Stereoselective additions to [60]fullerene

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1,3-Dipolar cycloaddition of chiral azomethine ylides to C_{60} affords mixtures of diastereoisomeric fulleropyrrolidines, which can be separated by flash chromatography; the structure of the adducts is supported by unambiguous NOE enhancements, and CD curves of the adducts can be of help in the assignment of the absolute configuration.

Although a large number of reactions with C_{60} have been carried out so far,[1] stereoselective additions have not received much attention.[2,3] However, the high symmetry of C_{60} and the curved shape of its double bonds[4] pose interesting questions on the stereochemical outcome of a chiral addition. Furthermore, the breaking of the fullerene symmetry in a stereoselective way can lead to dissymmetric compounds with interesting chiral π-systems.[5–8]

In this paper we describe three examples of diastereoselective additions to C_{60}, the isolation and characterization of the resulting diastereoisomers and discuss their chiroptical properties (CD spectra).

The addition of azomethine ylides to C_{60} is one of the most powerful and versatile methods for derivatising fullerenes.[9] The condensation of such readily available starting materials as α-amino acids and aldehydes gives rise to the reactive 1,3-dipole which adds to C_{60} leading to functionalised fulleropyrrolidines. Since the intermediate ylides are planar species, the chirality of the α-amino acid, when present, is lost during the addition. An additional chiral centre on the α-amino acid is thus required in order to achieve stereoselection. Alternatively, a chiral aldehyde can be employed.

When the O-protected (2*S*,4*R*)-4-hydroxypyrrolidine-2-carboxylic acid (L-4-hydroxyproline) **1** was heated in toluene at reflux temperature in the presence of paraformaldehyde and C_{60}, the two diastereoisomeric monoadducts **2** and **3** were isolated in 11 and 24% yield, respectively, after chromatography (Scheme 1).†‡ The diastereoisomeric ratio (31 : 69) was confirmed by HPLC and by integration of selected signals in the ^{1}H NMR spectrum of the reaction mixture. The configuration of the chiral carbon atom, α to nitrogen, formed in the cycloaddition, was readily assessed by differential NOE spectroscopy.

A readily available source of chirality is (+)-2,3-*O*-isopropylidene-D-glyceraldehyde **4**, which can be condensed with *N*-methylglycine (sarcosine) in toluene at reflux. The resulting chiral azomethine ylide adds to C_{60} in a highly stereoselective way, affording a mixture of the two diastereoisomeric fulleropyrrolidines **5** and **6** in 5 and 17% isolated yield respectively (diastereoisomeric ratio 23 : 77, confirmed by HPLC) after chromatography (Scheme 1).† The bulky dimethyldioxolane ring does not allow free rotation of the C–C bond that links it to the pyrrolidine ring, making the structural assignment possible by ^{1}H NMR spectroscopy. The major compound **6** shows a doublet for H_a at δ 4.19 ($J_{a,b}$ 7.9 Hz), derived from coupling with H_b, typical of a *trans* relationship for vicinal protons. In the minor isomer **5**, the same coupling constant is $J_{a,b}$ 2.4 Hz, which accounts for a *cis* relationship with a dihedral angle close to 60°. The assignment was confirmed by NOE measurements, where it was found that spatial interactions between H_a and H_b were stronger in **5** than in **6**.

Garner's aldehyde [*tert*-butyl (*S*)-4-formyl-2,2-dimethyloxazolidine-3-carboxylate] **7**, commercially available in high enantiomeric purity, possesses a chiral centre (*S*) with opposite configuration with respect to **4** (*R*). An inversion of the isomer ratio is then expected in the azomethine ylide cycloaddition to C_{60}. It was indeed found that condensation of **7** with sarcosine followed by cycloaddition to C_{60} gives fulleropyrrolidines **8** and **9** in 86 : 14 ratio (HPLC), with 22% overall yield (Scheme 1).† The presence of a urethane function in **8** and **9** (Boc–N<) causes a broadening of some signals in the ^{1}H NMR spectra recorded at room temperature, which resolve into sharp signals at 95 °C ([$^2H_8$]toluene). Under these conditions, proton H_a in **8** and **9** resonates as a doublet at δ 5.04 (J_{trans} 8.5 Hz) and 4.85 (J_{cis} 1.2 Hz), respectively. Also, in this case the structural assignment has been corroborated by NOE analysis.

The stereoselectivity observed in the above reactions is most probably due to steric reasons. In all the three cases, the chiral 1,3-dipole has a bulky group that directs the addition; on the other hand, C_{60} can offer only one reactive face. For instance, in the attack of the azomethine ylide generated from **1**, one face of the dipole is more hindered because of the presence of the *tert*-butyldiphenylsilyloxy (OTBDPS) group. The favoured approach with the bulky group away from C_{60} leads to **3**, the major isomer. Similar reasoning accounts for the preferred formation of **6** and **8** in the other two cases, where the steric hindrance of the *N*-methyl group with the acetonide and the *N*-Boc groups disfavours the formation of **5** and **9**.

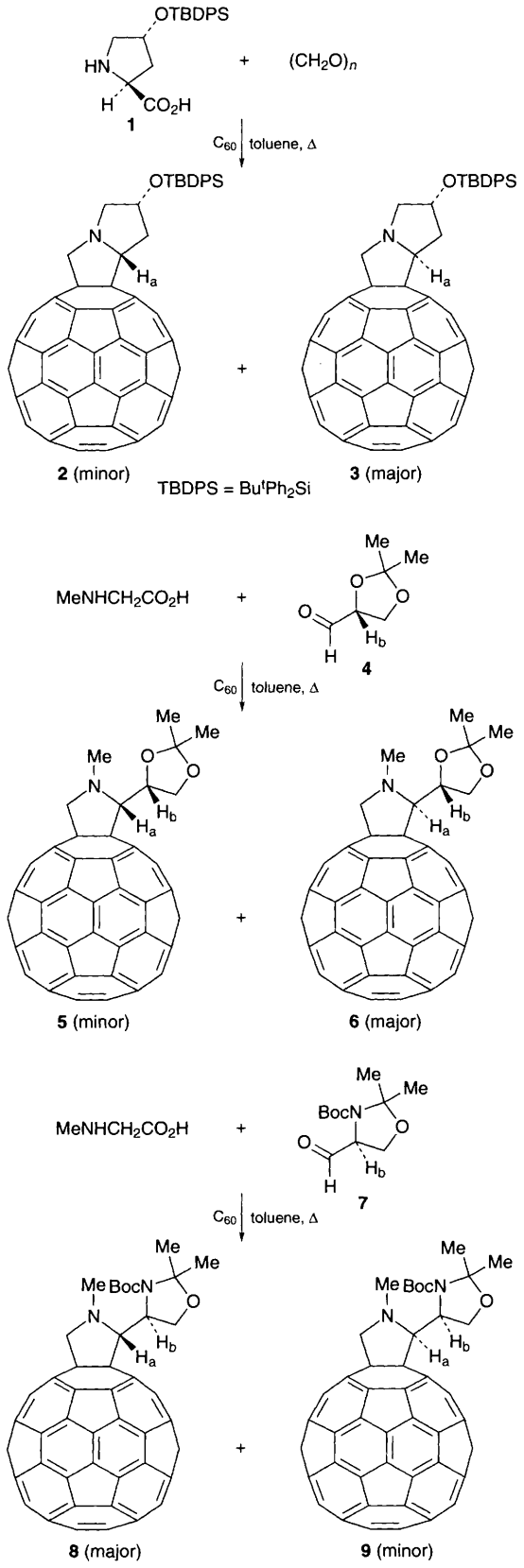
Inspection of the CD spectra shows that diastereoisomeric pairs **5/6** and **8/9** give nicely opposite signed curves, whereas **2/3** perform differently, essentially displaying less mirror-image bands. This finding may be due to different conformational effects of the more rigid pyrrolizidine bicyclic skeleton. Admittedly, however, neither the **5/6** nor the **8/9** pair possesses much conformational freedom, owing to the bulky acetonide and *tert*-butoxycarbonyl groups, respectively. Molecular model examinations and NOE effects are in excellent agreement with the locked conformations depicted in Scheme 1.

We have recently demonstrated that the presence of a Cotton effect in fulleroproline derivatives and peptides can be diagnostic for the assignment of the absolute configuration to that class of compounds.[2,10] In the present work, a strong maximum in the low energy region of the CD spectra, centred at about 430 nm, is common to all cycloadducts, suggesting that the dissymmetric C_{60}-fused pyrrolidine ring, the only common structural feature, might be responsible for that band. The maximum is negative for adducts **2**, **5** and **8**, while positive for **3**, **6** and **9**. The chiral pyrrolidine rings in the two groups of compounds can be considered homofacial, in the sense that all three molecules in each group (**2**, **5** and **8** on one side and **3**, **6** and **9** on the other) are characterized by H_a above the plane and below the plane, respectively. Thus, all the three examples reported in the present work point toward the conclusion that the

430 nm maximum in the CD spectra of fulleropyrrolidines can be of help in the assignment of the absolute configuration to the chiral centre generated during the addition of azomethine ylides to C_{60}. In the way they are drawn in Scheme 1, pyrrolidines with the H_a atom above the plane should exhibit a negative Cotton effect at 430 nm, whereas a positive maximum is expected when H_a is below the plane. This result is in full agreement with the presence of a Cotton effect at 428 nm in CD spectra of fulleroprolines,[2,10] and suggests that, in a general way, the same CD maximum might be common to all chiral fullerene monoadducts.[7]

In conclusion, according to previous work,[1] C_{60} is confirmed to be a reactive 2π component in cycloaddition reactions. However, this uniquely spherical substrate is very sensitive to steric factors and reacts with high diastereoselectivity with bulky chiral reagents. The resulting chiral adducts exhibit very interesting chiroptical properties, with typical Cotton effects in CD spectra that can be used to tentatively assign the absolute configuration to fulleropyrrolidines. Of course, before this evidence is taken as a rule, a wider range of supportive examples is required.

All the protecting groups in the fullerene adducts described in the present work can be removed under very mild conditions, so that further elaboration and functionalisation are possible. Work along these lines is currently underway.



Scheme 1

Footnotes

† All new compounds gave correct analytical and spectroscopic data.

‡ Representative experimental data for compounds **2** and **3**: Isomer **2**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.69 (m), 7.42 (m), 5.10 (d, *J* 12.21 Hz), 4.96 (m), 4.83 (d, *J* 12.21 Hz), 4.25 (dd, *J* 9.77, 6.71 Hz), 3.57 (dd, *J* 9.77, 7.63 Hz), 2.99 (m) and 1.06 (s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 157.74–128.22 (59 peaks), 79.19, 78.13, 75.14, 74.66, 65.94, 59.26, 38.75, 26.88 and 19.17; $\lambda_{max}(CHCl_3)$/nm 258, 314 and 431; ν_{max} (KBr)/cm^{-1} 2959, 2929, 2858, 1633, 1460, 1426, 1187, 1110, 699, 575 and 527; CD $\lambda_{max}(CHCl_3)$ ($\theta_T \times 10^{-3}$)/nm 428 (4600); MALDI-MS *m/z* 1057 (M^+); Isomer **3**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.74 (m), 7.42 (m), 5.31 (dd, *J* 7.32, 4.58 Hz), 5.02 (m), 4.85 (m), 4.05 (dd, *J* 11.29, 7.02 Hz), 3.52 (dd, *J* 11.29, 2.75 Hz), 3.11 (ddd, *J* 13.73, 7.32, 4.58 Hz), 2.82 (ddd, *J* 13.73, 7.32, 3.66 Hz) and 1.16 (s); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 156.86–127.80 (48 peaks), 79.58, 76.87, 74.91, 74.16, 66.66, 60.95, 39.68, 29.70 and 19.18; $\lambda_{max}(CHCl_3)$/nm 257, 316 and 431; ν_{max} (KBr)/cm^{-1} 2930, 2856, 1634, 1460, 1426, 1188, 1111, 699, 575 and 527; CD $\lambda_{max}(CHCl_3)$ ($\theta_T \times 10^{-3}$)/nm 428 (5400); MALDI-MS *m/z* 1057 (M^+) (Found C, 91.25; H, 2.4; N, 1.3 $C_{81}H_{27}NOSi$ requires C, 91.94; H, 2.57; N, 1.32%).

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