A Facile Method for the Synthesis of Amino Acid and Amido Derivatives of C_{60}

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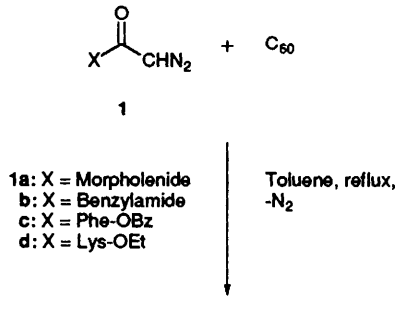
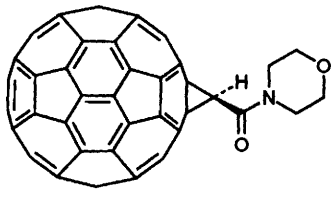
Amino acid and amido derivatives of C_{60} were synthesized by direct additions of the corresponding diazoamides to the fullerene core.

Buckminsterfullerene (C_{60}) is a molecule which can undergo a large variety of chemical transformations being mainly addition reactions.[1,2] Whereas so far most of the chemically modified fullerene derivatives are interesting from an academic point of view, F. Wudl *et al.*[3,4] have recently shown that water soluble methano bridged C_{60} compounds inhibit the HIV enzymes protease (HIVP) and reverse transcriptase (HIVRT). As suggested by molecular modelling the C_{60} molecule fits into the active sites of the enzymes. This first example of a biologically active fullerene is already impressive and it is obvious that more specific, tailor made derivatives, for example a C_{60} moiety attached as a target on a certain oligopeptide can be expected to show an even more potent and selective activity.

In the present work we report an efficient route to amino acid and amido derivatives **2–5** of C_{60} by the direct attachment of the corresponding diazoamides **1** to the fullerene core under a loss of N_2 (Scheme 1). A wide range of diazoamides **1** are easily accessible in high yields by direct diazoacetylation of primary and secondary amino groups in amino compounds including protected amino acids or peptides with succinimidyl diazoacetate.[5] Compound **1d** is the ω-diazoamide derivative. The syntheis of **2–5** was carried out by refluxing stoichiometric amounts of C_{60} and **1** in toluene for 48 h. After purification by flash chromatography with toluene–ethylacetate (10:1 v/v) the monoadducts **2–5** were obtained in a 20–30% yield. The analogous reactions with diazomethanes[6] and diazoesters[7] are reported to yield 1,2- or 1,6-methano bridged fullerenes[8] with a ring closed (1,2-derivatives) or a ring opened (1,6-derivatives) structure. For methano bridges with C_s-symmetry, two isomers of the 1,6-derivatives, one with methine proton above a pentagon, and one with the methine proton above a hexagon are possible and have been observed.[7] Indeed, the HPLC chromatogram of the monoadducts **2** (Fig. 1) show three peaks with significantly different UV–VIS spectra of the eluting components being simultaneously recorded with a diode array detector. Whereas the features of the spectra recorded at peaks *A* and *B* in Fig. 1 are almost identical to those of C_{60} (1,6-bridged derivatives **2a,b**)[6,7] the characteristic additional band at 430 nm[7,9–11] measured at *C* demonstrates that the 1,2-compound **2c** is eluting. In the ^{1}H NMR spectrum of the isomer mixture of **2** three resonances for the methine protons appear at δ 6.81, 4.86 and 3.76. These chemical shifts are in complete agreement with the reported values for alkoxycarbonylmethylene-bridged C_{60} adducts,[7] allowing the attribution of the corresponding signals to the 1,6 bridged system with H above a pentagon **2b**, the 1,2-bridged system **2c** and the 1,6 bridged system with H above a hexagon **2a**, respectively. The integration of the methine proton signals fits well to the ratios of the peak areas in Fig. 1 being 9:1:5 for A(**2a**):B(**2b**):C(**2c**). The chestnut brown **2c** could be separated from the ring opened isomers **2a,b** by flash chromatography with toluene as mobile phase.† Prolonged refluxing of **2a,b** in toluene leads to a decomposition rather than to an equilibration[7] to **2c**.

The regioisomers of **3–5**‡ are eluting simultaneously and are less retentive from silica gel columns (SC, HPLC) with various mixtures of toluene–ethylacetate. Compared to the morpholenide moiety in **2**, the more extended substituents in **3–5** increase the solubility and at the same time vanish the difference in retention behaviour of the regioisomers. The coexistance of the three regioisomers is demonstrated by the ^{1}H NMR spectra‡ showing the distinct methine resonances at δ 6.8, 4.8 and 3.8. The composition of compounds **2–4** was confirmed by field desorption (FD) mass spectrometry,





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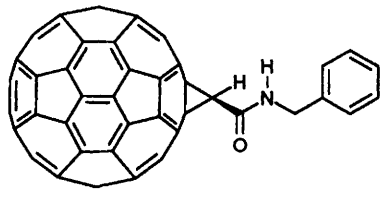

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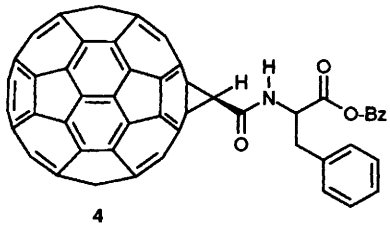

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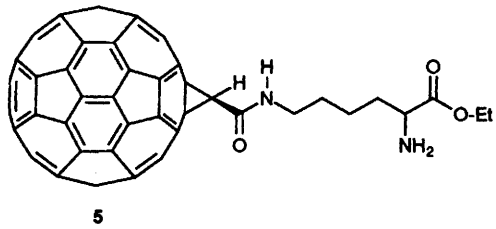

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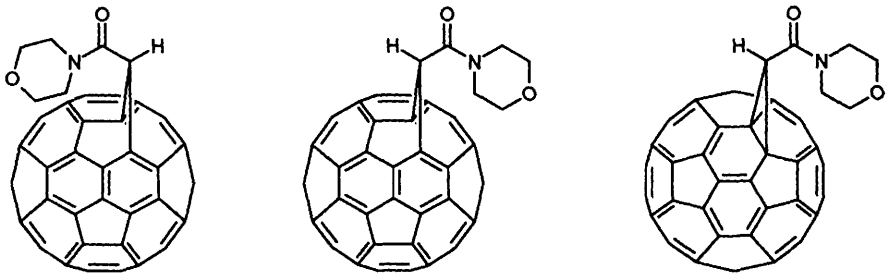
Scheme 1 Synthesis of amino acid and amide derivatives of C_{60} with the representation of the 1,2-methano bridged isomers



2a **2b** **2c**

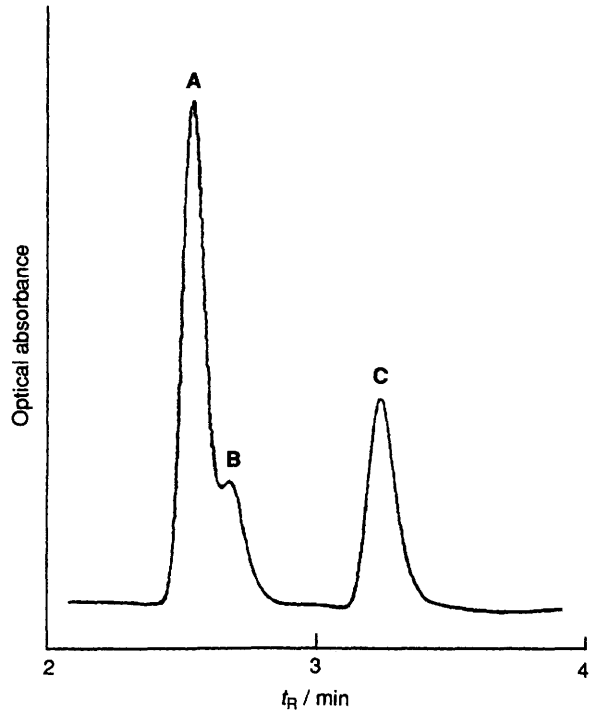


Fig. 1 HPLC profile of the isomer mixture of **2** (silca gel column 25 × 0.46 cm, particle size 5 μ, eluent toluene, flow rate, 1.5 mol min^{-1}, detection at 340 nm and with several diode array scans)

whereas with this technique **5**, due to fragmentation, gave only the mass at 720 (C_{60}). Using matrix assisted laser desorption mass spectrometry (LD-MS) the dimer of **5** at 1870 was detected. The formation of dimers and oligomers of **5** could proceed by the intermolecular nucleophilic attack of α-amino groups to double bonds of the fullerene core since C_{60} is known to undergo such hydroaminations with primary and secondary amines.[12]

In conclusion, we have shown that amino acid derivatives of C_{60} can be synthesized easily by one step reactions with **1**. The scope of the amide moieties in **1**, including peptides is very large, which is a key point for the synthesis of tailor made fullerene derivatives with possible biological relevance.§

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Footnotes

† Selected spectroscopic data of compounds **2a–2c**. **2a/b**: UV–VIS (λ_{max}, toluene) 333, 374sh, 490w. IR ν/cm^{-1} (KBr): 2950sh, 2922, 2852, 1733w, 1726w, 1652, 1645, 1635, 1456, 1434, 1298, 1269, 1226, 1114, 1033, 979, 906, 729, 572 w, sh, 526. FD-MS (toluene) *m/z* (% base): 720 (100, $[M - C_6H_9NO_2]^+$), 847 (76, M^+). ^1H NMR (250 MHz, CS_2–$CDCl_3$ 4:1, δ): 6.81 (s, 1H, CH), 3.82 (s, 1H, CH), 3.73 (m, *J* 5.2 Hz, 8H, CH_2). The mixture contains 10.8% of isomer **2b**, as shown by the peak intensities (HPLC, Fig. 1).

2c: UV–VIS (λ_{max}, toluene) 330, 346sh, 428, 462w. IR ν/cm^{-1} (KBr): 2958sh, 2921, 2852, 1716w, 1699w, 1652, 1456, 1434, 1269, 1230, 1114, 1041, 914, 730, 705, 667, 526. FD-MS (toluene) *m/z* (% base): 847 (100, M^+), 720 (12, $[M - C_6H_9NO_2]^+$). ^1H NMR (250 MHz, CS_2-$CDCl_3$ 4:1, δ): 4.86 (s, 1H, CH), 3.95 (m, *J* 5.1 Hz, 8H, CH_2).

‡ Selected spectroscopic data of compounds **3–5**. For **3**: UV–VIS (λ_{max}, hexane) 254, 270sh, 336sh, 354, 385w, 406sh, 430. IR ν/cm^{-1} (KBr): 3411br, 3060, 3024w, 2921, 2821, 1726, 1666, 1649sh, 1631, 1606, 1512, 1452, 1431sh, 1380, 1311sh, 1259sh, 1161, 1076, 927, 800, 760, 580sh, 527. FD-MS (toluene) *m/z* (% base): 867 (9, M^+), 720 (100, $[M - C_9H_9NO]^+$). ^1H NMR (250 MHz, CS_2–$[^2H_8]$THF 4:1, δ): 7.69 (m, 2H, Ph), 7.43 (m, 2H, Ph), 7.24 (m, 1H, Ph), 6.79 (s, 1H, CH), 6.13 (br, 1H, NH), 4.75 (s, 1H, CH), 4.13 (m, 2H, CH_2), 3.92 (s, 1H, CH).

For **4**: UV–VIS (λ_{max}, dichloromethane) 256, 286sh, 325sh, 360, 393, 432. IR ν/cm^{-1} (KBr): 3321, 3061, 3028, 2958, 2921, 2852, 1733, 1674, 1581, 1519, 1456, 1380, 1261, 1174, 1029, 804, 744, 700, 586, 526. FD-MS (toluene) *m/z* (% base): 1015 (100, M^+), 720 (13, $[M - C_{18}H_{17}NO_3]^+$). ^1H NMR (250 MHz, CS_2-$[^2H_8]$THF 4:1, δ): 7.74 (m, 2H, Ph), 7.42 (m, 2H, Ph) 7.17 (m, 6H, Ph), 6.79 (s, 1H, CH), 5.21 (br, 1H, NH), 5.09 (M, 2H, CH_2), 4.57 (s, 1H, CH), 3.91 (s, 1H, CH), 3.27 (s, 1H, CH), 3.18 (d, *J* 5.5 Hz, 2H, CH_2).

For **5**: UV–VIS (λ_{max}, hexane) 255, 329, 476w, 554w. IR ν/cm^{-1} (KBr): 3063, 3026, 2957, 2926, 2854, 1726, 1681, 1602, 1558, 1452, 1379, 1325, 1261, 1161, 1093, 1033, 804, 752, 688, 590, 526. FD-MS (toluene) *m/z* (% base): 720 (100, $[M - C_{10}H_{17}N_3O_2]^+$) LD-MS ($CS_2$–α-cyano-4-hydroxycinnamic acid) *m/z* (% base): 1870 (100, $2M^+$). ^1H NMR (250 MHz, CS_2–$[^2H_8]$THF 4:1, δ): 7.14 (br, NH), 5.00 (br, CH_2), 4.84 (s, CH), 4.50 (br, CH), 3.84 (s, CH), 3.14 (br, CH_2, NH_2), 2.31 (br, CH_2), 1.26 (br, Me).

§ *Note added in proof*: Two other papers on the synthesis of amino acid derivatives of C_{60} using different methods appeared during the course of this work: Y.-Z. An, L. J. Anderson and Y. Rubin, *J. Org. Chem.*, 1993, **58**, 4799; M. Prato, A. Bianco, M. Maggini, G. Scorrano, C. Toniolo and F. Wudl, *J. Org. Chem.*, 1993, **58**, 5578.

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