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Benzocyclotrimers: From the Mills–Nixon Effect to Gas Hosting

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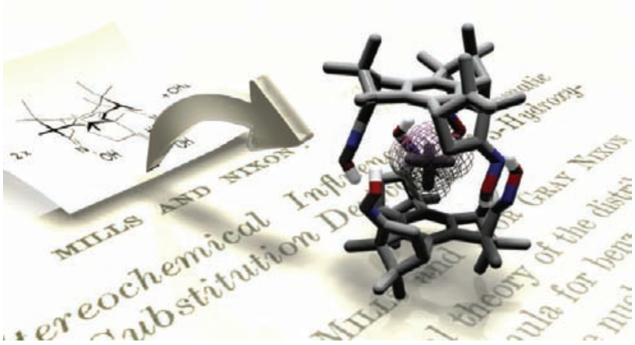

The formal annulation of three bicylic olefins yields a class of molecules termed benzocyclotrimers (BCTs), which have unusual electronic properties. The bonds in the central aromatic ring, for example, alternate in length: rather than resembling a substituted benzene, a BCT instead evokes comparison to a cyclohexatriene.

Forty years have passed since the synthesis of heptiptycene, the first BCT, was reported. In the interim, many methods have been developed for preparing tris-bicycloannulated benzenes. More than thirty different BCTs have so far been reported, with a variety of morphological features and properties. Over the same period, yields have increased from just a few percent to almost quantitative conversion. This improvement in synthetic access has expanded interest beyond the original theoretical considerations (bond-length fixation in aromatics) to functional applications (supramolecular scaffolds). In this Account, we describe the evolution of synthetic approaches to BCTs and their derivatives, as well as the applications that are now being explored for these compounds.

Early syntheses of BCTs involved chloroolefins treated with butyl lithium. A strained alkyne intermediate was postulated early on, and was indeed trapped in 1981. Subsequent efforts have focused on improving chemoselectivity by mitigating the drastic conditions required for the generation of the alkyne intermediate. Our introduction of Cu(I) to induce lithium–copper exchange was successful in this regard. Further improvement resulted from the use of bicylic bromo(trimethylstannyl)olefins. In an effort to avoid the toxicity of the tin reagents, the Heck reaction and Pd catalysis have been pursued for cyclotrimerizing bicylic bromo- and iodoolefins.

Depending on the symmetry of the starting bicylic olefin, two diastereomers can be obtained in the preparation of a BCT: a *syn* compound with C_3 symmetry and an *anti* compound with C_s symmetry. Studying the diastereomeric outcome in a variety of synthetic approaches has yielded valuable insight into the cyclotrimerization reaction. Moreover, highly symmetric compounds, such as a D_3-symmetric trindane and C_{3v}-symmetric sumanene, have been prepared as BCT derivatives.

The structure of BCTs offers a versatile three-dimensional scaffold for studying molecular recognition. Like calixarenes, BCTs form complexes with a variety of guest molecules. Recent developments include the trapping of gases in a hydrogen-bonded dimer and the encapsulation of larger molecules within a covalently linked condensation derivative. Future innovations in this fertile research area will likely include highly functionalized curved aromatics, receptors, and sensors.

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1. Introduction

Benzocyclotrimers (BCT) are synthetic molecules derived from the formal annelation of three bicyclic olefins. Such operation is usually referred to as "cyclotrimerization" and benzocyclotrimers or simply cyclotrimers the products thereof. The condensation of three suitably functionalized bicyclic olefins is the main way to obtain BCTs. The driving force for the cyclization is the extra stability gained with the formation of the central aromatic ring, though the aromaticity of these molecules is peculiar and it has been the original motivation for the synthesis. In fact, BCTs own unusual electronic properties as they are among the very few molecules that exhibit bond length alternation of the central aromatic ring: the central aromatic ring resembles a cyclohexatriene more than a substituted benezene.

Besides the central ring, in recent years attention has been focused in the molecular recognition properties resulting from the resemblance with the cavity exhibited by calixarenes, resorcinarenes or cycloveratrilenes, although BCTs differ from these molecular scaffolds for the stiffness of the structure and for the elements constituting the walls of the cavity, that can consist in saturated, unsaturated, or aromatic residues. Furthermore, enantiomerically pure BCTs can be directly obtained starting from enantiomerically enriched precursors. The availability of highly differentiated starting bicycles has offered the possibility to prepare a large variety of BCTs presenting structural and functional diversity. This assortment has been translated in recent years into a wide range of applications which range from molecular recognition to the synthesis of fullerene subunits.

In this accounts we are presenting the BCTs that have been obtained during the last four decades and the applications of these compounds studied in our and other research groups.

2. Benzocyclotrimers: Synthesis

Although alkenes, alkynes, and ketones were cyclotrimerized since the beginning of the last century,[1] the research aimed at the cyclotrimerization of polycyclic olefins is more recent. Among the reported methodologies for the preparations of BCT, cyclotrimerization of suitably substituted polycyclic olefins is the more affordable strategy.[2] This approach is based on olefins bearing two vicinal substituents able to act as anionic and cationic leaving groups in the presence of a suitable promoter. In the case of polycyclic alkenes, depending on the symmetry of the bicycle, it is possible to obtain two different compounds: the *syn*-diastereomer, exhibiting C_3-symmetry and the *anti*-diastereomer possessing C_S symmetry, which are formed in the statistical 1:3 diastereomeric ratio (Figure 1).

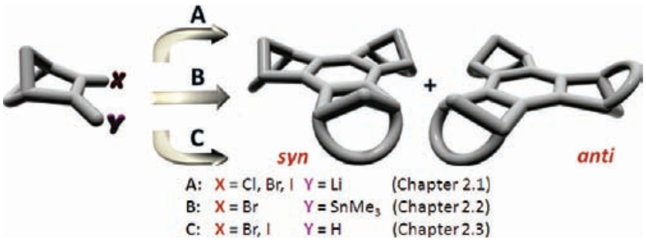

FIGURE 1. Viable pathways of cyclotrimerization leading to *syn* and *anti* diastereoisomers.

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FIGURE 2. Stick representation of X-ray crystal structure of heptiptycene **1**.[3]

Section 2 has been divided into three sections according to the nature of the anionic and cationic leaving groups present on the precursor bicyclic olefins.

2.1. BCT from Organolithium Bicyclic Olefins. The first benzocyclotrimer obtained from a bicyclic olefin was heptiptycene **1** (Figure 2), which was described in 1970 by a group of researchers of CIBA pharmaceutical company.[3] This D_{3h}-symmetric molecule was formed in low yield (much less than 30%)[3] from the corresponding bicyclic chloro-olefin, when treated with butyl lithium at room temperature.

Ten years later, P. G. Gassman reported the structure of two isomeric products **2** (Figure 3), obtained in nearly statistic ratio and 9−11% overall yield when treating 2-chloronorbornene with *t*-butyl lithium.[4] For the first time, Gassman assigned the prefix "*syn*" and "*anti*" to the two diastereoisomers. It was also postulated a strained alkyne as intermediate of the reaction, deriving from elimination of lithium chloride from the lithiated olefin.[4]

In 1981, H. Hart optimized the reaction conditions for the synthesis of heptiptycene **1**, obtaining a reproducible 20%

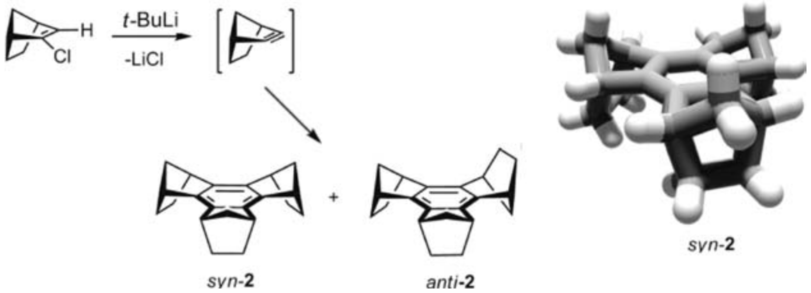


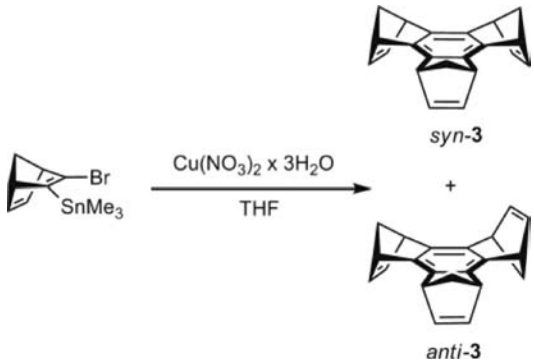
FIGURE 3. Synthetic pathway adopted by Gassman for the synthesis of BCTs **2** and crystal structure representation of *syn*-**2**.

yield, and demonstrated that the cyclotrimerization occurs through a strained alkyne intermediate, which was trapped during the reaction.[5] In a first attempt to improve the yields of the cyclotrimerization of 2,3-dibromobicyclo[2.2.2]oct-2-ene, K. Komatsu introduced nickel(0) to stabilize the alkyne intermediate, although finally the role of the metal resulted negligible.[6]

An important progress in the synthesis of BCTs has been the use of copper(I), which causes a copper–lithium exchange, leading to improved chemo-selectivity, presumably avoiding the alkyne intermediate. This procedure, that has been developed in 1996 in our group, allowed to prepare for the first time benzotrinorbornene and benzotribenzobornane in yields up to 50%.[7] A similar approach has been applied in 2001 by K. Komatsu,[8] allowing to access to good quantities of the highly strained benzotribicyclo[2.1.1]hexane.[9]

2.2. BCT from Organostannyl Bicyclic Olefins. *In situ* generation of *vic*-lithiumhalobicycloolefins furnished low yields of BCT and proved not be applicable in the presence of many functional groups. To overcame these disadvantages, less drastic conditions were studied. With this aim, we proposed the use of bromo(trimethyltin)olefins as milder alternative to cyclotrimerization of lithium derivatives.[10] The trimethyltin moiety can be introduced either in *vic*-dibromoolefins by metal–halogen exchange with *n*-butyl lithium followed by trans-metalation with trimethyltin chloride, or starting from bromoolefins by deprotonation with lithium diisopropylamide and subsequent quenching with trimethyltin chloride.[11] *vic*-Bromo(trimethylstannyl)bicyclic olefins can be conveniently obtained via cycloaddition of *vic*-bromo(trimethylstannyl)-1,3-dienes and suitable dienophiles.[12] The first reagent employed to promote the cyclotrimerization of *vic*-bromo(trimethyltin)bicycloolefins was $Cu(NO_3)_2 \cdot 3H_2O$ in THF, furnishing good yields of cyclotrimers, as exemplified by the synthesis of benzonorbornene **3**, which was obtained in 78% overall yield (Scheme 1).[10]

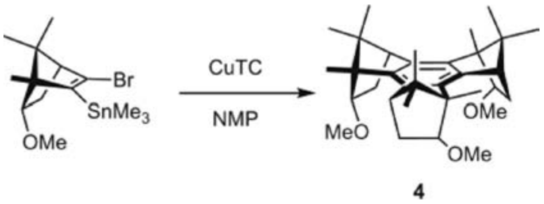
SCHEME 1. Synthesis of BCTs **3** Starting from the Corresponding *vic*-Bromo(trimethyltin)bicycloolefins using $Cu(NO_3)_2 \cdot 3H_2O$ as Promoter



To reverse the statistical 1:3 *syn* to *anti* ratio, enantiopure starting materials were tested, considering that a chemoselective tin–bromine coupling can led only to the formation of the *syn*-isomer. Disappointedly, the reactions afforded the *anti* isomers in almost quantitative yield.[13] This phenomenon was attributed to the fact that tin–tin homocoupling in the first step of the reaction is more favorable than tin–bromine heterocoupling. Moreover, the three molecules of water of the copper salt can easily quench the organocuprate resulting from the tin–copper exchange. This proto-destannylation process can be responsible of the low yields of cyclotrimers. As example, in the case of hindered bicycloolefins, such as bornene, the resulting proto-destannylated compound was the main product of the reaction. Optimization of the reaction conditions showed that the use of anhydrous copper(I) in the presence of lithium salts and a chelating cosolvent (DME) in DMF affords yields of cyclotrimers up to 80%, with minor amounts of byproduct.[14] In particular, the usually unfavorable statistical ratio was reversed to a maximum of 9:1 *syn* to *anti* diastereoselectivity, in the case of benzotribenzonorbornane.

However, this method was still not applicable to many substrates. The synthesis of BCTs from *vic*-bromo(trimethyltin)-bicycloolefins had a definitive improvement with the

SCHEME 2. Synthesis of (+)-*syn*-Benzotrimethoxyborneol **4** using Copper(I) 2-Thiophenecarboxylate (CuTC) as Promoter



introduction of copper(I) 2-thiophenecarboxylate (CuTC). This nonhygroscopic and stable reagent was known to afford excellent yields of homo- and heterocoupling products from vinylic or arylic halides and stannanes.[15] CuTC promoted the cyclotrimerization of bromostannanes under very mild conditions, affording BCTs, which could not be obtained with the previous methodologies.[16] Very importantly, CuTC furnished enantiopure functionalized benzocyclotrimers with almost complete *syn*-diasteroselectivity (Scheme 2).[17]

The copper-promoted cyclotrimerizations of *vic*-bromostannylbicycloolefins required stoichiometric amounts of copper salts. A possibility to overcome this problem is the use of Stille coupling conditions, which are known to provide good yields of dienes from one olefin bearing halides and one olefin substituted with a trialkyltin moiety. The reaction is catalyzed by palladium(0) complexes. In the case of cyclotrimerization *vic*-bromostannylbicycloolefins reacted smoothly with palladium(0) affording benzocyclotrimers with 38–58% yields, although with high *anti*-diastereoselectivity.[18] The trialkylstannane can be generated *in situ*, starting from the easily accessible dibromide and hexamethylditin, according to Grigg's methodology. The almost complete *anti*-diastereoselectivity of this reaction was reversed using a suitable metal as templating agent.[19]

2.3. BCT from Halo Bicyclic Olefins. The toxic effects of alkylstannanes bring toward the research of new precursors for cyclotrimerizations. Halobicycloolefins were tested for cyclotrimerization using the Heck reaction by our group in 2001.[20] However, the use of enantiomerically pure starting materials led to very low yields (5%) of *syn*-cyclotrimers.[21] More recently, the optimization of the reaction conditions by the group of H. Sakurai have opened an interesting alternative for the synthesis of BCT.[22] Pd-catalyzed cyclotrimerization of enantiopure iodonorbornens have been applied to preparation of C_3 or C_{3v} symmetric BCTs with various functional groups.

3. Benzocyclotrimers Derivatives

The tris-annelated benzene ring of BCT molecules can be used as starting point for the preparation of high-symmetry derivatives. We define as BCT-derivatives molecules in which the original bicyclic structures are removed. So far two very promising structures has been obtained using BCT as key compound in the synthetic strategy.

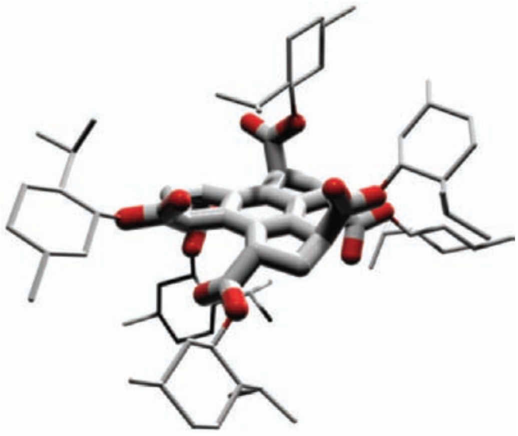
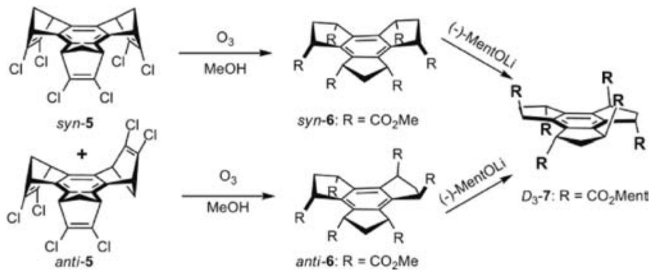
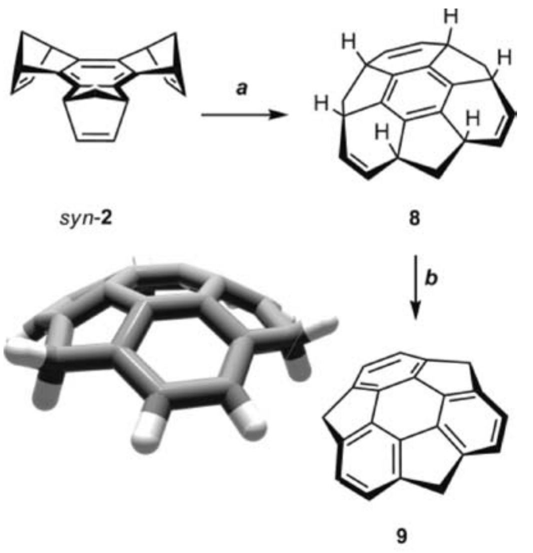


FIGURE 4. Stick representation of X-ray crystal structure of D_3-symmetric trindane hexacarboxylate **7**.

SCHEME 3. Synthesis of Diasteromerically Pure Trindane Hexacarboxylates **7** via trans-Esterification and Epimerization Using Lithium Mentholate ((−)-MentOLi)



In 2005, the first D_3 benzene rings with six directly bound homotopic groups was synthesized starting from a BCT.[23] The synthetic plan starts with the oxidative cleavage of the three vinyl bonds of a mixture of *syn* and *anti* isomers using ozone in methanol. This reaction furnishes quantitatively the two *syn* and *anti* isomeric trindane hexacarboxylates **6** in which the carboxylic groups reflect the same C_{3v} and C_s symmetries of the starting materials (Scheme 3). The carboxylic groups and base-sensitive benzylic hydrogens have been exploited in a trans-esterification and epimerization sequential process using a chiral alcohol. The resulting product is the diastereo- and enantio-pure D_3-symmetric trindane **7**, whose configuration of the homotopic benzylic carbons has been established to be *S* by single-crystal X-ray diffraction analysis (Figure 4). The removal of the chiral auxiliary affords the enantiopure hexaacid in quantitative yield. The trindane framework with homotopic faces is the



a: Grubb's I and II generation catalyst,Toluene

b: DDQ, Toluene

FIGURE 5. Synthesis and crystal structure representation of sumanene **9**.

first example of an enantiopure D_3 molecule with six reactive units joined directly in a rigid structure.

In 2003 benzotribornene **2** has been employed for the preparation of sumanene **8**, which is the smaller C_{3v}-symmetric nonplanar aromatic fragment of fullerene.[24] The synthesis consists in a one-pot sequential ring-opening and ring-closing metathesis promoted by Grubbs' I and II generation catalysts, followed by aromatization of the molecule with 2,3-dichloro-5,6-dicyanoquinone (DDQ) (Figure 5). Noteworthy, the procedure is short and very mild, avoiding severe conditions such as flash vacuum pyrolysis.

More recently, the same group has obtained the enantiopure C_3-symmetric trimethylsumanene, despite the facile racemization at room temperature, own to the concave-convex isomerization.[25]

4. Physical Organic Chemistry and Supramolecular Chemistry of Benzocyclotrimers

As described in the Introduction, BCTs have attracted the interest of many chemists. Beside the interest for the development of new synthetic methodologies, BCTs have been initially the focus of attention for the possibility to study the Mills−Nixon effect, or more properly, the bond-length fixation by strain in benzene ring.[26] Indeed, BCTs were good candidates to establish if a change in the aromatic character of the central aromatic ring could be induced by the strain of the three annelated bicyclic units. The maximum bond length alternation in a six-member ring was observed in the benzocyclotrimer **10** synthesized by J. S. Siegel, in which the difference among the exocyclic and endocyclic C−C distances is 0.089 Å (Figure 6).[27]

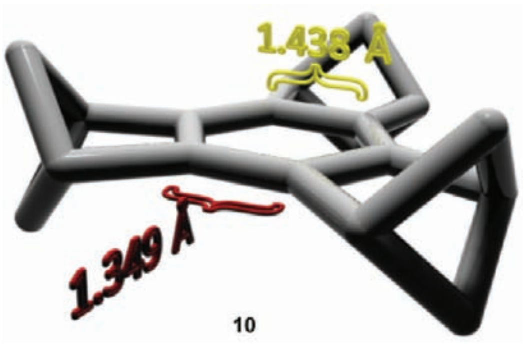


FIGURE 6. Crystal structure representation of BCT **10**.

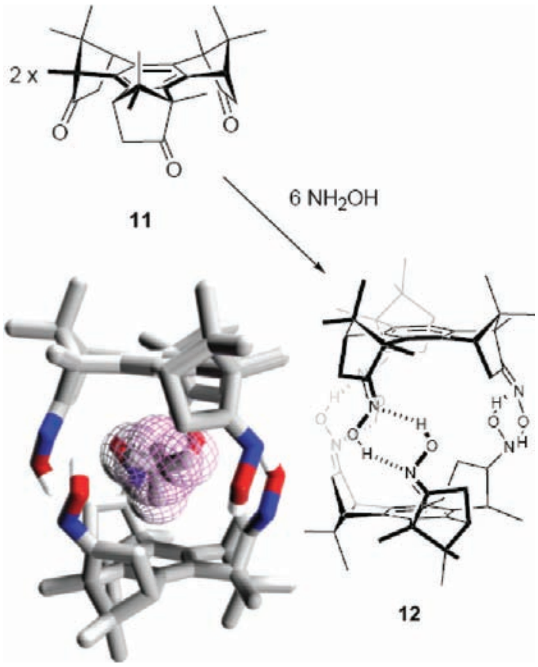


FIGURE 7. Formation of the (+)-benzotricamphor trioxime **12** capsule and model structure CH_4@**12**.

Further proofs of this behavior was demonstrated by NMR and crystal structure of chromium(0) η^6-coordinated with benzotrinorbornane **2**.[28] The same author reported also the first supramolecular behavior of a benzocyclotrimer, reporting the first crystal structure of a chlatrate of heptiptycene **1** with chlorobenzene.[29]

A further physical peculiarity of benzocyclotrimers regards the interaction of functional groups positioned at the rim of the structure, which generates high optical rotations and enhanced Cotton effect, as observed and calculated in the case of carbonyls.[30]

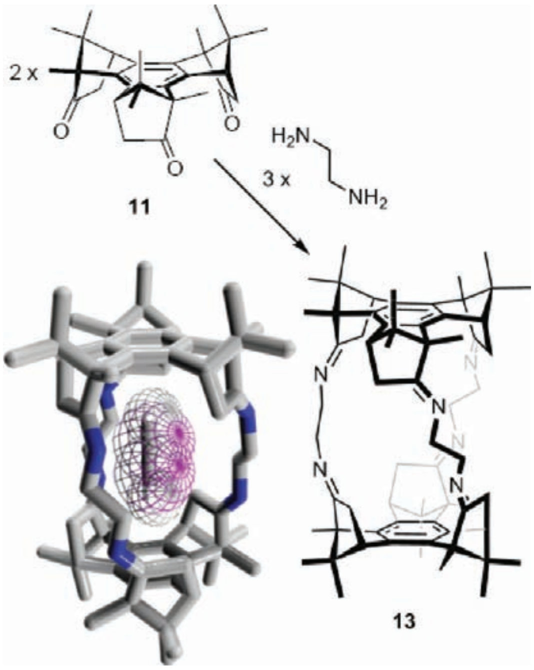


FIGURE 8. Formation of the cage compound **13** and model structure C_2H_2@**13**.

At the outset, practical applications of BCTs involved the synthesis of stabilized cationic derivatives or π-arene complexes of transition metals.[31] More recently, these molecules have been employed in molecular recognition studies, to observe complexation with fullerene C_{60} in analogy with calixarenes and resorcinares.[11] Reliable synthetic strategies for the preparation of functionalized BCTs allowed more challenging targets for molecular recognition studies. Enantiopure *syn*-benzotriborneol **11** was observed to efficiently bind water in solution or in the solid state[32] and to recognize chiral ammonium ions in solution.[33] The recently prepared enantiopure trioxime **12**, spontaneously forms a dimeric capsule held together by six hydrogen-bonds (Figure 7). The formation of the capsule requires the presence of a properly sized guest. The neat result is the inclusion of gases, such as argon, methane, nitrogen, oxygen, and carbon monoxide.[34]

Larger molecules, such as methane, ethyne, ethene, and ethane, can be selectively hosted by the hexa-imine **13** derived from the condensation of two benzotricamphor **11** and three 1,2-ethanediamine moieties. Compound **13** (Figure 8) represents the covalent version (cage) of the previously described capsule **12**.[35]

An other important contribution in the supramolecular chemistry of BCT has been given by the gated baskets prepared in the group of J. D. Badjic. In their research started from BCT **14** (Figure 9), they developed the synthesis of dynamic molecular containers having a set of functionalized aromatic rings installed at the rim.[36] These rings are able to act as gate for the molecular basket, able to respond to external stimulus: acid, silver,[37] and copper[38] ions. These baskets can be functionalized to tune the conformational dynamics of the gates, installed at their rim, and thereby to adjust the time that a guest molecule spends inside their cavity, or stabilizing the transition state of the guest molecule.[39]

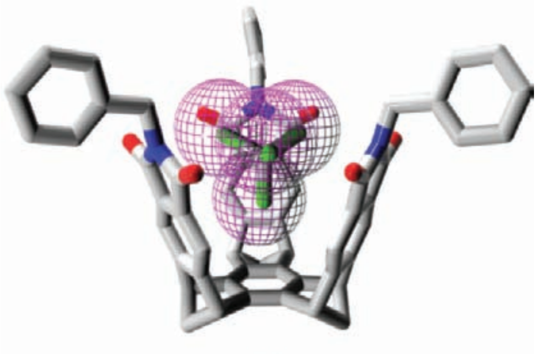


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FIGURE 9. Crystal structure representation of gated basket **14** including $CHCl_3$.

5. Perspective and Conclusions

The efficient cyclotrimerization techniques developed in the last two decades afforded cyclotrimers for specific purposes, giving access to unprecedented applications in physical-organic chemistry and supramolecular chemistry. Many other technological outcome within these discipline can be forecasted for the future, such as highly functionalized curved aromatics, receptors, sensors or more in general nanodevices. In practice, any application of these molecules can be speculated when a C_3-symmetric, rigid, functionalized scaffold is required.

We are deeply indebted with our collaborators, whose names are given in the references. These co-workers have played a fundamental role in the development of this subject. We are particularly grateful to professors Sergio Cossu, Arif Dastan and Vittorio Lucchini, which have contributed to the research in this field research since its very beginning. We thank the MIUR (Ministero dell'Istruzione, dell'Università e della Ricerca) for financial support of this research.

BIOGRAPHICAL INFORMATION

Fabrizio Fabris received his "Laurea" degree in Industrial Chemistry in 1992 and his Ph.D. in 1996 under the supervision of Prof. Ottorino De Lucchi from University Ca' Foscari Venezia, Italy. In 1996, he obtained the position of Researcher in the same

University. In 1999, he spent one year as Postdoctoral Fellow at The Ohio State University in Columbus, OH, under the supervision of Prof. Leo A. Paquette. During 2008, he was Visiting Professor at Brock University, ON, collaborating with Prof. T. Hudlicky. In 2008, he obtained the position of Associate Professor at the University Ca' Foscari Venezia (Italy). His main interests are mainly focused on cycloadditions, terpene chemistry, couplings and cyclotrimerization reactions.

Cristiano Zonta obtained his "Laurea" degree at the University Ca' Foscari Venezia, Italy, in 1999 under the supervision of Prof. Ottorino De Lucchi. He then moved to the University of Sheffield, GB, where he obtained his Ph.D. in 2004 under the supervision of Prof. Christopher A. Hunter. After a postdoctoral fellowship in University Ca' Foscari Venezia, Italy, in 2006 he moved to work with Prof. Giulia Licini at the University of Padova (Italy) where he holds a Researcher position from 2007. His main research interests concern the application of physical organic chemistry tools in the study of catalytic processes and intermolecular interactions.

Giuseppe Borsato received his "Laurea" degree in Industrial Chemistry in 1998 under the supervision of Prof. Ottorino De Lucchi, and his Ph.D. in 2003 under the supervision of Prof. Vittorio Lucchini from University Ca' Foscari Venezia, Italy. During 2007, he spent a Postdoctoral Fellow at the Neuchâtel University (CH) in under the supervision of Prof. R. Deschenaux. In 2007, he obtained a position as Organic Synthesis and NMR Laboratory Administrator in University Ca' Foscari Venezia, Italy. He is currently interested in the application of new generation high-performance pigments in the field of art conservation.

Ottorino De Lucchi obtained the "Laurea" degree in Chemistry in 1975 and in Pharmacy in 1977 from University of Padova, Italy, under the supervision of Prof. Giorgio Modena. From 1978 to 1981, he was Research Associate at the University of Puerto Rico, U.S., and at the University of Würzburg, D, with Prof. Waldemar Adam. In 1981, he obtained the position of Researcher at the University of Padova, Italy, and in 1986, the position of Full Professor at the University of Sassari, Italy. In 1990, he moved to University Ca' Foscari Venezia, Italy. Main interests are on the chemistry of organosulfur compounds, cycloadditions, synthetic chiral auxiliaries, unusual molecules with peculiar geometries and electronic distributions, C−C couplings, and cyclotrimerization reactions.

FOOTNOTES

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