Benzoins and Cyclobenzoins in Supramolecular and Polymer Chemistry

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ARTICLE

Benzoins and Cyclobenzoins in Supramolecular and Polymer Chemistry

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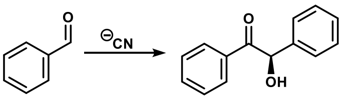
Benzoin condensation is one of the oldest rigorously described organic reactions, having been discovered in 1832 by Liebig and Wöhler. It creates a new C–C bond and a stereocenter from ubiquitous aldehyde starting materials under simple cyanide-catalyzed conditions. We have recently discovered cyclobenzoins: a class of macrocyclic compounds prepared by a benzoin cyclooligomerization of simple aromatic dialdehydes. Cyclobenzoins' internal cavities suggest they should be intriguing solution-phase supramolecular hosts, while their crystallographic packing aligns these cavities into potentially useful pores in the solid state. Well-precedented derivatization chemistry allows rapid functionalization into heteroacenes, which are optoelectronic materials and models for graphene defects. This Feature Article summarizes our work on cyclobenzoins, together with other applications of benzoins in supramolecular chemistry and materials science.

Faced with the prospect of writing a Feature Article on his group's body of work, the corresponding author suffered a mild crisis of faith. With a research program that is kindly described as "diverse", finding a unifying intellectual thread to the past ten years of research proved difficult. But another—more personal—thread emerged: that of a research program guided by the students who had the good fortune to make discoveries and the tenacity to develop them into scientific topics. This thread took former Miljanić group members to studies in dynamic covalent and systems chemistry (Dr. Karolina Osowska),[1] fluorophores (Dr. Jaebum Lim),[2] and porous materials (Prof. Teng-Hao Chen).[3] O.Š.M. was content to watch the science grow and busied himself with pleading for funding to governments and private foundations.

Presented here is the latest of these stories, on our discovery and study of cyclobenzoins—a story in which M.A. is a key player. This manuscript will begin with a mini-review of the uses of benzoin condensation at the interface of organic, inorganic, and materials chemistry. Then, we will proceed to discuss our discoveries of cyclobenzoins and their emerging applications. The voice of this manuscript will vary between "we"—signifying contributions of both co-authors or the entire research group, and "I"—which will be used for the more personal recollections of O.Š.M.

Introduction

Benzoin condensation is a carbon-carbon bond forming reaction in which one aldehyde adds over the C=O bond of another, forming an α-hydroxyketone (illustrated on the conversion of benzaldehyde **1** into parent benzoin **2**, Scheme 1). This addition reaction is in fact not a condensation—as no small molecule is eliminated—but the historical nomenclature persists. Benzoin condensation was discovered in 1832 by Wöhler and Liebig;[4,5] shortly thereafter, Liebig's student Nikolay Zinin established the cyanide-catalyzed version of the reaction that is in most common use today.[6,7] While initially discovered on aromatic aldehydes, benzoin condensation is readily expanded to their aliphatic counterparts as well.



1 2
benzoin

Scheme 1. Cyanide-catalysed benzoin condensation.

The mechanism of the benzoin condensation was established by Lapworth in 1903 and is shown in Scheme 2.[8] The reaction commences with the addition of cyanide to aldehyde **1** to form a tetrahedral anionic intermediate **3**. Its tautomerization results in a carbanionic nucleophile **4**; this newly created acyl anion equivalent then attacks the second molecule of **1** (which acts as the electrophile), forming the key C–C bond in **5**. Another tautomerization follows, setting the stage for the expulsion of cyanide catalyst from **6** and the formation of the final benzoin product **2**.[9,10]

In cases where two different aldehyde precursors are exposed to the cyanide catalyst, the reaction typically results in a mixture of the four possible products whose ratio is determined by their relative stabilities.[11,12] This outcome is a necessary consequence of the thermodynamic control generally observed in the benzoin condensation. In 2004, Johnson et al. have shown that this limitation can be circumvented by using an acyl silane as one of the coupling partners.[13] Its cyanation is followed by the [1,2]-Brook rearrangement which delivers a preferred acyl anion equivalent under the kinetic control, resulting in a single *O*-silyl protected benzoin adduct. An asymmetric version of this cross-benzoin condensation has been developed, using chiral metallophospites as catalysts.[14] Mixed aromatic benzoins can

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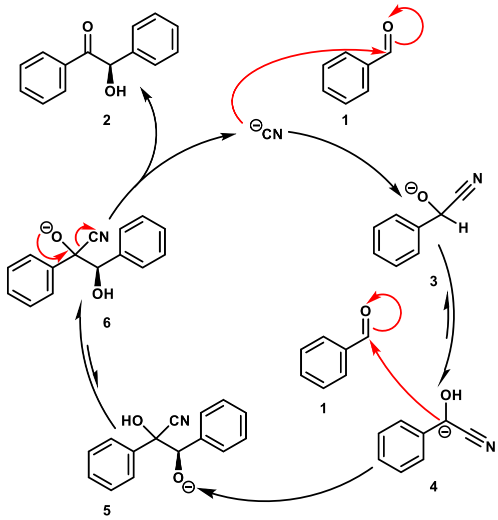
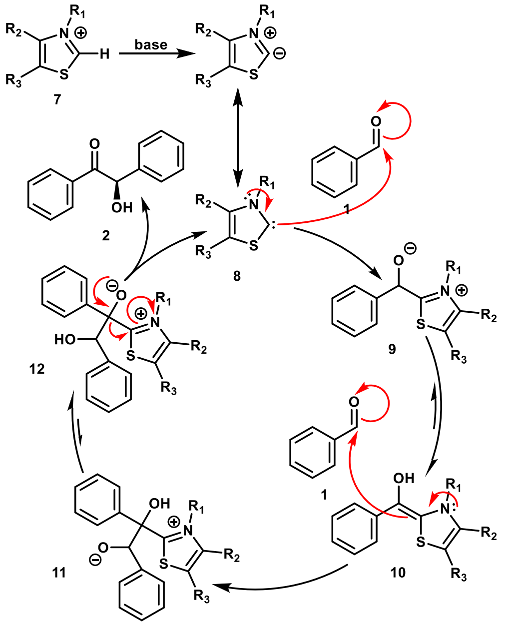
be made indirectly, by e.g. Friedel-Crafts reactions of glyoxals with aromatic hydrocarbons.[15]



Scheme 2. Mechanism of benzoin condensation, as first proposed by Lapworth.

Over a hundred years after the discovery of the cyanide-catalyzed benzoin condensation, Ugai et al. observed that thiazolium salts (**7**, Scheme 3) also catalyse benzoin condensation under basic conditions.[16] In 1958, Breslow suggested a mechanistic model for this reaction wherein the base deprotonates precatalyst **7** and generates carbene **8** that is the catalytically active species.[17] The initial inability to isolate the purported carbenes made this mechanism tentative, but doubts were dispelled by the mounting evidence for carbene intermediates—including the first isolation by Arduengo in 1991.[18]



Scheme 3. Mechanism of carbene-catalyzed benzoin condensation, as originally proposed by Breslow.

Benzoin condensation creates a chiral center on the carbon bearing the –OH group in the new α-hydroxyketone.[19] The use of carbene-based catalysts allowed the exploration of enantioselective variants of benzoin condensation. The first asymmetric benzoin condensation catalysed by a chiral thiazolium salt was reported by Sheehan et al. in 1966, but the enantiomeric excess (ee) in this reaction was just 22%.[20] The ee was soon improved to 51% (albeit benzoin was produced in a low yield) using a (*S*)-4-methyl-3-α-(1-naphthyl)ethyl-thiazolium salt **13** (Chart 1).[21] Several decades of investigation followed this initial report, but enantioselectivity remained modest.[22,23,24] Dramatic improvements came in the late 1990s with the work of Enders[25] and Leeper,[26] who discovered that triazolium-derived precatalysts **15** and **16** lead to higher enantioselectivity than their thiazolium counterparts, especially if the triazolium ring is a part of a bicyclic skeleton. With precatalyst **17**, Enders et al. subsequently improved the yields to 83% and optical purity to 90% in the case of parent benzoin.[27,28] Introduction of the pentafluorophenyl group into the structure of precatalyst **18** by Connon led to further improvement in the yield (90%) and to excellent 99% ee.[29]

More recently, asymmetric catalysts for benzoin condensation included desymmetrized rotaxanes substituted with a thiazolium group.[30] Observed ee's were low, but this work demonstrated that the rotaxane can be used to introduce a chiral field around an otherwise achiral catalytic thread molecule. Other competent precatalysts that were recently developed included bistriazolium,[31] hydrogen bonding,[32] and spirocyclic[33] motifs, with ee's ranging between 55% and 95%. An aqueous version of the NHC-catalyzed asymmetric benzoin condensation was recently reported.[34]

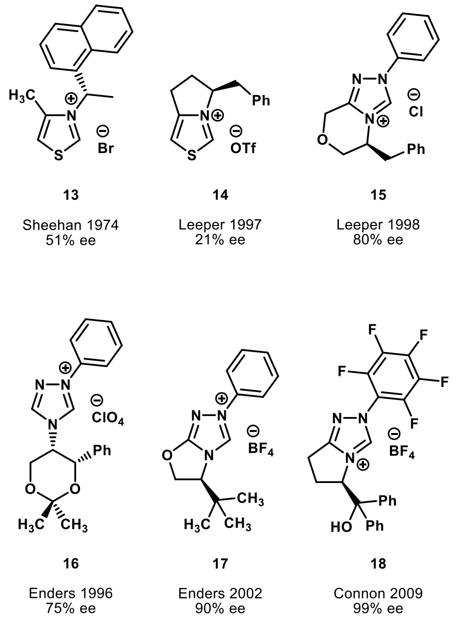
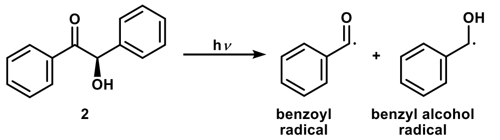


Chart 1. Examples of precatalysts to chiral carbene-based catalysts for asymmetric benzoin condensations.

Benzoins in Polymer Science

Benzoins can be easily reduced into hydrobenzoins or oxidized into benzils. Benzoins, their ethers, and benzils are common photoinitiators for radical polymerizations.[35]

Irradiation of benzoins with the light with wavelengths between 300 and 400 nm results in efficient α-cleavage, generating a benzoyl and benzyl alcohol radicals (Scheme 4).[36] One of the few drawbacks in using benzoin derivatives as photoinitiators is their poor absorption in the near-UV region; this feature can be easily corrected through substitution with e.g. methyl thioether groups.[37] Benzoin-terminated polyurethane was used as macrophotoinitiator in the synthesis of polyurethane–polymethyl methacrylate block copolymers.[38] Novel oligomeric benzoin-derived photoinitiators were synthesised by the reaction of the parent benzoin with depolymerization products of polyethyleneterephthalate (PET), and subsequently used in the block copolymerization of styrene and acrylonitrile.[39] Decoration of multi-walled carbon nanotubes (MWCNT) with benzoin functional groups allowed the photoinitiation of polymer growth from the surface of the MWCNT, allowing the creation of nanotube/polystyrene hybrids.[40] Propargyl ether of benzoin was used as a "clickable" photoinitiator that could be easily attached to azide-ornamented polymers.[41] Timpe and Rajendran studied the cationic ring-opening of epoxides using several benzoin derivatives as radical sources in polymerization process and diphenyliodonium hexafluoro-phosphate as the electron-acceptor.[42]



Scheme 4. Photolytic α-cleavage of benzoin is the basis of its use as a photoinitiator in polymerization reactions.

Attempts to incorporate benzoin motifs into polymeric structures date back to 1955, when Tinker and Jones and co-worker obtained an apparent benzoin pentamer by treating terephthalaldehyde with potassium cyanide.[43] This finding contradicted a previous report by Oppenheimer in which terephthalaldehyde was shown to form only its dimer upon exposure to cyanide.[44] Kuriakose and Pillai engaged pendant benzaldehyde chains of a polymer in a cross-benzoin condensation.[45] Angiolini et al. used free-radical copolymerization to produce optically active copolymer containing racemic α-methylolbenzoin methyl ether acrylate and (−)-menthyl acrylate monomer units.[46] Han's group used rigid threefold symmetric trisaldehydes **19**–**22** (Chart 2) as precursors to porous organic polymers (POPs) with benzoin linkages and Brunauer-Emmet-Teller (BET) surface areas as high as 726 $m^2 g^{-1}$.[47]

Benzoins as Ligands for Transition Metals

Nitrogen condensation derivatives of benzoins have been often used as chelating ligands for metals. Ghaedi and co-workers have shown that trace concentration of Cr^{3+} in water can be detected by complexing this ion with α-benzoin oxime in the presence of a non-ionic Triton X-100 surfactant,[48] building on the previous work on Cr^{3+} complexes of α-benzoin oxime.[49] Stamatatos's group employed α-benzoin oxime and Mn^{3+} to construct an unusual cluster with nine metal centers (Figure 1, left),[50] while Joshi and Habib used the same ligand to obtain mononuclear complexes with Co^{2+}, Cu^{2+}, Ni^{2+}, and Zn^{2+}.[51]

Narang, Lal, and co-workers studied complexes of benzoin's thiosemicarbazone with various Cu^{2+} salts and found that the coordinating atoms and the coordination geometry switch as a function of a counterion.[52] Zakir et al. synthesized Co^{2+} and Ni^{2+} complexes of benzoin thiosemicarbazone, and investigated their antibacterial activities.[53] El-Shahawi and co-workers studied homoleptic and heteroleptic complexes of benzoin thiosemicarbazone with Rh^{3+}, Ru^{3+}, Pd^{2+}, Cu^{2+}, and Ni^{2+}.[54]

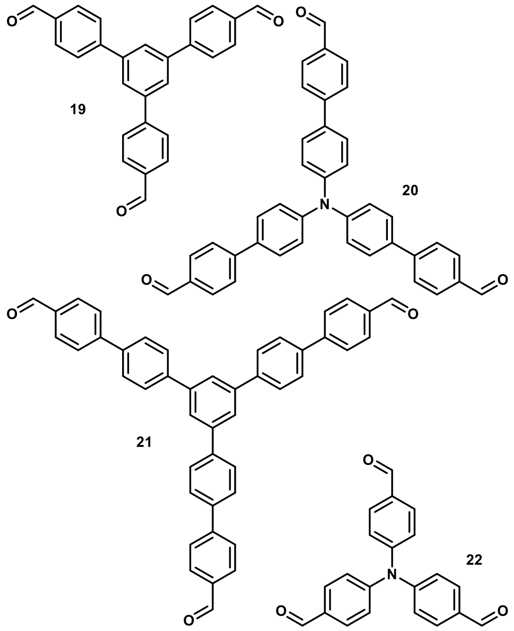


Chart 2. Examples of trigonally symmetric aldehydes used in the production of porous organic polymers through benzoin condensation.

Aliyu and co-worker prepared a Schiff base from benzoin and anthranilic acid and coordinated it with Fe^{2+} and Ni^{2+} salts to produce complexes with 1:1 metal-to-ligand ratio.[55] A Schiff base of benzoin and glycine was complexed with a series of transition metals, yielding complexes with 1:2 metal-to-ligand ratio.[56]

Benzoins themselves are also competent ligands for catalytically active metals. Benzoin-supported titanium catalyst (Figure 1, right) was shown as effective in the copolymerization of norbornene and ethylene.[57] Paine's group mimicked the action of non-heme enzymes in aliphatic C–C bond cleavage using complexes in which benzoins were coordinated with Fe^{2+} and supported by a facial N3 and a tripodal N4 ligand.[58] Benzoin complex with Mn^{2+} was also prepared and studied.[59]

Itoh, Fukuzumi, and co-workers have shown that a binuclear complex of Cu^{2+} with tridentate *N*,*N*-bis[2-(2-pyridyl)ethyl]-2-phenylethylamine can be quantitatively hydroxylated at the benzylic position using molecular oxygen and benzoin-derived 1,2-enediolate as the electron donor. This behaviour paralleled the activity of dopamine β-hydroxylase.[60]

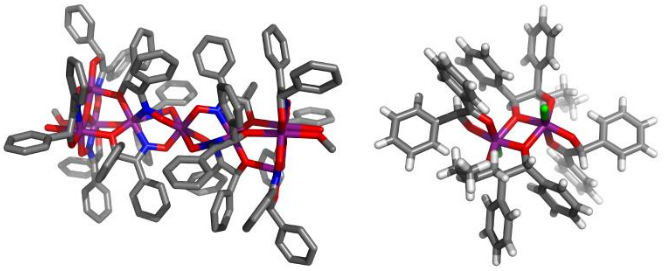
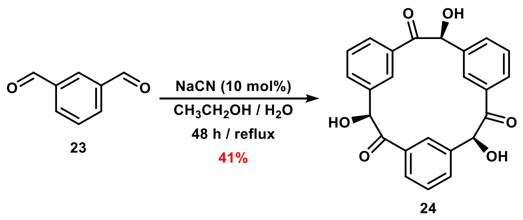


Figure 1. Complexes of benzoin oxime with Mn^{3+} (left, ref. 50) and benzoin with Ti^{4+} (right, ref. 57). Element colors in this and subsequent figures: C—gray, H—white, O—red, N—blue, Cl—green, metals—purple. In the structure on the left, hydrogen atoms have been ommitted for clarity.

First Cyclobenzoins

In 2014, I traveled to China with my graduate student Qing Ji, to attend the International Symposium on Macrocyclic and Supramolecular Chemistry (ISMSC) in Shanghai. My motivation for inviting Qing was manifold. First, he has proven himself competent and committed in the lab, and an exciting international conference was a good way to reward such dedication. Second, ISMSC is a premier gathering of supramolecular chemists and I still remember my first trip to this conference (in Victoria, Canada) as a veritable introduction to “Who Is Who” in our field. Finally, and quite selfishly, I thought that Qing would be an invaluable local guide on my first trip to China. This last point proved quite correct, especially in the culinary sense. Qing introduced me to what became one of my favorite dishes: Shanghainese baked dumplings (sheng jian bao, 生煎饅頭), whose crunchy outsides burst to release a surprise of hot soup found inside. Today, they are made by wrapping a cube a frozen soup in the dough and then baking it; traditionally, as Qing explained, they used to be a winter dish, made only when soup froze in cold weather.

Qing’s motivation for this trip was much more professional than mine, and he returned to Houston full of new ideas. Particularly inspiring was a talk by Prof. Amar Flood from Indiana University, in which he described his group’s synthesis of the first macrocycles of the cyanostar class[61]—and a very simple synthesis at that. Upon returning to Houston, Qing proposed to me to expand his research portfolio, which at the time focused on the dynamic covalent chemistry of esters[62,63] and imines,[64] onto the dynamic synthesis of rigid macrocycles through (reversible) benzoin condensation. My response that “this will probably not work” provided all the encouragement he needed and he retired to the lab to test out his ideas on isophthalaldehyde (**23**, Scheme 5) as the first substrate. Several weeks later, he reported that a discrete oligomer had been formed in 41% yield, but only if the ratio of EtOH and H$_2$O solvents was adjusted so that the precipitation occurs very selectively. In a couple of weeks, a crystal structure of the cyclic trimer **24** followed—dispelling all doubt that Qing indeed made a macrocyclic compound. We dubbed this molecule *cyclotribenzoin* to suggest its cyclic trimeric nature and its origins in the benzoin condensation.



Scheme 5. Synthesis of cyclotribenzoin (**24**).

Single crystal structure of cyclotribenzoin (Figure 2, left) showed that the molecule was formed as the all-*cis* diastereomer, which adopts a conical shape with three benzene rings expressing a cuplike cavity. The structure is not strained, as all its carbon atoms have bonding angles within 2 ° of their idealized geometries. Six C–H bonds—three coming from the aromatic rings and the other three coming from the secondary carbon atoms adjacent to the hydroxyl groups—are convergently positioned pointing towards the apex of the cone. In the crystal packing of cyclotribenzoin (Figure 2, right), the parallel orientation of stacked molecules to each other is clearly shown through the *a*–*b* crystallographic plane. Short [C–H···O] contacts connect each cyclotribenzoin molecule with twelve of its neighbours, with H···O distances between 2.50 and 2.60 Å. On each aromatic ring of cyclotribenzoin, the hydrogen located *ortho* to the C=O group establishes a short contact with the carbonyl oxygen atom from the adjacent molecule. Likewise, the hydrogen located *meta* to the C=O group establishes short contacts with the hydroxyl oxygen atoms from neighbouring molecules. This set of connections is repeated for each aromatic ring in the cyclotribenzoin molecule.

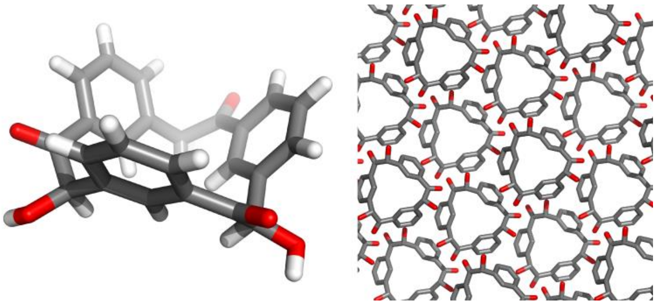
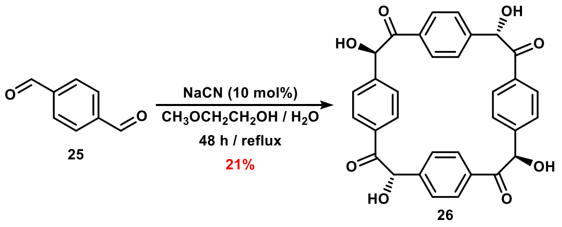


Figure 2. Crystal structure (left) and a segment of packing diagram (right) for **24**.

Qing’s continued dedication to this project took him next to terephthalaldehyde (**25**, Scheme 6), whose exposure to similar benzoin condensation conditions resulted now in a cyclic tetramer **26**, which we named *cyclotetrabenzoin*.[66] Cyclotetrabenzoin was isolated following precipitation and recrystallization from a MeOH/DMSO mixture. While the isolated yield of 21% may appear low, it is remarkable considering how many potential isomers can be formed in the process: even just among the cyclic tetramers, there are 37 possible stereoisomers and regioisomers. Only one is isolated: this diastereomer (shown in Scheme 6) is achiral on account of the presence of an S_4 rotation axis.

The crystal structure of cyclotetrabenzoin (Figure 3, top left) was obtained using synchrotron radiation. The tetrameric macrocycle is square-shaped, with a central cavity measuring 6.9 × 6.9 Å (distance between the centroids of two benzene rings located on the opposite sides). Judging by the bonding angles on all carbon atoms, cyclotetrabenzoin is not significantly strained either.

The individual macrocycles organize into 2D layers which resemble square grids (Figure 3, top right), perfectly stacked on top of one another. Molecules of cyclotetrabenzoin organize into infinite nanotubes, held in bundles through zigzagging hydrogen bonding connections (Figure 3, bottom, hydrogen bonds shown in green). Formed between the oxygens of the carbonyl and hydroxyl groups as acceptors and the hydrogen of the neighboring molecule's –OH group as the donor, these hydrogen bonds repeat themselves on each of the four corners of the square-shaped macrocycle. Because of this perfect alignment, cyclotetrabenzoin is somewhat porous in the solid state, with a Langmuir surface area of 47 $m^2\ g^{-1}$.



Scheme 6. Synthesis of cyclotetrabenzoin (**26**).

Publication of our results in *Chemistry—A European Journal* included an abstract in which the square-grid network of molecules of **26** (seen in Figure 2, top right) superimposes neatly on the city plan of Barcelona. Barcelona's district of Eixample is known for its visionary urban design, proposed by Ildefons Cerdà (1815–1876) in the mid-1800s. In it, city blocks are rectagonal in shape, but the corners of each rectangle are cut off to generate an octagon. Thus each intersection of two streets looks like a small square, arguably giving the city some of its famous charm. As Henrik Ottosson, a colleague from Uppsala University with a passion for urban design (and physical organic chemistry), was quick to point out, the ChemDraw representation of **26** is also a square with each corner cut off.[67]

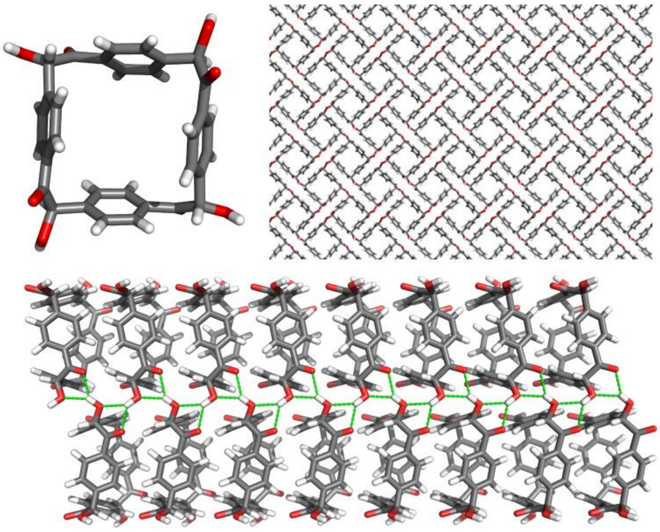


Figure 3. Crystal structure (top left) and a segment of the packing diagram (top right) for cyclotetrabenzoin (**26**). On the bottom, zigzagging arrays of hydrogen bonds organize molecules of **26** into perfectly aligned nanotubes.

Derivatization of Cyclobenzoins

Benzoins have a huge volume of well-precedented chemistry, which suddenly becomes new in the context of cyclobenzoins. The hydroxyl groups can be silylated[65] or esterified.[68] Both modifications remove the hydrogen bond donors, dramatically increasing the solubility and facilitating purification. Acetic ester of cyclotetrabenzoin (**27**, Figure 4, left), for example, can be routinely produced in >10 g batches.

Examination of the crystal packing diagram of **27** (Figure 4, right) shows that simple acetylation had a profound impact on the packing of the cyclotetrabenzoin moieties. Apart from the pore defined by the square-shaped cyclotetrabenzoin, another diamond-shaped pore is observed in the packing diagram. Together, they dramatically increase the guest-accessible surface area, from ~50 $m^2\ g^{-1}$ in **26** to ~500 $m^2\ g^{-1}$ in **27**. Similarly large pores were not observed in the crystal structures of the propionic or isobutyric esters of **26**; larger acyl groups occupied the pores, leaving little empty space.

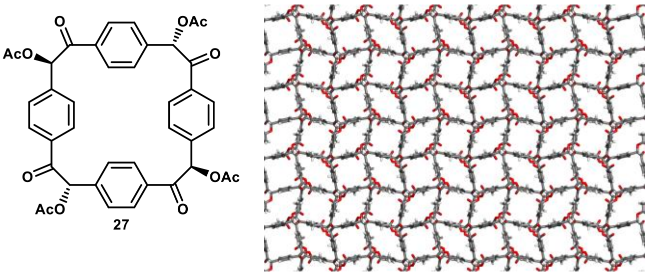
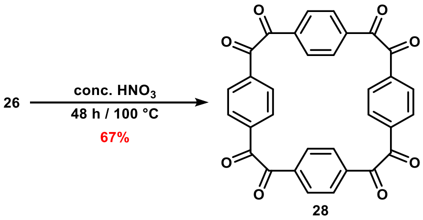


Figure 4. Chemical structure (left) and a segment of the packing diagram (right) for the acetic ester of cyclotetrabenzoin (**27**).

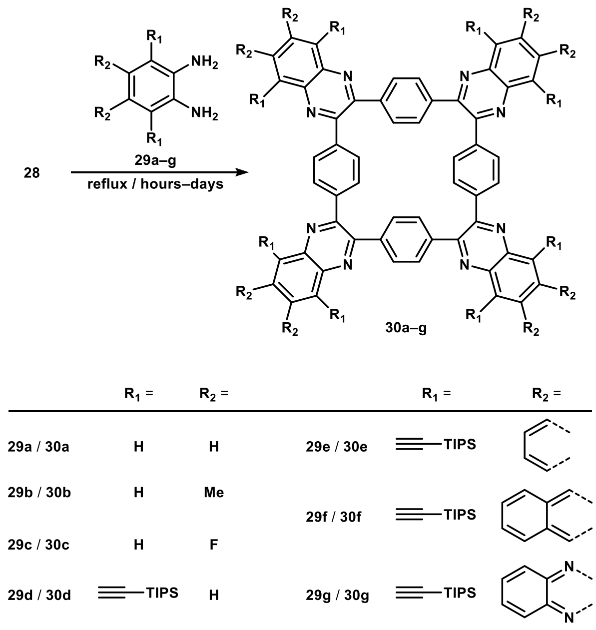
Oxidation of benzoin's –OH group to produce 1,2-diketone known as benzil has also been widely explored. Benzils are important building blocks in synthesis of pharmaceuticals[69] and porphyrins,[70] and common photoinitiators for free radical polymerizations.[71] Using concentrated HNO_3, cyclotetrabenzoin could be readily oxidized into the corresponding octaketone **28** in 67% yield (Scheme 7). In cyclotetrabenzil **28**, hydrogen bond donors are no longer present, making its solubility much higher than that of **26**.



Scheme 7. Oxidation of cyclotetrabenzoin into octaketone **28**.

Synthesis of **28** opened up a very productive collaboration between our group and the team of Prof. Uwe Bunz at the Ruprechts-Karls-Universität in Heidelberg (Germany). Bunz pioneered the chemistry of azaacenes:[72,73] heterocyclic analogs of acenes which offer many new lessons in electron mobility and fundamental studies of (anti)aromaticity.[74] As most azaacenes are synthesized through a convenient condensation of 1,2-diketones with 1,2-phenylenediamines, compound **28** presented itself as an interesting precursor that could orient four azaacenes around the central macrocyclic core.

A series of fully π-conjugated functionalized heteroaromatic cycles was synthesized using acid-mediated condensation reaction between 1,2-phenylenediamine derivatives **29a**–**g** and the octaketone **28** producing the corresponding tetraquinoxaline macrocycles **30a**–**g** in yields ranging from 61% to 85% (Scheme 8). The central cavities of these macrocyclic molecules consist of an all-carbon macrocycle in which adjacent benzenoid rings connect in para- and ortho-positions, alternately. Interestingly, when the relative amount of 1,2-phenylenediamine in the coupling was decreased to 2 equiv, bisquinoxalines could be isolated in which two quinoxaline condensations occurred on the opposite corners of the cyclic octaketone.[75]



Scheme 8. Condensation of cyclotetrabenzil (**28**) with a variety of 1,2-phenylenediamines **29a**–**g** produces heteroacenes **30a**–**g**.

The optical and electronic properties of **30d**–**g** were studied by UV/Vis spectroscopy and cyclic voltammetry, and were found to be dominated by the linear acene fragments. Only small bathochromic shifts have been observed upon incorporation of these subunits in the cyclic skeleton. The stepwise nature of the condensation allows incorporation of different heteroacene fragments into the same molecule, opening up space for modulation of optoelectronic properties.

Diffraction-quality crystals of all prepared quinoxalines could be grown by vapour diffusion. An exemplary crystal structure of **30b** is shown in Figure 5. The macrocyclic molecule is twisted into the saddle shape by the rigidifying fusions of quinoxaline rings around the central cavity.

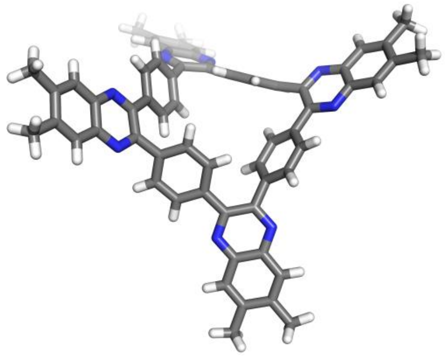
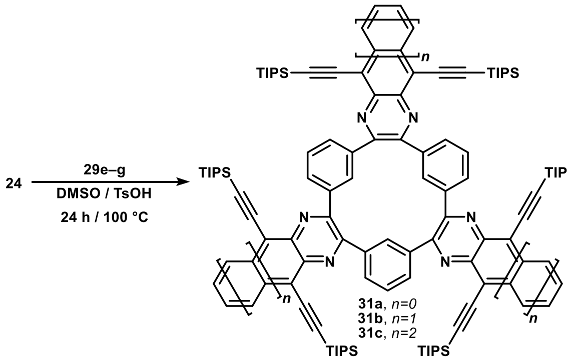


Figure 5. Crystal structure of **30b** shows the saddle-shaped structure.

Cyclotribenzoin (**24**) could be similarly elaborated into trisquinoxalines, but with one important difference. Its oxidation could not cleanly produce the corresponding hexaketone; instead, a significant amount of ring-opened product was observed, wherein the macrocyclic ring was cleaved between the carbonyl and alcohol carbon atoms. By performing this oxidation *in situ*, and immediately proceeding with the condensation with requisite 1,2-phenylenediamines, trisquinoxalines **31a**–**c** could be isolated (Scheme 9) in yields between 29% and 34%.[76] Compound **31b** was found to have a very twisted structure and shown to be a reasonably good green-yellow emitter for organic light-emitting diode (OLED) devices.



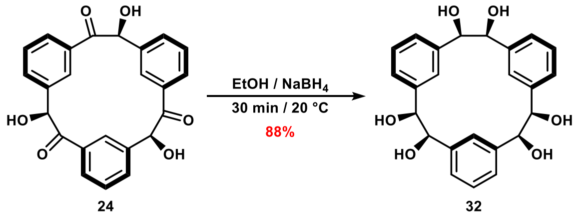
Scheme 9. *In situ* oxidation of cyclotribenzoin (**24**) followed by condensation with [tris(isopropyl)silyl]ethynylated diaminoarenes **29e**–**g** yielded novel heteroarenes **31a**–**c**.

Apart from their inherent interest as emissive materials, heterocyclic cyclobenzoin condensates **30** and **31** are also of relevance as models for heteroatom-doped[77] and curved[78,79,80] graphene fragments.

Water Confinement within the Crystals of Cyclotrihydrobenzoin

Reduced benzoins—known as *hydrobenzoins*—are 1,2-diols which have been used as chiral auxiliaries and catalysts,[81] and as precursors to chiral crown ethers,[82,83] liquid crystals,[84,85] and materials with non-linear optical (NLO) properties.[86] We were thus intrigued to see whether reduced cyclobenzoins would have similarly interesting properties.

Using $NaBH_4$ as the reductant, cyclotribenzoin (**24**) was diastereoselectively reduced to the all-cis hexaol **32** (Scheme 10).[87] We speculated that the diastereoselectivity of this simple reduction stemmed from the conical shape of cyclotribenzoin, which mandated the attack of the hydride reducing agent from one side only.



Scheme 10. Reduction of cyclotribenzoin **24** into hexaol **32**.

Diffraction quality crystals of **32** were obtained from off-the-shelf THF. The crystal structure of **32** is shown in Figure 6, top left. The cone-shaped cyclotribenzoin was deformed after reduction: one of the three aromatic rings in the macrocycle was flipped, while the other two aromatic rings still pointed in the same direction as well as all the hydroxyl groups. The hydroxyl groups were convergently positioned, with neighbouring –OH groups in a gauche orientation and dihedral angles ranging from 54 to 63 °.

Molecules of **32** co-crystallized with water (which was present in THF) in a 1:3 ratio. These water molecules were extremely well-ordered within the crystal structure: atomic positions of their hydrogens could be refined directly from X-ray data and elemental analysis also supported a well-defined trihydrate. Closer inspection of the packing diagram (Figure 6, top right) shows small voids within which ordered pentameric water clusters[88,89,90] are found. In these clusters, five water molecules are organized in a tetrahedral structure with the central water molecule hydrogen bonded to four of its neighbours (Figure 6, bottom left). This pentameric water cluster was first identified in 1964 by Walrafen, who suggested it to be one of the simplest subunits of hydrogen-bonded water networks.[91,92,93,94,95,96] In 2012, Bowman-James and coworkers isolated the Walrafen pentamer within a supramolecular host capsule.[97,98]

To enclose the tetrahedral water pentamer, six molecules of **32** come together in a fashion reminiscent of protein subunit assembly: they orient their hydrophobic exteriors toward the outside to enclose a highly hydrophilic interior. The central water molecule hydrogen bonds to its four neighbours (Figure 6, bottom left), forming a distorted tetrahedron. The O···O distances in this tetrahedron are comparable to the shortest observed distances in Fujita's “molecular ice” encapsulated in a self-assembled metal-organic cage (2.72 Å) and those found in the I_h-type ice (2.75 Å).[99] The O···O···O angles range from 97.7 to 141.8 °, suggesting a “squeezed” tetrahedron relative to the I_h ice, in which the corresponding angles are 109 °. Externally, the water cluster is stabilized by hydrogen bonding and [O–H···π] interactions with the six neighbouring molecules of **32**, color-coded in Figure 6, bottom right.

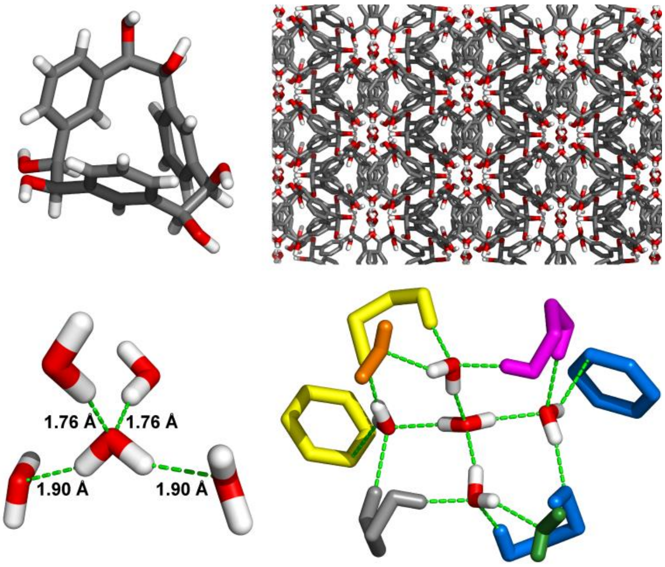


Figure 6. Crystal structure (top left) and crystal packing (top right) of molecule **32**. Within the voids of the crystal structure, Walrafen's water pentamers are found (bottom left), stabilized by interactions with six neighboring molecules of **32** (bottom right).

Conclusions and the Future

Perhaps old dogs can be taught new tricks. In the hands of talented young scientists, an old reaction attempted on an apparently trivial substrate revealed cyclobenzoins: a whole new class of macrocycles with interesting structures and potentially useful functions. Made in a single air- and moisture-tolerant step, cyclobenzoins are easily reduced into cyclohydrobenzoins or oxidized into cyclobenzils. While closely synthetically related, these three groups of macrocycles show diverse solubility profiles and self-assembly properties.

We believe that cyclobenzoins and their relatives offer some advantages over the existing classes of macrocycles. They are inexpensive to make, with even unoptimized laboratory-scale preparations producing them at costs of ~$1 per gram. Their synthesis is doubly modular, as both the size of the oligocyclic assembly and the nature of the linking group can be modified. Their macrocyclic skeletons are highly stable, and can tolerate functionalization of their aromatic rings; at the same time, their pendant functionalities are reactive, allowing easy and stepwise derivatization. Self-assembly of cyclotetrabenzoin derivatives into nanotubular arrays in the solid state bodes well for the construction of porous materials and binding of gaseous guests.

Continued work in our lab focuses on: (*a*) the understanding and control of the dynamic equilibrium involved in the preparation of cyclobenzoins (Schemes 2 and 3), (*b*) exploration of their properties as supramolecular hosts in solution and the solid state, (*c*) use of their porous solid-state structures to construct sensing devices, and (*d*) preparation of new, larger cyclobenzoins. Results of these studies will be reported in due course.

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