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Systematic Enantiomeric Separation of [60]Fullerene Bisadducts Possessing an Inherent Chiral Addition Pattern

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The optical resolution of *trans*-2 and *trans*-3 [60]fullerene bisadducts with an inherent chiral addition pattern, modified by Bingel reaction, cycloaddition by benzyne, Prato reaction, and cycloaddition by *o*-quinodimethane, was systematically investigated by using chiral HPLC columns (Chiralcel OD and Chiralpak AD). The chiroptical properties of enantiomers separated were also examined.

Introduction

The preparation and characterization of [60]fullerene bisadducts have attracted increasing interest in the field of fullerene chemistry.[1−6] A series of regioisomers were isolated and characterized for some typical bisadducts, although bisadditions generally proceed with low regioselectivity to give seven or eight regioisomers.[1−6] Several research groups independently accomplished regioselective synthesis of bisadducts using tether-constraint strategies.[7−11] The electronic and photophysical properties characteristic of the resulting bisadducts have been also disclosed.[12−16] These properties were generally dependent on the addition sites rather than the nature of addends. Among bisadducts, *cis*-3, *trans*-3, and *trans*-2 regioisomers have a chirality on the π-system of fullerene chromophore derived from their addition pattern, even though two identical, achiral addends are introduced. For some of these bisadducts, enantiomeric separation of racemates was successful, and the CD spectra of resolved enantiomers (^{f}A and ^{f}C) were reported.[17−20] Enantiopure *cis*-3 bisadducts were also obtained by using a tether-constraint method.[20−24] The assignments of absolute configuration were also accomplished for some bisadducts on the basis of comparison between the theoretical and experimental CD spectra.[25,26] Among chiral bisadducts, there seem to be limited examples on the enantiomeric separation and chiroptical properties of *trans*-3 and *trans*-2 isomers relative to that of *cis*-3,[17] although they gather much interest in recent years in not only organic chemistry but also physical chemistry. Recently, we have successfully resolved *trans*-3 and *trans*-2 isomers of *o*-quinodimethane- (**4a**,**b**)[5] and benzyne-modified bisadducts (**2a**,**b**)[6] by using chiral HPLC columns (Chiralcel OD and/or Chiralpak AD). Thus, we

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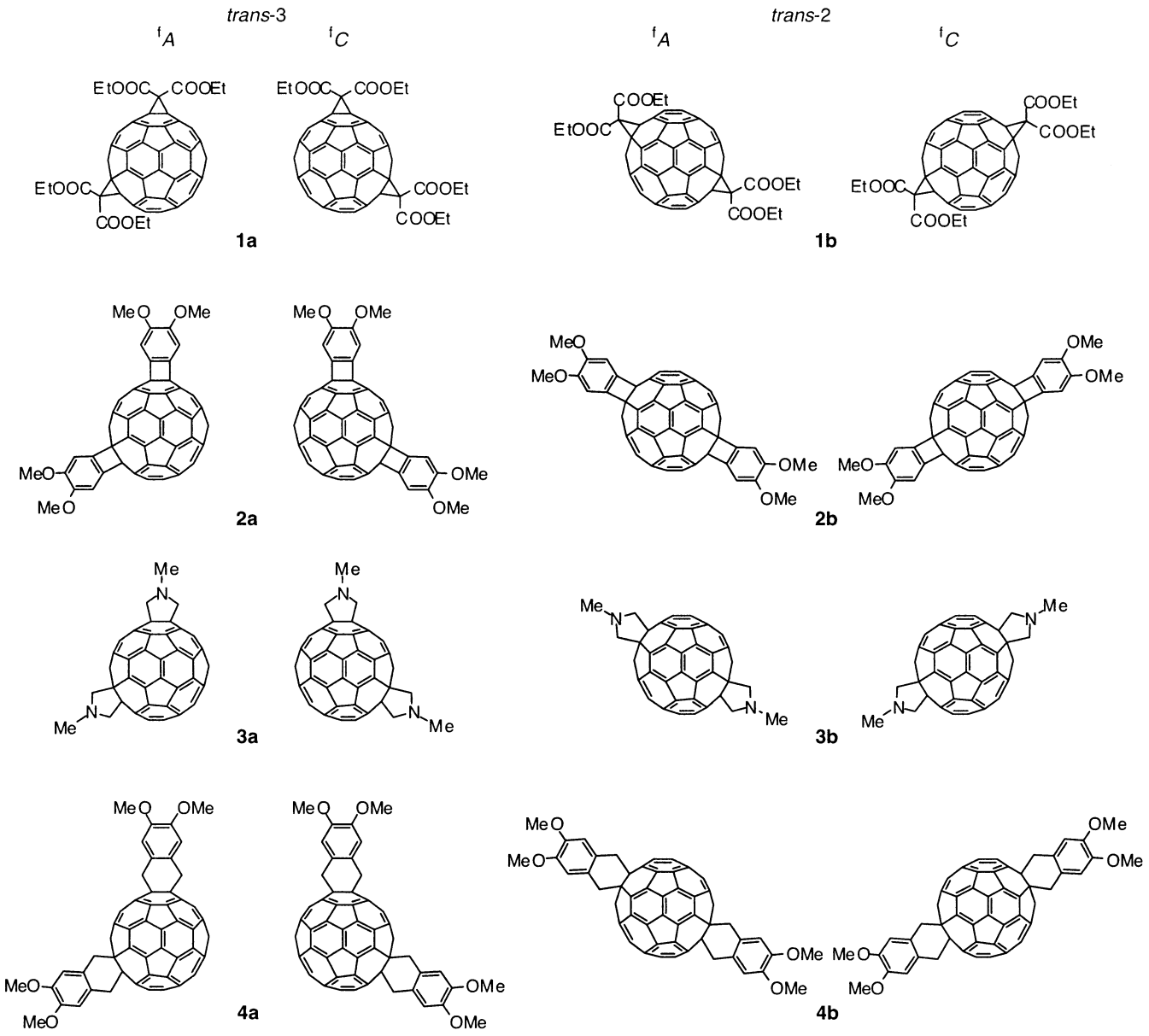
CHART 1



were stimulated to examine the enantiomeric separation of *trans*-3 and *trans*-2 bisadducts modified by other typical reactions such as Bingel reaction (**1a**,**b**)[1,2] and Prato reaction (**3a**,**b**)[3,4] and to compare with that of **2a**,**b** and **4a**,**b**. In this paper, we report the systematic enantioseparation of bisadducts **1a**−**4a** (*trans*-3) and **1b**−**4b** (*trans*-2) with a series of modifications by three- to six-membered rings in detail. The effects of columns or eluents onto the elution order and separation factors (α) of enantiomers are discussed. The CD spectra of separated enantiomers are presented and compared with one another.

Results and Discussion

Enantioseparation of Each Bisadduct. The enantioseparation of bisadducts **1a**−**4a** (*trans*-3) and **1b**−**4b** (*trans*-2) was examined by using Chiralcel OD and Chiralpak AD as chiral columns and hexane/2-propanol and hexane/ethanol as eluent. In several cases, a Chiralpak AD-H column with higher theoretical plates was also employed. The representative chromatogram for each bisadduct is illustrated in Figure 1. The elution order, separation factor (α), and resolution factor (R_s) are summarized in Table 1. The absolute configuration, ^{f}A or ^{f}C, of each fraction was assigned on the basis of comparison with the calculated CD spectra of *trans*-3 and *trans*-2 bismethanofullerenes $C_{62}H_4$ in the literature, as described below.[26]

1. Benzyne Bisadducts 2a and 2b. We have already succeeded in the complete enantioseparation of **2a** and **2b** with using Chiralpak AD, as reported in the literature.[6] Here, we also examined the use of Chiralcel OD as stationary phase. As the α and R_s values suggest, this column was much less effective for the enantioseparation of both **2a** and **2b**. Intriguingly, in using Chiralpak AD, the kind of alcohol involved in eluent significantly affected the α and R_s values; for **2a**, hexane/ethanol (9/1) was much more preferable than hexane/2-propanol

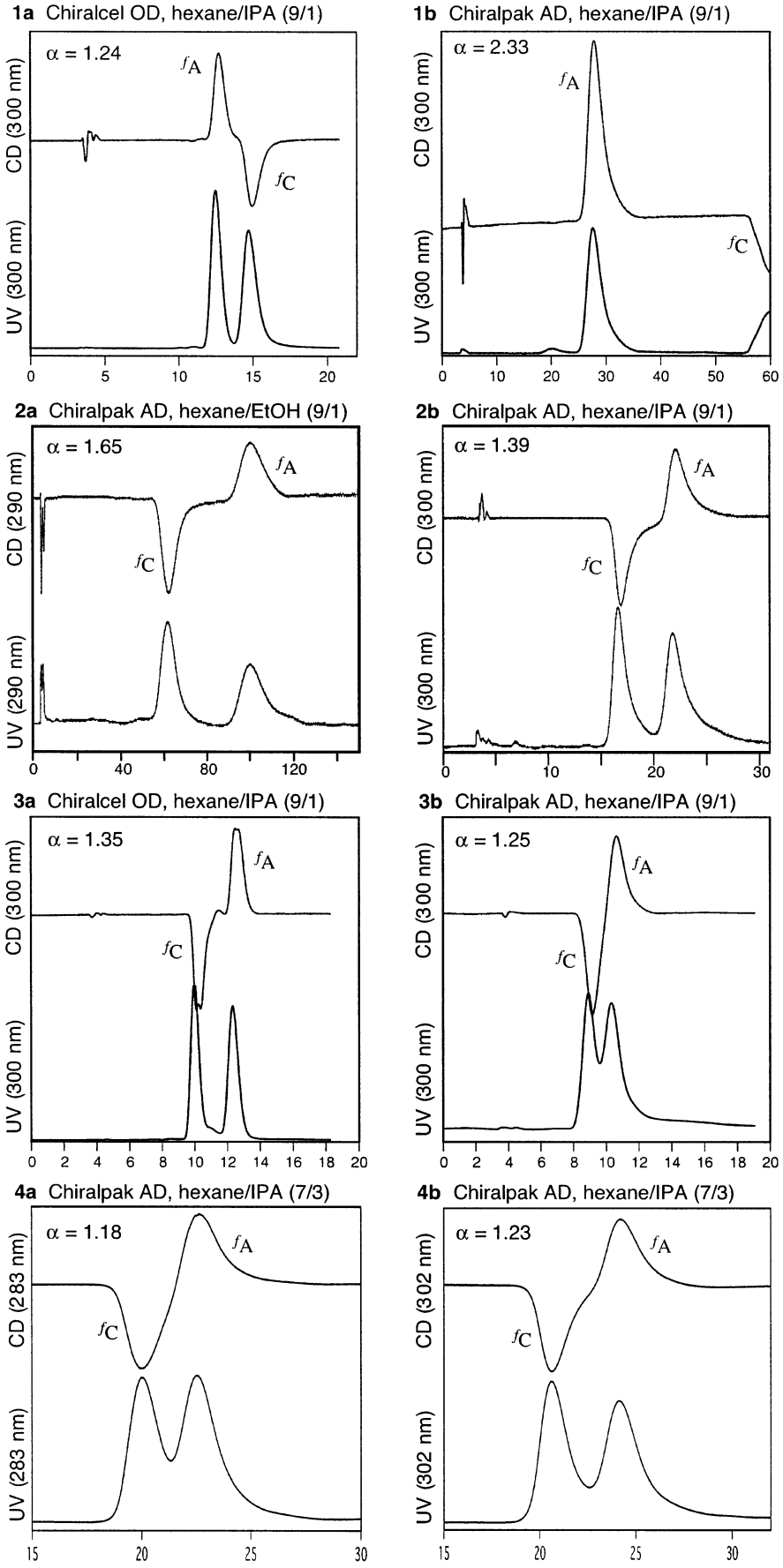


FIGURE 1. Chromatograms for the optical resolution of bisadducts **1a**−**4a** and **1b**−**4b**.

TABLE 1. Elution Order, α,[a] and R_s[a] in Enantioseparation of Bisadducts

	trans-3, stationary phase				*trans*-2, stationary phase			
eluent	**1a** elution order α, *Rs*[b]	**2a** elution order α, *Rs*[b]	**3a** elution order α, *Rs*[b]	**4a** elution order α, *Rs*[b]	**1b** elution order α, *Rs*[b]	**2b** elution order α, *Rs*[b]	**3b** elution order α, *Rs*[b]	**4b** elution order α, *Rs*[b]
Chiralcel OD hexane/IPA	^{f}A **1.24**, **1.43**	^{f}A 1.07, 0[d]	^{f}C **1.35**, **2.06**	^{f}C 1.07, 0[d]	^{f}C 1.10, 0[d]	^{f}A 1.09, 0[d]	^{f}C 1.07, 0[d]	^{f}C 1.10, 0[d]
Chiralcel OD hexane/EtOH	^{f}A 1.15, 0.43	^{f}A 1.08, 0[d]	^{f}C 1.22, 1.70	^{f}A 1.07, 0[d]	^{f}C 1.08, 0[d]	^{f}A 1.08, 0[d]	$^{f}C \sim {}^{f}A$ 1.0, 0	^{f}C 1.07, 0[d]
Chiralpak AD hexane/IPA	^{f}A 1.07, 0[d]	^{f}C 1.13, 0[d]	^{f}A 1.22, 0.70 (1.54)[c]	^{f}C **1.18**, **0.81**	^{f}A **2.33**, **4.76**	^{f}C **1.39**, **1.79** (**1.53**, **2.51**)[c]	^{f}C **1.25**, **0.72** (**1.83**)[c]	^{f}C **1.23**, **1.07**
Chiralpak AD hexane/EtOH	^{f}A 1.10, 0[d]	^{f}C **1.65**, **2.18**	^{f}C 1.16, 0.38 (0.87)[c]	^{f}C 1.09, 0.38	^{f}A 1.40, 1.47	^{f}A 1.08, 0[d] (1.06, 0)[c]	^{f}A 1.07, 0[d] (0)[c]	^{f}C 1.09, 0.57

[a] The highest value is depicted in boldface for each compound. [b] Enantiomer eluted in the earlier retention time is denoted. [c] Values obtained by using Chiralpak AD-H are shown in parentheses. [d] The α values were estimated by the elution times of positive and negative peaks detected by polarimeter, since the UV detector showed a single peak.

(9/1), whereas for **2b** the applicability was reversed. For **2b**, the use of Chiralpak AD-H with hexane/2-propanol further enhanced the α and R_s values.

2. *o*-Quinodimethane Bisadducts 4a and 4b. As reported previously, with Chiralcel OD and hexane/2-propanol, **4a** and **4b** gave only an almost unresolved peak on a UV detector, although the front and tail parts of the peak afforded mirror-imaged CD spectra.[5] In contrast, the utilization of Chiralpak AD resulted in distinct resolution into two peaks with slight overlapping for both **4a** and **4b**. This stationary phase had an advantage in that the retention time was much reduced compared to that with Chiralcel OD. As eluent, hexane/2-propanol (7/3) was superior to hexane/ethanol (7/3) for both **4a** and **4b**.

3. Bingel Bisadducts 1a and 1b. The enantioseparation of **1a** and **1b** has so far been unknown, although the resolution of the corresponding *cis*-3 isomer was reported.[18] As Table 1 apparently suggests, Chiralcel OD was suitable for **1a**, whereas Chiralpak AD was suitable for **1b**. In both cases, hexane/2-propanol was preferable to hexane/ethanol as an eluent. The high α and R_s values of 2.33 and 4.76, respectively, for **1b** with Chiralpak AD and hexane/2-propanol are noteworthy.

4. Prato Bisadducts 3a and 3b. There have been no reports on the optical resolution of Prato bisadducts with chiral addition pattern. The tendency for resolution of **3a** and **3b** was rather similar to that of **1a** and **1b**; Chiralcel OD was effective for **3a**, while Chiralpak AD for **3b**. However, the α and R_s values for **3b** were much small compared to those for **1b**, and the use of hexane/ethanol as an eluent gave only a single peak on a UV detector, even with Chiralpak AD. On the contrary, the α and R_s values of **3a** were slightly higher than those for **1a**.

CD Spectrum of Each Enantiomer and Assignment of Absolute Configuration. The CD spectra of resolved enantiomers are shown in Figure 2. Each pair of enantiomers obviously exhibited mirror images to each other for all the bisadducts.

The spectra of Bingel bisadducts **1a** with a (−) sign at 450 nm and **1b** with a (+) sign at 500 nm, exhibiting characteristic band shapes between 400 and 700 nm, are quite similar to the calculated spectra of (^{f}A)-*trans*-3 and (^{f}C)-*trans*-2 bismethanofullerenes $C_{62}H_4$, respectively.[26] They are also in good agreement with the experimental spectra of corresponding bis(oxazoline) bisadducts in the literature.[19,26] Therefore, the absolute configuration of enantiomeric pairs of **1a** and **1b** was definitely assigned as shown in Figure 2.

The spectra of *trans*-3 bisadducts **2a**, **3a**, and **4a** bearing four-, five-, and six-membered rings, respectively, are also similar to that of **1a** with three-membered rings, though their band shapes and wavelength are slightly different from **1a**. Noticeably, the spectral shapes of **2a**, **3a**, and **4a** are almost superimposable on one another. These results apparently indicate that the observed chiroptical properties are derived from the π-system of fullerene moiety with an inherent chiral addition pattern and almost independent of the nature of addends, although the functionalization by cyclopropanation appears to impose relatively much strain on the fullerene surface and also allow Walsh-type σ−π interaction, leading to the perturbation of its π-electron system. Therefore, for **2a**−**4a**, the enantiomer with a (+) sign at 400 nm and a (−) sign at 300 nm was reasonably assigned as ^{f}C and the other one as ^{f}A. Similar tendencies are clearly observed in *trans*-2 bisadducts **1b** and **2b**−**4b**. Thus, the enantiomer with a (+) sign at 480 nm and a (−) sign at 300 nm was reasonably assigned as ^{f}C and the other one as ^{f}A for **2b**−**4b**. On the basis of this assignment of absolute configuration, the elution order was readily determined, as listed in Table 1. Thus, the measurement of CD spectra can be a quite useful tool for the assignment of not only addition sites but also the absolute configuration for such chiral bisadducts.

Consideration on the Effects of Stationary Phase (Column) or Eluent onto the Elution Order and Separation Factor. 1. Elution Order. As Table 1 suggests, there seems to be no general, definite correlation between the elution order and absolute configuration on the whole. The elution order varies with the nature of addends, columns, and eluents. Nonetheless, several features are observed as described below.

Only in the case of **1a**, among *trans*-3 bisadducts, the ^{f}A-enantiomer was always eluted before the ^{f}C-one regardless of columns or eluents. However, the elution order for **2a**−**4a** was dependent on columns employed. In the cases of **3a** with Chiralpak AD and **4a** with Chiralcel OD, the elution order was also reversed by the kind of alcohol, ethanol or 2-propanol, in eluent. On the other hand, for *trans*-2 bisadducts **3b** and **4b**, ^{f}C-enan-

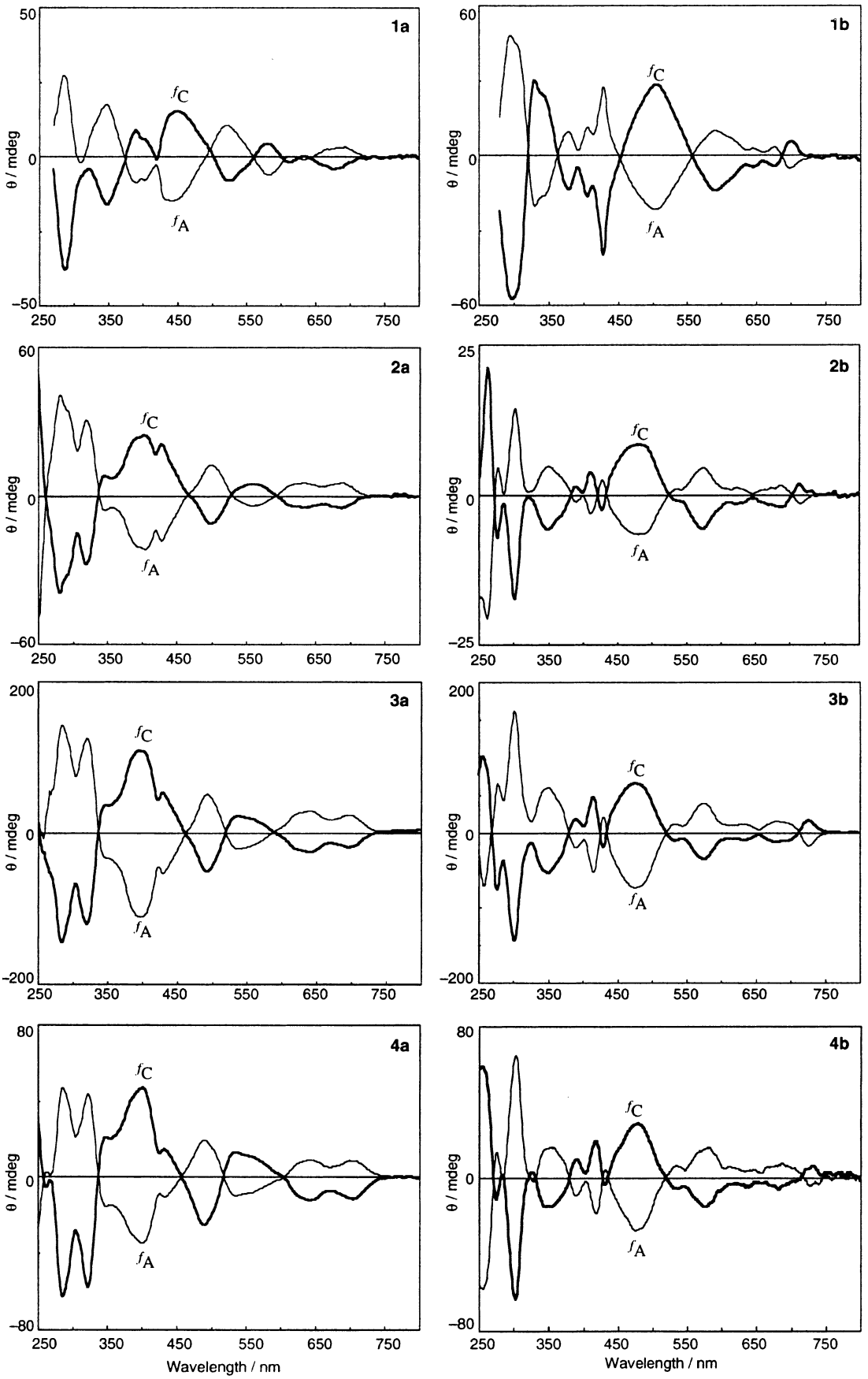


FIGURE 2. CD spectra of enantiomers of bisadducts **1a**−**4a** and **1b**−**4b** in $CHCl_3$.

tiomers were always eluted earlier than ^{f}A-ones, although enantiomers of **3b** were not resolved by Chiralcel OD with hexane/ethanol. The elution order for **1b** and **2b** depended on columns and/or eluents employed. Chiralcel OD and Chiralpak AD are polysaccharide-based chiral stationary phases consisting of tris(3,5-dimethylphenylcarbamate) of cellulose and amylose, respectively. Possible structures are a left-handed 3/2 (Chiralcel OD)[27] and 4/1 helical structure (Chiralpak AD),[28] and owing to this difference in the structure, these two chiral columns often show complementary chiral recognition ability.[29] Actually, some enantiomers were eluted in the reverse order on the two columns in the present study.

In surveying Table 1 along the horizontal rows, we cannot find any general tendency. Apparently, there are no elution conditions (combinations of column and eluent) that allow one specific enantiomer of ^{f}C or ^{f}A to elute preferentially for all of **1a**−**4a** (or **1b**−**4b**); under certain conditions, the elution order varies with the nature of addends. No correlation can be also observed in the elution order between the *trans*-3 and *trans*-2 bisadducts carrying the same addends (e.g., **1a**−**4a** vs **1b**−**4b**). Thus, it seems to be difficult to estimate the absolute configuration only from the elution order of enantiomers under any elution conditions. The elution order is apparently dependent on the nature of addends and stationary phases rather than the absolute configuration itself, in contrast with CD spectra. To clarify the factors governing the elution order more closely, it is necessary to examine the behavior in enantioseparation of bisadducts carrying other addends.

2. Separation Factor and Resolution Factor. For the enantioseparation of *trans*-2 bisadducts **1b**−**4b**, Chiralcel OD column is apparently unsuitable irrespective of eluents, as demonstrated by the low α and R_s values. On the contrary, Chiralpak AD combined with hexane/2-propanol exhibited excellent enantioseparation abilities. For all of **1b**−**4b**, the highest α and R_s values were accomplished under this combination. In particular, quite high α and R_s values for **1b** are noticeable, as described above. Surprisingly, the use of ethanol instead of 2-propanol remarkably depressed the separation and resolution factors. Thus, Chiralpak AD with hexane/2-propanol is expected to be generally applicable to the enantioseparation of *trans*-2 bisadducts with high efficiency, though further investigation on the resolution of other *trans*-2 bisadducts is necessary in order to prove the generality.

For *trans*-3 bisadducts **1a**−**4a**, enantioseparation is accomplishable by either of Chiralcel OD and Chiralpak AD. However, the more suitable column depends on compounds; **1a** and **3a** prefer Chiralcel OD, whereas **2a** and **4a** prefer Chiralpak AD. As eluent, hexane/2-propanol appears to be slightly better than (or comparable to) hexane/ethanol on the whole, but the resolution of **2a** by Chiralpak AD represented a quite exceptional case; the utilization of ethanol significantly increased the resolution ability. Although the selection of column depends on compounds, all of **1a**−**4a** can be sufficiently resolved into enantiomers at least on either of the two columns.

The most important adsorbing sites for chiral recognition of both the stationary phases are considered to be the polar carbamate groups of the polysaccharides. The carbamate groups can interact with the polar groups of enantiomers through hydrogen bond or dipole−dipole interactions, so that the structure of alcohols used as the eluent influences the enantioselectivity. However, the enantioselectivity may be governed by a delicate balance of interactions between the carbamate groups and enantiomers and alcohols. Besides hydrophilic interactions, hydrophobic interactions such as $\pi-\pi$ interaction is also responsible for chiral recognition, since chiral fully hydrocarbons and C_{76} can be resolved on either Chiralcel OD or Chiralpak AD.[29,30]

Conclusion

The enantioseparation of [60]fullerene bisadducts **1a**−**4a** (*trans*-3) and **1b**−**4b** (*trans*-2) was systematically investigated by using both Chiralcel OD and Chiralpak AD. For **1a**−**4a**, the preferable column depended on the addends, although enantioseparation was possible on either column. Noticeably, Chiralpak AD combined with hexane/2-propanol exhibited excellent enantioseparation abilities for all of **1b**−**4b**, irrespective of addends. The CD spectra of resolved enantiomers were apparently dependent on addition pattern and almost independent of addends, although the band shapes and maximum wavelength for **1** with three-membered rings were rather different from those for **2**−**4**. Therefore, CD spectra are applicable to the determination of addition pattern, *trans*-3 or *trans*-2, and the assignments of absolute configuration.

Experimental Section

Materials. Bisadducts **1**−**4** were prepared according to the literature procedures.[1−6] From the regioisomeric mixture of each bisadduct, **1a**−**4a** (*trans*-3) and **1b**−**4b** (*trans*-2) were separated and isolated by HPLC using a Develosil RP-FULLERENE column (20 × 250 mm, Nomura Chemical Co., Ltd.) with an eluent of toluene/acetonitrile (1/3 (v/v)) as reported previously.[5,6] They were characterized by mass, NMR, and UV−vis spectroscopy.

Optical Resolution with Chiral HPLC Columns and Measurement of CD Spectra. Optical resolution of [60]-fullerene bisadducts **1a**−**4a** (*trans*-3) and **1b**−**4b** (*trans*-2) were performed with a JASCO PU-1580 liquid chromatograph equipped with UV−vis (JASCO UV-1570, 300 nm) and CD (JASCO CD-1595, 300 nm) detectors. A chiral HPLC column (Chiralcel OD, Chiralpak AD, or Chiralpak AD-H (**2b**, **3a**, and **3b**) (25 × 0.46 cm i.d.)) was connected in series, and hexane/2-propanol mixtures (9/1 for **1a**−**3a** and **1b**−**3b** and 7/3 for **4a** and **4b**) or hexane/ethanol mixtures (9/1 for **1a**−**3a** and **1b**−**3b** and 7/3 for **4a** and **4b**) were used as the eluent at a flow rate of 1.0 mL/min. A solution of a racemate (chloroform/cyclohexane/2-propanol = 1/5/5, 1.0 mg/mL) was injected into the chromatographic system (50 μL) using a Rheodyne model 7125 injector with a 0.2 mL loop. The column effluents of each enantiomer were collected in a 50-mL flask, and the solvent was evaporated to dryness. When the resolution was not

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baseline separated, fractions rich in each enantiomer were collected monitored by both UV and CD detectors. The absorption and CD spectra of each fractionated enantiomer were measured in a 1.0-mm quartz cell in dry chloroform at room temperature (ca. 25 °C) with a JASCO V-570 spectrophotometer and a JASCO J-725 spectropolarimeter, respectively.

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