Tetrahedron Letters 49 (2008) 6831–6834

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Anti to *syn* isomerization of oxacalix[4]arene bearing two methyl groups at the intra-annular distal positions

Hisatoshi Konishi *, Takayuki Mita, Yusuke Yasukawa, Osamu Morikawa, Kazuhiro Kobayashi

Department of Chemistry and Biotechnology, Graduate School of Engineering, Tottori University 4-101 Koyama-minami, Tottori, Tottori 680-8552, Japan

ARTICLE INFO

Article history:
Received 25 July 2008
Revised 9 September 2008
Accepted 12 September 2008
Available online 17 September 2008

Keywords:
Oxacalixarenene
Metacyclophane
Inversion barrier
VT NMR

ABSTRACT

The thermal isomerization of *anti* to *syn* stereoisomers of oxacalix[4]arene bearing two methyl groups at the intra-annular distal positions was investigated by temperature-dependent NMR spectroscopy. The conversion followed a first-order kinetics, and very slowly proceeded at 473 K in nitrobenzene-d_5 with a half-life of 7.2 h. The free energy of activation ($\Delta G^{\neq}$ 139 kJ mol^{-1}) is much higher than those for the ring inversion of related calix[4]arene derivatives.

Heteroatom-bridged [1$_n$]metacyclophane compounds[1] are promising molecular scaffolds for designing sophisticated functional molecules. Their molecular frameworks vary in size and properties depending on the bridging atoms and on the presence of introduced functional groups at the intra- and/or extra-annular positions (Fig. 1). It is well documented that the introduction of bulky substituents to the intra-annular positions of the calix[4]-arene can lead to the formation of four non-interconvertible stereoisomers, *cone*, *partial cone*, *1,2-alternate*, and *1,3-alternate* conformers. These stable conformers represent a special three-dimensional arrangement with different potential applications as molecular scaffolds.

Recently, much effort has been focused on the synthesis of oxygen atom-bridged [1$_n$]metacyclophanes, the so-called oxacalix[*n*]arenes.[2] Although a small number of oxacalix[4]arenes with substituents at the intra-annular positions are known, information on the dynamic conformational properties of this molecular framework is limited. As we reported previously,[2e] the oxacalix[4]arene **1a**, with two propyl groups at the *distal* positions on the intra-annular rim, can exist in two stereoisomers, that is, the *syn*-isomer

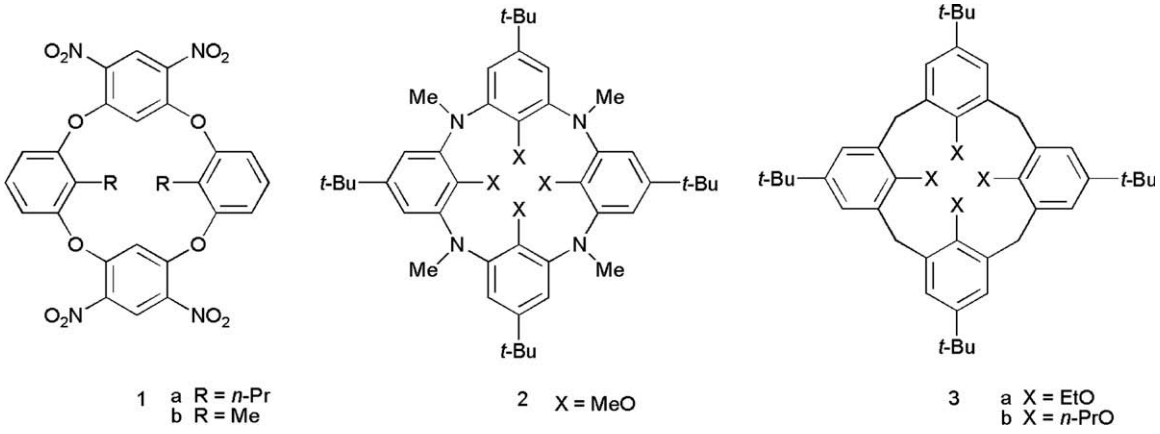


Figure 1. [1$_n$]Metacyclophane compounds having substituents on the intra-annular rim.

* Corresponding author. Tel.: +81 857 31 5262; fax: +81 857 31 5331.
E-mail address: konis@chem.tottori-u.ac.jp (H. Konishi).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.075

(*1,3-alternate* conformation) and the *anti*-isomer (*partial cone* conformation). Furthermore, their conformational interconversion in solution could not be observed by ^{1}H NMR spectroscopy at high temperatures. Recently, it was reported that the 1,3-alternate conformation of the azacalix[4]arene tetramethoxy derivative **2** is stable in solution.[3] These observations are in contrast to the properties of calix[4]arene tetraalkyl ether derivatives **3**. For instance, on the NMR time scale, the tetraethoxy derivative **3a** equilibrates in solution above 100 °C to a mixture of all four possible conformers, although immobilization of the conformational interconversion is achieved in the tetrapropoxy derivative **3b**.[4] To gain further insight into the rigidity of the oxacalix[4]arene core, we have carried out a temperature-dependent ^{1}H NMR spectroscopic study of the dimethyl derivative **1b**, which bears two smaller methyl groups at the distal position. Although the synthesis of the oxacalix[4]arene **1b** has been reported,[5] its conformational properties in solution and in the solid state were not described.

The CsF-catalyzed aromatic nucleophilic substitution of 2-propylresorcinol **4a** with 1,5-difluoro-2,4-dinitrobenzene **5** in DMF produces a mixture of two cyclic tetramers (***syn*-1a** and ***anti*-1a**) and the cyclic hexamer. Since the substitution is reversible in the presence of CsF, the product ratio depends on the reaction time. Eventually, the thermodynamically most stable product ***syn*-1a** is obtained in good yield.[2e]

On the other hand, under analogous conditions, the reaction of 2-methylresorcinol **4b** with **5** gave a mixture of ***syn*-1b** and ***anti*-1b** in a ratio of about 3:2.[†] This is because the cyclic tetramers have very low solubility in DMF, and therefore, the *anti*-isomer was not smoothly converted to the *syn*-isomer. In fact, upon heating the mixture of two isomers in the presence of CsF at 130 °C in nitrobenzene, which is a slightly better solvent for the cyclic oligomers, the minor component was converted to the major component. On the other hand, in the absence of CsF under the same conditions, the conversion could not be observed. These experiments demonstrate that the thermodynamically less stable ***anti*-1b** isomerizes to the more stable ***syn*-1b** via a C–O bond cleavage mechanism.[2e] Furthermore, when the CsF-catalyzed reaction was conducted in nitrobenzene, only ***syn*-1b** was isolated in good yield.[‡]

The structure of ***syn*-1b** was unequivocally confirmed by X-ray[§] crystallography. Single crystals suitable for X-ray analysis were obtained by recrystallization from hot nitrobenzene. Its ORTEP drawing

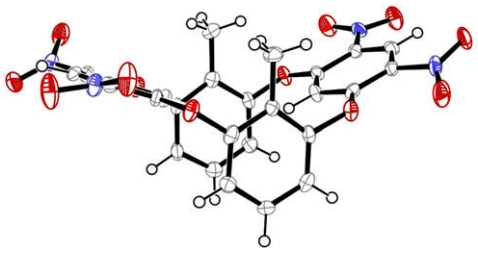


Figure 2. ORTEP drawing of ***syn*-1b.** Thermal ellipsoids were drawn at the 50% probability level.

is shown in Figure 2. Four bridging oxygen atoms are located almost in the same plane with a deviation of less than 0.096 Å. The two methylbenzene rings are almost perpendicular to this plane. On the other hand, the dihedral angle between the two dinitrobenzene rings is 135.0°. The molecular structure is very similar to that of the dipropyl derivative ***syn*-1a**.[2e] ^{1}H NMR analysis provided information about the conformation of ***syn*-1b** in solution. In the 400 MHz ^{1}H NMR spectrum (DMSO-d_6, 130 °C), ***syn*-1b** showed one methyl signal at 1.80 (s, 6H) and four aromatic signals at 5.42 (s, 2H), 7.21 (d, 4H, J = 8.0 Hz), 7.45 (t, 2H), and 8.93 (s, 2H). The aromatic signal at a quite higher field (δ 5.42) compared to the other aromatic protons is assigned to the intra-annular aromatic protons (H_{in}, see Scheme 1). This is because the H_{in} is located within the shielding region of the neighboring methylbenzene rings. Hence, the preferred conformation of ***syn*-1b** in solution is presumed to be similar to the one observed in the solid state.

All attempts failed to isolate the *anti*-isomer from the mixture due to its extremely limited solubility in common organic solvents. On the basis of the ^{1}H NMR spectrum, the major component was identified as ***syn*-1b**, whereas the minor component was assigned to the ***anti*-1b** by comparison of the chemical shifts for the H_{in} protons with ***anti*-1a**, 5.67 and 5.63 ppm, respectively.

Next, we examined the thermal conversion of ***anti*-1b** to ***syn*-1b**. In this process, the intra-annular methyl groups pass through the cavity annulus (Scheme 2). Since the reaction requires a high temperature, we chose nitrobenzene as the solvent for our kinetic experiments. A sample of higher ***anti*-1b** content (70%) was obtained by repeated recrystallization from hot nitrobenzene, and its conversion was followed by ^{1}H NMR (Fig. 3). The relative concentration of ***anti*-1b** and ***syn*-1b** was determined by integrating the peak areas of their H_{in} signals (normalizing against the total H_{in} peak areas for both isomers). At 473 K, a plot of $\ln(C_0/C)$ versus time (Fig. 4) gave a straight line (r^2 = 0.998) over a period of three half-lives. From the slope of this line, a first-order rate constant of 2.67×10^{-5} s^{-1}[¶] is obtained. The conversion is a very slow process with a half-life of 2.60×10^4 s (7.2 h). The linear plots obtained at 463 K and 453 K are also depicted in Figure 4. Based on these data, an Eyring plot of $\ln(k/T)$ versus $1/T$ was constructed (Fig. 5); from the slope and intercept of this straight line (r^2 = 0.999), $\Delta H^{\neq}$ = 105 kJ mol^{-1} and $\Delta S^{\neq}$ = −113 J K^{-1} mol^{-1} were calculated. The free energy of activation for the isomerization ($\Delta G^{\neq}$) is deduced to be 139 kJ mol^{-1} under standard conditions. This value is extremely high compared with the free energy of activation for the ring inversion of the calix[4]arenes bearing four small substituents at the intra-annular positions. For example, the $\Delta G^{\neq}$ value for the tetramethoxy derivative is ca. 65 kJ mol^{-1}.[6]

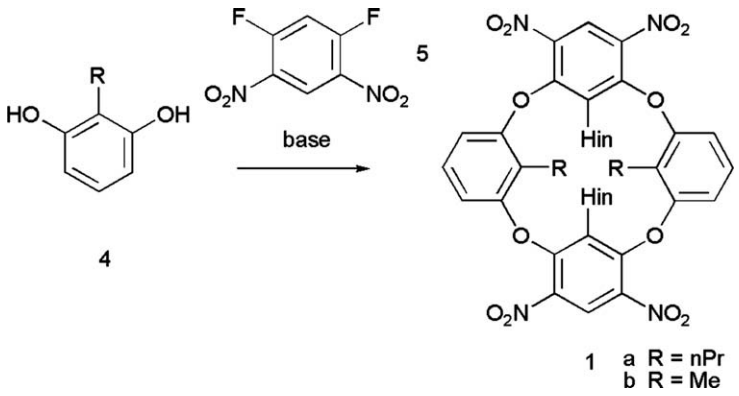
The increase in the energy barrier reflects the fact that the cavity of the oxacalix[4]arene is smaller than that for the calix[4]-arene. The annulus defined by the four bridging atoms is about 4.82 Å × 4.81 Å, whereas the annulus of calix[4]arene tetramethyl

[†] A mixture of ***syn*-1b** and ***anti*-1b**: The reaction in DMF was conducted as described above at 100 °C for 2 h. Recrystallization of the crude product from nitrobenzene gave a mixture of ***syn*-1b** and ***anti*-1b** in a ratio of about 3:2 (total yield 68%). ***Anti*-1b**: 400 MHz ^{1}H NMR (DMSO-d_6, 130 °C) 1.89 (s, 6H), 5.67 (s, 2H, H_{in}), 7.15 (d, 4H, J = 8.0 Hz), 7.45 (t, 2H), 8.90 (s, 2H).

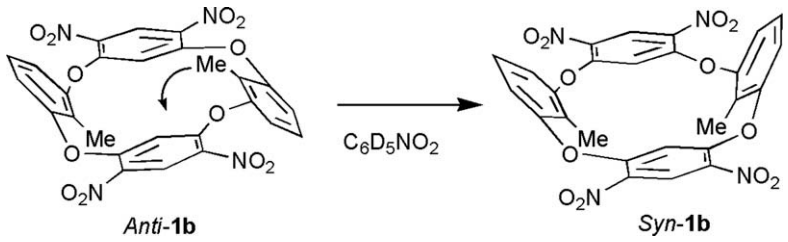
[‡] Synthesis of ***syn*-1b**: A mixture of 2-methylresorcinol **4b** (124 mg, 1 mmol), 1,5-difluoro-2,4-dinitrobenzene **5** (204 mg, 1 mmol), and CsF (300 mg, 2 mmol) in nitrobenzene (5 ml) was stirred at 130 °C for 3 h. After removal of most of the solvent under reduced pressure, the residual material was washed with methanol and water, and then recrystallized from nitrobenzene to yield ***syn*-1b** in 70% yield. 400 MHz ^{1}H NMR (DMSO-d_6, 130 °C) 1.80 (s, 6H), 5.42 (s, 2H, H_{in}), 7.21 (d, 4H, J = 8.0 Hz), 7.45 (t, 2H), 8.93 (s, 2H).

[§] 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 SHELXL-86 and refined with SHELXL-97.[8] The non-hydrogen atoms were anisotropically refined. All hydrogen atoms were included at the calculated positions and isotropically refined. All calculations were performed using the WINGX crystallographic software package.[9] Crystals of ***syn*-1b** were obtained by recrystallization from nitrobenzene: $C_{26}H_{16}N_4O_{12}$, M = 576.43, monoclinic, space group $P2_1/a$ (No. 14), a = 11.525(2), b = 11.090(2), c = 19.061(4), β = 95.498(7), V = 2424.9(8) Å^3, Z = 4, ρ_c = 1.579 g cm^{-3}, 2θmax = 55°. F(000) = 1184. A total of 38,844 reflections were measured, and 5544 were unique. The final cycle of the full-matrix least squares refinement was based on all the observed reflections, 380 variable parameters, with factors of R = 0.051, wR_2 = 0.128, GOF = 0.956, and max./min. residual electron density of 0.43/−0.42 Å^3. Crystallographic data in cif format (ref. CCDC 695851) can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

[¶] $k_{453} = 7.82 \times 10^{-6}$ s^{-1}, $k_{463} = 1.45 \times 10^{-5}$ s^{-1}, $k_{473} = 2.67 \times 10^{-5}$ s^{-1}. $\Delta G^{\neq} = \Delta H^{\neq} - T\Delta S^{\neq}$, T = 298 K.



Scheme 1. Base-catalyzed synthesis of oxacalix[4]arenes.



Scheme 2. The conversion of ***anti*-1b** to ***syn*-1b.**

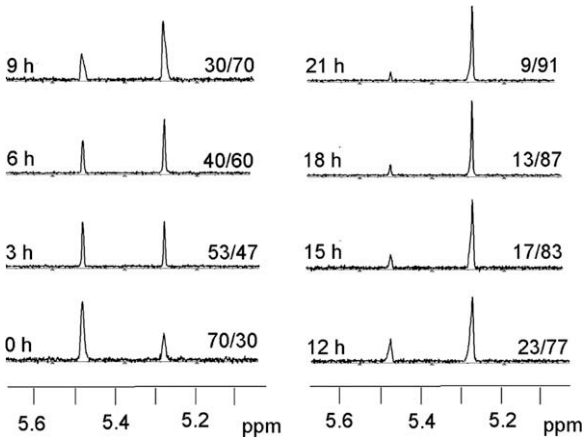


Figure 3. ^{1}H NMR spectral changes for the H_{in} protons of ***anti*-1b** (5.49 ppm) and ***syn*-1b** (5.29 ppm) during isomerization at 473 K in nitrobezene-d_5. The ratios are the relative intensities of the H_{in} signals.

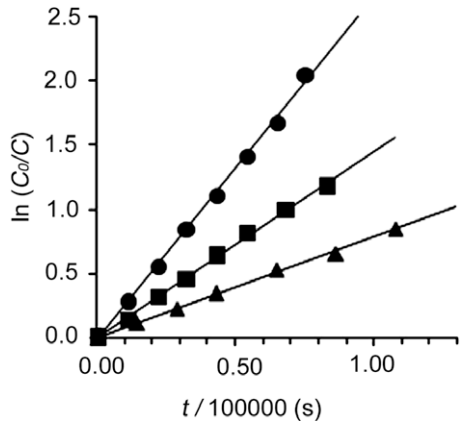


Figure 4. First-order plots for *anti* to *syn* isomerization of **1b** in nitrobenzene-d_5 at 473 (●), 463 (■), and 453 K (▲).

ether is about 5.07 Å × 5.07 Å (Fig. 6).[7] It is likely that the steric hindrance due to the small annulus suppresses the passage of the methyl groups through the annulus. Furthermore, the conjugation between the bridging oxygen atoms and dinitrobenzene rings increases the conformational rigidity of the macrocyclic framework. In fact, the bond lengths between the oxygen atom and its connecting aromatic carbons, 1.356 Å for dinitrobenzene and 1.411 Å for methylbenzene, indicate that oxygen atoms are conjugated with the dinitrobenzene rings.

In conclusion, we have determined the thermodynamic parameters for the ring conversion of oxacalix[4]arene. In comparison to the calix[4]arenes, an extremely high-energy barrier was observed. Further investigations are planned to provide additional information with regard to the effect of the nitro groups on the conformational properties of oxacalix[4]arenes and related compounds.

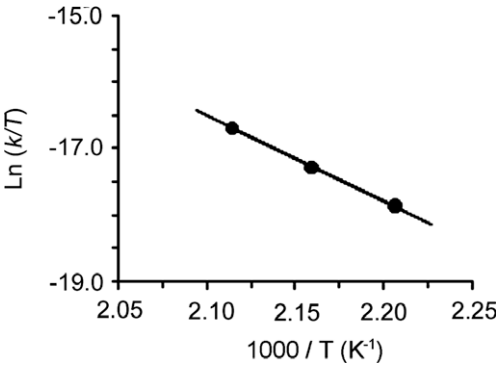


Figure 5. Eyring plot for *anti* to *syn* isomerization of **1b** in nitrobenzene-d_5.

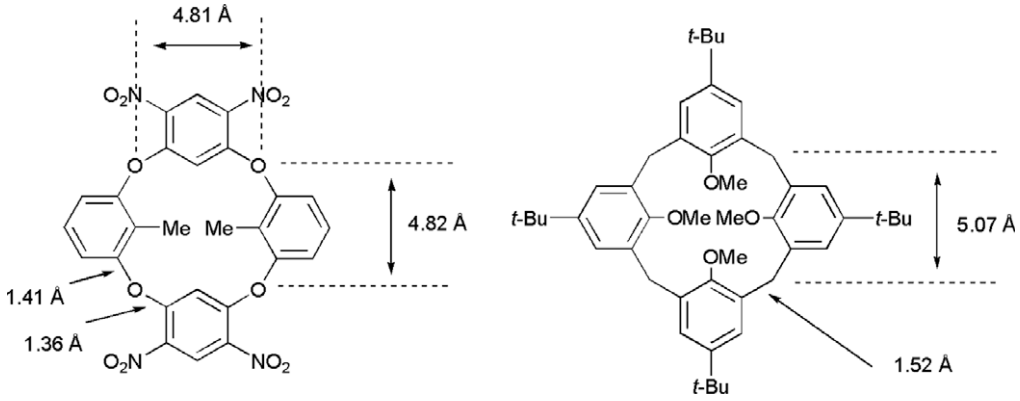


Figure 6. The averaged bond lengths and the distance between bridging atoms of oxacalix[4]arene ***syn*-1b** and calix[4]arene octamethyl ether (partial cone conformation).

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