Water-soluble Malonic Acid Derivatives of C_{60} with a Defined Three-dimensional Structure

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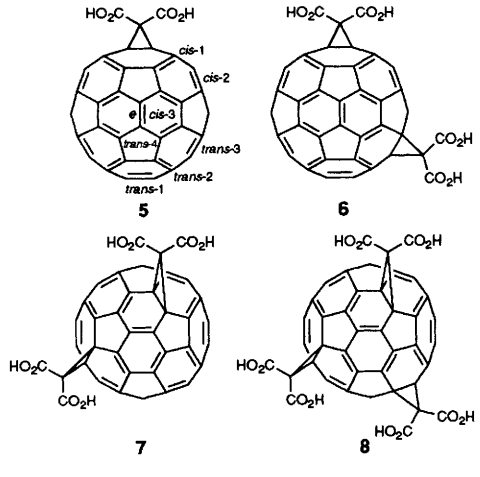
Water-soluble malonic acid derivatives of C_{60} have been synthesised by hydrogenolysis of stereochemically defined mono-, bis- and tris-adducts of C_{60} and di(ethoxycarbonyl)methylene.

Buckminsterfullerene (C_{60}) can be chemically modified by a large variety of addition reactions[1,2] which allows the combination of its properties with those of other classes of materials. Recently, it has been shown that some fullerene derivatives exhibit biological activity.[3–6] In this respect two properties of C_{60} are of special significance. The first is its spherical shape, which can be used for molecular recognition, for example in the inhibition of HIV protease (HIVP),[3,4] and the second is the ability of the fullerene core to efficiently photosensitise the conversion of triplet to singlet oxygen,[7–9] which can be applied to DNA cleavage.[5,6] An important requirement for the investigation of the biological activity of a fullerene derivative is water solubility. This can be achieved by the attachment of polar functional groups. So far either defined water-soluble monoadducts[3–6] or polyadducts as mixtures of a huge number of regioisomers such as fullerols[10–14] or ethylenediamine adducts[15] have been synthesised. However, for biological applications, such as molecular recognition of enzymes, stereochemically defined water-soluble adducts (single regioisomers) with a higher degree of addition would be very interesting. In systematic regiochemistry studies of the three-dimensional 'workspace' of C_{60}[16,17] we isolated a variety of defined regioisomers of bis- to hexakis-adducts with di(ethoxycarbonyl)methylene and found a remarkable regioselectivity for successive attacks in *e*- and *trans*-3-positions† to addents already bound to the fullerene core. In this paper we report the synthesis of water-soluble malonic acid derivatives of C_{60} obtained by the hydrogenolysis of the corresponding stereochemically defined diethyl malonates.

As starting materials for the synthesis of fullerene–malonic acids we chose the di(ethoxycarbonyl)methylene adducts $C_{61}(CO_2Et)_2$-C_{2v} **1**, *trans*-3-$C_{62}(CO_2Et)_4$-C_2 **2**, *e*-$C_{62}(CO_2Et)_4$-C_s **3** and *e,e,e*-$C_{63}(CO_2Et)_6$-C_3 **4** which were synthesised by the reaction of fullerene with diethyl bromomalonate in the presence of base.[16–18] A saponification of these malonates under basic conditions has been shown to be inappropriate since either the conversion to the acids is incomplete or it is accompanied by nucleophilic additions of hydroxide to the fullerene core. A clean formation of the malonic acid derivatives $C_{61}(CO_2H)_2$-C_{2v} **5**, *trans*-3-$C_{62}(CO_2H)_4$-C_2 **6**, *e*-$C_{62}(CO_2H)_4$-C_s **7** and *e,e,e*-$C_{63}(CO_2H)_6$-C_3 **8** was obtained by stirring the corresponding diethyl malonate (100 mg) dissolved in toluene (50 ml) under nitrogen in the presence of a twentyfold molar excess of NaH for 3 h at 60 °C. After this procedure the NaH was almost homogeneously suspended in toluene while the diethyl malonate was unaffected. The transformation of the malonate was accompanied by a vigorous gas evolution and the quantitative precipitation of the sodium salt of the fullerene malonic acid took place after the addition of methanol (1 ml). The formation of the acids occurs presumably by hydrogenolysis of the OEt bonds. After centrifugation and removal of the liquid phase, the precipitate was washed with toluene, 2 mol dm^{-3} H_2SO_4, then water and finally dried under vacuum at 60 °C for 12 h. The resulting malonic acids **5–8** are soluble in solvents such as THF, methanol and water. The water solubility increases with increasing numbers of malonic acid groups attached to the fullerene. Whereas the monoadduct **5** is moderately soluble in basic water (pH > 9), the bisadducts **6** and **7** are very soluble in weakly basic (pH > 8) solution and the trisadduct **8** is very soluble even in neutral water. In aqueous acids all adducts **5–8** are completely insoluble.

The UV–VIS spectra‡ of **5–8** are similar to those of the corresponding diethyl malonates **1–4** (Fig. 1).[16] The symmetry of **5–8** can be deduced from their ^{13}C NMR spectra‡ which again, except for the missing resonances of the ethyl groups, are similar to those of **1–4**.[16] Spectra either from the acids in THF or in methanol or from the corresponding carboxylates in D_2O–K_2CO_3 (pH = 9) have been recorded. The C_{2v}-symmetrical **5** exhibits 13 signals for partly overlapping resonances of the fullerene C-atoms in the sp^2-region and one signal at δ 73 for the sp^3 C-atoms of the fullerene core. The signal for the C-atom of the methylene bridge, expected at δ 50 is too weak



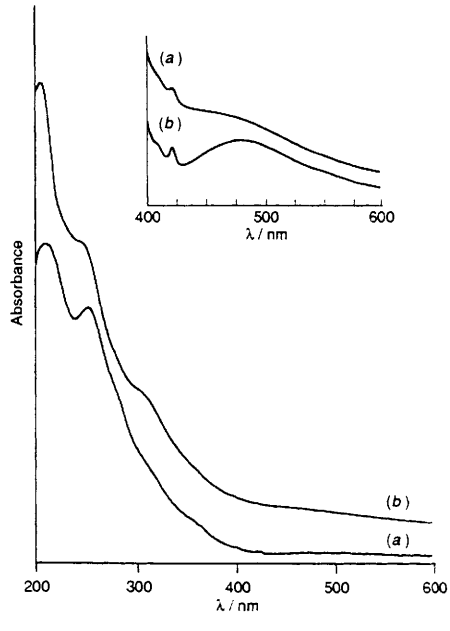


Fig. 1 Comparative UV–VIS spectra of compound **7** (*a*) and **3** (*b*) in MeCN. The inset shows the region 380–600 nm in THF.

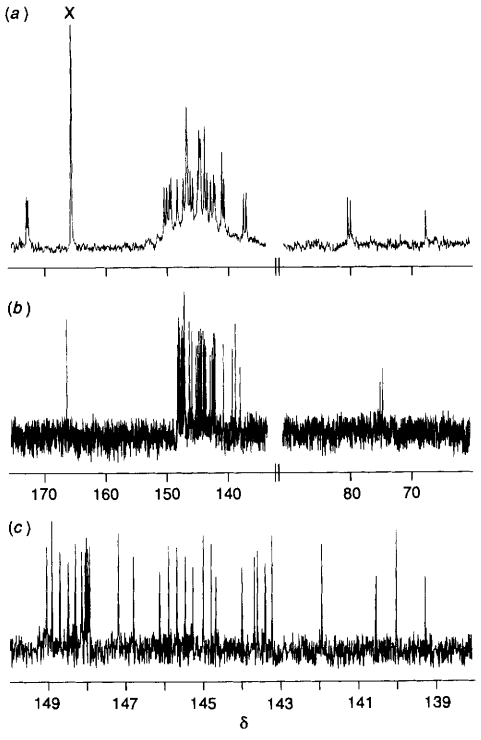


Fig. 2 ^{13}C NMR spectra of **6** (*a*) in D_2O–K_2CO_3 (62.9 MHz, the signal denoted with X is due to K_2CO_3), (*b*) in CD_3OD (100 MHz, the signal for the methylene bridge is covered by the solvent) and (*c*) the expanded region of the sp^2 fullerene C-atoms in CD_3OD

to be unambiguously identified. Owing to its C_2-symmetry, **6** shows 28 resonances§ (Fig. 2) with equal intensities in the sp^2-region and two resonances at δ 80 or 74 for the sp^3 carbons. Compound **7** has a C_s-symmetry with the cyclopropyl rings located in the mirror plane. This is especially reflected by three signals for the sp^3-fullerene C-atoms at δ 74, 69 and 62 with a 2 : 1 : 1 intensity ratio and also three signals at δ 166 for the quarternary carboxylic C-atoms. Two of the 29 signals of the sp^2-fullerene C-atoms are overlapping. The chiral C_3-symmetric trisadduct **8** shows two signals for the carboxylic groups, 18 signals for the sp^2-fullerene C-atoms with two of them overlapping, two signals for the sp^3-fullerene C-atoms and one signal for the cyclopropane methylene C-atom at δ 69. Significantly, the locations of the NMR signals strongly depend on whether the acids or the carboxylates are investigated (Fig. 2). The carbons of the carboxylates (D_2O–K_2CO_3, pH = 9), especially those for the carboxylate C-atoms, the fullerene sp^3 C-atoms as well as that of the C-atom of the methylene bridge resonate downfield compared to those of the free acids, as can be seen from compound **6** in Fig. 2. In addition to absorptions due to the fullerene core the IR spectra‡ of **5–8** show typical bands for carboxylic acid groups. By mass spectrometry (FD, FAB and LD) a pronounced fragmentation of the parent acids is observed.

The synthesis of further fullerene–malonic acids starting from other adducts of di(ethoxycarbonyl)ethylene and C_{60}, *e.g.* tetrakis- to hexakis-adducts, as well as coupling reactions of such malonic acids with amino acids, peptides and other classes of compounds are currently under way.

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Footnotes

† For a clear description of the 8 spatial relationships of the addents bound to 6–6-bonds of the fullerene core we introduced the relations[16] *cis* for addents bound in the same hemisphere, *e* for addents bound in equatorial positions and *trans* for addents bound in two hemispheres. The *cis*- and *trans*- cases are subdivided in *cis*-3, *cis*-2 and *cis*-1 as well as in *trans*-1, *trans*-2, *trans*-3 and *trans*-4 in the order of increasing polarity of the corresponding bisadducts.

‡ *Selected spectroscopic data* for compounds **5–8**. 5: UV–VIS (λ_{max}/nm, THF) 256, 320(sh), 370(sh), 430. IR ν/cm^{-1} (KBr): 3050, 2505, 1796, 1738, 1433, 1377, 1232s, 1059s, 883, 852, 594, 527. ^{13}C NMR (100 MHz, [$^2H_8$]THF): δ 163.26, 147.03, 145.73, 145.37, 145.30, 144.93, 144.86, 144.59, 144.11, 143.16, 142.43, 142.22, 140.97, 139.35, 73.48.

6: UV–VIS (λ_{max}/nm, MeCN) 203, 249, 325(sh), 369(sh), 405, 422, 436, 500w. IR ν/cm^{-1} (KBr): 3472, 1801w, 1724, 1429, 1400, 1231, 1057, 833w, 735w, 581w, 528, 520(sh). LD-MS (% base): *m/z* 835 (6, [M − 2 CO_2H]$^+$), 720 (100, [M − 2 $C(CO_2H)_2$]$^+$). ^{13}C NMR (100 MHz, CD_3OD): δ 166.35, 149.04, 148.90, 148.69, 148.47, 148.29, 148.13, 148.04, 148.01, 147.96, 147.92, 147.18, 146.78, 146.10, 145.87, 145.66, 145.44, 145.24, 144.98, 144.77, 144.64, 143.96, 143.65, 143.56, 143.35, 143.19, 141.89, 140.49, 139.97, 139.22, 74.47, 74.04. ^{13}C NMR (62.9 MHz, D_2O–K_2CO_3): δ 172.53, 172.32, 151.20, 150.79, 150.36, 150.12, 149.15, 148.24, 147.74, 147.67, 147.13, 146.76, 145.95, 145.72, 145.56, 144.89, 144.48, 143.95, 143.48, 143.27, 142.18, 141.86, 138.84, 138.43, 79.61, 79.14, 67.11.

7: UV–VIS (λ_{max}/nm, MeCN) 212, 253, 306(sh), 354(sh), 399, 413, 426, 490w. IR ν/cm^{-1} (KBr): 3443, 1726, 1425, 1398, 1352, 1159, 1130, 1051, 739w, 706w, 582w, 544w, 525. ^{13}C NMR (62.9 MHz, CD_3OD): δ 166.57, 166.54, 166.27, 150.04, 148.79, 148.09, 147.91, 147.85, 147.59, 147.05, 146.86, 146.74, 146.68, 146.47, 146.24, 146.15, 146.12, 145.90, 145.68, 145.53, 145.33, 144.85, 144.54, 144.47, 143.54, 143.28, 143.16, 143.07, 140.40, 140.13, 74.32, 69.16, 62.25.

8: ^{13}C NMR (62.9 MHz, D_2O–K_2CO_3): δ 173.72, 173.36, 152.53, 151.06, 149.29, 148.85, 148.73, 148.35, 147.76, 147.50, 146.17, 145.96, 145.77, 144.56, 143.39, 142.66, 82.76, 79.62, 68.60.

§ The ^{13}C NMR spectrum of **6** [Fig. 2(*c*)] shows 29 signals in the sp^2-region. One signal is due to an unidentified impurity.

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