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Preparation and identification of bis(formylmethano)[60]-fullerene isomers: the first systematic study on bifunctionalized [60]fullerenes with dissymmetric addends

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Abstract—Fourteen isomers of bis(formylmethano)C_{60} were isolated and characterized. A mixture of the bisadducts was obtained by the reaction of C_{60} with an α-formylsulfonium ylide, and then separated into 15 fractions by preparative HPLC, preparative TLC, and recycling preparative HPLC. Fourteen of the fifteen fractions were found to consist of a single isomer, respectively, which were assigned to the *trans*-2 (3 diastereo-isomers), *trans*-3 (3 diastereo-isomers), *trans*-4 (3 diastereo-isomers), *equatorial* (2 diastereo-isomers), and *cis*-2 (3 diastereo-isomers) bisadducts by the comparison of their UV/vis spectra with those of the bisadducts obtained by the Bingel–Hirsch reaction. The ^{1}H and ^{13}C NMR analysis, the transformation of the formyl groups, and the dipole moment calculation clarified the stereochemistry of the substituents on the two cyclopropane bridge-head carbons (*in*/*in*, *in*/*out*, and *out*/*out*).

Bifunctionalized [60]fullerenes (C_{60}s) are of special attention as versatile building blocks of C_{60}-containing materials.[1] In general, separation and identification of bifunctionalized C_{60}s require considerable effort, because a large number of regio- and diastereo-isomers may be produced by the bisaddition reaction of C_{60}, in which as much as 30 equivalent [6,6] double bonds potentially participate in the reaction. A series of bisadducts with a different addition pattern can be prepared by a tandem C_{60} functionalization, followed by the chromatographic separation of the resultant mixture of the regio- and diastereo-isomers.[2] Although the method is not advantageous in terms of the yield and the isolation efficiency, the thorough investigation of such a series of regio- and diastereo-isomers is of significant importance; their chemical, physical, and spectroscopic properties are very valuable as reliable 'fingerprints' for the anticipation of the properties and the identification of other bifunctionalized C_{60}s, especially obtained by tether-directed reactions which often result in regio- and/or diastereo-selective bifunctionalization.

To date, systematic investigations have been conducted for several series of bisadducts of C_{60}, including the products of the double Bingel reaction (the Bingel–Hirsch reaction) and those of the double Prato reaction.[2] As far as we know, however, only C_{2v} symmetric addends have been utilized in these reports most likely in order to avoid complexity arising from the relative orientation of two addends; for bifunctionalized C_{60}s, eight regio-isomers are possible due to a variety of the positions of the bisaddition on the [6,6] junctions of C_{60} (*trans*-1, *trans*-2, *trans*-3, *trans*-4, *equatorial*, *cis*-3, *cis*-2, and *cis*-1), and furthermore two or three diastereo-isomers are possible for each of the eight bisadducts with respect to the relative orientation of the addends (*in*/*in*, *in*/*out*, and *out*/*out*).[3] Although the isolation and characterization of these isomers are very important as reliable references for bifunctionalized C_{60}s, there are few reports on the separation and identification of diastereo-isomers. Here, we report the first systematic study on C_{60} bisadducts with dissymmetric addends, bis(formylmethano)C_{60}s.

Among nucleophilic addition reactions to the [6,6] junction of C_{60} reported so far, we selected the cyclopropanation with an α-formylsulfonium ylide, which has been recently developed as a versatile method for the preparation of 2,2-[60]fullerenoalkanals,[4] for the present study

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Keywords: Bifunctionalization; Diastereo-isomer; α-Formylsulfonium ylide; Fullerene; Regio-isomer.

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with the following expectations: (i) The proper dipole moment of the formyl group would bring difference in polarity between the bisadducts to make the chromatographic separation of regio- and diastereo-isomers easier. (ii) The ^{1}H NMR signal of the formyl group (–C*H*O), which is usually observed at a highly down field almost without overlapping with other peaks, would be a suitable probe for the determination of the addition pattern and orientation of two addends in the bisadducts. (iii) Taking into account the fact that the bridge-head carbon of methano[60]fullerenes possesses sp^{2} character to some extent, the proton of the formyl group and the C_{60} core are connected with partially conjugated bonds so that the chemical shift of the formyl signal would efficiently sense the environment of the C_{60} core.

The α-formylsulfonium ylide **1** possessing an octyl group was synthesized and utilized for the bisaddition to C_{60}, according to the method we previously reported:[4] The sulfonium ylide **1** (2.5 equiv) was allowed to react with C_{60} in toluene (Scheme 1), and the resultant mixture was successively subjected to silica gel column chromatography and gel permeation column chromatography to afford four fractions of unreacted C_{60} (trace), the monoadduct (**2**, 51%), a mixture of the bisadducts (**3**, 34%), and a mixture of polyfunctionalized C_{60}s possessing more than two addends. Further separation of **3** on a preparative HPLC (nakalai COSMOSIL 5PBB) gave five fractions (F1–F5, Table 1). Each of the five fractions was then subjected to preparative TLC to give fourteen fractions (F1-1–F5-2). Because the ^{1}H NMR and HPLC studies clearly showed that F4-1 contained two isomers, F4-1 was subjected to recycling preparative HPLC (Japan Analytical Industry, Co., JAIGEL-SIL-SH) to give two fractions, F4-1-1 and F4-1-2. All of the products in the fractions gave a simple ^{1}H NMR spectrum with one set of signals, respectively, indicating that each fraction was composed of one isomer or a few isomers with quite similar character (**3a**–**o**, Table 1).

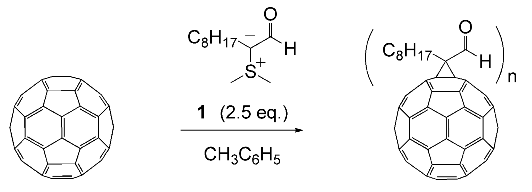
Table 1. Chromatographic separation of the C_{60} bisadducts **3**

Fraction[a]			Compound	Isolated yield/%	Ratio/%[b]
1	1-1		**3a**	0.2	0.5
	1-2		**3b**	1.9	5.2
2	2-1		**3c**	2.7	7.4
	2-2		**3d**	3.4	9.3
	2-3		**3e**	1.0	2.7
3	3-1		**3f**	2.9	7.9
	3-2		**3g**	1.3	3.6
	3-3		**3h**	0.9	2.5
	3-4		**3i**	8.1	22.2
	3-5		**3j**	7.7	21.1
4	4-1	4-1-1	**3k**	3.4	9.3
		4-1-2	**3l**	0.5	1.3
	4-2		**3m**	1.0	2.7
5	5-1		**3n**	0.6	1.6
	5-2		**3o**	0.9	2.5

[a] The fraction was numbered in the order of chromatographic elution. For the procedure of separation, see the text.

[b] The relative yield of each product.

The comparison of the UV/vis spectra of the isomers thus obtained in a range of 400–700 nm with those of the isomers of bis[bis(ethoxycarbonyl)methano]C_{60} (the Hirsch bisadducts) made the addition pattern of the isomers definite, because each isomer gave a UV/vis spectrum very similar to that of one of the seven regio-isomers of the Hirsch bisadducts (Table 2).[2a,5] At first, the regiochemistry of **3a** was confirmed to be *trans*-1. Other 12 kinds of isomers (**3b**–**i**, **3l**–**o**) were classified into four groups of three isomers, and the groups were assigned to the *trans*-2, *trans*-3, *trans*-4, and *cis*-2 bisadducts, respectively. Moreover, the remaining two isomers were identified to be the *equatorial* bisadducts (**3j** and **3k**). For each of these addition patterns, one diastereo-isomer was selected as a representative isomer and characterized by ^{13}C NMR, which was in good agreement with the theoretically expected symmetry (**3a**, **3b**, **3d**, **3e**, **3j**, and **3o**).[5,6] Thus, in the present biscyclopropanation, at least 15 isomers were found to be produced among 22 isomers driven theoretically on the basis of eight possible addition patterns (*trans*-1, *trans*-2, *trans*-3, *trans*-4, *equatorial*, *cis*-3, *cis*-2, and *cis*-1) and relative orientation of the formyl groups (*in*/*in* and *in*/*out* diastereo-isomers for the *trans*-1 bisadduct; *in*/*in*, *in*/*out*, and *out*/*out* diastereo-isomers for the *trans*-2, *trans*-3, *trans*-4, *cis*-3, *cis*-2, and *cis*-1 bisadducts; *in*/*out* and *out*/*out* diastereo-isomers for the *equatorial* bisadduct). Worth to note is that no fraction was assigned to the *cis*-1 and *cis*-3 bisadducts. The absence of the *cis*-1 bisadduct in the resultant mixture would be reasonably explained by considering the fact that *cis*-1 bisaddition hardly takes place in the biscyclopropanation of C_{60} because of the steric hindrance between the two addends. Although the reason for no production of the *cis*-3 bisadduct is unclear at present, the *cis*-3 bisadduct would be hardly generated due to the characteristic chemoselectivity of the biscyclopropanation of C_{60} with sulfonium ylides.[2]



n = 0:	Unreacted	trace
n = 1:	Monoadduct (**2**)	51%
n = 2:	Bisadducts (**3**)	34%
n ≧ 3:	Multiadducts (**4**)	

Scheme 1. Cyclopropanation of C_{60} with the α-formylsulfonium ylide **1**.

In the next stage, we attempted to assign the relative stereochemistry of the formyl groups at the bridge-head carbons of the diastereo-isomers on the basis of the symmetry deduced from the ^{1}H NMR spectra (Table 2).[5]

For each regio-isomer with an addition pattern of *trans*-2, *trans*-3, *trans*-4, and *cis*-2, there existed two diastereo-isomers with C_2/C_s symmetry and one diastereo-isomer with C_1 symmetry, which are in good agreement with

Table 2. Assignment of the C_{60} bisadducts **3**

Compound	Addition pattern (UV/vis)	Orientation	Symmetry	^{1}H NMR[a] δ/ppm	Intramolecular double imination[b]	Dipole moment[c], μ calcd/debye	Elution time[d] /min
3a	*trans*-1	*in/out*	C_{2h}	10.81			
	trans-1	*in/in*	C_{2v}				
3g	*trans*-2	*out/out*	C_2	10.87		0.4621	15.68
3c	*trans*-2	*in/out*	C_1	10.46, 10.86			
3b	*trans*-2	*in/in*	C_2	10.46		0.8097	16.22
3f	*trans*-3	*out/out*	C_2	10.58		0.0113	15.46
3i	*trans*-3	*in/out*	C_1	10.39, 10.57			
3d	*trans*-3	*in/in*	C_2	10.39		0.5717	15.63
3l	*trans*-4	*out/out*	C_s	10.48	No	0.5110	15.79
3h	*trans*-4	*in/out*	C_1	10.39, 10.47			
3e	*trans*-4	*in/in*	C_s	10.36	Yes	0.9383	17.38
3k	*equatorial*	*out/out*	C_1	10.44, 10.45	No		
3j	*equatorial*	*in/out*	C_1	10.18, 10.42	Yes		
3n	*cis*-2	*out/out*	C_s	10.21	No	1.1239	16.86
3m	*cis*-2	*in/out*	C_1	10.11, 10.20			
3o	*cis*-2	*in/in*	C_s	10.10	Yes	1.7711	17.90

[a] The chemical shift(s) of the ^{1}H NMR signal(s) of the formyl groups.

[b] The bis-imine formation was attempted by using the *trans*-4-(*out*/*out*), *trans*-4-(*in*/*in*), *equatorial*-(*in*/*out*), *equatorial*-(*in*/*in*), *cis*-2-(*out*/*out*), and *cis*-2-(*in*/*in*) isomers. For the reaction conditions, see the text.

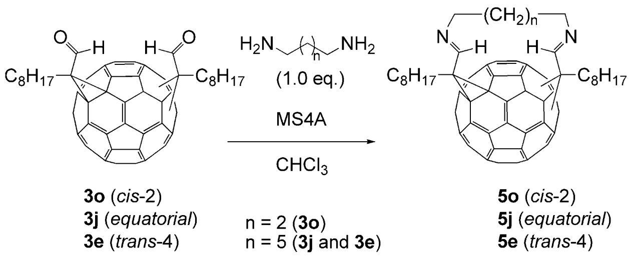
[c] Dipole moment calculated for an energy-minimized structure by the AM1 method. In order to simplify the calculation, the octyl group was substituted with a methyl group.

[d] Column, Merck LiChrosorb Si 60 (250 × 4 mm); eluent, toluene; flow rate, 1.0 mL/min.

the theoretical expectation. Among them, the diastereo-isomers with C_1 symmetry could be unequivocally assigned to the *in*/*out* diastereo-isomers (**3c**, **3h**, **3i**, and **3m**). However, we could not deduce the relative stereochemistry of the diastereo-isomers with C_2/C_s symmetry on the basis of their ^{1}H NMR spectra (**3b**, **3d**, **3e**, **3f**, **3g**, **3l**, **3n**, and **3o**). Moreover, the stereochemistry of the two isomers of the *equatorial* bisadducts (**3j** and **3k**) could not be assigned, because they were equally C_1 symmetric. On the other hand, the product in F1-1 (**3a**) was assigned to be *trans*-1, although two diastereo-isomers are possible for this addition pattern (*trans*-1-(*in*/*in*) and *trans*-1-(*in*/*out*)). Selective formation of either of the two isomers was unlikely to occur, considering the fact that all of the possible diastereo-isomers were generated in the cases of the other addition patterns. Therefore, **3a** was most likely to be a mixture of two isomers, *trans*-1-(*in*/*in*) and *trans*-1-(*in*/*out*), of which the physical properties, such as polarity and chemical shifts of the resonances in ^{1}H and ^{13}C NMR spectroscopies, would be very similar to each other.

For the structural assignment of the bisadducts, of which two formyl groups are located closely to each other, such as the *cis*-2, *equatorial* and *trans*-4 bisadducts, we applied the transformation of the formyl groups to imino groups as a probe.[3] It was generally expected for each of these addition patterns that the distance between the two formyl groups of the *out*/*out* diastereo-isomer is obviously longer than that of the *in*/*in* diastereo-isomer. This means that a diamine with a proper molecular length would form the corresponding intramolecularly bis-iminated product with the *in*/*in* diastereo-isomer while the diamine would not afford such a bis-iminated product with the *out*/*out* diastereo-isomer. The molecular modeling of the *in*/*in* and *out*/*out* diastereo-isomers was conducted for each of the *cis*-2, *equatorial*, and *trans*-4 addition patterns, which indicates that the intramolecular bis-imine formation is possible only for the *in*/*in* isomer, when 1,4-diaminobutane (for the *cis*-2 bisadducts) or 1,7-diaminoheptane (for the *equatorial* and *trans*-4 bisadducts) is used as the linker; the length of the diamine is too short to intramolecularly connect the two formyl groups of the *out*/*out* isomer.

On the basis of the prediction as described above, two diastereo-isomers of the *cis*-2 bisadducts, **3n** and **3o** were allowed to react with 1,4-diaminobutane in the presence of MS4A, respectively (Scheme 2). The products were directly monitored by MALDI-TOF-MS spectroscopy, because the imines thus produced would be not so stable to be easily hydrolyzed. For the reaction mixture of **3o** with 1,4-diaminobutane, a very strong molecular ion peak was observed at $m/z = 1081.91$, which is in good agreement with the calculated value



Scheme 2. Intramolecular double imination of the *cis*-2, *equatorial*, and *trans*-4 bisadducts **3o**, **3j**, and **3e**.

for the intramolecularly double iminated product (**5o**, calcd for $[M+H]^+$ $C_{84}H_{45}N_2$, $m/z = 1081.36$). In contrast, in the case of the reaction mixture of **3n** with 1,4-diaminobutane, the ion peak corresponding to the intramolecularly double iminated product (**5n**) was quite weak in intensity. Therefore, **3n** and **3o** could be assigned to be the *cis*-2-(*out*/*out*) and *cis*-2-(*in*/*in*) isomers, respectively. Under the same conditions 1,7-diaminoheptane in the place of 1,4-diaminobutane was allowed to react with the diastereo-isomers of the *equatorial* (**3j** and **3k**) and *trans*-4 (**3e** and **3l**) bisadducts, respectively. For each of the two addition patterns, one diastereo-isomer (**3j** and **3e** for the *equatorial* and *trans*-4 addition patterns, respectively) was found to have a high propensity to form the intramolecularly double iminated product (**5j** and **5e**), whereas the other diastereo-isomer (**3k** and **3l** for the *equatorial* and *trans*-4 addition patterns, respectively) sluggishly afforded the corresponding product. Therefore, **3l**, **3e**, **3k**, and **3j** were assigned to be the *trans*-4-(*out*/*out*), *trans*-4-(*in*/*in*), *equatorial*-(*in*/*out*), and *equatorial*-(*in*/*in*) bisadducts, respectively.

The methods for the assignment of *in*/*in* and *out*/*out* diastereo-isomers described above would be unsuitable for the identification of the bisadducts, of which the cyclopropane rings are placed at relatively remote positions (the *in*/*in* and *out*/*out* isomers of the *trans*-2 and *trans*-3 bisadducts). Therefore, in order to assign the diastereo-isomers of the bisadducts, the chromatographic elution order was compared with their calculated dipole moments, which has been generally utilized for the assignment of C_{60} bisadducts.[2,7] Dipole moments were calculated for the energy-minimized structures of all the isomers (AM1, Table 2). For all of the bisadducts with C_2/C_s symmetry, (the *in*/*in* and *out*/*out* diastereo-isomers of the *trans*-2, *trans*-3, *trans*-4, and *cis*-2 addition patterns), the dipole moments of the *in*/*in* isomers were larger than those of the *out*/*out* isomers with the same addition pattern, indicating that there was high correlation between the orientation of the formyl groups and the dipole moment. In addition, the elution order of the *in*/*in* and *out*/*out* diastereo-isomers of the *trans*-4 and *cis*-2 bisadducts was in good agreement with the order of the calculated dipole moment; the fact strongly supports the assignment on the basis of the elution order. Thus, the identification of the *in*/*in* and *out*/*out* diastereo-isomers of the *trans*-2 and *trans*-3 could be achieved, as shown in Table 2.

From the ^1H NMR data in Table 2, the following general rules might be driven: (i) The ^1H NMR chemical shift of the formyl signal strongly influenced by the addition pattern and its orientation, but the orientation of the other formyl group has little influence. (ii) The formyl group taking the *in* orientation gives an upfield-shifted signal, compared to the signal of the formyl group with the *out* orientation. For example, the *trans*-2-(*in*/*out*) isomer (**3c**) showed ^1H NMR signals of the formyl groups at 10.46 and 10.86 ppm, which were quite near to the chemical shifts of the corresponding signals of the *trans*-2-(*in*/*in*) and *trans*-2-(*out*/*out*) isomers (**3b** and **3g**, 10.46 and 10.87 ppm, respectively). This tendency is plausibly explained in terms of the ring-current effect of the C_{60} core being the determinant factor for the ^1H NMR chemical shift of the formyl proton.[2]

In conclusion, we prepared and characterized bis(formylmethano)C_{60}, of which the bridge-head carbon was substituted in a dissymmetric manner. Fourteen isomers could be isolated as a diastereomerically pure form. Their addition pattern could be assigned by the comparison of their UV/vis spectra with those of the bisadducts from the Bingel–Hirsch reaction. In terms of the relative stereochemistry of the substituents on the bridge-head carbons, assignments were made on the basis of ^1H NMR spectroscopy, chemical reactivity, and the comparison of the chromatographic elution order with the order of the calculated dipole moments. The data of the isomers obtained here would contribute to the development and application of novel bifunctionalized C_{60}s, especially to the identification of the addition pattern and the relative orientation of the addends.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.10.027.

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5. For the spectroscopic data of **3a**–**o** (^1H and ^{13}C NMR, and UV/vis spectra), see Supplementary data.
6. As the representative isomer of each addition pattern, an isomer with the highest symmetry was chosen in order to know the inherent symmetry of the C_{60} moiety.
7. The retention time was measured by loading each of the isolated isomers on a HPLC column packed with silica gel (Merck LiChrosorb Si 60) by using toluene as an eluent. The elution order thus obtained is not necessarily consistent with the order of the fraction number in Table 1, because the process for the isolation of these isomers involved the chromatography on a nakalai COSMOSIL 5PBB; the stationary phase of this column is silica gel modified with pentabromobenzyl groups. Therefore, the elution time might be not only reflected by the dipole moment of the C_{60} bisadducts but also influenced by other factors, such as the π–π interaction between the C_{60} bisadducts and the stationary phase.