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Tetranitroresorcin[4]arene: synthesis and structure of a new stereoisomer

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ABSTRACT

The direct reaction between 2-nitroresorcinol and acetaldehyde in alkaline medium yields tetranitro-C_1-resorcin[4]arene in a moderate 8.2% overall yield which was characterized by single crystal X-ray crystallography, ^{1}H NMR spectroscopy and electrospray ionization mass spectrometry (ESI-MS). In solution and in the solid state, the product adopts a unique, thermally stable and unprecedented *rcct-boat* conformation.

The C_x-resorcin[4]arenes ($x \geq 1$) are typically prepared under reflux conditions in alcoholic acidic medium of resorcinol and aliphatic or aromatic aldehydes.[1] Substitution of resorcinol at position 2 with an electron-withdrawing group such as a nitro group deactivates the phenyl ring and it is generally accepted[1] that the acid and Lewis acid-catalyzed condensation reactions do not lead to the cyclic oligomers due to the effective quenching of the reaction after the formation of the dimer **1** (Scheme 1). Yet, under alkaline conditions from 0 °C to room temperature, it has been shown that the more reactive paraformaldehyde and 2-nitroresorcinol do form a cyclic tetramer in high yield.[2]

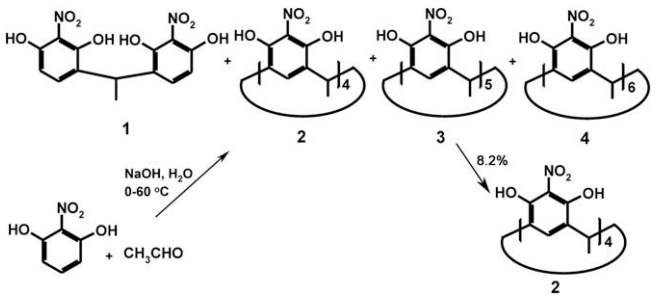
A series of new structures that adopt specific geometry and shapes have been reported previously. Amongst these compounds are resorcin[4]arenes and pyrogall[4]arenes[1] which usually adopt the crown conformation and act as hosts for a range of guest species.[3] Resorcin[4]arenes also act as building blocks in the synthesis of a wide variety of materials such as metal complexing agents[4] and have been useful hosts for open inclusion complexes,[5a–f] dimers,[5g,h] hexamers[5i–k] and tubular assemblies.[5l]

Several conformations[1,3] with different arrangements of the benzene rings and R groups on the methine bridges with respect to one another, and to the macrocycle plane are known for resorcin[4]arenes. These include crown, boat, chair, diamond and saddle. Unusual resorcin[4]arene and pyrogall[4]arene conformations such as the rarely observed *rcct-diamond* isomer of C_1-resorcin[4]arene[6a] and the C_{4t}-pyrogall[4]arene (4t = *tert*-butyl) in the *rcct-crown* conformation[6b] have been reported.

Careful tuning of the direct reaction between acetaldehyde and 2-nitroresorcinol under alkaline ($NaOH/H_2O$) conditions, resulted in the formation of a mixture of the dimer **1** and cyclic oligomers **2**, **3** and **4** (Scheme 1). Using either $Ca(OH)_2$ or K_2CO_3 instead of NaOH resulted in similar mixtures containing the dimer and the same oligomers, but in slightly lower yields. In all cases, an increase in temperature to 100 °C did not improve the yield.

The ^{1}H NMR spectrum of the crude product in DMSO-d_6 at 303 K confirmed a mixture of the dimer and the three cyclic oligomers, the tetramer **2** being most abundant as highlighted in Figure 1. To shed light on the nature of the complexity of the reaction products, an electrospray ionization mass spectrometric (ESI-MS) study was performed, the result of which showed the mixture to consist of the dimer **1** and cyclic oligomers, that is, tetramer **2**, pentamer **3** and hexamer **4** (Fig. 2, bottom). The measured isotope pattern of the cyclic oligomers is in line with the calculated pattern on the basis of natural abundance.

Further purification of the reaction product via flash chromatography led to the isolation of the cyclic tetramer **2** in an 8.2% overall yield. The larger cyclic oligomers could not be isolated from the mixture. The ESI mass spectrum and the elemental analysis of the isolated cyclic tetramer **2** confirmed the compound to be pure and showed neither the presence of dimer **1** nor any of the larger cyclic oligomers **3** and **4** (Fig. 2, top). The measured isotope pattern of the cyclic tetramer **2** is in line with the calculated pattern. The ^{1}H NMR spectrum in $CDCl_3$ at 303 K showed a complicated set of signals for such a simple compound. A temperature-dependent



Scheme 1. Synthesis and isolation of tetranitro-C_1-resorcin[4]arene **2**.

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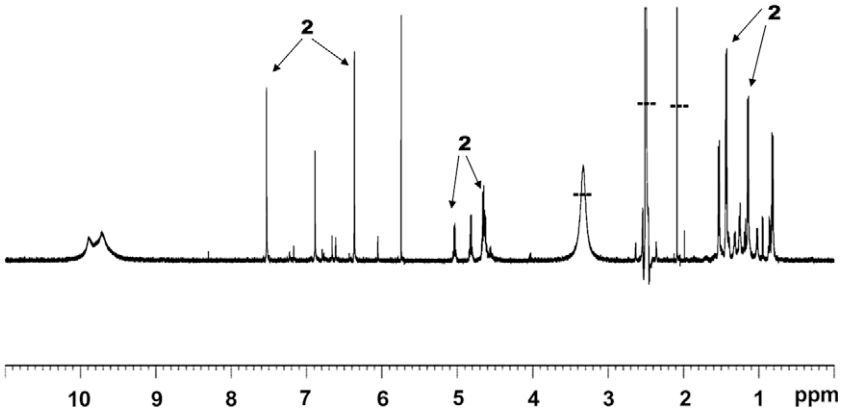

Figure 1. ^{1}H NMR of the product mixture containing **1**, **2**, **3** and **4**, signals of **2** are highlighted.

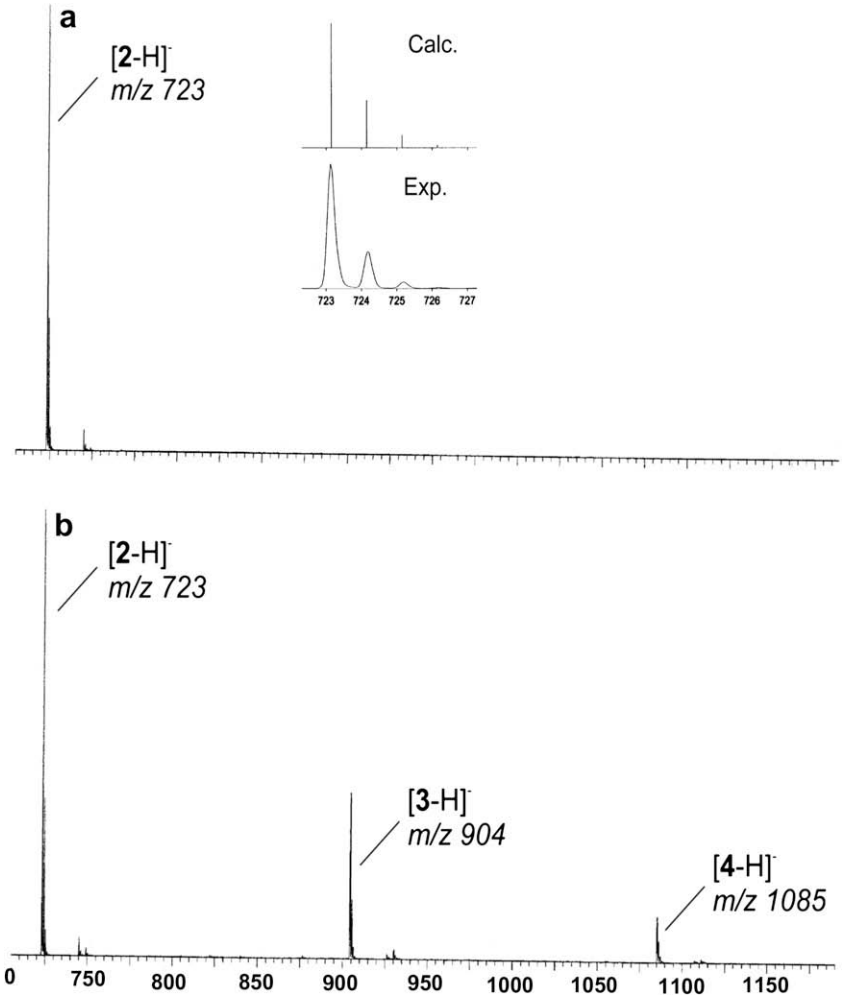

Figure 2. ESI-MS spectra of (top) tetranitro-C_1-resorcin[4]arene **2** (inset: calculated and experimental isotope patterns of **2**), and (bottom) the mixture of cyclic tetrameric **2**, pentameric **3** and hexameric **4** oligomers.

^{1}H NMR measurement was then carried out to study the conformational dynamics of **2** and similarly a ^{1}H^{1}H COSY 2D NMR spectrum was recorded to study the interactions between the protons. The temperature-dependent ^{1}H NMR shows that **2** possesses a stable conformation between 223 and 323 K. At 253 K, for example (Fig. 3), 4 equiv singlets were observed for the hydroxy groups between 11.0 and 11.3 ppm. There was slight overlapping of these protons at 223 K. These peaks shifted up-field on increasing the temperature with no overlapping. Two singlets were evident for the aromatic hydrogens between 7.7 and 6.5 ppm which were relatively constant at all temperatures. Three quartets for the C*H* protons were apparent between 4.6 and 5.3 ppm in a statistical 1:2:1 ratio. The smaller signals broadened at lower temperature and one of them eventually overlapped with the larger signal at higher temperatures. Similarly, three doublets in a statistical 1:2:1 ratio were observed between 0.9 and 1.7 ppm for the CH_3 protons. These

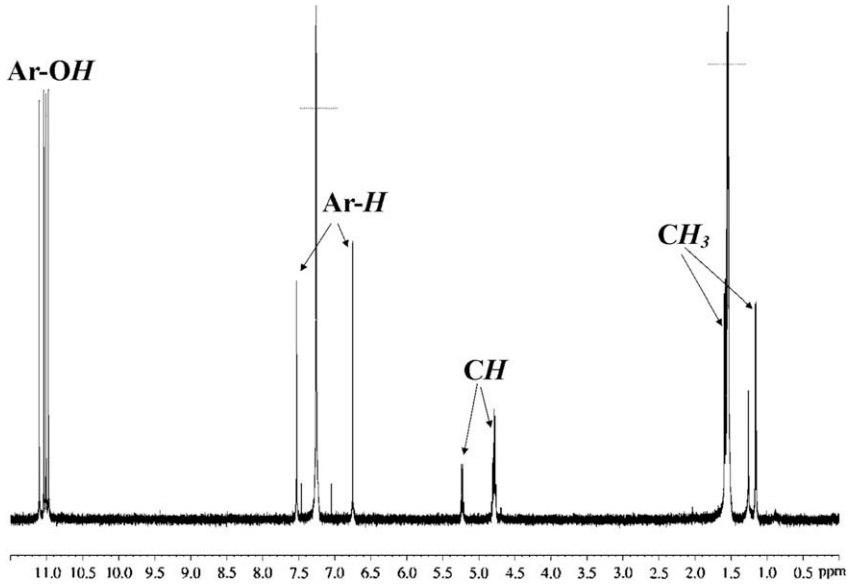

Figure 3. ^{1}H NMR of **2** at 253 K. Four singlets for the hydroxy groups, two singlets for the aromatic protons, three quartets for the CH protons in a statistical 1:2:1 ratio, and similarly three doublets for the CH_3 protons in a statistical 1:2:1 ratio.

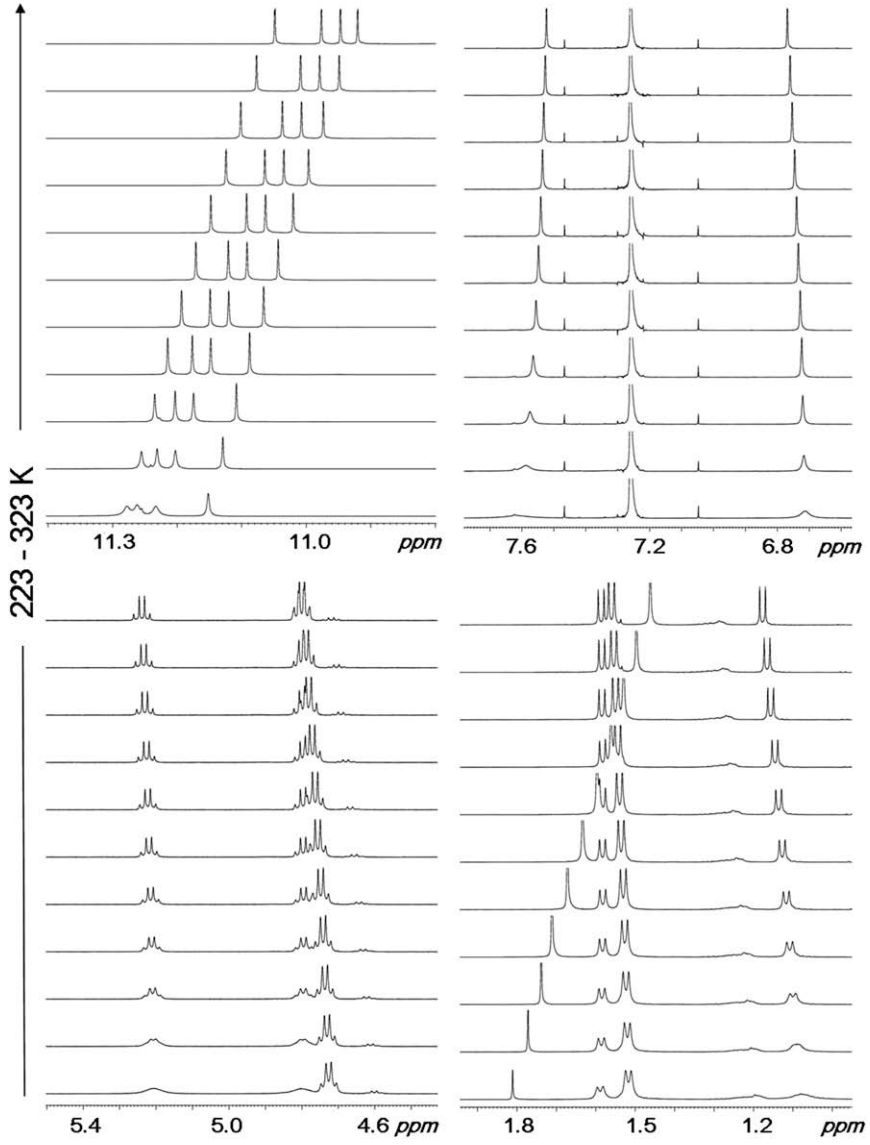

Figure 4. ^{1}H NMR temperature-dependent measurements on tetranitro-C_1-resorcinarene **2** from 223 to 323 K.

signals were relatively constant and a slight overlap of two of these resonances at higher temperature was observed. The complete set of ^{1}H NMR spectra from 223 K to 323 K is shown in Figure 4. The same phenomenon was apparent with the aromatic and aliphatic protons in DMSO-d_6, even at higher temperatures. The hydroxy protons appeared as one broad peak in DMSO-d_6. A similar pattern was also observed in the ^{13}C NMR spectrum in $CDCl_3$.

Fortunately, single crystals of tetranitro-C_1-resorcin[4]arene **2** suitable for X-ray analysis were obtained via slow evaporation from acetone. The X-ray structure confirmed an unprecedented new stereoisomer for the resorcin[4]arene and pyrogall[4]arene family which fully explains the rather strange ^{1}H NMR spectra obtained. The asymmetric nature of **2** is manifested by the low symmetry of the unit cell (triclinic) and the conformation can be described as *rcct-boat* (Fig. 5), being clearly different from the *rcct-diamond*[6a] C_1-resorcin[4]arene and the *rcct-crown*[6b] C_{4t}-pyrogall[4]arene conformations. All the hydroxy hydrogens are hydrogen bonded to the nitro group oxygens, thus disrupting the normal circular hydrogen bonding system observed in *rccc* resorcin[4]arenes.[1,2,4,5] The ^{1}H NMR spectrum is consistent with the *syn–syn–syn–anti* configuration of the methyl groups. The two parallel nitrobenzene rings are twisted towards each other, the contact (O10A···N23 distance) between the nitro groups is only 2.99 Å, and is slightly shorter than the sum of the van der Waals radii of the O and N atoms (3.07 Å). The angles between the nitrobenzene rings and the plane defined by the four methane carbons, 73.3° and 83.3° and −24.7° and −4.2°, deviate significantly from the regular boat conformation where the angles are 90° and 0°. The probable cause of this distortion is the steric repulsion caused by the *anti*-methyl group [C(29)].

In conclusion, we have presented here the first example of a direct synthesis of a tetranitro-C_{alkyl}-resorcin[4]arene from 2-nitroresorcinol and acetaldehyde under alkaline conditions. The ^{1}H NMR studies and X-ray structure of the tetranitro-C_1-resorcin[4]arene **2** confirm a unique, thermally stable and completely asymmetric *rcct-boat* stereoisomer. By careful application and tuning of the known procedures to reactions or conditions reported to be unsuccessful can lead to the synthesis and isolation of interesting novel compounds. Our results show that there are probably many unprecedented resorcin[4]arene conformations to be discovered and this could help in the design of novel molecular architectures.

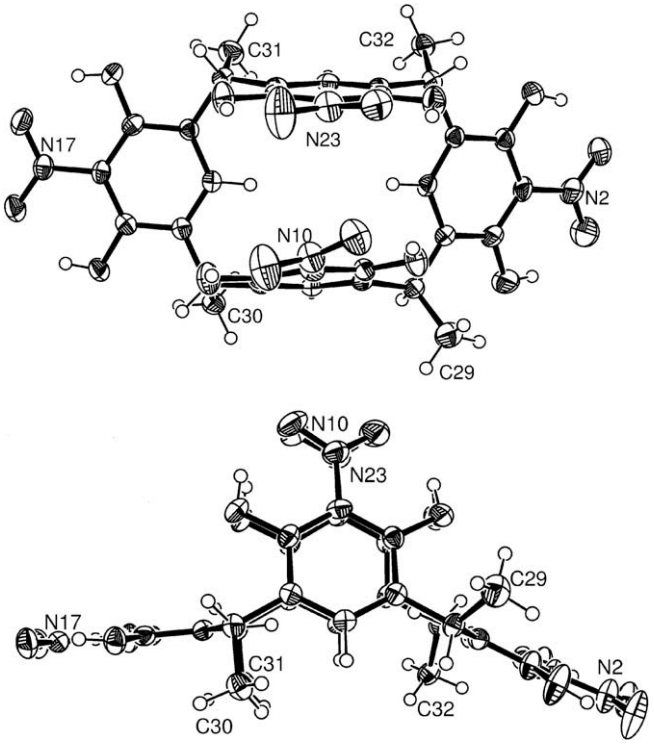

Figure 5. ORTEPs of the top and side view presentation of the X-ray crystal structure of tetranitro-C_1-resorcin[4]arene **2**. Acetone solvent molecules have been omitted for clarity.

To a solution of 2-nitroresorcinol (5.0 g, 0.0322 mol) in H_2O (100 ml) and NaOH (2.6 g, 0.0645 mol) at 0 °C, acetaldehyde (1.42 g, 0.0322 mol) was added in one portion. The mixture was maintained at 0 °C for 2 h with stirring under an N_2 atmosphere. After stirring for 24 h at 60 °C, the dark-coloured mixture was cooled to 0 °C before being neutralized with HCl (0.2 mol). A red precipitate was separated from the aqueous medium and was filtered, washed with H_2O to eliminate HCl and NaCl and dried. The reddish solid obtained was recrystallized from MeOH (~50 ml). The recrystallized product was further purified via column chromatography (eluent: CH_2Cl_2/MeOH, 95:5) to give 4.08 g of a mixture of the dimer **1**, and tetramer **2**, pentamer **3** and hexamer **4**. This mixture was subjected to further purification via flash chromatography (eluent: CH_2Cl_2/hexane, 40–20% gradient) which resulted in a partial extraction of tetramer **2** (0.48 g, to give an overall 8.2% yield) as a reddish powder. Mp >300 °C, (found C, 43.06; H, 3.52; N, 5.83; $C_{32}H_{28}N_4O_{16}\cdot1.5CHCl_3\cdot1.5H_2O$ requires C, 43.23; H, 3.52; N, 6.02). [$C_{32}H_{28}N_4O_{16}$ requires 724.604; ESI-TOF MS [M−H]$^-$ found 723.02]. ^{1}H NMR (500 MHz, $CDCl_3$, 50 °C) δ: 11.10, 11.03, 11.00, 10.97 (s, 8H, Ar–O*H*), 7.53, 6.75 (s, 4H, Ar–*H*), 5.23, 4.78 (q, 4H, *J* 7.2 Hz, C*H*), 1.59, 1.55, 1.16 (d, 12H, *J* 7.3 Hz, C*H*$_3$); ^{13}C NMR (126 MHz, $CDCl_3$, 30 °C,) δ:152.1, 152.0, 151.8, 151.6 (Ar–*C*–OH) 135.0, 134.6 (Ar–*C*–H) 124.8, 124.5, 124.0, 123.8, 123.7, 123.3 (Ar–*C*–C/Ar–*C*–N), 31.3, 29.7, 27.3 (*C*–H) 20.5, 20.2, 19.1 (*C*–H$_3$).

Suitable single crystals for X-ray analysis were obtained by slow evaporation of tetranitro-C_1-resorcinarene **2** from acetone. Crystal data $C_{32}H_{28}N_4O_{16}\cdot2C_3H_6O$, red prisms 0.3 × 0.2 × 0.1 mm, Bruker–Nonius Kappa APEXII diffractometer, M_r = 840.74, D_{calcd} = 1.448 Mg/m^3, triclinic, $P\bar{1}$, Z = 2, MoK$_\alpha$ radiation [λ = 0.71073 Å], a = 12.9107(3), b = 13.2590(3), c = 13.5419(4) Å, α = 74.086(2), β = 70.667(2), γ = 63.052(2)°Å, V = 1928.55(8) Å^3, μ = 0.12 mm^{-1}, T = 173.0(1) K, 21,883 measured reflections, 6716 independent, 4650 reflections with $I > 2\sigma(I)$, θ_{max} = 25°, refinement on F^2, 571 parameters, R_{int} = 0.042, R = 0.064 [$F^2 > 2\sigma(F^2)$], $wR(F^2)$ = 0.178, S = 1.02, $\Delta\rho_{max}$ = 0.78 e Å^{-3} and $\Delta\rho_{min}$ = −0.39 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structures in this Letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. 725579. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

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