Cyclotribenzoin

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Dedicated to Peter Vollhardt, for fifteen years of chemistry- and lifestyle-related inspiration

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Abstract

Using cyanide-assisted benzoin condensation of isophthaldehyde, we prepared cyclotribenzoin: a cone-shaped macrocycle whose three benzene rings define a cuplike cavity, while six of its C–H bonds convergently point in the opposite direction. This combination of convergently oriented cation- and anion-binding groups, coupled with an exceedingly simple synthesis, promises to make cyclotribenzoin an appealing platform for supramolecular chemistry studies.

Key words condensation, macrocycles, host–guest systems, molecular recognition, supramolecular chemistry

Chemistry of macrocycles has evolved into a broad research area that spans the fields of organic, inorganic, and supramolecular chemistry.1 To list just a handful of applications, macrocycles play a role in the studies of aromaticity,2 porous materials,3 and supramolecular binding.4 At the same time, macrocyclic molecules still present a synthetic challenge: macrocyclization reactions are entropically unfavorable, an obstacle that often has to be circumvented through long and indirect synthetic routes. On the other hand, the few macrocycle classes that are easily synthesized or obtained from nature – such as cyclodextrins4 or cucurbiturils5 – present challenges in terms of selective derivatization. Because of these two factors, synthetic research on macrocycles is still an active area; for example, the recent dramatic ascent of pillar[n]arenes6 happened in large part due to their facile synthesis, which – coupled with easy preparation of derivatives – presented the supramolecular chemists with a class of receptors that could be easily diversified. In this contribution, we demonstrate a one-step synthesis of a benzoin-based macrocycle ornamented with multiple oxygen-based functional groups.

Benzoin condensation (the use of the term ‘condensation’ is purely historic, as no small molecule is eliminated in this addition reaction) was developed by the two fathers of modern organic chemistry – Liebig and Wöhler – as early as 1832.7 In this well-known reaction, two molecules of an aldehyde add together in the presence of a nucleophile (typically CN–), forming a single bond between their former carbonyl carbon atoms. Very early in the development of this reaction, attempts were made to extend its scope to dialdehydes;8 however, benzoin reaction of simple isophthaldehyde was reported to have resulted only in polymers.9 In recent years, renewed interest in benzoin condensation has been stimulated by the development of enantioselective versions10 and has led to applications in the production of benzoin-based porous polymers.11

We revisited the reaction of isophthaldehyde (1, Scheme 1) with NaCN and found that the outcome of this reaction depends on the solvent and concentration of 1. We were pleasantly surprised to observe that heating of 1 with NaCN at reflux in 1:1 mixtures of H2O with either MeOH, EtOH, or t-BuOH resulted in the predominant formation of trimer 2. This trimer conveniently precipitated from the solution if the starting concentration of 1 was 0.5 M. At higher concentrations of 1, mixtures of 2 with other non-cyclic oligomers and insoluble (presumed) polymers were obtained, and similar results were observed if the reaction mixtures were not heated. Alcoholic solvents appear essential for the success of this reaction, as switching to a 1,4-dioxane–H2O solvent combination completely suppressed the reaction, while the use of ethylene glycol as the solvent led to the formation of mixtures. Ultimately, reaction in the EtOH–H2O mixture was chosen as the most convenient and was optimized to produce 2 in 41% yield after recrystallization from 2-methoxyethanol.12 While this yield is moderate, one-step synthesis and low cost of isophthaldehyde mean that 2 can easily be prepared on multigram scale. We
Propose to name this compound ‘cyclotribenzoin’, to emphasize its origin (benzoin condensation) and cyclic trimeric nature.

Crystal packing diagram of 2 is shown in Figure 2. Within the a-b crystallographic plane, molecules of 2 orient parallel to each other. Along the c axis, they similarly stack in a parallel orientation. Each molecule of 2 establishes twelve short [C–H···O] contacts (H···O distances between 2.50 and 2.60 Å) with twelve of its neighbors. Specifically, on each benzene ring of 2, the hydrogen positioned ortho relative to the carbonyl group establishes a short contact with a carbonyl oxygen from a neighboring molecule. Similarly, the hydrogen positioned meta to the carbonyl group has contact with the hydroxyl oxygen atoms from three neighboring molecules. As this relationship is reciprocal, C=O and O–H groups from the ‘other side’ of 2 establish short contacts with C–H groups from six additional molecules of 2.

To circumvent the problems associated with the poor solubility of 2 in common organic solvents, we converted it into a tert-butyldimethylsilyl (TBDMS) derivative 3 by treatment with TBDMSCl in CH₂Cl₂.¹⁵ As anticipated, this derivative is significantly more soluble in most organic solvents. This increased solubility allowed us to probe its conformational flexibility using variable-temperature ¹H NMR spectroscopy. Upon cooling to –85 °C in CD₂Cl₂, no decoalescence of peaks was observed, although some shifting of peak positions was noticeable – possibly suggesting aggregation or changes in the intermolecular hydrogen-bonding configurations.

In conclusion, we have developed a one-step synthesis of a novel highly oxygenated and shape-persistent macrocycle. This method starts with commercially available materials and is easily scalable. Convergent positioning of aromatic rings on one, and multiple C–H functionalities on the other side of the macrocyclic systems bodes well for its applications as a receptor for cationic anions, or possibly both. This and other supramolecular applications of 2 will be explored in our labs. Additional lines of inquiry will include attempts to synthesize enantiopure 2 (possibly using asymmetric N-heterocyclic carbene organocatalysis), substituted derivatives of 2, as well as its larger congeners.
Figure 2 Segment of a crystal packing diagram of 2, viewed along the crystallographic c axis. Hydrogen atoms and disordered THF molecules were removed for clarity.

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Supporting Information

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References and Notes


(12) Synthesis of Macrocycle 2

Isophthaldehyde (1, 684 mg, 5.10 mmol), ETOH (5 mL), and deionized H2O (5 mL) were added to a round-bottom flask equipped with a stirring bar, and the mixture was heated at reflux under nitrogen until all of 1 dissolved. At that time, NaCN (25 mg, 0.51 mmol) was added into the round-bottom flask and heating was continued for 48 h. The precipitate obtained was filtered and then washed with deionized H2O (10 mL), ETOH (10 mL), and Et2O (10 mL). After recrystallization from 2-methoxyethanol, pure 2 was obtained (280 mg, 41%) as a white solid; mp 245 °C (decomp.). UV/vis (THF): θmax (log ε) = 248 (4.29), 288 (3.46) nm. IR (neat): 3456 (w, O–H), 326 (3.18) nm. IR (neat): 3070 (w, O–H), 3044 (w, C=O), 1713 (s, C=O), 1583 (s), 1471 (s), 1362 (s), 1257 (m), 1182 (m), 1083 (m), 796 (s), 743 (s), 692 (s) cm–1. 1H NMR (400 MHz, DMSO-d6): δ = 8.78 (s, 3 H), 7.63 (d, JH–H = 7.8 Hz, 3 H), 7.45 (d, JH–H = 7.8 Hz, 3 H), 7.35 (dd, JH–H = 7.8, 7.3 Hz, 3 H), 6.42 (d, JH–H = 5.5 Hz, 3 H), 6.01 (d, JH–H = 5.5 Hz, 3 H) ppm. 13C NMR (100 MHz, DMSO-d6): δ = 198.4, 140.8, 134.9, 132.4, 130.2, 128.2, 74.7 ppm. ESI-LRMS: m/z [M − H+] calcd for C42H60O6Si3: 1511.73; found: 1511.09.

(13) Crystallographic information file (CIF) for compound 2 has been deposited with Cambridge Structural Database under deposition code CCDC 1055400.


(15) Synthesis of Macrocyle 3

Compound 2 (128 mg, 0.32 mmol), imidazole (1.30 g, 19.1 mmol), and dry CH2Cl2 (15 mL) were added to a thick-walled 20 mL microwave vial. The mixture was stirred under nitrogen for 10 min. The reagent TBDMSCl (2.90 g, 19.1 mmol), EtOH (5 mL), and dry CH2Cl2 (10 mL) were added to the mixture. The vial was sealed, and then placed into a Biotage microwave reactor, where it was heated for 10 h at 40 °C. The reaction mixture was diluted with CHCl3 (50 mL), washed with H2O (50 mL), and the organic layer was separated and dried over anhydrous MgSO4. After removal of solvent, the crude product was isolated as a light yellow oil. Pure compound 3 was obtained after recrystallization from pentane at −78 °C (142 mg, 60%); mp 167 °C. UV/vis (THF): θmax (log ε) = 286 (3.61), 326 (3.18) nm. IR (neat): 3070 (w, νC–H), 2929 (w, νC–H), 1713 (s, νC=O), 1674 (s), 1581 (s), 1471 (s), 1362 (s), 1257 (m), 1120 (m), 1028 (m), 862 (m), 781 (m), 735 (s), 698 (s) cm–1. 1H NMR (500 MHz, CDCl3): δ = 7.88 (s, 3 H), 7.72 (d, JH–H = 8.0 Hz, 3 H), 7.73 (d, JH–H = 7.6 Hz, 3 H), 7.33 (dd, JH–H = 8.0, 7.4 Hz, 3 H), 5.82 (s, 3 H), 0.87 (s, 27 H), 0.09 (s, 9 H), 0.08 (s, 9 H) ppm. 13C NMR (125 MHz, CDCl3): δ = 198.3, 139.2, 135.7, 131.6, 129.5, 128.9, 120.7, 79.4, 25.9, 18.5, –4.6, –4.7 ppm. ESI-LRMS: m/z [M + Na+] calcd for C33H53O4N6Si4: 767.36; found: 767.38; m/z [2M + Na+] calcd: 1511.73; found: 1511.09.