Tandem reductive ring opening-retro-Bingel reactions of bismethano[60]fullerenes to give 1,2-dihydro[60]fullerylglycines

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Bismethano[60]fullerene derivatives 1 and 3 give 1,2-dihydro[60]fullerylglycines 2 and 4 respectively by a novel tandem reductive ring opening-retro-Bingel reaction.

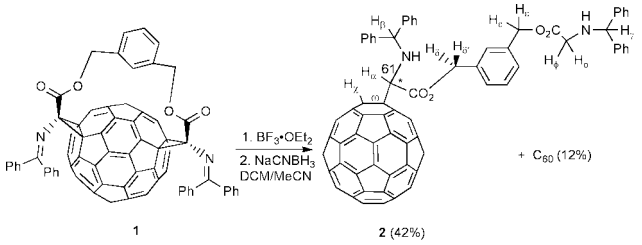
The addition of a single bis(ethoxycarbonyl)methylene unit [$C(CO_2Et)_2$] to [60]fullerene is readily achieved by treatment of C_{60} with diethyl bromomalonate under Bingel reaction conditions.[1] Sequential Bingel additions have been used to prepare the corresponding bis- and tris-adducts as mixtures of regioisomers.[2] The regiochemistry of these reactions however, improves as the fullerene becomes more substituted, as exemplified by the regioselective synthesis of $C_{60}[C(CO_2Et)_2]_6$ with the all-*e* addition pattern starting from *e-e-e*-$C_{60}[C(CO_2Et)_2]_3$.[3] The regioselective formation of bis- through to hexakis-adducts can now be realized using tethered-directed remote functionalization.[4] Anthracene and 9,10-dimethylanthracene have been employed as reversible covalent templates to regioselectively prepare tetrakis- and hexakis-derivatives ($C_{60}[C(CO_2Et)_2]_n$ n = 4,6).[5] Non-tethered bis-adducts ($C_{60}[C(CO_2Et)_2]_2$) can be isomerised under carefully controlled electrochemical conditions to afford predominantly a thermodynamically favoured mixture of bis-adducts ('walk-on-the-sphere rearrangements').[6] While one or more of the methano groups of higher adducts can be removed under reductive conditions (retro-Bingel reaction), either electrochemically[7] or chemically,[8,9] to give less substituted methano[60]fullerenes or C_{60} itself. The potential of using a malonate addend as a reversible directing group or a protecting group of more reactive double bonds on the fullerene sphere for the synthesis of functionalised fullerenes has been recently demonstrated.[7d,8]

Earlier we reported a method for preparing the protected cyclopropane amino acid fullerene derivative $C_{60}[C(N{=}CPh_2)(CO_2\,Bu^t)]$ from the reaction C_{60} and *tert*-butyl *N*-diphenylmethyleneglycinate under Bingel reaction conditions.[10] Treatment of this methano[60]fullerene derivative with sodium cyanoborohydride under protic conditions resulted in reduction of the C61 imino group and concomitant ring opening of the cyclopropane ring to give, after a further reduction step and protonolysis, the novel 1,2-dihydro[60]fullerylglycine derivative, $C_{60}H[C(NHCHPh_2)(CO_2Bu^t)]$.[10] More recently we have extended this study to the synthesis of the corresponding tethered *trans*-4 bismethano[60]fullerene derivative **1**.[11] Interestingly, the regiochemistry of this tethered reaction was different to that found using the analogous tethered bismalonate system. We report here our study on the reductive ring opening reactions of the bis-adduct **1** and that of its corresponding untethered diethyl ester analogue **3**.

Treatment of a solution of **1** in THF–MeOH at pH 4 with sodium cyanoborohydride at ambient temperature, as described by us previously,[10] resulted in only recovered starting material. However, after much experimentation, we discovered that treatment of a solution of **1** in DCM with 5 equiv. of boron trifluoride–diethyl ether, initially at 0 °C with warming to rt over 30 min (presumably to activate the imine by complexation to the imine nitrogen), followed by the addition of acetonitrile and 10 equiv. of sodium cyanoborohydride gave, after 90 min, a mixture of the 1,2-dihydro[60]fullerylglycine **2** and C_{60}. Separation of this mixture by column chromatography on silica gel gave pure samples of **2** and C_{60} in yields of 42 and 12%, respectively (Scheme 1).[12] These fullerene compounds arise formally from a tandem reductive ring opening-retro-Bingel reaction and a double retro-Bingel reaction, respectively. Interestingly, none of the double reductive ring-opened bisfullerylglycine adduct $\{C_{60}H_2[C(NHCHPh_2)(CO_2R)]_2\}$ was isolated. The structure of **2** was clearly evident from NMR spectroscopy. The UV-vis spectrum of **2** in DCM showed distinct absorbances at 430, 640 and 705 nm, similar to that found in the derivative $C_{60}H[C(NHCHPh_2)(CO_2Bu^t)]$.[10] The ^{1}H NMR spectrum of **2** revealed a one proton singlet at δ 6.84 that corresponded to the single fullerene proton (H_χ). An upfield shift of the aromatic protons of the benzhydryl moiety was consistent with the chemical transformation of the imine to the secondary amino functionality. The addend region of **2** revealed two doublets at δ 5.41 and 5.24 (J = 11.9 Hz) corresponding to the diastereotopic benzyl protons ($H_\delta/H_{\delta'}$). The other benzylic protons (H_ε) resonated as a two proton singlet at δ 5.08, whereas the two proton singlet at δ 3.40 was identified as corresponding to the methylene protons (H_ϕ). A singlet one proton resonance at δ 4.84 corresponded to the benzhydryl resonance (H_γ). A three proton coupled spin system was identified as H_α (δ 4.97, d, J 12.3 Hz), H_β (δ 5.24, d, J 2.5 Hz) and NH (δ 3.67, dd, J 12.3, 2.5 Hz).

The ^{13}C NMR spectrum of the fulleryl sp^2 region of **2**, like that of $C_{60}H[C(NHCHPh_2)(CO_2Bu^t)]$, revealed a structure lacking a plane of symmetry due to the newly formed stereogenic centre at C61. This centre gives rise to diastereotopic pairs of fulleryl sp^2 carbons that lie either side of the plane bisecting C1 and C2 of the fullerene sphere. A single set of fulleryl sp^3 resonances at C_χ (δ 58.9), and C_ω (δ 67.3) were observed in addition to resonances corresponding to the addend C_α (δ 70.4), C_β (δ 66.3) C_δ (δ 67.8), C_ε (δ 66.2), C_ϕ (δ 47.5) and C_γ (δ 66.5). These carbons were readily assigned from HSQC and HMBC experiments.

In principle, the product **2** could arise from the anionic intermediates **A** or **B**. The driving force for mono-elimination of the tether from **A** or **B** might be the relief of ring strain upon expulsion of one arm of the tether. In the case of **A**, a further driving force may be the conversion of a fulleryl dianion intermediate to a thermodynamic more stable fulleryl monoanionic system. Clearly the rate of mono-elimination of the



Scheme 1

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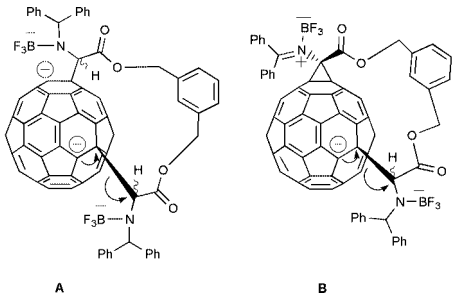
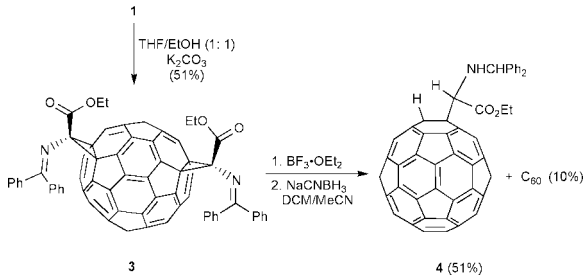
addend is much faster than the rate of elimination of the entire addend as indicated by the relative isolated yields of **2** and C_{60}.



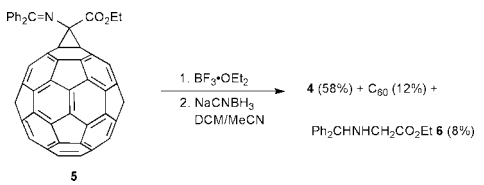
A B

To examine the influence of the tether on this ring opening-retro-Bingel reaction, the diethyl ester **3** was prepared from the base-catalysed trans-esterification of **1** with ethanol–THF–sodium carbonate as shown in Scheme 2. Treatment of **3** under similar reduction conditions to those described for **1** above also resulted in formation of a ring opened-retro-Bingel product, the ethyl ester **4**. This compound was obtained pure in 51% yield after column chromatography. A smaller amount of C_{60} (10%) was also isolated (Scheme 2). Compound **4** exhibited ^{1}H NMR and ^{13}C NMR resonances that were almost identical to those of $C_{60}H[C(NHCHPh_2)(CO_2Bu^t)]$[10] and **2**, except for those resonances associated with the different ester groups. The mono-ester **4** was also prepared in 58% yield from reductive ring opening of the methano[60]fullerene **5** (Scheme 3). In this case C_{60} (12%) and the reduced addend **6** (8%) were also isolated. The isolation of **6** supports our earlier proposed mechanism for these ring-opening reactions.[10,13]



Scheme 2

Thus we have demonstrated a general method for reductive ring opening of [60]fullerenes having a fused cyclopropane imino ester moiety. Both bis- and monomethano[60]fullerenes of this type give 1,2-dihydro[60]fullerylglycines, the latter by a novel tandem reductive ring opening-retro-Bingel reaction. In light of these results it can be concluded that the presence of the tether is not the driving force for the mono-elimination of one of the addends. While C_{60} is formed in all of these reactions it is only a minor component and thus the rate of elimination of one of these addends from the bismethanofullerene derivatives appears to be higher than the corresponding elimination of both addends. These results suggest that a dianion like **A** may be an intermediate in the tandem reductive ring opening-retro-Bingel reactions of **1** and **3**.



Scheme 3

The application of this chemistry to prepare more highly functionalised fullerenes is in progress. In principle, bis-cyclopropane imino esters can also function as directing and protecting groups for the synthesis of more highly functionalised fullerenes. For example, after the addition of further addends to the fullerene surface of **1** or **3** the bis-cyclopropane imino ester group could be then converted, under relatively mild conditions that would be compatible with a variety of other functional groups, to the mono-fullerylglycine moiety to give a variety of novel multifunctionalised fullerenes.

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12 Synthesis of **2**: Boron trifluoride–diethyl ether (0.104 g, 732.80 μmol) was added dropwise over 1 min to a solution of **1**[11] (0.095 g, 73.19 μmol) in DCM (100 mL) at 0 °C. The reaction mixture was allowed to warm to rt over a 30 min period when MeCN (50 mL) was added. Sodium cyanoborohydride (0.046 g, 732.80 μmol) was added to the reaction mixture which was stirred for 90 min and then concentrated *in vacuo*. The reaction mixture was redissolved in chloroform (100 mL) and washed with saturated ammonium chloride solution (10 mL), followed by saturated sodium bicarbonate solution (10 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Column chromatography, eluting with DCM–hexane (90:10) provided [60]fullerene (0.006 g, 12%) and **2** (0.043 g, 42%) as a brown amorphous solid. UV/vis (DCM) 330 nm (sh, 15000), 435 nm (3000). ^{1}H NMR ($CDCl_3$ CS_2 (80 : 40), 600 MHz): d 3.37 (s, 2H), 3.66 (dd, 1H, J = 12.3, 2.7 Hz), 4.84 (s, 1H), 4.98 (d, 1H, J = 12.3 Hz), 5.07 (s, 2H), 5.24 (d, 1H, J = 11.9 Hz), 5.28 (d, 1H, J = 2.7 Hz), 5.41 (d, 1H, J = 11.9 Hz), 6.84 (s, 1H), 7.19 (t, 2H, J = 7 Hz), 7.23–7.38 (m, 14H), 7.41 (t, 2H, J = 7.9 Hz), 7.47 (t, 2H, J = 7.6 Hz), 7.64 (d, 2H, J = 7.8 Hz), 7.74 (d, 2H, J = 7.8 Hz). ^{13}C NMR ($CDCl_3$ CS_2 (80 : 40), 125 MHz): δ 172.39, 172.31, 154.03, 152.99, 152.17, 151.05, 147.50, 147.20, 147.07, 146.97, 146.43, 146.43, 146.42, 146.38, 146.33, 146.25, 146.19, 146.18, 146.16, 145.88, 145.75, 145.71, 145.58, 145.44, 145.42, 145.35 (2 × C), 145.31, 145.22, 144.74, 144.68, 144.38, 144.35, 143.17, 143.13, 143.11, 142.63, 142.58, 142.56, 142.43, 142.23, 142.14, 142.09, 142.06, 142.04, 142.01, 141.72, 141.70, 141.54, 141.49, 141.47, 140.39, 140.37, 139.62, 139.23, 137.34, 136.43, 136.32, 136.14, 135.45, 129.32, 129.12, 129.07, 129.04, 128.91, 128.71, 128.04, 127.68, 127.29, 127.26, 70.38, 67.74, 67.32, 66.56, 66.35, 66.09, 58.87, 49.08. MS(ES): *m/z* 1327 (M + 23), 720 (C_{60}).

13 The reduced addend was not isolated from the reactions involving **1** and **3** because of the small scales of these reactions.