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Mannich Reaction Involving Calix[4]resorcinarenes and Aminoacetals

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Abstract—The Mannich reaction involving calyx[4]resorcinarenes, aminoacetals, and formaldehyde in the molar ratio 1:4:4 yields calixarenes containing aminoacetal fragments on the upper molecule rim. Four oxazinyl rings formed with the retention of acetal groups as the formaldehyde amount was twofold increased.

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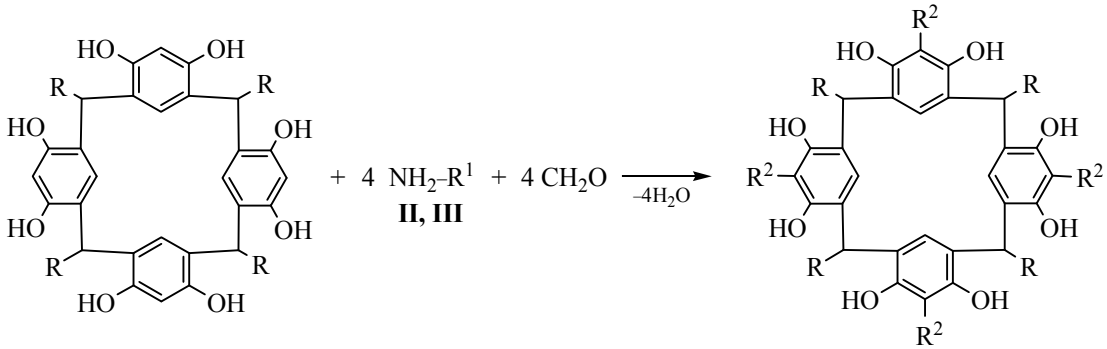
Recently researchers showed an increased interest in the calixarenes chemistry, for the latter were able to include and retain a wide range of organic molecules and ions due to their bowl-shaped form. In this connection the development of functionalization methods of calixarenes aiming to incorporate certain structural fragments into the molecule composition and to create on this matrix effective complexing agents, extractants etc. is an actual problem [1–3]. Calyx[4]-resorcinarenes containing aminoacetyl fragments in the *ortho*-position of aromatic rings relative to hydroxy groups are of undoubted interest as an initially sterically ordered matrix. The first representative of these compounds was obtained by Mannich reaction, when calyx[4]resorcinarene was reacted with formaldehyde and secondary amine [4]. Also Yohichi and Tahanao showed that the use of primary amines gave rise to the complex mixture of products. Recently aminomethylated derivatives of calix[4]resorcinarenes were successfully obtained with NH-groups on the upper molecule rim by involving *N*,*N*-dimethylethylenediamine into Mannich reaction [5]. In this work this approach was used for synthesis of calixarenes containing on the upper molecule rim structural fragments containing simultaneously acetal and secondary amino groups. Synthesis of the compounds containing aminoacetal fragments with the tertiary nitrogen atoms was reported earlier [6].

In Mannich reaction we used calyx[4]resorcinarenes **Ia–Ic**, aminoacetals **II** and **III** containing primary amino group, and formaldehyde in the molar

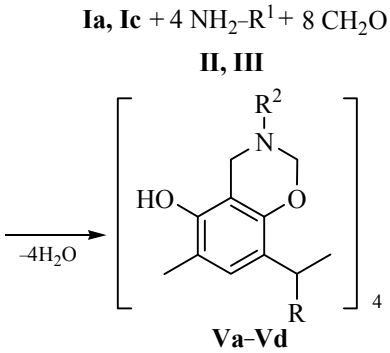


Ia–Ic **IVa–IVc**

I: R = Me (**a**), C_5H_{11} (**b**), C_7H_{15} (**c**); **II**: R^1 = $CH_2CH(OMe)_2$; **III**: R^1 = $(CH_2)_3CH(OEt)_2$; **IV**: R = Me, R^2 = $CH_2NHCH_2CHOMe)_2$ (**a**), R = C_5H_{11}, R^2 = $CH_2NHCH_2CH(OMe)_2$ (**b**), R = C_7H_{15}, R^2 = $CH_2NH(CH_2)_3CH(OEt)_2$ (**c**).

ratio 1:4:4 and 1:4:8. At the use of four equivalents of formaldehyde, the reaction products are calyx[4] resorcinarenes **IVa–IVc** containing acetal and secondary amino groups in the molecule.

Compounds **IVa–IVc** are pink powders soluble in chloroform, acetone, diethyl ether and insoluble in alcohols, DMSO, hexane, and water. Their structures were proved by the IR and ^{1}H NMR spectroscopy, the composition, by elemental analysis. In the IR spectra hydroxy and secondary amino groups are observed as a wide absorption band in the range of 3200–3300 cm^{-1}. When the twofold formaldehyde amount relative to the primary amine was used (the molar ratio of the starting materials 1:4:8), the formation of four oxazinyl fragments on the upper molecule rim occurs to give cavitands **Va–Vc**. It should be noted that the products **Va–Vc** can be obtained also in the two-stage reaction: at the initial use of the reagents ratio 1:4:4 to form calixarenes **IVa–IVc** followed by adding 4 more equivalents of formaldehyde.



V: R = Me, R^2 = $CH_2CH(OMe)_2$ (**a**); R = Me, R^2 = $(CH_2CH(OEt)_2$ (**b**); R = C_7H_{15}, R^2 = $CH_2CH(OMe)_2$ (**c**); R = C_7H_{15}, R^2 = $(CH_2)_3CH(OEt)_2$ (**d**).

Note that in the ^{1}H NMR spectra of compounds **Va–Vc** the doubling of signals is observed for aromatic protons, methyl (**Va**) and methylene protons **Vb**, **Vc** of acetal fragment that is probably due to the formation of intramolecular hydrogen bonds between hydroxy groups and oxygen atoms of acetal groups.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on an Avance 600 instrument at operating frequencies 600.13 and 150.90 MHz respectively relative to the residual protons of deuterated solvent (D_2O, CD_3OD). The IR spectra were registered on a UR-20 spectrometer in the range of 400–3600 cm^{-1} in mineral oil.

4,6,10,12,16,18,22,24-Tetrahydroxy-5,11,17,23-tetrakis[(2,2-dimethoxyethyl)aminomethyl]-2,8,14,20-tetramethylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (IVa). To a solution of 1.0 g of calixarene **Ia** in a mixture of 15 ml of benzene and 15 ml of ethanol were dropwise added 0.97 g of aminoacetal **II** and 0.75 g of 37% aqueous formaldehyde solution. The reaction mixture was kept for 1 day at 20°C. Then the solvent was removed in a vacuum of the water-jet pump. The precipitate was filtered off, washed with ethanol, and dried in a vacuum (30°C, 0.06 mm Hg) to the constant weight. Yield 1.58 g (49.4%), mp 120–125°C. IR spectrum, ν, cm^{-1}: 1075, 1140 (HC–O–CH_2), 1608 (CH_{Ar}), 2669 (NH···OH), 3236, 3299(OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.75 d (12H, CH_3, $^3J_{HH}$ 6.79 Hz), 2.77–2.78 m (8H, CH_2), 3.38 s (24H, OCH_3), 4.04 br.s (8H, CH_2Ar), 4.48 br.s (4H, CHO), 4.57 q (4H, CHMe, $^3J_{HH}$ 6.79 Hz), 7.28 s (4H, CH_{Ar}). Found, %: C 62.08; H 7.61; N 5.42. $C_{52}H_{76}N_4O_{16}$. Calculated, %: C 61.66; H 7.51; N 5.53.

4,6,10,12,16,18,22,24-Tetrakishydroxy-5,11,17,23-tetrakis[(2,2-dimethoxyethyl)aminomethyl]-2,8,14,20-tetrapentylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (IVc) was prepared similarly from 2.0 g of calixarene **IIb**, 1.08 g of aminoacetal **II**, and 1.24 g of 37% aqueous formaldehyde solution. Yield 56%, mp 119–124°C. IR spectrum, ν, cm^{-1}: 1075, 1140 (HC–O–CH_2), 1608 (CH_{Ar}), 2669 (NH···OH), 3231, 3297(OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm, Hz: 0.90 t (12H, CH_3CH_2, $^3J_{HH}$ 6.96 Hz), 1.32 m [24H, Me(CH_2)$_3$], 2.19 br.s (8H, CH_2CH_2CH), 2.76 m (8H, CH_2NHCH), 3.39 s (24H, CH_3O), 4.04 br.s (8H, $NHCH_2Ar$), 4.28 m (4H, CHO), 4.49 m (4H, CHAr), 7.04–7.13 br.s (4H, CH_{Ar}). Found, %: C 65.87; H 8.70; N 3.97. $C_{68}H_{108}N_4O_{16}$. Calculated, %: C 65.99; H 8.80; N 4.53.

4,6,10,12,16,18,22,24-Tetrahydroxy-5,11,17,23-tetrakis[(2,2-dimethoxybutyl)aminomethyl]-2,8,14,20-tetraheptylpentacyclo[19.3.1.1^{3,7}.1^{9,13}.1^{15,19}]octacosa-1(25),3,5,7(28),9,11,13(27),15,17,19(26),21,23-dodecaene (IVc) was prepared similarly from 3.0 g of calixarene **IIc**, 2.2 g of acetal **III**, and 1.24 g of 37% aqueous formaldehyde solution. Yield 93.1%, mp 119-123°C. IR spectra, ν, cm^{-1}: 1060, 1125 (HC–O–CH_2), 1608 (CH_{Ar}), 2669 (NH···OH), 3190, 3272 (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 t (12H, $CH_3CH_2CH_2$, $^3J_{HH}$ 6.96 Hz), 1.15–1.21 m (24H,

CH_3CH_2O), 1.29 m [40H, Me(CH_2)$_5$], 1.63 m [16H, OCH(CH_2)$_2$], 2.18 m (8H, ArCHCH_2), 2.67 m (8H, CH_2NH), 3.46 m (8H, CH_2O), 3.63 m (8H, CH_2O), 4.10 br.s (8H, CH_2Ar), 4.47–4.52 m (8H, CHO, CHAr), 7.06 br.s (4H, CH_{Ar}). Found, %: C 70.17; H 9.90; N 3.57. $C_{96}H_{156}N_4O_{16}$. Calculated, %: C 70.19; H 9.99; N 3.56.

2,12,22,32-Tetramethyl-4,14,24,34-tetrahydroxy-7,17,27,37-tetradimethoxyethyl-7,17,27,37-tetraaza-nonacyclo[31.7.1.1^{3,11}.1^{13,21}.1^{23,31}.1(41).3.5(10).11(44).13.-1^{23,31}.0^{5,10}.0^{15,20}.0^{25,35}.0^{35,40}]tetraconta[15(20),21(43),23,-25(30)31(42),33,35(41)]dodecaene (Va). To a solution of 1.27 g of calixarene **Ia** in a mixture of 10 ml of benzene and 10 ml of ethanol was dropwise added 1.19 g of aminoacetal **II** and 2.12 g of 37% aqueous formaldehyde solution under stirring. The reaction mixture was heated for 2 h at 70°C. Then the solvent was evaporated in a vacuum of the water-jet pump. The residue was reprecipitated from chloroform into hexane and dried in a vacuum (30°C, 0.06 mm Hg) to the constant weight. Yield 2.16 g (87.1%), mp 110–112ºC. IR spectrum, ν, cm^{-1}: 1075, 1128 (HC–O–CH_2), 1601, 1608 (CH_{Ar}), 3384 (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.75 d (12H, CH_3CH, $^3J_{HH}$ 6.97 Hz), 2.80 d. d, 2.86 d. d (8H, NCH_2CH, $^2J_{HH}$ 13.94, $^3J_{HH}$ 5.50 Hz), 3.33 s, 3.34 s (24H, CH_3O), 3.87 d, 4.01 d (8H, C_{Ar}, CH_2N, $^2J_{HH}$ 17.24 Hz), 4.48 q (4H, $CHCH_3$, $^3J_{HH}$ 6.97 Hz), 4.49 t (4H, CH_2CHO, $^3J_{HH}$ 5.50 Hz), 4.90 d, 4.95 d (8H, NCH_2O, $^2J_{HH}$ 9.54 Hz), 7.28 s (4H, CH_{Ar}), 7.74 s (4H, OH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 149.48 (C_{Ar}OH), 147.83 ($C_{Ar}OCH_2$), 125.29, 124.78 (C_{Ar}CH), 121.05 (CH_{Ar}), 108.62 ($C_{Ar}CH_2$), 103.60 (CHO), 84.09 (NCH_2O), 53.83 (CH_3O), 53.74 (NCH_2CH), 53.69 (CH_3O), 47.84 (NCH_2C_{Ar}), 27.19 ($CHCH_3$), 19.95 (CH_3CH). Found, %: C 63.82; H 7.06; N 4.84. $C_{56}H_{76}N_4O_{16}$. Calculated, %: C 63.38; H 7.22; N 5.28.

2,12,22,32-Tetramethyl-4,14,24,34-tetrahydroxy-7,17,27,37-tetradiethoxybutyl-7,17,27,37-tetraaza-nonacyclo[31.7.1.1^{3,11}.1^{13,21}.1^{23,31}.1(41).3.5(10).11(44).-13.1^{23,31}.0^{5,10}.0^{15,20}.0^{25,35}.0^{35,40}]tetraconta[15(20),21(43),-23,25(30),31(42),33,35(41)]dodecaene (Vb) was prepared similarly from 2.5 g of calixarene **Ia**, 3.70 g of acetal **III**, and 3.73 g of 37% aqueous formaldehyde solution. Yield 5.77 g (97.8%), mp 138–142°C. IR spectrum, ν, cm^{-1}: 1060, 1125 (HC–O–CH_2), 1599, 1613 (CH_{Ar}), 3352 (OH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.16–1.23 m (24H, CH_3CH_2), 1.60–1.64 m (16H, CH_2CH_2CH), 1.74 d (12H, CH_3CH, $^3J_{HH}$ 6.97 Hz), 2.62–2.70 m (8H, CH_2N), 3.46 m, 3.65 m (16H, CH_2O), 3.79 d, 3.92 d (8H, NCH_2Ar, $^2J_{HH}$ 17.24 Hz), 4.48–4.51 m (8H, CHAr, CHO), 4.87 d, 4.92 d (8H, NCH_2O, $^2J_{HH}$ 9.54 Hz), 7.24 s, 7.80 (4H, CH_{Ar}). Found, %: C 67.82; H 8.06; N 4.44. $C_{72}H_{108}N_4O_{16}$. Calculated, %: C 67.26; H 8.47; N 4.36.

2,12,22,32-Tetraheptyl-4,14,24,34-tetrahydroxy-7,17,27,37-tetradimethoxyethyl-7,17,27,37-tetra-azanonacyclo[31.3(7).1.1^{3,11}.1^{13,21}.1^{23,31}.1(41).3.5(10).-11(44).13.1^{23,31}.0^{5,10}.0^{15,20}.0^{25,30}.0^{35,40}]tetraconta[15(20),-21(43),23,25(30),31(42),33,35(41)]dodecaene (Vc) was obtained similarly from 4.0 g of calixarene **Ic,** 2.39 g of aminoacetal **II**, and 4.26 g of 37% aqueous formaldehyde solution. Yield 6.0 g (94.4%), mp 99–104°C. IR spectrum, ν, cm^{-1}: 1076, 1128 (HC–O–CH_2) 1607 (CH_{Ar}), 3183, 3313 (OH). ^{1}H NMR spectroscopy ($CDCl_3$), δ, ppm: 0.89 m (12H, CH_3CH_2), 1.28 m [40H, $(CH_2)_5$], 2.19 br.s (8H, CH_2CHC_{Ar}), 2.81 m (8H, NCH_2CH), 3.34–3.41 br.s (24H, CH_3O), 4.03 br.s (8H, NCH_2C_{Ar}), 4.32-4.51 m (8H, CHO, CHC_{Ar}), 4.80–4.93 m (8H, NCH_2O), 7.02–7.13 br.s (CH_{Ar}). Found, %: C 68.24; H 9.08; N 3.98. $C_{80}H_{124}N_4O_{16}$. Calculated, %: C 68.74; H 8.94; N 4.01.

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