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Synthesis of tetrathiacalix[4]arene functionalised by acetylhydrazone fragments

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The reactions of tetrathiacalix[4]arene functionalised by acetylhydrazide groups with an excess of 4-nitrobenzaldehyde or tetrathiacalix[4]arene functionalised by chlorocarbonylmethoxy groups with an excess of 4-nitrobenzaldehyde hydrazone lead to the preferable formation of tetrathiacalix[4]arene with an additional *N*,*N*′-diacetylhydrazine bridge, but in the case of pyridine-2-carboxaldehyde, only to the formation of tetrathiacalix[4]arene functionalised by four acetylhydrazone fragments.

Recently,[1] we have reported the synthesis of a number of calix[4]-arenes (calix[4]phenols, calix[4]resorcinols and calix[4]pyrogallols) functionalised by acetylhydrazide groups. On the basis of them, new nitrogen-containing calix[4]arenes can be prepared. It is known that acetylhydrazones can be obtained by the interaction of carboxylic acid hydrazides with aldehydes. Compounds with such functional groups possess high complexability properties,[2,3] which can be controlled by varying substituents in the ylidene fragment during the synthesis procedure. Moreover, acetylhydrazones and their complexes can exhibit biological activity[2] and serve as key reagents in the synthesis of heterocyclic compounds.[4] The introduction of these functional groups into calixarene molecules could promote the preparing of effective and highly selective complexones due to the macrocyclic cooperative effect,[5] as it was observed for calix[4]phenols modified by acetylhydrazide fragments.[1] However, in spite of great interest to the chemistry of calixarenes,[6,7] there is no information concerning acetylhydrazone derivatives on their basis. In this connection, we have investigated the preparation of tetrathiacalix[4]phenols bearing acetylhydrazone groups.

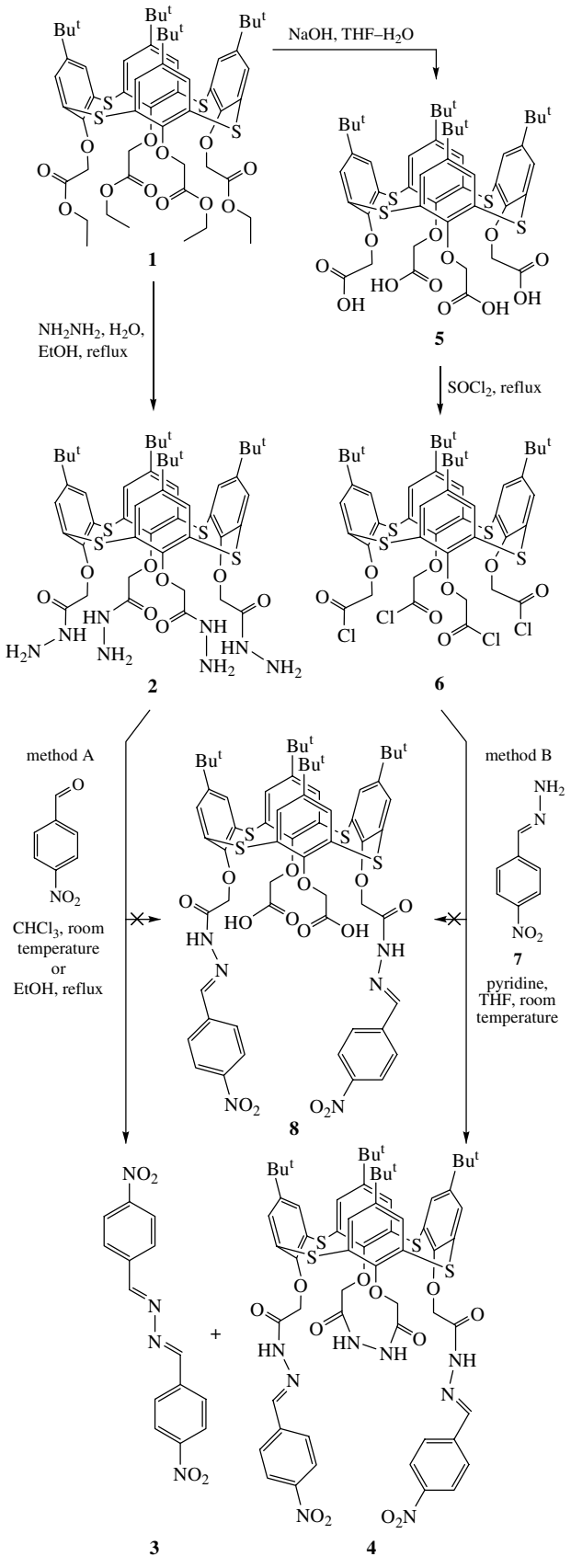
For this purpose, the following two methods can be used (Scheme 1). By the reaction of tetraester **1** with hydrazine hydrate, tetrahydrazide **2** can be obtained. It would be expected that the condensation of compound **2** with aldehyde would result in the conversion of acetylhydrazide groups to acetylhydrazone ones (method A). As the alternative approach, tetracarboxylic acid **5**, then the acid chloride **6** and the corresponding hydrazone could be synthesised from ester **1** (method B).

During the reaction of calix[4]arene **2** with 4-nitrobenzaldehyde at room temperature in $CHCl_3$ or at refluxing in ethanol (method A, Scheme 1) and at the reaction of calix[4]arene **6** with 4-nitrobenzaldehyde hydrazone **7** (method B, Scheme 1), precipitate formation was observed. We found that the azine of 4-nitrobenzaldehyde **3** was a by-product of these reactions, which was described previously.[8] In both of the methods of synthesis, the same composition precipitates have been isolated after removing solvent from filtrate and repeated dissolution in ethyl acetate. The most intense signal (*m*/*z* 1245 $[M + H]^+$) in the MALDI-TOF† mass spectra of reaction mixtures was assigned to this isolated product. It was proposed that this molecular peak in spectra corresponds to calix[4]arene **8** bearing two 4-nitrobenzaldehyde acetylhydrazone and two carboxymethyl fragments (M = 1246). In the method A, its formation could be caused by the hydrolysis of hydrazide groups in tetrathiacalixarene **2**. If we use synthetic method B, the hydrolysis of unreacted chloranhydride groups could also take place. The ^1H and ^{13}C NMR spectra are consistent with the structure proposed for the isolated compound.

However, according to pH-potentiometry measurements, the isolated product exhibits the properties of weak acids ($pK_a > 10$) in comparison with acid properties for the derivatives of carboxylic acids ($pK_a \sim 5$–6).[9] Moreover, the elemental analysis data show a higher content of nitrogen (9.03%) compared with calculated (6.74%) for calix[4]arene having two 4-nitrobenzaldehyde acetylhydrazone and two carboxymethyl fragments. Furthermore, no wide complicated Fermi resonance bands below 3000 cm^{-1}, usually detected in carbonyl compounds,[10] and absorption bands of free vibrations ν_{OH} at ~3500 cm^{-1} are observed in the IR spectra of dilute $CHCl_3$ solutions. The analysis of other ranges of spectra, where acid groups become apparent, particularly ν_{C-O}, does not confirm their presence.

In this connection for an unambiguous identification of the synthesised compound structure, we used a combination of 2D NMR spectroscopy methods [HSQC (^{13}C and ^{15}N) and HMBC (^{13}C and ^{15}N)]. From the detailed investigation, it was established that the isolated product corresponds to calix[4]arene **4**, where two opposite phenoxy fragments are additionally connected by an *N*,*N*′-diacetylhydrazine bridge. If the bridge was formed between two neighbouring phenoxy groups, the symmetry of aromatic rings would be disturbed, which would lead to their

† Mass spectra were detected on a Finnigan MALDI-TOF Dynamo mass spectrometer. NMR spectra were recorded on Bruker Avance-600 (^1H, 600 MHz; ^{13}C, 150.9 MHz; ^{15}N, 60.81 MHz) spectrometers. Chemical shifts were reported relative to solvent signals as an internal standard ($CDCl_3$, δ_H 7.27 ppm, δ_C 77.7 ppm; DMSO, δ_H 2.5 ppm, δ_C 39.5 ppm). The IR spectrum was recorded on a Bruker Vector instrument in Nujol.



Scheme 1

magnetic non-equivalence and as a result to the splitting of aromatic proton signals in ^{1}H NMR spectra with the coupling constants ^4J ~ 1–3 Hz.[11] Such a phenomenon has not been observed. The *N*,*N*′-diacetylhydrazine bridge formation has been proved by the presence of cross peaks between nitrogen (122 ppm) and NH group protons (~9.5 ppm) in HSQC (^{15}N) spectra and with oxymethyl protons (4.86 and 5.0 ppm) in HMBC (^{15}N) spectra. According to published data,[12] the nitrogen and carbon chemical shifts are typical of the *N*,*N*′-diacetylhydrazine fragment. The intensity of proton signals of the *N*,*N*′-diacetylhydrazine fragment is the same in the solutions with different polarity ($CDCl_3$, DMSO) and in the wide concentration range. This indicates that one of the amide fragments in the *N*,*N*′-diacetylhydrazine bridge has a *trans* conformation, but another one shows a *cis* conformation.[13] No considerable changes in the $\nu_{C=O}$ (~1705 cm^{-1}) absorption band frequencies were observed in IR spectra in $CHCl_3$ solutions under dilution. This is typical of *N*,*N*′-diacetylhydrazine bridge containing compounds.[14] The presence of conformers about C(O)–N bond in *N*,*N*′-diacetylhydrazine bridge, binding one pair of aromatic rings, as well as in acetylhydrazone fragments, attached to another two aromatic rings, leads to the appearance of four signals for *tert*-butyl group protons and a number of signals for protons of aromatic and amide fragments in NMR spectra.

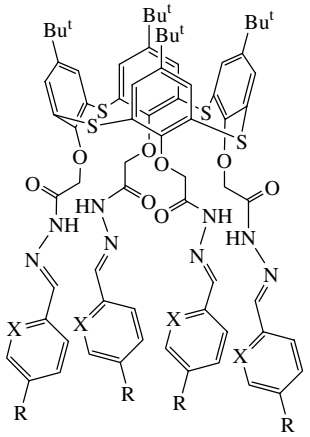
Calix[4]arene **4** can form as a result of an intramolecular reaction.‡ Probably, the bonding of an aldehyde molecule (method A) is accompanied by a nucleophilic attack of the hydrazide group terminal nitrogen atom in calix[4]arene toward the carbonyl group of neighbouring oppositely disposed hydrazide or acetylhydrazone fragments, which leads to the formation of intramolecular cross-links. The following reaction of hydrazine or 4-nitrobenzaldehyde hydrazone with an excess of aldehyde results in azine **3** formation, which precipitates during the process.

It is known that hydrazones are highly reactive compounds, and under heating, moisture or catalyst effect they are capable to change into azines with the liberation of hydrazine or into the products of resinification.[15,16] Indeed, the reaction of 4-nitrobenzaldehyde hydrazone with calix[4]arene **6** (method B) is accompanied by azine **3** formation. The interaction of hydrazine,

‡ *Synthesis of 5,11,17,23-tetra*-tert-*butyl-25,27-bis[(4-nitrobenzylidene)-hydrazinocarbonylmethyloxy]-26,28-[*N,N′-*hydrazinylene-bis(carbonyl-methyleneoxy)]-2,8,14,20-tetrathiacalix[4]arene* **4**.

Method A. A solution of 4-nitrobenzaldehyde (1.64 mmol) in $CHCl_3$ (10 ml) was added dropwise to a solution of tetrahydrazide **2** (0.4 mmol) in $CHCl_3$ (50 ml). The reaction mixture was stirred at room temperature for 20 h. (Similar procedure was carried out in EtOH at the reflux for 5 h). The precipitate of **3** (mp 310 °C) was filtered off. After removing the solvent from the filtrate under a reduced pressure, ethyl acetate (20 ml) was added to the residue, and the mixture was heated. After cooling, the precipitate was filtered off, washed several times with ethyl acetate and recrystallised from EtOH–DMF. Yield 26%, mp 242–246 °C. ^{1}H NMR (600 MHz, [$^2H_6$]DMSO, 30 °C) δ: 0.75 and 0.85 (s, 18H, Bu^t), 1.31 and 1.32 (s, 18H, Bu^t), 4.7–5.3 (m, 8H, OCH_2), 6.8–7.0 (m, 4H, ArH), 7.8–8.4 (m, 12H, ArH), 9.3–9.9 (m, 2H, NHNH), 11.68 and 11.78 [2s, 2H, NHC(O)]. ^{13}C NMR (150.9 MHz, [$^2H_6$]DMSO, 30 °C) δ: 30.81, 30.85, 31.45 and 31.48 (Me), 34.09, 34.19, 34.61 and 34.77 (CMe_3), 71.68, 73.13, 74.56 and 77.20 (OCH_2), 128.39, 128.59, 157.86 and 157.95 [C(2) in 4-Bu^t-Ar], 132.29, 132.48, 132.95, 136.76, 136.96 and 137.23 [C(3) in 4-Bu^t-Ar], 146.89, 147.27, 147.48 and 148.26 [C(4) in 4-Bu^t-Ar], 156.62, 156.27, 161.62 and 161.50 [C(1) in 4-Bu^t-Ar], 164.77, 166.25, 166.42, 169.66 and 171.55 (C=O). ^{15}N NMR (60.81 MHz, [$^2H_6$]DMSO, 30 °C) δ: 121 and 122 (NHNH), 169 and 175 [NHC(O)], 321 and 322 (N=C), 366 (NO_2). IR (ν/cm^{-1}): 3326, 3271, 3200 (ν_{NH}), 1707, 1680 ($\nu_{C=O}$), ~1650 (sh, $\nu_{C=N}$), ~1550 (sh, $\delta_{NH\ (trans)}$), 1520 ($\nu_{as\ NO_2}$), 1342 ($\nu_{s\ NO_2}$), 1273, 1250 ($\nu_{as\ COC}$), 1094 ($\nu_{s\ COC}$), 835 ($\gamma_{=CH}$). MS (MALDI-TOF), *m*/*z*: 1245 [M + H]$^+$, 1269 [M + Na]$^+$, 1284 [M + K]$^+$. Found (%): C, 59.53; H, 5.72; N, 9.03; S, 10.02. Calc. for $C_{62}H_{66}N_8O_{12}S_4$ (%): C, 59.88; H, 5.35; N, 9.01; S, 10.31.

Method B. A solution of 4-nitrobenzaldehyde hydrazone **7** (5 mmol) in THF (25 ml) was added dropwise to a solution of calix[4]arene **6** (1.2 mmol) and pyridine (6 mmol) in THF (40 ml). The reaction mixture was stirred at room temperature for 2 h. The precipitate of **3** was filtered off. After removing the solvent from the filtrate under a reduced pressure, $CHCl_3$ was added to the residue, and the mixture was washed several times with water. The organic layer was dried with $MgSO_4$. After removing the solvent from the filtrate under a reduced pressure, 30 ml of ethyl acetate was added to the residue, and the mixture was heated. After cooling, the precipitate was filtered off, washed several times with ethyl acetate and recrystallised from EtOH–DMF. Yield 32%, mp 242–245 °C. Found (%): C, 60.64; H, 5.54; N, 9.15, S, 10.10. Calc. for $C_{62}H_{66}N_8O_{12}S_4$ (%): C, 59.88; H, 5.35; N, 9.01; S, 10.31. The IR and NMR spectra of compound **4** obtained by methods A and B are identical.



9 X = C, R = NO_2
10 X = N, R = H

released during the process, with two oppositely located C(O)Cl groups of calix[4]arene **6** leads to the intramolecular *N*,*N*′-diacetylhydrazide bridge formation.

The low-intensity molecular peak (*m*/*z* 1541 $[M + H]^+$) was found in the MALDI-TOF mass spectra of the reaction mixture (method B), which can be explained by the presence of calix[4]arene **9** (*M* = 1540). We failed to isolate **9** as an individual product.

The test reaction with benzaldehyde (method A) in $CHCl_3$ showed that the most intense peak in MALDI-TOF mass spectra corresponds to a product similar to **4**. At the same time, the use of pyridine-2-carboxaldehyde as a reagent leads to the disappearance of the molecular peak corresponding to the compound similar to **4** from the MALDI-TOF spectra of the reaction mixture. Instead of it, the desired product (tetrahydrazone **10**) was isolated in a quantitative yield.§ It is known that nitrogen in the pyridine ring is one of the strongest proton acceptors.[10] Obviously, the formation of an intramolecular hydrogen bond between nitrogen of pyridine ring and the NH group of the neighbouring acetylhydrazone fragment or with the NH group of the fragment in $Z_{C=N}$ isomer prevents from breakage of amide bond and facilitates the formation of tetrathiacalix[4]arene **10** bearing four acetylhydrazone groups.

Thus, the formation of the acetylhydrazone derivatives of tetrathiacalix[4]arene has been studied. In particular, the unusual formation of an *N*,*N*′-diacetylhydrazine bridge in the calixarene structure has been discovered. The synthesis of similar calix(aza)-crown compounds is of interest in the context of obtaining high selectivity complexones.[17]

§ *Synthesis of 5,11,17,23-tetra*-tert-*butyl-25,26,27,28-tetrakis[(2-pyridinylidene)hydrazinocarbonylmethyloxy]-2,8,14,20-tetrathiacalix[4]arene* **10**. A solution of pyridine-2-carboxaldehyde (1.64 mmol) in ethanol (10 ml) was added dropwise to a solution of tetrahydrazide **2** (0.4 mmol) in ethanol (10 ml). The reaction mixture was stirred at room temperature for 1 h and then refluxed for 5 h. After removing the solvent, hexane (20 ml) was added to the residue, and the mixture was heated. After cooling, the precipitate was filtered off, washed several times with hexane and recrystallised from MeOH. Yield 80%, mp 190–195 °C. ^{1}H NMR (600 MHz, [$^2H_6$]DMSO, 30 °C) δ: 1.12 (s, 36H, Bu^t), 5.37 (s, 8H, OCH_2), 7.14 [s, 4H, C(3) in 4-Bu^t-Ar], 7.28 [s, 4H, C(4) in 2-Py], 7.68 [s, 4H, C(5) in 2-Py], 7.81 [s, 4H, C(6) in 2-Py], 8.36 (s, 4H, N=C–H), 8.52 [s, 4H, C(3) in 2-Py], 11.3 (s, 4H, NH). ^{13}C NMR (150.9 MHz, [$^2H_6$]DMSO, 90 °C) δ: 30.12 (Me), 33.11 (CMe), 71.99 (OCH_2), 119.40 [C(6) in 2-Py], 123.18 [C(4) in 2-Py], 127.84 [C(2) in 4-Bu^t-Ar], 133.66 [C(3) in 4-Bu^t-Ar], 135.57 [C(5) in 2-Py], 145.87 [C(4) in 4-Bu^t-Ar], 148.49 [C(3) in 2-Py], 152.64 [C(1) in 2-Py], 157.34 [C(1) in 4-Bu^t-Ar], 168.66 (C=O). IR (ν/cm^{-1}): 3232 (ν_{NH}), 3069 ($\nu_{=CH}$), 2961–2870 (ν_{Me}, ν_{CH_2}), 1690 ($\nu_{C=O}$), ~1650 (sh, $\nu_{C=N}$), 1614, 1586, ~1450 (ν_{Ph}), ~1557, 1540 ($\delta_{NH_{trans}}$), 1362, 1349 (σ_{Me}), 1266, 1243 ($\nu_{as\ COC}$), 1095 ($\nu_{s\ COC}$), 749 ($\gamma_{=CH}$). MS (MALDI-TOF), *m*/*z*: 1390 $[M + Na]^+$, 1412 $[M + 2Na]^+$, 1430 $[M + Na + K]^+$. Found (%): C, 63.57; H, 5.86; N, 11.60; S, 9.78. Calc. for $C_{72}H_{76}N_{12}O_8S_4$ (%): C, 63.32; C, 5.61; N, 12.31; S, 9.39.

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