COC).