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Selective Mono-O-acylation of C_{2V}-Symmetrical Calix[4]arenediols with Acylisocyanates

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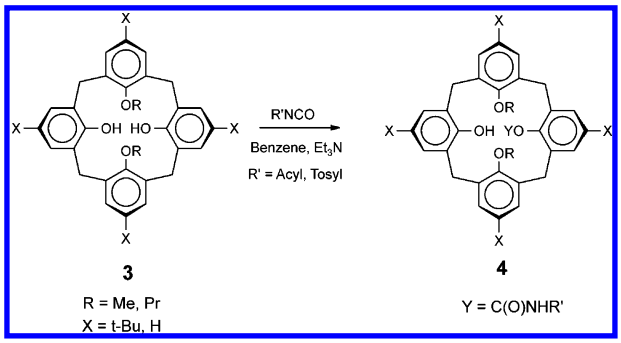
ABSTRACT



Calix[4]arenedialkyl ethers 3 react with an excess of acylisocyanates to give selectively monoacylated products 4. Intramolecular hydrogen bonds and steric effects of the acylcarbamate fragments are most likely responsible for the high selectivity of this monoprotection.

Calixarenes[1] are versatile building blocks for the construction of functional supramolecular systems through conventional and noncovalent synthesis. Partial protection−deprotection synthetic procedures have been developed in order to attach different functional groups (or binding sites) to the calixarene framework. For example, carefully controlled acylation of tetraaminocalix[4]arene tetrapentyl ether with BOC anhydride afforded mono-, 1,2-di-, and tri-BOC-protected calixarenes in preparative yields.[2] Subsequent acylation−deprotection procedures gave a wealth of calix[4]arenes bearing two different kinds of functional groups at the wide rim. The molecules containing hydrogen bonding fragments (amides, ureas) were shown to form self-assembling tetramers and dimeric molecular capsules.[3] One amine group of a 1,3-diaminocalix[4]arene tetraether was protected by BOC anhydride[4] in 67% yield. The resulting aminocalixarene was used for the construction of nanosized molecular assemblies. Selective protection of four hydroxyls of resorcinol-based calixarenes by aroyl, CbZ, and BOC groups provided a general method for the synthesis of C_{2V}-symmetrical derivatives.[5] Some of these compounds form highly stable dimeric capsules in the presence of complementary guests.[6]

It is known that acylisocyanates readily react with phenols to produce acylcarbamates,[7] which can be easily cleaved

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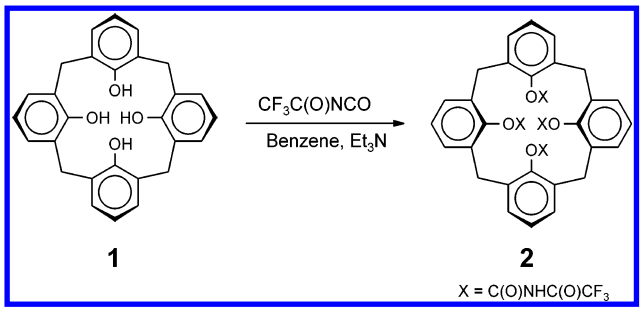
under mild conditions. Therefore we decided to use acylisocyanates as protecting agents for the hydroxy groups of hydroxycalix[4]arene. Herein we report on the unexpected selective monoprotection of the 1,3-dialkyl ethers of calix[4]arene with acylisocyanates.

The reaction of calix[4]arene **1** with 4 equiv of trifluoroacetylisocyanate[8] in benzene, in the presence of a catalytic amount of Et_3N, afforded tetracarbamate **2** in 55% yield (Scheme 1).[9]

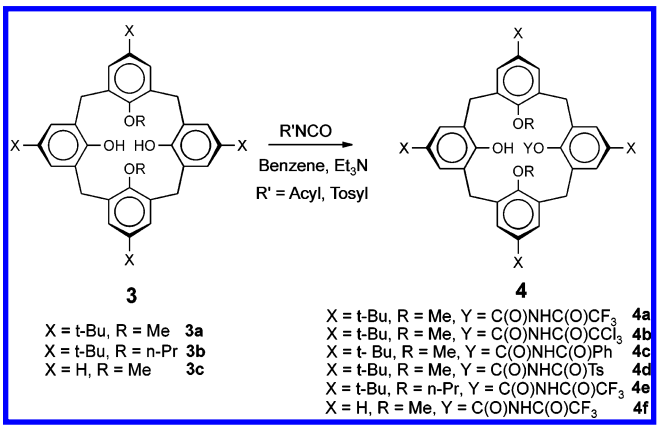
Scheme 1



The ^{1}H NMR spectrum of this product contains one singlet for the methylene protons of the bridges (δ = 3.67 ppm) and one set of signals for the aromatic protons. This pattern corresponds to the 1,3-alternate conformation of the calixarene skeleton that has no intramolecular cavity. Accordingly, the ^{13}C NMR signal for the carbons of the methylene bridges appears at 36.96 ppm, which is characteristic of an anti orientation of adjacent phenolic rings in a 1,3-alternate conformation.[10] The IR spectrum of **2** contains two broadened bands at 3380 and 1816 cm^{-1} corresponding to N−H and C═O bonds, respectively. These bands do not shift upon dilution, apparently as a result of the formation of intramolecular N−H···O═C hydrogen bonds.

Surprisingly, the reaction of C_{2v}-symmetrical calix[4]arenediols **3a**−**c** with a 2-fold excess of the acylisocyanate in benzene or dichloromethane, in the presence of catalytic amounts of Et_3N, resulted in the selective acylation of one hydroxy group (Scheme 2). Complete acylation did not occur

Scheme 2



even at elevated temperature and in the presence of a large excess of the acylating agent. Calix[4]areneacylcarbamates **4** were obtained in 44−75% yields by simple crystallizations.[11] Interestingly, the reaction of C_s-symmetrical dipropyl ether of calix[4]arene **3d** (Figure 2) with 2 equiv of acylisocyanates led to the complete acylation of the hydroxy groups. The ^{1}H NMR spectrum revealed that the mixture of cone and partial cone conformers of calixdiacylcarbamates

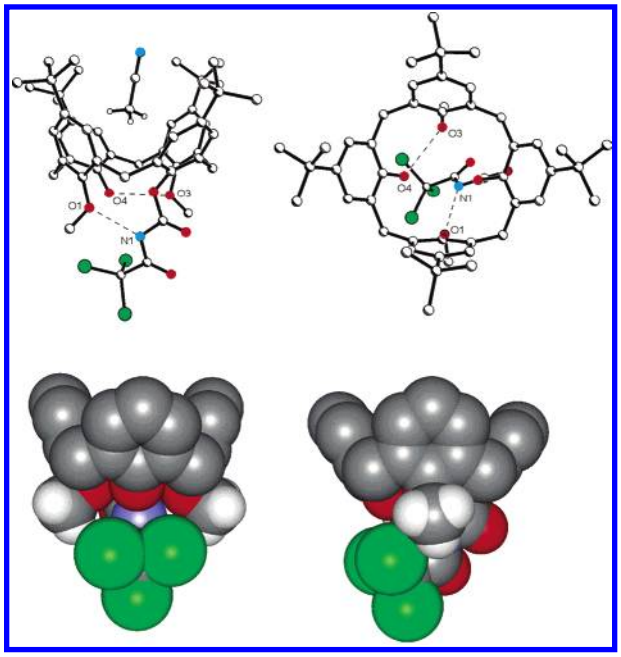


Figure 1. Single-crystal X-ray structure of **4b**. (Top) Side and top view in ball-and-stick presentation. Hydrogen bonds are shown as dashed lines. Only hydrogen atoms of the acetonitrile molecule are shown for the sake of clarity. (Bottom) Side views in the space filling presentation. *tert*-Butyl groups, some hydrogen atoms, and the included acetonitrile molecule are not shown.

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(9) **Calix[4]arenetetracarbamate 2.** A solution of trifluoroacetyl isocyanate (0.83 g, 5.94 mmol) in dry benzene (3 mL) was added to a solution of 0.57 g (1.35 mmol) of calix[4]arene **1** in dry benzene (5 mL). The reaction mixture was stirred at room temperature for 1 h. Then a drop of triethylamine was added, and the reaction mixture was stirred for an additional 5 h. After 24 h the solvent and excess isocyanate were removed under reduced pressure. The crude residue was crystallized from acetone, yielding 55% of **2** as colorless crystals, mp (complex with acetone) 182−186 °C (decomp). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 2.08 (s, 12H, acetone), 3.67 (s, 8H), 6.84 (t, J = 7.6 Hz, 4H), 7.14 (d, J = 7.6 Hz, 8H), 10.47 (s, 4H). ^{19}F NMR (CH_2Cl_2) δ ppm: −74.4. ^{13}C NMR (acetone-d_6) δ ppm: 36.96, 115.74 (q, J_{CF} = 284.8 Hz), 127.63 (Ar, C.-H, meta), 130.11, 134.55 (Ar), 148.03, 148.31, 154.82 (q, J = 40.3 Hz). IR (CH_2Cl_2) cm^{-1}: 1760 (CF_3C═O), 1785 (C═O), 1816 (O−C═O), 3380 (ass. NH). Anal. Calcd for $C_{40}H_{24}F_{12}N_4O_{12}$·2 acetone: C 50.28, H 3.49, N 5.10. Found: C 50.44, H 3.40, N 5.30.

(10) Margans, J. O.; de Mendoza, J.; Pons, M.; Prados, P. *J. Org. Chem.* **1997**, *62*, 4518.

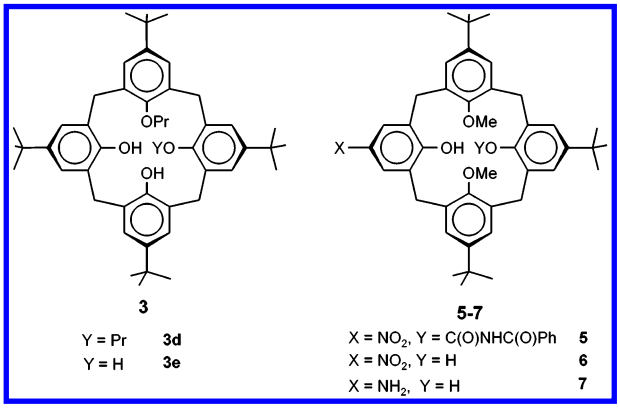

Figure 2. Line formulas of compounds **3** and **5**−**7**.

was formed. In the case of calixarene monopropyl ether **3e** the acylation with 5-fold excess of acylisocyanates resulted in a complicated mixture of partially acylated products. Thus the arrangement of groups at the narrow rim is somehow responsible for the selective monoacylation of **3a**−**c** with acylisocyanates. To identify the reason for the low reactivity of the OH group in monoacylcarbamates **4**, single-crystal X-ray analysis was carried out.

Diffraction quality crystals of trichloroacetylcarbamate **4b** were grown from acetonitrile.[12,13] The molecule of **4b** adopts a slightly distorted cone conformation whose cavity is filled with one acetonitrile molecule (Figure 1). The dihedral angles between the aromatic rings and the main plane of calixarene (the plane defined by the four bridging carbon atoms) are 74.2°, 54.0°, 67.2°, and 47.5°. The distances between the methyl group of the included acetonitrile and the centers of the calixarene aromatic rings (3.5−3.6 Å) clearly indicate some C−H···π interactions. The trichloroacetylcarbamate fragment forms an intramolecular hydrogen bond with the methoxy group (N1−O1 distance is 2.8 Å). The hydroxyl is hydrogen bonded to one of the methoxy groups (O4−O3 = 2.8 Å), while the short distance to the other methoxy fragment is 3.16 Å. Molecule **4b** is chiral as a result of the orientation of the hydrogen bonding groups at the narrow rim. As shown in Figure 1 (bottom) the hydroxy group of **4b** is nearly completely shielded by the two methoxy groups and the trichloroacetylcarbamate residue.

The ^{1}H NMR spectra of compounds **4** in $CDCl_3$ contain doublets for the methylene protons of the bridges (J = 13.2−13.7 Hz), which indicates the calixarene skeleton exists in a cone conformation. The pattern of aromatic protons reflects the C_s-symmetry of the structure with a symmetry plane passing through the unsubstituted and acylated phenolic rings. The NH and OH protons emerge as somewhat broadened singlets at 9.93−10.94 and 7.49−6.85 ppm, respectively. They do not shift considerably upon dilution, suggesting that the NH and OH hydrogens are involved in intramolecular hydrogen bonds in solution as well. Accordingly, the corresponding IR bands also showed no concentration dependence.

Molecular mechanics calculations have been performed on the basis of the crystallographic coordinates of **4b**.[14] The conformation of the calixarene and the hydrogen bonding pattern do not change considerably during the optimization procedure. Variations in the orientation of the acylcarbamate fragment resulted in a sharp increase of the energy and, in some cases, led to unrealistic distortions of the aromatic rings. These results in combination with the NMR studies suggest that the crystal structure of **4b** can be considered as a realistic snapshot of the structure in solution. Fast interconversion between the two C_1-symmetrical enantiomeric arrangements may explain the average C_s-symmetrical NMR patterns of compounds **4**. The hydroxyl of the optimized structure is completely shielded by the acylcarbamate fragment and two methoxy groups (as in the crystal structure). The low reactivity of compounds **4** and the high selectivity of the monoprotection of calixdiols **3a**−**c** with acylisocyanates are, most probably, caused by this steric effect.

The *ipso*-nitration[15] of **4c** with 75% HNO_3 in CH_2Cl_2/AcOH occurs in the most reactive phenolic ring to afford mononitrocalixarene **5** in 63% yield (Figure 2).[16] The benzoycarbamate group was readily cleaved by KOH in aqueous methanol to give mononitro calixarene **6** in 68% yield.[17] Catalytic hydrogenation of **6** (H_2, Raney-Ni) afforded aminocalixarene **7** in 83% yield.[18] Standard bromination (NBS, acetone)[19] of **4f** resulted in a selective monobromination of the unsubstituted phenol ring.[20]

(11) **Trichloroacetylcarbamate (4b).** A solution of trifluoroacetyl, trichloroacetyl, or benzoyl isocyanate (1.6 mmol) in dry benzene (3 mL) was added to a benzene solution containing calix[4]arene **3a** (0.74 mmol) and one drop of Et_3N. The reaction mixture was stirred for 8 h at room temperature (288 K). After 24 h the reaction mixture was evaporated in vacuo. The residue was crystallized from a benzene−hexane mixture, yielding 67% of **4b** as colorless crystals, mp 263−265 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm.: 0.83 (s, 18H), 1.34 (s, 9H), 1.37 (s, 9H), 3.33 (d, J = 13.4 Hz, 2H), 3.34 (d, J = 13.4 Hz, 2H), 3.80 (s, 6H), 4.18 (d, J = 13.4 Hz, 4H), 6.60 (br s, 4H), 6.95 (s, 1H), 7.12 (br s, 2H). 7.24 (br s, 2H), 10.58 (s, 1H). IR (CCl_4) cm^{-1}: 1733 (CCl_3C═O), 1809 (O−C═O), 3425 (NH), 3310 (ass. OH). Anal. Calcd for $C_{49}H_{60}Cl_3NO_6$: C 68.01 H 6.99, N 1.62. Found: C 68.13, H 6.80, N 1.80.

(12) **Crystal data for compound 4b·2MeCN:** monoclinic, $P21/n$, a = 12.750(3) Å, b = 12.540(2) Å, c = 33.750(7) Å, β = 99.36(3)°, V (Å^3) = 5324(2), Z = 4, D_x (mg cm^{-3}) = 1.168, $2\theta_{max}$ = 52.62°, R1 = 0.0835, wR2 = 0.2157 (for 7136 reflns $F > 4\sigma(F)$), R1 = 0.1335, wR2 = 0.2841 (for 10567 independent reflns), 635 parameters, S = 1.036, $\Delta\rho$(min/max) = −0.82/0.59 e Å^{-3}

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(14) MMX force field was used as implemented in the PC Model program PCMODEL for Windows V. 7.50.00, 2000, Serena Software.

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(16) **Mononitrocalix[4]arenebenzoylcarbamate 5.** Nitric acid (3 mL, 75%) was added dropwise at 0 °C to a solution, containing methylene chloride (15 mL), glacial acetic acid (15 mL), and calix[4]arene **4c** (1 g, 1.21 mmol). The reaction mixture was stirred at room temperature for 2 h and quenched with water (15 mL). The water layer was separated and washed with dichloromethane (2 × 5 mL). The combined organic solution was washed with water again and dried over Na_2SO_4. The solvent was removed, and the crude residue was dissolved in dichloromethane and precipitated with methanol, yielding 63% of **5** as pale yellow crystals: mp 229−231 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.84 (s, 18H), 1.36 (s, 9H,), 3.37 (d, J = 13.3 Hz, 2H), 3.52 (d, J = 13.7 Hz, 2H), 3.74 (s, 6H), 4.26 (d, J = 13.3 Hz, 2H), 4.27 (d, J = 13.7 Hz, 2H), 6.58 (d, J = 2.2 Hz. 2H), 6.71 (d, J = 2.2 Hz, 2H), 7.26 (s, 2H), 7.60 (m, 3H), 8.13 (s, 2H), 8.40 (d, 2H), 8.68 (s, 1H), 10.59 (s, 1H). Anal. Calcd for $C_{50}H_{56}N_2O_8$: C 73.87, H 6.94. Found: C 74.02, H 6.83.

In conclusion, acylisocyanates are efficient agents for selective protection of one hydroxyl group in calixarenediols **3a**−**c**. It seems that this selectivity is caused by a low reactivity of the hydroxyl group in the monocarbamate **4**, which is in turn the result of intramolecular hydrogen bonds[21] and steric effects.

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(17) **Mononitrocalix[4]arene 6.** A water solution of KOH (0.4 mL, 0.772 mmol of KOH) was added to a solution of calix[4]arene **5** (0.2 g, 0.234 mmol) in methanol (5 mL). The reaction mixture was refluxed for 12 h. The reaction mixture was diluted with water (2 mL) and acidified with concentrated sulfuric acid until the yellow color of the suspension disappeared. The precipitate was filtered off, washed with water (3 × 25 mL) and dried: yield 68%, mp 273−275 °C (decomp), white solid. ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 0.98 (s, 18H,), 1.29 (s, 9H), 3.37 (d, J = 13.4 Hz, 2H), 3.47 (d, J = 13.4 Hz, 2H), 3.78 (s, 6H), 4.28 (d, J = 13.4 Hz, 4H), 6.78 and 6.90 (two m, 2H each), 7.08 (s, 2H), 7.40 (s, 1H), 8.06 (s, 2H), 8.84 (s, 1H). Anal Calcd for $C_{42}H_{51}NO_6$: C 75.76, H 7.72 N 2.10. Found: C 73.10, H 7.46, N 2.19.

Supporting Information Available: Characterization details for compounds **4a**,**c**−**f** and details of crystal structure solution and refinement in cif format. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) **Monoaminocalixarene 7.** To a suspension of mononitrocalix[4]-arene **6** (31.4 mg, 0.0472 mmol) in 5 mL of ethanol (96%) was added 0.5 mL of hydrazine hydrate. The mixture was heated to 35 °C, and Raney-Ni catalyst, as water suspension, (0.2 mL) was added dropwise. An immediate release of gas was observed. After the essential part of the gas had dissipated the reaction mixture was refluxed for 30 min. The solid disappeared, and the solution became colorless. The catalyst was filtered off. The water−ethanol solution was evaporated in a vacuum. The residue was washed with water and filtered off. After drying in a vacuum calixarene **7** was obtained as pale-pink solid: yield 83%, mp 154−156 °C. ^{1}H NMR ($CDCl_3$) δ ppm.: 1.00 (s, 18H), 1.28 (s, 9H), 3.24 (d, 2H, J = 13.0 Hz), 3.34 (d, 2H, J =13.0 Hz), 3.94 (s, 6H), 4.26 and 4.30 (2d, 4H, J =13.0 Hz each), 6.48 (bs, 2H), 6.80 (d, 2H, J = 2.5 Hz), 6.85 (d, 2H, J = 2.5 Hz), 7.05 (bs, 2H), 7.40 (bs, 1H). Anal. Calcd for $C_{42}H_{53}NO_4$: C 79.33, H 8.40 N 2.20. Found: C 79.44, H 8.36, N 2.17.

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(20) Selective transformations of the monoacycarbamates of type **4f** will be published in a due course.

(21) Rudkevich, D. M. *Chem. Eur. J.* **2000**, *6*, 2679−2686.