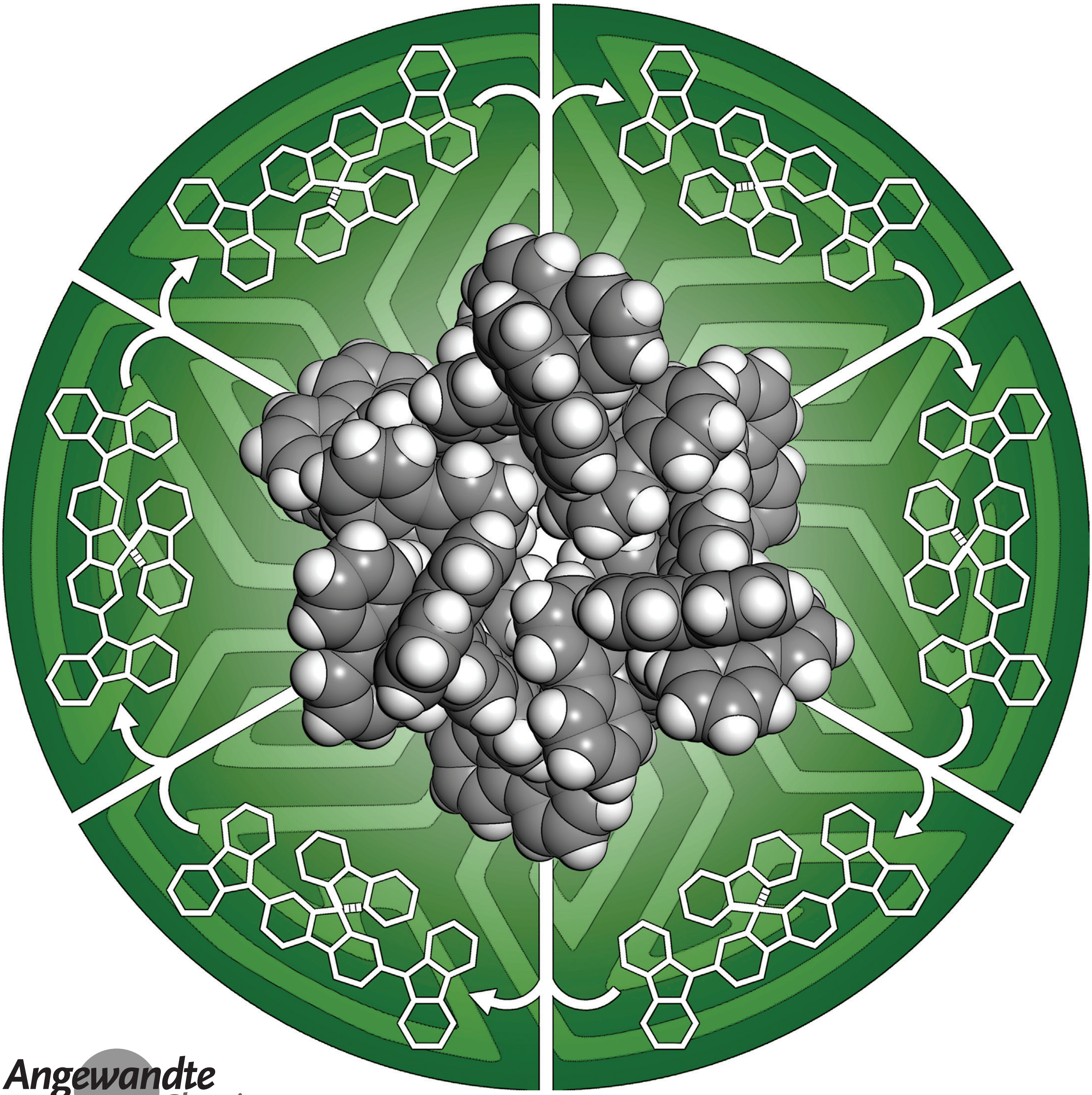
Dynamic Covalent Chemistry **Hot Paper**

International Edition: DOI: 10.1002/anie.201509608
German Edition: DOI: 10.1002/ange.201509608

Building Giant Carbocycles by Reversible C–C Bond Formation

Daniel Beaudoin, Olivier Levasseur-Grenon, Thierry Maris, and James D. Wuest**

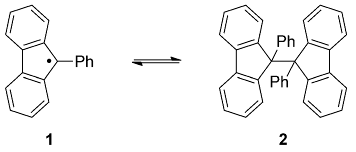
Dedicated to Professor Junes Ipaktschi on the occasion of his 75th birthday



Abstract: *We describe a simple way to build giant macrocyclic hydrocarbons by the reversible formation of carbon–carbon bonds. Specifically, extended spirobifluorene-substituted derivatives of Wittig's hydrocarbon were synthesized and found to undergo oligomerization, giving the largest hydrocarbon that has been crystallized and characterized by X-ray diffraction to date.*

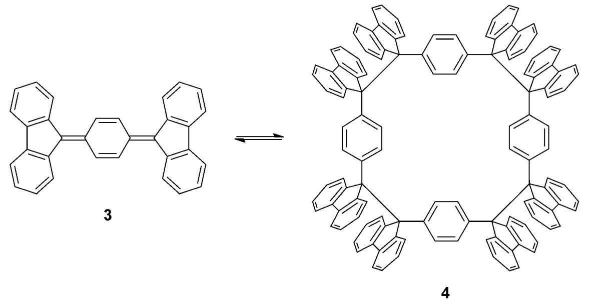
An effective way to build complex chemical structures by design is to assemble them from molecular subunits that are chosen so that their topology and interactions work in harmony to hold neighbors in predetermined relative positions. Various interactions can be used to hold the subunits together, but the use of covalent bonds of intermediate strength is a particularly promising way to control molecular assembly and create unique ordered materials. The suitability of such bonds has recently been highlighted by the preparation of single crystals of covalent organic networks[1] and by the formation of self-healing polymers.[2] An exciting new opportunity is to exploit the reversible oligomerization of stabilized carbon-centered radicals, which can in principle yield complex ordered analogues of diamond and graphite held together solely by carbon–carbon bonds.

The feasibility of this approach is shown in Scheme 1 by the dimerization of the 9-phenylfluorenyl radical (**1**), which produces 9,9′-diphenyl-9,9′-bi-9*H*-fluorene (**2**). The value of ΔH° for dissociation of dimer **2** is 15.1 kcal mol^{-1},[3] making such C–C bonding suitable for use in dynamic covalent chemistry under mild conditions.[4] The related dimerization of triphenylmethyl radicals and analogues thereof is also readily reversible, but steric factors normally prevent the formation of hexaarylethanes by symmetric benzylic coupling.[5]



Scheme 1. Dimerization of the 9-phenylfluorenyl radical (**1**).

Monomers with multiple 9-arylfluorenyl radicals attached to a suitable core should therefore undergo benzylic coupling to give oligomers or polymers with structures determined by the number of radical sites and the geometry of the core. Related monomers are known, but the general class of compounds remains little studied and exploited. In 1969, Wittig and co-workers described the synthesis and behavior of a hydrocarbon that can be represented by structure **3** or by a related diradical.[6] Solutions of Wittig's hydrocarbon (**3**) were found to be deep blue, but concentration produced a colorless solid that was determined to be cyclic tetramer **4** (Scheme 2). No further study of this intriguing system was published for nearly 30 years, until Ipaktschi and co-workers examined substituted derivatives of Wittig's hydrocarbon.[7] These compounds also produced colored solutions from which colorless crystals could be obtained, and analysis by X-ray diffraction confirmed the formation of cyclic tetramers.



Scheme 2. Wittig's hydrocarbon (**3**) and its cyclic tetramer (**4**).

The behavior of Wittig's hydrocarbon and simple derivatives encouraged us to examine the use of arylfluorenyl couplings to create more complex covalently bonded molecular structures by modular assembly. Our initial work reported herein has yielded the largest carbocycle generated by a process of self-assembly, as well as the largest hydrocarbon that has been crystallized and characterized by X-ray diffraction to date.

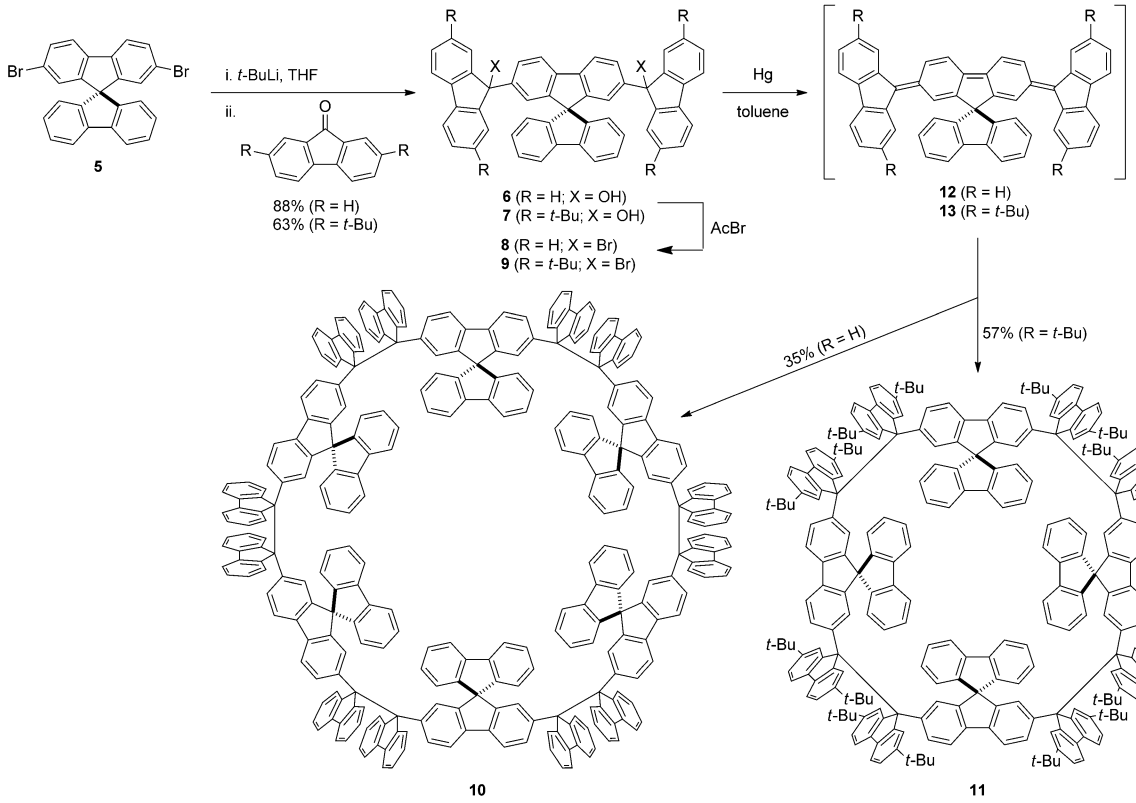
Using established general methods,[7,8] we made analogues of Wittig's hydrocarbon with spirobifluorenyl cores by the routes summarized in Scheme 3. Specifically, lithiation of 2,7-dibromo-9,9′-spirobifluorene (**5**),[9] followed by addition of 9-fluorenone or 2,7-di-*tert*-butyl-9-fluorenone,[10] provided diols **6** and **7** in good yields. Treatment of the diols with acetyl bromide (AcBr) gave the corresponding crude dibromides **8** and **9**, which were used without extensive purification to make hydrocarbons **10** and **11**. Heating crude dibromide **8** with Hg in toluene gave a green supernatant solution, and a colorless solid separated when the solution was cooled. Inorganic material was removed from the solid by extraction, and the residual product was heated in boiling mesitylene to give a green solution. Colorless crystals grew slowly from the cooled solution. These observations are consistent with the hypothesis that reduction with Hg produces intermediate **12**, which resembles Wittig's hydrocarbon and reacts similarly by reversible oligomerization. The poor solubility of the crystalline product prevented extensive spectroscopic characterization and analysis, but its structure could be determined by X-ray diffraction, unlike that of the putative cyclic tetramer derived from Wittig's hydrocarbon.

The oligomer derived from dibromide **8** proved to be macrocyclic hexamer **10**, which crystallized from mesitylene in the triclinic space group $P\bar{1}$ to form a structure with two very similar but non-equivalent chair-shaped molecules in the

---

[*] Dr. D. Beaudoin, O. Levasseur-Grenon, Dr. T. Maris,
Prof. Dr. J. D. Wuest
Département de Chimie, Université de Montréal
Montréal, Québec, H3C 3J7 (Canada)
E-mail: daniel.beaudoin.1@umontreal.ca
james.d.wuest@umontreal.ca

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201509608.



Scheme 3. Synthesis of macrocyclic oligomers **10** and **11**.

unit cell and an overall composition of $C_{306}H_{180}\cdot 12\,C_9H_{12}$ (Figure 1 A). The structural analysis of macrocyclic hexamer **10** is noteworthy for multiple reasons. In particular, the compound is the largest hydrocarbon that has been characterized by X-ray diffraction to date,[11] and its 54-membered carbocyclic ring is among the largest analyzed crystallographically. Larger carbocyclic rings are known, but they have been obtained by strategies involving templation, high dilution, and/or lengthy step-wise synthesis; in contrast, macrocyclic hexamer **10** results simply from self-assembly.[12]

The macrocycle can be considered to be built from six spirobifluorenyl units linked in alternation by six bifluorenyl units. The geometry of the intracyclic fluorenyl units is normal, but the benzylic bonds of the bifluorenyl units are conspicuously lengthened to minimize steric repulsion (1.619(6)–1.645(6) Å). A similar phenomenon of significant elongation relative to the normal length of a $C(sp^3){-}C(sp^3)$ bond (1.588 Å)[13] has been observed in other 9,9′-disubstituted bifluorenes.[14] Furthermore, the bifluorenyl units in macrocyclic hexamer **10** adopt a gauche conformation, as found in the structure of other 9,9′-disubstituted bifluorenes.[14] The characteristic preference for gauche bifluorenyl units promotes cyclization and helps account for the chair-shaped conformation of hexamer **10**. The resulting conformation places the fluorenyl groups of the bifluorenyl units in alternating orientations that can be considered to be axial and equatorial.

The preference for a gauche orientation does not by itself explain why a cyclic hexamer is preferred instead of the cyclic tetrameric alternative favored by derivatives of Wittig's hydrocarbon. We suggest that hexamer **10** results selectively from arylfluorenyl coupling of monomer **12** because it allows formation of an extensive network of intramolecular $C{-}H\cdots\pi$ interactions not possible in other cyclic oligomers. Specifically, axial fluorenes serve as donors in six $C{-}H\cdots\pi$ interactions with spirobifluorenyl units as acceptors (Figure 1 B). Furthermore, a cyclic pinwheel array of six other intramolecular $C{-}H\cdots\pi$ interactions is formed by the mutual embrace of adjacent spirobifluorenyl units (Figure 1 C). The observed pinwheel motif is closely related to the classic sixfold phenyl embrace,[15] in which two triphenylmethyl groups or analogues adopt propeller-shaped conformations of opposite configuration and interdigitate to create a compact cyclic array of six phenyl rings. Within this array, each ring of each triphenylmethyl group engages simultaneously in edge-to-face $C{-}H\cdots\pi$ interactions with two rings provided by the other group, often across a center of inversion. As established by Dance and co-workers through computation and analysis of structural data,[16] the sixfold phenyl embrace is a strongly attractive supramolecular motif. The net stabilization attributed to the cyclic concerted edge-to-face interaction of six phenyl rings is approximately 10–20 $\text{kcal}\,\text{mol}^{-1}$, making its strength similar to that of strong hydrogen bonds. As a result, it is plausible that the formation of these special arrays of intramolecular $C{-}H\cdots\pi$ interactions leads preferentially to the formation of cyclic hexamer **10**, rather than to other cyclic oligomers or a linear polymer. Based on these observations, we suggest that hexamer **10** is the enthalpically favored

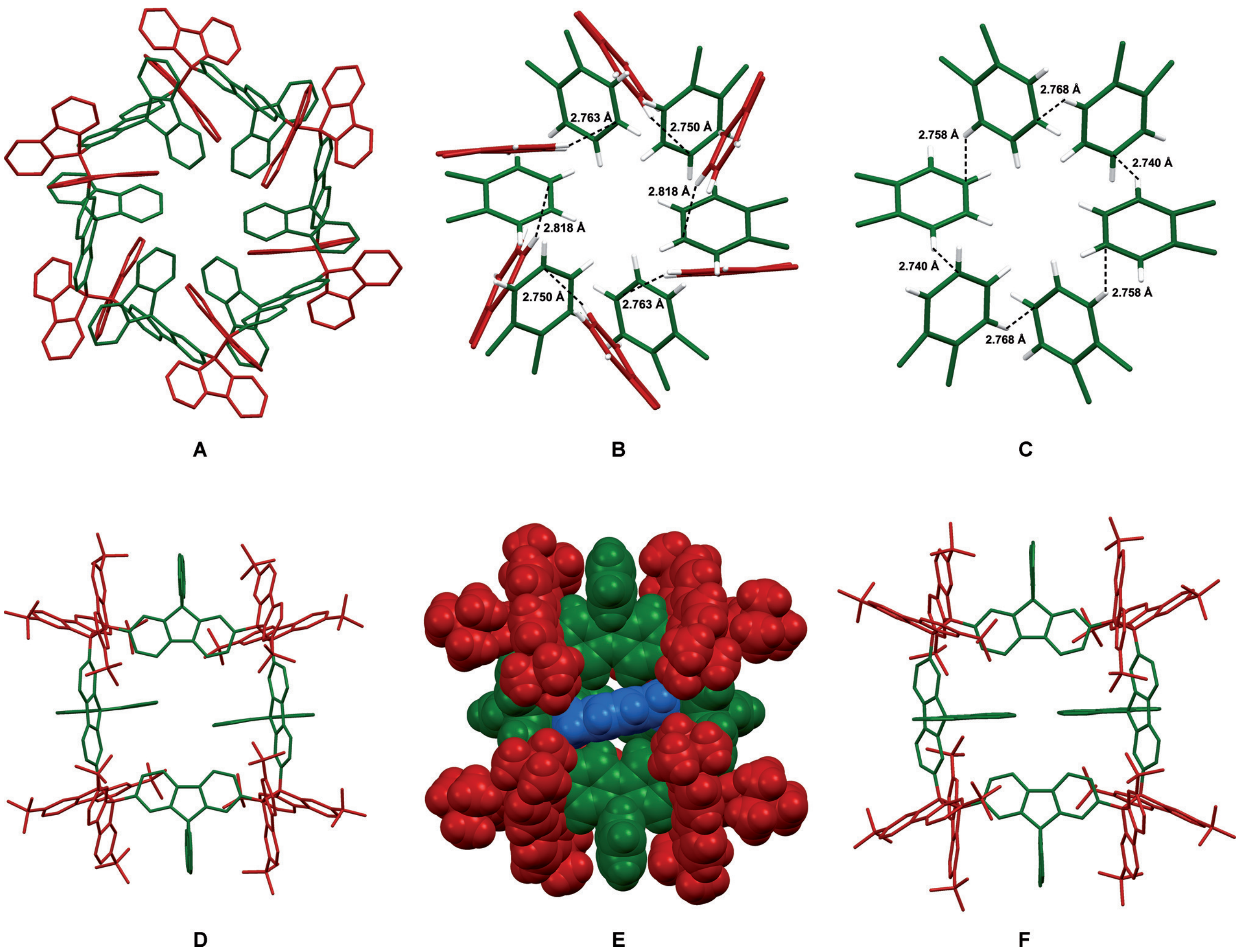


Figure 1. A) Solid-state structure of hexamer **10** crystallized from mesitylene, with hydrogen atoms omitted for clarity. B) Intramolecular array of C–H···π interactions involving axial fluorenes and spirobifluorenyl subunits in hexamer **10**. C) The intramolecular cyclic pinwheel array of C–H···π interactions involving spirobifluorenyl subunits in hexamer **10**. D) Solid-state structure of tetramer **11** crystallized from *para*-xylene/CS$_2$, with hydrogen atoms omitted for clarity. E) Corey–Pauling–Koltun representation of the host–guest complex between tetramer **11** and included *para*-xylene. F) Solid-state structure of tetramer **11** crystallized from *ortho*-xylene/CS$_2$, with hydrogen atoms omitted for clarity. All atoms of the spirobifluorenyl subunits are depicted in green, atoms of the bifluorenyl subunits in red, and atoms of *para*-xylene in blue.

product of the oligomerization of monomer **12** by reversible arylfluorenyl coupling.

The poor solubility of macrocyclic hexamer **10** led us to replace unsubstituted monomer **12** by *tert*-butyl-substituted analogue **13**. Treatment of the corresponding dibromide **9** with Hg in hot toluene produced a green supernatant solution, and a colorless solid precipitated when the solution was cooled. In this case, however, the organic product showed significant solubility in CS$_2$, allowing it to be purified by flash chromatography and crystallized by slow evaporation of solutions in CS$_2$ containing *para*-xylene. The crystalline product, which proved to be macrocyclic tetramer **11** as shown below, was obtained in 57 % yield, and other oligomers were not detected. Heating compound **11** in refluxing mesitylene produced a green solution, as in the case of hexameric analogue **10**, and the colorless tetrameric form **11** was quantitatively recovered after the solution had been cooled and the solvent removed by evaporation. Together, these observations provide strong circumstantial evidence that both cyclic oligomers are formed reversibly from monomeric precursors analogous to Wittig's hydrocarbon.

Analysis by X-ray diffraction revealed that macrocyclic tetramer **11** crystallized from CS$_2$/*para*-xylene in the monoclinic space group *C*2/*c*, and the crystals had the composition $C_{268}H_{248}\cdot 9\,C_8H_{10}$. The unit cell contains four equivalent molecules of tetramer **11**, which adopt a conformation of S_4 symmetry in the solid state (Figure 1 D). The tetramer incorporates a ring of 36 carbon atoms, including four spirobifluorenyl units and four intervening bifluorenyl units, which adopt a normal gauche conformation. As observed in the structure of macrocyclic hexamer **10**, the benzylic bonds of the bifluorenyl units in tetramer **11** are notably lengthened (1.635(3) and 1.617(3) Å).

Inspection of the molecular structure of macrocyclic hexamer **10** reveals that introducing *tert*-butyl groups at the 2- and 7-positions of the bifluorenyl units would be expected to disrupt all twelve characteristic intramolecular C–H···π interactions. Furthermore, careful comparison of the geometric parameters in hexamer **10** and tetramer **11**, including the bond lengths, bond angles, and dihedral angles in the bifluorenyl units, provides no evidence that the two oligomers differ markedly in strain. In the observed S_4 conformation of macrocyclic tetramer **11**, two of the spirobifluorenyl units adopt an exocyclic orientation and the two others are endocyclic, thereby creating a pocket suitable for the inclusion of *para*-xylene, which is bound by various close C···H contacts (Figure 1E). There are no notable intramolecular interactions within the macrocycle itself or between adjacent macrocycles. The high solubility of tetramer **11** in CS_2 allowed us to record ^{1}H and ^{13}C NMR spectra in solution, which showed four distinct *tert*-butyl resonances at 25°C rather than a single one, which would have been expected for a fully symmetric structure. This observation is consistent with a preference for an S_4 conformation or a related structure in solution.

Macrocyclic tetramer **11** also crystallized efficiently from CS_2/*ortho*-xylene, and the crystals were shown to belong to the triclinic space group $P\bar{1}$ and to have the composition $C_{268}H_{248}\cdot 15\,C_8H_{10}$. The unit cell contains a single molecule of tetramer **11**, which adopts a conformation that is more compact and symmetric than the one observed in crystals grown from CS_2/*para*-xylene (Figure 1F). In this new conformation, no space for guests is available within the macrocycle, and all included *ortho*-xylene molecules occupy intermolecular voids.

In summary, we have shown that the synthesis of giant carbocycles can be accomplished by a simple self-assembly process, which has yielded the largest hydrocarbon characterized by single-crystal X-ray diffraction to date. These results set the stage for using the oligomerization of stabilized carbon-centered radicals to produce other complex molecular assemblies held together by carbon–carbon bonds.

Acknowledgements

We are grateful to the Natural Sciences and Engineering Research Council of Canada, the Ministère de l'Éducation du Québec, the Canada Foundation for Innovation, the Canada Research Chairs Program, NanoQuébec, and the Université de Montréal for financial support.

Keywords: carbocycles · dynamic covalent chemistry · macrocycles · radicals · spirobifluorenes

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 894–898
Angew. Chem. **2016**, *128*, 906–910

---

[1] D. Beaudoin, T. Maris, J. D. Wuest, *Nat. Chem.* **2013**, *5*, 830–834.
[2] K. Imato, M. Nishihara, T. Kanehara, Y. Amamoto, A. Takahara, H. Otsuka, *Angew. Chem. Int. Ed.* **2012**, *51*, 1138–1142; *Angew. Chem.* **2012**, *124*, 1164–1168.
[3] M. Frenette, C. Aliaga, E. Font-Sanchis, J. C. Scaiano, *Org. Lett.* **2004**, *6*, 2579–2582.
[4] a) Y. Jin, C. Yu, R. J. Denman, W. Zhang, *Chem. Soc. Rev.* **2013**, *42*, 6634–6654; b) J. M. Lehn, *Chem. Soc. Rev.* **2007**, *36*, 151–160; c) P. T. Corbett, J. Leclaire, L. Vial, K. R. West, J. L. Wietor, J. K. M. Sanders, S. Otto, *Chem. Rev.* **2006**, *106*, 3652–3711; d) S. J. Rowan, S. J. Cantrill, G. R. L. Cousins, J. K. M. Sanders, J. F. Stoddart, *Angew. Chem. Int. Ed.* **2002**, *41*, 898–952; *Angew. Chem.* **2002**, *114*, 938–993.
[5] For exceptions, see: a) B. Kahr, D. Van Engen, K. Mislow, *J. Am. Chem. Soc.* **1986**, *108*, 8305–8307; b) M. Stein, W. Winter, A. Rieker, *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 692–694; *Angew. Chem.* **1978**, *90*, 737–738.
[6] G. Wittig, E. Dreher, W. Reuther, H. Weidinger, R. Steinmetz, *Justus Liebigs Ann. Chem.* **1969**, *726*, 188–200.
[7] a) J. Ipaktschi, R. Hosseinzadeh, P. Schlaf, T. Eckert, *Helv. Chim. Acta* **2000**, *83*, 1224–1238; b) J. Ipaktschi, R. Hosseinzadeh, P. Schlaf, *Angew. Chem. Int. Ed.* **1999**, *38*, 1658–1660; *Angew. Chem.* **1999**, *111*, 1765–1768; c) J. Ipaktschi, R. Hosseinzadeh, P. Schlaf, E. Dreiseidler, R. Goddard, *Helv. Chim. Acta* **1998**, *81*, 1821–1834.
[8] L. K. Montgomery, J. C. Huffman, E. A. Jurczak, M. P. Grendze, *J. Am. Chem. Soc.* **1986**, *108*, 6004–6011.
[9] W. L. Yu, J. Pei, W. Huang, A. J. Heeger, *Adv. Mater.* **2000**, *12*, 828–831.
[10] C. Poriel, J. Rault-Berthelot, F. Barrière, A. M. Z. Slawin, *Org. Lett.* **2008**, *10*, 373–376.
[11] For X-ray crystallographic studies of hydrocarbons containing >200 atoms of carbon, see: a) F. E. Golling, S. Osella, M. Quernheim, M. Wagner, D. Beljonne, K. Müllen, *Chem. Sci.* **2015**, *6*, 7072–7078; b) F. E. Golling, M. Quernheim, M. Wagner, T. Nishiuchi, K. Müllen, *Angew. Chem. Int. Ed.* **2014**, *53*, 1525–1528; *Angew. Chem.* **2014**, *126*, 1551–1554; c) X. Zhu, H. Tsuji, J. T. L. Navarrete, J. Casado, E. Nakamura, *J. Am. Chem. Soc.* **2012**, *134*, 19254–19259; d) X. Shen, D. M. Ho, R. A. Pascal, *J. Am. Chem. Soc.* **2004**, *126*, 5798–5805; e) R. E. Bauer, V. Enkelmann, U. M. Wiesler, A. J. Berresheim, K. Müllen, *Chem. Eur. J.* **2002**, *8*, 3858–3864; f) P. Müller, I. Usón, V. Hensel, A. D. Schlüter, G. M. Sheldrick, *Helv. Chim. Acta* **2001**, *84*, 778–785; g) M. B. Nielsen, M. Schreiber, Y. G. Baek, P. Seiler, S. Lecomte, C. Boudon, R. R. Tykwinski, J.-P. Gisselbrecht, V. Gramlich, P. J. Skinner, C. Bosshard, P. Gunter, M. Gross, F. Diederich, *Chem. Eur. J.* **2001**, *7*, 3263–3280.
[12] a) R. May, S. Jester, S. Höger, *J. Am. Chem. Soc.* **2014**, *136*, 16732–16735; b) W.-J. Liu, Y. Zhou, Q.-F. Zhou, Y. Ma, J. Pei, *Org. Lett.* **2008**, *10*, 2123–2126; c) R. Jasti, J. Bhattacharjee, J. B. Neaton, C. R. Bertozzi, *J. Am. Chem. Soc.* **2008**, *130*, 17646–17647; d) S. Höger, *Chem. Eur. J.* **2004**, *10*, 1320–1329; e) V. Hensel, A. D. Schlüter, *Chem. Eur. J.* **1999**, *5*, 421–429.
[13] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc. Perkin Trans. 2* **1987**, S1–S19.
[14] a) M. H. Al-Afyouni, T. A. Huang, F. Hung-Low, C. A. Bradley, *Tetrahedron Lett.* **2011**, *52*, 3261–3265; b) Y. Liu, D. Ballweg, T. Müller, I. A. Guzei, R. W. Clark, R. West, *J. Am. Chem. Soc.* **2002**, *124*, 12174–12181; c) R. A. Kemp, L. Chen, I. A. Guzei, A. L. Rheingold, *J. Organomet. Chem.* **2000**, *596*, 70–76; d) Y.-L. Lam, L.-L. Koh, H.-H. Huang, L. Wang, *J. Chem. Soc. Perkin Trans. 2* **1999**, 1137–1142.
[15] a) M. Scudder, I. Dance, *J. Chem. Soc. Dalton Trans.* **1998**, 329–344; b) I. Dance, M. Scudder, *New J. Chem.* **1998**, *22*, 481–492; c) I. Dance, M. Scudder, *J. Chem. Soc. Chem. Commun.* **1995**, 1039–1040.
[16] a) I. Dance, M. Scudder, *CrystEngComm* **2009**, *11*, 2233–2247; b) I. Dance, *Mol. Cryst. Liq. Cryst.* **2005**, *440*, 265–293.

Received: October 13, 2015