Toulhoat et al., we found the typical volcano plot. It is evident that TMSs with either too high or too low $\rho(b_{MS})$ values possess only low HDS activity. The most active catalysts are characterized by intermediate values of the electronic density at the M–S bond critical point. This result corroborates, by means of a bond concept that is rigorously defined by the topological theory of $\rho(\mathbf{r})$, the consistency of TMS-catalyzed HDS with the Sabatier principle.

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Higher Adducts of C_{60} by Tether-Directed Remote Functionalization: X-Ray Crystal Structure and Reactivity of a Chiral Hexakis-Cyclopropanated Fullerene with all Addends Located along an Equatorial Belt**

Craig R. Woods, Jean-Pascal Bourgeois, Paul Seiler, and François Diederich*

Hexakis adducts of C_{60} are increasingly attracting interest as three-dimensional building blocks for advanced materials applications.[1, 2] Among those, derivatives with a pseudooctahedral (T_h) addition pattern have been the earliest and most widely investigated ones.[3–7] Recently, Rubin and co-workers reported the synthesis of a hexakis adduct with a novel, D_3-symmetric addition pattern, which features unusually strong fluorescence and electroluminescence properties.[1] Both types of hexakis adducts are accessible by stepwise additions and their addends are evenly distributed over the entire carbon sphere. In recent years, regio- and stereoselective tether-directed remote functionalization techniques[8] have provided access to a great variety of higher adducts of C_{60}, which either cannot be synthesized by stepwise additions or are obtained only in small yield from complex isomeric mixtures. Using such a methodology,[9] we became interested in preparing hexakis adducts with completely novel addition patterns, that feature the location of all addends along an equatorial belt rather than evenly distributed over the entire carbon sphere. In the chiral D_2-symmetric structure **A** (Figure 1) the addition sites are aligned in a distinct helical array, whereas structure **B**, with a D_{3d}-symmetric addition pattern, features a circumferential ("Saturn"-like) functionalization about the equator which dissects the residual π-electron chromophore of the fullerene into two polar halves with no direct π-electron conjugation. Here, we report the synthesis,

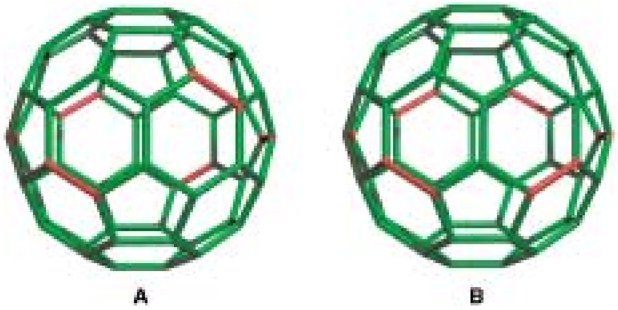

Figure 1. Novel hexakis addition patterns of C_{60} with the addend sites located along an equatorial belt.

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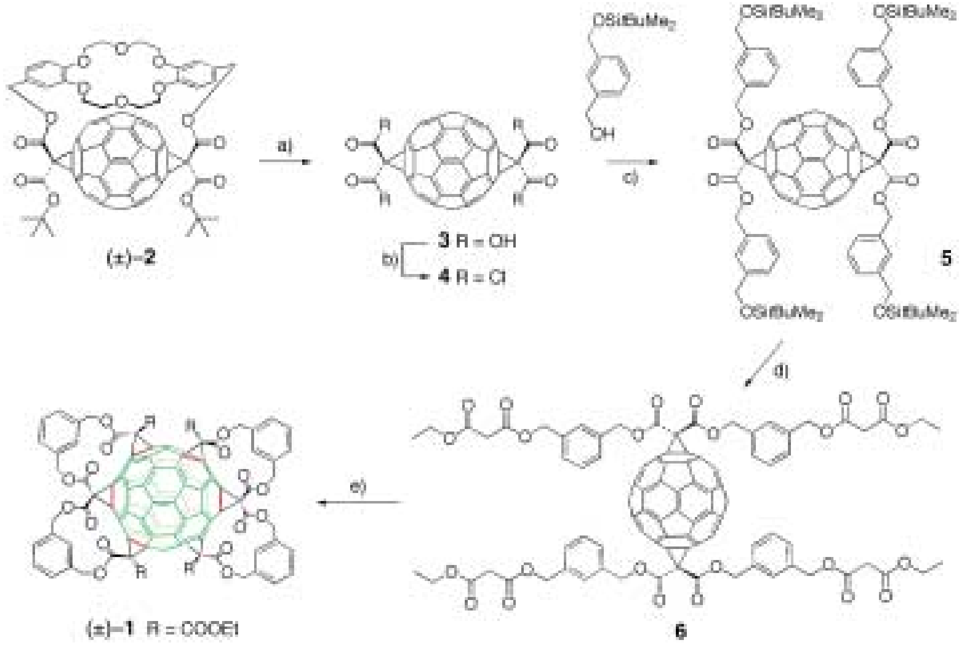
crystal structure, and chemical reactivity of the D_2-symmetric hexakis adduct (±)-**1**, which features addition pattern **A**.



Scheme 1. Synthesis of the hexakis adduct (±)-**1**. a) p-TsOH · H_2O, PhMe, reflux, 16 h; b) $(COCl)_2$, CH_2Cl_2, reflux, 48 h; c) Py, CH_2Cl_2, 20 °C, 12 h, 21 % (from (±)-**2**); d) 1) HF/Py, CH_2Cl_2, 0 °C, 1 h; 2) $ClCOCH_2CO_2Et$, DMA, CH_2Cl_2, 20 °C, 80 %; e) I_2, DBU, $PhMe/Me_2SO$, 20 °C, 12 h, 10 %. DMA = *N*,*N*-dimethylaniline; DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Target compound (±)-**1** was synthesized by a short route that involves two sequential tether-directed remote functionalization steps. The first consisted in the preparation of *trans-1* bis-adduct (±)-**2** by Bingel macrocyclization of C_{60} with dibenzo[18]crown-6 appended with two bis-malonate moieties. The reaction is templated by K^+ ions and gives the product in a 50 % yield, as previously described.[10] Cleavage of the crown ether template and the *tert*-butyl ester groups with 4-toluenesulfonic acid monohydrate (p-TsOH · H_2O) in toluene afforded tetraacid **3**,[10b] which was transformed into tetrakis(acyl chloride) **4** (Scheme 1). Coupling with mono-tBuMe$_2$Si-protected 1,3-benzenedimethanol[11] yielded **5**, which was then deprotected with HF/pyridine and converted with ethyl malonyl chloride into **6**.[12] Fourfold intramolecular Bingel addition[13] of **6** under high dilution conditions, flash-chromatographic workup (SiO_2-*H*; CH_2Cl_2/AcOEt (99/1)), and further chromatographic separation of the middle fraction (SiO_2-*H*; CH_2Cl_2/AcOEt (99.5/0.5)) gave (±)-**1** as a single hexakis adduct in 10 % yield.

The molecular formula of the hexakis adduct was unambiguously revealed by high-resolution matrix-assisted laser desorption-ionization mass spectrometry (MALDI-TOF MS) which showed the sodium complex of the molecular ion as parent ion at $m/z = 1875.275$ (100 %, $[M+Na]^+$, $C_{118}H_{52}NaO_{24}^+$; calcd: 1875.275). 1,3-Benzenedimethanol-tethered bis-malonates are well known to yield regioselectively *cis-2* addition patterns on the fullerene.[8, 9, 14] Fourfold intramolecular Bingel addition of **6** with *cis-2* selectivity can only give (with equiprobability) two hexakis adducts, D_2-symmetric (±)-**1** with addition pattern **A**, or a C_{2h}-symmetric compound with addition pattern **B** (Figure 1). Whereas the symmetry of the two regioisomers does not allow differentiation using ^1H NMR, this can, in principle, be performed by ^{13}C NMR spectroscopy. In the C_{2h}-symmetric compound, the mirror plane cuts through four sp^2-hybridized carbon atoms, to give 22 $^{13}C_{sp^2}$ (three C=O, six benzene, and 13 fullerene) resonances. On the other hand, the C_2 axes in D_2-symmetric (±)-**1** do not pass through any carbon atoms and therefore 21 $^{13}C_{sp^2}$ (three C=O, six benzene, and 12 fullerene) resonances were expected. Unfortunately, the ^{13}C NMR spectrum (125.8 MHz, $CDCl_3$) of the isolated compound displayed only 20 distinguishable $^{13}C_{sp^2}$ resonances due to accidental isochrony; hence, it was not useful for assigning symmetry and molecular constitution.

Fortunately, one small red-black crystal, suitable for an X-ray analysis, was successfully grown from a solution of CH_2Cl_2, hexane, and benzene. The molecular structure (Figures 2 and 3) nicely reveals the distinct helical nature of addition pattern **A** and allows an unambiguous assignment of structure (±)-**1** to the isolated hexakis adduct.[15] Distortion of the C_{60} sphere in (±)-**1** due to the belt of six fused cyclopropane rings is small and its overall shape closely resembles that determined for the bis-adduct (±)-**2**.[10]

π-Electron conjugation between the two unsubstituted poles in (±)-**1** is maintained through two *trans*-stilbene-like bridges (Figure 4). As a result of this retained, extended conjugation, the compound is red in solution with an end

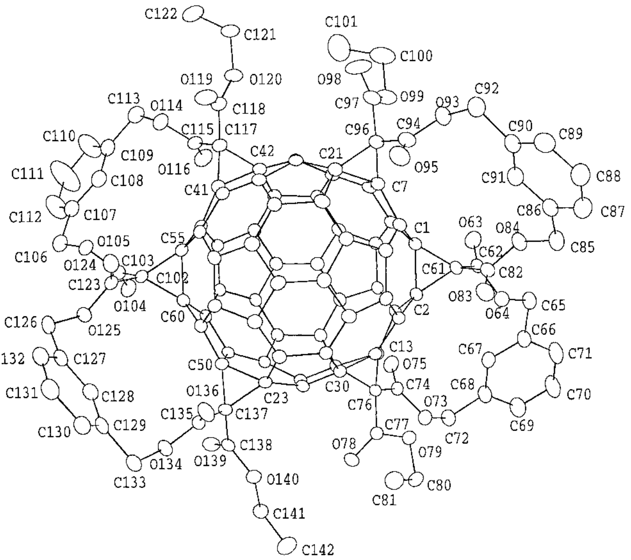


Figure 2. X-ray crystal structure of (±)-**1**. Atomic displacement parameters obtained at 228 K are drawn at the 20 % probability level.

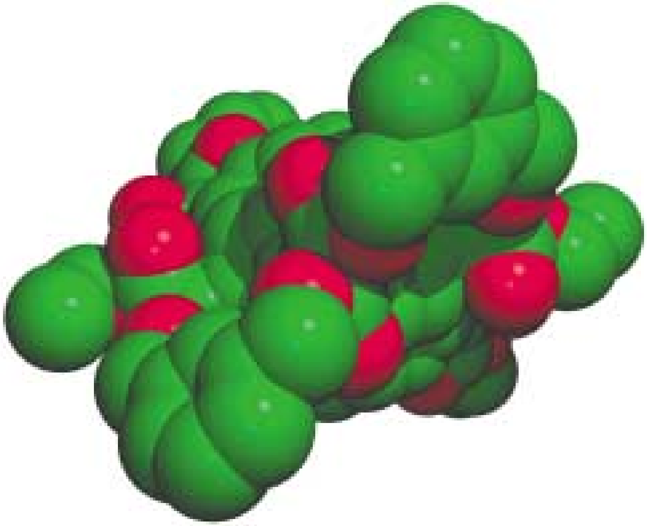


Figure 3. Space-filling representation of the X-ray crystal structure of (±)-**1**, which shows the distinct helical nature of the addition pattern.

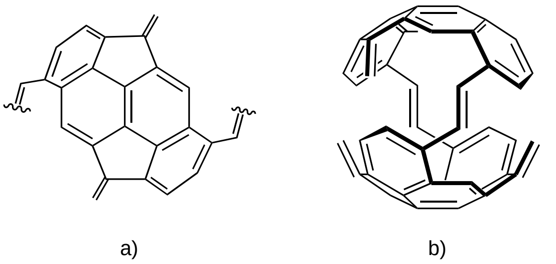
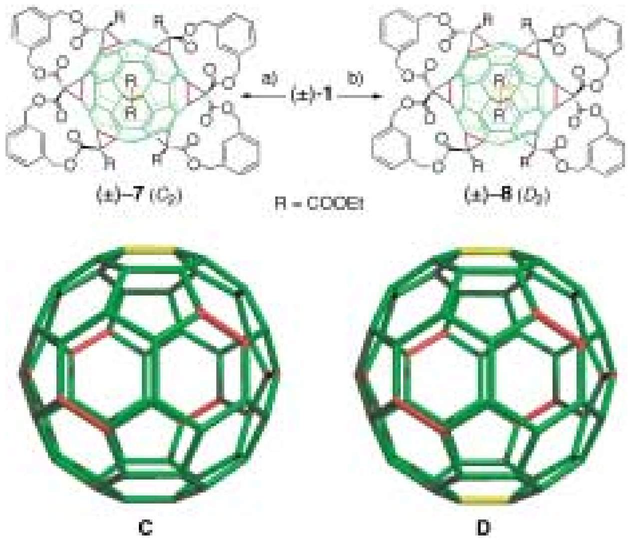


Figure 4. Residual π-electron chromophore in (±)-**1**: a) view atop one of the two unfunctionalized poles and b) side view onto the *trans*-stilbene-like moiety, which maintains electronic communication between the two polar regions.

absorption extending to 600 nm. This contrasts with the light-yellow color (end absorption around 450 nm) of the hexakis adducts with pseudooctahedral addition patterns, in which the residual π-electron chromophore is reduced to a benzenoid "cubic cyclophane"-type substructure.[1–7]

The novel hexakis-adduct (±)-**1** undergoes further functionalization at the central 6–6 bond of each pole. A Bingel reaction with diethyl 2-bromomalonate (2 equiv) in toluene/DMSO (1/1) in the presence of DBU afforded the heptakis-adduct (±)-**7** as a single new product together with some starting material. Addition of a 20-fold excess of the same 2-bromomalonate to (±)-**1** produced another unique compound, the octakis-adduct (±)-**8**, along with traces of (±)-**7** (Scheme 2). The high-resolution MALDI-TOF mass spectra showed the sodium complexes of the molecular ions as parent ions, which correspond to the heptakis and octakis adducts from a single and double Bingel addition, respectively ((±)-**7**: $m/z = 2033.331$ (100%, $[M+\mathrm{Na}^+]$, $C_{125}H_{62}NaO_{28}^+$; calcd: 2033.332); (±)-**8**: $m/z = 2191.388$ (100%, $[M+\mathrm{Na}^+]$, $C_{132}H_{72}NaO_{32}^+$; calcd: 2191.390)). Unambiguous proof for the proposed addition patterns was provided by the ^{1}H NMR spectra (300 MHz, $CHCl_3$). The spectrum of (±)-**7** corresponds to a C_2-symmetric compound, with four AB systems for four different benzylic CH_2 groups, whereas the spectrum of (±)-**8** displays only two such AB systems, in agreement with a higher, D_2 symmetry. Addition patterns of this symmetry can only be obtained starting from (±)-**1** by mono- and bis-cyclopropanation at the central polar 6–6 bonds. Attack at these specific 6–6 bonds is favored since they are sterically the least hindered ones and are in an equatorial (*e*) relationship with respect to the two malonate addends with *trans-1* relationship introduced in the first tether-directed remote functionalization step.[4a] Since the *trans*-stilbene type conjugation between the two polar chromophoric regions is still maintained, the hypsochromic shift upon passing from (±)-**1** (longest wavelength absorption maximum at $\lambda_{max} = 576$ nm), to (±)-**7** ($\lambda_{max} = 556$ nm, sh), and to (±)-**8** ($\lambda_{max} = 551$ nm) is not large and solutions of the latter still display an orange-yellow color.



Scheme 2. Synthesis of the heptakis and octakis adducts (±)-**7** and (±)-**8** with addition patterns **C** and **D**, respectively. a) $(EtOOC)_2CHBr$ (2 equiv), DBU (6.6 equiv), PhMe/Me_2SO, 20 °C, 12 h; ≈40%; b) $(EtOOC)_2CHBr$ (20 equiv), DBU (66 equiv), PhMe/Me_2SO, 20 °C, 12 h, ≈80%. The indicated yields have high uncertainty due to the small quantities of materials used.

We were unable to isolate the regioisomer of (±)-**1** with addition pattern **B**, although molecular modeling calculations[16] predicted only little energetic differences between the two compounds. There may, however, exist differential steric interactions between adjacent EtOOC groups in the transition states of the two final cyclopropanation steps. The geometric relationship between two adjacent ethyl malonate addends in (±)-**1** is *cis-3*, whereas it is *cis-2* in the regioisomer (Figure 1), and the closer proximity of adjacent EtOOC groups in the latter could render its formation unfavorable. We intend to test this hypothesis with an analog of **6** that contains four smaller, terminal methyl malonate moieties, which we expect to yield hexakis adducts with both **A** and **B** addition patterns. The pronounced helical nature of the inherently chiral addition pattern of (±)-**1** promises interesting chiroptical properties.[17] Therefore, we are now introducing chiral tethers instead of the 1,3-benzenedimethanol moieties in **6** to prepare optically active derivatives of (±)-**1** in a diastereoselective way.[8, 9]

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[15] X-ray crystal data of (±)-**1** ($C_{118}H_{52}O_{24}\cdot\approx 3.5\,CH_2Cl_2$, $M_r = 2150.8$): monoclinic, space group $P2_1/c$ (no. 14), $\rho = 1.495\ \mathrm{g\,cm^{-3}}$, $Z = 4$, $a = 20.332(3)$, $b = 19.860(3)$, $c = 23.696(3)$ Å, $\beta = 93.02(1)^\circ$, $V = 9555(2)$ Å^3, $T = 228$ K. Nonius-CAD4 diffractometer, $\mathrm{Cu_{K\alpha}}$ radiation, $\lambda = 1.5418$ Å. One red-black, slightly twinned crystal (linear dimensions approximately $0.3 \times 0.2 \times 0.1$ mm) was obtained by liquid – liquid diffusion of hexane into a CH_2Cl_2/C_6H_6 solution of (±)-**1**. The crystal was mounted at low temperature to prevent evaporation of the enclosed solvents. The twinning led to asymmetric reflection profiles for many reflections; an appropriate background correction was made to compensate for this effect. In addition, a semiempirical absorption correction, based on psi-scans, was applied to the data ($T_{\max} = 0.99$, $T_{\min} = 0.61$). The structure was solved by direct methods (SIR92: A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435) and refined by full-matrix least-squares analysis (SHELXL-97, G. M. Sheldrick, University of Göttingen, Germany, **1997**) with the use of an isotropic extinction correction and $w = 1/[\sigma^2(F_0^2) + (0.125\,P)^2 + 25.85\,P]$, where $P = (F_0^2 + 2\,F_c^2)/3$. It consists of one ordered molecule of (±)-**1** and five disordered CH_2Cl_2 molecules with population parameters between about 0.5 and 0.75. All heavy atoms were refined anisotropically (hydrogen atoms of the ordered fullerene isotropically, in which hydrogen atomic positions are based on stereochemical considerations). Final $R(F) = 0.085$, $wR(F^2) = 0.235$ for 1365 parameters and 8593 reflections with $I > 2\sigma(I)$ and $2.2 < \theta < 57.0^\circ$ (corresponding R values based on all 12832 reflections are 0.125 and 0.274, respectively). Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145416. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK (fax: (+44)1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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High-Throughput Structure Verification of a Substituted 4-Phenylbenzopyran Library by Using 2D NMR Techniques**

Harald Schröder,* Peter Neidig, and Gérard Rossé

Innovative technologies for combinatorial chemistry and automated synthesis make possible the synthesis of large collections of compounds as potential sources of lead structures in medicinal chemistry. While the synthesis, purification, and biological screening of combinatorial libraries can be performed automatically, purity control and structure verification remain bottlenecks. Insufficient purity or ambiguous structures of screened samples hinder the exploitation of structure – activity relationships, which are critical elements for the further design of libraries. The HPLC, MS, and liquid chromatography mass spectrometry (LC-MS) techniques are generally accepted as the most appropriate means of characterization.[1] These analytical methods are fast and easy to automate, but they do not provide sufficient structural and quantitative data on the desired product. The existing automated methods based on ^{13}C and ^{1}H NMR spectroscopy[2] are not routinely applied due to the intrinsic low sensitivity of ^{13}C NMR spectroscopy and the lack of reliable proton-based automated structure verification methods. We report here a novel approach for the automated structure verification of compound libraries by using the experimental data from 2D

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