Journal of Molecular Structure 1098 (2015) 47–54

Contents lists available at ScienceDirect

Journal of Molecular Structure

journal homepage: http://www.elsevier.com/locate/molstruc

Synthesis and conformational studies of calixarene analogue chiral [3.3.1]metacyclophanes

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ARTICLE INFO

Article history:
Received 8 April 2015
Received in revised form
11 May 2015
Accepted 28 May 2015
Available online 30 May 2015

Keywords:
Metacyclophanes
Macrocycles
Calixarenes
Intramolecular hydrogen bonding
O–methylation
Chirality

ABSTRACT

Trihydroxy[3.3.1]metacyclophane, which can be regarded as an unsymmetrical or incomplete "homocalix[3]arene", has been prepared from trimethoxy[3.3.1]metacyclophane by demethylation with trimethylsilyl iodide in MeCN. Di-*O*-methylation at the lower rim of trihydroxy[3.3.1]metacyclophane in the presence of K_2CO_3 in acetone afforded a novel, inherently chiral calixarene–analogue, namely a macrocyclic [3.3.1]metacyclophane, possessing C_1 symmetry. The inherent chirality of the two conformers was characterized by ^{1}H NMR spectroscopy by addition of an excess of Pirkle's chiral shift reagent [(*S*)-(+)-1-(9-anthryl)-2,2,2-trifluoroethanol], which caused a splitting of the OMe group and AB patterns corresponding to the methylene protons.

1. Introduction

Calixarenes and related macrocycles have been receiving considerable attention due to their host–guest chemistry as ionophoric receptors [1,2] and potential enzyme mimics in biology [3–5]. The conformational characteristics of macrocyclic cyclophanes, especially those of calix [*n*]arenes, have been extensively investigated in the past decade [6,7]. Their phenolic hydroxyl groups are well ordered in a cyclic array due to strong intramolecular hydrogen bonding. C.D Gutsche reported [8] the role of hydrogen bonding in conformational mobolities of calix[*n*]arenes (n = 4–20). Kanters et al. have reported [9] that 27,28-diethoxy-*p*-*tert*-butylcalix[4]arene exhibits interconversion due to intramolecular hydrogen bonding. Considering the role of the hydrogen bonding, it is surprising that reports on the preparation of calix[3]arenes and their analogues containing three aromatic rings and the characterization of their conformational mobility due to hydrogen bonding has been very limited [10–14]. The first successful preparation of *p*-halocalix[3]arenes was reported in 1982 and no follow up reports have appeared [10]. This lack of research seems to be due to the much more strained structure of calix[3]arenes than larger calix[*n*]arenes. Homocalixarenes have been the subject of scientific interest for a couple of decades [14] and belong to a general class of calixarenes [1,2] in which the linker methylene bridges are partly or completely replaced by ethano or longer bridges [2,15,16]. Introduction of longer bridge into the methylene bridges of the conventional calixarenes, has rendered the homocalixarenes unique structural characteristics. One of the salient structural features is the self fine tuning of the conformations and the cavity sizes of the macrocycles. Such compounds have significantly different properties to those of their corresponding calixarene analogues.

Shinkai and co-workers have reported [11,12] that the introduction of substituents at the hydroxyl groups of hexahomotrioxacalix[3]arene led to conformationally rigid structures, *i.e.* fixed conformations such as *cone* and *partial-cone*. Among the numerous methods of chemical modification of calixarenes, the *O*-alkylation of the phenolic hydroxyl groups or modification at the upper rim is of great importance which leads to inherent chirality in

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http://dx.doi.org/10.1016/j.molstruc.2015.05.036
0022-2860/

conventional calixarenes [12,17–21]. Inherently chiral calixarenes are unusual types of chiral calixarenes which are not based on a chiral subunit but are due to the absence of a plane of symmetry or an inversion center in the molecule [22–25]. Inherently chiral calixarenes are considered as promising host molecules for molecular recognition [26,27] and as asymmetric catalysts [17]. A large number of racemic, inherently chiral calixarenes have been reported and some of them have been resolved into the enantiomerically pure form [22–25]. Replacement of the bridging methylene linkage by hetero-atoms has attracted considerable interest as a way of forming new members of calixarene family [28–31] and most recently as a technique to synthesize inherent chiral calixarene analogues [32]. However, there are few reports concerning the introduction of substituents at the hydroxyl groups of asymmetric or incomplete homocalix[3]arenes having three conformers; *i.e. cone* and 2-*partial-cone* and 3-*partial-cone* conformers (Fig. 1).

Due to the intramolecular hydrogen bond interactions between the lower-rim phenolic hydroxy groups of conventional calix[4] arenes, it adopts stable *cone*, *partial-cone*, 1,3-*alternate* and 1,2-*alternate* conformations [6,7]. In contrast to the conventional calix [4]arenes, the conformational isomerism in the present system is relatively simple. Owing to the intrinsic structural features, we envisaged that calix [3]arenes would provide a unique platform for the construction of inherently chiral macrocycles and prompted us to attempt the synthesis of inherently chiral propane bridged homocalixarenes [33]. The main objective of this research is to synthesize asymmetric or incomplete calixarene analogues of the inherently inherently chiral [3.3.1]metacyclophane bearing two propane bridges.

2. Experimental

2.1. General procedures

All melting points (Yanagimoto MP-S1) are uncorrected. Proton nuclear magnetic resonance (^{1}H NMR) and ^{13}C NMR spectra were recorded on a Nippon Denshi JEOL FT-300 NMR spectrometer and Varian-400 MR-vnmrs400 spectrometer. Chemical shifts are reported as δ values (ppm) relative to internal Me_4Si. Mass spectra were obtained on a Nippon Denshi JMS–01SA–2 mass spectrometer at an ionization energy of 70 eV; *m/z* values reported include the parent ion peak. Infrared (IR) spectra were obtained on a Nippon Denshi JIR-AQ2OM spectrophotometer as KBr disks. Elemental analyses were performed by Yanaco MT-5. G.L.C. analyses were performed by Shimadzu gas chromatograph, GC-14A; Silicone OV–1, 2 m; programmed temperature rise, 12 °C min^{-1}; carrier gas nitrogen, 25 mL min^{-1}. Silica gel columns were prepared by use of Merk silica gel 60 (63–200 μm).

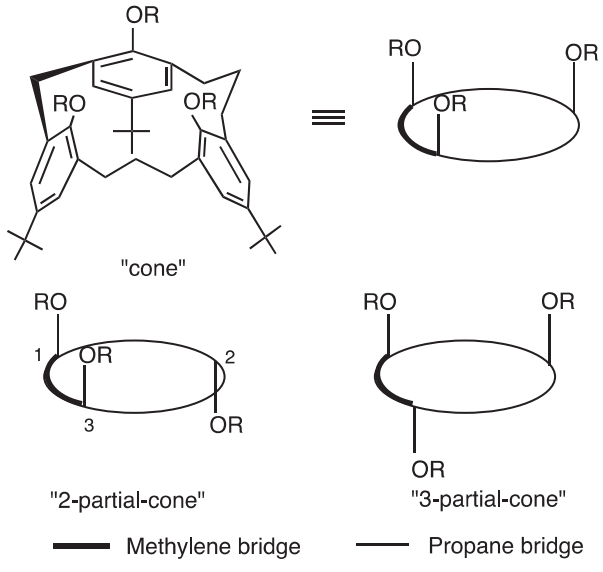

Fig. 1. Possible conformers for [3.3.1]metacyclophanes.

2.2. Materials

TosMIC adduct **1** was prepared according to our reported data [34,35] and 1,1-bis(3-bromomethyl-5-*tert*-butyl-2-methoxyphenyl) methane **2**, was previously described [36]. 6,15,22-Tri-*tert*-butyl-9,18,25-trimethoxy[3.3.1]metacyclophane-2,11-dione **3** was synthesized by the coupling reaction of TosMIC adduct **1** with **2** according to the reported procedure [37].

2.3. Synthesis of 6,15,22-tri-tert-butyl-9,18,25-trimethoxy[3.3.1] metacyclophane (*4*)

A mixture of **3** (200 mg, 0.33 mmol), NaOH (200 mg, 5.0 mmol), 100% hydrazine hydrate (0.35 mL, 6.2 mmol), and triethylene glycol (5 mL) was heated at 120 °C for 2 h and then at 200 °C for 3 h. The cooled mixture was poured into water (50 mL), acidified with diluted HCl, and extracted with CH_2Cl_2 (5 × 30 mL), washed with water (2 × 20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified on silica gel using benzene as eluent to give crude **4** as a white solid. Recrystallization from hexanes afforded 6,15,22-tri-*tert*-butyl-9,18,25-trimethoxy [3.3.1]metacyclophane **4** (129 mg, 68%) as a white solid. M.p. 199–200 °C. IR: ν_{max} (KBr)/cm^{-1}: 2900, 2800, 1480, 1180 and 1000. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.19 (9H, s, *t*Bu), 1.27(18H, s, *t*Bu × 2), 1.80 (3H, s, O*Me*), 1.98–2.28 (10H, m, *CH*$_2$), 3.01 (2H, d, *J* = 2.19, *CH*$_2$), 3.43 (1H, d, *J* = 12.1 Hz, *CH*$_2$), 3.77 (6H, s, O*Me*), 4.50 (1H, d, *J* = 12.1 Hz, *CH*$_2$), 6.81 (2H, s, Ar–*H*), 6.96 (2H, d, *J* = 2.5, Ar–*H*) and 7.35 (2H,d, *J* = 2.5 Hz, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.67 (CH_2), 30.45 (CH_2), 31.59 ($C(CH_3)_3$), 31.77 ($C(CH_3)_3$), 32.66 (CH_2), 34.02 (CH_2), 34.08 (CH_2), 58.41 (OCH_3), 61.11 (OCH_3), 124.08 (ArC), 125.40 (ArC), 126.72 (ArC), 134.29 (ArC), 134.68 (ArC), 136.35 (ArC), 145.04 (ArC), 145.21 (ArC), 154.32 (ArC) and 155.56 (ArC) ppm. FABMS: *m/z*: 584.45 [M$^+$]. $C_{40}H_{56}O_3$ (584.89): calcd. C 82.14, H 9.65. Found: C 81.98, H 9.67.

2.4. Synthesis of 6,15,22-tri-tert-butyl-18,25-dihydroxy-9-methoxy [3.3.1]metacyclophane (*5*)

A solution of BBr_3 (1 mL, 10.6 mmol) in CH_2Cl_2 (3 mL) was added gradually to a solution of **4** (100 mg, 0.17 mmol) in CH_2Cl_2 (5 mL) at 0 °C. After the reaction mixture had been stirred at room temperature for 4 h, it was poured into ice-water (20 mL), extracted with CH_2Cl_2 (2 × 50 mL), washed with water (2 × 10 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give crude **5** as a white solid. Recrystallization from benzene afforded 6,15,22-tri-*tert*-butyl-18,25-dihydroxy-9-methoxy[3.3.1]metacyclophane **5** (60 mg, 63%) as white powder. M.p. 209–210 °C. IR: ν_{max} (KBr)/cm^{-1}: 3625, 3320 (OH), 1495 and 1215. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.22 (9H, s, *t*Bu), 1.28(18H, s, *t*Bu × 2), 1.72 (3H, s, O*Me*), 1.76–2.35 (10H, m, *CH*$_2$), 3.04 (2H, m, *CH*$_2$), 3.61 (1H, d, *J* = 13.3 Hz, *CH*$_2$), 4.36 (1H, d, *J* = 13.3 Hz, *CH*$_2$), 6.29 (2H, s, *OH*, Exchanged by D_2O), 6.90 (2H, s, Ar–*H*), 6.96 (2H, d, *J* = 2.5 Hz, Ar–*H*) and 7.25 (2H, s, Ar–*H*) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.58 (CH_2), 29.92 (CH_2), 31.42 (CH_2), 31.56 ($C(CH_3)_3$), 31.58 ($C(CH_3)_3$), 31.76 (CH_2), 33.93 (CH_2), 34.15 (CH_2), 58.25 (OCH_3), 124.31 (ArC), 125.21 (ArC), 126.81 (ArC), 127.58 (ArC), 128.16 (ArC), 136.36 (ArC), 143.15 (ArC), 145.78 (ArC), 149.15 (ArC) and 154.17 (ArC) ppm. FABMS: *m/z*: 556.44 [M$^+$]. $C_{38}H_{52}O_3$