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The First Synthesis of Functionalized Oxacalix[4]crown Ethers

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O-alkylation and cyclization of 25,27-dihydroxy-4,6,16,18-tetranitro-oxacalix[4]arene were performed with mono- and bifunctional alkylating agents under basic conditions. In this way several 1,3-alt oxacalix[4]-crown-4, 5 and 6 ethers were synthesized and characterized

Keywords: Oxacalix[4]arene; Alkylation; Cyclization; Crown ethers

INTRODUCTION

Reports on hetero atom (O, S, N, etc.)-bridged calixarenes **1** (Fig. 1) have seldom been found in the chemical literature [1]. Among them thiacalix[4]arenes are the only exception that have attracted great interest since their first synthesis in 1997 [2]. Although, a number of oxygen-linked macrocycles **1** (X=O) and related compounds have been published in the past decades [3–8], these molecules cannot be regarded as real calixarenes, as they do not contain phenolic OHs. Synthetic approaches to the strictly analogous oxacalix[4]arenes comprised of four hydroxy groups on the lower rim have still remained unexplored, but recently an important contribution, a simple access to oxacalix[4]arene diols **2** (Fig. 1) utilizing the commonly applied S_NAr based strategy, was reported by Katz *et al.* [9] opening the way to extend the research activity in this field.

Their efficient route using pyrogallol derivatives condensed with 1,5-difluoro-2,4-dinitrobenzene in DMSO at 25°C afforded a variety of tetranitro-oxacalix[4]arenes in excellent yields (86–92%) (Scheme 1). They found that K_2CO_3 or Cs_2CO_3 is the base of choice, which effect the cyclization selectively to the direction of tetramers in extremely short time without using high-dilution technics. The authors suggest that ring opening and closing may be reversible and that oxacalix[4]arene structure may be the thermodynamic product of these cyclizations.

RESULTS AND DISCUSSION

This mild, effective and variable method prompted us to reproduce it and investigate the reactivity of the OH groups in different alkylation reactions. Following the original description and starting from pyrogallol **4** or methyl gallate **5** using finely ground anhydrous K_2CO_3 base, oxacalixarene diols **2a** (R=H) and **b** (R=COOMe) were successfully prepared but in substantially lower yields. Changing the solvent to acetone proved to be beneficial and similar high yields (89–90%) were attained.

Products **2a**,**b** in hand allowed to investigate *O*-alkylation reactions. First, **2a** was attempted to alkylate with alcohols under Mitsunobu conditions using TPP/DEAD coupling agents according to our recent method used for the selective distal dialkylation of *p-tert*-butyl-thiacalix[4]arene [10]. Unfortunately, no reaction took place, the starting **2a** was recovered. The failure may be due to the weak acidity of the phenolic OHs as compared with that of the distal hydroxy groups in TCA [11]. Subsequently, the classical base-promoted alkylation performed with a large excess of PrI and K_2CO_3 in MeCN solvent at 80°C (12 h) led to success and **3a**,**b** were obtained, but in low yields (20–40%) (Scheme 2).

The reaction was accompanied by a large amount of polymeric side-products insoluble in common

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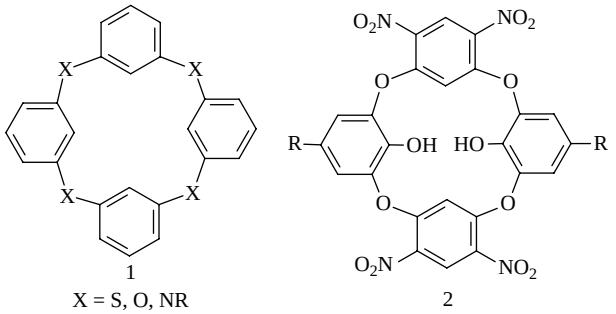
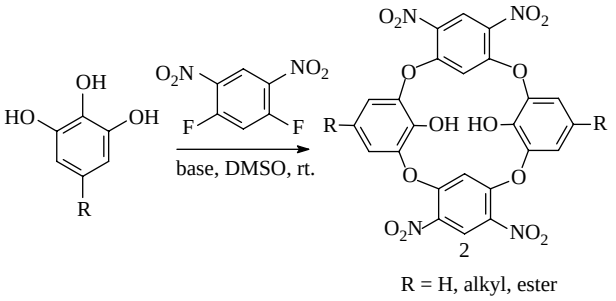


FIGURE 1 Heterocalix[4]arenes **1** and oxacalix[4]arene diols **2**.

organic solvents, which were ascribed to the ring opening of **2** prior to alkylation performed at elevated temperature. Notably, when the preparation of **2a** was carried out in boiling acetone, the yield was markedly decreased and similar side-products were obtained. If the propylated **3a** was subjected to vigorous basic conditions, ring cleavage was not observed, **3a** was totally recovered indicating that the reversible ring opening and closing is characteristic of diols **2** only. To increase the yield, the preparation of **2a** and the subsequent propylation was carried out in MeCN in one-pot procedure producing **3a** with 70% overall yield.

The steric structure of diol **2a** was determined by X-ray diffraction analysis by Katz *et al*. and they found it adopts a distorted 1,3-alt conformation where the nitroaromatic rings are oriented to maintain conjugation to the bridging oxygen atom (124.6° average angle between ring planes) [9]. This structure was retained in solution as reflected by the ^{1}H NMR spectrum of **2a**, where the anisotropic effect of the adjacent and nearly parallel aromatic rings causes an unusual upfield shift of the interior nitroaromatic ring protons H_a (δ 5.66) [9]. Oxacalixarenes derived from resorcines and, therefore, not containing free phenolic OHs, adopt a highly distorted (flattened) 1,3-alt conformation with almost coplanar nitroaromatic rings where the H_a protons does not place inside the anisotropic shielding cone of the adjacent rings (δ 6.5–6.8) [9]. The chemical shift of the H_a protons is, therefore, of diagnostic value in respect of the conformational distortion. This signal of our diethers **3a** (5.79) and **3b** (5.80) was assigned in the range of **2a,b** evidencing that the original distorted 1,3-alt conformation was not altered by the *O*-alkylation.



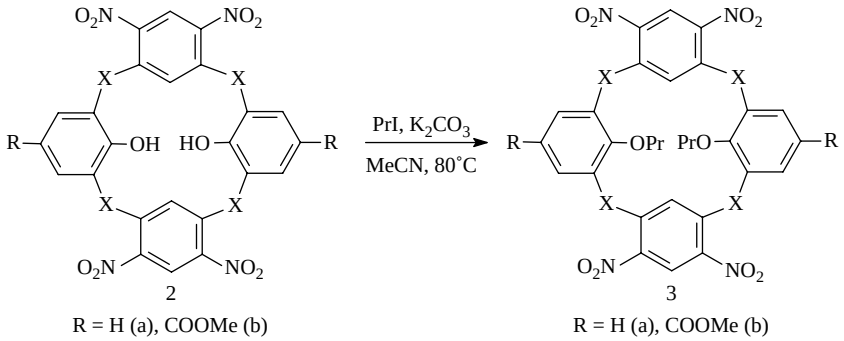
SCHEME 1 Synthesis of oxacalix[4]arene diols **2**.

After these preliminaries, bifunctional alkylating agents of different length were used under the same conditions to link the two phenolic units of **2a**. Dialkylation but not ring closure was achieved with 1,3-dibromopropane affording bis(3-bromopropyl) ether **4** (40%). Olygoethylene glycol ditosylates **5**--**8**, however, effected cyclization in generally low to moderate yields (20–60%) resulting in the first representatives of functionalized oxacalix[4]crown ethers **9a–d** (Fig. 2). This reaction was also accompanied by the formation of a large quantity of polymeric side-product lowering the yields that, however, could be improved by using one-pot procedure described for the preparation of dipropylether **3a**.

The H_a proton signals of **9a–d** appear at 5.74–5.86 ppm indicating the retention of the original distorted 1,3-alt conformation.

As part of ongoing work, we have synthesized a number of calix-and thiacalix[4]crown ether ionophores and their alkali cation complexing abilities were assessed by biphasic picrate extraction method. The most significant extraction capacities were found with 1,3-alt-calix[4]crowns [12], where the adjacent parallel aromatic rings contribute to binding by π-cation interactions. The same measurements performed with ligands **9** using chloroform-aqueous alkali picrate systems did not show appreciable cation extractabilities. This result clearly proves that the crown ether moiety in oxacalix[4]arenes **9** itself cannot stabilize cations sufficiently without the contribution of the adjacent aromatic rings, which in turn, are not parallel but flattened and of electron-deficient character (Fig. 3).

As crown ethers generally, calix[4]crowns can also bind with primary or secondary ammonium cations, where the complex is stabilized by ion-dipole interaction and H-bonds with the etheric oxygens [13]. Therefore, we tested the complexation ability of oxacalix[4]crown-6 **9c** towards benzylammonium perchlorate by mixing the components in $CDCl_3/CD_3OD = 4:1$ solvent and found that the ^{1}H NMR spectra did not change beyond 1:1 stoichiometry. The broad signals of the crown ether methylene protons in **9c** became sharp and well-resolved triplets indicative of a more organized and rigid crown ether ring due to complexation. At the same time, the skeletal aromatic protons were split but exhibited only insignificant shifts indicating, as expected, the lack of π-π contact between the host and the guest phenyl groups (Fig. 4). This observation gave the idea to utilize ligands **9c,d**



SCHEME 2 *O*-alkylation of oxacalix[4]arene diols **2**.

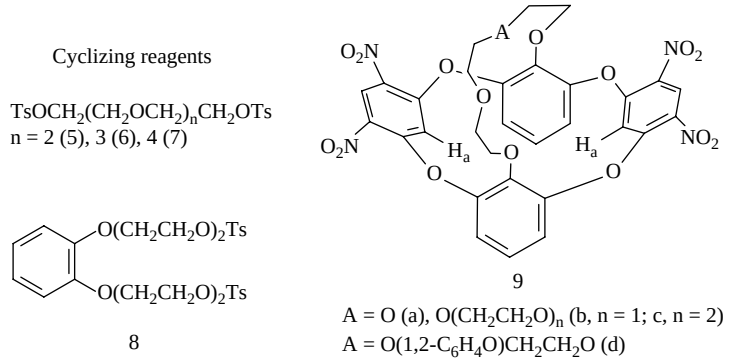


FIGURE 2 Survey of oxacalix[4]crown ethers **9**.

or analogues with larger crown ether rings as wheels in construction of pseudo [2]rotaxanes. These interesting supramolecules generally consist of 24-crown-8 wheels threaded by different dibenzylammonium axles [14]. This work is in progress in our laboratory and will be published in due course.

CONCLUSIONS

In conclusion, we have demonstrated for the first time the O-alkylation of oxacalix[4]arene **2a** with mono-and bifunctional reagents under classical base-promoted conditions. During the reactions, a large amount of insoluble side-products were formed due to the opening of the oxacalixarene ring under elevated temperature prior to alkylations. Nevertheless, a series of oxacalix[4]crown ethers were synthesized and established by ^{1}H NMR that they retained the distorted 1,3-alt conformation characteristic of the starting oxacalixarene diols. Biphasic picrate extraction experiments revealed that oxacalix[4]crowns **9** did not extract alkali cations due to the lack of contribution of the flattened and strongly electron-deficient nitroaromatic rings to binding. Preliminary observations revealed that these molecules may be utilized as wheels in construction of pseudo [2]rotaxanes.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) at 500/125 MHz on a Bruker Avance DRX-500 spectrometer. Precoated silica gel plates (Merck 60 F_{254}) were used for analytical TLC and Kieselgel 60 for column chromatography. All chemicals were reagent grade and used without further purification.

General Procedure for the Synthesis of Oxacalix[4]arene Diols 2a,b

To the vigorously stirred mixture of pyrogallol or methyl gallate (12 mmol) and powdered K_2CO_3 (4.2 g, 30 mmol) in dry acetone (70 ml) was dropped a solution of 1,3-difluoro-2,4-dinitrobenzene (3.05 g, 15 mmol) in acetone (10 ml) at ambient temperature and allowed to react for 1 h. The solvent was then removed under reduced pressure and the residue was partitioned between EtOAc and 10% aqueous HCl. The organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue was triturated with MeOH to give **2a**,**b** as pale yellow solids in essentially pure form.

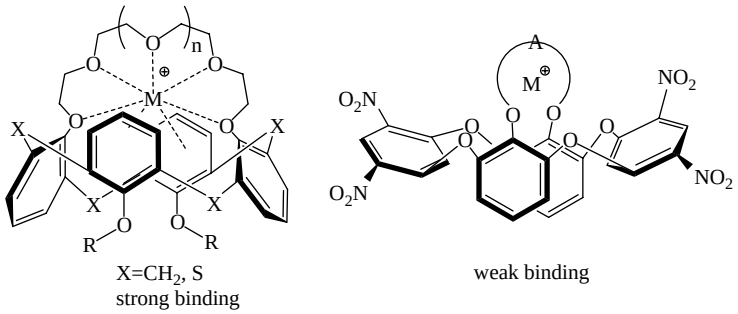


FIGURE 3 Conformation and cation binding mode of 1,3-alt calix[4]crowns *vs.* oxacalix[4]crowns.

25,27-Dihidroxy-4,6,16,18-tetranitro-oxacalix[4]arene (2a)

Yield: 89%, mp 228–231°C (dec.). All spectroscopic data were identical with those described by Katz *et al*. [9].

25,27-Dihidroxy-11,23-di(methoxycarbonyl)-4,6,16,18-tetranitro-oxacalix[4]arene (2b)

Yield: 80%, mp 290°C (dec.). ^{1}H NMR (DMSO-d_6): δ 11.83 (br s, 2H, O*H*), 8.91 (s, 2H, Ar*H*), 7.61 (s, 4H, Ar*H*), 5.78 (s, 2H, Ar*H*), 3.58 (s, 6H, OCH_3). ^{13}C NMR: δ 163.7 (*C*O), 155.3, 146.3, 140.4, 131.6, 125.9, 122.9, 121.4, 100.9 (Ar), 52.6 (O*C*H$_3$). anal. calcd for $C_{28}H_{16}N_4O_{18}$ (696.05): C, 48.29; H, 2.32; N, 8.04, found: C, 48.42; H, 2.25; N, 8.13%.

GENERAL PROCEDURE FOR THE ALKYLATION/CYCLIZATION OF 2A

The mixture of **2a,b** (1 mmol), powdered K_2CO_3 (0.56 g, 4 mmol) and PrI (1.02 g, 6 mmol) in MeCN (20 ml) was stirred under reflux for 12 h. The solvent was then removed under reduced pressure and the residue was partitioned between $CHCl_3$ and 10% aqueous HCl. After removal of the insoluble side-products by suction filtration, the organic layer was separated, washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue was triturated with MeOH to give **3a** (40%)**, 3b** (16%) as pale yellow solid. The same procedure was applied for the cyclization of **2a** (1 mmol) using 1,3-dibromopropan or **5**–**8** (2 mmol), K_2CO_3 (0.56 g, 4 mmol) in MeCN (30 ml). The crude products were purified by column chromatography on silica using toluene–MeOH = 9:1 eluent mixture to give **4** (40%), **9a** (62%), **b,c** (20%), **d** (16%) as pale yellow solids.

ONE-POT PROCEDURE FOR THE SYNTHESIS OF 3A AND 9C,D

To the vigorously stirred mixture of pyrogallol (0.73 g, 6 mmol) and powdered K_2CO_3 (8.4 g, 60 mmol) in dry MeCN (60 ml) was dropped a solution of 1,3-difluoro-2,4-dinitrobenzene (1.5 g, 7.5 mmol) in MeCN (10 ml) at ambient temperature and allowed to react for 1 h. Subsequently, PrI (5.1 g, 30 mmol), **7** or **8** (4.5 mmol), respectively, was added and refluxed for 12 h. After workup described above **3a** (70%), **9c** (50%) and **9d** (30%) were obtained in improved yields.

25,27-Dipropoxy-4,6,16,18-tetranitro-oxacalix[4]arene (3a)

Mp 290°C (dec.). ^{1}H NMR: δ 8.88 (s, 2H, Ar*H*), 7.18–7.21 (d,d, 2H, J = 7.0, J = 9.0 Hz, Ar*H*), 7.13 (d,d, 4H,

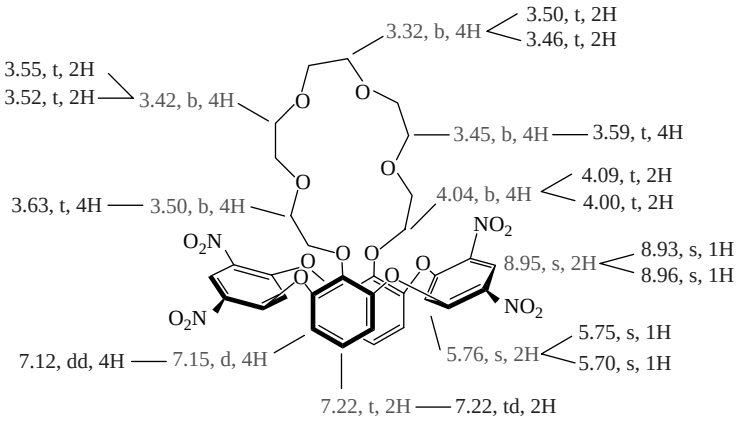


FIGURE 4 The ^{1}H NMR signals of **9c** without (red) and with addition of equimolar amount of benzylammonium perchlorate (blue).

$J = 7.5$, $J = 1.0$ Hz, Ar*H*), 5.79 (s, 2H, Ar*H*), 3.88 (t, 4H, $J = 6.5$ Hz, OCH_2), 1.35 (t,q, 4H, $J = 6.5$, $J = 7.5$ Hz, CH_2), 0.56 (t, 6H, $J = 7.5$ Hz, CH_3). ^{13}C NMR: δ 156.3, 146.9, 143.1, 131.8, 125.9, 125.8, 121.9, 102.9 (Ar), 77.1 (OCH_2), 23.3 (CH_2), 10.0 (CH_3). anal. calcd for $C_{30}H_{24}N_4O_{14}$ (664.13): C, 54.22; H, 3.64, N, 8.43, found: C, 54.34; H, 3.66, N, 8.41%.

25,27-Dipropoxy-11,23-di(methoxycarbonyl)-4,6,16, 18-tetranitro-oxacalix[4]arene (3b)

Mp 280°C (dec.). ^{1}H NMR: δ 8.87 (s, 2H, Ar*H*), 7.84 (s, 4H, Ar*H*), 5.80 (s, 2H, Ar*H*), 4.12 (t, 4H, $J = 6.5$ Hz, OCH_2), 3.92 (s, 6H, CH_3O), 1.34 (t,t, 4H, $J = 6.5$, $J = 7.0$ Hz, CH_2), 0.57 (t, 6H, $J = 7.0$ Hz, CH_3). ^{13}C NMR: δ 164.4 (*C*O), 155.5, 146.9, 146.2, 132.2, 128.0, 126.0, 123.4, 102.6 (Ar), 77.2 (OCH_2), 53.1 (CH_3O), 23.3 (CH_2), 10.0 (CH_3); anal. calcd for $C_{34}H_{28}N_4O_{18}$ (780.14): C, 52.31; H, 3.62, N, 7.18, found: C, 52.22; H, 3.68, N, 7.09%.

25,27-bis(3-Bromoethoxy)-4,6,16,18-tetranitro-oxacalix[4]arene (4)

Mp 220°C (dec.); ^{1}H NMR: δ 8.90 (s, 2H, Ar*H*), 7.25 (t, 2H, $J = 8.0$ Hz, Ar*H*), 7.15 (d, 4H, $J = 7.5$ Hz, Ar*H*), 5.74 (s, 2H, Ar*H*), 4.12 (t, 4H, $J = 5.0$ Hz, ArOCH_2), 3.12 (t, 4H, $J = 5.5$ Hz, BrCH_2), 1.93 (q, 4H, $J = 5.5$ Hz, CH_2). ^{13}C NMR: δ 156.0, 146.4, 142.9, 131.9, 126.4, 126.2, 122.2, 102.3 (Ar), 73.0 (OCH_2), 32.7 (CH_2Br), 28.8 (CH_2); anal. calcd for $C_{30}H_{22}Br_2N_4O_{14}$ (819.95): C, 43.82; H, 2.70; Br, 19.43; N, 6.81; found: C, 43.74; H, 2.77; Br, 19.52; N, 6.72%.

4,6,16,18-Tetranitro-oxacalix[4](25,27)-crown-4 (9a)

Mp 260°C (dec.); ^{1}H NMR: δ 8.89 (s, 2H, Ar*H*), 7.20–7.23 (d,d, 2H, $J = 7.0$, $J = 9.0$ Hz, Ar*H*), 7.16 (d,d, 4H, $J = 7.5$ Hz, $J = 1.5$ Hz, Ar*H*), 5.86 (s, 2H, Ar*H*), 4.00 (t, 4H, $J = 2.0$ Hz, ArOCH_2), 3.21 (t, 4H, $J = 1.5$ Hz, OCH_2), 3.19 (t, 4H, OCH_2). ^{13}C NMR: δ 156.5, 147.3, 142.1, 132.2, 125.9, 125.7, 121.5, 103.7 (Ar), 73.5 (ArOCH_2), 68.2, 67.7 (OCH_2); anal. calcd for $C_{30}H_{22}N_4O_{16}$ (694.10): C, 51.88; H, 3.19; N, 8.07, found: C, 52.01; H, 3.27; N, 7.98%.

4,6,16,18-Tetranitro-oxacalix[4](25,27)-crown-5 (9b)

Mp 255°C (dec.); ^{1}H NMR: δ 8.96 (s, 2H, Ar*H*), 7.21–7.24 (d,d, 2H, $J = 7.5$, $J = 9.0$ Hz, Ar*H*), 7.16 (d, 4H, $J = 8.0$, Ar*H*), 5.76 (s, 2H, Ar*H*), 4.00 (t, 4H, $J = 4.0$ Hz, ArOCH_2), 3.38 (t, 4H, $J = 4.0$ Hz, OCH_2), 3.33-3.36 (t,t, 8H, $J = 5.0$ Hz, OCH_2). ^{13}C NMR: δ 156.7, 147.2, 143.0, 131.8, 126.3, 126.1, 121.9, 103.1 (Ar), 75.2 (ArOCH_2), 70.8, 70.5, 69.8 (OCH_2); anal. calcd for $C_{32}H_{26}N_4O_{17}$ (738.13): C, 52.04; H, 3.55; N, 7.59, found: C, 52.17; H, 3.47; N, 7.67%.

4,6,16,18-Tetranitro-oxacalix[4](25,27)-crown-6 (9c)

Mp 230-232°C; ^{1}H NMR: 8.94 (s, 2H, Ar*H*), 7.21 (t, 2H, $J = 7.5$ Hz, Ar*H*), 7.15 (d, 4H, $J = 8.0$ Hz, Ar*H*), 5.77 (s, 2H, Ar*H*), 4.03 (br s, 4H, ArOCH_2), 3.50 (br s, 4H, OCH_2), 3.44 (br s, 4H, OCH_2), 3.41 (br s, 4H, OCH_2), 3.32 (br s, 4H, OCH_2). ^{13}C NMR: δ 156.5, 146.7, 142.9, 131.8, 126.1, 125.9, 122.0, 103.0 (Ar), 75.3 (ArOCH_2), 71.0, 70.9, 70.7, 69.9 (OCH_2); anal. calcd for $C_{34}H_{30}N_4O_{18}$ (782.16): C, 52.18; H, 3.86; N, 7.16, found: C, 52.04; H, 3.79; N, 7.18%.

4,6,16,18-Tetranitro-oxacalix[4](25,27)-benzocrown-6 (9d)

Mp 265°C (dec.); ^{1}H NMR: δ 8.71 (s, 2H, Ar*H*), 7.20 (t, 2H, $J = 8.0$ Hz, Ar*H*), 7.11 (d, 4H, $J = 8.0$ Hz, Ar*H*), 6.97 (d, 2H, $J = 3.0$ Hz, Ar*H*), 6.89 (d, 4H, $J = 3.0$ Hz, Ar*H*), 5.75 (s, 2H, Ar*H*), 4.08 (br s, 4H, ArOCH_2), 3.91 (br s, 4H, OCH_2), 3.56 (br s, 4H, OCH_2), 3.53 (br s, 4H, OCH_2). ^{13}C NMR: δ 156.4, 149.1, 146.6, 143.0, 131.7, 126.3, 125.9, 122.4, 122.0, 115.8, 102.7 (Ar), 75.2 (ArOCH_2), 70.2, 70.0, 69.9 (CH_2O); anal. calcd for $C_{38}H_{30}N_4O_{18}$ (830.16): C, 54.95; H, 3.64; N, 6.74, found: C, 55.12; H, 3.72; N, 6.68%

Acknowledgements

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