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First Protection of a Wide-Rim Tetraamino Calix[4]arene in Opposite Positions

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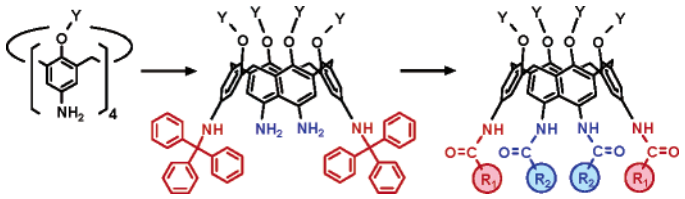
ABSTRACT



The importance of tetraamino calix[4]arenes as starting materials is distinctly increased by the first versatile protective group for opposite amino functions. Reaction with trityl chloride leads to the 1,3-dialkylated derivative easily isolated in 34% yield; after a first acylation of the remaining amino groups, the trityl residues can be removed by TFA to introduce a second acyl group.

Wide-rim tetraamino calix[4]arenes are rather interesting and useful macrocyclic compounds. They are easily available in large quantities[1] and serve as attractive starting material for various fascinating structures. Extractants for lanthanides and actinides,[2] different anion receptors,[3] intriguing self-assembled structures,[4,5] sophisticated rotaxanes and catenanes,[6] and building blocks for self-assembled dendrimers[7] were prepared starting from tetraamino calix[4]arenes.

In some cases, the combination of (different) functional groups is very important. For example, the introduction of

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(1) Ipso-nitration of tetraethers of calix[4]arene followed by catalytic hydrogenation affords respective tetraamines in high yields. See: Verboom, W.; Durie, A.; Egberink, R. J. M.; Asfari, Z.; Reinhoudt, D. N. *J. Org. Chem.* **1992**, *57*, 1313−1316. Jakobi, R. A.; Böhmer, V.; Grüttner, C.; Kraft, D.; Vogt, W. *New J. Chem.* **1996**, *20*, 493−501.

(2) Delmau, L. H.; Simon, N.; Schwing-Weill, M.-J.; Arnaud-Neu, F.; Dozol, J.-F.; Eymard, S.; Tournois, B.; Böhmer, V.; Grüttner, C.; Musigmann, C.; Tunayar, A. *Chem. Commun.* **1998**, 1627−1628. Delmau, L. H.; Simon, N.; Schwing-Weill, M.-J.; Arnaud-Neu, F.; Dozol, J.-F.; Eymard, S.; Tournois, B.; Grüttner, C.; Musigmann, C.; Tunayar, A.; Böhmer, V. *Sep. Sci. Technol.* **1999**, *34*, 863−876.

(3) For a recent review, see: Matthews, S. E.; Beer, P. D. In *Calixarenes 2001*; Asfari, Z., Böhmer, V., Harrowfield, J., Vicens, J., Eds.; Kluwer Academic Publishers: Dordrecht, 2001; Chapter 23, pp 421−439. For some selected examples, see: Dudič, M.; Lhoták, P.; Stibor, I.; Lang, K.; Prošková, P. *Org. Lett.* **2003**, *5*, 149−152. Casnati, A.; Massera, C.; Pelizzi, N.; Stibor, I.; Pinkassik, E.; Ugozzoli, F.; Ungaro, R. *Tetrahedron Lett.* **2002**, *43*, 7311−7314. Sansone, F.; Baldini, L.; Casnati, A.; Lazzarotto, M.; Ugozzoli, F.; Ungaro, R. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 4842−4847. Morzherin, Y.; Rudkevich, D. M.; Verboom, W.; Reinhoudt, D. N. *J. Org. Chem.* **1993**, *58*, 7602−7605.

(4) For a short review, see: Rebek, J., Jr., *Chem. Commun.* **2000**, 637−643. For some selected examples, see: Castellano, R. K.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1998**, *120*, 3657−3663. Brody, M. S.; Schalley, C. A.; Rudkevich, D. M.; Rebek, J., Jr. *Angew. Chem., Int. Ed.* **1999**, *38*, 1640−1644. Pop, A.; Vysotsky, M. O.; Saadioui, M.; Böhmer, V. *Chem. Commun.* **2003**, 1124−1125. Rudzevich, Y.; Fischer, K.; Schmidt, M.; Böhmer, V. *Org. Biomol. Chem.* **2005**, *3*, 3916−3925.

(5) Shivanyuk, A.; Saadioui, M.; Broda, F.; Thondorf, I.; Vysotsky, M. O.; Rissanen, K.; Kolehmainen, E.; Böhmer, V. *Chem.−Eur. J.* **2004**, *10*, 2138−2148.

(6) For a recent review, see: Bogdan, A.; Rudzevich, Y.; Vysotsky, M. O.; Böhmer, V. *Chem. Commun.* **2006**, 2941−2952.

(7) Rudzevich, Y.; Rudzevich, V.; Moon, C.; Schnell, I.; Fischer, K.; Böhmer, V. *J. Am. Chem. Soc.* **2005**, *127*, 14168−14169.

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several ligating functions at well-defined positions can significantly influence selectivity or effectivity of extractants.[8] Also, the well-known dimerization of the tetraurea calix[4]arene does not occur if just one urea group is replaced by an acetamide function; instead, an astonishing tetrameric assembly with a totally different hydrogen-bonding pattern is formed.[5] Novel catenanes with different sizes of the loops are also worth being mentioned.[9]

The controlled synthesis of such intriguing compounds is strongly facilitated by the selective protection of amino functions. Although simple and effective procedures for mono-Boc (36%), 1,2-di-Boc (48%), and tri-Boc (54%) protection were formerly developed, the 1,3-di-Boc-substituted derivative was not even detected.[10] However, calixarenes possessing two different acyl residues in alternating order are often the most interesting examples due to their higher symmetry. The dimerization of tetraurea derivatives with alternating urea functions (ABAB), for instance, leads to a single regioisomer with supramolecular chirality, whereas two regioisomeric dimers are formed from an AABB isomer.[11]

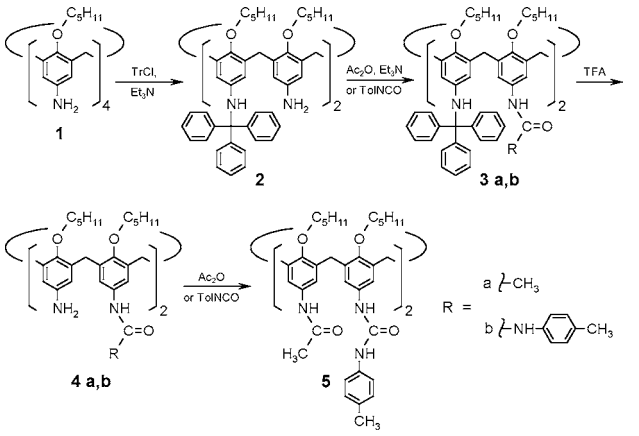
Two different strategies were proposed for the synthesis of precursors possessing two nitro and two amino groups in alternating order.[12] Both ways comprise seven steps, each starting from the parent calix[4]arene, and afford the target products in 8−20% overall yield. Thus, the synthesis of 1,3-diprotected tetraamino calix[4]arenes remains quite complicated and the corresponding derivatives are almost not studied. Therefore, a direct selective protection is still of great interest.

The absence of 1,3-diacylation products can be explained by the formation of a trans-cavity hydrogen bond[13] between the first amide function and the opposite amino group, which is thus deactivated. This observation suggests that in alkylated amines such hindrance should be absent.

On the basis of these considerations, we have tried to attach triphenylmethyl as a protecting group by direct 1,3-dialkylation of the tetraamino calix[4]arene under the following conditions (Scheme 1). Two equivalents of trityl chloride were added dropwise to the chloroform solution of **1** (c = 1 g/L) in the presence of triethylamine. Indeed, the target product was detected by ^{1}H NMR and it was *easily* separated from the mixture of all possible derivatives by a simple crystallization in ∼20% yield.

To optimize the reaction conditions, the alkylation was carried out at different concentrations (1−10 g/L) of starting calix[4]arene **1** using trityl chloride or trityl bromide.[14]

Scheme 1. Synthesis of a Tetraacyl Calix[4]arene Bearing Two Different Acyl Groups in Alternating Order



Neither concentration nor the alkylating agent significantly influenced the yield of the 1,3-dialkylated compound and the ratio between the products. A slow addition of trityl chloride was also not important because similar yields were obtained when the reagents were rapidly mixed. Obviously, the substitution occurs statistically and not selectively.

Remarkable differences were observed when the alkylation was carried out without triethylamine. Only mono-[15] and disubstituted derivatives were observed by TLC in the reaction mixture, whereas all possible alkylation products were formed in the presence of triethylamine.

Thus, to reduce the amount of the tetra- and trialkylated products, the trityl chloride was added to the substrate in two portions. The first 2.2 mol of alkylating agent was reacted with the tetraamine, also used as base. Subsequently, the triethylamine and the extra portion of trityl chloride (1.1 mol) were added. This sequence afforded the 1,3-disubstituted compound which crystallized in 34% yield from the reaction mixture.[16]

Mono-, tri-, and tetrasubstituted derivatives were also separated and characterized, but their yields were not optimized because analogous derivatives are easily obtained by Boc protection.[10] Complete deprotection of this mixture allowed recovery of 56% of the tetraamino calix[4]arene **1**.[16,17] Thus, only 10% of the starting material was lost.

The remaining amino groups were easily acylated with tolyl isocyanate or with acetic acid anhydride. As expected, the cleavage of the trityl groups with TFA in dichloromethane occurs selectively, leading to 1,3-disubstituted diaminocalix[4]arenes **4** in 90−95% yields. Acylation of the last two amino groups gives product **5** (as an example) bearing two different acyl groups in alternating order.

The structures of all products were unambiguously proved by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry.

(8) For a recent example at the narrow rim, see: Mikulášek, L.; Grüner, B.; Danila, C.; Böhmer, V.; Cáslavský, J.; Selucký, P. *Chem. Commun.* **2006**, 4001−4003.

(9) Molokanova, O.; Bogdan, A.; Vysotsky, M. O.; Bolte, M.; Ikai, T.; Okamoto, Y.; Böhmer, V., manuscript in preparation.

(10) Saadioui, M.; Shivanyuk, A.; Böhmer, V.; Vogt, W. *J. Org. Chem.* **1999**, *64*, 3774−3777.

(11) See: Pop, A.; Vysotsky, M. O.; Saadioui, M.; Böhmer, V. *Chem. Commun.* **2003**, 1124−1125.

(12) Bogdan, A.; Vysotsky, M. O.; Böhmer, V. *Collect. Czech. Chem. Commun.* **2004**, *69*, 1009−1026. van Wageningen, A. M. A.; Timmerman, P.; van Duynhoven, J. P. M.; Verboom, W.; van Veggel, F. C. J. M.; Reinhoudt, D. N. *Chem.−Eur. J.* **1997**, *3*, 639−654.

(13) Scheerder, J.; Vreekamp, R. H.; Engbersen, J. F. J.; Verboom, W.; van Duynhoven, J. P. M.; Reinhoudt, D. N. *J. Org. Chem.* **1996**, *61*, 3476−3481.

(14) Because of its hygroscopic properties, trityl bromide should be freshly opened or dried.

(15) Trityl chloride is partly hydrolyzed to the trityl alcohol during the reaction. As an example, see: Canle, M. L.; Clegg, W.; Demirtas, I.; Elsegood, M. R. J.; Haider, J.; Maskill, H.; Miatt, P. C. *J. Chem. Soc., Perkin Trans. 2* **2001**, 1742−1747.

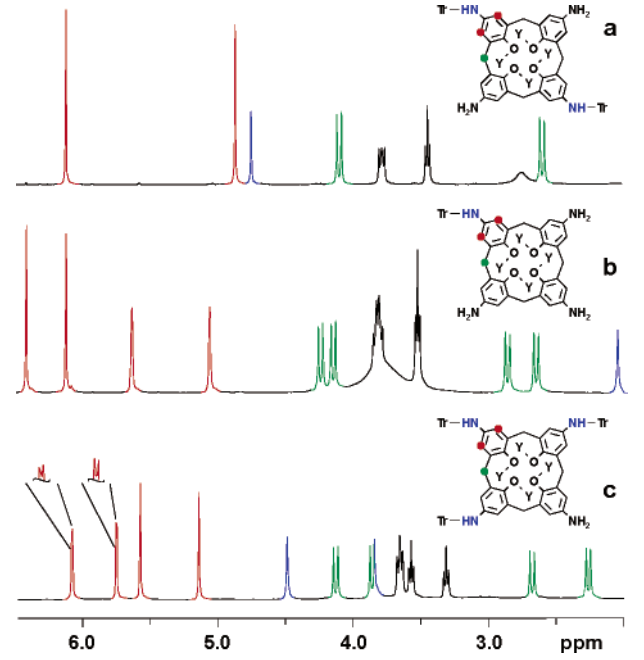


Figure 1. Sections of the ^{1}H NMR spectra of **2** (a), mono- (b), and trisubstituted (c) tetraamino calix[4]arenes proving the absence of other alkylation products in **2**.

The ^{1}H NMR spectrum of compound **2** (Figure 1) contains two singlets for the aromatic protons of the calixarene skeleton, one singlet for N*H*, and one pair of doublets for the protons of the methylene bridges showing the expected pattern for a molecule of the ABAB type.

(16) Synthesis of **2**: A solution of triphenylmethyl chloride (1.6 g, 5.75 mmol) in chloroform (50 ml) was added in one portion (fast) to the vigorously stirred solution of tetraamino calix[4]arene **1** (2.0 g, 2.61 mmol) in chloroform (100 ml). After 6 h, triethylamine (2.9 mL, 20.91 mmol) was added to the reaction mixture, and after the next 2 h, the second portion of triphenylmethyl chloride (0.73 g, 2.61 mmol) in chloroform (50 mL) was added. Stirring was continued for 6 h, and the solvent was removed under reduced pressure. The residue was dissolved in chloroform (100 ml), washed with water, and dried over $MgSO_4$. After evaporation, the residue was dissolved in the mixture of diethyl ether (7 ml) and hexane (10 ml) and kept at −14 °C. The formed precipitate was filtered off, washed with a cold mixture of diethyl ether/hexane (1:1), and dried on the air to give compound **2** (1.1 g, 34 %), mp 162−164 °C: ^{1}H NMR (400 MHz, $CDCl_3$), δ_H 0.889 (t, 6H, ^3J = 7.0 Hz, C*H*$_3$), 0.894 (t, 6H, ^3J = 7.0 Hz, C*H*$_3$), 1.07−1.48 (m, 16H, C*H*$_2$), 1.65−1.83 (m, 8H, C*H*$_2$), 2.60 (d, 4H, ^2J = 13.2 Hz, ArC*H*$_2$Ar), 2.78 (br s, 4H, N*H*$_2$), 3.45 (t, 4H, ^3J = 6.4 Hz, OC*H*$_2$), 3.78 (m, 4H, OC*H*$_2$), 4.10 (d, 4H, ^2J = 13.2 Hz, ArC*H*$_2$Ar), 4.74 (s, 2H, N*H*), 4.87 (s, 4H, Ar*H*), 6.11 (s, 4H, Ar*H*), 7.2−7.5 (m, 30H, Ph*H*); ^{13}C{^{1}H} NMR (100.6 MHz, $CDCl_3$), δ_C 14.0 (s, *C*H$_3$), 14.3 (s, *C*H$_3$), 22.7 (s, *C*H$_2$), 22.9 (s, *C*H$_2$), 28.1 (s, *C*H$_2$), 28.7 (s, *C*H$_2$), 29.5 (s, *C*H$_2$), 30.1 (s, *C*H$_2$), 31.1 (s, *C*H$_2$), 72.0 (s, *C*Ph$_3$), 74.7 (s, O*C*H$_2$), 74.9 (s, O*C*H$_2$), 114.8 (s, *C*H$_{Ar}$), 117.5 (s, *C*H$_{Ar}$), 126.5 (s, *C*H$_{Ar}$), 127.8 (s, *C*H$_{Ph}$), 129.4 (s, *C*H$_{Ph}$), 133.6 (s, *C*$_{Ar}$), 136.6 (s, *C*$_{Ph}$), 140.1 (s, *C*$_{Ar}$), 140.4 (s, *C*$_{Ar}$), 146.1 (s, *C*$_{Ph}$), 148.9 (s, *C*$_{Ar}$), 150.6 (s, *C*$_{Ar}$); *m*/*z* (FD) 1248.8 (100) $[M]^+$, 1006.7 (30) $[M - Ph_3C]^+$, calcd 1249.75. The mother solution was evaporated. Its deprotection (see below) afforded 1.12 g (56 %) of the starting tetraamino calix[4]arene **1**.

(17) General procedure for the cleavage of the trityl groups: The trityl-containing compound was dissolved in methylene chloride. After addition of trifluoroacetic acid (10 mol per group), the mixture was stirred for 2 h. The solvent and acid were removed under reduced pressure. The residue was dissolved in chloroform, washed with an aqueous solution of K_2CO_3 (10 %) and water, and dried over $MgSO_4$. Precipitation with hexane or Et_2O from the chloroform solution leads to product **4** (80−85 %).

Colorless crystals of **3b** suitable for X-ray crystallographic analysis[18] were obtained by slow crystallization from DMSO. The asymmetric unit comprises two calixarenes and six molecules of DMSO. One of the urea fragments of each calixarene forms bifurcated hydrogen bonds with the oxygen of a single DMSO, whereas the second urea group is bound to the two solvent molecules. The calixarene assumes the pinched cone conformation (Figure 2), in which surprisingly

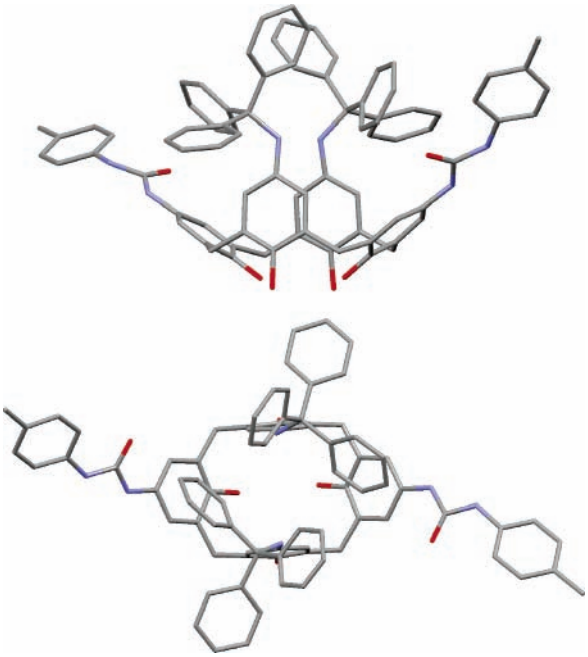


Figure 2. Molecular conformation of compound **3b** seen from the side (top) and from the top (bottom). Hydrogen atoms, pentyl substituents, and solvent molecules are omitted for clarity.

the phenolic rings bearing bulky trityl substituents are almost parallel (the shortest distance between the closest carbons of the opposite trityl groups is 3.6 Å). The patch angles of two opposite trityl- and tolyl-substituted aromatic units to the reference plane passing through the methylene bridges are 84.5 ± 0.6 and 127.5 ± 0.8°, respectively. Some other typical angles and distances are shown in Table 1.

In conclusion, the first preparatively useful procedure for the direct protection of a wide-rim tetraamino calix[4]arene at opposite positions was elaborated. The facile synthesis and the simple purification allow us to obtain the target compound on a multigram scale. It was also shown that the further functionalization of the remaining amino groups, the

(18) Crystal data for **3b**: $C_{102}H_{106}N_6O_6 \times 3SO(CH_3)_2$, M = 1746.31, triclinic, a = 16.6852(5) Å, b = 18.6076(6) Å, c = 19.9047(6) Å, α = 99.238(1)°, β = 112.682(1)°, γ = 113.338(1)°, V = 4864.2(3) Å^3, T = 183 K, space group P-1 (No. 2), Z = 2, μ(Mo Kα) = 0.14 mm^{-1}, 33 300 reflection measured, 21 641 unique (R_{int} = 0.0360) which were used in all calculations. The final w$R(F_2)$ was 0.35 (all data). $\Delta\rho_{max}$ = 1.93 eÅ^{-3}. The crystals obtained from **3b** had very low reflecting power at higher diffraction angles. The whole structure is highly disordered due to the included solvent molecules and to the pentyl chains. Therefore, the *R* values are rather high, but the molecular structure is proved nevertheless.

Table 1. Selected Geometric Parameters of **3b**

parameter	value
angles (°)[a]	
Ar_{Tol} / Ar_{Tol}	74.95
Ar_{Trt} / Ar_{Trt}	11.07
MP[b] / Ar_{Tol}	126.72/128.23
MP[b] / Ar_{Trt}	83.92/85.10
distances (Å)	
$(O)C_{Tol}-(O)C_{Tol}$[c]	5.48
$(N)C_{Tol}-(N)C_{Tol}$[d]	9.87
$(O)C_{Trt}-(O)C_{Trt}$[c]	5.37
$(N)C_{Trt}-(N)C_{Trt}$[d]	4.81

[a] Ar: aromatic rings of the calixarene skeleton. [b]MP: plain passing through the methylene bridges of the calixarene skeleton. [c](O)C: carbon atom to which the alkoxy residue is attached. [d](N)C: carbon atom to which the urea/trityl is attached.

following deprotection, and exhaustive acylation occur selectively and in high yields. This reaction sequence opens wide possibilities for the preparation and investigation of calix[4]arenes bearing different *N*-acyl groups in alternating order and closes a significant gap in the synthetic repertoire.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of synthesized compounds and crystallographic details for **3b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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