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Synthesis and conformational properties of tetranitroazacalix[4]arenes

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ABSTRACT

Tetranitroazacalix[4]arenes have been synthesized by the nucleophilic aromatic substitution of 1,5-difluoro-2,4-dinitrobenzene with 1,3-diaminobenzenes. An X-ray crystal structure analysis revealed that the azacalixarenes adopt a non-symmetrical 1,3-alternate conformation, and the dinitrobenzene rings strongly conjugate with the bridging nitrogen atoms. In the ^{1}H NMR spectrum ($CDCl_3$, 30 °C), the tetraisopropyl derivative **3b** displays a pair of diastereotopic methyl signals of the isopropyl groups in agreement with the frozen 1,3-alternate conformation on the NMR time scale. The free energy of activation ($\Delta G^{\neq}_{298}$) for the macrocyclic inversion was determined to be 87.5 kJ mol^{-1} by temperature-dependent NMR spectroscopy.

Calixarenes, or [1$_n$]metacyclophanes, are some of the most widely used molecular scaffolds for designing sophisticated functional molecules. This is due to their easy availability, interesting conformational properties, and versatile introduction of functional groups.[1] Recently, much attention has focused on the synthesis of hetero atom-bridged calixarenes[2] because of their fine tunable molecular structures. Among them, the oxacalix[4]arenes are readily prepared by the nucleophilic aromatic substitution of activated 1,3-dihalobenzenes with 1,3-dihydroxybenzenes.[3] The high selectivity for the formation of cyclic tetramers observed during their synthesis without using high dilution conditions is a consequence of the thermodynamic product control.[4] Thus, the C–O bond formation is reversible and the cyclic tetramer is the most stable product. An analogous thermodynamically controlled synthesis of the thiacalixarenes has also been reported.[5]

On the other hand, several types of nitrogen atom-bridged calixarenes, that is, azacalixarenes, have been prepared by Pd-catalyzed aryl amination reactions.[6] These reactions require a long reaction time at high temperature and produce a mixture of cyclic oligomers of various ring sizes.[7] Meanwhile, some azacalixarenes containing 1,3,5-triazine units have been synthesized by the reaction of cyanuric chloride with 1,3-diaminobenzenes in the absence of metal catalysts.[8] We have developed the facile synthesis of the azacalix[4]arenes (Scheme 1). Our synthetic route involves the aromatic nucleophilic substitution of 1,5-difluoro-2,4-dinitrobenzene **1**. This synthetic approach provided azacalix[4]arenes consisting of two dinitrobenzene moieties at the distal positions. The strong conjugation between the dinitrobenzenes and the bridging nitrogen atoms was revealed by X-ray crystallography. In order to investigate the energy barrier of the macrocyclic ring inversion by temperature-dependent NMR spectroscopy, the azacalix[4]arene bearing isopropyl substituents at the 4,6-positions of the aromatic rings was synthesized.

The reaction of **1** with 1,3-diaminobenzene **2a** was conducted in DMF in the presence of K_2CO_3 at 100 °C for 2 h. Recrystallization of the precipitated crude product from DMSO produced the tetranitroazacalix[4]arene **3a** in 49% yield.[9] On the other hand, under analogous conditions, the reaction of **1** with 1,5-diamino-2,4-diisopropylbenzene **2b** produced the cyclic tetramer **3b** in rather low yield (12%) accompanied by the significant formation of lower linear oligomers.[10] Moreover, the GPC separation of the crude reaction mixture from **2b** provided no evidence for the formation of larger macrocyclic compounds. These results appear to be due to the sterically encumbering isopropyl substituents at the *ortho* positions of the amino groups.

The ^{1}H NMR spectroscopic analysis demonstrates the highly symmetrical structure of **3**. In DMSO-d_6 at 50 °C, the signals of the aromatic protons in **3a** appear as an AB_2C-spin system and two singlets. Its intra-annular protons (H_{in}) of the dinitrobenzene moieties resonate at 5.48 ppm. The ^{1}H NMR spectrum (400 MHz, $CDCl_3$, 30 °C) of the tetraisopropyl derivative **3b** shows the aromatic protons as four singlets, and the H_{in} protons resonate at 5.30 ppm. The H_{in} signals of **3a** and **3b** are shifted to a higher field when compared to the corresponding aromatic protons of **2**. These high field shifts are attributed to the influence of the ring current effect by the two adjacent benzene rings. Thus, it can be presumed that the preferred conformations of **3** are more likely to be the

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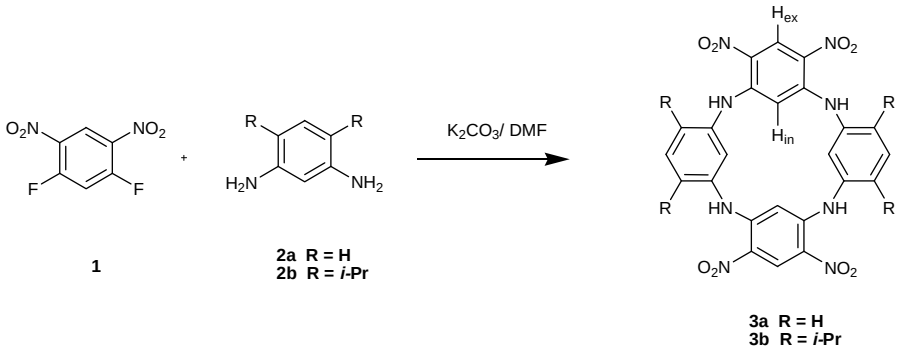

Scheme 1. Preparation of azacalix[4]arene **3** by nucleophilic aromatic substitution.

1,3-alternate ones. Interestingly, the resonance of the isopropyl groups in **3b** appears as a pair of doublets (1.07 and 1.18 ppm) and a septet (2.97 ppm). Furthermore, in the ^{13}C NMR spectrum (125 MHz, $CDCl_3$, 30 °C) of this compound, two methyl carbon signals (22.0 and 22.5 ppm) are observed. These observations indicate that the two methyl groups in the isopropyl group are diastereotopic.

Moreover, the temperature-dependent ^1H NMR analysis demonstrated the spectral changes of the signals in the isopropyl methyl protons in the range of 363–423 K, which are shown in Fig. 1 (left). The exchange of the magnetic environment of two methyl groups can be interpreted as a result of the ring inversion process. This interpretation is supported by molecular mechanics calculations. The energy-minimized structure of **3b** optimized by the MM3 force field adopt 1,3-alternate conformation, and the isopropyl substituents are bisected by the attached aromatic rings. Furthermore, the computed rotational barrier about the Ar-C bond of the isopropyl group is 25.7 kJ mol^{-1}, indicating its free rotation at ambient temperature on the NMR time scale. Therefore, these calculations support the fact that the diastereotopicity of the geminal methyl groups is not due to the restricted rotation of the isopropyl groups, but due to the slow macrocyclic ring inversion. The simulation spectra are shown in Figure 1 (right).[11] Based on these data, the Eyring plot of ln(k/T) versus 1/T was constructed (Fig. 2). Based on the slope and intercept of this straight line (r^2 = 0.999), $\Delta H^{\neq}$ = 78.0 kJ mol^{-1} and $\Delta S^{\neq}$ = −31.8 J K^{-1} mol^{-1} were determined. Thus, the free energy of activation for the inversion ($\Delta G^{\neq}_{298}$) was estimated to be 87.5 kJ mol^{-1}. This value is considerably higher than that of the azacalix[4]arene **4** ($\Delta G^{\neq}_{301}$ 58.5 kJ mol^{-1}),[7j] bearing *N*-benzyl moieties and no nitro groups (Fig. 3).

The solid state structures of **3a** and **3b** were determined by a single-crystal X-ray crystallographic analysis.[12] Their ORTEP drawings are shown in Figure 4. In both molecules, the four nitrogen atoms at the bridging positions are located nearly in the mean plane defined by these atoms with a maximum deviation of 0.022 Å for **3a** and 0.045 Å for **3b**. The benzene rings of **3a** and the diisopropylbenzene of **3b** are almost perpendicular to these mean planes, whereas the dinitrobenzene rings are oriented outward. The dihedral angles between the opposite dinitrobenzene rings are 127.2° for **3a** and 103.4° for **3b**. The difference in these dihedral angles may be ascribed to the steric repulsion of the isopropyl groups and nitro groups. Overall, the calix[4]arenes **3** adopt a non-symmetrical 1,3-alternate conformation.

Each of the nitro groups is essentially coplanar with the attached benzene ring, and all the nitrogen atoms in the bridging

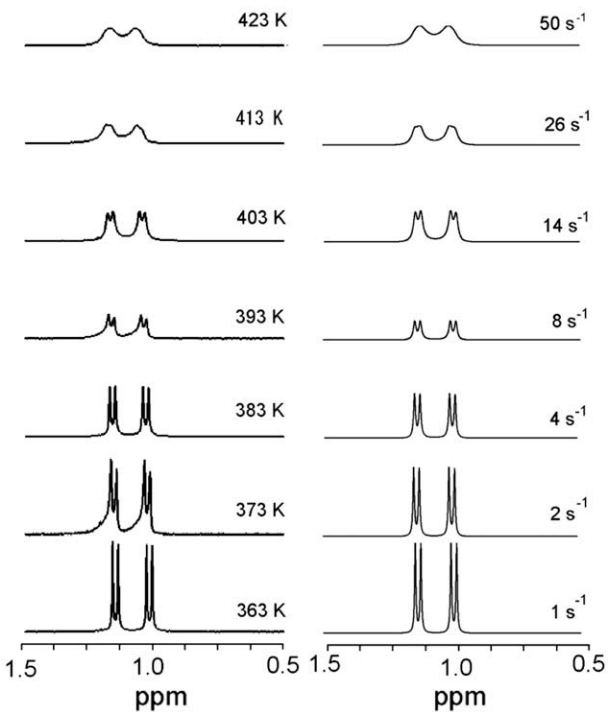

Figure 1. Left: temperature dependent ^1H NMR spectra of the isopropyl methyl signals of **3b** at 400 MHz in DMSO-d_6. Right: line-shape simulations obtained with the indicated rate constants.

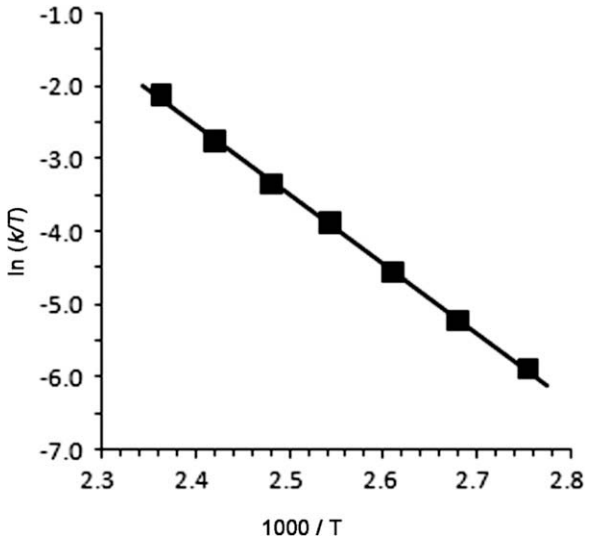

Figure 2. The Eyring plot for the ring inversion of azacalix[4]arene **3b** in DMSO-d_6.

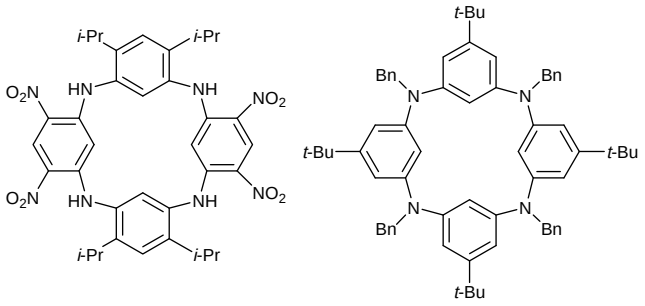

Figure 3. Azacalix[4]arenes possessing diastereotopic protons used for temperature-dependent NMR experiments.

positions adopt the sp^2 configuration. These structural features demonstrate that the dinitrobenzene rings conjugate with the bridging nitrogen atoms. This is further corroborated by comparison of the bond lengths between the nitrogen atom and its connecting aromatic carbons, which are shown in Figure 5. In compound **3a**, the bond length between the nitrogen atom and the dinitrobenzene carbon (1.29 Å) is significantly shorter than that between the nitrogen atom and the benzene carbon (1.41 Å). A similar situation exists in compound **3b**, in which the corresponding bond lengths are 1.35 and 1.44 Å. Obviously, the shortening of the C–N bond lengths as compared to that of the azacalix[4]arene **5**[7j] arises from the conjugation of the dinitrobenzene rings with the bridging nitrogen atoms.

In the solid state, there are intramolecular hydrogen bonding interactions between one of the oxygen atoms of nitro group at the ortho position and the N–H proton (O···H–N hydrogen bonding), which are shown in Figure 4. The O···H–N distances ranging from 1.86 to 2.12 Å are much shorter than the overall mean O···H–N hydrogen bond length (2.30 Å), which was retrieved from the Cambridge Structural Database.[13] Thus, the 1,3-alternate conformation is considered to be stabilized by the hydrogen bonding interactions. In the ^{1}H NMR spectra, the low field chemical shifts (9.62 ppm for **3a**, 9.64 ppm for **3b**) of the N–H protons as compared to the azacalix[4]arene **5** (5.58 ppm)[7j] are observed, which indicate the presence of the O···H–N hydrogen bondings in solution.

The 1,3-alternate conformation of the azacalix[4]arene bearing four methoxy groups at the intra-annular positions is inflexible

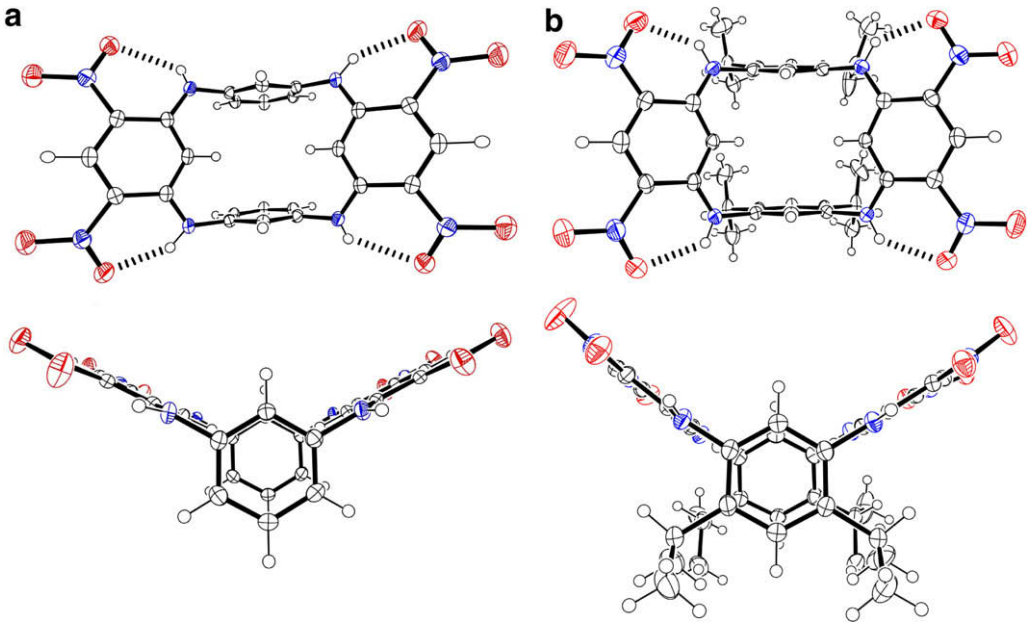

Figure 4. X-ray crystal structure of azacalix[4]arene (a) **3a** and (b) **3b** with thermal ellipsoids drawn at the 50% probability level. Atom coloring: O, red; N, blue; C and H, white. The dotted lines show the intramolecular hydrogen bondings between the N-H proton and one of the oxygen atoms of nitro group. Solvent molecules are omitted for clarity.

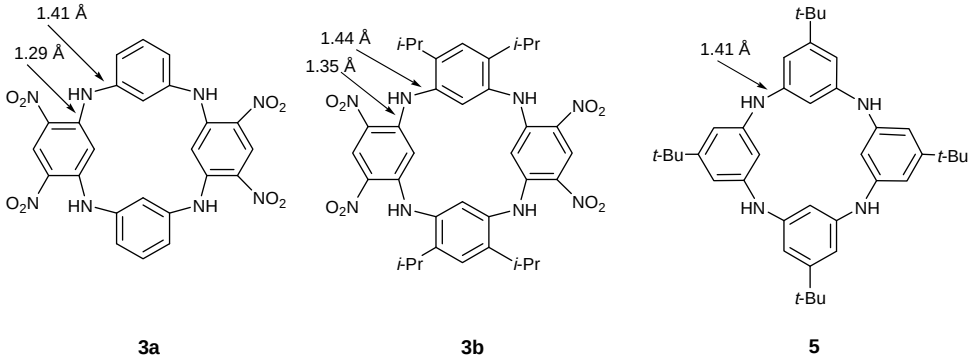

Figure 5. The averaged C-N bond lengths of azacalix[4]arenes.

in solution.[14] This is because its small annulus prevents the passage of the methoxy groups. On the other hand, in the present case, the nitro groups at the extra-annular position play an important role in producing a more rigid macrocyclic framework. There are three reasons which may explain the effect of the nitro group on the conformational inflexibility. The first is the conjugation between the dinitrobenzene rings and the bridging nitrogen atoms, by which the bridging CN bonds are considerably shortened. The second is the intramolecular hydrogen bondings between the N–H proton and one of the oxygen atoms of nitro group at the *ortho* position. This interaction is expected to reduce the mobility of the 1,3-dinitrobenzene rings. The third is the steric hindrance between the nitro groups and the neighboring isopropyl substituents. The bulky alkyl groups may destabilize the transition state of the ring inversion, thus increasing the macrocyclic inversion barrier. For all these reasons, the conformational flexibility of **3b** is significantly diminished when compared to **4.**

In summary, we have found that the tetranitroazacalix[4]arenes can be synthesized by facile nucleophilic aromatic substitution, and that the dinitrobenzene units strongly affect the conformational properties of the azacalix[4]arenes both in the solid state and in solution. Further investigations are planned to provide additional information with regard to the effect of the nitro groups on the conformational properties of the heteroatom-bridged calixarenes.

Supplementary data

Supplementary data (Experimental procedures for the preparation of compound **2b**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.11.095.

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9. *1^4,1^6,5^4,5^6-Tetranitro-2,4,6,8-tetraaza-1,3,5,7(1,3)-tetrabenzenacyclooctaphane* (**3a**): A mixture of **1** (5.0 mmol, 1.02 g), **2a** (5.0 mmol, 0.54 g), and K_2CO_3 (10 mmol, 1.38 g) in DMF (25 ml) was stirred at 100 °C for 2 h under Ar. To this solution were added water and methanol, and the crude product that precipitated was collected by suction and washed with methanol. The insoluble material was recrystallized from DMSO to produce the pure azacalix[4]arene **3a** (0.66 g, 49%). Mp 270 °C (dec.), 400 MHz ^{1}H NMR (DMSO-d_6, 50 °C) δ 5.48 (s, 2H), 7.14 (m, 4H), 7.15 (m, 2H), 7.47 (t, 2H, J = 8.0 Hz), 9.03 (s, 2H), 9.62 (s, 4H, NH), 125 MHz ^{13}C NMR (DMSO-d_6, 50 °C) δ 96.0, 124.7, 125.3, 125.7, 127.2, 131.0, 138.7, 147.1.
10. *1^4,1^6,5^4,5^6-Tetraisopropyl-3^4,3^6,7^4,7^6-tetranitro-2,4,6,8-tetraaza-1,3,5,7(1,3)-tetrabenzenacyclooctaphane* (***3b***): The reaction of **1** and **2b** was analogously conducted as above for 4 h. Recrystallization of the crude product from toluene/ethyl acetate produced the azacalix[4]arene **3b** (42 mg, 12%). Mp 320 °C (dec.), 400 MHz ^{1}H NMR ($CDCl_3$, 30 °C) δ 1.07 (d, 12H, J = 7.0 Hz, –CH(CH_3)$_2$), 1.18 (d, 12H, J = 7.0 Hz, –CH(CH_3)$_2$), 2.97 (sept, 4H, J = 7.0 Hz, –*CH*(CH_3)$_2$), 5.30 (s, 2H, H_{in}), 6.95 (s, 2H, H), 7.36 (s, 2H, H), 9.34 (s, 2H, H_{out}), 9.64 (s, 4H, NH), 125 MHz ^{13}C NMR (DMSO-d_6, 130 °C) δ 22.0 (CH_3), 22.5 (CH_3), 27.5 (CH), 94.5, 124.2, 124.4, 127.7, 128.3, 133.7, 146.0, 147.9.
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12. *X-ray crystal structure analysis*: The X-ray data were collected at 173 K using a Rigaku R-AXIS RAPID-S imaging plate area detector with graphite monochromated Mo Kα (λ = 0.7107 Å) radiation using the ω scan mode. The structure was solved by direct methods with SIR2004[15] and refined with SHELXL-97.[16] Non-hydrogen atoms were anisotropically refined. All hydrogen atoms excluding the N–H groups were included at the calculated positions, and the nitrogen-bonded hydrogens were located by difference electron density map, and refined isotropically. All calculations were performed using the WINGX crystallographic software package.[17] Crystallographic data in cif format (Refs. CCDC 697464, 697465) can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Crystals of **3a** were obtained by recrystallization from dimethylsulfoxide: $C_{24}H_{16}N_8O_8{\cdot}(C_2H_6OS)_2$, M = 700.70, monoclinic, space group $C2/c$ (No. 15), a = 23.367(13), b = 8.649(5), c = 14.379(5), β = 98.90(3), V = 2871(3) Å^3, Z = 4, ρ_c = 1.621 g cm^{-3}, $2\theta_{max}$ = 55°. F(000) = 1456. A total of 20,241 reflections were measured, 3297 unique. The final cycle of full-matrix least squares refinement was based on all observed reflections, 226 variable parameters, with factors of R = 0.068, wR_2 = 0.227, GOF = 1.108, max./min. residual electron density 0.41/−0.55 Å^3.Crystals of **3b** were obtained by recrystallization from acetone: $C_{36}H_{40}N_8O_8{\cdot}(C_3H_6O)_2$, M = 828.92, triclinic, space group $P\bar{1}$ (No. 2), a = 12.471(1), b = 12.644(2), c = 16.263(2), α = 68.632(1), β = 89.778(2), γ = 67.134(2) Å, V = 2171.9(4) Å^3, Z = 2, ρ_c = 1.268 g cm^{-3}, $2\theta_{max}$ = 55°. F(000) = 880. A total of 21,124 reflections were measured, 9864 unique. The final cycle of full-matrix least squares refinement was based on all observed reflections, 557 variable parameters, with factors of R = 0.045, wR_2 = 0.114, GOF = 1.042, max./min. residual electron density 0.42/−0.26 Å^3.
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