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Mendeleev Commun., 2011, **21**, 44–45
Mendeleev Communications

New calix[4]resorcinols with diarylmethane fragments on the upper rim of the molecule

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DOI: 10.1016/j.mencom.2011.01.018

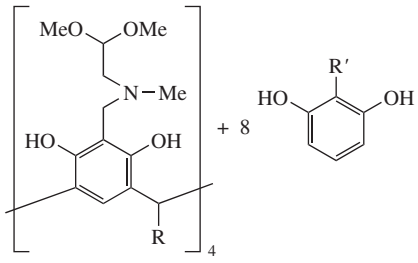
Reaction of calix[4]resorcinols, containing acetal moieties on the upper rim, with resorcinols leads to calixarenes bearing four diarylmethane fragments on the upper rim of the molecule.

Calixarenes are widely used as building blocks for the design of supramolecular and coordination systems[1–3] and manufacture of novel types of materials, extragents and catalysts.[4–6] Therefore, search for new expedient syntheses of calix[4]resorcinols and development of the methods of their functionalization still remain topical.[3]

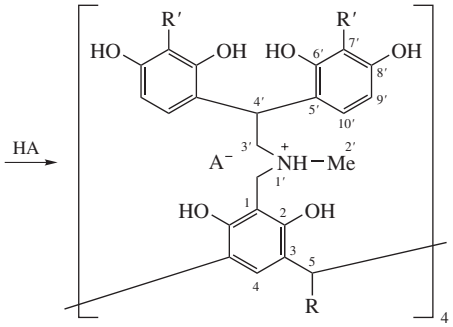
One of the most convenient ways of the modification of the calix[4]resorcinol framework is the Mannich reaction.[7–19] Within this approach, we obtained the first representatives of calix[4]-resorcinols, equipped with aminoacetal fragments at the upper rim of the molecule.[20–22] In the meantime, condensation of resorcinols with α-amino acetals in water–alcohol media is a good access to functionalized diarylmethanes,[23,24] which can serve as important components of dyes[25] and biologically active compounds.[26,27]

Assuming the abovementioned, calix[4]resorcinols, bearing diarylmethane fragments on the upper rim of the molecule, can be of considerable interest. Compounds of this type due to their chemical structure and large cavity size can be the promising receptors and possess various biological activities. We supposed that their synthesis can be performed by the reaction of amino acetal-supplied calix[4]resorcinols with resorcinols (Scheme 1).

In fact, HCl-assisted condensation of amino acetal calix[4]-resorcinols **1a–c** with 2-methylresorcinol and resorcinol in water–alcohol medium leads to the products containing four diarylmethane fragments on the upper rim of the molecule **2a–c**,† **3**.‡



1a R = Me
1b R = Et
1c R = C_7H_{15}



2a R = R′ = Me, A^- = Cl^-
2b R = Et, R′ = Me, A^- = Cl^-
2c R = C_7H_{15}, R′ = Me, A^- = Cl^-
3 R = Et, R′ = H, A^- = Cl^-
4 R = C_7H_{15}, R′ = Me, A^- = Br^-
5 R = R′ = Me, A^- = CF_3COO^-

Scheme 1

† The ^1H and ^{13}C NMR spectra were recorded on an Avance 600 instrument with working frequencies of 600.13 (^1H) and 150.86 (^{13}C) MHz. The IR spectra were recorded on a Vector 22 (Bruker) spectrometer. Mass spectra were measured on a MALDI Ultraflex III 'Bruker'.

General procedure for the synthesis of calix[4]resorcinols **2a–c**. To a stirred solution of 1.00 g (0.94 mmol) of calix[4]resorcinol **1a** in the mixture of ethanol (7 ml), water (7 ml), and HCl (1.8 ml), cooled to 0 °C, a solution of 2-methylresorcinol 0.93 g (7.5 mmol) in ethanol (2 ml) was added dropwise. The mixture was refluxed for 3 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in ethanol and this solution was poured into diethyl ether, the precipitate thus formed was filtered off and dried *in vacuo* to a constant weight. The purity of the compound was confirmed by TLC (Merck Silica gel 60 F_{254} plates, ethyl acetate as eluent). Yield of **2a**, 1.7 g (93%), mp > 330 °C. IR (ν/cm^{-1}): 1606 (C=C_{ar}), 2725 (NH^+), 3201 (OH), 3440 (OH). ^1H NMR (CD_3OD) δ: 1.65 (d, 12H, Me, J 6.24 Hz), 2.08 (s, 24H, $H^{11'}$), 2.82 (s, 12H, NMe), 3.74 (br. s, 8H, $H^{3'}$), 4.37 (br. s, 8H, $H^{1'}$), 4.52 (br. s, 4H, H^5), 5.05 (t, 4H, $H^{4'}$, J 5.22 Hz), 6.35 (br. s, 8H, $H^{9'}$), 6.66 (br. s, 8H, $H^{10'}$), 7.18 (s, 4H, H^4). ^{13}C-{^1H} NMR (CD_3OD) δ: 156.4 ($C^{6'}$), 154.3 (C^2), 152.1 ($C^{8'}$), 128.3 (C^3), 126.9 (C^4), 126.4 ($C^{10'}$), 119.4 (C^1), 116.9 ($C^{7'}$), 110.1 ($C^{9'}$), 107.5 ($C^{5'}$), 61.2 ($C^{3'}$), 53.5 ($C^{1'}$), 41.6 ($C^{2'}$), 35.0 ($C^{4'}$), 30.9 (C^5), 20.3 (CH*Me*), 9.0 ($C^{11'}$). MS, *m/z*: 1828.79 [M – 4HCl + Na]$^+$. Found (%): C, 63.26; H, 6.45; Cl, 7.28; N, 2.74. Calc. for $C_{104}H_{120}Cl_4N_4O_{24}$ (%): C, 63.56; H, 6.15; Cl, 7.28; N, 2.87.

Analogously, 1.6 g (91%) of **2b**, mp > 330 °C, was obtained from 1 g (0.89 mmol) of calix[4]resorcinol **1b**, in EtOH (10 ml), HCl (5 ml) and 0.88 g of 2-methylresorcinol. IR (ν/cm^{-1}): 1606 (C=C_{ar}), 2720 (NH^+), 3163 (OH). ^1H NMR (CD_3OD) δ: 0.93 (t, 12H, Me, J 6.97 Hz), 2.13 (br. s, 24H, C_{ar}Me), 2.34 (m, 8H, CH_2Me), 2.78–2.83 (m, 12H, NMe), 3.61–3.70 (br. s, 8H, CH_2N), 4.28 (br. s, 8H, $H^{1'}$), 4.36 (br. s, 4H, H^5), 5.04 (t, 2H, CH, J 6.97 Hz), 5.07 (t, 2H, CH, J 6.97 Hz), 6.35 (br. s, 8H, $H^{9'}$), 6.67 (br. s, 8H, $H^{10'}$), 7.13 (s, 2H, H^4), 7.33 (s, 2H, H^4). ^{13}C-{^1H} NMR (CD_3OD) δ: 155.6 ($C^{6'}$), 153.5 (C^2), 151.2 ($C^{8'}$), 127.3 (C^3), 126.2 (C^4), 125.7 ($C^{10'}$), 119.5 (C^1), 118.7 ($C^{7'}$), 112.6 ($C^{9'}$), 106.1 ($C^{5'}$), 60.7 ($C^{3'}$), 52.5 ($C^{1'}$),

The outcome of the reaction is little substrate- and temperature-dependent (25 – 78 °C) (see Scheme 1). Carrying out the reaction in the presence of hydrobromic acid and in trifluoroacetic acid afford products **4**,§ **5**¶ in high yields (91% and 74%, respectively).

The structure of the synthesized compounds **2a–c**, **3–5** was confirmed by ^{1}H, ^{13}C NMR, IR spectroscopy, mass spectrometry and elemental analysis. The correlation of signals in ^{13}C NMR spectra of compounds **2a** and **4** was performed on the basis of HSQC, HBMC and COSY NMR experiments.

In conclusion, the developed method is the promising approach to the synthesis of calix[4]resorcinols bearing various substituted diarylmethane and heteroarene fragments on the upper rim of the molecule.

This work was supported by the Russian Foundation for Basic Research (grant no. 08-03-00512) and the grant of the President of the Russian Federation for the state support of young Russian scientists (MK-919.2009.3). The authors are grateful to Dr. R. Z. Musin and Dr. D. Sharafutdinova for recording the mass spectra.

38.9 ($C^{2'}$), 35.1 ($C^{4'}$), 32.7 (C^5), 26.8 (CH_2Me), 12.3 (CH_2*Me*), 8.5 ($C^{11'}$). MS, *m/z*: 1883.89 [M – 4HCl + Na]$^+$. Found (%): C, 64.39; H, 6.43; Cl, 7.16; N, 2.80. Calc. for $C_{108}H_{128}Cl_4N_4O_{24}$ (%): C, 64.60; H, 6.38; Cl, 7.08; N, 2.79.

By the same procedure, 0.58 g (72%) of compound **2c**, mp > 330 °C, was obtained from 0.50 g (0.36 mmol) of calix[4]resorcinol **1c** in EtOH (3 ml), H_2O (3 ml), HCl (1.5 ml) and 0.35 g (2.82 mmol) of 2-methylresorcinol in EtOH (2 ml). IR (ν/cm^{-1}): 1605 (C=C$_{ar}$), 2726 (NH$^+$), 3161, 3339 (OH). ^{1}H NMR (CD_3OD) δ: 0.93 (br. s, 12H, Me), 1.32–1.42 [m, 40H, $(CH_2)_5$], 2.06–2.09 (m, 24H, C_{ar}Me), 2.21 (br. s, 8H, CHCH_2CH$_2$), 2.64 (br. s, 12H, NMe), 3.34–3.62 (m, 8H, CHCH_2N), 4.33–4.42 (m, 12H, CHC_7H_{15}, $C_{ar}CH_2$), 5.03 (s, 4H, CH), 6.36 (br. s, 8H, $H^{9'}$), 6.71 (m, 8H, $H^{10'}$), 7.24–7.30 (m, 4H, H^4). MS, *m/z*: 2163.75 [M – 4HCl + Na]$^+$. Found (%): C, 66.78; H, 7.53; Cl, 6.16; N, 2.45. Calc. for $C_{128}H_{168}Cl_4N_4O_{24}$ (%): C, 67.18; H, 7.40; Cl, 6.20; N, 2.45.

‡ Analogously, 1.46 g (87%) of compound **3**, mp > 330 °C, was obtained from 1.00 g (0.89 mmol) of calix[4]resorcinol **1b** and 0.98 g (8.90 mmol) of resorcinol. IR (ν/cm^{-1}): 1605 (C=C$_{ar}$), 2728 (NH$^+$), 3164 (OH). ^{1}H NMR (CD_3OD) δ: 0.92 (br. s, 12H, H^{12}), 2.08–2.26 (m, 8H, CH_2), 2.59–2.76 (m, 12H, NMe), 3.70 (br. s, 8H, $H^{3'}$), 4.31 (br. s, 8H, $H^{1'}$), 4.37 (br. s, 4H, H^5), 5.04 (s, 4H, $H^{4'}$), 6.33 (s, 8H, $H^{7'}$), 6.66 (br. s, 8H, $H^{9'}$), 7.31 (br. s, 8H, $H^{10'}$), 7.87 (s, 4H, H^4). MS, *m/z*: 1771.29 [M – 4HCl + Na]$^+$. Found (%): C, 63.27; H, 6.05; Cl, 7.89; N, 2.87. Calc. for $C_{100}H_{112}Cl_4N_4O_{24}$ (%): C, 63.36; H, 5.91; Cl, 7.50; N, 2.96.

§ Analogously, 0.80 g (91%) of compound **4**, mp > 300 °C, was obtained from the mixture of 0.50 g (0.36 mmol) of calix[4]resorcinol **1c** in EtOH (3 ml), HBr (1 ml) and 0.35 g (2.82 mmol) of 2-methylresorcinol. IR (ν/cm^{-1}): 1605 (C=C$_{ar}$), 2726 (NH$^+$), 3100, 3313 (OH). ^{1}H NMR (acetone-d_6) δ: 0.85 (br. s, 12H, H^{12}), 1.24 (br. s, 40H, CH_2), 2.12–2.15 (m, 24H, $H^{11'}$), 2.25 (br. s, 8H, H^6), 2.82–2.87 (m, 12H, NMe), 4.01–4.03 (m, 8H, $H^{3'}$), 4.36 (br. s, 4H, H^5), 4.51–4.85 (m, 8H, $H^{1'}$), 5.25 (t, 4H, $H^{4'}$, *J* 7.2 Hz), 6.49–6.70 (m, 8H, $H^{9'}$), 6.86–6.93 (m, 8H, $H^{10'}$), 7.68 (m, 4H, H^4), 8.50 (s, OH). ^{13}C-{^{1}H} NMR (acetone-d_6) δ: 154.6 (C^2), 156.7 ($C^{6'}$), 152.2 ($C^{8'}$), 128.3 (C^3), 127.8 ($C^{10'}$), 126.7 (C^4), 119.5 (C^1, $C^{7'}$), 109.3 ($C^{5'}$), 109.8 ($C^{9'}$), 61.0 ($C^{1'}$), 53.9 ($C^{3'}$), 41.5 ($C^{2'}$), 36.8 ($C^{4'}$), 35.1 (C^5), 33.8, 33.3, 31.1, 31.0, 29.5, 23.9 [$(CH_2)_6$], 15.06 (CH_2*Me*), 10.1 ($C^{11'}$). MS, *m/z*: 2163.29 [M – 4HBr + Na]$^+$. Found (%): C, 61.99; H, 6.94; Br, 12.86; N, 2.32. Calc. for $C_{128}H_{168}Br_4N_4O_{24}$ (%): C, 62.33; H, 6.87; Br, 12.96; N, 2.27.

¶ Solution of 1.00 g (0.94 mmol) of calix[4]resorcinol **1a** and 0.93 g (7.5 mmol) of 2-methylresorcinol in trifluoroacetic acid (5 ml) was refluxed for 5 h, cooled to room temperature and concentrated *in vacuo*. The residue was dissolved in ethanol and this solution was poured into diethyl ether, the precipitate thus formed was filtered off and dried *in vacuo* to a constant weight to give 1.62 g (74%) of compound **5**, mp > 330 °C. IR (ν/cm^{-1}): 1607 (C=C$_{ar}$), 1672 (COO$^-$), 2725 (NH$^+$), 3220 (OH). ^{1}H NMR (acetone-d_6) δ: 1.75 (br. s, 12H, Me), 2.07–2.15 (m, 24H, C_{ar}Me), 2.87–2.94 (m, 12H, NMe), 3.78 (br. s, 8H, $H^{3'}$), 4.37 (br. s, 4H, H^5), 4.60 (br. s, 8H, $H^{1'}$), 5.11–5.15 (m, 4H, $H^{4'}$), 6.37–6.44 (m, 8H, $H^{9'}$), 6.77–6.91 (m, 8H, $H^{10'}$), 7.25 (s, 4H, H^4). MS, m/z: 1828.59 [M – CF_3COOH + Na]$^+$. Found (%): C, 60.26; H, 5.86; N, 2.34. Calc. for $C_{118}H_{132}F_{12}N_4O_{32}$ (%): C, 60.40; H, 5.67; N, 2.39.

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Received: 19th May 2010; Com. 10/3528