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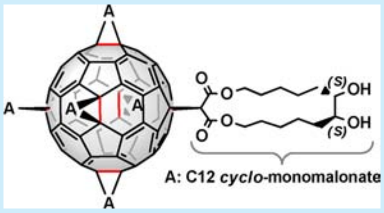
Synthesis of Enantiopure *T*-Symmetrical [6:0]-Hexakis Adducts of C_{60} Equipped with 1,2-Glycol Substituted *cyclo*-Monomalonate Addends

Maria Riala, Katerina L. Maxouti, Charalambos P. Ioannou, and Nikos Chronakis*

Department of Chemistry, University of Cyprus, University Str 1, Building no. 13, 2109 Aglantzia, Nicosia, Cyprus

S *Supporting Information*

ABSTRACT: The synthesis of *T*-symmetrical [6:0]-hexakis adducts of C_{60} bearing enantiopure *cyclo*-monomalonate addends equipped with 1,2-glycol groups masked as isopropylidene acetals is presented. The deprotection of the acetals afforded functional fullerene building blocks bearing six 1,2-glycol moieties in an octahedral geometry as connection sites with appropriate linear organic spacers targeting 3D chiral extended networks with cubic building units. Evaluation of the experimental results revealed the advantageous synthetic accessibility to hexakis adduct (−)-**9** which carries six homochiral C12 *cyclo*-monomalonate addends.



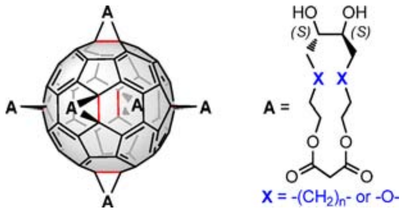
T_h-Symmetrical [6:0]-hexakis adducts of C_{60} are derived from the functionalization of the six *equatorial* double bonds at the octahedral sites with identical addends.[1] The first synthesis was reported by Fagan and co-workers in 1991[2] by reacting C_{60} with $(Et_2P)_4Pt$ to obtain the metal complex $[(Et_2P)_2Pt]_6C_{60}$ which was characterized by X-ray crystallography. In 1994,[3] Hirsch reported the synthesis of the first organic [6:0]-hexaadduct of C_{60} by stepwise nucleophilic cyclopropanations with diethyl bromomalonate, and one year later, Kräutler[4] published the direct synthesis of a [6:0]-hexaadduct by a 6-fold [4 + 2] cycloaddition of 2,3-dimethyl-1,3-butadiene to C_{60}.

The great potential of this family of hexakis adducts of C_{60} was readily recognized after the experimental confirmation of their octahedral addition pattern and was followed by the investigation of reaction conditions, which can improve the hexa-functionalization yield of the *equatorial* bonds of C_{60} and facilitate their separation from other oligo-adducts by silica gel column chromatography. An efficient approach developed by Hirsch[5] employed 9,10-dimethylanthracene (DMA) as a templating reagent, while in 2006, Sun[6] reported a different modification to the original Bingel reaction by using a large excess of carbon tetrabromide without the use of DMA. These improvements allowed the birth of [6:0]-hexakis adducts of C_{60} with spectacular 3D structures and properties depending on the nature of the six addends placed at the octahedral positions of C_{60}. As such, lipofullerenes,[7] dendrofullerenes,[8] liquid crystals,[9] fullerene sugar balls,[10] polycationic fullerene hexakis adducts,[11] glycofullerenes,[12] giant fullerene polyelectrolytes,[13] photosynthetic mimics,[14] and ionic liquids[15] were synthesized, and their properties have been investigated. The design of addends with functional groups as connecting sites provides unique octahedral organic building units for the construction of extended molecular networks. Beuerle[16] synthesized a [6:0]-hexakis adduct of C_{60} bearing 12 glycolic acid side chains and characterized by X-ray crystallography the 3D network which was formed in the solid state by hydrogen bonding. Recently, Bein[17] reported the first 3D Covalent Organic Framework (COF) of a *T_h*-symmetrical hexakis adduct of C_{60} functionalized with silane malonates using a templated evaporation-induced self-assembly strategy.

The octahedral arrangement of the addends in [6:0]-hexaadducts of C_{60} is unique in organic chemistry. If the addends bear terminal functionalities able to cross-link the fullerene units via linear bifunctional spacers, extended molecular structures such as COFs with cubic building units can be envisioned. This strategy can be extended to Metal Organic Frameworks (MOFs) with cubic lattices by covalently connecting an appropriate ligand on the addends, followed by coordination with a metal center that favors a linear geometry. Bräse[18] reported the synthesis of [6:0]-hexakis adducts of C_{60} functionalized with enantiopure bisoxazoline addends and attempted the construction of their metal complexes with palladium and copper. Due to the insolubility of the products formed, their structural characterization was not feasible.

Fascinated by the perspective of building such aesthetically beautiful extended structures, we attempted in this work to synthesize *T*-symmetrical [6:0]-hexakis adducts of C_{60} bearing enantiopure *cyclo*-monomalonate addends[19] equipped with 1,2-glycol moieties (Scheme 1). The choice of these addends was based on (a) their macrocyclic structure which restricts their

Scheme 1. Enantiopure *T*-Symmetrical Hexakis Adducts of C_{60} Equipped with 1,2-Glycol Substituted *cyclo*-Monomalonate Addends



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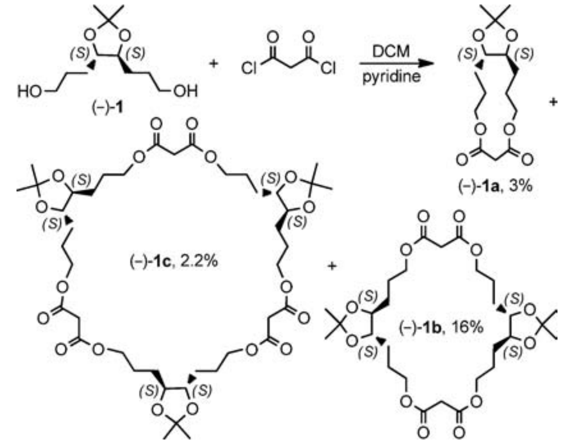
flexibility compared to opened-structure malonates, (b) the synthetic access to *cyclo*-monomalonates which differ in the size and the nature of the spacers, (c) the 1,2-glycol groups which play the role of the connecting points, and (d) the chirality due to the asymmetric carbon atoms carrying the hydroxyl groups. In the literature, there are only three examples of T_h-symmetrical [6:0]-hexakis adducts of C_{60} functionalized with *cyclo*-monomalonate addends. In the first report,[20] *o*-phenylenediamine and 9,10-dialkoxyanthracene moieties were incorporated in the monomalonate addends and the synthesized hexakis adducts were studied in energy and electron transfer processes. The second report[21] deals with the synthesis and postfunctionalization of hexakis adducts decorated with azido-, iodo-, and bromo-monomalonate crown ethers, and the third,[22] with the synthesis of a [6:0]-hexakis adduct equipped with benzo[25]crown-8 ether monomalonates which was used in the construction of pseudorotaxanes. The novelty of our design lies in the presence of the 1,2-diol groups which can be utilized in reversible coupling reactions, for example with boronic acids, and the chirality.

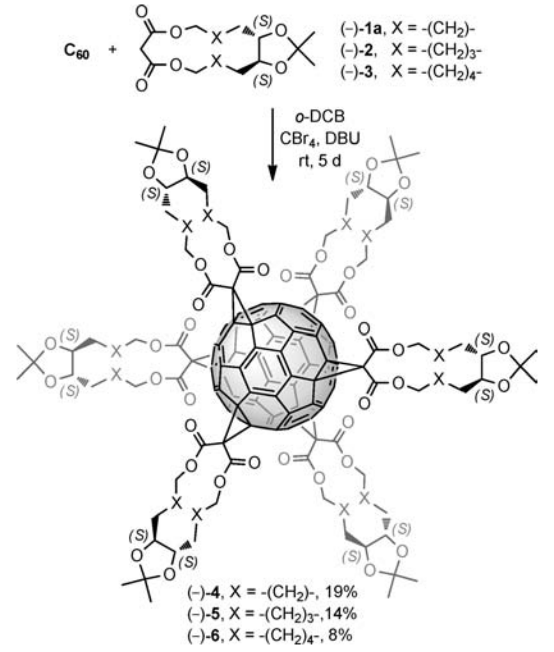
In the first step of our investigation, we synthesized optically pure, acetal-protected *cyclo*-monomalonates with alkyl chains consisting of 8 [C8 *cyclo*-monomalonate (−)-**1a**], 12 [C12 *cyclo*-monomalonate (−)-**2**], and 14 [C14 *cyclo*-monomalonate (−)-**3**] carbon atoms (Scheme 3). (−)-**1a** was synthesized by the condensation of the known diol (−)-**1**[23] with malonyl dichloride under the experimental conditions reported earlier (Scheme 2).[19] With the exception of (−)-**1a**, bis-(−)-**1b** and trismalonate (−)-**1c** were also isolated by column chromatography and fully characterized (Supporting Information (SI)). The synthesis of *cyclo*-monomalonates (−)-**2** and (−)-**3** (Scheme 3) has been reported previously by us.[23]

Scheme 2. Synthesis of the *cyclo*-Monomalonate (−)-1a



For the hexa-functionalization of C_{60} with the synthesized *cyclo*-monomalonates, we employed the synthetic protocol of Sun.[6] (−)-**1a** was reacted with C_{60}, in *o*-DCB, using a 100-fold excess of CBr_4 and DBU (1,8-diazabicyclo[5.4.0]undec-7-ene) as a base (Scheme 3). The isolation of hexakis adduct (−)-**4** was attempted by SiO_2 column chromatography, but the eluted fractions were very complicated and (−)-**4** was detected in traces (MALDI-TOF). This result could not be explained by the presence of other oligo-adducts formed during the Bingel cyclopropanation, and careful TLC experimentation revealed that deprotection of the acetal groups occurred on SiO_2. That was quite surprising as *anti* acetonides are known[24] to be cleaved under strongly acidic conditions. We tackled this problem by carrying out the column chromatographic separation of (−)-**4** using freshly distilled dry solvents (hexane/EtOAc = 3:7) and some drops of triethylamine in the eluent in order to neutralize the acidity of SiO_2. In this manner, hexakis adduct (−)-**4** was isolated in 19% yield and fully characterized by NMR, UV/vis, IR spectroscopies and by MALDI-TOF mass spectrometry (SI). Hexaadduct (−)-**4** was the most polar product compared to the pentakis- and tetrakis-adducts, which were isolated from the column and characterized by MALDI-TOF. Notably, the facile deprotection of the acetonide group was also observed for *cyclo*-monomalonate (−)-**1a**. After recording its ^1H NMR spectrum in $CDCl_3$, the sample was left in solution for 12 h and the spectrum was recorded again. A 50% conversion to the deprotected product was calculated by integrating the appropriate peaks. We believe that the strain of the macrocyclic ring facilitates the deprotection of the acetonide group in the presence of traces of water in the solvents and the slightly acidic conditions attributed to either the solvent or the SiO_2 during the chromatographic procedure.

Scheme 3. Synthesis of Hexaadducts (−)-4, (−)-5, and (−)-6



We next employed C12 *cyclo*-monomalonate (−)-**2** targeting the corresponding hexakis adduct (−)-**5** (Scheme 3). The 6-fold Bingel cyclopropanation was carried out under the Sun[6] experimental conditions, and after completion, the crude reaction mixture was subjected to SiO_2 column chromatography. Elution with a mixture of toluene/EtOAc (7:3) afforded three fractions which were analyzed by HPLC. Hexaadduct (−)-**5** was found in the second fraction and was separated by SiO_2 column chromatography using a mixture of $CHCl_3$/CH_3CN (10:0.4) as an eluent. After precipitation form DCM/hexane, (−)-**5** was isolated in 14% yield as a yellowish waxy solid. Its structure was assigned by NMR, UV/vis, IR spectroscopies and by MALDI-TOF mass spectrometry (SI). In opposition to hexakis adduct (−)-**4**, (−)-**5** did not show signs of deprotection during the chromatographic separation, and thus, dry solvents and triethylamine were not required for its successful purification.

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Hexakis adduct (−)-**6** was also synthesized following the protocol of Sun[6] by reacting C_{60} with the C14 *cyclo*-monomalonate (−)-**3** (Scheme 3). The crude reaction mixture was chromatographed on a SiO_2 column using a mixture of toluene/CH_3CN (9:1) as an eluent. Two fractions were collected, and the eluent was then changed to toluene/CH_3CN (8:2) to afford a third fraction where (−)-**6** was detected (HPLC). Hexakis adduct (−)-**6** was separated by SiO_2 column chromatography using a mixture of toluene/$CHCl_3$/EtOAc (6:4:1) and isolated in 8% yield after precipitation from DCM/hexane. All spectroscopic data were in full agreement with the proposed structure (SI). (−)-**6** was not deprotected during chromatography, thus strengthening our hypothesis that the facile deprotection of the acetal groups in (−)-**4** is due to the strain of the C8 macrocyclic rings.

[6:0]-Hexakis adducts of C_{60} bearing achiral addends have a T_h symmetry. As a consequence, in their ^{13}C NMR spectra, two signals are observed in the region between 140 and 150 ppm due to the two kinds of magnetically nonequivalent sp^2 carbon atoms of the fullerene skeleton. The attachment of enantiomerically pure addends such as the *cyclo*-monomalonates we employed in this study lowers the symmetry of the hexaadducts to T. In this case, four absorptions are expected in the ^{13}C NMR spectra due to the presence of two pairs of diastereotopic sp^2 carbon atoms of the fullerene core. The distance between the chiral carbon centers of the addends and the fullerene carbon network is expected to affect their environment and, consequently, differentiate their chemical shifts. This is nicely reflected in the ^{13}C NMR spectra of the synthesized hexaadducts bearing the alkyl monomalonates (−)-**1a**, (−)-**2**, (−)-**3** (Figure 1). Hexaadduct (−)-**4** functionalized with the smallest C8 *cyclo*-monomalonate addend shows four well-resolved signals due to the shortest distance between the chiral centers of the attached addends and the fullerene skeleton compared to the corresponding hexaadducts (−)-**5**, (−)-**6** which bear the larger C12 and C14 *cyclo*-monomalonate addends, respectively.

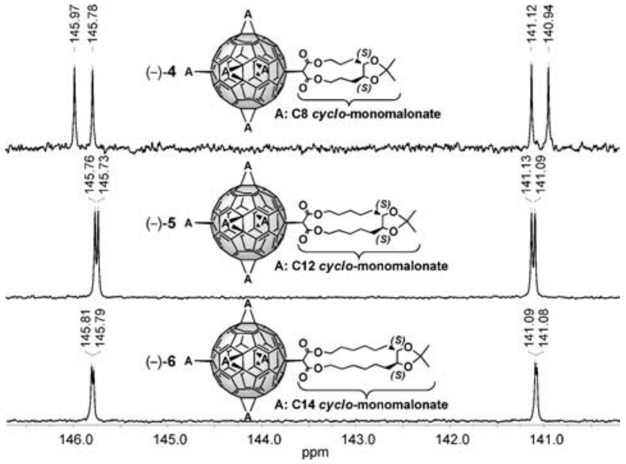
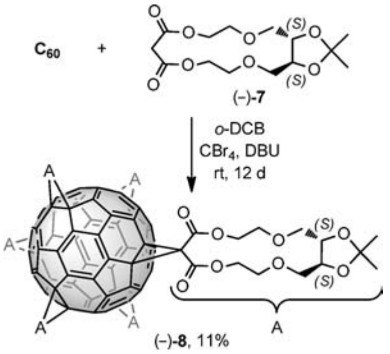


Figure 1. ^{13}C NMR spectra of (−)-**4**, (−)-**5**, and (−)-**6** in the region 140.20−146.71 ppm (sp^2 carbon atoms of C_{60}).

To this end, the evaluation of the results derived from the synthesis of hexakis adducts (−)-**4**, (−)-**5**, and (−)-**6** clearly demonstrates the advantageous synthetic accessibility to (−)-**5** taking into account that the chromatographic separation of (−)-**4** requires dry solvents and not acidic conditions due to the acetal deprotection. This conclusion is supported not only by the higher yield of adduct (−)-**5** (14%) compared to (−)-**6** (8%) but also considering the number of synthetic steps required for the construction of *cyclo*-monomalonates (−)-**2** and (−)-**3**,[23] respectively. In an effort to reduce the number of steps for the synthesis of the monomalonate addend, we employed in our study (−)-7 (Scheme 4). This macrocycle is synthesized in four steps and isolated in 33% overall yield.[25] The 6-fold cyclopropanation of C_{60} with (−)-**7** afforded hexakis adduct (−)-**8** (Scheme 4) in 11% yield after SiO_2 column chromatography and precipitation from DCM/pentane (SI). (−)-**8** was the most polar product in the crude reaction mixture, and thus, monitoring of the reaction progress by TLC and product purification by column chromatography were much easier compared to hexaadducts (−)-**4**, (−)-**5**, and (−)-**6**. Despite the lower yield compared to (−)-**4** and (−)-**5**, the synthesis of hexakis adduct (−)-**8** was the most advantageous considering the shorter and higher yielding synthesis of *cyclo*-monomalonate (−)-**7** in conjunction with the facile SiO_2 column chromatographic purification of the hexaadduct.

Scheme 4. Synthesis of Hexakis Adduct (−)-8



With the synthesized hexakis adducts (−)-**4**, (−)-**5**, (−)-**6**, and (−)-**8** available, we then attempted the deprotection of their acetal groups in order to obtain the functional fullerene building blocks equipped with six 1,2-glycol moieties in an octahedral geometry. Amberlyst-15 was the acidic catalyst of choice, and the reactions were carried out under MW irradiation which facilitated the completion of the 6-fold deprotection. The reaction progress of hexaadducts (−)-**5**, (−)-**6** was monitored by TLC and confirmed the quantitative cleavage of the acetonide groups. Hexakis adducts (−)-**9**, (−)-**10** (Scheme 5) were isolated by SiO_2 column chromatography in quantitative yields and were fully characterized (SI). In contrast, the deprotection reaction progress of hexaadducts (−)-**4**, (−)-**8** was followed by MALDI-TOF due to the high polarity of the fully deprotected adducts which rendered TLC analysis inappropriate. After the deprotection reached completion, the catalyst was removed by filtration and the enantiopure fullerene polyalcohols were subjected to SiO_2 column chromatography. Their chromatographic behavior did not allow the isolation of analytically pure samples due to the extreme tailing on SiO_2. The utilization of stationary phases such as reversed-phase silica gel combined with polar solvents failed to improve the isolation/purification.

In conclusion, we have presented the synthesis of four T-symmetrical [6:0]-hexakis adducts of C_{60} bearing enantiopure *cyclo*-monomalonate addends differing in the size and nature of their spacers and equipped with 1,2-glycol moieties masked as

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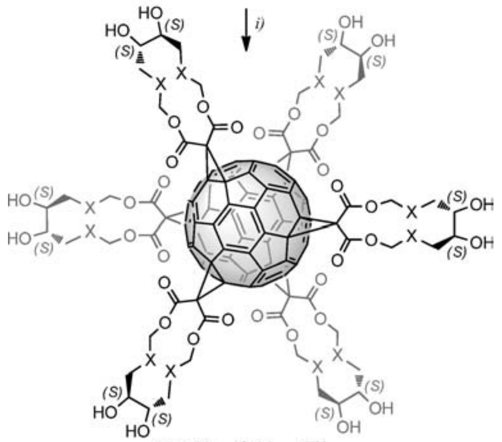
Scheme 5. Deprotection of (−)-5, (−)-6[a]

(−)-**5**, X = -$(CH_2)_3$-
(−)-**6**, X = -$(CH_2)_4$-



(−)-**9**, X = -$(CH_2)_3$-, 97%
(−)-**10**, X = -$(CH_2)_4$-, 99%

[a](*i*) DCM/MeOH/H_2O, Amberlyst-15, MW: 250W, 80 °C, 75 min then 100 °C, 30 min.

isopropylidene acetals. The deprotection of the acetal groups afforded functional fullerene building blocks bearing six 1,2-glycol moieties in an octahedral geometry as connection sites with appropriate linear organic spacers functionalized with boronic acid moieties targeting COFs with chiral cubic building units. Evaluation of the experimental results revealed the advantageous synthetic accessibility to hexakis adduct (−)-**9** which carries six homochiral C12 *cyclo*-monomalonate addends.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00220.

Detailed experimental procedures and spectral data for all compounds; copies of ^1H, ^{13}C NMR, UV/vis, and MALDI-TOF spectra (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nchronak@ucy.ac.cy.

Notes

The authors declare no competing financial interest.

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