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Letter

Cycloglycolurils: Hybrid Glycoluril–Cyclobenzil Macrocycles

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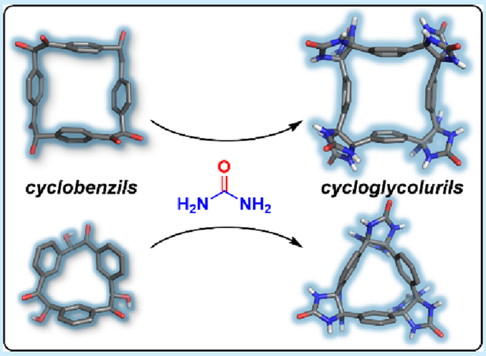
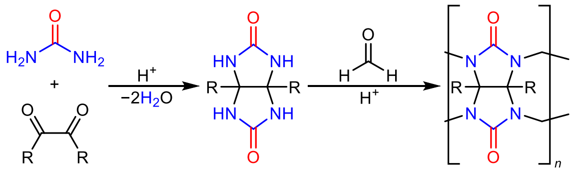
ABSTRACT: Two novel glycoluril macrocycles have been synthesized from cyclotetrabenzil and cyclotribenzoin precursors using solvent-free condensations with urea. The crystal structure of the cyclotetra(*p*-phenylene)glycoluril macrocycle shows a twisted ring conformation, while that of the cyclotri(*m*-phenylene)glycoluril hybrid exhibits a distinct tubular supramolecular packing. These structures establish a potentially broad new class of macrocycles with intriguing guest binding properties owing to their available N–H motifs.



The glycoluril monomer is among the most widely used building blocks in the synthesis of diverse supramolecular hosts that can interact with cationic, anionic, or neutral guest molecules. Acyclic supramolecular hosts based on glycoluril oligomers show distinct curvature around their bridgehead carbon atoms, forming molecular clips[1] and exhibiting molecular recognition properties.[2] On the contrary, cyclic glycoluril-based hosts are best represented by the cucurbit[*n*]uril family,[3] synthesized by the acid-catalyzed condensation of glycoluril and formaldehyde (Scheme 1). Cucurbit[*n*]urils have attracted a great deal of attention because of their host–guest binding properties and their applications in drug delivery, catalysis, and nanomaterials.[4] Related macrocycles synthesized from ethyleneurea and formaldehyde were named hemicucurbit[*n*]urils, as their structures resemble the corresponding cucurbit[*n*]urils cut in half along the equator. Bambus[*n*]urils are a special case of hemicucurbit[*n*]urils; in this unique configuration, both nitrogen atoms on one of the urea groups are capped with methyl groups, and the macrocycle is formed via methylene bridges at the other urea.[5] Hemicucurbit[*n*]urils are known for their high affinity for inorganic anions in both organic solvents and aqueous environments.[6] Thiocucurbit[*n*]urils are expected to show interesting ligation properties to metal ions and metal surfaces;[7] although thiocucurbit[*n*]urils are expected to be thermodynamically stable, their synthesis poses significant challenges.[8] A unifying feature of all these supramolecular hosts is the connectivity of glycoluril units to one another, through methylene bridges linking their nitrogen atoms. Notably, there are no literature reports of glycoluril-derived macrocycles in which glycolurils connect to one another through the central carbon atoms, leaving N–H groups available for interactions with potential guest molecules. Generally, the presence of N–H motifs enhances a macrocycle's ability to act as a receptor due to the possibility of [N–H···X] hydrogen bonding.[9] In the absence of guests, these N–H motifs can alternatively contribute to intermolecular hydrogen bonding and result in the formation of highly ordered supramolecular structures.[10]

Scheme 1. Synthesis of Glycolurils and Cucurbit[*n*]urils



Here, we report a new class of hybrid macrocycles consisting of glycoluril units that alternate with phenylene groups and are connected entirely through C–C bonds. These new macrocycles, dubbed cycloglycolurils, were synthesized by the condensation of oxidized cyclobenzoins with urea. Cyclobenzoins, discovered by our group in 2015,[11] are readily synthesized from aromatic dialdehydes in a benzoin condensation catalyzed by either cyanide or N-heterocyclic carbenes (NHCs).[12] Cyclobenzoins and their derivatives have since been used as components of lithium-ion batteries,[13] platforms for the capture of CO_2 and its separation from N_2, CH_4,[14] and CO,[15] and iodine-capture agents.[16]

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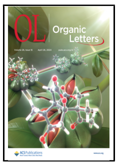

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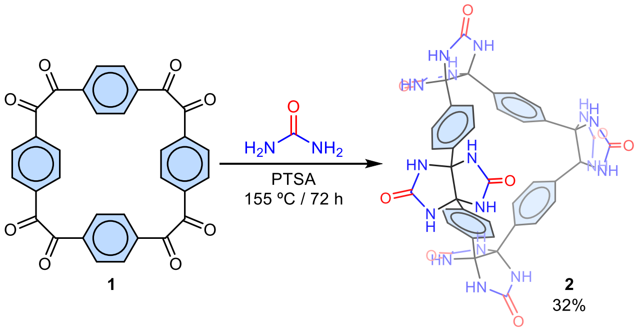
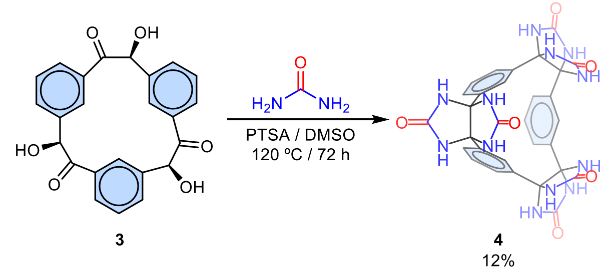
The synthesis of the first cycloglycolurils commenced with octaketone **1**,[17] which was obtained by the oxidation of cyclotetrabenzoin.[11b] This octaketone was first reacted with an excess of urea in the presence of *p*-toluenesulfonic acid (PTSA) and in dimethyl sulfoxide (DMSO) as the solvent, but no condensation product was observed. Eliminating DMSO and instead using molten urea as both the reagent and the reaction solvent at 155 °C (Scheme 2) resulted in a different outcome with a change in color from yellow to light brown. Macrocycle **2**, obtained from the reaction mixture after washing the unreacted urea with water and recrystallization from DMSO, appeared as a yellow solid in 32% yield. We named this compound cyclotetra(*p*-phenylene)glycoluril.

Scheme 2. Synthesis of Cyclotetra(*p*-phenylene)glycoluril



We next shifted our attention to cyclotribenzoin **3** (Scheme 3) as the starting material. Our group and Bunz's group were not previously able to isolate its hexaketone oxidation product but instead developed a protocol for an *in situ* oxidation of **3** in DMSO.[18] Using this method and an excess of urea, in the presence of PTSA as the catalyst, the reaction produced a light-yellow precipitate, which was isolated in 12% yield and identified as cyclotri(*m*-phenylene)glycoluril **4**.

Scheme 3. Synthesis of Cyclotri(*m*-phenylene)glycoluril



Our attempts to prepare sulfur and nitrogen analogues of **2** and **4** by condensation of **1** and **3**, respectively, with either thiourea, guanidine, or guanidinium salts were unsuccessful.

Spectroscopic information about new macrocycles **2** and **4** is consistent with their presented structures. The ^1H nuclear magnetic resonance (NMR) spectrum of **2** in DMSO-d_6 shows only two singlets at δ 6.75 and 7.76 ppm, suggesting a highly symmetric structure of the hybrid macrocycle, or a quick exchange between several lower-symmetry conformers (*vide infra* for its structure in the solid state). The addition of D_2O leads to the disappearance of the signal at δ 7.76 ppm, indicating that this signal corresponds to the N−**H** protons of **2**. Similarly, the ^1H NMR spectrum of **4** in DMSO-d_6 shows two singlets at δ 7.22 and 7.58 ppm for the N−**H** protons and three signals for the phenyl protons at δ 7.05, 6.99, and 6.94 ppm. The signals corresponding to the N−**H** protons were identified via deuterium exchange reactions.

Diffraction-quality single crystals of macrocycle **2** were grown by vapor diffusion of Me_2CO into its dilute solution in DMSO over 5 days. Macrocycle **2** crystallizes in monoclinic space group $P2_1/n$ with two molecules of **2** and three molecules of the ordered DMSO solvent in the unit cell. The molecular structure shows that the glycoluril and phenylene are connected through C−C bonds in an alternating fashion (Figure 1A,B). The molecule is largely unstrained, with minimal (<4.3°) deplanarization of the glycoluril carbon atoms relative to the neighboring aryl rings. Glycoluril carbons show a distorted tetrahedral geometry, with $C_{glycoluril}-C_{glycoluril}-C_{aryl}$ angles of 116.9−119.5° being significantly larger than the ideal angle of 109.5°; these are compensated for by the smaller-than-ideal $C_{glycoluril}-C_{glycoluril}-NH$ angles of 99.7−102.0°. The glycoluril units do not have all of their possible hydrogen bonding sites satisfied. One of the NH groups of the urea subunit participates in intermolecular hydrogen bonding with [N−H···O=C] distances ranging between 1.92 and 2.25 Å, while the other NH group does not engage in hydrogen bonding or does so only with the molecules of the DMSO solvent. The macrocycle adopts a distinctively twisted structure with all four glycoluril units extending outward. This lower-symmetry structure, relative to that observed in solution, is chiral, and **2** crystallizes as a pair of twisted enantiomers (Figure 1C). This duality of geometries observed in solution and the solid state has been previously reported for larger macrocyclic (thio)ureas.[19] The extended solid-state structure of **2** (Figure S8) is rather closely packed with no observable pores or channels.

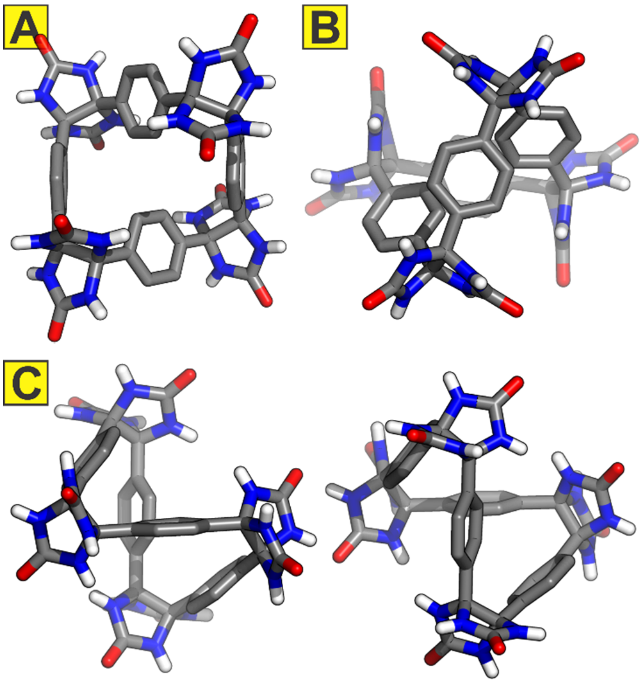


Figure 1. (A) Side and (B) top views of the X-ray crystal structure of **2**, along with (C) the pair of enantiomers observed in the unit cell. Nonpolar hydrogen atoms and solvent molecules have been removed for the sake of clarity.

Single crystals of trimeric macrocycle **4** suitable for X-ray analysis were obtained by vapor diffusion of THF into its solution in DMF over 7 days. The macrocycle crystallizes in trigonal space group *R*3*c* with highly disordered solvent molecules within the cavity of the macrocycle, which were removed using the PLATON/SQUEEZE routine. Macrocycle **4** adopts a capped trigonal pyramid shape, with three phenyl rings serving as the outer sides of the pyramid and three glycoluril units acting as vertices, extending outward (Figure 2A). The three phenyl rings in **4** are nearly parallel with an interplanar angle of 10.5°, in contrast to its precursor **3**, where the phenyl rings form a conical shape, bent at an angle of 36.4°. Much like in **2**, the deplanarization of the glycoluril carbon atoms relative to the phenylene rings in **4** is minimal (<2.3°), and the most distorted moieties are the glycoluril carbons, which show $\mathrm{C_{glycoluril}{-}C_{glycoluril}{-}C_{aryl}}$ angles of 116.0−116.8° and $\mathrm{C_{glycoluril}{-}C_{glycoluril}{-}NH}$ angles of 99.7−102.1°.

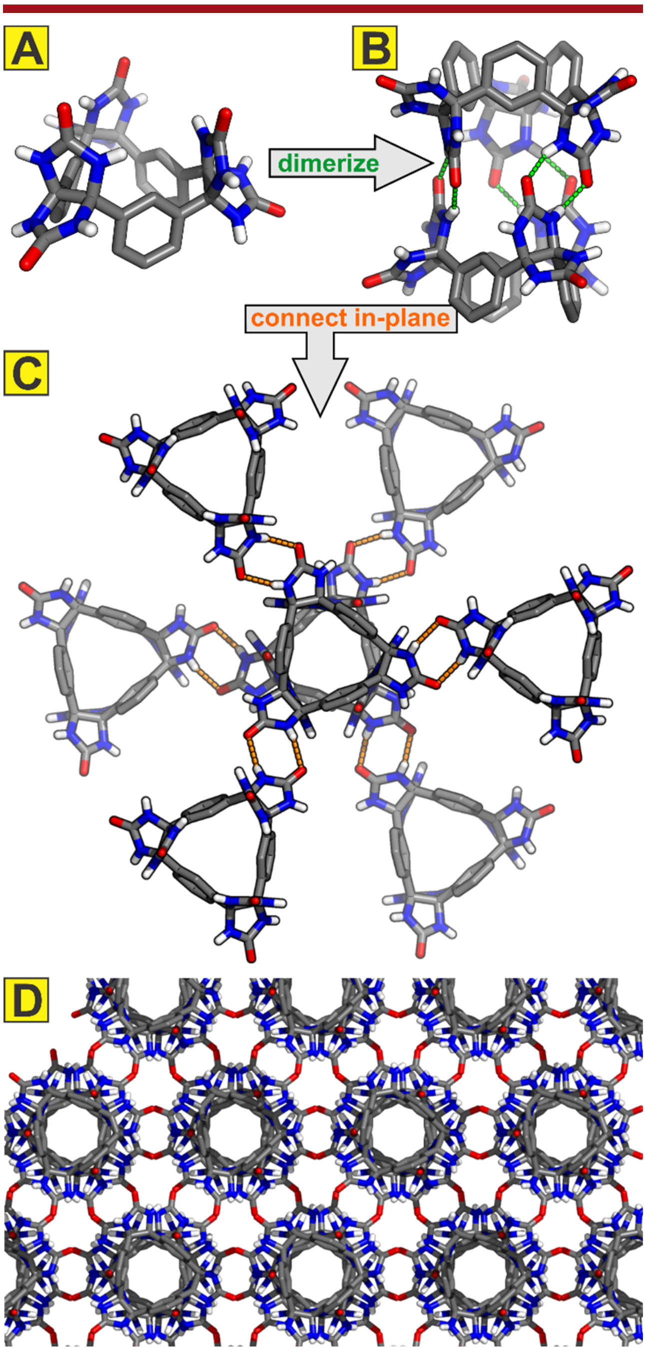


Figure 2. X-ray crystal structures of (A) **4** and (B) its hydrogen-bonded dimer, with hydrogen bonds colored green. (C) Each dimer of **4** connects to six other molecules of **4** via hydrogen bonds (orange). (D) Overall, compound **4** packs in a superstructure that shows tubular channels. Nonpolar hydrogen atoms have been omitted for the sake of clarity.

In each glycoluril unit of **4**, the *meta* substituton pattern of the neighboring phenylene rings desymmetrizes the two urea moieties: one points upward and the other outward. These orientations play a pivotal role in the formation of the extended supramolecular structure of **4**. Each molecule of **4** dimerizes with its neighbor (Figure 2B) via six strong hydrogen bonds established between the N−H and C═O moieties of the upward-pointing ureas, with [N−H···O═C] distances of 1.94 Å (green in Figure 2B). The two molecules in the dimer stack on top of one another but are rotated by 60°. Each such dimer then connects to six additional molecules of **4** (Figure 2C) through [N−H···O═C] hydrogen bonds established between the urea units pointing outward, which are characterized by [N−H···O═C] distances of 2.04 Å (orange in Figure 2C). The overall packing diagram of **4**, shown in Figure 2D along the crystallographic *c* axis, reveals a tubular-shaped supramolecular structure in the solid state. In this supramolecular architecture, the highly polar exterior groups and nonpolar internal cavities of **4** present an interesting combination of properties, which might be explored in the development of, e.g., synthetic ion channels.

In conclusion, our work has expanded the family of glycoluril-derived macrocycles by adding the first new family of C−C-connected cycloglycolurils. Cyclobenzil precursors were instrumental in allowing this synthesis to proceed in a single and simple step. The structural analysis revealed that macrocycle **2** is more flexible than its trimeric counterpart **4**. These intriguing new macrocycles pave the way for promising avenues of exploration. The molecular recognition ability of these glycoluril macrocycles is currently being explored in our laboratories on both neutral and ionic guest molecules that could engage in hydrogen bonding with **2** and **4**. Concurrently, we are also synthesizing expanded cycloglycolurils from larger cyclotetrabenzoins[12] and exploring guest binding preferences of these novel macrocycles. The results of these studies will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.4c00835.

> Experimental procedures, copies of ^{1}H and ^{13}C NMR spectra, IR spectra, and mass spectra (PDF)

Accession Codes

CCDC 2330573 and 2330577 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Author Contributions

A.B. designed, synthesized, and crystallized compounds **2** and **4**. X.W. determined the crystal structures of **2** and **4**. A.B. and O.Š.M. wrote the manuscript. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Sijbesma, R. P.; Nolte, R. J. M. Molecular Clips and Cages Derived from Glycoluril. *Top. Curr. Chem.* **1995**, *175*, 25−56. (b) Rowan, A. E.; Elemans, J. A. W.; Nolte, R. J. M. Molecular and Supramolecular Objects from Glycoluril. *Acc. Chem. Res.* **1999**, *32*, 995−1006. (c) Sokolov, J.; Lizal, T.; Sindelar, V. Dimeric Molecular Clips Based on Glycoluril. *New J. Chem.* **2017**, *41*, 6105−6111.

(2) (a) Huang, W.-H.; Zavalij, P. Y.; Isaacs, L. Cucurbit[*n*]uril Formation Proceeds by Step-growth Cyclo-oligomerization. *J. Am. Chem. Soc.* **2008**, *130*, 8446−8454. (b) Huang, W.-H.; Zavalij, P. Y.; Isaacs, L. Metal-ion-induced Folding and Dimerization of a Glycoluril Decamer in Water. *Org. Lett.* **2009**, *11*, 3918−3921.

(3) (a) Kim, J.; Jung, I.-S.; Kim, S.-Y.; Lee, E.; Kang, J.-K.; Sakamoto, S.; Yamaguchi, K.; Kim, K. New Cucurbituril Homologues: Syntheses, Isolation, Characterization, and X-ray Crystal Structures of Cucurbit[*n*]uril (*n* = 5, 7, and 8). *J. Am. Chem. Soc.* **2000**, *122*, 540−541. (b) Assaf, K.; Nau, W. M. Cucurbiturils: From Synthesis to High-affinity Binding and Catalysis. *Chem. Soc. Rev.* **2015**, *44*, 394−418. (c) Lagona, J.; Mukhopadhyay, P.; Chakrabarti, S.; Isaacs, L. The Cucurbit[*n*]uril Family. *Angew. Chem., Int. Ed.* **2005**, *44*, 4844−4870.

(4) (a) Barrow, S. J.; Kasera, S.; Rowland, M. J.; del Barrio, J.; Scherman, O. A. Cucurbituril-based Molecular Recognition. *Chem. Rev.* **2015**, *115*, 12320−12406. (b) Lü, J.; Lin, J. X.; Cao, M.; Cao, R. Cucurbituril: A Promising Organic Building Block for the Design of Coordination Compounds and Beyond. *Coord. Chem. Rev.* **2013**, *257*, 1334−1356. (c) Wang, Z.; Sun, C.; Yang, K.; Chen, X.; Wang, R. Cucurbituril-based Supramolecular Polymers for Biomedical Applications. *Angew. Chem., Int. Ed.* **2022**, *61*, No. e2022067.

(5) (a) Miyahara, Y.; Goto, K.; Oka, M.; Inazu, T. Remarkably Facile Ring-Size Control in Macrocyclization: Synthesis of Hemicucurbit[6]uril and Hemicucurbit[12]uril. *Angew. Chem., Int. Ed.* **2004**, *43*, 5019−5022. (b) Svec, J.; Necas, M.; Sindelar, V. Bambus[6]uril. *Angew. Chem., Int. Ed.* **2010**, *49*, 2378−2381.

(6) (a) Yawer, M. A.; Havel, V.; Sindelar, V. A Bambusuril Macrocycle that Binds Anions in Water with High Affinity and Selectivity. *Angew. Chem., Int. Ed.* **2015**, *54*, 276−279. (b) Lizal, T.; Sindelar, V. Bambusuril Anion Receptors. *Isr. J. Chem.* **2018**, *58*, 326−333.

(7) (a) Singh, M.; Solel, E.; Keinan, E.; Reany, O. Dual-functional Semithiobambusurils. *Chem. - Eur. J.* **2015**, *21*, 536−540. (b) Pichierri, F. Nanosoldering of Thiacucurbituril Macrocycles with Transition Metals Affords Novel Tubular Nanostructures: A Computational Study. *Chem. Phys. Lett.* **2005**, *403*, 252−256.

(8) (a) Singh, M.; Parvari, G.; Botoshansky, M.; Keinan, E.; Reany, O. The Synthetic Challenge of Thioglycolurils. *Eur. J. Org. Chem.* **2014**, *2014*, 933−940. (b) Pichierri, F. Density Functional Study of Cucurbituril and Its Sulfur Analogue. *Chem. Phys. Lett.* **2004**, *390*, 214−219.

(9) (a) Gale, P. A.; Howe, E. N. W.; Wu, X. Anion Receptor Chemistry. *Chem* **2016**, *1*, 351−422. (b) Blažek Bregović, V.; Basarić, N.; Mlinarić-Majerski, K. Anion Binding with Urea and Thiourea Derivatives. *Coord. Chem. Rev.* **2015**, *295*, 80−124.

(10) (a) Steed, J. W. Anion-tuned Supramolecular Gels: A Natural Evolution from Urea Supramolecular Chemistry. *Chem. Soc. Rev.* **2010**, *39*, 3686−3699. (b) Prusinowska, N.; Szymkowiak, J.; Kwit, M. Enantiopure Tertiary Urea and Thiourea Derivatives of Trianglamine Macrocycle: Structural Studies and Metallogeling Properties. *J. Org. Chem.* **2018**, *83*, 1167−1175.

(11) (a) Alrayyani, M.; Miljanić, O. Š. Benzoins and Cyclobenzoins in Supramolecular and Polymer Chemistry. *Chem. Commun.* **2018**, *54*, 11989−11997. (b) Ji, Q.; Le, H. T. M.; Wang, X.; Chen, Y.-S.; Makarenko, T.; Jacobson, A. J.; Miljanić, O. Š. Cyclotetrabenzoin: Facile Synthesis of a Shape-persistent Molecular Square and Its Assembly into Hydrogen-bonded Nanotubes. *Chem. - Eur. J.* **2015**, *21*, 17205−17209. (c) Ji, Q.; Do, L. H.; Miljanić, O. Š. Cyclotribenzoin. *Synlett* **2015**, *26*, 1625−1627.

(12) Eisterhold, A. M.; Puangsamlee, T.; Otterbach, S.; Bräse, S.; Weis, P.; Wang, X.; Kutonova, K. V.; Miljanić, O. Š. Expanded Cyclotetrabenzoins. *Org. Lett.* **2021**, *23*, 781−785.

(13) (a) Meng, J.; Robles, A.; Jalife, S.; Ren, W.; Zhang, Y.; Zhao, L.; Liang, Y.; Wu, J. I.; Miljanić, O. Š.; Yao, Y. Cyclotetrabenzil Derivatives for Electrochemical Lithium-ion Storage. *Angew. Chem., Int. Ed.* **2023**, *62*, No. e202300892. (b) Yen, Y.-J.; Chen, T.-H.; Wang, Y.-T.; Robles, A.; Đerić, M.; Miljanić, O. Š.; Kaveevivitchai, W.; Chung, S.-H. Selective Chemisorption of Polysulfides by Porous Molecular Crystal: Cathode Host Materials for Lean-electrolyte Lithium-sulfur Cells with High Electrochemical Stability. *J. Power Sources* **2023**, *565*, 232891.

(14) (a) Wang, Y.-T.; McHale, C.; Wang, X.; Chang, C.-K.; Chuang, Y.-C.; Kaveevivitchai, W.; Miljanić, O. Š.; Chen, T.-H. Cyclotetrabenzoin Acetate: A Macrocyclic Porous Molecular Crystal for CO_2 Separations by Pressure Swing Adsorption. *Angew. Chem., Int. Ed.* **2021**, *60*, 14931−14937. (b) Ashirov, T.; Alrayyani, M.; Song, K.-S.; Miljanić, O. Š.; Coskun, A. Cyclotetrabenzil-based Porous Organic Polymers with High CO_2 Affinity. *Org. Mater.* **2021**, *3*, 346−352.

(15) Wang, Y.-T.; Jalife, S. J.; Robles, A.; Đerić, M.; Wu, J. I.; Kaveevivitchai, W.; Miljanić, O. Š.; Chen, T.-H. Efficient CO_2/CO Separation by Pressure Swing Adsorption Using an Intrinsically Porous Molecular Crystal. *ACS Appl. Nano Mater.* **2022**, *5*, 14021−14026.

(16) Robles, A.; Alrayyani, M.; Wang, X.; Miljanić, O. Š. Cyclobenzil Hydrazones with Exceptional Iodine Capture Capacities in Solutions and on Interfaces. *Cell Rep. Phys. Sci.* **2023**, *4*, 101509.

(17) Hahn, S.; Alrayyani, M.; Sontheim, A.; Wang, X.; Rominger, F.; Miljanić, O. Š.; Bunz, U. H. F. Synthesis and Characterization of Heterobenzenacyclo-octaphanes Derived from Cyclotetrabenzoin. *Chem. - Eur. J.* **2017**, *23*, 10543−10550.

(18) Hahn, S.; Koser, S.; Hodecker, M.; Seete, P.; Rominger, F.; Miljanić, O. Š.; Dreuw, A.; Bunz, U. H. F. Phenylene Bridged Cyclic Azaacenes: Dimers and Trimers. *Chem. - Eur. J.* **2018**, *24*, 6968−6974.

(19) Prusinowska, N.; Szymkowiak, J.; Kwit, M. Unravelling Structural Dynamics, Supramolecular Behavior, and Chiroptical Properties of Enantiomerically Pure Macrocyclic Tertiary Ureas and Thioureas. *J. Org. Chem.* **2023**, *88*, 285−299.