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First Isolation and Characterization of Eight Regioisomers for [60]Fullerene–Benzyne Bisadducts

Yosuke Nakamura,[†] Nobutoshi Takano,[†] Tatsuya Nishimura,[‡] Eiji Yashima,[‡] Mitsuo Sato,[†] Takako Kudo,[†] and Jun Nishimura*,[†]

Department of Chemistry, Gunma University, Tenjin-cho, Kiryu, Gunma 376-8515, Japan, and Department of Molecular Design and Engineering, Graduate School of Engineering, Nagoya University, Chikusa-ku, Nagoya 464-8603, Japan

nisimura@chem.gunma-u.ac.jp

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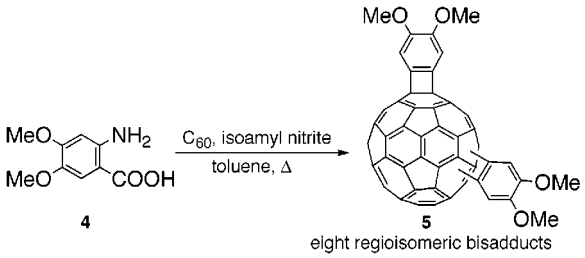
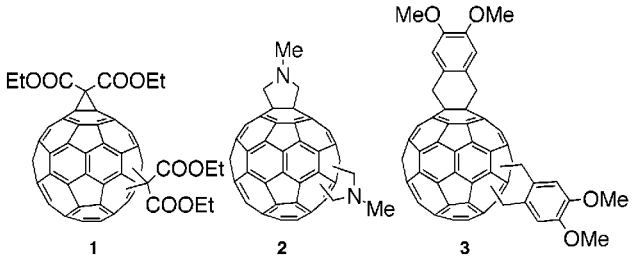
ABSTRACT



The [2 + 2] cycloaddition between [60]fullerene and benzyne generated from 4,5-dimethoxyanthranilic acid (4) afforded bisadducts 5 along with the monoadduct. All of the eight possible regioisomers were first isolated by HPLC and then characterized on the basis of MS, NMR, UV–vis, and CD spectroscopies.

Bisadditions at [6,6]-junctions of [60]fullerene enable eight regioisomers in principle, whose preparation and isolation have attracted much attention recently.[1] For some typical bisadducts, such as Bingel−Hirsch **1**,[2] Prato **2**,[3] and *o*-quinodimethane **3**,[4] a series of regioisomers were successfully



isolated by various chromatographic techniques and characterized on the basis of NMR, UV−vis, and other spectroscopic methods.[5] Although the second addition processes in these reactions proceeded with insufficient regioselectivity, the regioisomer distribution of bisadducts was qualitatively correlated with the coefficients of frontier orbitals in the corresponding monoadducts; *e* and *trans*-3 bisadducts were generally formed preferentially among the eight isomers. In contrast, *cis*-1 bisadduct was absent in all three cases. This observation is readily explained by the lower thermodynamic stability of *cis* bisadducts due to the steric hindrance between the two addends.[2b] Therefore, it is meaningful to examine

[†] Gunma University.
[‡] Nagoya University.

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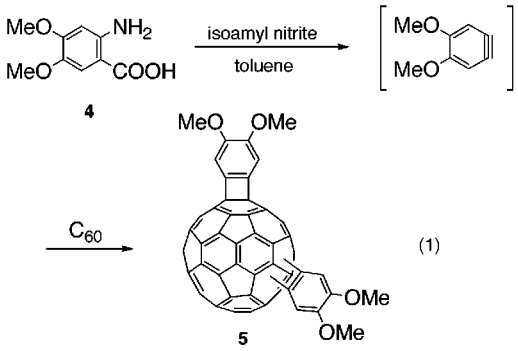
the bisaddition suffering from less steric hindrance, to correlate the experimental results with theoretical calculation more closely. Benzyne species, which are known to add to [60]fullerene by [2 + 2] cycloaddition,[6] appear to be candidates for such addends. While [60]fullerene−benzyne monoadducts were reported by several research groups,[6] the corresponding bisadducts are unknown to the best of our knowledge. Thus, we were prompted to investigate the bisaddition of 4,5-dimethoxybenzyne generated from **4**. The purification of the reaction mixture by preparative HPLC resulted in the successful isolation and identification of all eight regioisomeric bisadducts **5**. Here, we report the regioselectivity in the bisaddition using **4** and the spectroscopic properties of **5** and compare them with those of other bisaddition products.

A mixture of [60]fullerene, benzyne precursor **4** (4 equiv), and isoamyl nitrite (4 equiv) was refluxed in toluene for 30 min (eq 1). Purification by column chromatography on silica



gel (eluent: toluene → toluene/AcOEt) afforded a regioisomeric mixture of bisadducts **5** in 18%, after the elution of unchanged [60]fullerene (17%) and the monoadduct[6d] (20%). These bisadducts **5** were further subjected to preparative HPLC using a Develosil RPFULLERENE column (eluent: toluene/acetonitrile (1:3 (v/v)) in a manner similar to that for bisadducts **3**.[4] As shown in Figure 1, seven peaks (**5a**−**g**) were detected and each fraction was repeatedly collected.

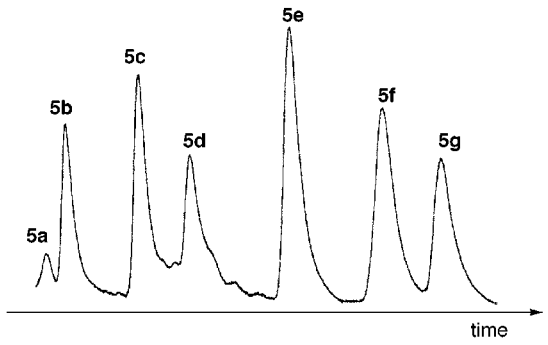


Figure 1. HPLC chromatogram of regioisomeric bisadducts **5**. Conditions: stationary phase, Develosil RPFULLERENE column (20 × 250 mm); eluent, toluene/acetonitrile (1:3 (v/v)); flow rate, 10 mL/min; detection, UV 335 nm.

The structures of **5a**−**g** were characterized by MS, ^{1}H and ^{13}C NMR, and UV−vis spectroscopy. **5a**−**g** all clearly indicated the molecular ion peak (m/z = 992) corresponding to the desired bisadduct in FAB-MS spectra. Their ^{1}H NMR spectra were quite simple; only the singlet peaks of aromatic and methoxy protons were observed, as summarized in Table 1.

Table 1. ^{1}H NMR Spectral Data of Bisadducts **5a**−**h**[a]

compd	δ (Ar)	δ (OMe)
5a	7.69 (4H)	4.19 (12H)
5b	7.65 (2H), 7.56 (2H)	4.17 (6H), 4.14 (6H)
5c	7.62 (2H), 7.37 (2H)	4.15 (6H), 4.04 (6H)
5d	7.48 (2H), 7.33 (2H)	4.09 (6H), 4.02 (6H)
5e	7.40 (1H), 7.33 (2H), 7.20 (1H)	4.05 (3H), 4.02 (6H), 3.96 (3H)
5f	7.33 (2H), 7.29 (2H)	4.05 (6H), 3.99 (6H)
5g	7.50 (2H), 7.26 (2H)	4.16 (6H), 4.00 (6H)
5h	7.35 (2H), 7.26 (2H)	3.96 (6H), 3.93 (6H)

[a] Measured in $CDCl_3$, except for **5h** in CD_2Cl_2, at room temperature.

The ^{1}H NMR spectrum of **5a** exhibits a quite high symmetry as demonstrated by only two singlets corresponding to the equivalent 4 aromatic and 12 methoxy protons. This observation apparently indicates the D_{2h}-symmetrical *trans*-1 bisadduct. The number of ^{13}C NMR peaks also supports this addition pattern. In the ^{1}H NMR spectrum of **5e**, both aromatic and methoxy protons were observed as three singlet peaks with an integral ratio of 2:1:1. This spectral pattern can be accomplished from only the *e* bisadduct with C_s symmetry in which the mirror plane contains one of the two benzene rings. Its ^{13}C NMR spectrum, in which 38 sp^2 carbon peaks are observed, is also compatible with this addition pattern. On the other hand, **5b**−**d**, **5f**, and **5g** afforded two aromatic and two methoxy proton peaks, suggesting C_s or C_2 symmetry. Their addition sites, however, cannot be determined only by consideration of symmetry, since C_s symmetry can result from the *cis*-1, *cis*-2, and *trans*-4 and C_2 symmetry from *cis*-3, *trans*-3, and *trans*-2 bisadducts.[7]

The characterization of these bisadducts was established on the basis of the order of chromatographic elution, the order of chemical shifts in ^{1}H NMR spectra, the comparison of UV−vis spectra, and the optical resolution.

In the separation of regioisomeric mixture of **3** using the same HPLC column, the bisadducts were eluted in the order *trans*-1, *trans*-2, *trans*-3, *trans*-4, *e*, *cis*-2, and *cis*-3.[4] This elution order apparently corresponds to the positional

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(7) Although the total number of the [60]fullerene sp^2 carbon peaks is theoretically different in case of C_2 (28 signals) and C_s (30 signals) symmetry, it was difficult to distinguish between C_2 and C_s due to the overlapping of some peaks.

relationship between the two addition sites, except for *cis*-2 and *cis*-3; the regioisomers with addends at more remote positions were eluted in fractions with shorter retention times. Since bisadducts **5** carry *o*-dimethoxybenzene moieties similar to those of **3**, and **5a** and **5e** were assigned as *trans*-1 and *e*, respectively, as described above, it is reasonable to tentatively assign **5b**, **5c**, and **5d** as *trans*-2, *trans*-3, and *trans*-4, respectively, and **5f** and **5g** as *cis*-1, *cis*-2, or *cis*-3.

The order of chemical shifts in the ^{1}H NMR of bisadducts has been also available for determining the addition sites, since it is closely related to the relative position of addition sites.[3] Both aromatic and methoxy protons of **3** were deshielded in the order *trans*-1, *trans*-2, *trans*-3, *trans*-4, and *e*.[4] This tendency, ascribable to the curvature of the fullerene surface, was also observed in both **1** and **2** including the *cis*-3 isomer.[3] As shown in Table 1, the deshielding in both aromatic and methoxy protons of **5** decreases from **5a** to **5f**, although **5g** has rather deshielded protons. These observations support the assignment described above. The large deshielding in **5g** is likely to suggest the *cis*-2 addition pattern, since the aromatic protons of some of the *cis*-2 *o*-quinodimethane bisadducts prepared so far are remarkably deshielded due to the steric compression effect.[8] According to the molecular mechanics calculations, the two inner aromatic protons in the *cis*-2 isomer of **5** are located within 2.2 Å. Such situations cannot be accomplished in the other regioisomers, even in the *cis*-3 or *cis*-1 isomer. Furthermore, the ring current effect of benzene rings is also expected to induce a low-field shift of the inner aromatic and methoxy protons in the *cis*-2 isomer.

Additional evidence for the assignment of **5g** was provided by its UV−vis spectrum (Figure 2), which is quite similar to that of the *cis*-2 *o*-quinodimethane bisadducts in the literature.[4,8] This similarity proves the *cis*-2 addition mode in **5g**, since the UV−vis spectra of [60]fullerene bisadducts are known to be generally dependent on the addition patterns. The spectra of the other regioisomers of **5** except for **5e**, namely, **5a**, **5b**, **5c**, and **5d**, also resemble those of the *trans*-1, -2, -3, and -4 isomers, respectively, of **2** and **3**.

The remaining isomer **5f**, which is either *cis*-1 or *cis*-3, was identified as the former on the basis of the following observations. The UV−vis spectrum of **5f**, showing a sharp band around 430 nm, is quite similar to those of *cis*-1 bisadducts in the literature, such as diepoxy[60]fullerene[9] and bisadducts by nitrile oxide and azomethine ylide,[10] while obviously different from those of the *cis*-3 bisadducts reported previously, which generally afford the longest absorption band extending up to more than 750 nm.[8] The results of optical resolution are also compatible with this assignment. Among the bisadducts **5**, *trans*-2, *trans*-3, and *cis*-3 are chiral with a C_2 symmetry. The optical resolution of **5b** (*trans*-2) and **5c** (*trans*-3) was successful by using a CHIRALPAK AD column (eluent: hexane/ethanol (9:1 (v/v)), to give two distinct peaks. The CD spectra of the respective peaks displayed mirror images to each other, undoubtedly indicating the enantiomeric relationship. These spectra also resemble those of *trans*-2 and *trans*-3 *o*-quinodimethane bisadducts.[4] On the contrary, **5f** has not been separated into two peaks despite attempts under various conditions, though *cis*-3 bisadducts such as *o*-quinodimethane bisadducts[8a,11] and Bingel−Hirsch bisadducts[12] were enantiomerically separated in most cases. Therefore, it is reasonable to assign **5f** as *cis*-1 rather than *cis*-3. Of course, the chiral HPLC analysis of achiral **5e** (*e*) and **5g** (*cis*-2) with C_s symmetry afforded only a single peak.

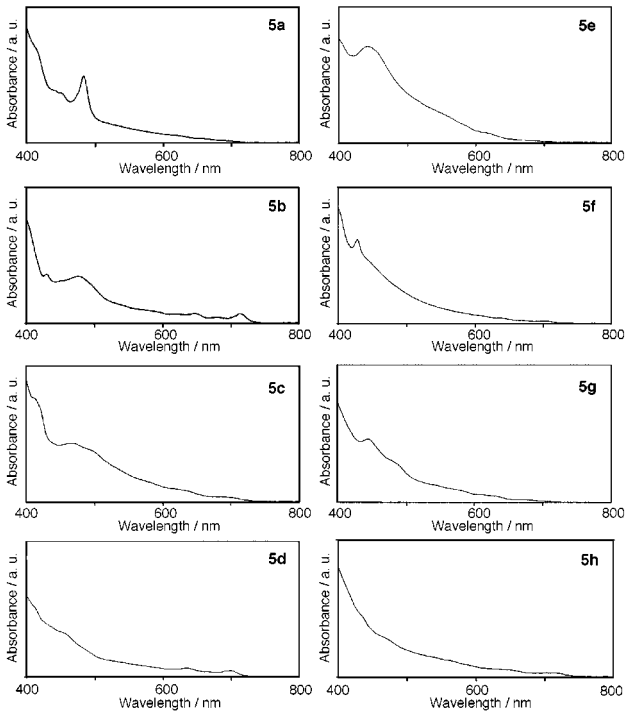

Figure 2. UV−vis spectra of **5a**−**h** in chloroform at room temperature.

At this stage, seven isomers (except for *cis*-3) were isolated and fully identified. Thus, in search of this isomer, the sum of fractions from **5f** to **5g** of the HPLC chromatogram in Figure 1 was further analyzed by gel permeation chromatography (GPC) (eluent: chloroform). A small peak was detected before the two main peaks, corresponding to **5f** and **5g**. This fraction (**5h**) was repeatedly collected and characterized in a manner similar to that used above. Similar to **5a**−**g**, the FAB-MS spectrum of **5h** gave a molecular ion peak of $m/z = 992$. Two aromatic and two methoxy proton peaks in the ^{1}H NMR suggest C_s or C_2 symmetry. Its UV−vis spectrum exhibits absorption bands around 740 nm, characteristic of *cis*-3 bisadducts. Furthermore, the enantio-

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meric separation of **5h** was accomplished under conditions similar to those in **5b** and **5c**. The CD spectra of the respective fractions are almost superimposable on the mirror images of each other, indicating the enantiomeric relationship. The spectral shapes, such as bands around 720 nm, are also analogous to those of *cis*-3 bisadducts reported in the literature.[11,12] These spectroscopic behaviors apparently demonstrate the *cis*-3 addition pattern in **5h**. In the HPLC chromatogram, the peak of **5h** appears to be hidden in those of **5f** and **5g** or between them due to its low intensity. On the basis of the peak area ratio of **5f** (*cis*-1), **5g** (*cis*-2), and **5h** (*cis*-3) in the GPC chromatogram and that of **5a**−**g** in HPLC (Figure 1), the regioisomeric ratio of *trans*-1, *trans*-2, *trans*-3, *trans*-4, *e*, *cis*-3, *cis*-2, and *cis*-1 was finally determined as 1:12:15:10:25:3:14:20.

In summary, all possible regioisomers of [60]fullerene−benzyne bisadducts, **5a**, **5b**, **5c**, **5d**, **5e**, **5f**, **5g**, and **5h**, were isolated and assigned as *trans*-1, *trans*-2, *trans*-3, *trans*-4, *e*, *cis*-1, *cis*-2, and *cis*-3, respectively. Figure 3 illustrates a comparison of regioselectivity in the formation of benzyne bisadducts **5** with those in the Bingel−Hirsch (**1**) and *o*-quinodimethane bisaddition (**3**). The regioselectivity for **5** is remarkably different from those in other bisadditions. The ratio of *cis* isomers in **5** is much larger than that in **1** or **3**. Noticeably, *cis*-1 isomer was obtained in the ratio of 20% second to the *e* isomer, whereas no *cis*-1 isomers were obtained from **1**−**3**. The increased ratio for *cis* isomers is apparently ascribed to the less steric hindrance in the flat addends of **5**. Consequently, the regioselectivity for **5** is roughly in agreement with the coefficients of frontier orbitals, especially HOMO, of the monoadduct. A detailed mechanistic analysis of this reaction on the basis of MO calculations is now in progress. The UV−vis spectrum of each isomer of **5** possessing four-membered rings is analogous to that of **2** and **3** with five- and six-membered rings, respectively, rather than **1** with three-membered rings, indicating the similarity of electronic properties among **2**, **3**, and **5**.

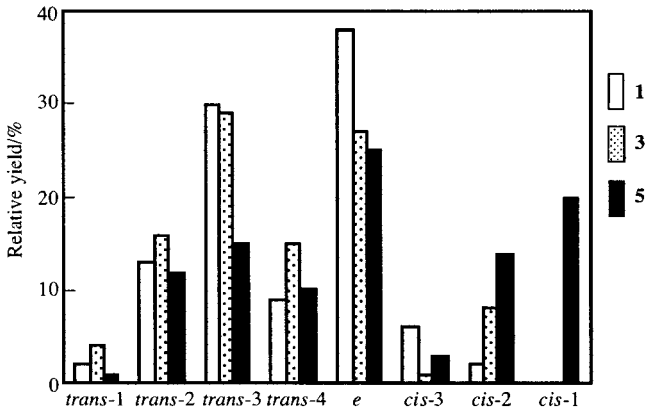

Figure 3. Comparison of regioselectivity in the formation of bisadducts **1**, **3**, and **5**.

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Supporting Information Available: Preparation and spectroscopic data of bisadducts **5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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