Unexpected Isomerism in *cis*-2 Bis(pyrrolidino)[60]Fullerene Diastereomers**

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Fullerene functionalization has been studied extensively since they became available in macroscopic quantities in 1990.[1] Because of its versatility, utility, and ease of implementation, the 1,3-dipolar cycloaddition reaction of azomethine ylides is probably the most frequently used method for the synthesis of fullerene derivatives.[2,3] The asymmetric version of this reaction has also been recently reported by Martín et al., thus giving rise to enantiomerically pure fullerenes.[4]

Bis(functionalization) of fullerenes is challenging because of the many isomeric products that are typically obtained. Since C_{60} has 30 reactive double bonds, eight bis(adduct)s can be obtained when the two addends are identical (*cis*-1, *cis*-2, *cis*-3, equatorial, *trans*-4, *trans*-3, *trans*-2, and *trans*-1). Prato and co-workers found that when monoaldehydes are used as reactants, the main bis(addition) products are the *trans*-3 and equatorial isomers,[5] although others have reported that the *cis*-3 bis(adduct) is the most abundant one.[6] Bis(adduct)s *cis*-1 and *cis*-2 are hardly ever observed because of the steric congestion.[7]

Controlled multifunctionalization of C_{60} is crucial to improving the yield of specific bis(adduct) isomers and to avoiding tedious HPLC chromatographic separations.[8] One approach to achieve controlled bis(functionalization) is the tether-directed remote method,[9] which was introduced by Diederich and co-workers in 1994.[10] This method was used to conduct bis(1,3-dipolar cycloaddition)s to C_{60} by D'Souza et al. and Zhou et al.[11,12]

Examples of regioselective syntheses of bis(adduct)s with a *cis*-1 addition pattern were reported by Martín et al., who used an intramolecular Pauson–Khand reaction, thermal [2+2] cycloaddition,[13] and nucleophilic addition.[14] Also, selective tether-controlled tandem additions of nitrile oxides

and azomethine ylides to yield *cis*-1 bis(adduct)s were reported by Prato et al.[15]

Herein we report the one-step synthesis and characterization of three pure [60]fullerene bis(adduct)s, including the X-ray crystal structure of two *cis*-2 bisadducts (**1** and **2**; see Scheme 1 for structures) which are individual *meso* forms. Although there are multiple reports of chirality for fullerene derivatives,[16,4] the isomerism reported here is unprecedented. These *meso* bis(adduct)s, easily isolable by silica gel chromatography, show a unique isomerization and the proposed mechanism is supported by computational studies.

Three pure bis(adduct)s, **1**, **2**, and **3**, were prepared by the 1,3-dipolar cycloaddition of an ylide, resulting from *o*-phthalaldehyde (OPA) and *N*-ethylglycine, in the presence of C_{60} by using the procedure reported by Prato et al.[2a,17] To prevent the formation of monoadducts, an excess of *N*-ethylglycine was added. The purification of the crude reaction mixture by silica gel column chromatography (CS_2) gave rise, in order of elution, to unreacted C_{60}, the three compounds denoted **1**, **2**, and **3**, and finally the polyadducts. The major product of the reaction was the bis(adduct) **2**, which was isolated in 26% yield, followed by **1** and **3** in 9% and 8% yield, respectively.

The compounds **1** and **2** were characterized by UV/Vis and NMR spectroscopy, mass spectrometry, and X-ray crystallography (see the Supporting Information). OPA has the formyl groups in the *ortho* positions, therefore after the first 1,3-cycloaddition occurs, the most accessible double bonds on C_{60} for a second cycloaddition are the *cis*-1 and *cis*-2. Three diastereomers could in principle be formed for each regioisomer (*cis*-1 and *cis*-2) depending on the orientation of the hydrogen atoms at the stereogenic centers, so a total of six isomers are possible (Figure 1).

The compounds **1** and **2** have almost identical UV/Vis spectra, and these indicate that they are *cis*-2 isomers (see Figure S4 in the Supporting Information). These assignments are based on the unique UV/Vis absorption patterns for each [60]fullerene bis(adduct)s in the $\lambda = 400$ to 750 nm region, reported for the first time by Hirsch et al.[7,5] After the first cycloaddition, the *cis*-1 bond should be more reactive than the *cis*-2 for the second addition, however the former leads to a more sterically strained compound, and is thus disfavored.[7,18]

The ¹H NMR spectra of **1** and **2** showed half of the possible number of signals, thus evidencing the presence of a plane of symmetry for both compounds.[19] The most pronounced difference between **1** and **2** corresponds to the protons of the methylene groups of the pyrrolidine ring, the signals for which appear as two doublets centered at $\delta = 4.65$

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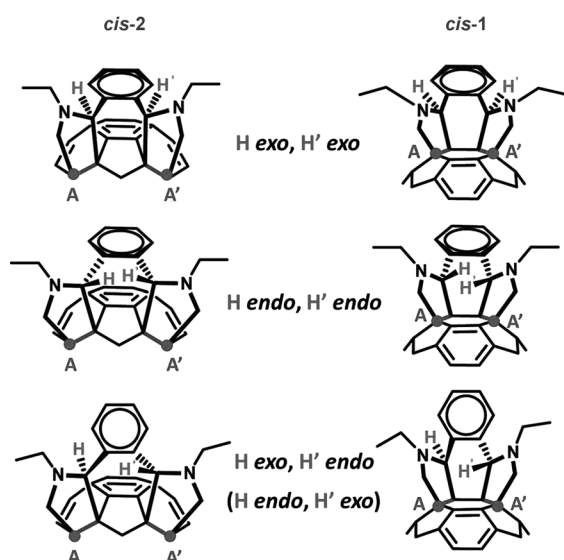
Figure 1. Structures of the six possible bis(adduct)s that can be formed from the 1,3-dipolar cycloaddition to C_{60} of the ylide resulting from OPA and *N*-ethylglycine. If the hydrogen atoms at the stereogenic centers are pointing away from A and A′ they are "*exo*" and if they are in the direction of A and A′ they are "*endo*".

and 4.55 ppm for **1** and at $\delta = 4.81$ and 3.81 ppm for **2** (Figure 2). The singlet for the CH proton of the pyrrolidine ring appears at $\delta = 5.63$ ppm for **1** and at $\delta = 4.73$ ppm for **2** (shifted 0.92 ppm). The methylene signals of the ethyl group are diasterotopic, thus showing two multiplets centered at $\delta =$
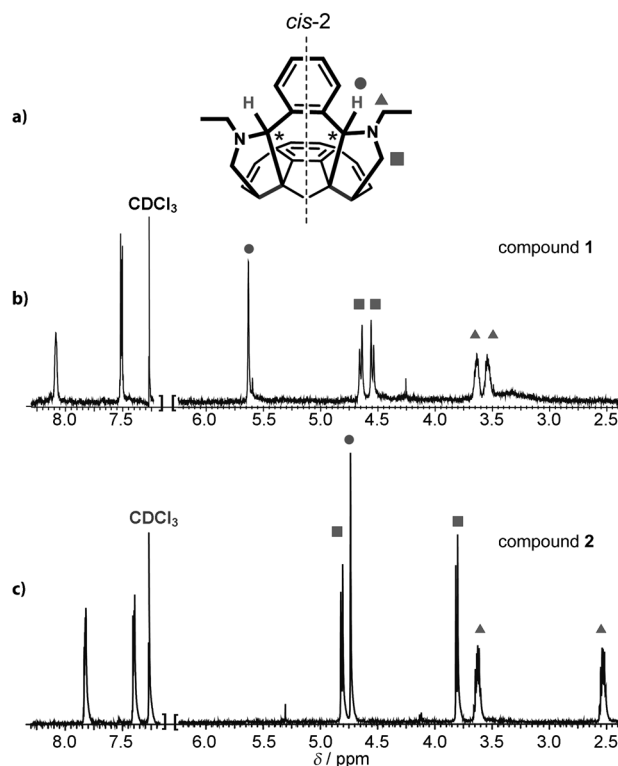

Figure 2. a) Representation of **1** and **2** without stereochemical information. ¹H NMR (600 MHz, CDCl₃, 298 K) of b) **1** and c) **2**.

3.63 and 3.53 ppm ($\Delta\delta = 0.1$ ppm) for **1** and at $\delta = 3.63$ and 2.53 ppm ($\Delta\delta = 1.1$ ppm) for **2**.

Both **1** and **2** have a symmetry plane, and the presence of the two stereogenic centers establishes that these are non-chiral and correspond to two diastereoisomers, each in a different *meso* form. It is not common to have two *meso* isomeric forms of one compound.[20] The *cis*-2 compounds reported here have two stereogenic centers, thus suggesting, at most, four configurational isomers: *RR*, *SS*, *RS*, and *SR*. In this case, *RR* and *SS* are the enantiomeric pair, which is not observed because they are only possible if the molecule is not symmetric. Usually the *RS* and *SR* are the same, thus a single *meso* compound is observed,[21] but in this case they are two different and isolable *meso* forms (**1** and **2**). This peculiar result is due to the three dimensionality of the molecule, and to the best of our knowledge, this phenomenon has never been reported for fullerene compounds.

Surprisingly, these two diastereomeric bis(adduct)s having the same *cis*-2 addition pattern also differ in electronic and redox properties (Table S1), polarity, and especially solubility (solubility in CS₂: 0.695 mg mL⁻¹ for **1** and 11.26 mg mL⁻¹ for **2**). Stereochemical assignments were possible by X-ray crystallography.

The compound **3** was characterized by spectroscopic techniques and mass spectrometry (see the Supporting Information). NMR and UV/Vis experiments on **3** were sufficient to establish its structure. The UV/Vis spectrum of **3** is typical for a *cis*-1 addition pattern (Figure S4). The compound **3** does not possess a symmetry plane as evidenced by the ¹H and ¹³C NMR spectra, which exhibit unsymmetrical pyrrolidines (Figures S12 and S13).

Bis(addition) at the *cis*-1 positions leads to an inherently symmetric pattern. However, the ¹H and ¹³C NMR spectra clearly show that the molecule is unsymmetric. The lack of symmetry must arise from the relative orientation of the hydrogen atoms in an opposite arrangement (*exo,endo* or *endo,exo*) at the stereogenic centers, thus **3** is a racemic mixture.

Single crystals of **1** and **2** were grown from CS₂/toluene. The bond distances and bond angles are comparable to those of similar compounds in the literature.[10b] Analysis of the crystal structures showed the configuration at the chiral centers (**1**: *S,R* and **2**: *R,S* from left to right based on the arbitrary orientations introduced in Figure 1). The restricted motion of the N-Et groups in the crystal of **1** (Figure 3) reduces the symmetry in the solid state to the $P2_1/c$ spatial group. **2** has symmetric N-Et groups making it a *meso* compound with spatial group *Pnnm*. Both compounds exhibit the same symmetry in solution because of the free rotation of the ethyl groups. Changing the chirality of the two stereogenic centers results in the two possible diastereoisomers (Figure 3).

The crystal packing of **1** shows that each fullerene interacts with two other fullerenes through C···C interactions [3.315 and 3.367 Å] (Figure S16a). In the case of **2**, each fullerene interacts with five other fullerenes through C···C interactions [3.208–3.385 Å] (Figure S18). A particularly interesting motif is observed in the packing of **2**, where two phenyl groups from adjacent molecules show π···π interac-
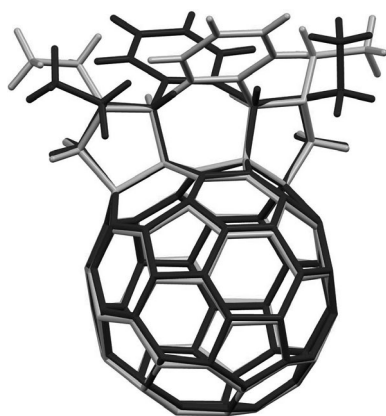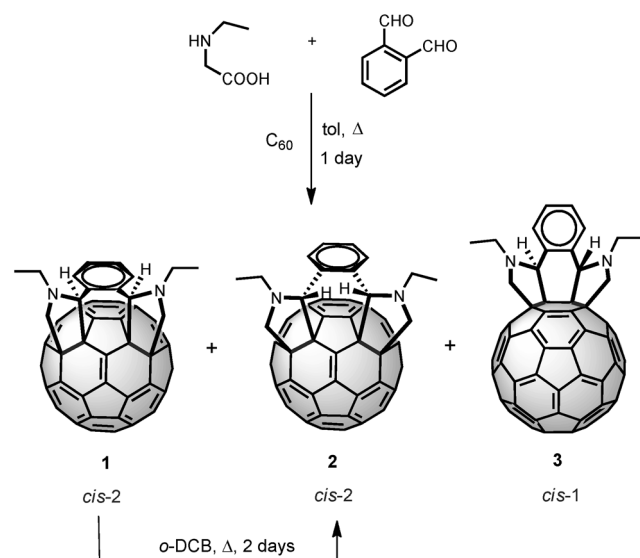
Figure 3. Superposition of the crystal structures of **1** (black) and **2** (grey) showing the difference in orientation of the phenylene group for both compounds and the lack of symmetry for the N-Et groups in **1**.

tions [3.853 Å] (Figure S16b). Based on the X-ray data it is possible to assign the stereochemistry (summarized in Scheme 1) for the pure bisadducts **1** and **2** (*cis*-2).

Scheme 1. Synthesis of **1** (*cis*-2), **2** (*cis*-2), and **3** (*cis*-1).

The compound **1** was heated at 180 °C (*o*-dichlorobenzene reflux) for two days, and was found to almost quantitatively convert into **2**, and some pristine C_{60} was also detected by TLC and HPLC (Figure S11). These data suggest that retro-1,3-dipolar cycloadditions are involved in the interconversion processes, and such reactions have received considerable attention recently since their discovery in 2006.[22] Once the retro cycloaddition occurs for one of the pyrrolidines, the ylide can add again to any of three additional double bonds as well as the original one (reverse reaction): two *cis*-1 bonds and another *cis*-2 bond. This hypothesis has been confirmed by theoretical calculations. The only migration observed was that towards the other *cis*-2 bond to obtain **2** exclusively (Figure 4). It is remarkable that shifting the attachment position of one pyrrolidine from a *cis*-2 bond to the other very
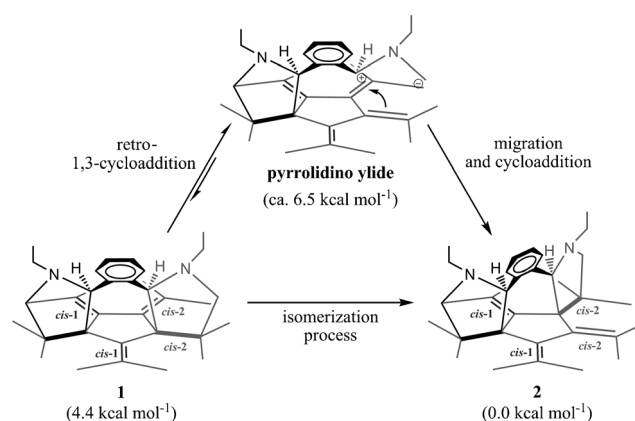

Figure 4. Isomerization of **1** into **2**. One of the two pyrrolidines undergoes a retro-1,3-dipolar-cycloaddition, migrates, and reacts preferentially with the other available *cis*-2 bond to obtain a totally different isolable compound. Two intermediates and three transition states were identified for the transformation from **1** to **2** (Figure S19). The highest-energy point in the profile, at 41 kcal mol^{-1} with respect to **1**, is easily achieved at 180 °C.

proximal *cis*-2 bond results in a totally different compound with drastically different properties. The small amount of pure C_{60} observed corresponds to the unlikely, but not impossible, bis(retro-1,3-dipolar cycloaddition) occurring almost simultaneously. Although the stereogenic carbon centers do not rotate during the isomerization, and thus retain their intrinsic stereochemistry, upon reattachment at the other *cis*-2 position the absolute stereochemistry is inverted (from *SR* to *RS*, Figure 3). Another mechanistic possibility was analyzed and found more unlikely based on their computed energy profiles (Figure S20).

Thermalization of **2** at 180 °C does not lead to **1**, but results in a small amount of pure C_{60}, so most of the compound remains unchanged. Heating **3** under the same conditions gave rise to C_{60} and some uncharacterized insoluble compounds. No isomerization to other compounds was observed.

In conclusion, we successfully prepared, isolated, and characterized three pure [60]fullerene bis(adduct)s, from a double 1,3-dipolar cycloaddition, without using HPLC techniques. This reaction exhibits regio- and diastereoselectivity towards *cis*-1 and *cis*-2 bisadducts. The compounds **1** and **2** are two independent *meso* forms confirmed by X-ray crystallography which have never been isolated before. Although **1** and **2** are very similar structurally, they exhibit very different chemical, physical, and electrochemical properties.

We also observed a unique isomerization of **1** to **2**, which can be accounted for as a consequence of a retro-cycloaddition of one pyrrolidine with subsequent migration and a conformational change of the pyrrolidine ylide intermediate.

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