Enantiomeric separation of [60]fullerene derivatives with an inherent chiral addition pattern

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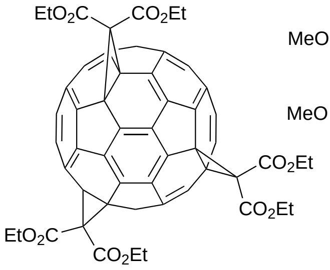
Enantiomeric separation of bis-, tris- and hexakis-adducts of [60]fullerene with achiral addends and an inherent chiral addition pattern is achieved by HPLC using a chiral Whelk-O1 phase.

Investigations on chiral fullerene derivatives is a topic attracting increasing interest.[1] Recently there has been a lot of effort directed towards the synthesis and characterization of various chiral [60]fullerene adducts. If the addends themselves are achiral, chirality is still possible due to the nature of the addition pattern. In these cases the fullerene based π-systems themselves are chiral, and the chiroptical properties are due to an asymmetric fullerene chromophore.

We recently reported the synthesis and characterization of several regioisomeric bis- and tris-adducts of [60]fullerene with both identical and different addends, *e.g.* diethoxycarbonylmethylene $C(CO_2Et)_2$, dianisylmethylene $C(anisyl)_2$ and ethoxycarbonylnitrene NCO_2Et.[2,3] Some of these isomers are chiral due to their addition pattern and they were isolated and characterised as racemates. In order to isolate single enantiomers[4,5,6] of chiral fullerene derivatives two different approaches can be considered: (1) enantioselective synthesis of enantiomerically enriched or pure products, which has been demonstrated, *e.g.* with asymmetric bisosmylation[4] and enantioselective addition of malonates[5] and (2) enantiomeric separation by means of preparative chromatography (HPLC) on a chiral stationary phase.



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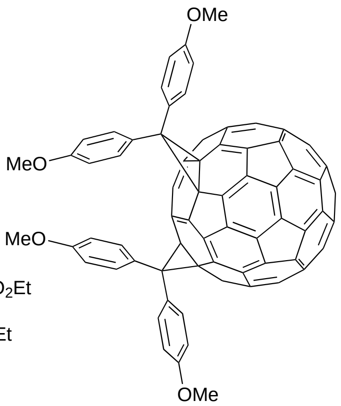

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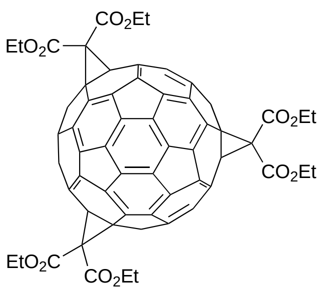

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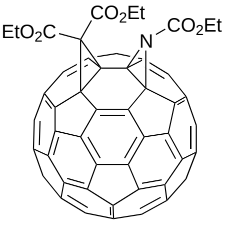

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Chiral Whelk-O1 HPLC columns are well suited to the separation of enantiomers with either π-acidic or π-basic groups. Welch *et al.* were the first to resolve enantiomeric monoadducts of [60]fullerene on a Whelk-O1 column.[7] [76]Fullerene monoadducts[8] as well as a [70]fullerene monoadduct[9] were also successfully separated using this chiral stationary phase. Recently, a malonate bisadduct of [60]fullerene was resolved into its enantiomers.[5]

Here we report the enantiomeric separation of several racemic bis-, tris- and hexakis-adducts of [60]fullerene by chiral HPLC using a (*R,R*)-Whelk-O1 column† and we show the circular dichroism spectra of the single enantiomers. The HPLC separation of the enantiomers of the C_3-symmetric trisadduct **1** (^{f}C)-I,eI,eII[11,12] and (^{f}A)-I,eI,eII with an *e,e,e*-addition pattern and of the D_3-symmetric trisadduct **2** (^{f}C)-I,III*,III* and (^{f}A)-I,III*,III* with a *trans*-3, *trans*-3, *trans*-3 addition pattern represents the first resolution of racemic fullerene trisadducts. A chiral C_1-symmetrical hexakisadduct $C_{66}(CO_2Et)_{12}$ **3** of unknown structure, which is a side product in the synthesis of the corresponding T_h-symmetrical hexakisadduct,[13] is the first example of the separation of a racemic hexakisadduct of [60]fullerene. Successful chromatographic resolution was also achieved with the enantiomers of bisadduct **4** (^{f}C)-I,III and (^{f}A)-I,III as well as **5** (^{f}C)-I,II and (^{f}A)-I,II. The chromatogram of the enantiomeric separation of **3** is shown in Fig. 1. Several solvent compositions were tested for the five racemic derivatives. Usually fullerene adducts are only sparingly soluble in solvents like MeCN, MeOH or water. Therefore all the fullerene separations described in the literature so far are carried out in the normal phase mode, using toluene or solvent mixtures with *e.g.* either hexane or CH_2Cl_2. The bisadducts **4** and **5** are very soluble in toluene and hexane or heptane mixtures. Trisadducts **1** and **2** as well as the hexakisadduct **3** were separated using a reversed phase mode. Whereas with MeOH only broad peaks leading to poor resolution were observed, the use of MeCN–

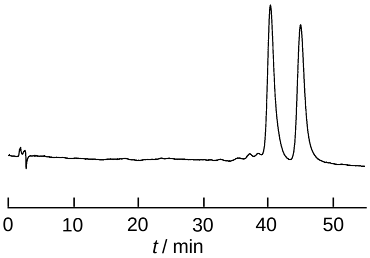

Fig. 1 Chromatogram of the enantiomer separation of **3** on Whelk-O1 Eluent: MeCN–H_2O, 75:25; flow rate: 0.8 ml min^{-1}; UV detection: 254 nm.

water mixtures guaranteed a good separation into the corresponding enantiomers **1**–**3** with chiral separation factors α in the range 1.04–1.12. The best separation was achieved with the hexakisadduct **3** showing a resolution R_s = 2.37. In pure toluene the resolution for the bisadducts **4** and **5** was very poor. Increasing percentages of hexane or heptane lead to an improvement of the α- and R_s-values. As these adducts are less soluble in hexane or heptane, a higher percentage of these solvents in toluene leads to bad peak shapes and no further improvement in separation.

After separation of the enantiomers of **1**–**5** on a semipreparative scale CD spectra were recorded (Fig. 2),‡ which are comparable to those reported for other fullerene adducts.[4–10] Since in our case chirality arises exclusively from the addition pattern on the carbon cluster itself, the CD originates from the chiral functionalized fullerene chromophore. Each derivative gives rise to mirror image CD curves for the enantiomers (Fig. 2).

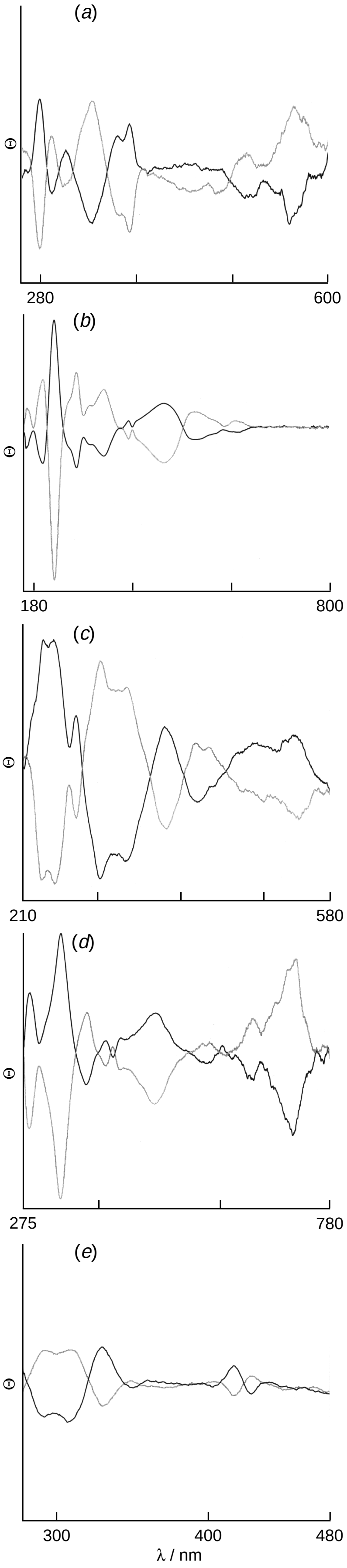

Fig. 2 Circular dichroism spectra of the enantiomers **1**–**5**: (*a*) **1**, (*b*) **2**, (*c*) **3**, (*d*) **4** and (*e*) **5**. — First eluted enantiomer. **—** Second eluted enantiomer.

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Footnotes

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† Chromatographic analysis was performed using a GRAS (CPISOS/LC) pump (Chrompack, Frankfurt, Germany) and a Chrompack UV-variable wavelength UV detector. Injections were performed using a Rheodyne model 7125 injector with a 20 μl sample loop. An analytical 250 mm × 4.6 mm i.d. (*R*,*R*)-Whelk-O1 column was a gift from Regis Chemical Company (Morton Grove, IL, USA). Conditions: MeCN–H_2O mixtures for **1**–**3**, 85:15 (**1**), 90:10 (**2**), 75:25 (**3**); toluene–hexane mixtures for **4** and **5**, 65:35 (**4**), 80:20 (**5**).

‡ CD spectra were obtained on a J720 spectrometer from Asco (Tokyo, Japan) using a 0.02 cm pathlength quartz cell with a resolution of 0.5 nm. **1**–**3** were recorded in acetonitrile, **4**–**5** in toluene.

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