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Expanded Cyclotetrabenzoins

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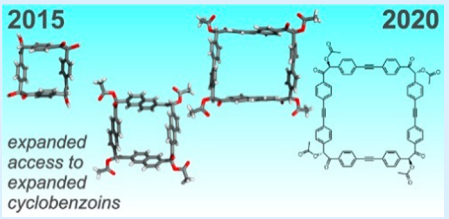
ABSTRACT: Cyclobenzoins are shape-persistent macrocycles of interest in the preparation of optoelectronic and porous materials. New cyclotetrabenzoins derived from biphenyl, naphthalene, and tolane skeletons were synthesized using *N*-heterocyclic carbene-catalyzed benzoin condensation. Their preparation proceeded with different regioselectivity than that observed in the cyanide-catalyzed preparation of the parent cyclotetrabenzoin. Crystal structures of two new cyclotetrabenzoin acetic esters have been obtained. Alkyne groups of the tolane-based cyclotetrabenzoin were postsynthetically functionalized with $Co_2(CO)_6$ moieties.



Cyclobenzoins[1] are cyclic oligomers of aromatic dialdehydes formed by benzoin condensation.[2] These readily made macrocycles[3] bode well for applications as supramolecular hosts, porous molecular crystals,[1b] and precursors to optoelectronic materials.[4] Cyclotetrabenzoin (**2a**, Scheme 1) was first prepared by tetramerization of terephthaldehyde (**1a**) using catalytic NaCN.[1b] Its synthesis was remarkably selective: out of 40 possible cyclic tetramers of **1a** (Figure S1), only **2a** was isolated, on account of its lowest solubility. Compound **2a** has a low surface area (~50 $m^2\ g^{-1}$); its acetic ester **4a** exhibited a much-improved solubility as well as a surface area of 570 $m^2\ g^{-1}$.[5] In this Letter, we report the extension of the cyclotetrabenzoin family onto larger aromatic scaffolds. We also report the X-ray crystal structures of two of these expanded cyclotetrabenzoins, and the postsynthetic modification of one of them. These new cyclotetrabenzoins were prepared using a more environmentally friendly *N*-heterocyclic carbene (NHC) catalyst.[6,2d]

After screening potential NHC catalysts, we found that 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide[7] was the most efficient precatalyst for the conversion of **1a** into **2a**. Its exposure to **1a** and Et_3N produced the parent cyclotetrabenzoin **2a** in 19% yield, comparable to the 21% observed in the cyanide-catalyzed reaction.[1b] This finding was doubly encouraging: it demonstrated that a less dangerous catalyst can be used to produce cyclobenzoins and that the cyclization can happen in low polarity solvents such as CH_2Cl_2. The latter point allowed us to explore other less polar dialdehyde precursors to cyclobenzoins, which were not soluble in the originally used EtOH/H_2O mixture required to dissolve the NaCN catalyst. We focused our attention on precursors **1b−d**, which were expected to produce macrocycles with larger central cavities. Starting from 4,4′-biphenylenedicarbaldehyde (**1b**), NHC-mediated benzoin condensation yielded evidence of the formation of a cyclic species. However, efforts to purify this new cyclotetrabenzoin proved futile because of its low solubility and high polarity. We instead proceeded to acetylate the crude material and perform the purification at the stage of its acetic ester. Ultimately, an acetylated cyclotetrabenzoin was isolated in a 24% yield after two steps. Its spectroscopic data were consistent with both the S_4-symmetric **4b** and the D_2-symmetric **5b**; X-ray crystallographic analysis (vide infra) resolved this dilemma in favor of **5b**. Tolane-derived precursor **1c** was subjected to an analogous set of reaction conditions and gave two products in the combined yield of 23%. The two products could be separated but not on a preparative scale; given that their spectral information is virtually identical, we tentatively assigned their identities as **4c** and **5c** but were not able to tell which one is which in the absence of crystal structures. Finally, starting with 2,6-diformylnaphthalene (**1d**), **4d** and **5d** were isolated in 9 and 5% overall yields, respectively. Structural assignment of **4d** came from its crystal structure (vide infra), while the structure of the other isolated isomer was consistent with **5d**, but also, it should be noted, with several other possible cyclic tetramers of **1d** which have identical NMR spectroscopic patterns and molecular masses.

Five additional dialdehydes were tested as substrates. Terphenyl-based **1e**[8] produced only traces of its dimer upon exposure to the NHC catalyst. Precursors with electron-withdrawing (**1f**) and electron-donating (**1g**, **1h**) groups were tested to see whether electronic effects of substituents[9] on the biphenyl skeleton affect cyclotetrabenzoin formation. The paracyclophane-based linker **1i** was selected to establish whether different cyclobenzoin topologies could be derived

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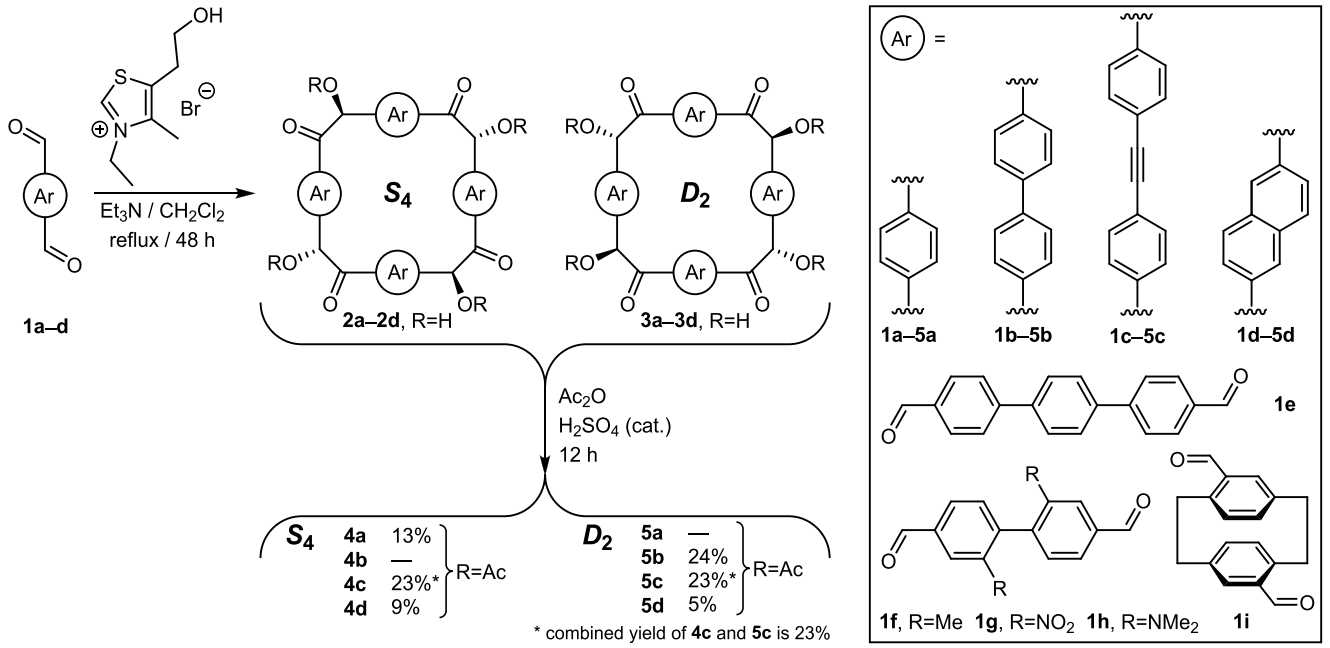
Org. Lett. 2021, 23, 781−785

Scheme 1. Synthesis of Novel Cyclotetrabenzoins and Their Acetylated Derivatives[a]



[a]Precursors **1e**−**1i** yielded no cyclobenzoins.

from its unusual geometry.[10] Exposure of **1f**−**1i** to the benzoin condensation conditions did not result in macrocycle formation: only starting materials were recovered.

Compounds **4c**, **4d**, and **5b**−**5d** are white powders. Their ^{1}H NMR spectra are consistent with the regio- and stereoisomers shown in Scheme 1, and the diagnostic benzoin C−H peaks are found at δ = 6.93 ppm for **5b**, 6.84 ppm for **4c**/**5c**, and 7.10 ppm for **4d**/**5d** (in $CDCl_3$). Aromatic regions of the NMR spectra of naphthalene-based cyclobenzoins are complicated by the restricted rotation around the offset long axis of the Ar groups in Scheme 1.

Single crystals of **5b** suitable for X-ray diffraction analysis were grown by diffusion of MeOH into a solution of **5b** in THF. Compound crystallizes in the *F*dd2 space group with eight molecules of **5b** per unit cell. The obtained structure is shown in Figure 1A. Its overall shape, defined here by the four corners represented by benzoin CHOAc carbon atoms, is that of a puckered rectangle with angles of 86.3° and 86.6° and sides that vary in length between 10.1 and 11.9 Å. The crystal structure showed that **5b** crystallized as a racemic mixture of the *R*,*R*,*R*,*R* and the *S*,*S*,*S*,*S* isomer (only the latter is shown in Scheme 1 and Figure 1B). Pairs of phenylene rings in the biphenylene moieties are distorted from coplanarity by 15.7°, 37.4°, and 36.7°. The packing diagram of **5b**, viewed along the crystallographic *a* axis (Figure 1B), shows diamond-shaped channels of approximate dimensions 15.7 × 7.5 Å. These channels appear to be filled with disordered solvent molecules which have been treated with the PLATON/SQUEEZE routine. Notable short contacts are established between the ester carbonyl oxygens and hydrogens of the benzoin functionality and those in the *ortho*-position of the biphenylene with [C═O···H−C] distances of 2.38 and 2.47 Å, respectively. Formation of this different regioisomer relative to the precedent of **2a**/**4a** is puzzling. Tentatively, we ascribe it to the differences in the solubility between isomers, which strongly favored **2a**, being diminished and inverted in the case of the longer biphenyl precursor, now favoring the D_2-symmetric structure.

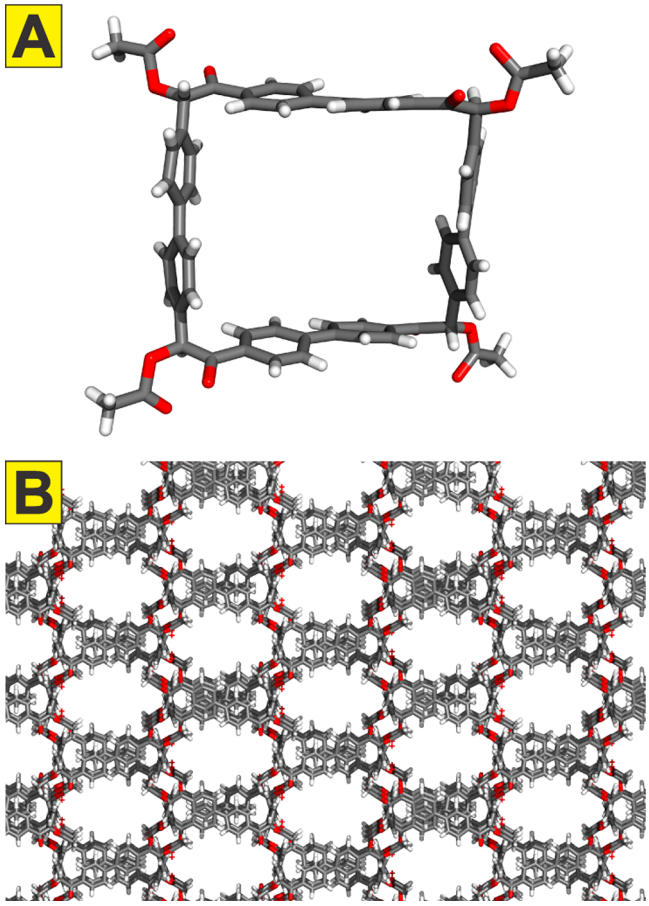


Figure 1. X-ray crystal structure of **5b** (A) and its packing diagram (B), viewed along the crystallographic *a* axis. Element colors: C, gray; H, white; O, red. Solvent molecules were removed for clarity.

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Single crystals of **4d** were fortuitously obtained after one of the column chromatography fractions (eluted with EtOAc/CH_2Cl_2 solvent mixture) was left to stand at room temperature overnight. Compound **4d** crystallizes in $I\bar{4}$ space group with two molecules per unit cell. Its molecular structure is shown in Figure 2A, indicating the *S*,*R*,*S*,*R* stereochemistry of the four

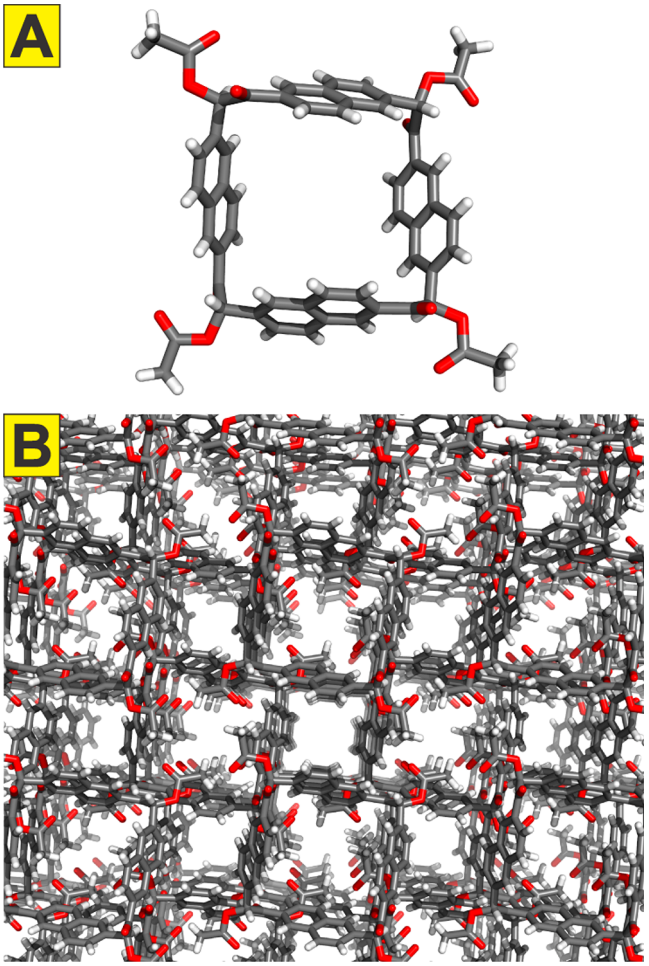


Figure 2. X-ray crystal structure of **4d** (A) and its packing diagram (B), viewed along the crystallographic *c* axis. Element colors: C, gray; H, white; O, red. Solvent molecules were removed for clarity.

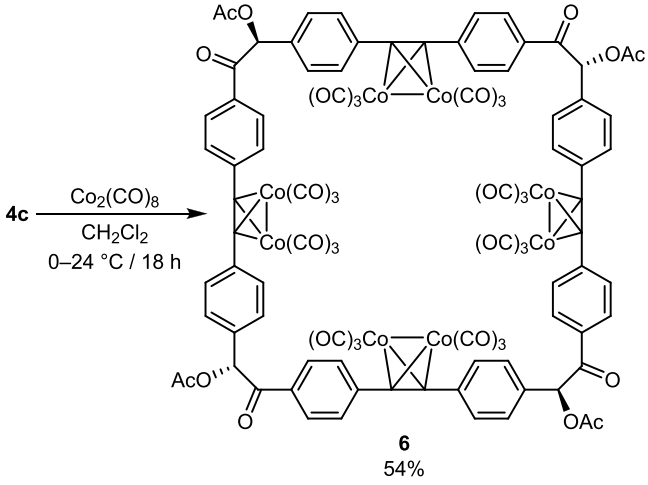
stereogenic centers. The overall shape of **4d**, defined by the four corners represented by benzoin CHOAc carbon atoms, is that of a puckered square (more symmetric than that observed for **5b**) with angles of 86.7° and sides of 8.63 Å. At the same time, naphthalene "walls" are very much distorted from a parallel arrangement: those on the opposite sides of the molecule form an angle of 52.2° with each other, while those on the neighboring sides stand at an angle of 78.9°. The crystal packing diagram of **4d** is shown in Figure 2B and reveals two kinds of one-dimensional channels running in parallel when viewed along the crystallographic *c* axis: a larger one with approximate dimensions of 8.4 × 7.3 Å and a smaller one, measuring ∼6.5 × 5.4 Å. Close contacts established between molecules of **4d** include [C−H···O] hydrogen bonds between the ester carbonyl oxygen and the benzoin hydrogen (2.69 Å) as well as the α-hydrogen on the naphthalene nucleus (2.61 Å).

Despite extensive experimentation, we were unable to produce crystals of **4c**, **5c**, or **5d** suitable for X-ray diffraction.

Our observation of the solvent-filled channels in the crystal structure of **5b** and **4d** prompted us to examine the porosity of isolated cyclotetrabenzoin esters through gas sorption experiments. Disappointingly, miniscule nitrogen sorption suggested that the samples activated at 60 °C for 14 h are not porous.[11]

The presence of alkyne moieties in the cyclotetrabenzoins **4c** and **5c** opens many opportunities for further modifications.[12] In this work, we attempted one of them: hexacarbonyl dicobalt complexation of triple bonds in **4c**/**5c**. The reaction of the mixture of **4c** and **5c** with $Co_2(CO)_8$ in CH_2Cl_2 smoothly proceeded to give complex **6**, which was isolated as a red solid in 54% yield (Scheme 2, only **4c** is shown for simplicity). In

Scheme 2. Postsynthetic Modification of Cyclotetrabenzoin 4c by Complexation with $Co_2(CO)_6$ Groups



comparison with **4c**/**5c**, compound **6** shows significant visible light absorption between 300 and 400 nm with the maximum at 310 nm and an additional band at 260 nm. IR spectra of **6** shows the appearance bands at 2092, 2053, and 2003 cm^{-1} related to the cobalt carbonyls,[13] and the disappearance of the low-intensity 2220 cm^{-1} band, associated with the C≡C vibration in the starting materials. High resolution electrospray ionization mass spectrometry (HR-ESI MS) provided strong evidence in determining the composition of **6** as $C_{96}H_{48}Co_8O_{36}$. HR-ESI MS spectra in negative mode showed a peak at m/z = 2375.565, which was assigned to the $[M + I]^-$ adduct, with iodine stemming from the added CsI. Even more diagnostic was a series of fragment peaks $[M + I - 28n]^-$, where n indicates the number of lost CO molecules. We have observed the sequential loss of all CO molecules, i.e. up to n = 24. In the ^{1}H NMR spectra, strong downfield shift of aromatic signals is observed, together with expected peak broadening[13c] due to the presence of the metal. Signals at ∼199 ppm in the ^{13}C NMR spectra additionally confirm the presence of CO groups. Unfortunately, our attempts to obtain single crystals of **6** were unsuccessful.

In conclusion, the work presented in this contribution advances the chemistry of cyclobenzoins in three significant ways. We have (a) shown that these macrocycles can be prepared using environmentally friendly NHC catalysts, (b) expanded the family of cyclotetrabenzoins with larger members, and (c) postsynthetically modified functional groups within the cyclobenzoin skeletons. The roughly square-shaped cavities of **4d** and **5b** are about 60 and 125% greater in volume, respectively, that those of **2a**/**4a**. We presume that they will be

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able to include aromatic and other small molecular guests and are currently investigating the use of these expanded cyclotetrabenzoin esters as supramolecular hosts as well as their further postsynthetic modifications. We will report our results in due course.[14]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c04014.

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

Accession Codes

CCDC 2019826 and 2019827 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.M.E. and T.P. synthesized **3b**, **2d**, **3d**, **5b**, **4d**, and **5d**. X.W. solved the crystal structures of **4d** and **5b**. S.O. and K.V.K. prepared **1c**−**5c** and **6** and the aldehydes **1e**−**1i**. P.W. performed the HR-ESI mass analysis of **6**. O.Š.M. wrote the manuscript with the input from all authors, who have given their approval to the final version.

Notes

The authors declare no competing financial interest.

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