

First example of ring *carbo*-mer of 1,4-cyclohexadiene

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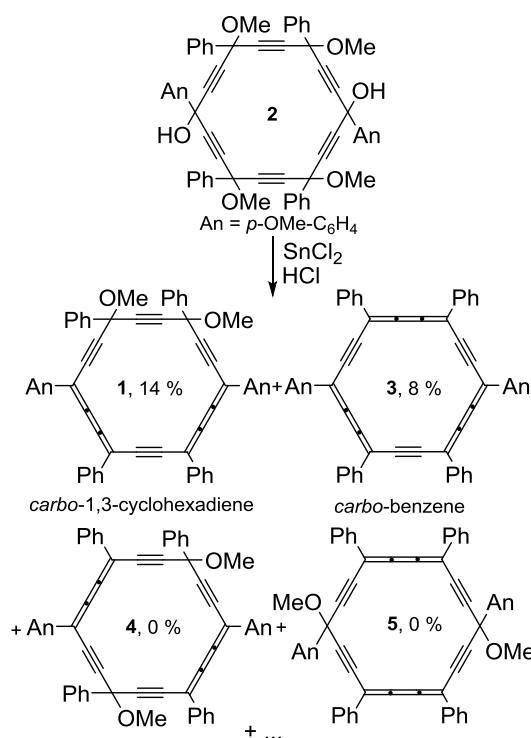
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While a series of *carbo*-mers of 1,3-cyclohexadienes was reported through the use of a specifically developed synthetic strategy, no example of their 1,4-regioisomers was known. Inspired by the methodology elaborated for the preparation of the 1,3-isomers, the synthesis of the first example of *carbo*-mer of 1,4-cyclohexadiene is presented. Comparison of physico-chemical properties of this first representative with those of the recently described 1,3-regioisomer, especially UV-vis absorption properties, is also addressed.

Introduction

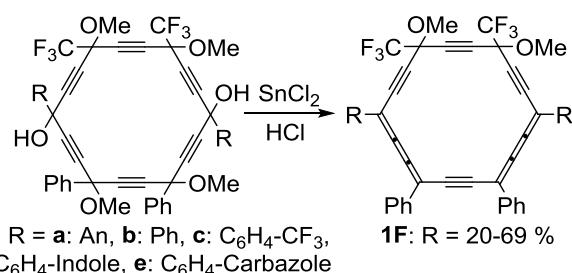
The first example of *carbo*-cyclohexadiene **1**, reported in 2012 [1,2], resulted from an incomplete reduction of a [6]pericyclic precursor **2** of the corresponding *para*-dianisyl-*carbo*-benzene original target **3** [3,4]. The conjugated ring *carbo*-mer of 1,3-cyclohexadiene **1** was the sole sub-reduced product separated from the reaction mixture by semi-preparative HPLC, without evidence of non-conjugated 1,4-isomers **4** or **5** (Scheme 1). Since then, a series of bis-trifluoromethylated conjugated *carbo*-1,3-cyclohexadienes **1F** was developed on the basis of a synthesis procedure involving bis-trifluoromethylated [6]pericyclic precursors of type **2F** (Scheme 2) [5].



Scheme 1. First isolation in the tetraphenyl-dianisyl series of a *carbo*-mer of 1,3-cyclohexadiene **1**, sub-reduction side-product of the [6]pericyclic diol **2** to the *carbo*-benzene **3** [1].

The two trifluoromethyl groups of **2F**, replacing two phenyl groups of **2**, at two adjacent vertices allowed the selective four-electron reduction to the *carbo*-cyclohexadiene target **1F**, through the destabilization of the carbenium intermediate possibly generated by the acidic character of the reducing SnCl₂/HCl system [6].

The *carbo*-mers of 1,3-cyclohexadienes **1** and **1F**, isolated as *cis/trans* diastereoisomeric mixtures, were found to be stable chromophores, some of them exhibiting the rare property of dichromism in solution [1,5,7].



Scheme 2. Synthesis of bis-trifluoromethylated ring *carbo*-mers of 1,3-cyclohexadienes **1F** [5]. An = Anisyl = 4-MeO-C₆H₄.

The conjugated nature of the tetraphenylated *carbo*-mer of 1,3-cyclohexadiene **1** was inferred by confrontation of the experimental UV-vis absorption spectrum, exhibiting two intense bands at 437 and 602 nm, with calculated spectra at the ZINDO level, reproducing with high accuracy the two intense bands at 433 and 615 nm: the calculated spectrum of the 1,4-regioisomer **4** (**Scheme 1**) was indeed calculated to exhibit a

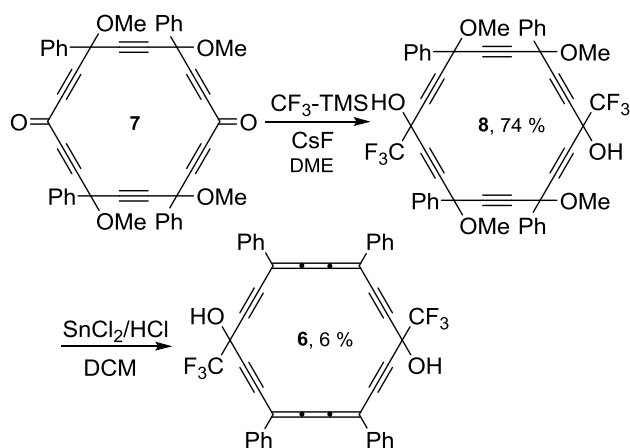
completely different pattern, with a single intense band at 449 nm [1]. Nevertheless, *carbo*-mers of 1,4-cyclohexadienes with non-conjugated dialkynylbutatriene edges (DAB), such as **4** and **5** remain unknown (**Scheme 1**). Numerous chromophores containing isolated DAB motifs were however recently described, their stability varying significantly with the nature of the substituents [8,6].

The first synthesis of a *carbo*-mer of 1,4-cyclohexadiene, **6**, is presented hereafter. Physico-chemical properties of **6** are then compared with both those of the 1,3-isomer **1Fb** and known acyclic DABs.

Results and discussion

The preparation of the *carbo*-cyclohexadiene **6** relies on a two-step strategy starting from the known [6]pericyclynedione **7** [3e], a key precursor for the synthesis of quadrupolar *para*-disubstituted *carbo*-benzenes [4d,f,g]. In order to prevent the formation of two conjugated endocyclic butatriene edges, i.e. to orientate the reaction towards the formation of two butatriene moieties on two facing edges of the C₁₈ macrocycle, the two trifluoromethyl substituents were envisaged at opposite vertices (C1 and C10) (**Scheme 3**). It was indeed recently evidenced that trifluoromethyl substituents inhibit the dissociation of geminal hydroxy or methoxy group and subsequently the formation of a butatriene unit upon treatment with SnCl₂/HCl [5,6]. Trifluoromethyl

substituents were anchored at the macrocycle using a known procedure consisting in the addition of the Ruppert-Prakash reagent $\text{CF}_3\text{-TMS}$ on the two carbonyl groups of **7** in the presence of CsF as initiator (**Scheme 3**) [9]. The putative bis-silylether intermediate was not isolated, but *in situ* hydrolyzed by treatment with aqueous 2 M HCl. The resulting bis-trifluoromethylated diol **8** was then reacted with SnCl_2/HCl in DCM to afford the *carbo*-cyclohexadiene target **6**, which was isolated as a red-orange solid in 6 % yield. This first *carbo*-mer of 1,4-cyclohexadiene could be fully characterized by spectroscopic methods (^1H , ^{13}C , ^{19}F NMR, IR, ...) but it was found to be much less stable than the 1,3-isomer **1Fb** (which was isolated in a higher yield of 20 %).



Scheme 3. First synthesis of a *carbo*-mer of 1,4-cyclohexadiene **6**, non-conjugated isomer of **1Fb** (**Scheme 2**).

The formation of **6** is evidenced by the disappearance of all the methoxy ^1H NMR signals of **8** at 3.40–3.65 ppm, accompanied by a simplification of the aromatic ^1H signals due

to the decrease of the number of diastereoisomers (2 in **6** vs 14 in **8**) [3e].

In spite of the non-conjugated nature of the DAB edges, the *carbo*-cyclohexadiene **6** remains chromophoric, giving intense yellow solutions in usual organic solvents. The absorption spectrum, recorded in CHCl_3 solution, exhibits one intense band at $\lambda_{\text{max}} = 418$ nm (**Figure 1a**). This UV-vis spectrum can be naturally compared with those of **9** containing a non-conjugated DAB motif, and of the *carbo*-cyclohexadiene conjugated isomer **1Fb** (**Figure 1b**).

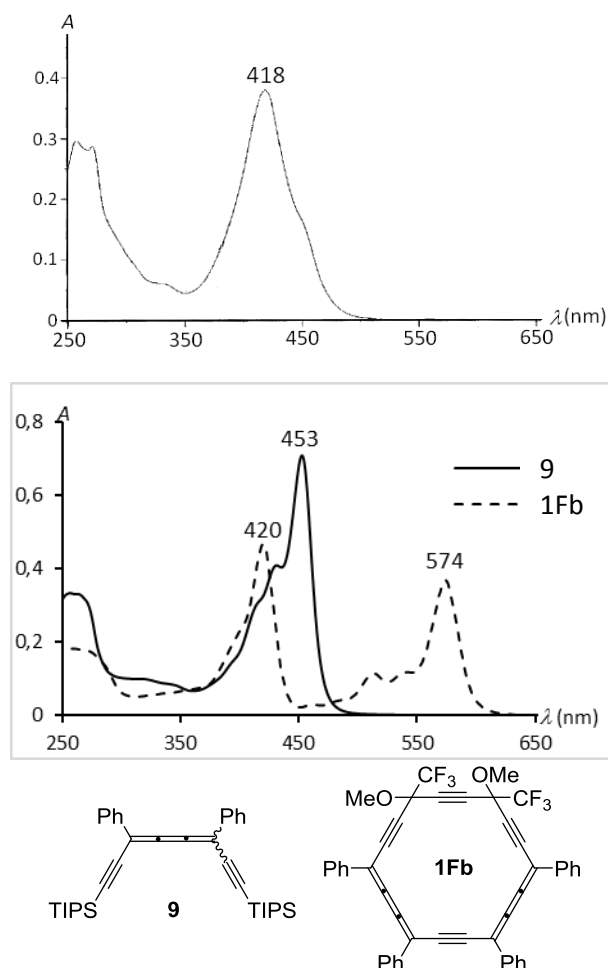


Figure 1. 1a. UV-vis spectrum of **6** (top); **1b.** UV-vis spectra of the DAB **9** and *carbo*-cyclohexadiene **1Fb** (bottom). Spectra recorded in CHCl_3 solutions.

The one-band spectral profile of **6** resembles that of **9** and is reminiscent of the ZINDO-calculated spectrum of **4** (albeit at higher energy because the DAB motifs are not conjugated with the methoxy groups of the anisyl substituents). It is also completely different from the two-band profile of the conjugated isomer **1Fb** [5]. The hypsochromic shift of the λ_{\max} value of **6** (418 nm) with respect to **9** (453 nm) is attributed to the withdrawing effect of the CF₃ groups of **6**. In the dibutatrienylacetylene (DBA) series, namely the *carbo-n*-butadienes, it was indeed observed that electron withdrawing substituents induce a relative hypsochromic shift [10]. Nevertheless, the two products exhibit comparable molar extinction coefficients of $\epsilon_6 = 73400 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$ and $\epsilon_9 = 53400 \text{ L}\cdot\text{mol}^{-1}\cdot\text{cm}^{-1}$. It is remarkable that the λ_{\max} value of **6** (418 nm) is almost identical to the first λ_{\max} value of the conjugated isomer **1Fb** (420 nm). Nevertheless, the second strong band of **1Fb** at $\lambda'_{\max} = 574 \text{ nm}$ is correlated with the π -conjugation extension in **1Fb** (over 14 C atoms in a row).

Conclusions

Though less stable than the 1,3-regioisomer **1Fb**, the first *carbo*-mer of 1,4-cyclohexadiene **6** has been isolated, and characterized. Its relative stability and spectroscopical properties are fully consistent with general principles in the chemistry of π -

conjugated systems and with previous semi empirical and TDDFT calculations.

In prospect of these advances in the synthesis of trifluoromethylated ring *carbo*-mers of 1,3- or 1,4-cyclohexadienes, the synthesis of hexa-trifluoromethyl-*carbo*-benzene, C₁₈(CF₃)₆, appears as a natural challenge. The influence of a crown of six electron-withdrawing CF₃ substituents on the macro-aromatic character of a highly π -electron-rich core is indeed a fundamental issue. Although the present results confirm that this target cannot be accessible by reductive elimination from a hexa(trifluoromethyl)-hexaoxy-[6]pericyclyne, alternative strategies and future efforts deserve to be envisaged [11].

Experimental part

General remarks. THF and dimethoxyethane (DME) were dried and distilled over sodium/benzophenone, dichloromethane (DCM) and pentane over calcium hydride. All others reagents were used as commercially available, particularly solution of *n*-butyllithium were 2.5 M in hexane, and solution of HCl were 2 M in Et₂O. All reactions were carried out under argon atmosphere, using Schlenk and vacuum line techniques. Column chromatography was carried out on silica gel (60 Å, C.C 70-200 μm). Silica gel thin layer chromatography plates (60F254, 0.25 mm) were revealed by treatment with an ethanolic solution of phosphomolybdic acid (20 %). The following analytical

instruments were used: ^1H and ^{13}C NMR: Brüker Avance 300 and Avance 400 spectrometers; mass spectroscopy: Quadrupolar Nermag R10-10H spectrometer; IR: Perkin-Elmer Spectrum 100 FT-IR spectrometer. NMR chemical shifts are given in ppm with positive values to high frequency relative to the tetramethylsilane reference for ^1H and ^{13}C , and CCl_3F reference for ^{19}F . Coupling constants J are in Hertz. Previously described procedures were used for the preparation of **7** [3e].

Experimental procedures and characterizations.

4,7,13,16-tetramethoxy-4,7,13,16-tetraphenyl-1,10-bis(trifluoromethyl)cyclooctadeca-2,5,8,11,14,17-hexayne-1,10-diol **8**.

[6]Pericyclynedione **7** (0.100 g, 0.146 mmol) and CsF (0.022 g, 0.146 mmol) were dried under vacuum in a Schlenk tube. Dry DME (0.2 mL) and $\text{CF}_3\text{-TMS}$ (0.087 mL, 0.59 mmol) were added and the resulting mixture was stirred under argon overnight. After dilution with Et_2O (0.2 mL) and treatment with aqueous 2 M HCl (2 mL), the mixture was stirred at room temperature for 2.5 h. Water was then added, and the aqueous layer was extracted with Et_2O . The combined organic layers were washed with brine, dried over MgSO_4 and concentrated under reduced pressure to give **8** as an orange solid (0.089 g, 74 %).

^1H NMR (CDCl_3 , 400 MHz): $\delta = 3.25$ (m, 2H, OH), 3.35-3.64 (m, 12H, OCH_3), 7.33-7.42 (m, 12H, m -, p - C_6H_5), 7.62-7.73 (m, 8H, o - C_6H_5);

^{19}F NMR (CDCl_3 , 282 MHz): $\delta = -81.28$ -(-81.02) (m, CF_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (CDCl_3 , 75 MHz): $\delta = 53.4$ (OCH_3), 64.5 (q, $J = 37$ Hz, C-CF_3), 76.6 (C-OCH_3), 79.2-79.7, 83.7-84.4 ($\text{C}\equiv\text{C}$), 121.8 (q, $J = 285$ Hz, CF_3), 126.3, 128.7 (o -, m - C_6H_5), 129.4 (p - C_6H_5), 138.2-138.6 (i - C_6H_5). HRMS (DCI- CH_4): m/z calcd for $\text{C}_{48}\text{H}_{34}\text{O}_6\text{F}_6$: 820.2260, found: 820.2255.

4,7,13,16-tetraphenyl-1,10-bis(trifluoromethyl)cyclooctadeca-4,5,6,13,14,15-hexaen-

2,8,11,17-tetrayne-1,10-diol **6**. To a solution of **8** (0.050 g, 0.061 mmol) in DCM (25 mL) under stirring at -78 °C were added SnCl_2 (0.116 g, 0.61 mmol) and HCl (0.61 mL, 1.22 mmol). The resulting mixture was allowed to warm up to room temperature and stirred overnight, before treatment with 1 M aqueous NaOH (1.2 mL). The aqueous layer was extracted with DCM and the combined organic layers were washed with brine, dried over MgSO_4 . The DCM solution was filtered through a pad of silica and concentrated to dryness. The residue was dissolved in the minimum amount of DCM and a solid was precipitated by addition of pentane. The obtained red-orange powder was finally washed with acetone to give **6** (3 mg, 6 %).

^1H NMR (THF-D_8 , 300 MHz): $\delta = 7.44$ -7.55 (m, 12H, m -, p - C_6H_5), 7.86-7.88 (m, 8H, o - C_6H_5); ^{19}F NMR (THF-D_8 , 282 MHz): $\delta = -81.21$ (CF_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (THF-D_8 , 75 MHz): $\delta = 65.3$ (q, $J = 36$ Hz, C-CF_3), 82.1, 93.1 ($\text{C}\equiv\text{C}$), 104.3 ($=\text{C}=\text{C-C}_6\text{H}_5$), 122.6 (q, $J = 285$

Hz, CF₃), 127.2, 128.9 (*o*-, *m*-C₆H₅), 129.7 (*p*-C₆H₅), 133.6 (*i*-C₆H₅), 150.1 (C=C=C=C). MS (MALDI-TOF/DCTB): *m/z*: 696.0 [M]⁺. HRMS (MALDI-TOF): *m/z* calcd for C₄₄H₂₂O₂F₆: 696.1548, found: 696.1590. UV (CHCl₃): ν = 418 (ϵ = 73400).

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References

- [1] L. Leroyer, C. Lepetit, A. Rives, V. Maraval, N. Saffon-Merceron, D. Kandaskalov, D. Kieffer, R. Chauvin, *Chem.–Eur. J.* **2012**, *18*, 3226-3240.
- [2] For references on *carbo*-mers see: (a) R. Chauvin, *Tetrahedron Lett.* **1995**, 397-400; (b) V. Maraval, R. Chauvin, *Chem. Rev.* **2006**, *106*, 5317-5343.
- [3] For references on [5] and [6]pericyclines, see: (a) L. T. Scott, G. J. DeCicco, J. L. Hyun, G. Reinhardt, *J. Am. Chem. Soc.* **1983**, *105*, 7760-7761; (b) L. T. Scott, G. J. DeCicco, J. L. Hyun, G. Reinhardt, *J. Am. Chem. Soc.* **1985**, *107*, 6546-6555; (c) L. Maurette, C. Tedeschi, E. Sermot, M. Soleilhavoup, F. Hussain, B. Donnadiou, R. Chauvin, *Tetrahedron* **2004**, *60*, 10077-10098; (d) C. Saccavini, C. Tedeschi, L. Maurette, C. Sui-Seng, C. Zou, M. Soleilhavoup, L. Vendier, R. Chauvin, *Chem.–Eur. J.* **2007**, *13*, 4895-4913; (e) L. Leroyer, C. Zou, V. Maraval, R. Chauvin, *C. R. Chimie*, **2009**, *12*, 412-419.
- [4] For references on *carbo*-benzenes, see: (a) Y. Kuwatani, N. Watanabe, I. Ueda, *Tetrahedron Lett.* **1995**, *36*, 119-122; (b) R. Suzuki, H. Tsukude, N. Watanabe, Y. Kuwatani, I. Ueda, *Tetrahedron* **1998**, *54*, 2477-2496; (c) R. Chauvin, *Tetrahedron Lett.* **1995**, *36*, 401-404; (d) C. Saccavini, C. Sui-Seng, L. Maurette, C. Lepetit, S. Soula, C. Zou, B. Donnadiou, R. Chauvin, *Chem.–Eur. J.* **2007**, *13*, 4914-4931; (e) C. Zou, C. Duhayon, V. Maraval, R. Chauvin, *Angew. Chem. Int. Ed.* **2007**, *46*, 4337-4341; (f) A. Rives, I. Baglai, V. Malyskiy, V. Maraval, N. Saffon-Merceron, Z. Voitenko, R. Chauvin, *Chem. Commun.* **2012**, *48*, 8763-8765; (g) I. Baglai, V. Maraval, C. Bijani, N. Saffon-Merceron, Z. Voitenko, Y. M. Volovenko, R. Chauvin, *Chem. Commun.* **2013**, *49*, 8374-8376.
- [5] A. Rives, I. Baglai, C. Barthes, V. Maraval, N. Saffon-Merceron, Z. Voitenko, Y. Volovenko, R. Chauvin, *Chem. Sci.* **2015**, *6*, 1139-1149.
- [6] V. Maraval, L. Leroyer, A. Harano, C. Barthes, A. Saquet, C. Duhayon, T. Shinmyozu, R. Chauvin, *Chem.–Eur. J.* **2011**, *17*, 5086-5100.
- [7] (a) H. Cartwright, *J. Chem. Educ.* **1986**, *63*, 984-987; (b) S. Kreft, M. Kreft, *Naturwissenschaften* **2007**, *94*, 935-939.
- [8] (a) J.-D. van Loon, P. Seiler, F. Diederich, *Angew. Chem. Int. Ed.* **1993**, *32*, 1187-1189; (b) A. Auffrant, F. Diederich, C. Boudon, J.-P. Gisselbrecht, M. Gross, *Helv. Chim. Acta*, **2004**, *87*, 3085-3105; (c) A. Auffrant, B. Jaun, P. D. Jarowski, K. N. Houk, F. Diederich, *Chem.–Eur. J.* **2004**, *10*, 2906-2911; (d) L. Leroyer, V. Maraval, R. Chauvin, *Chem. Rev.* **2012**, *112*, 1310-1343.
- [9] (a) R. P. Singh, G. Cao, R. L. Kirchmeier, J. M. Shreeve, *J. Org. Chem.* **1999**, *64*, 2873-2876; (b) J. Simon, T. T. Nguyen, E. Chelain, N. Lensen, J. Pytkowicz, G. Chaume, T. Brigaud, *Tetrahedron : Asymm.* **2011**, *22*, 309-314 ; (c) J. Simon, E. Chelain, T. Brigaud, *Org. Lett.* **2012**, *14*, 604-607 ; (c) A. Fleury, E. Chelain, T. Brigaud, manuscript in preparation.
- [10] A. Rives, V. Maraval, N. Saffon-Merceron, R. Chauvin, *Chem.–Eur. J.* **2014**, *20*, 483-492.
- [11] K. Black, A. Rives, C. Barthes, E. Chelain, T. Brigaud, V. Maraval, R. Chauvin, *unpublished results*.