Synthesis of a 1,2-dihydro[60]fullerylglycine derivative by a novel cyclopropane ring opening of a methano[60]fullerene

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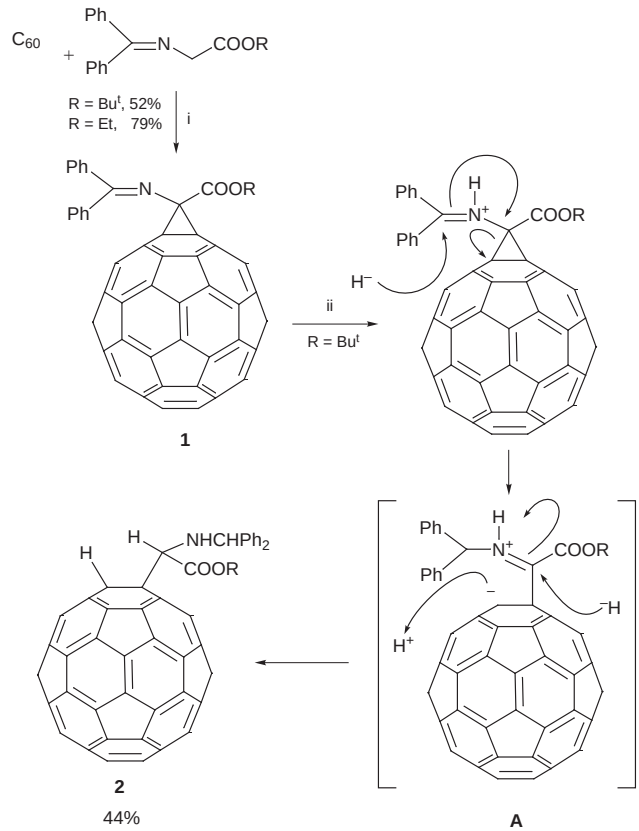
The 1,2-dihydro[60]fullerylgylcine derivative 2 has been prepared by a novel cyclopropane ring opening reaction of the methano[60]fullerene derivative 1.

[60]Fullerenes exhibit a range of interesting biological activities including inhibition of HIV-1 protease,[1] cytotoxicity[2] and the selective cleavage on DNA.[3] Furthermore, the covalent tethering of fullerenes to peptides and proteins has been the goal of a number of studies concerned with the application of fullerene–peptide conjugates to biological problems.[4–8] These conjugates not only enhance the water-solubility of the fullerene and make this molecule more amenable to biological studies, but the fullerene itself can modify the conformation of the tethered peptide and often enhance its biological activity.[6] Such investigations could be greatly enhanced if an α-substituted fulleryl amino acid was available that could be directly incorporated into a peptide sequence. The resulting fulleryl peptides would be expected to have novel secondary structures because of the possibility of π–π and hydrophobic interactions between the peptide and the fullerene surface. Furthermore, these conjugates may have unique biological properties or applications. While a number of fullerylproline derivatives have been prepared[9] the synthesis of an acyclic α-fulleryl amino acid has not been realised. We describe here the synthesis of the 1,2-dihydro[60]fullerylgylcine derivative **2** by a novel ring opening reaction of the methano[60]fullerene derivative **1** (Scheme 1).

Treatment of a solution of [60]fullerene, under Hirsch cyclopropanation conditions,[10] with *tert*-butyl *N*-diphenylmethyleneglycinate, CBr_4 and DBU gave the cyclopropane imino ester **1** in 52% yield after purification by column chromatography. Apart from the signals due to the aryl and *tert*-butyl group (δ 28.3) the ^{13}C NMR spectrum (C_6D_6–CS_2, 1:1) of **1** showed the expected downfield resonances for the sp^2 hybridized carbonyl (δ 162.3) and imine carbons (δ 153.7), 25 sp^2 fullerene carbon resonances (δ 149.3–135.0) and resonances for the quaternary sp^3 carbons at δ 95.0 (C-61), 84.3 (Me_3CO) and 83.8 (C1, C2). The electrospray ionization mass spectrum of **1**, using PhMe–MeCN (30 : 1) as solvent showed a molecular ion at *m/z* 1013. The related ethyl ester **1** (R = Et) could be obtained in 79% yield from C_{60} and ethyl *N*-diphenylmethyleneglycinate. Attempts at the acid hydrolysis (6 M HCl, TFA or TsOH) of **1** (R = Bu^t or Et) have not proven successful and none of the desired cyclopropane amino acid could be isolated.

Reduction of **1** (R = Bu^t) with $NaBH_3CN$ in THF–MeOH at pH 4 gave not the expected reduced imine compound but the novel ring opened 1,2-dihydro[60]fullerylglycine derivative **2** in 44% yield after purification by column chromatography on silica gel. The ring opened structure of **2** was evident from its ^1H NMR (C_6D_6–CS_2, 1:1) spectrum which showed a singlet resonance at δ 6.84 typical of H-2 in a 1-substituted 2-H-C_{60}.[11,12] The structure of **2** was further supported by single proton resonances at δ 5.27 (d, J = 3 Hz, Ph_2CHNH), 4.83 (d, J = 11.7 Hz, H-61) and 3.62 (dd, J = 3, 11.7 Hz, NH). The ^{13}C NMR spectrum of **2** showed 47 sp^2 fullerene resonances in the region δ 154.4–136.2 and resonances for 5 sp^3 carbons in the region δ 83–58. These latter resonances were unequivocally assigned by ^1H–^{13}C NMR correlation experiments (HMBC) as δ 82.8 (Me_3CO), 70.9 (C-61), 68.1 (C-1) , 66.7 (Ph_2CH) and 58.8 (C-2). The two fullerene carbons alpha to C-1 (C-6 and C-9) and C-2 (C-3 and C-12) were observed downfield of the other fullerene resonances and occurred in the region δ 154.4–152.4. Interestingly, C-6 and C-9 and C-3 and C-12 appeared as diastereotopic pairs due to the stereogenicity of C-61 (Fig. 1). The number of different sp^2 fullerene signals suggested that most other fullerene carbons formed diastereotopic pairs.† The assignmements made to individual carbons are shown in Fig. 1. Furthermore, the HMBC experiments confirmed that the 1,2-substituted rather than the 1,4-substituted fullerene had formed.‡

The formation of **2** can be rationalized as occuring by a mechanism similar to that shown in Scheme 1, although this process may not be concerted and the protonation steps may occur at different stages along the reaction pathway. Clearly the driving force for such a ring opening must be stabilization of the incipient C-2 fulleryl carbanion **A** by delocalization over the fullerene ring. Such ring opening of cyclopropane amino esters and acids is known when a β-electron-withdrawing group is



Scheme 1 *Reagents and conditions*: i, DBU, CBr_4, PhCl, room temp.; ii, $NaBH_3CN$, pH 4.

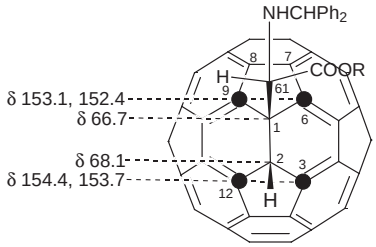


Fig. 1 ^{13}C NMR (C_6D_6–CS_2, 1:1) chemical shifts and assignments for **2** (R = Bu^t).

present on the ring that can stabilize a developing carbanionic centre.[13] The ring opening of fullerene derivatives has been observed before but not on cyclopropane derivatives or under such mild conditions.[14]

In conclusion, we have discovered a novel ring opening reaction of a methano[60]fullerene derivative under reductive conditions that allows the synthesis of 1,2-dihydro[60]fullerylglycine derivatives that would have potential for many interesting biological applications.§

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Notes and references

† Simple achiral 1-substituted 2-H fullerenes should show 30 different carbons due to their C_s symmetry (ref. 11, 12).

‡ While the structure of **2** was clear from its ^{1}H and ^{13}C NMR and IR spectral data, we have been unable to obtain a useful mass spectrum (ESMS or MALDI) of this compound.

§ To date attempts at the acid hydrolysis of the ester group (6 M HCl, TFA or TsOH) or the hydrogenolysis of the *N*,*N*-diphenylmethylamino group in **2** have not proven successful.

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