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Disciplines

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Reactions of Iminoglycines with C_{60} Fullerene and their Unambiguous Characterisation using NMR Spectroscopy

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Abstract

This review examines the addition of iminoglycine derivatives to C_{60}, yielding protected fullerenyl pyrroline derivatives. Subsequent reduction with sodium cyanoborohydride produces ring-opening adducts which are protected fullerenyl α-amino acids. Pyrroline bisadducts can be produced using tethers to link two iminoglycine units together, and variations include combining with malonate reactive groups this giving rise to interesting observations as to the regioselectivity of such reactions. All derivatives are fully characterised by NMR spectroscopy, and in the case of bis-adducts, the regioselectivity is determined from $^{1}H/^{13}C$ and $^{13}C/^{13}C$ connectivity patterns using HMBC and INADEQUATE experiments, respectively, thus eliminating the need for comparative techniques or X-ray crystallography to determine the structures.

Keywords:

fullerenyl amino acid, iminoglycine, fullerene, regioselectivity, fullerene characterisation, NMR spectroscopy

Introduction

The pioneering investigations into the chemical reactivity of [60]fullerene have provided a precedent towards the design and synthesis of novel and sophisticated architectures that may have

applications in medicinal chemistry and the material sciences.[1,2] Further, with the increasing degree of complexity of fullerenyl derivatives comes the necessity for a larger range of reliable techniques for the unequivocal characterisation of such molecules. Such techniques should rely heavily on direct methods of characterisation, *e.g.* NMR spectroscopy, rather than the current, well used comparative techniques.

The concept of using the fullerene cage as a three-dimensional template in all aspects of medicinal chemistry, nanotechnology and materials science is well established. The momentum for our initial investigations into fullerenyl chemistry was the notion that the complete chemical control of functionality on the surface of the C_{60} sphere would allow the precise placement of specific binding groups, permitting subsequent applications in medicinal chemistry with a large array of enzymatic binding pockets to be easily targeted. Clearly, this level of synthetic achievement is still a significant distance from reality, with not only current limitations on the available synthesis technology, but additional limitations in the unambiguous characterisation of these multifunctionalised fullerenyl derivatives.

With these principles in mind we embarked on a program to investigate the regioselective synthesis and characterisation of fullerenyl derivatives with multiple amino acid functionalities with a view to utilise such molecules as templates for molecules to be used in medicinal chemistry and nanotechnology. Our starting point was to try and synthesise fullerenyl α-amino acids, as such binding groups could have clear applications in biological systems - a number of such systems are illustrated in Figure 1. The proline derivative **1** is already well known whereas the more generic fullerenyl α-amino acids **2** and **3** had not been reported at the beginning of our studies.

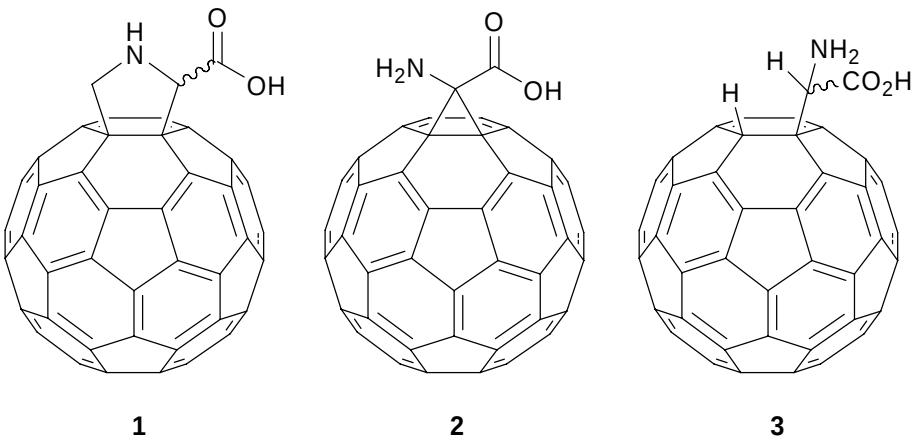
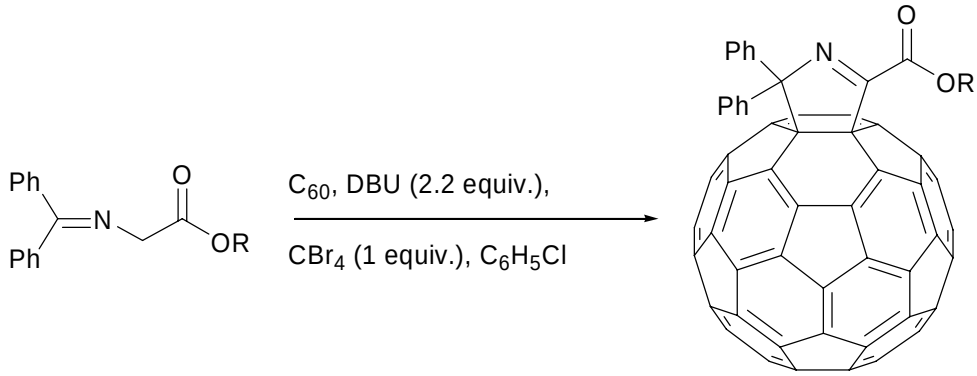


Figure 1: Possible forms of fullerenyl α-amino acids

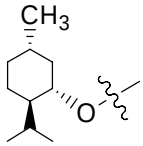
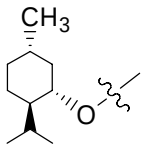
Reaction of Imino Glycines

Our initial studies began with an examination of the addition of *N*-(diphenylmethylene)glycinate esters **4a-d** to [60]fullerene under Bingel conditions (Scheme 1). We reported the synthesis of the methano[60]fullerenyl iminoesters **6** (Figure 2) based upon extensive structural characterisation including the observation of a single sp^3 fullerene resonance (between δ 82-83) in the ^{13}C NMR spectra (4:6 $CDCl_3$:CS_2) of these compounds at 75 or 100 MHz, which implied to us that these molecules had C_S symmetry. Subsequent examination of the ^{13}C NMR spectra (4:6 $CDCl_3$:CS_2) of these compounds at higher field (150 MHz) showed two sp^3 fullerene resonances separated by 0.02-0.03 ppm (3 - 4.5 Hz) in this chemical shift region. When pure $CDCl_3$ was employed as the solvent, these resonances were resolved by 16 Hz. This prompted us to re-examine our initial NMR and structural assignments and to perform INADEQUATE NMR experiments to unequivocally determine that the products of these reactions were [60]fullerenyldihydropyrroles **5a-d**, as illustrated in Scheme 1.[3] Further key evidence to this assignments were the HMBC experiments which indicated a strong correlation from the *ortho* protons of the phenyl substituents to a fullerenyl sp^3 carbon atom (**5**, Fig 2) and no correlation to any downfield resonance attributable to the imine group (as would be necessary in the presence of a 3-membered ring structure, **6**, Fig 2). The assignment of the entire fullerene sphere was unequivocally determined by 2D-INADEQUATE and ^{13}C NMR experiments using 10% ^{13}C enriched fullerene. Fullerenyl resonances were distinguished

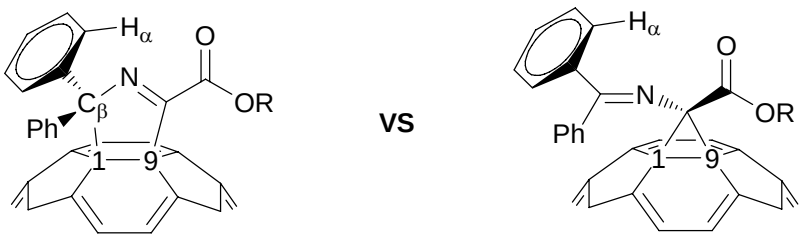
from non-fullerenyl resonances by the presence of ^{13}C-^{13}C coupled satellites situated on either side of a central resonance peak. Assignment of the carbon sphere was achieved on the basis of one-bonded ^{13}C-^{13}C connectivities and examination of the carbon-carbon coupling ($^{1}J_{CC}$) values knowing typical values for $C(sp^2)$-$C(sp^3)$ bonds (~48 Hz), the longer 5,6 ring-fused bonds (54-57 Hz) and the shorter 6,6 ring-fused bonds (65-71 Hz).[3-5]



4a-d **5a-d**

			Yields
a	R = ^{t}Bu	R = ^{t}Bu	46%
b	R = Et	R = Et	72%
c	R = 	R = 	31%
d	R = $EtCO_2CH_2$-	R = $EtCO_2CH_2$-	46%

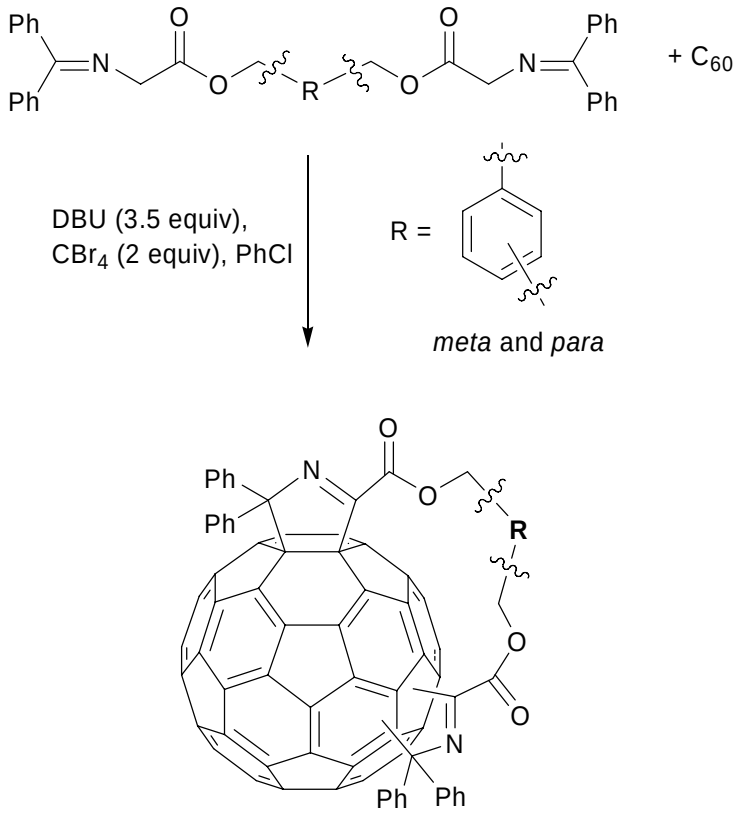
Scheme 1:



5 **6**

Figure **2**:

The corresponding bisadducts, connected by the well known benzene dimethanol tether, reacted with C_{60} to give the expected [60]fullerenyldihydropyrroles bis-adducts with the regiochemical outcome *trans*-4 and *cis*-3 in a 3.2 : 1 ratio for the '*meta*' tether and *trans*-3 and *trans*-4 in a 3.7 : 1 ratio for the '*para*' tether (Fig 3). There was no bisadduct formed using the '*ortho*' tether.[5]



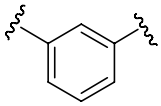
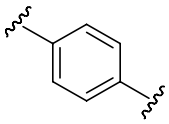
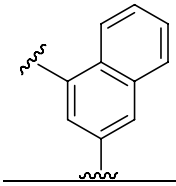
R	Regiochemistry and yield (%)	
	**7** *trans-4* (32)	**8** *cis-3* (10)
	**9** *trans-3* (37)	**10** *trans-4* (10)
	**11** *trans-4* (9)	**12** *cis-3* (5)

Figure 3: Synthesis of the bisadducts using iminoglycine addition chemistry

The corresponding bis-malonate derivative, linked by the identical '*meta*' tether, yielded exclusively the *cis*-2 bis-methano[60]fullerene.[6] Given the differences in regiochemistry using an identical tether, we decided to examine the regiochemical outcome of a mixed-tethered system utilizing 1,3-benzene dimethanol to tether a *N*-(diphenylmethylene)glycinate and a malonate unit.

The reaction of **13** with [60]fullerene under Bingel conditions using CBr_4 (2 equiv) and DBU (4 equiv) gave the *e*-edge-[60]fullerenylmethanodihydropyrrole **14** in a yield of 30%. This regiochemical outcome was the sole product regardless of the order of addition (initial reaction of the malonate moiety *vs* iminoglycine addition) or whether the reaction was done in the presence of excess reagent or in a stepwise fashion. The regiochemical outcome was found to be independent of the order of addition of either the *N*-(diphenylmethylene)glycinate or the malonate moieties. The mixed tethered-system **13** gave a different regiochemical outcome (exclusively the *e*-edge-isomer) to the corresponding symmetrical tethered systems comprising a bis-malonate (*cis*-2 isomer) or a bis-iminoglycine (*trans*-4 and *cis*-3, 3 : 1). These differences indicate that these regiochemical outcomes are not dependent on the nature of the tether alone, but must incorporate additional factors including the mechanism of each reaction, the orientation of the tether based upon the first addend, and the electronic nature of the mono-substituted-fullerenyl changing the likely kinetic and thermodynamic outcomes of subsequent additions.[7] The first step in the cyclisation reactions of mono-adducts of these reactions to give bis-adducts**,** was expected to involve the addition of an α-bromoenolate anion to a mono-substituted-[60]fullerene. This initial step may be reversible, however, the final step, attack of a fullerenyl anion on either the bromomalonate or the bromoiminoglycinate moiety would be expected to be irreversible and thus under kinetic control. Clearly both cyclisations favour formation of the *e*-edge-regioisomer in the second reaction step, independent of the nature of the first addend.

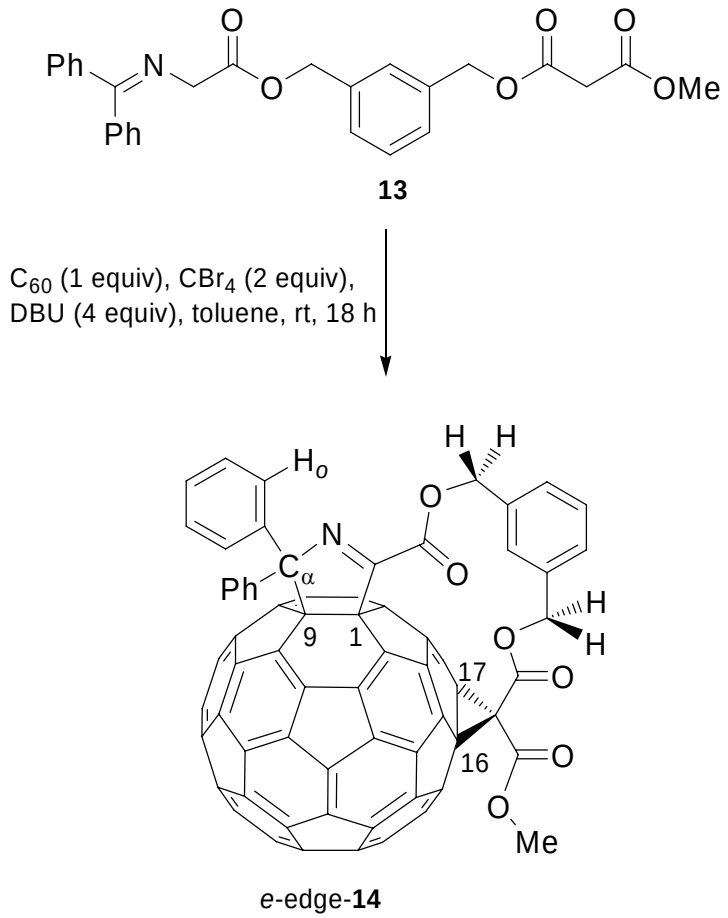
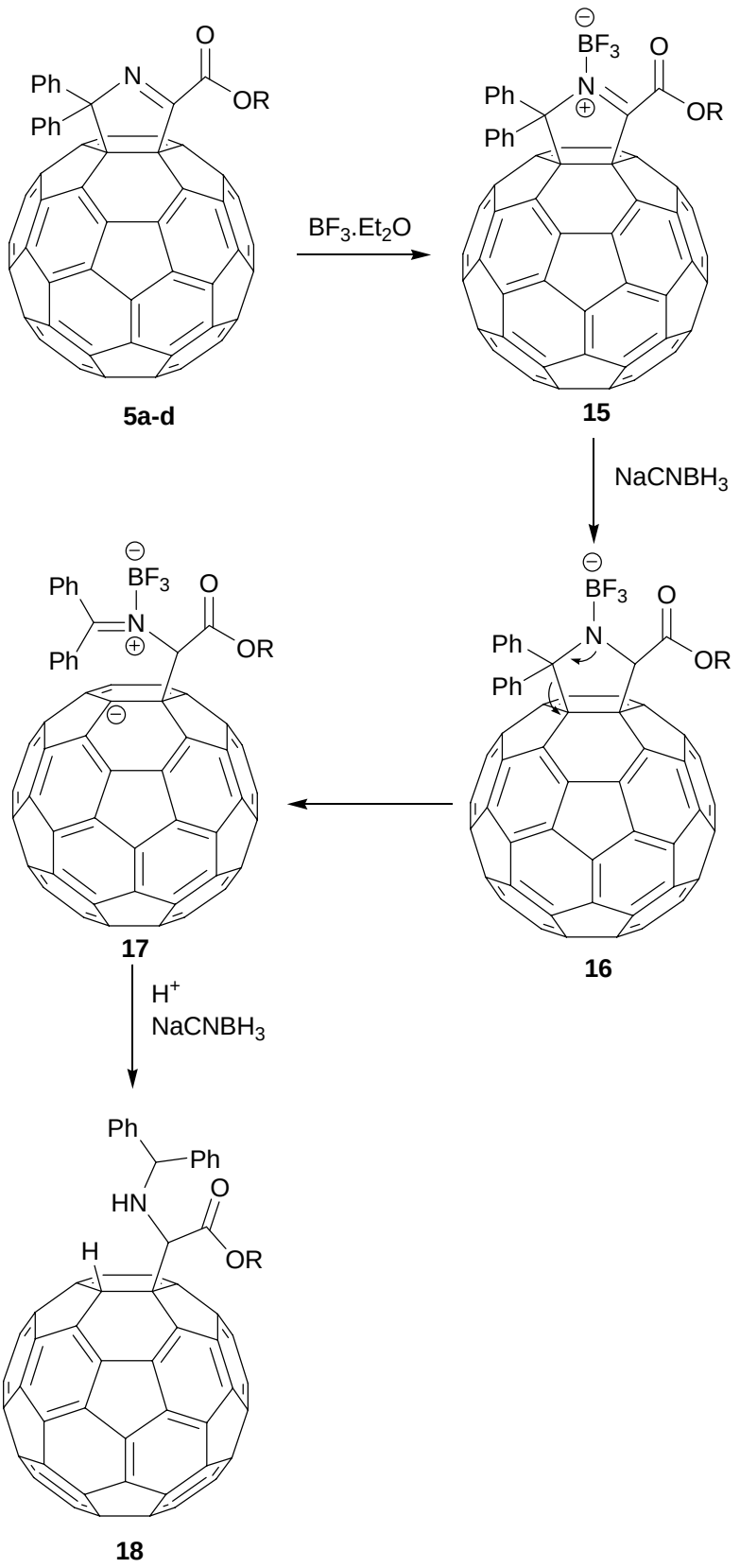


Figure 4: Addition of the mixed malonate-iminoglycine tether to C_{60}.

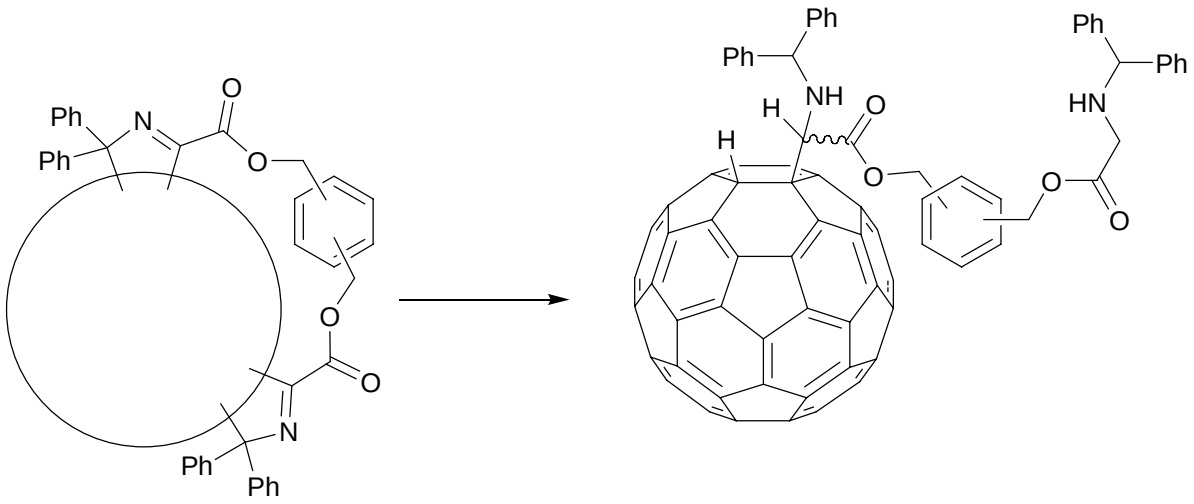
Ring Opening Reactions

In an interesting reaction, reductive ring-opening products of methano[60]fullerenyl iminoesters **5a-d** with sodium cyanoborohydride yields the novel ring-opened 1,2-dihydro[60]fullerenylglycinates **18a-d** in good yields.[8] The mechanism of this reaction is proposed to proceed via the intermediate **15** (Scheme 2) which undergoes ring-opening to give the more conjugated (stable) diphenylmethyleneimine, fullerenyl anion intermediate **17**, rather than the less conjugated $Ph_2CHN{=}C(fullerenyl)(CO_2R)$ imine, fullerenyl anion intermediate (not shown). Further reduction of the imine moiety of **17** and protonation gives the ring-opened 1,2-dihydro[60]fullerenylglycinates.[3] Extension of this reaction to the corresponding bisadducts **7-10** gives rise to the reduced 'mono-adduct' **19** presumably via a transient unstable dianion species and the driving force of addend removal arising from the transformation of sp^3 to sp^2 hybridisation. Using identical reaction conditions the mixed-bisadduct **13** also yielded the corresponding ring-

opened product in good yield.[9] Subsequent transesterification of **20** removed the tether and, in principal, indicated the ability to develop further chemistry around such systems. In general, one of the most interesting aspects of this unique ring-opening reaction is the possibilities for further chemistry, either utilising the protected amino or carboxylate functionalities, or the acidic fullerenyl hydrogen in a range of possible chemistries.

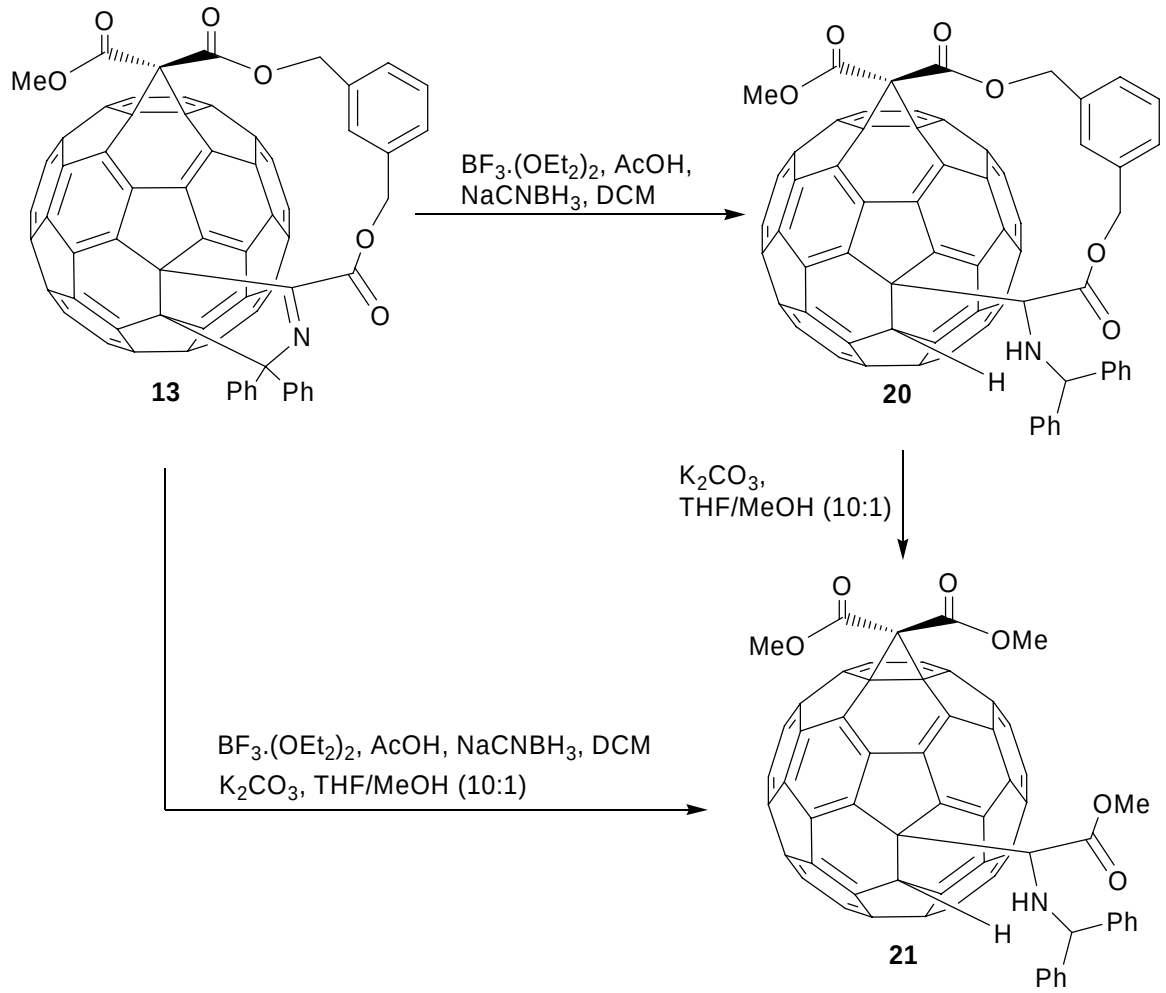


Scheme 2: Reaction mechanism of the reductive ring-opening of 1,2-dihydro[60]fullerenylglycinates.



7-10 **19**

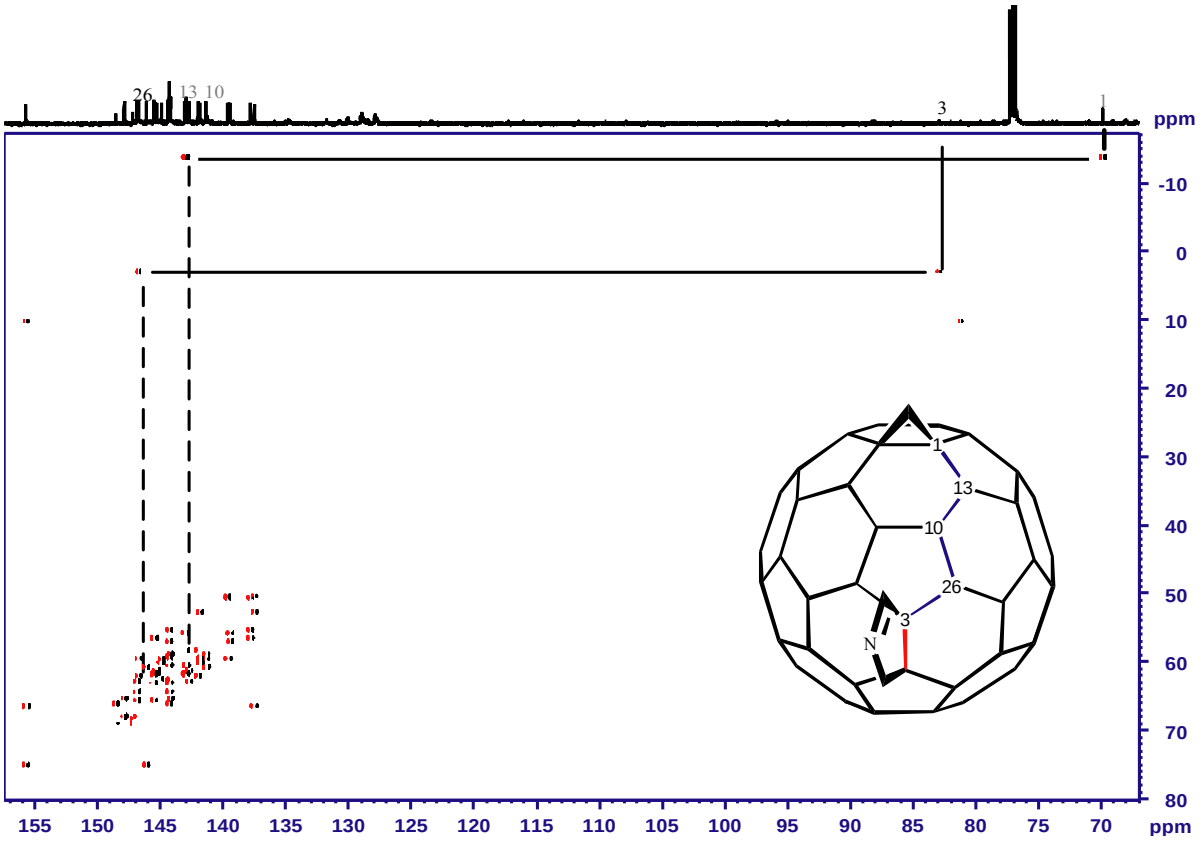
Figure 5: Ring-opening of the bis-adducts **7-10**.



Scheme 3: Reductive ring–opening of the mixed-tether biadduct. Ring opening followed by transesterification yields the identical outcome as the inverse order of reaction.

NMR Characterisation of C_{60} Adducts

The unambiguous characterisation of our fullerenyl adducts by NMR spectroscopy is a key component of our studies. By assigning as completely as possible all carbon atoms in the molecule we ensure that there is no ambiguity in the structural assignment with no reliance on comparative techniques. The establishment of symmetry is a key initial step in this process with the identification of the number of full intensity and half-intensity peaks in the fullerenyl region of the ^{13}C NMR spectra. A further key element is the unambiguous assignment of at least two different carbon atoms present on the surface of the sphere – these two atoms will be starting and finishing points for the sequence of stepwise correlations that will establish the relative positions of substituents present. As a straightforward example of this process, the mixed-tether bisadduct **13** was assigned using the INADEQUATE experiment illustrated in Figure 6. The unambiguous assignment of the sp^3 carbon atoms C1 and C3 was facilitated by previous well established experiments on the corresponding monoadducts and represent the starting and finishing points for the series of correlations. The stepwise correlations are illustrated by dotted arrows and the 'walk across the sphere' from C1 to C3 unambiguously establishes the *e*-regiochemistry for this bisadduct. This particular example of the process is a relatively easy example as the two addends themselves are different (a cyclopropyl derivative and a 5-membered pyrrolidine ring) and this gives rise to a greater dispersion of signals to assign to the sp^2 fullerenyl carbon atoms. Further, due to the plane of symmetry that bisects the tether (Figure 7), there are only 29 different fullerenyl carbon atoms to assign. These conditions significantly simplify the analysis and reduce the possibility of overlapping signals.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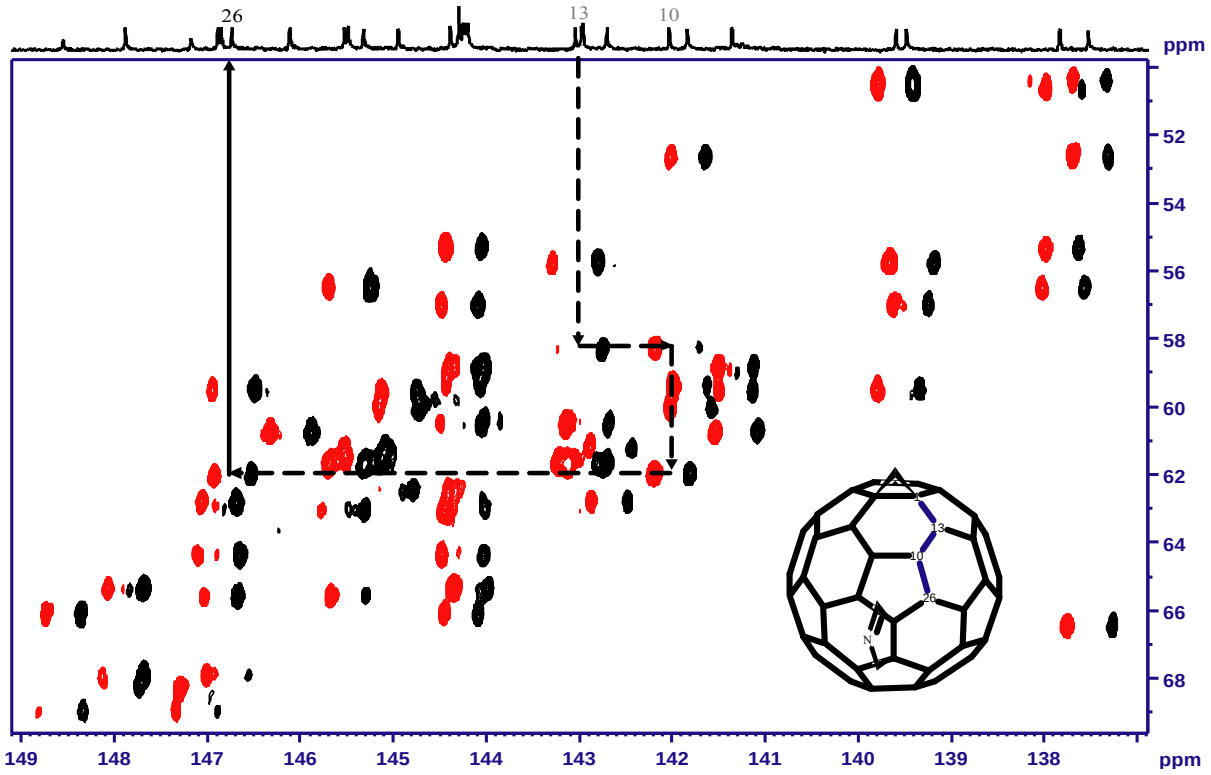
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Figure 6: Assignment of the regiochemistry of the C_{60} mixed-tether adduct **13**. The upper portion illustrates the entire spectrum and shows the starting and finishing points of C1 and C3. The lower portion is an expansion of the fullerenyl section of the spectrum.

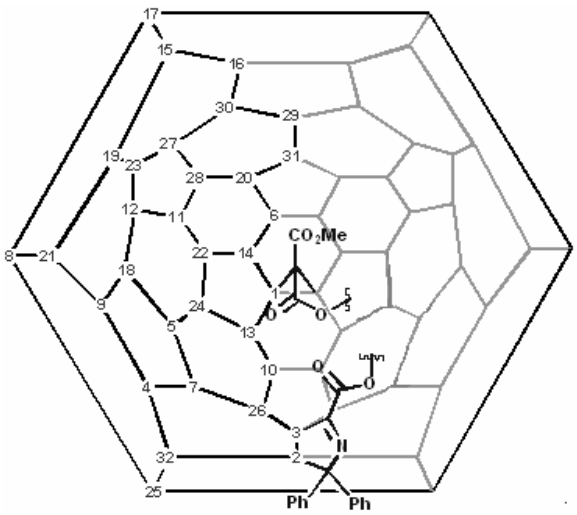

Figure 7: Schlegel diagram of the mixed-tether adduct **13** showing the plane of symmetry – the 1,3-dimethylbenzene component of the tether is omitted for clarity.

Conclusions

Our initial studies on the addition of iminoglycines to C_{60} in attempts to produce protected amino acid derivatives led us to investigate other chemistry of significance to the fullerene area. This includes the synthesis of pyrrolidinofullerenyl adducts and subsequent reductive ring-opened derivatives. The chemistry is also applicable to multifunctionalised fullerenyls. The importance of full characterisation of adducts is also highlighted with the complete assignment of our structures by NMR spectroscopic techniques. We are currently extending this chemistry to include the synthesis of α-amino acid fullerenyl derivatives – as originally planned – and the investigation of higher order fullerenyl adducts.

Acknowledgements

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