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Isolation and Characterization of Nine Tris-adducts of *N*-Methylfulleropyrrolidine Derivatives

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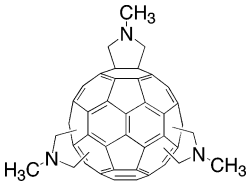

We report the isolation and characterization of bis- and tris-adducts of fulleropyrrolidine derivatives. First, all eight *N*-methyl regioisomers with two addends on the C_{60} sphere have been isolated; second, C_{60} was used as starting material for the synthesis of tris-adducts, and the products formed in detectable quantities have been isolated and characterized. Third, the same compounds were obtained by introducing the third addend on each previously isolated bis-derivative: this approach facilitated the assignment of the relative geometry through chromatographic comparison of the diverse reaction mixtures. Finally, the obtained tris-adducts have been characterized by means of ES-MS, UV−vis, ^{1}H NMR, as well as comparison with UV spectra and elution order of Bingel and Diels−Alder tris-adducts described in the literature.

Introduction

During the last 15 years, the chemistry of fullerene has developed at a fast pace.[1−4] In the initial period, the researchers explored the chemical reactivity of the third allotropic form of carbon; later, attention focused on the synthesis of new derivatives to study the electrochemical,[5,6] spectroscopic,[7−10] and biological[11−14] properties of fullerene and the possibility to modulate these characteristics and their exploitation in medical and material science.[15,16] The cycloaddition reactions have been widely used for these purposes,[17,18] while new reactions continue to be reported.[19]

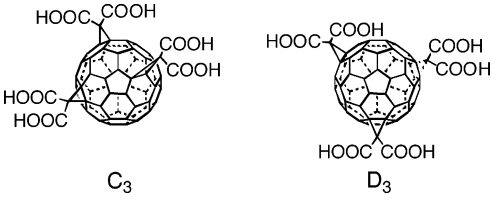

FIGURE 1. Tris-adduct C3 (*equatorial, equatorial, equatorial*) and D3 (*trans*-3, *trans*-3, *trans*-3).

At the beginning, the research was centered on the monofunctionalization of the fullerene and, only later, on the multiple additions, which cause the formation of several regioisomers. The pioneering work to stereochemically define multiple derivatives has been developed by Hirsch and co-workers, who undertook the first extensive work on the isolation and characterization of multiple adducts of C_{60} and reported the first tris-adducts, the so-called C_3 and D_3 (Figure 1),[20] widely used for biomedical purposes.[21−26]

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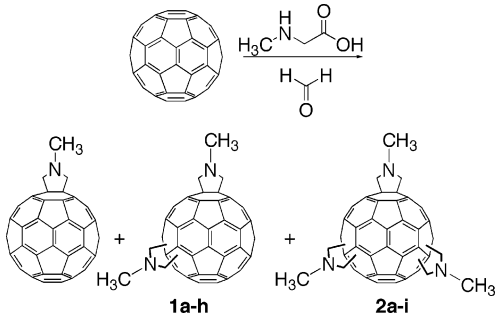
Hirsch and collaborators clarified the addition pattern of multiple cyclopropanation reactions. If two of the 30 double bonds of C_{60} are functionalized with a symmetrical addend, there are eight possible bis-adducts. In particular, if the groups are not sterically demanding, all the products can be observed;[27−30] otherwise, only seven are formed other than *cis*-1,[31−34] although in the Bingel reaction the second addition rather favors *equatorial* and *trans*-3 bis-adducts. In a very elegant approach toward the selective synthesis of polyadducts, different macrocyclic malonate addends were used to obtain the desired bis- and tris-adducts.[35] In the case of tris-adducts, in which three 6−6 bonds have been functionalized, the number of possible regioisomers increases to 46, still considering a symmetrical addend; otherwise, the number of possible isomers is much higher. To date, a limited amount of work[20,31,35−43] has been carried out on such compounds, due to the increased complexity of their separation and characterization. In addition, most of the research has dealt with either Bingel or Diels−Alder reactions, mainly using tethers to direct the regioselectivity.[44] As a result, little is known on the relative yields of tris-adduct formation without steric constrictions, in particular using fullerene functionalization other than cyclopropanation.

SCHEME 1. Synthesis of Mono-, Bis-, and Tris-fulleropyrrolidine Derivatives



We have extensively studied the 1,3-dipolar cycloaddition of azomethine ylides, yielding fulleropyrrolidines.[18,45,46] This reaction presents a remarkably lower selectivity compared to other cycloadditions, thus allowing the formation of a higher number of isomers. Moreover, using the less sterically hindered reagents (HCHO and N-Me-Gly) the possibility exists of formation of isomers otherwise not observed (*cis* positions). Moreover, this reaction gives bis- and tris-adducts, which are coeluted in chromatography due to their extremely similar polarity.[8,27] This event adds more difficulties to the isomer isolation and relative structural assignment. However, we deemed it important to finally attribute the structure to bis- and tris-fulleropyrrolidines, as these molecules are increasingly used and show electronic properties different from those of cyclopropano- and aziridino-fused systems.[47,48]

The main target of the present work is the exploration of the regioselectivity in multiple additions, as well as the investigation of the absorption spectroscopy, due to the change in the conjugation of the π-electron cromophore.[49] We report for the first time the isolation and characterization of nine fulleropyrrolidine tris-analogues, three of which present an addition pattern never observed before.

Results and Discussion

The *N*-methylfulleropyrrolidine bis-adducts were synthesized by reaction of 2 equiv of *N*-methylglycine (sarcosine), 1 equiv of C_{60}, and 10 equiv of HCHO in refluxing toluene for 1 h (Scheme 1).

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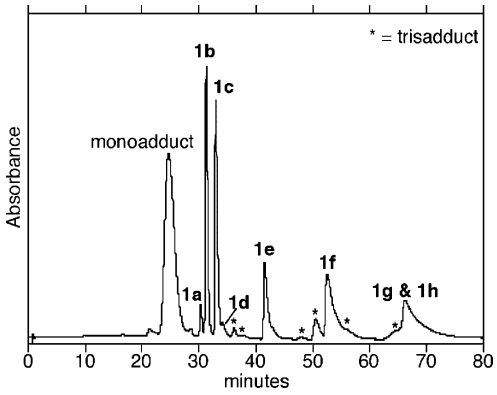

FIGURE 2. HPLC chromatogram of the bis-addition reaction, after 30 min, registered at 320 nm (method A, see the Experimental Section).

The reaction was followed by HPLC, equipped with a diode array detector, which allows UV−vis spectra comparisons. After 30 min, the chromatogram presented one peak for the monoadduct, seven peaks corresponding, respectively, to the isomers *trans*-1, *trans*-2, *trans*-3, *cis*-1, *trans*-4, *equatorial*, *cis*-2 (named **1a**−**g** following the elution order), and tris-adducts in traces (Figure 2).

After 1 h, the reaction mixture appeared too complex to allow the assignment of each peak: electrospray mass spectrometry (ES-MS) analysis revealed the formation of various tris-adducts. In addition, as previously observed,[27] it was not possible to identify the peak corresponding to the *cis*-3 (**1h**), even if the compound was eventually obtained after tedious chromatographic separations. In fact, some isomers have extremely similar polarities: repeated HPLC analysis revealed the coelution of different bis- and tris-adducts combined under the same peak. In certain cases, the UV−vis spectra of the coeluted compounds were similar, so that ES-MS analysis proved essential to unambiguously assign the number of adducts (Figure 3).

All the *N*-methylfulleropyrrolidine bis-adducts were separated by repeated medium-pressure column chromatography, preparative TLC, and further purification by semipreparative HPLC. The eight isomers were isolated and fully characterized by ES-MS, UV−vis, and ^{1}H and ^{13}C NMR and are in accordance with the previously reported data.[8,48] The UV−vis absorption profiles, which are diagnostic for the addition pattern, were identical to those observed for analogue addition patterns, in particular for C_{60} derivatives with five- and six-membered rings.[27,50,51] The number and intensities of the ^{1}H and ^{13}C NMR signals, as well as the elution order, were compatible with the assigned structure symmetry.

Since there has been no systematic study of the structure of bis-adducts of *N*-methylfulleropyrrolidine, we discuss briefly their structural assignments. In its ^{1}H NMR spectrum, compound **1a** displays one singlet at 4.68 ppm for the eight pyrrolidine protons and one singlet at 3.15 ppm for the two methyl groups, consistent with the D_{2h} symmetry of the *trans*-1 isomer, as confirmed by the peculiar UV−vis absorption pattern and by the elution order, as reported in the literature.[8,27,47] Compounds **1b** and **1c** show ^{1}H NMR spectra, ^{13}C NMR spectra, UV−vis absorption pattern, and elution order in agreement with the geometry assigned to isomers *trans*-2 and *trans*-3, respectively.

Compound **1f** is the only bis-adduct possessing a vivid red color. Its ^{13}C NMR spectrum is the only one consistent with the C_s symmetry of an *equatorial* structure, displaying 27 peaks integrating two carbons each and two peaks integrating one carbon each between 135 and 159 ppm. This isomer is also characterized by the relative 90° orientation of the two pyrrolidines, which are nonequivalent and in ^{1}H NMR display one multiplet at 4.01 ppm integrating six protons and one broad singlet at 3.87 ppm integrating 2H; finally, the six nonequivalent methyl protons resonate at 2.80 ppm. The UV−vis absorption pattern and elution order are in agreement with the *equatorial* N-mTEG-fulleropyrrolidine previously characterized.[27] The elution order and the relative yield of **1f** are also consistent with *equatorial* attribution.

The isomer **1h** presents a ^{13}C NMR spectrum with 28 signals integrating two carbons each, reflecting C_2 symmetry, displayed by *trans*-2, *trans*-3, and *cis*-3 isomers. Since the first two have been already identified, the only isomer consistent with the data is the *cis*-3. Indeed, visible spectra comparisons with the *cis*-3 reported by Nishimura[48] corroborate this assignment. Notably, the ^{1}H NMR signals are shifted downfield with respect to the *trans*-2 and *trans*-3 isomers, displaying two doublets at 4.21 and 3.99 ppm and other two doublets at 3.99 and 3.93 ppm.

The NMR spectra of the last three compounds (**1d**, **1e**, and **1g)** display C_s symmetry as expected for *cis*-1, *trans*-

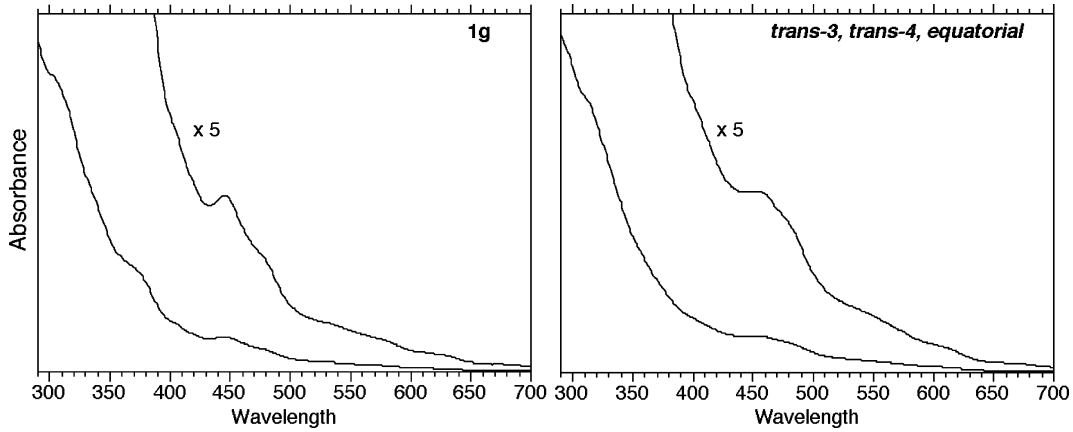

FIGURE 3. UV−vis spectra of compound bis-**1g** (*cis*-2) and tris-**2g** (*trans*-3, *trans*-4, *equatorial*).

4, and *cis*-2. The most abundant is **1e**, which is characterized by an olive green color, in contrast with the brown-orange color generally displayed by the other adducts. Visible spectra comparisons clearly indicate a *trans*-4 geometry: the absorption pattern and elution order are identical to the analogue N-mTEG-bis-fulleropyrrolidine. Isomers **1d** and **1g** also show visible spectra and elution order identical to the N-mTEG-bis-fulleropyrrolidines *cis*-1 and *cis*-2, respectively.[14] The extremely low yield of **1d** is typical of *cis*-1, if we consider that this isomer is the least favored due to steric repulsion between addends.

The 1,3-dipolar cycloaddition of azomethine ylides leads to the formation of not only all the eight possible bis-adducts but also of many tris-derivatives, whose isolation and characterization represent an impressive challenge. If, on one hand, the systematic investigation of bis-addition regioselectivity has been extensively pursued, no work has been carried out on tris-fulleropyrrolidines. The only tris-pyrrolidine derivative isolated so far (*trans*-3, *trans*-3, *trans*-3) has been reported by Rubin and collaborators.[52]

The approach adopted in the present work includes, first, the synthesis and isolation of the bis-adducts using C_{60} as starting material and, second, the introduction of the third group on each previously purified bis-derivative. This has been revealed to be crucial for the geometry assignment, since the reaction is irreversible and thus the positional relationships among addends present in the bis-adduct are preserved in any tris-derived. The addition pattern of the products has been deduced on the basis of the precursor known geometry and verified via analysis of the NMR spectra, which reflect the symmetry of the compounds. In fact, in this sense, there are three possible cases: adducts with all the addends in the same relative position (e.g., *trans*-3, *trans*-3, *trans*-3) which present a 3-fold symmetry; adducts with two addends in the same relative position (e.g., *trans*-3, *trans*-3, *trans*-4) which possess a 2-fold symmetry; and, finally, asymmetrical adducts with the addends in three different positional relationships (e.g., *trans*-3, *trans*-4, *equatorial*). Furthermore, when possible, the data obtained were further verified via comparison of the UV−vis spectra and elution order of Bingel or Diels−Alder tris-derivatives.

The nomenclature of tris-adducts has been adopted from Hirsch et al.[31] Basically, if we call the three addends 1, 2, and 3, the first sterochemical relationship is between 1 and 2, the second between 2 and 3, and the third is between 3 and 1. For example, *trans*-3, *trans*-4, *equatorial* means that addend 1 and 2 are in *trans*-3 relation, 2 and 3 in *trans*-4 relation, and 1 and 3 in *equatorial* relation.

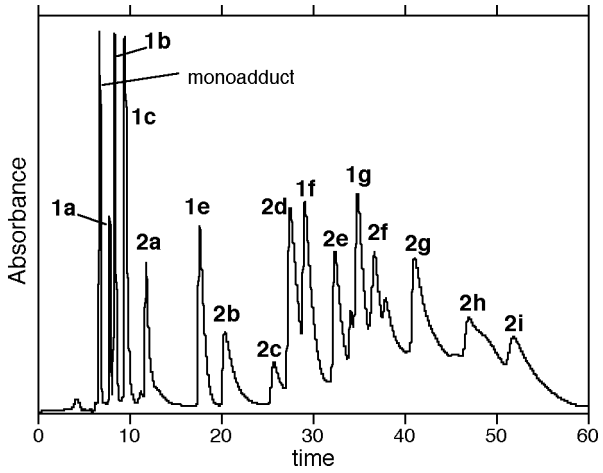

FIGURE 4. HPLC chromatogram of the tris-addition reaction, registered at 320 nm (method B, see the Experimental Section).

The reaction of C_{60} with 3 equiv of *N*-methylglycine and an excess of HCHO in refluxing toluene was followed by HPLC: the crude was very complex, and at least 17 products (bis- and tris-adducts) were detected. We proceeded with the chromatographic separations using repeated columns and preparative TLC in silica gel and eluant mixtures of toluene/ethyl acetate. Nine isomers (named **2a**−**i** after the elution order) were purified, and ES-MS analysis corroborated that all the molecules are *N*-methylfulleropyrrolidine tris-adducts (Figure 4).

Next, we heated each bis-adduct with 1 equiv of *N*-methylglycine and an excess of HCHO in toluene. The reactions proceeded with difficulty compared to reaction with C_{60}. Nonetheless, due to the reduced material availability, the bis-isomers *trans*-1, *cis*-1, and *cis*-3 did not allow the identification of their relative addition tris-products. However, a thorough study of the chromatograms related to the other isomer additions (Figure 5), paying particular attention to the peaks which presented identical retention times and UV−vis spectra in the 400−800 nm range, allowed a first partial assignment of the addition patterns of compounds **2a**−**i**.

Compound **2a** exhibits a cherry red color and can be easily recognized as the *trans*-3, *trans*-3, *trans*-3 already reported by Rubin.[52] The high symmetry of the compound (D_3) is reflected in its NMR spectra. The protons give two singlets, one at 2.85 ppm for the equivalent methyl groups and one broad at 4.06 ppm for the pyrrolidine protons. The C_{60} sp^2 carbons give only nine signals between 160 and 140 ppm, the sp^3 fullerene and pyrrolidine carbons give two signals at 69.40 and 69.20 ppm, and finally the equivalent methyl groups resonate at 42.36 ppm. This isomer is one of the first tris isomers to be formed and shows an extremely similar polarity to the *trans*-4 isomer, which can be easily distinguished by sight, the first being cherry red and the second olive green.

Compound **2b** also shows a vivid red color and was found in the addition reactions carried out on the *trans*-3 and *trans*-4 isomers; thus, two addition patterns are known. The ^1H NMR spectrum highlights a simplicity due to the presence of one plane of symmetry: there are three AB systems (dd) for the pyrrolidines and two

(48) While the present work was already completed, a thorough investigation of formation of *N*-methyl-bis-pyrrolidines has appeared: Nishimura, T.; Tsuchiya, K.; Ohsawa, S.; Maeda, K.; Yashima, E.; Nakamura, Y.; Nishimura, J. *J. Am. Chem. Soc.* **2004**, *126*, 11711−11717.

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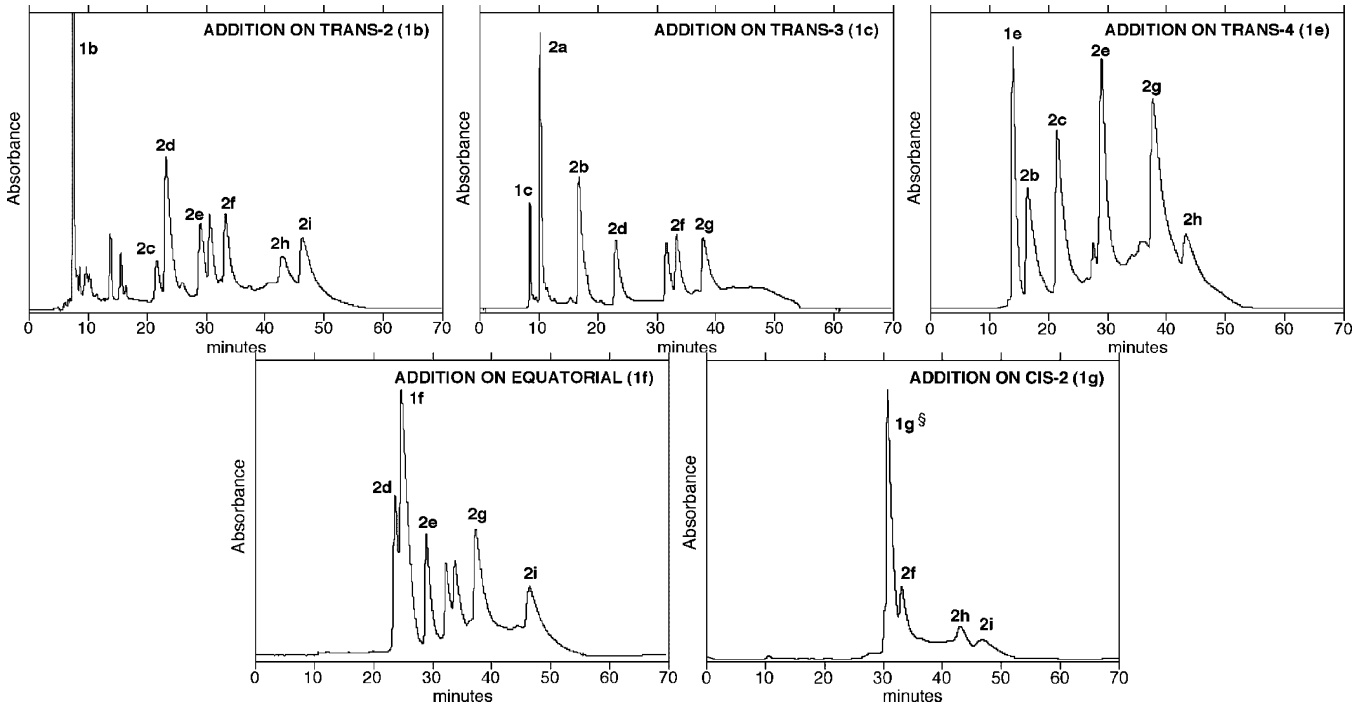

FIGURE 5. HLPC chromatograms of tris-addition on each bis-adduct, registered at 320 nm (program B, see Experimental Section). §The peak, attributed to **1g**, also contains two tris-adducts which are not completed identified. They present, respectively, the *equatorial* and *cis*-2 geometries the first and the *trans*-3 and *cis*-2 geometries the second, but it was not possible to identified the third addition pattern.

singlets for the methyl groups. The only compatible geometry is *trans*-3, *trans*-3, *trans*-4, confirmed via comparison with elution order and UV−vis spectrum of the analogue Bingel derivative (Figure 6).[38]

Compound **2c** is olive green and was found in the reaction mixtures of *trans*-2 and *trans*-4. In this case, the ^{1}H NMR spectrum also reflects the presence of an element of symmetry, being very similar to that of compound **2b**. The only possible addition pattern is *trans*-2, *trans*-4, *trans*-4, in accordance with the data related to the corresponding Bingel tris-adduct.[38]

Compounds **2d**, **2e**, and **2g** are brown-orange and were found in the crudes of *trans*-2, *trans*-3, *equatorial*; *trans*-2, *trans*-4, *equatorial*; and *trans*-3, *trans*-4, *equatorial*, respectively; thus, their geometries are known. The ^{1}H NMR spectra reflect their asymmetry, showing all six AB systems for the pyrrolidine protons and the three singlets for the methyl groups. The elution order and UV−vis spectra of **2d**, **2e**, and **2g** were compatible with the corresponding tris-malonates known in the literature.[38] Surprisingly, in contrast to the cyclopropanation reaction, compound **2d** is the most favored isomer, the only one formed in sufficient quantities to allow ^{13}C NMR analysis, which shows all 54 signals of the C_{60} sp^2 carbons as well as the 15 fullerene and pyrrolidine sp^3 carbons.

Compounds **2f**, **2h**, and **2i** are brown and were immediately identified as the isomers *trans*-2, *trans*-3, *cis*-2; *trans*-2, *trans*-4, *cis*-2; and *trans*-2, *equatorial*, *cis*-2. Their asymmetry is confirmed by their ^{1}H NMR spectra, where the 6 AB systems and the three methyl singlets can be distinguished.

The relative yields of the tris-adducts clearly indicate the favored formation of *trans*-2, *trans*-3, *equatorial* (27%), followed by *trans*-3, *trans*-4, *equatorial* (13%), and by the tris-adducts displaying a *cis*-2 addition pattern (approximately 10% each). This result is not very surprising if we consider that the azomethine ylide 1,3-dipolar cycloaddition is less chemoselective compared to cyclopropanation, as already reported.[47] Furthermore, it is well-known that addends on the *cis*-2 position are favored by the HOMO−LUMO coefficients, but such derivatives are not generally recovered if the groups are sterically demanding: the choice for small molecules such as HCHO and *N*-methylglycine for our study proved essential for their isolation.

Conclusions

N-Methylfulleropyrrolidine bis-adducts constitute a series of isomers whose polarity is extremely similar, as the groups introduced on the C_{60} sphere are small and do not display particularly polar functional groups. Their separation is a task also complicated by other factors, mainly the coformation and coelution of diverse tris-adducts. Here, we have reported the isolation and characterization of the complete series. Higher adducts have become a topic of great interest, and until now, all of the work conducted on tris-derivatives has concentrated on Bingel or Diels−Alder functionalizations. For the first time, nine fulleropyrrolidine tris-adducts have been purified and unambiguously characterized, including three isomers (*trans*-2, *trans*-3, *cis*-2; *trans*-2, *trans*-4, *cis*-2; and *trans*-2, *equatorial*, *cis*-2) which possess an addition pattern never described before for fullerene adducts. The most abundant product is the asymmetrical *trans*-2, *trans*-3, *equatorial*, in accordance with the diverse regioselectivity already noticed for the azomethine ylide 1,3-dipolar cycloaddition compared to cyclopropanation.[47]

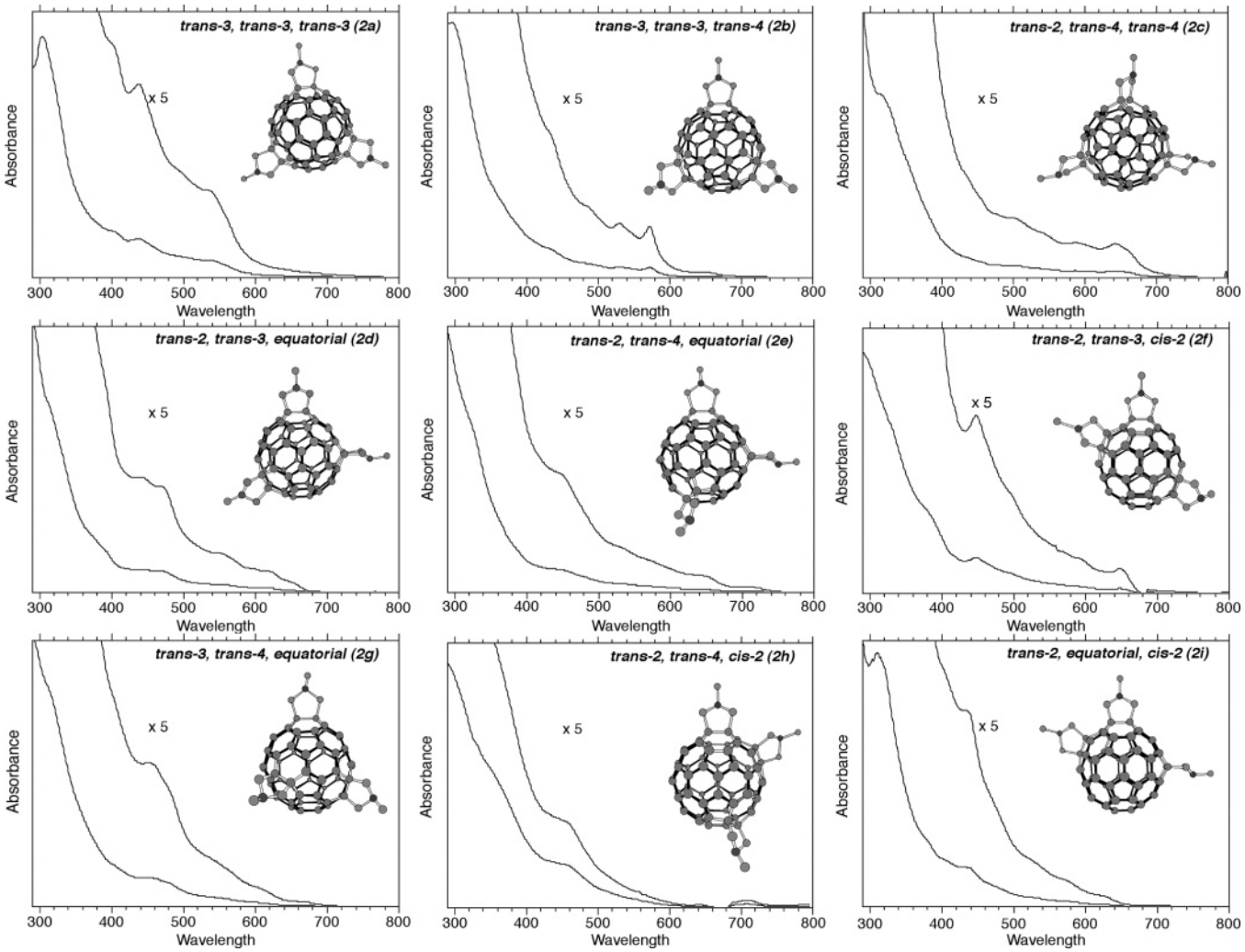

FIGURE 6. Tris-adduct models and UV−vis spectra.

Visible spectra comparisons were a very useful tool for addition pattern assignment, and the absorption profiles in the range of 400−800 nm have proved to be independent from the nature of the addend and distinctive of the geometry of each isomer, as long as the C_{60} derivatives present five- or six-membered rings. Therefore, we suggest the use of the UV−vis spectra of the tris-pyrrolidines (Figure 6) as a reference for future geometry attribution on tris-adducts presenting five- or six-membered rings.

Experimental Section

Materials and Methods. To record electrospray mass spectra, compounds were dissolved in THF/MeOH 1/1 solutions unless otherwise noted. The NMR spectra have been recorded in $CDCl_3$ solutions, unless otherwise stated. TMS has been used as internal standard, and chemical shifts are given in parts per million (ppm) relative to that of tetramethylsilane. The HPLC analysis was conducted with a Phenomenex Prodigy 5 μm silica 100 Å column for the direct-phase purifications.

Synthesis of *N*-Methyl-bis-fulleropyrrolidines. A solution of 1.00 g of C_{60} (1.38 mmol), 0.25 g of *N*-methylglycine (2.78 mmol), and 0.21 g of formaldehyde (6.94 mmol) in 700 mL of toluene was heated to reflux for 1 h. The reaction was followed by HPLC, using the following elution program A: t = 0 min, toluene 100%, flow 0 mL/min; t = 3 min, toluene 100%, flow 1 mL/min; t = 33 min, toluene/ethyl acetate 1/4, flow 1 mL/min; t = 83 min, toluene 100%, flow 1 mL/min; t = 86 min, toluene 100%, flow 0 mL/min

Retention time: monoadduct, 23 min; *trans*-1, 30 min; *trans*-2, 31 min; *trans*-3, 32 min; *cis*-1, 34 min; *trans*-3, *trans*-3, *trans*-3, 35 min; *trans*-4, 38 min; *equatorial*, 53 min; *cis*-2 and *cis*-3, 66 min. The solution was concentrated under reduced pressure, and bis- and tris-adducts were purified from unreacted C_{60} and monoadduct by medium-pressure column chromatography on silica gel (0.063−0.200 mm), eluting with toluene. C_{60} and the monoadduct are precipitated by CS_2/MeOH and dried under vacuum. The monoadduct (0.49 g, 0.63 mmol) was then dissolved in 250 mL of toluene with *N*-methylglycine (56.3 mg, 0.63 mmol) and formaldehyde (37.9 mg, 1.26 mmol). The reaction was followed by HPLC using the previously reported program A. All the bis- and tris-adducts were separated by medium-pressure column chromatography on fine silica gel (0.015−0.04 mm), eluting with toluene/petroleum ether 4/1, toluene, then toluene/ethyl acetate, and finally toluene/methanol. Bis-adducts *trans*-1, *trans*-2, *trans*-3, and *cis*-1 eluted with toluene/petroleum ether 4/1; *trans*-4 and the tris *trans*-3, *trans*-3, *trans*-3 eluted with toluene/ethyl acetate 9/1; bis-adducts *equatorial*, *cis*-2, *cis*-3 eluted with toluene/ethyl acetate 85/15; finally, higher adducts elute with toluene/methanol 1/1. Bis-adducts *trans*-1, *trans*-2, *trans*-3, and *cis*-1 were separated through a medium-pressure column chromatography on fine silica gel (0.015−0.04 mm), using a mixture of toluene/ethyl acetate 99/1. The impure fractions were further separated by semipreparative HPLC eluting with toluene/ethyl acetate 85/15 (t_R: *trans*-1, 22 min; *trans*-2, 24 min; *trans*-3, 28 min; *cis*-1, 29 min). Bis-adduct *trans*-4 (green) was separated from tris-adduct *trans*-

3, *trans*-3, *trans*-3 (cherry red) by a preparative TLC in CH_2Cl_2. The fractions with the *equatorial* and *cis*-2 were separated by repeated column chromatography on fine silica gel (0.015−0.04 mm) eluting first with 100% toluene and then adding ethyl acetate until reaching 10%. Finally, *cis*-3 isomer (retention time 25 min) was separated by semipreparative HPLC using the following eluting program with a constant flow of 1 mL/min: t = 0 min, toluene/2-propanol 49/1; t = 10 min, toluene/2-propanol 49/1; t = 11 min, toluene/2-propanol 9/1; t = 26 min, toluene/2-propanol 9/1; t = 27 min, toluene/2-propanol 49/1.

Each bis-adduct was dissolved in CS_2, precipitated with acetone, washed with MeOH, and dried under vacuum.

1a: *trans*-1 *N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 0.6% (1.0 mg, 0.012 mmol); ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.68 (s, 8H), 3.15 (s, 6H); UV−vis (cyclohexane) λ_{max} 246, 330 (sh), 457, 491, 712, as reported by Lu et al.[47]

1b: *trans*-2 *N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 24.4% (35 mg, 0.042 mmol); ES-MS *m/z* 834 (M^+), 417 (M^{2+}); ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.64 (d, J = 9.2 Hz, 2H), 4.46 (d, J = 8.8 Hz, 2H), 4.35 (d, J = 6.6 Hz, 2H), 4.30 (d, J = 6.5 Hz, 2H), 3.05 (s, 6H); its low solubility did not allow ^{13}C NMR analysis; UV−vis (cyclohexane) λ_{max} 245, 262 (sh), 310 (sh), 428, 474, 650, 722.

1c: *trans*-3 *N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 18.5% (26 mg, 0.031 mmol); ES-MS *m/z* 834 (M^+); ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.42 (d, J = 9.1 Hz, 2H), 4.33 (d, J = 9.1 Hz, 2H), 4.17 (d, J = 9.3 Hz, 2H), 4.07 (d, J = 9.2 Hz, 2H), 2.94 (s, 6H); ^{13}C NMR (50 MHz) δ 158.0 (2C), 155.5 (2C), 155.4 (2C), 154.7 (2C), 152.6 (2C), 149.0 (2C), 148.7 (2C), 148.6 (2C), 148.1 (2C), 148.1 (2C), 146.5 (2C), 145.2 (2C), 145.1 (2C), 145.0 (2C), 145.0 (2C), 144.8 (2C), 144.5 (2C), 143.6 (2C), 143.5 (2C), 142.4 (2C), 141.5 (2C), 141.3 (2C), 141.1 (2C), 140.9 (2C), 139.7 (2C), 138.4 (2C), 136.3 (2C), 135.4 (2C), 70.4 (2C), 70.1 (2C), 70.1 (2C), 69.2 (2C), 41.6 (2C); UV−vis (cyclohexane): λ_{max} 246, 411 (sh), 463, 486 (sh), 640 (br), 695.

1d: *cis*-1 *N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 0.6% (0.9 mg, 0.0011 mmol); ES-MS *m/z* 834 (M^+), 418 ($MH^+/2$); ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.22 (d, J = 8.7 Hz, 4H), 4.03 (d, J = 8.5 Hz, 2H), 3.61 (d, J = 9.8 Hz, 2H), 2.85 (s, 6H); UV−vis (cyclohexane) λ_{max} 246, 330 (sh), 429, 648, 714. Its low yield did not give enough material for ^{13}C NMR analysis.

1e: *trans*-4 *N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 17.8% (25 mg, 0.030 mmol);. ES-MS *m/z* 834 (M^+); ^{1}H NMR (200 MHz, $CDCl_3/CS_2$) δ 4.29 (d, J = 9.2 Hz, 2H), 4.16 (d, J = 9.2 Hz, 2H), 4.08 (m, 4H), 2.88 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3/CS_2$) δ 154.2 (2C), 152.3 (2C), 151.1 (2C), 150.6 (1C), 150.3 (2C), 149.4 (1C), 148.9 (2C), 148.0 (2C), 147.6 (2C), 147.3 (1C), 147.1 (2C), 146.0 (2C), 145.8 (4C), 145.3 (2C), 144.7 (2C), 144.7 (2C), 144.3 (2C), 143.1 (1C), 142.4 (2C), 141.9 (2C), 141.5 (2C), 141.5 (2C), 141.1 (2C), 141.0 (2C), 138.9 (2C), 138.4 (2C), 135.9 (2C), 135.2 (2C), 131.0 (2C), 70.0 (2C), 69.7 (2C), 69.5 (2C), 69.3 (2C), 41.4 (2C); UV−vis (cyclohexane) λ_{max} 225, 241, 265, 306, 411 (sh), 450, 639, 705.

1f: *equatorial N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 35.0% (50 mg, 0.060 mmol); ES-MS *m/z* 835 (MH^+); ^{1}H NMR (200 MHz) δ 4.01 (m, 6H), 3.87 (s, 2H), 2.79 (s, 6H); ^{13}C NMR (50 MHz) δ 158.7 (2C), 153.2 (2C), 152.7 (2C), 152.5 (2C), 149.6 (1C), 148.7 (2C), 147.9 (2C), 147.9 (1C), 147.5 (2C), 147.0 (2C), 147.0 (2C), 146.5 (2C), 146.4 (2C), 145.6 (2C), 145.0 (2C), 144.8 (2C), 144.5 (2C), 144.5 (2C), 144.2 (2C), 143.5 (2C), 143.1 (2C), 142.1 (2C), 141.6 (2C), 141.5 (2C), 141.3 (2C), 140.5 (2C), 139.0 (2C), 136.6 (2C), 135.4 (2C), 70.2 (2C), 69.9 (2C), 69.5 (2C), 69.0 (2C), 41.6 (1C), 41.4 (1C); UV−vis (cyclohexane) λ_{max} 241, 256 (sh), 316, 422, 440 (sh).

1g: *cis*-2 *N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 1.7% (2.5 mg, 0.0030 mmol); ES-MS *m/z* 835 (MH^+); ^{1}H NMR (200 MHz) δ 3.93 (m, 4H), 3.77 (m, 4H), 2.78 (s, 6H); UV−vis (cyclohexane) λ_{max} 241, 256, 316, 446, 712, 743.

1h: *cis*-3 *N*-methyl-bis-fulleropyrrolidine; $C_{66}H_{14}N_2$ (MW 834.852); relative yield 1.4% (2 mg, 0.0024 mmol); ES-MS *m/z* 835 (MH^+); ^{1}H NMR (200 MHz) δ 4.21 (d, J = 9.2 Hz, 2H), 3.99 (d, J = 9.5 Hz, 2H), 3.99 (d, J = 9.5 Hz, 2H), 3.93 (d, J = 9.5 Hz, 2H), 2.85 (s, 6H); ^{13}C NMR (50 MHz) δ 151.8 (2C), 149.7 (2C), 149.0 (2C), 148.5 (2C), 148.3 (2C), 148.0 (2C), 147.5 (2C), 146.9 (2C), 146.2 (2C), 145.9 (2C), 145.7 (2C), 145.4 (2C), 145.4 (2C), 145.4 (2C), 145.1 (2C), 145.0 (2C), 144.7 (2C), 142.1 (2C), 142.1 (2C), 141.8 (2C), 141.7 (2C), 141.3 (2C), 139.7 (2C), 138.5 (2C), 136.7 (2C), 135.0 (2C), 134.0 (2C), 130.3 (2C), 71.4 (2C), 69.9 (2C), 69.8 (2C), 66.1 (2C), 41.5 (2C); UV−vis (cyclohexane) λ_{max} 241, 256 (sh), 316, 462, 560 (br), 654, 720.

Synthesis of *N*-Methyl-tris-fulleropyrrolidines. From C_{60}. A solution of 1.00 g of C_{60} (1.38 mmol), 0.37 g of *N*-methylglycine (4.17 mmol), and 0.42 g of formaldehyde (13.9 mmol) in 700 mL of toluene was heated to reflux for 1 h and followed by TLC in toluene/ethyl acetate 4/1 as well by HPLC (program A). The solution was concentrated under reduced pressure, and bis- and tris-adducts were purified from unreacted C_{60} and monoadduct by medium-pressure column chromatography on silica gel, eluting with toluene. All the bis-adducts were separated using the same methodology previously described: due to the complexity of the isomers mixture, it is necessary to separate the bis-adducts first. The cherry red **2a** (*trans*-3, *trans*-3, *trans*-3) was found in the fraction containing the bis-isomer *trans*-4 (green) from which it can be separated by preparative TLC in CH_2Cl_2. Compounds **2b** (*trans*-3, *trans*-3, *trans*-4), **2c** (*trans*-2, *trans*-4, *trans*-4), and **2d** (*trans*-2, *trans*-3, equatorial) were contained in the same fraction as the *equatorial* bis-adduct. They were separated by HPLC in toluene/ethyl acetate 85/15 (t_R: **2b**, 46 min; **2c**, 55 min; **2d**, 59 min).

Compounds **2e** (*trans*-2, *trans*-4, *equatorial*), **2f** (*trans*-2, *trans*-3, *cis*-2), **2g** (*trans*-3, *trans*-4, equatorial), **2h** (*trans*-2, *trans*-4, *cis*-2), and **2i** (*trans*-2, *equatorial*, *cis*-2) were eluted together with bis-adducts *cis*-2 and *cis*-3. They were separated by HPLC using the following eluting program B with a constant flow of 1 mL/min: t = 0 min, toluene/ethyl acetate 4/1; t = 20 min, toluene/ethyl acetate 4/1; t = 40 min, toluene/ethyl acetate 7/3; t = 52 min, toluene/ethyl acetate 4/1. t_R: **2e**, 29 min; **2f**, 34 min; **2g**, 38 min; **2h**, 43 min; **2i**, 46 min.

From *N*-Methyl-bis-fulleropyrrolidines. A solution of 10 mg of each *N*-methylfulleropyrrolidine bis-adduct ($1.2\cdot10^{-2}$ mmol), 1.07 mg of *N*-methylglycine ($1.2\cdot10^{-2}$ mmol), and 3.60 mg of formaldehyde ($1.2\cdot10^{-1}$ mmol) in 5 mL of toluene (*o*-dichlorobenzene for *trans*-1 and *trans*-2 isomers) was heated to reflux overnight and followed by TLC in toluene/ethyl acetate 4/1. The solution was concentrated under reduced pressure, and tris-adducts were purified from unreacted bis-adduct by medium-pressure column chromatography on fine silica gel (0.015−0.040 mm), eluting with toluene/ethyl acetate 95/5. Both the fraction with the products and the fraction with the unreacted bis-adduct were analyzed by HPLC using the eluting program B. Retention times: **2a**, 10 min; **2b**, 17 min; **2c**, 22 min; **2d**, 23 min; **2e**, 29 min; **2f**, 34 min; **2g**, 38 min; **2h**, 43 min; **2i**, 46 min. *Equatorial* and *cis*-2 bis-adducts were eluted together with tris-adducts and therefore were separated through careful repeated semipreparative HPLC.

2a: *N*-methyl-tris-fulleropyrrolidine *trans*-3, *trans*-3, *trans*-3; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 4.6% (2.7 mg, 0.003 mmol); ES-MS *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.06 (s, 12H), 2.85 (s, 9H); ^{13}C NMR (50 MHz) δ 158.20 (6C), 155.9 (6C), 152.0 (6C), 149.3 (6C), 148.5 (6C), 144.4 (6C), 142.9 (6C), 140.5 (6C), 69.4 (6C), 69.2 (6C), 42.4 (3C); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 440, 490 (br), 538.

2b: *N*-methyl-tris-fulleropyrrolidine *trans*-3, *trans*-3, *trans*-4; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 5.5% (3.2 mg, 0.004

mmol); ES-MS *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.22 (d, 2H), 4.15 (d, 2H), 4.08 (d, 2H), 4.00 (d, 2H), 3.89 (m, 4H), 2.87 (s, 3H), 2.77(s, 6H); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 475 (sh), 530, 572.

2c: *N*-methyl-tris-fulleropyrrolidine *trans*-2, *trans*-4, *trans*-4; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 8.6% (5.0 mg, 0.006 mmol); ES-MS *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.28 (d, J = 8.8 Hz, 2H), 4.23 (d, J = 13.2 Hz, 4H), 4.33 (d, J = 8.8 Hz, 2H), 3.99 (d, J = 10.9 Hz, 2H), 3.90 (d, J = 10.9 Hz, 2H), 2.91 (s, 6H), 2.76 (s, 3H); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 503, 591, 644.

2d: *N*-methyl-tris-fulleropyrrolidine *trans*-2, *trans*-3, *equatorial*; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 27.0% (15.7 mg, 0.018 mmol); ES-MS (THF−MeOH 1:1) *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.38 (d, J = 9.4 Hz, 1H), 4.32 (d, J = 9.4 Hz, 1H), 4.31 (d, J = 9.4 Hz, 1H), 4.19 (d, J = 11.0 Hz, 1H), 4.10 (d, J = 11.1 Hz, 1H), 4.01 (d, J = 8.0 Hz, 1H), 3.92 (d, J = 7.8 Hz, 1H), 3.89 (d, J = 9.5 Hz, 1H), 3.85 (m, 2H), 3.80 (m, 2H), 2.96 (s, 3H), 2.81 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (50 MHz) δ 161.5 (1C), 161.1 (1C), 159.5 (1C), 156.5 (1C), 156.1 (1C), 154.0 (1C), 153.2 (1C), 153.1 (1C), 152.6 (1C), 151.6 (1C), 151.5 (1C), 151.4 (1C), 151.0 (1C), 150.4 (1C), 150.2 (1C), 149.5 (1C), 149.1 (1C), 149.0 (1C), 148.8 (1C), 148.5 (1C), 148.3 (1C), 148.3 (1C), 148.0 (1C), 147.3 (1C), 147.1 (1C), 146.9 (1C), 146.4 (1C), 146.3 (1C), 146.0 (1C), 145.9 (1C), 145.7 (1C), 145.6 (1C), 145.0 (1C), 144.4 (1C), 144.1 (1C), 143.7 (1C), 143.7 (1C), 143.4 (1C), 142.7 (1C), 142.2 (1C), 141.8 (1C), 141.8 (1C), 141.5 (1C), 141.4 (1C), 141.2 (1C), 141.2 (1C), 140.8 (1C), 140.6 (1C), 140.3 (1C), 139.8 (1C), 139.7 (1C), 139.5 (1C), 133.5 (1C), 132.7 (1C), 70.0 (1C), 69.9 (1C), 69.9 (1C), 69.6 (1C), 69.5 (1C), 69.4 (1C), 69.1 (1C), 68.93 (1C), 69.0 (1C), 68.7 (1C), 68.4 (1C), 41.8 (1C), 41.7 (1C), 41.5 (1C); UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 441, 475 (sh), 554 (br), 618.

2e: *N*-methyl-tris-fulleropyrrolidine *trans*-2, *trans*-4, *equatorial*; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 7.2% (4.2 mg, 0.005 mmol); ES-MS *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.38 (d, J = 11.1 Hz, 2H), 4.17 (d, J = 11.1 Hz, 2H), 4.12 (m, 2H), 4.03 (m, 2H), 3.94 (m, 4H), 2.89 (s, 3H), 2.88 (s, 3H), 2.76 (s, 3H); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 455, 540 (br), 655, 709.

2f: *N*-methyl-tris-fulleropyrrolidine *trans*-2, *trans*-3, *cis*-2; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 10.2% (5.9 mg, 0.007 mmol); ES-MS *m/z* 893 (MH_2^+); ^{1}H NMR (400 MHz) δ 4.51 (d, J = 11.7 Hz, 1H), 4.31 (d, J = 9.8 Hz, 1H), 4.07 (m, 4H), 3.92 (m, 2H), 3.77 (d, J = 11.7 Hz, 1H), 3.60 (m, 2H), 3.48 (d, J = 9.8 Hz, 1H), 2.94 (s, 3H), 2.78 (s, 3H), 2.70 (s, 3H); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 448, 649.

2g: *N*-methyl-tris-fulleropyrrolidine *trans*-3, *trans*-4, *equatorial*; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 13.4% (7.8 mg, 0.009 mmol); ES-MS *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.12 (m, 2H), 4.04 (m, 2H), 3.84 (m, 4H), 3.72 (m, 4H), 2.81 (s, 3H), 2.79 (s, 3H), 2.70 (s, 3H); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 307, 457 (br).

2h: *N*-methyl-tris-fulleropyrrolidine *trans*-2, *trans*-4, *cis*-2; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 5.8% (3.4 mg, 0.004 mmol); ES-MS *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.37 (d, J = 9.2 Hz, 1H), 4.29 (d, J = 9.5 Hz, 1H), 4.08 (d, J = 9.2 Hz, 1H), 3.95 (m, 4H), 3.82 (m, 4H), 3.66 (d, J = 9.2 Hz, 1H), 2.91 (s, 3H), 2.82 (s, 3H), 2.72 (s, 3H); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 460, 642, 709.

2i: *N*-methyl-tris-fulleropyrrolidine *trans*-2, *equatorial*, *cis*-2; $C_{69}H_{21}N_3$ (MW 891.956); relative yield 11.0% (6.4 mg, 0.007 mmol); ES-MS *m/z* 893 (MH^+); ^{1}H NMR (400 MHz) δ 4.16 (d, J = 6.8 Hz, 2H), 4.98 (d, J = 9.2 Hz, 1H), 3.94 (d, J = 9.2 Hz, 1H), 3.84 (m, 2H), 3.66 (m, 4H), 3.57 (d, J = 11.4 Hz, 1H), 3.39 (d, J = 11.44 Hz, 1H), 2.80 (s, 6H), 2.65 (s, 3H); the low amount of obtained compound did not allow recording of the ^{13}C NMR spectrum; UV−vis (CH_2Cl_2) λ_{max} 225, 241, 265, 306, 440.

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