Pergamon

Tetrahedron Letters 41 (2000) 1393–1396

TETRAHEDRON
LETTERS

Synthesis and structure of new cyclophanes containing benzofuran and benzene rings

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Received 13 October 1999; revised 12 November 1999; accepted 3 December 1999

Abstract

Macrocycles **2**–**3** are synthesized by reacting 2,4-dihydroxybenzophenone with α,α′-dibromo-*p*-xylene and then 1,6-diiodohexane. Photoirradiation of **2** yields a new type of cyclophane **5** containing two benzo[*b*]furan rings via intramolecular δ-hydrogen abstraction. X-Ray analysis shows that **5** has a rectangular cavity of ca. 5.9 Å×7.6 Å. © 2000 Elsevier Science Ltd. All rights reserved.

The design and synthesis of medium- and large-sized ring systems is an area of current interest in supramolecular chemistry.[1] In particular, cyclophanes, macrocycles containing aromatic groups, represent the central class of synthetic receptors in molecular recognition due to the hydrophobicity and π-stacking interactions of their aromatic groups.[2] Here, we describe the synthesis of new macrocycles **2**–**3** utilizing 2,4-dihydroxybenzophenone as a connecting unit. Photochemical irradiation of **2** yields benzo[*b*]furan ring-containing cyclophane **5** via intramolecular δ-hydrogen abstraction. X-Ray analysis shows that **5** has a well-defined rectangular cavity.

The synthesis of **2**–**3** is shown in Scheme 1. The reaction mixture of 2,4-dihydroxybenzene (0.500 g, 2.33 mmol), α,α′-dibromo-*p*-xylene (0.305 g, 1.16 mmol), and K_2CO_3 (0.930 g, 6.73 mmol) was stirred in acetone (20 ml) at room temperature for 27 h. After water (10–20 ml) was added to the reaction mixture, the precipitate was filtered and washed with acetone to afford pure **1** (0.500 g, 0.94 mmol, 81% yield).[3] The high yield of **1** without any significant side products can be attributed to the differential reactivity between two hydroxyl groups in 2,4-dihydroxybenzophenone: the *o*-hydroxyl group to carbonyl forms an intramolecular hydrogen bond and becomes less reactive. *o*-Hydroxyl groups of **1** were then reacted with 1,6-diiodohexane: to the suspension of **1** (0.400 g, 0.75 mmol) and K_2CO_3 (0.622 g, 4.50 mmol) in acetone (80 ml) at reflux was added a solution of 1,6-diiodohexane (0.263 g, 0.78 mmol) in acetone (20 ml) very slowly and reflux was continued for 36 h. The reaction mixture was filtered, and the filtrate was concentrated and treated with chloroform. The undissolved solid which was mostly the unreacted starting material **1** was removed by filtration and the filtrate was purified by silica

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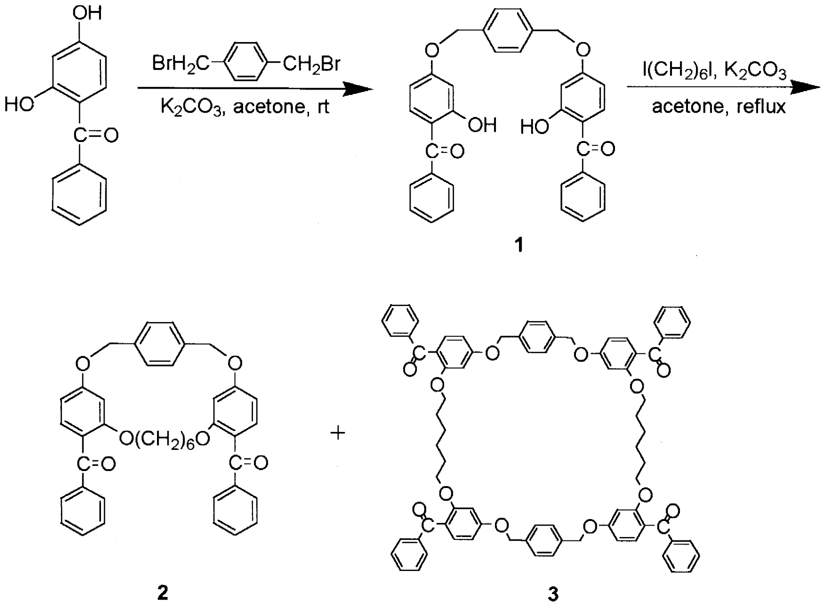
PII: S0040-4039(99)02300-X

gel chromatography eluting with dichloromethane and then 40:1 dichloromethane:ethyl acetate to give 0.100 g (21% yield) of **2**. Washing the precipitates obtained from the original reaction mixture with water to remove potassium carbonate yielded 15 mg (3% yield) of **3** after recrystallization from chloroform.

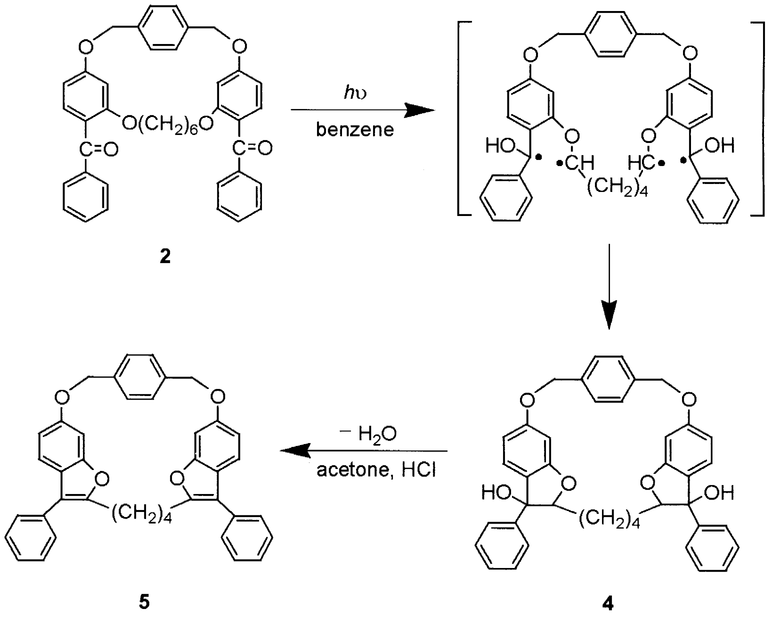


Scheme 1.

The structure of **1** was confirmed by ^{1}H NMR spectrum: the broad singlet at very low field (δ 11.95) corresponds to the *o*-hydroxyl proton hydrogen-bonded to carbonyl, proving the differential reactivity between two hydroxyl groups in 2,4-dihydroxybenzophenone. The macrocycles **2** and **3** were characterized by ^{1}H and ^{13}C NMR spectra, mass spectra and elemental analysis:[4,5] the molecular weight of **3** was found to be exactly twice that of **2** and the patterns of their ^{1}H and ^{13}C NMR spectra are very similar.

It has been known that *o*-alkoxybenzophenones photocyclize readily to benzofuranols via δ-hydrogen abstraction.[6] Since the macrocycle **2** contains two *o*-alkoxybenzophenone moieties, it is hoped that photoirradiation of **2** would lead to a new type of cyclophane containing two benzo[*b*]furan ring. The photocyclization reaction is shown in Scheme 2. A solution of **2** (0.100 g) in benzene (10 ml) was irradiated using a low pressure mercury lamp[7] for 3 h under a nitrogen atmosphere and then the reaction mixture showed several spots with virtually no starting material remaining. Without attempting isolation and separation of diastereoisomers of the benzofuranol derivative **4**, the concentrated reaction mixture was treated with a few drops of 1 M HCl in acetone, which produced **5** (20 mg, 21% yield) after silica gel chromatography eluting with 1:1 dichloromethane:hexane. The structure of the compound **5** was characterized by ^{1}H and ^{13}C NMR spectra, mass spectra and elemental analysis.[8] Formation of **5** starting from **1** is firm proof that the structures **1** and **2** are correct, which is, on the other hand, an additional clear indication that the initial alkylation of 2,4-dihydroxybenzophenone occurs selectively at the *p*-hydroxyl group.

The structure of the macrocycle **5** was further determined by single crystal X-ray analysis[9] and the ORTEP drawing is shown in Fig. 1. The cyclophane **5** has 2-fold symmetry along the *b*-axis. The dihedral angle between a benzofuran ring and the benzene ring of the *p*-xylyl group is 85.9°, and two benzofuran rings which are related by 2-fold symmetry are almost parallel to each other with a dihedral angle of



Scheme 2.

171.8°. These conformations make the molecule form such a rectangular cavity that the distances of O1–O1′=7.37 Å, O2–O2′=4.49 Å, O2–C8′=5.88 Å, and C1–C20=7.56 Å.

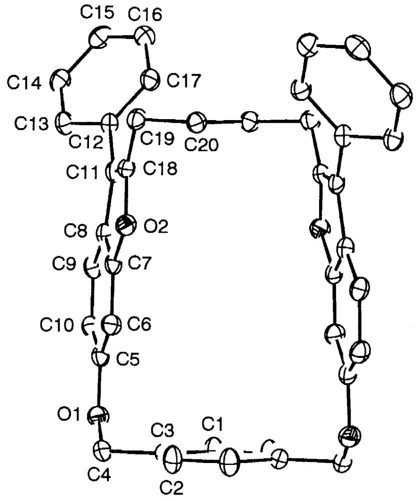


Fig. 1. ORTEP drawing of the X-ray structure of **5**

In summary, we have developed a facile route for new cyclophanes containing benzofuran and/or benzene rings utilizing 2,4-dihydroxybenzophenone as the connecting unit. Differential reactivity between two hydroxyl groups in 2,4-dihydroxybenzophenone and photocyclization of two *o*-alkoxybenzophenone moieties in the cyclophane **2** via δ-hydrogen abstraction have been demonstrated. Single crystal X-ray analysis showed that the macromolecule **5** has a rectangular cavity. Synthesis of other cyclophanes using this scheme and investigation on the molecular recognition properties of these macrocycles as synthetic receptors are underway.

Acknowledgements

Support for this work by the Ministry of Education of the Republic of Korea (BSRI-98-3433) and by the Center for Biofunctional Molecules is gratefully acknowledged. NMR and mass spectra were taken at the Center for Research Facilities at the Chungnam National University and the Korea Basic Science Center, respectively.

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3. Compound **1**: mp 175–176°C; ^{1}H NMR (DMSO-d_6) δ 5.21 (s, 4H, $\text{-O}\mathit{CH}_2\text{-C}_6\text{H}_4\text{-}\mathit{CH}_2\text{O-}$), 6.65–6.58 (m, 4H, two Ar-H *ortho* to -OH and two Ar-H *para* to -OH), 7.7–7.4 (m, 16H, Ar-H), 11.95 (broad s, 2H).
4. Compound **2**: mp 172°C; ^{1}H NMR (CDCl_3) δ 1.0–0.9 (m, 4H, $\text{-OCH}_2\text{CH}_2\mathit{(CH_2)_2}\text{CH}_2\text{CH}_2\text{O-}$), 1.35–1.2 (m, 4H, $\text{-OCH}_2\mathit{CH}_2\text{-(CH}_2)_2\mathit{CH}_2\text{CH}_2\text{O-}$), 3.59 (t, *J*=6 Hz, 4H, $\text{-O}\mathit{CH}_2\text{(CH}_2)_4\mathit{CH}_2\text{O-}$), 5.27 (s, 4H, $\text{-O}\mathit{CH}_2\text{-C}_6\text{H}_4\text{-}\mathit{CH}_2\text{O-}$), 6.26 (d, *J*=2 Hz, 2H, Ar-H *ortho* to $\text{-O(CH}_2)_6\text{-}$), 6.71 (dd, *J*=8 and 2 Hz, 2H, Ar-H *para* to $\text{-O(CH}_2)_6\text{-}$), 7.5-7.3 (m, 12H, Ar-H), 7.70 (dd, *J*=7 and 2 Hz, 4H, Ar-H *ortho* to C=O in two benzoyl groups); ^{13}C NMR (CDCl_3) δ 23.6, 27.0, 67.8, 69.8, 99.1, 109.3, 121.7, 126.7, 127.9, 129.3, 131.9, 132.1, 136.8, 139.0, 158.9, 162.0, 195.8; mass (EI) 104 (100), 105 (96), 215 (26), 316 (42), 317 (90), 508 (53), 612 (99, M$^+$), 613 (43); anal. calcd for $\text{C}_{40}\text{H}_{36}\text{O}_6$: C, 78.41; H, 5.92. Found: C, 78.34; H, 5.60.
5. Compound **3**: mp 220–223°C; ^{1}H NMR (CDCl_3) δ 0.9–0.8 (m, 8H, $\text{-OCH}_2\text{CH}_2\mathit{(CH_2)_2}\text{CH}_2\text{CH}_2\text{O-}$), 1.35–1.2 (m, 8H, $\text{-OCH}_2\mathit{CH}_2\text{(CH}_2)_2\mathit{CH}_2\text{CH}_2\text{O-}$), 3.72 (t, *J*=6 Hz, 8H, $\text{-O}\mathit{CH}_2\text{(CH}_2)_4\mathit{CH}_2\text{O-}$), 5.14 (s, 8H, $\text{-O}\mathit{CH}_2\text{-C}_6\text{H}_4\text{-}\mathit{CH}_2\text{O-}$), 6.51 (d, *J*=2 Hz, 4H, Ar-H *ortho* to $\text{-O(CH}_2)_6\text{-}$), 6.62 (dd, *J*=8 and 2 Hz, 4H, Ar-H *para* to $\text{-O(CH}_2)_6\text{-}$), 7.5–7.3 (m, 24 H, Ar-H), 7.71 (dd, *J*=7 and 2 Hz, 8H, Ar-H *ortho* to C=O in four benzoyl groups); ^{13}C NMR (CDCl_3) δ 24.7, 28.3, 67.8, 69.9, 100.3, 111.5, 122.2, 127.8, 127.9, 129.4, 132.0, 132.2, 136.5, 139.3, 159.0, 162.4, 198.0; mass (positive ion FAB) 1225.50 (M$^+$+H$^+$); anal. calcd for $\text{C}_{80}\text{H}_{72}\text{O}_{12}$: C, 78.41; H, 5.92. Found: C, 78.67; H, 5.95.
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7. Ace micro photochemical reactor with quartz well purchased from Aldrich was used.
8. Compound **5**: mp 271°C; ^{1}H NMR (CDCl_3) δ 1.67 (broad s, 4H, $\text{-CH}_2\mathit{(CH_2)_2}\text{CH}_2\text{-}$), 2.78 (broad s, 4H, $\text{-}\mathit{CH}_2\text{(CH}_2)_2\mathit{CH}_2\text{-}$), 5.28 (s, 4H, $\text{-O}\mathit{CH}_2\text{-C}_6\text{H}_4\text{-}\mathit{CH}_2\text{O-}$), 6.49 (d, *J*=2 Hz, 2H, C_7-H of benzofuran ring), 6.98 (dd, *J*=8 and 2 Hz, 2H, C_5-H of benzofuran ring), 7.5–7.3 (m, 16 H, Ar-H); ^{13}C NMR (CDCl_3) δ 26.3, 27.2, 69.7, 96.9, 113.4, 117.3, 119.7, 121.8, 126.7, 126.9, 128.7, 129.1, 132.9, 136.9, 153.0, 154.5, 155.5; mass (EI) 104 (21), 165 (13), 444 (19), 576 (100, M$^+$), 577 (44); anal. calcd for $\text{C}_{40}\text{H}_{32}\text{O}_4$: C, 83.31; H, 5.59. Found: C, 83.47; H, 5.33.
9. Slow evaporation from chloroform solution afforded a colorless crystal suitable for diffraction study. Crystal data for **5**: monoclinic, space group C2/*c*, a=16.945(3) Å, b=11.339(1) Å, c=16.529(5) Å, β=109.45(2)°, V=2994(1) Å, Z=4. A list of atomic coordinates and bond distances has been deposited at the Cambridge Crystallographic Data Center.