

Regiochemistry of Multiple Additions to the Fullerene Core: Synthesis of a T_h -Symmetric Hexakisadduct of C_{60} with Bis(ethoxycarbonyl)methylene

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The spherical all-carbon molecule C_{60} exhibits a spherical "workspace" with 30 reactive 6–6 double bonds. Since these double bonds are accessible to a variety of different addition reactions,¹ the polyfunctionality of C_{60} implies an enormous multitude of possible regioisomeric fullerene adducts. Oligoadducts of C_{60} , with a defined three-dimensional structure, have a potential for applications, like molecular recognition, especially since it has been shown recently that a water soluble monoadduct of C_{60} inhibits the HIV enzymes protease and reverse transcriptase.² Tailor-made oligoadducts of C_{60} with a defined three-dimensional structure could dramatically increase the binding capability to a given enzyme. So far, the synthesis of isomerically pure oligoadducts of C_{60} has been reported only for a few cases.³ For example, it has been shown by Fagan et al. that allowing an excess of the metal reagent $Pt(PEt_3)_4$ to react with C_{60} leads exclusively, in a thermodynamically controlled reaction, to the formation of $[(Et_3P)_2Pt]_6C_{60}$ as the T_h -symmetric regioisomer.^{3a} This very pronounced regioselectivity is possible because the metal complexations are reversible. However, in order to synthesize stable and stereochemically defined adducts with a variable degree of addition which are useful for further applications, irreversible reactions, like cycloadditions, have to be employed. We have shown recently^{3d} that in nucleophilic cyclopropanations of C_{60} an attack into specific positions (Figure 1), namely, *e* and *trans*-3, relative to addends already bound to the fullerene core, are significantly preferred. In this work we report for the first time a systematic and stepwise synthesis of a T_h -symmetric hexakisadduct **6** of C_{60} with an increasing regioselectivity. Furthermore, we present a theoretical explanation for the regioselectivity of nucleophilic additions on the basis of the calculated coefficients of low-lying unoccupied orbitals (LUMO, LUMO+1, LUMO+2) as well as the thermodynamic stability of the adducts.

As model reaction we chose the cyclopropanation of C_{60} with diethyl bromomalonate in the presence of sodium hydride at room temperature.^{3d,4} The starting compound is the chiral C_3 -symmetric trisadduct **3** (*e,e,e* isomer), which we synthesized previously.^{3d} The synthesis of **6** has been carried out by successive *e* additions via the C_2 -symmetric tetrakisadduct **4** and the C_{2v} -symmetric pentakisadduct **5** (Scheme 1). Both **4** and **5** have been isolated by preparative HPLC on an aminopropyl phase

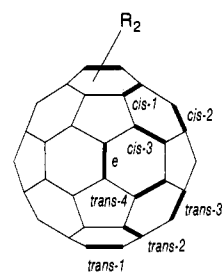


Figure 1. Positional relationships of the eight different double bonds in a C_{60} monoadduct relative to the 6–6 bond carrying the first addend R_2 ($R_2 = \text{e.g., methylene}$).

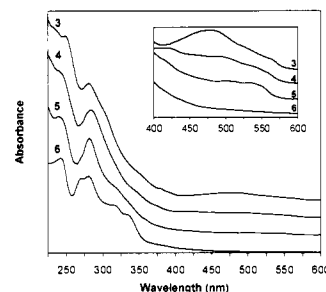
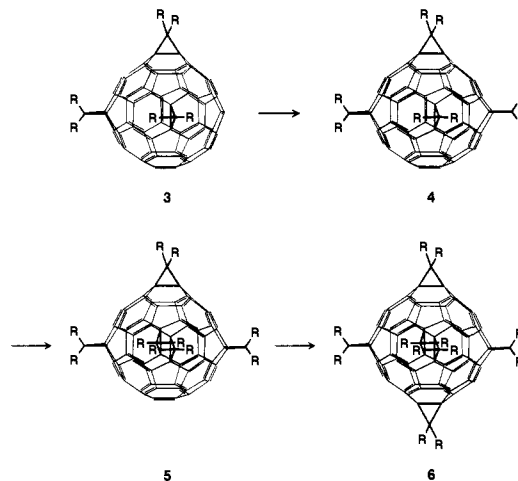


Figure 2. Electronic absorption spectra of **6** ($2.0 \times 10^{-5} \text{ mol L}^{-1}$), **3**, **4**, and **5** (each $1.5 \times 10^{-5} \text{ mol L}^{-1}$) in acetonitrile, $T = 25 \text{ }^\circ\text{C}$.

Scheme 1. Synthesis of the Hexakisadduct **6** by Successive *e* Additions^a



^a $R = \text{COOEt}$.

with toluene as eluent and characterized (see supplementary material) prior to the next addition step. Significantly, next to **4** only one other tetrakisadduct with C_1 -symmetry has been formed. On the basis of consumed **3** the yield (HPLC, gravimetry) of **4** is 64%. The cyclopropanation of **4** and **5** is even more regioselective. The regioisomers **5** and **6** are the only pentakis- and hexakisadducts formed. The more addends bound in *e* positions to a certain double bond, the more favorable is an attack of this bond. The required reaction times increase with an increasing degree of addition. Even when a large excess of diethyl bromomalonate has been used, the formation of a heptakisadduct has not been observed since only benzoid rings are left in **6**. In addition, very unfavorable *cis*-1 positions would be present in this heptakisadduct. The increasing rupture of the conjugated fullerene π -electron system leads to a lightening of the color (Figure 2). While the trisadduct **3** is orange-red, **4** exhibits an orange, **5** a light-orange and the hexakisadduct **6** a yellow color. The structure of the corresponding adducts can be deduced from their ^{13}C NMR spectra on the basis of symmetry considerations. For example, in the ^{13}C NMR spectrum of **6** due to the T_h -

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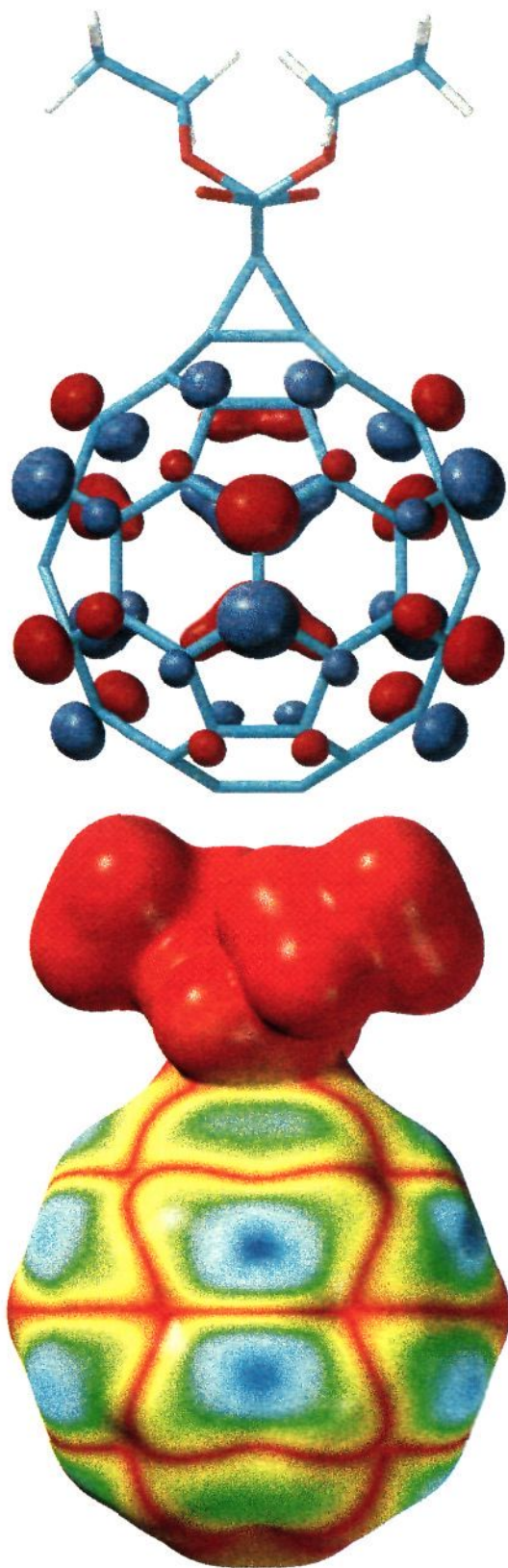


Figure 3. (a, top) LUMO of $C_{61}(\text{COOEt})_2$ (**1**) and (b, bottom) projection of the LUMO onto the electron density surface (SPARTAN 3.0). The density of the surface is 0.002 electron/ au^3 . The highest orbital coefficients are located in the blue areas and the lowest in the red areas.

symmetry only two lines for the fullerene C atoms appear in the sp^2 region at $\delta = 145$ and 141 and one line in the sp^3 region at $\delta = 69$ (see supplementary material).

The calculation of the AM1 heats of formation of the eight possible bisadducts of $C_{62}(\text{COOEt})_4$ **2** demonstrates that thermodynamic reasons are not significant to explain the preferred *e* and *trans*-3 additions.^{3d} Due to the steric repulsion of the ester groups the *cis*-1 adduct is considerably destabilized, while the *cis*-3 and *cis*-2 adducts are only slightly unfavored. To demonstrate experimentally that the *e* and *trans*-3 isomers do not have an extra thermodynamic stability, we treated *trans*-2- $C_{62}(\text{COOEt})_4$ for several days at 180 °C in refluxing dichlorobenzene. Only at this elevated temperature does a slow isomerization to the *trans*-1, *trans*-3, *trans*-4, and *e* isomers take place. A preferred isomerization to the *e* or *trans*-3 isomers, however, has not been observed. There are, however, kinetic reasons that govern the regiochemistry at room temperature. This is supported by MO calculations (AM1). The preferred sites for nucleophilic attack exhibit enhanced orbital coefficients of low-lying unoccupied MOs. In the LUMO of $C_{61}(\text{COOEt})_2$ (**1**) the highest orbital coefficients (± 0.22) are located at two equatorial double bonds (*e* positions) on the mirror plane perpendicular to the cyclopropanated bond (Figure 3). The other two equatorial double bonds have the highest coefficients (± 0.22) in the LUMO + 1. The next higher LUMO coefficients (± 0.10 – 0.16) are located at the *trans*-3 and *cis*-2 double bonds. The observed preference of *trans*-3 over *cis*-2 additions can be explained by the higher thermodynamic stability of the *trans*-3 adduct (lower steric repulsion). Enhanced orbital coefficients at other positions are observed only in the LUMO+1 and LUMO+2, for example at the *trans*-1 position in the LUMO+2. The energy difference between LUMO/LUMO+1 and LUMO+1/LUMO+2 is 0.08 and 0.12 eV, respectively.

A completely analogous picture results for the MOs of *e*- $C_{62}(\text{COOEt})_4$, **3**, **4**, and **5**. In each case the LUMO and LUMO+1 coefficients are significantly highest at *e* positions (then *trans*-3 if available). This trend even increases with an increasing degree of addition. Upon the exclusive formation of **6** from **5**, additional thermodynamic arguments are of importance. The regioisomer **6** is stabilized by at least 5 kcal/mol (AM1) compared to all the other 43 hexakisadducts, which in principle can be formed from **3** without introducing energetically very unfavorable *cis*-1 positions.⁵

Interestingly, the HOMO of **1** has the highest coefficients at the *cis*-1 and *e* positions. An electrophilic attack of sterically nondemanding addends should therefore preferably take place at these positions, which corroborates the findings of Cahill^{3e} where the *cis*-1 isomer of $C_{60}H_4$ is the major product obtained by hydroboration/protonation.

In conclusion, we have shown that a systematic investigation of multiple additions to C_{60} with chromatographic, spectroscopic, and theoretical methods deeply increases the knowledge of fullerene chemistry and provides access to a variety of stable fullerene derivatives with a defined three-dimensional structure.

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Supplementary Material Available: Experimental details for the syntheses of **4**–**6**, ^{13}C NMR and IR data and spectra for **4**–**6**, and ^1H NMR spectrum for **6** (9 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(5) The different possible regioisomers formed by additions to 6–6 double bonds have been generated systematically and are represented by interatomic square distances d_{ij}^2 . Many of the regioisomers generated in this way are identical for symmetry reasons. The eigenvalues of the squared distance matrices are independent of the atomic numbering. Regioisomers having squared distance matrices with the same eigenvalues have been considered identical. With this simple numerical method, for example, 314 different hexakisadducts without *cis*-1 positions can be determined. Starting from the trisadduct **3**, however, only 43 different regioisomers are found.