RSC Advances

ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/advances

RSC Advances RSCPublishing

REVIEW

[*60*]Fullerenyl Amino Acids and Peptides: A Review of their Synthesis and Applications

Sreenu Jennepalli[a,b], Stephen G. Pyne*[a] and Paul A. Keller*[a,b]

Cite this: DOI: 10.1039/x0xx00000x

Received 00th January 2012,
Accepted 00th January 2012

DOI: 10.1039/x0xx00000x

www.rsc.org/

This review reports on the latest progress in the synthesis of fullerenyl amino acids and related derivatives, and categorises the molecules into functional types for different uses: these include directly attached fullerenyl amino acids, fullerenyl N- and C-capping amino acids, and those amino acids in which the [*60*]fullerene group is attached to the amino acid side chain. These first and last mentioned derivatives have the potential to be incorporated into non-terminal positions of peptides. The applications of these substrates, by integration into different biological and materials chemistry programs, are also highlighted.

Introduction

A large portion of synthetic [*60*]fullerene chemistry is directed towards its functionalization, often providing biologically active derivatives and molecules with applications in material science.[1] The impetus for such work was to exploit the physical properties of [*60*]fullerene (such as sensitization of singlet oxygen and electron acceptor characteristics) and combine this with the properties of biomolecules (water solubility and precise secondary and tertiary structure).[1e, 2] For example, [*60*]fullerene derivatives covalently linked to peptides and proteins has been the goal of a number of research groups concerned with the application of [*60*]fullerene-peptide conjugates to biological problems.[3] It was anticipated that the addition of biologically active compounds to [*60*]fullerene in a strict regioselective fashion would aid the activity and specificity of future therapies. From a material science and a medicinal chemistry perspective, fullerenyl amino acids are important targets potentially serving as central hubs in architecturally defined nanostructures or 3D-templates in drug design.[1e, 4] To date fullerenyl amino acids and peptide derivatives have been prepared by the initial attachment of a handle to the fullerene followed by coupling to a protected amino acid or peptide.[5] In recent times,[1f, 5c] the field has matured significantly such that there are many different types of fullerenyl amino acids that can be categorised according to the properties of the amino acid itself, allowing for a broader perspective of how they could be incorporated into different research programs. This review not only reports on latest progress in the synthesis of fullerenyl amino acids and related derivatives, but attempts to categorise the molecules into functional types for different uses: these include directly attached fullerenyl amino acids, fullerenyl *N*- and *C*-capping amino acids, and those amino acids in which the [*60*]fullerene group is attached to the amino acid side chain. These first and last mentioned derivatives have the potential to be incorporated into non-terminal positions of peptides. The applications of these substrates by integration into different biological and materials chemistry programs are then highlighted.

1 Synthesis of Derivatives with Fullerenyl Substituents Directly Substituted to the Amino Acid α-Carbon

There are surprisingly few examples of fullerenyl amino acids that are direct analogues of α-amino acids, *i.e.* the α-carbon is bonded directly to a C_{60} carbon atom. There are two examples of this type of molecule, the well-established fullerenoprolines, and there are reports of protected versions of amino acids whereby the fullerenyl substituent is directly coupled to the α-carbon.

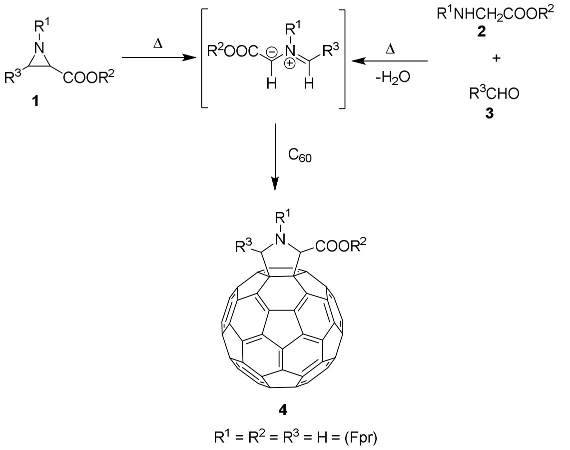
Fullerenoproline derivatives

The first synthesis of α-substituted fullerenyl amino acids, the fullerenoprolines (Fpr) (**4**) was achieved by the addition of azomethine ylides to [*60*]fullerene.[6] The azomethine ylide intermediate can be generated in two different ways, either *via* a thermal ring-opening of aziridines **1** or *via* tautomerisation of iminium salts formed by the condensation of α-amino esters **2** with aldehydes **3** (Scheme 1). These reactions allow for a

---

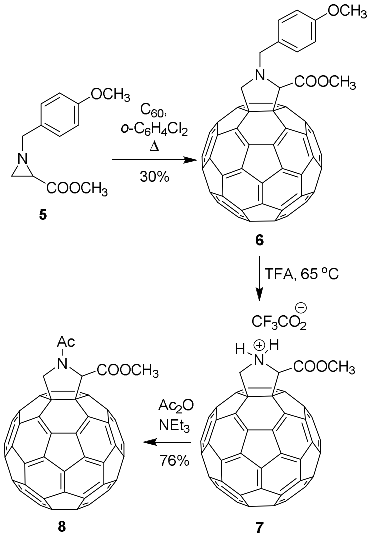
[a] *School of Chemistry, University of Wollongong, Wollongong, NSW 2522, Australia*
Fax: (+) +61 2 4221 4287
E-mail: keller@uow.edu.au spyne@uow.edu.au
Homepage: http://smah.uow.edu.au/chem/contacts/UOW008575.html
[b] *ARC Centre of Excellence for Electromaterials Science, University of Wollongong, NSW 2522, Australia.*

significant number of Fpr derivatives to be generated by using different combinations of aldehydes and amino esters.



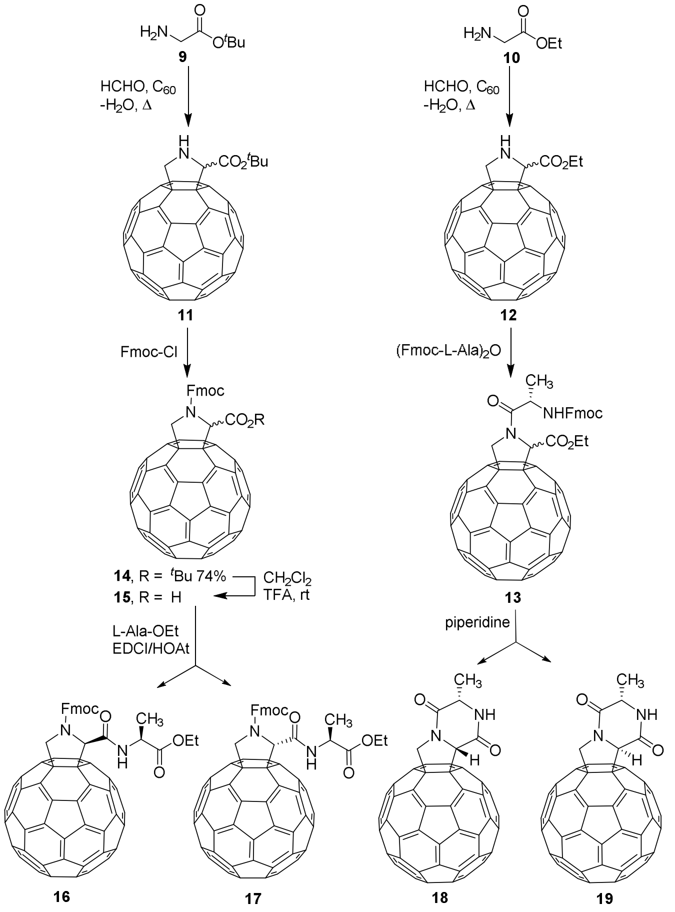
Scheme 1: The synthesis of fulleropyrrolidines **4** can be achieved by thermal addition of aziridines or iminium salts to [*60*]fullerene.

Fpr analogues can be prepared with the pyrrolidine nitrogen protected (Scheme 2) or unprotected (Scheme 3).[7] Addition of the aziridine **5** to [*60*]fullerene under thermal conditions formed the protected *N*-protected-Fpr **6**. Subsequent treatment with TFA provided the secondary amine salt **7**, which could then be acylated with acetic anhydride to provide **8** (Scheme 2).[7]



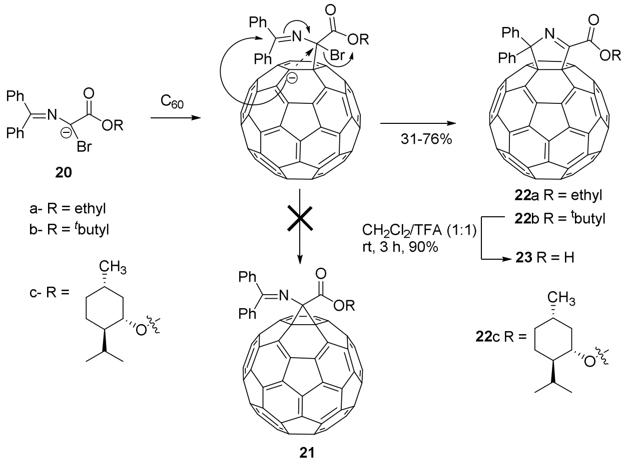
Scheme 2: Synthesis of **8** was achieved through thermal addition of aziridine **5** to [*60*]fullerene.

To obtain more useful Fpr derivatives for peptide synthesis, the azomethine ylides, which are generated *in situ* from the reaction of glycinate esters **9** and **10** with paraformaldehyde, can be added to [*60*]fullerene to produce the free Fprs **11** and **12**, respectively. These were relatively unstable and had to be kept as dilute solutions in the dark.[7] However, the amine group was readily functionalized using standard acylation procedures with acid anhydrides and acid chlorides (Scheme 3), to deliver diastereomeric mixtures of fullerenyl amino esters of the type **13**. Alternatively the amine **11** was protected as the *N*-Fmoc derivative **14**, and then the *tert*-butyl ester converted to the acid **15** by treatment with TFA. Subsequent coupling with ethyl L-alaninate under EDCI/HOAt conditions afforded the diastereomers **16** and **17**. The diastereomeric ratio of **13** was determined by formation of the dioxopiperazines **18** and **19**, thus eliminating the additional complexity in characterization imposed by amide rotamers.[7]



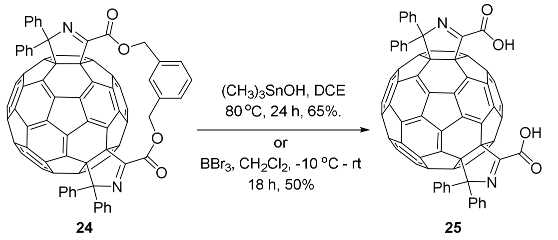
Scheme 3: Synthesis of Fpr peptide derivatives **16-19**.

A second type of fullerenyl amino acid was initially envisaged as a methanofullerene of the type **21** (Scheme 4). Strategies towards such molecules include the addition of diphenyliminoglycinates to [*60*]fullerene under Bingel cyclopropanation reaction conditions which was originally reported to furnish the corresponding methano[*60*]fullerene derivatives **21** (Scheme 4).[8] However subsequent extensive NMR studies revealed that the structure of the products was that of the dihydrofullerenoproline derivatives[8b] **22**, and not the more strained three-membered (cyclopropane) ring products **21**. The dihydrofullerenoproline derivative **22b** was hydrolysed to its carboxylic acid using TFA yielded **23** in 90% yield.



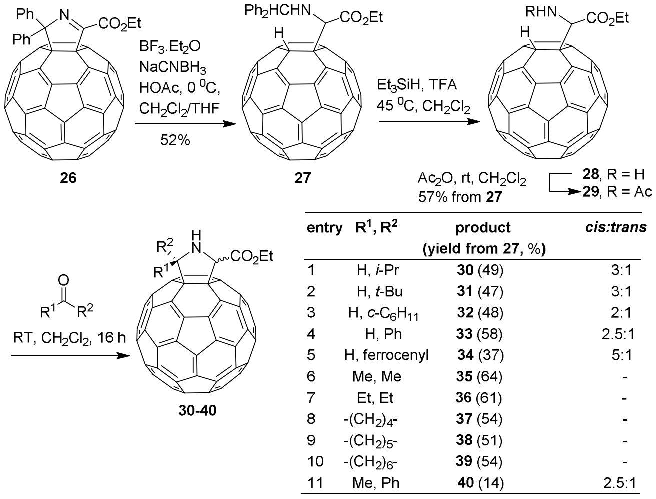
Scheme 4: The addition of iminoglycinate to [*60*]fullerene under Bingel cyclopropanation reaction conditions provides the analogous [*60*] dihydrofullerenoproline derivative **22**, with a proposed mechanism, and not the previously reported methano[*60*]fullerene **21**.

The diacid[9] **25** (Scheme 5) was synthesised from the previously reported bis-adduct **24**[8b] by hydrolysing the diester functionality with $(CH_3)_3SnOH$ or BBr_3 in 65% and 50% yields respectively. This diacid **25** has been used to synthesise potential biologically useful fullerene amino acid derivatives.



Scheme 5: Synthesis of diacid **25**.

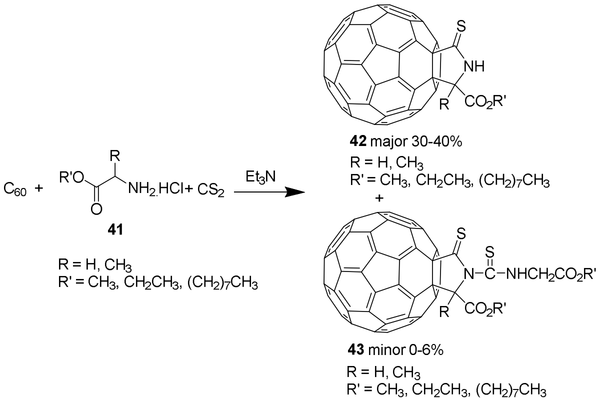
$BF_3.Et_2O$ and $NaCNBH_3$ mediated reductive ring-opening of the dihydrofullerenoproline derivative[8b] **26** yields ethyl *N*-benzhydrylfullerenyl[*60*]glycinate **27**, which was N-deprotected to give ethyl fullerenylglycinate[10] **28**, a true fullerenyl α-amino ester, which was fully characterized as its more stable N-acetyl derivative **29**. Therefore, the original structure **26** could be considered as a protected version of **28**. The free amine of **28** reacted with a variety of aldehydes and ketones in a Mannich-type process to produce 5-substituted and 5,5-disubstituted fullerenoprolines **30-40**. This process represents a versatile and general strategy to synthesise fullerenoprolines.



entry	R^1, R^2	product (yield from 27, %)	*cis:trans*
1	H, *i*-Pr	**30** (49)	3:1
2	H, *t*-Bu	**31** (47)	3:1
3	H, *c*-C_6H_{11}	**32** (48)	2:1
4	H, Ph	**33** (58)	2.5:1
5	H, ferrocenyl	**34** (37)	5:1
6	Me, Me	**35** (64)	-
7	Et, Et	**36** (61)	-
8	$-(CH_2)_4-$	**37** (54)	-
9	$-(CH_2)_5-$	**38** (51)	-
10	$-(CH_2)_6-$	**39** (54)	-
11	Me, Ph	**40** (14)	2.5:1

Scheme 6: Synthesis of 5-substituted and 5,5-disubstituted fullerenoprolines **30-40**.

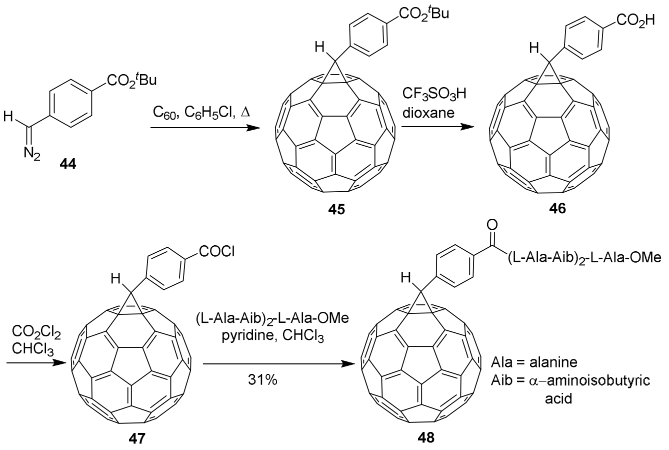
The reactions of amino acid ester hydrochlorides and CS_2 with [*60*]fullerene in the presence of Et_3N yields novel [*60*]fullerene derivatives **42** (major) and **43** (minor) containing biologically active amino acids,[11] thioamide, and thiourea units. The thiolactam groups in compounds **42** are sensitive to moisture and can easily be hydrolyzed to the corresponding lactams.



Scheme 7: Reactions of [*60*]fullerene with amino acid esters and CS_2.

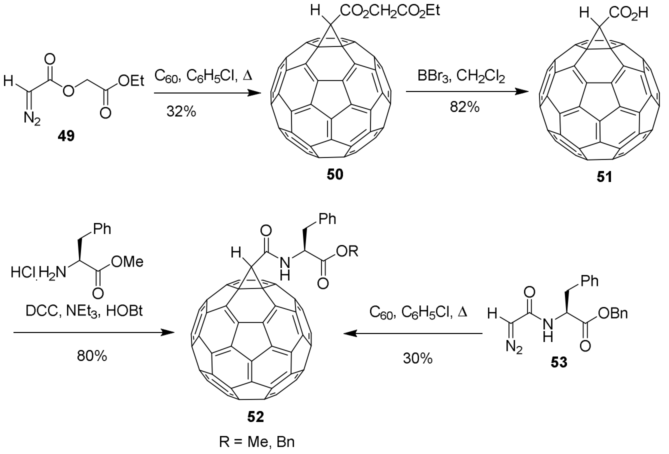
2 Synthesis of [*60*]fullerenyl N-Capped Peptides and Amino Acids

The thermal addition of the diazomethane derivative **44** to [*60*]fullerene and subsequent deprotection of the ester of the resulting methano[*60*]fullerene **45** provided the acid **46**.[12] This represented the first synthesis of a fullerenyl compound which had a synthetic handle to readily allow for peptide functionalization (Scheme 8). The acid **46** was converted to the reactive acid chloride **47** which underwent amide coupling with a pentapeptide under basic conditions to provide the first reported fullerenyl peptide **48**.[12]



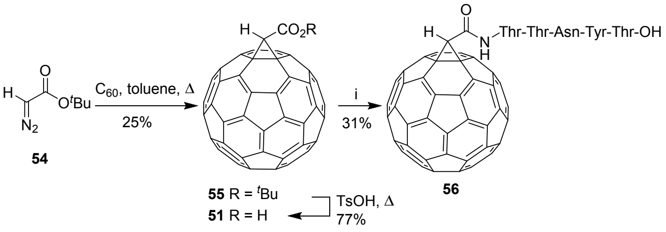
Scheme 8: Synthesis of **48** through a diazo-addition of **44** to [*60*]fullerene.

This work was extended to alkyl diazoacetates of the type **49**, which was added to [*60*]fullerene forming the methano[*60*]fullerene **50**, which was deprotected to the carboxylic acid **51** and then coupled to amino acids under standard DCC coupling reaction conditions to form fullerenyl amino acid esters of the type **52**.[13] Alternatively, a more efficient route was developed, that allowed the direct addition of diazoamides to [*60*]fullerene. For example, a solution of [*60*]fullerene in toluene was treated with the diazoamide **50** at reflux for 48 h providing the fullerenyl amino acid **53** (R = Bn) in 30% yield (Scheme 9).[14]



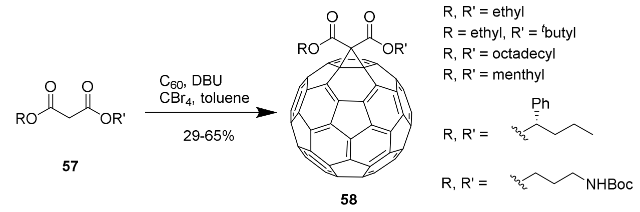
Scheme 9: Synthesis of **51** through a diazo-addition of **49** or **53** to [*60*]fullerene.

Thermal reactions of [*60*]fullerene with other diazo compounds such as diazomethanes,[15] diazoacetates,[16] diazoamides, diazomethylphosphonates,[17] and diazoketones, provides a broad variety of methano[*60*]fullerenes, having handles for further functionalization. The methano[*60*]fullerene **51** can be accessed from either the *tert*-butyl ester **54** (Scheme 10) or the *O*-glycolic ester **49** (Scheme 9), followed by ester deprotection of the fullerenyl adducts **55** and **50**, respectively. The synthetic utility of the methano[*60*]fullerenyl carboxylic acid **51** was demonstrated by its DCC/HOBt mediated amine coupling with peptides to produce the fullerenyl peptides **56** and **52**.[18]



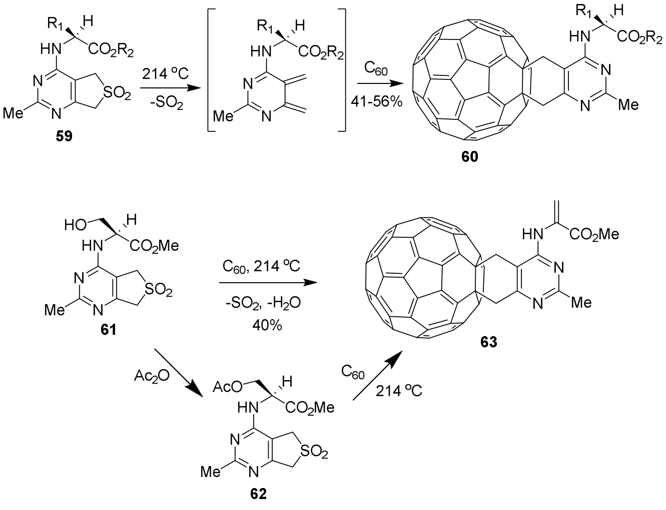
Scheme 10: Synthesis of peptide **56** was achieved through addition of **54** to [*60*]fullerene. i) H-Thr-Thr-Asn-Tyr-Thr-OH, DCC, HOBt, C_6H_5Br/DMSO (6:1).

The Bingel reaction conditions have been modified to work, in moderate to excellent yields, with ketones, esters and iminoglycinates. This modification has allowed for the generation of the analogous α-haloanion *in situ* rather than the previous isolation of the halogenated intermediate.[19] This efficient and reliable one-pot reaction has been used extensively with malonic esters **57** and derivatives, as illustrated in Scheme **11**.[19a, 20]



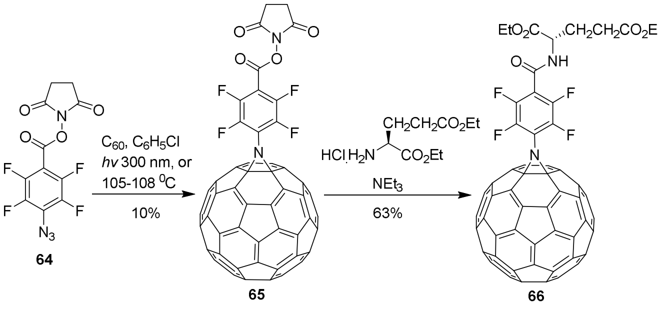
Scheme 11: Malonates add to [*60*]fullerene under Bingel cyclopropanation conditions to provide methanofullerenes **58**.

Thermolysis of sulfones **59** in the presence of [*60*]fullerene in 1,2,4-trichlorobenzene at reflux under a nitrogen atmosphere afforded the fullerene derivatives **60** (*via* the corresponding pyrimidine *o*-quinodimethanes) (Scheme 12). A similar reaction with **61** did not give the expected adduct but the dehydration product **63** (Scheme 12).[21] Acetylation of **61** to **62** before the cycloaddition reaction did not prevent the formation of compound **63**.



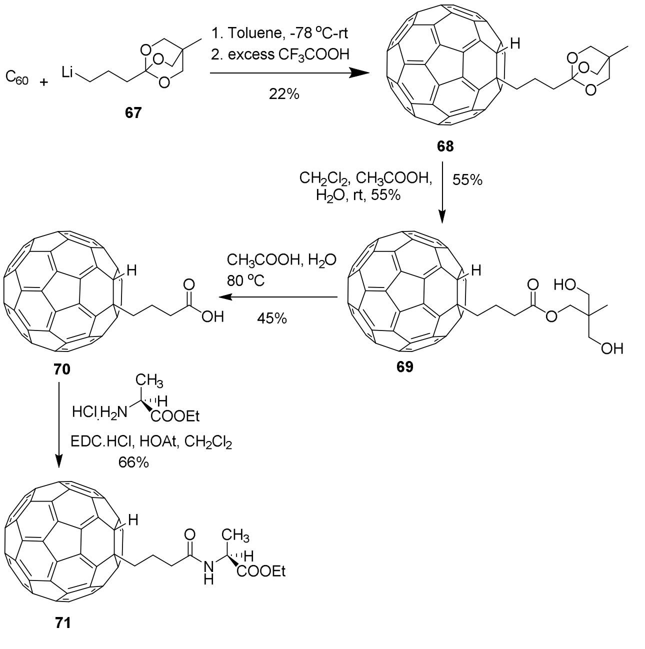
Scheme 12: Synthesis of [*60*]fullerene based tetrahydroquinazolines.

Organic azides act as 1,3-dipoles and can undergo [3+2]-cycloaddition reactions (either photochemically or thermally) with [*60*]fullerene to yield fulleroaziridines (Scheme 13).[22] Of these organic azides, photochemical or thermal reactions of [*60*]fullerene with perfluorophenylazide **64** produces the fulleroaziridine **65** with an activated *N*-hydroxysuccinamide ester. This active ester allows further functionalization, such as peptide coupling resulting in the formation of **66**.



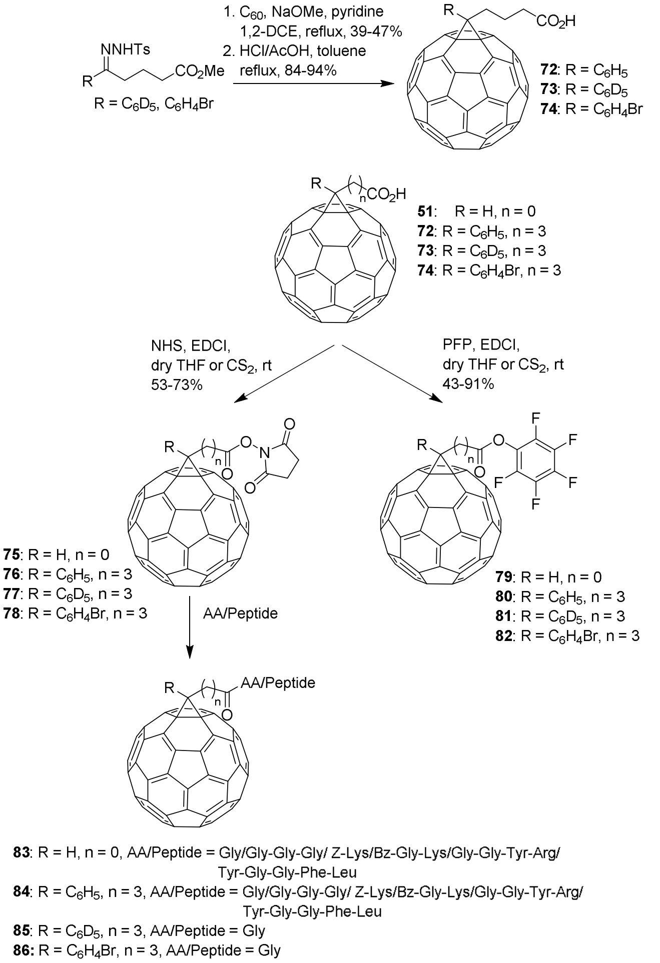
Scheme 13: Synthesis of fulleroaziridine

The reaction of [*60*]fullerene with organolithium and Grignard reagents have been exploited to incorporate a protected carboxylic acid functionality onto the C_{60} sphere.[23] The organometallic reagent made from the stable bicyclic orthoester **67**, prepared by following the general procedure described by Corey,[24] has been successfully added to [*60*]fullerene to give adduct **68**. This was converted to the acid **70** by two sequential hydrolysis steps and then coupled with L-alanine ethyl ester hydrochloride to give **71** (Scheme 14).



Scheme 14: Synthesis of 1-hydro-2-[3′-(L-Ala-OEt)propyl]-1,2-dihydro[*60*]fullerene **71**.

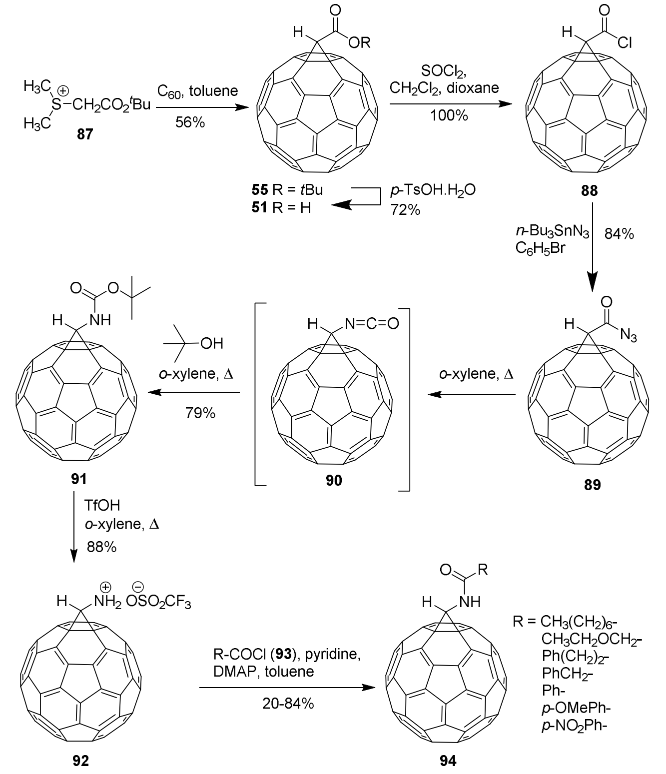
Methano[*60*]fullerene carboxylic acid derivatives **51** and **72-74** were converted to their active esters of *N*-hydroxysuccinimide (NHS) **75-78** and pentafluorophenol (PFP)[25] **79-82** and coupled with amino acids and peptides. These active esters have been reacted selectively with the amine group of the amino acid or peptide, or the hydroxy group but only under DMAP catalysis.



Scheme 15. Derivatization of **51** and **72-74** with amino acids and peptides.

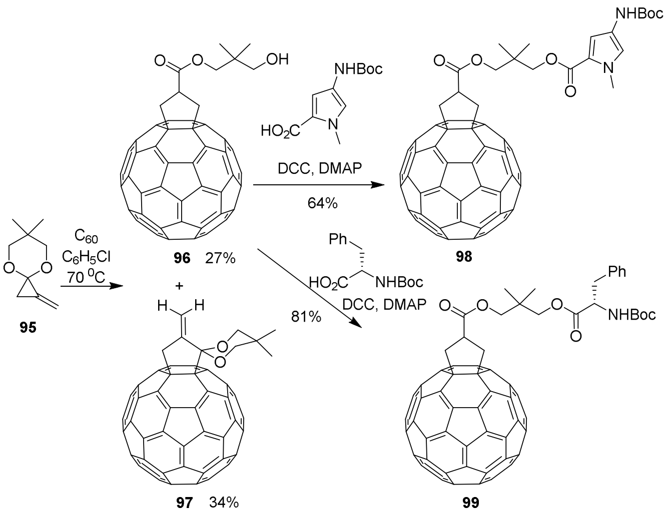
3 Synthesis of [*60*]Fullerenyl C-Capped Peptides and Amino Acids

Alternative methods to generate methano[*60*]fullerene derivatives *via* addition/elimination mechanisms have employed sulfonium and phosphonium ylides.[26] Deprotection of the ester moieties in these methano[*60*]fullerenes, as well as the malonate derivatives, has provided access to versatile handles, including the carboxylic acid **51** which was generated by the addition of the sulfonium ylide **87** to [*60*]fullerene, followed by cleavage of the *tert*-butyl ester **55** with *p*-TsOH (Scheme 16).[27] The acid **51** was then converted to its acid chloride **88**, which was subsequently treated with tributyltin azide to deliver the acyl azide **89** in good yield. Exposure of **89** to *o*-xylenes at reflux was expected to have afforded the isocyanate **90**, which was not isolated but trapped as the *tert*-butyl carbamate derivative **91**. Treatment of **91** with TfOH provided the amine salt **92**, which was coupled to various acyl chlorides **93** to generate the corresponding amide derivatives **94** (Scheme 16).[28]



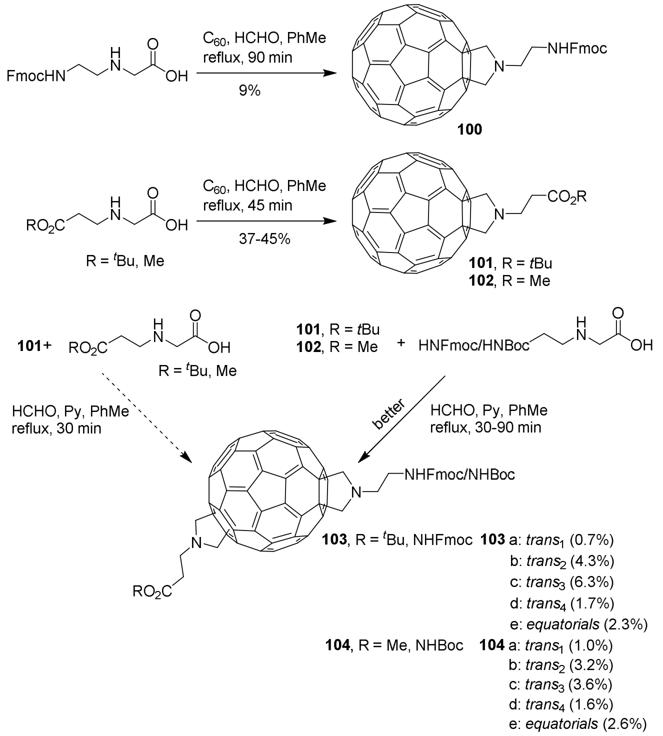
Scheme 16: Synthesis of amides **94** was achieved through a Curtius rearrangement.

Thermal ring opening of methylenecyclopropanone ketal **95** in chlorobenzene in the presence of [*60*]fullerene followed by silica gel hydrolysis of the resulting ketene acetal gave a mixture of cycloadducts **96** and **97**.[29] The corresponding fullerenyl amino ester derivatives **98** and **99** were subsequently prepared from **96** by DCC coupling (Scheme 17).[30]



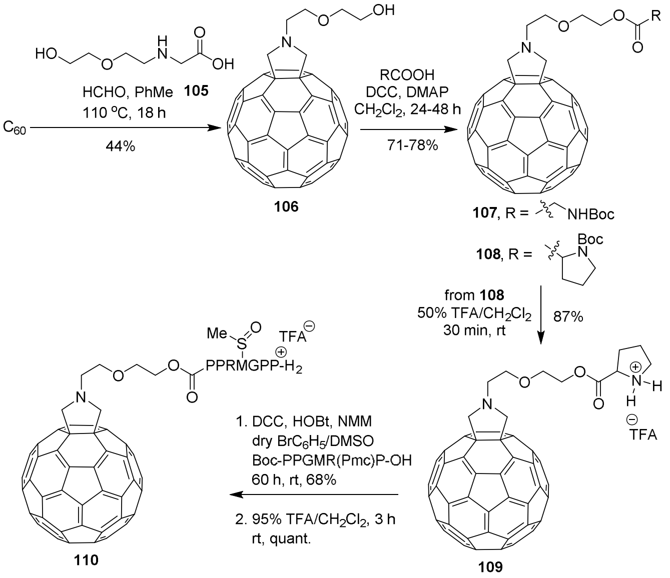
Scheme 17: Synthesis of fullerenyl amino ester derivatives via [3+2]-cycloaddition reactions.

Protected bis-fulleropyrrolidine amino acids derivatives **103** and **104** have been synthesised and characterised from two successive [3+2]-cycloaddition reactions of azomethine ylides to [60]fullerene, prepared *in situ* from the reactions of *N*-glycine derivatives and formaldehyde (Prato reaction). These reactions resulted in two different fullereopyrrolidine couples having unsymmetrical, orthogonally protected amino and acid functional groups.[31] These peptides could be used as models for fullerene-based peptidomimetics with the carbon sphere inserted into the peptide backbone (Scheme 18).



Scheme 18: Synthesis of mono-fulleropyrrolidines and unsymmetrical bis-fulleropyrrolidines.

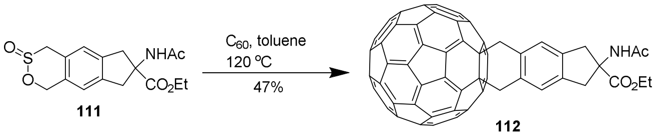
The 1,3-dipolar cycloaddition reaction of the N-substituted glycine derivative **105** to [*60*]fullerene produced the fulleropyrrolidine **106** having a hydroxyl group at the terminus of the N-substituent (Scheme 19). Subsequent esterification of this alcohol with the *C*-terminus of the protected amino acids gave **107** and **108**. Deprotection of **108** to its TFA salt **109** and then coupling with a hexapeptide followed by final deprotection with TFA resulted in the fullereno peptide **110**, having an oxidised methionine residue.[32]



Scheme 19: Synthesis of [*60*]fulleropeptides.

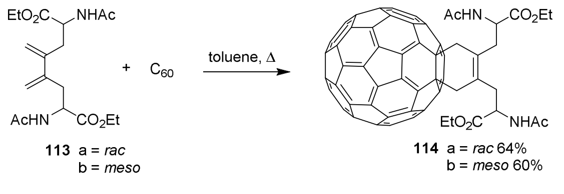
4 Synthesis of Fullerenyl Amino Acids That Could Potentially be Incorporated into Peptide Chains

The synthesis of highly functionalized benzo-annulated indane-based α-amino acid (AAA) derivatives was reported via a [4+2]-cycloaddition strategy using the sultine derivative **111**, containing an AAA ester moiety, as a reactive diene component. By adopting this strategy, a new α,α-dialkylatedindane-based [*60*]fullerene containing a rigid AAA unit **112** was realized (Scheme 20).[33]



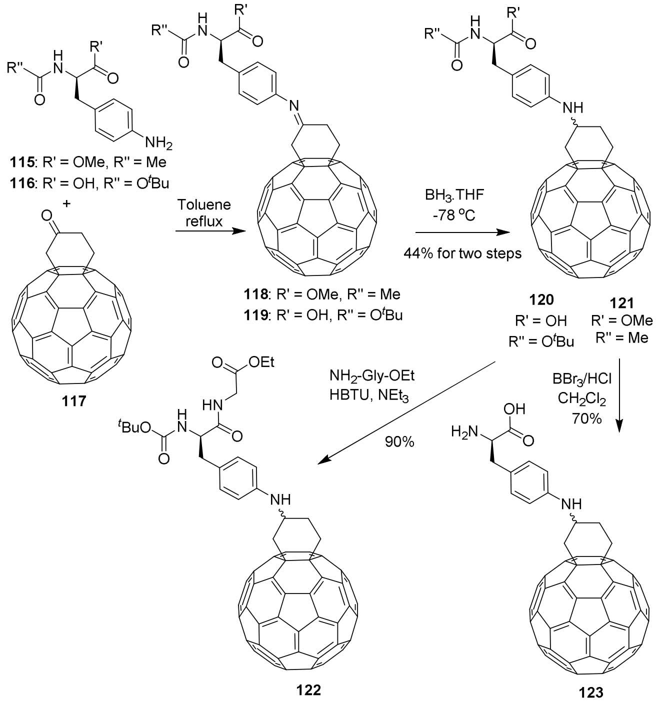
Scheme 20: Synthesis of α,α-dialkylatedindane-based [*60*]fullerene containing AAAs.

A Diels-Alder approach has been developed to prepare dicarba analogues of cystine. Treatment of diene **113** with [*60*]fullerene in toluene at reflux furnished the stable cycloadduct **114** in good yield (Scheme 21).[34]



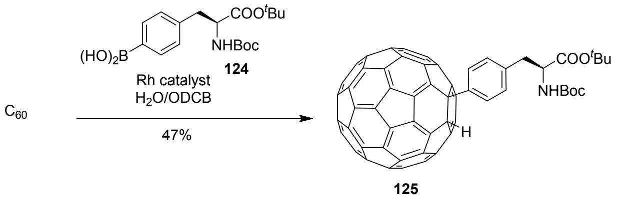
Scheme 21: [*60*]Fullerene-based dicarba analogue of cysteine **114**

Ketone **117** has been used to synthesise [*60*]fullerene substituted *D*-phenylalanine derivatives (Scheme 22).[3d] The *para*-amino substituted phenylalanine derivatives **115** and **116** readily undergo condensation reactions with **117** forming the analogous imines **118** and **119**, which were converted to their corresponding amines **120** and **121** by borane reduction. The *N*-Boc-glycine derivative **120** was coupled to ethyl glycinate under HBTU mediated coupling conditions to provide the peptide **122**. Treatment of the methyl glycinate derivative **121** with BBr_3 led to the isolation of the free glycine analogue **123**.



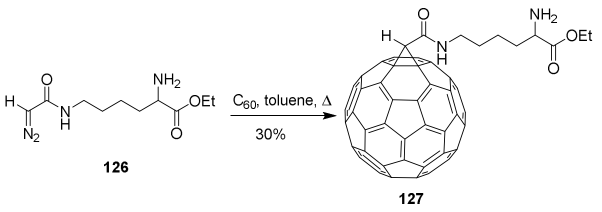
Scheme 22: Synthesis of [*60*]fullerenyl amino acids **122** and **123**.

A rhodium catalyzed reaction of [*60*]fullerene with the boronic acid derivative of phenylalanine **124** is shown in Scheme 23. This reaction gave the fullerene-tagged amino acid **125** in 47% yield.[35]



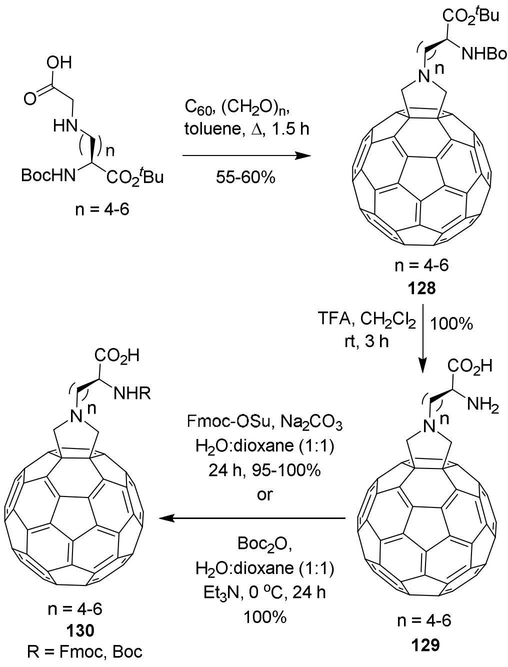
Scheme 23: Synthesis of 1-substituted 1,2-dihydro[*60*]fullerene derivatives.

A direct route was developed to produce fullerenyl peptides **127** by prolonged thermolysis of various diazoamides (e.g. **126**) in the presence of [*60*]fullerene (Scheme 24).[14]



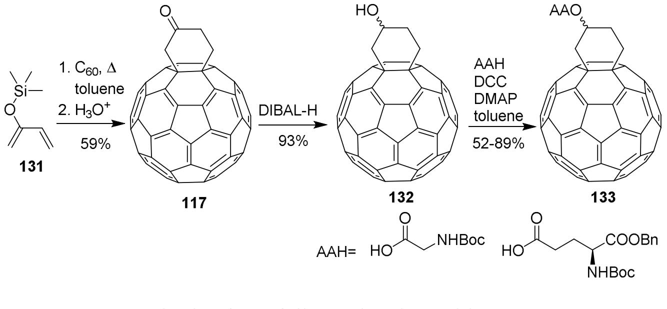
Scheme 24: Thermal addition of diazoamide to [*60*]fullerene provides direct access to fullerenyl amino esters.

[*60*]Fullerene functionalized amino acids with 4–6 methylene spacers from the α-carbon to the nitrogen atom of fulleropyrrolidine **128**, and their corresponding fullerene peptides **130**, have been synthesized from the reactions of *N*-glycine derivatives, formaldehyde and [*60*]fullerene under Prato's reaction conditions as shown in Scheme 25.[36]



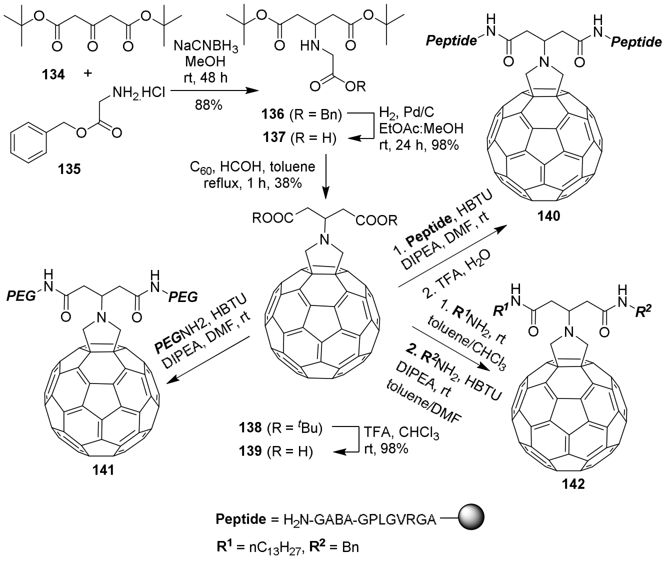
Scheme 25: Synthesis of [*60*]fullerene functionalized amino acids with 4-6 methylene spacers.

The [4+2]-cycloaddition of the 2-silyloxybutadiene **131** to [*60*]fullerene provided the ketone **117**, after hydrolysis. Subsequent reduction with DIBAL-H afforded the racemic alcohol **132**, a versatile synthon for the generation of fullerenyl amino acid derivatives (Scheme 26). For example, the DCC mediated esterification of **132** with alanine and glutamate derivatives provided the protected fullerenyl amino acids **133**.[3c]



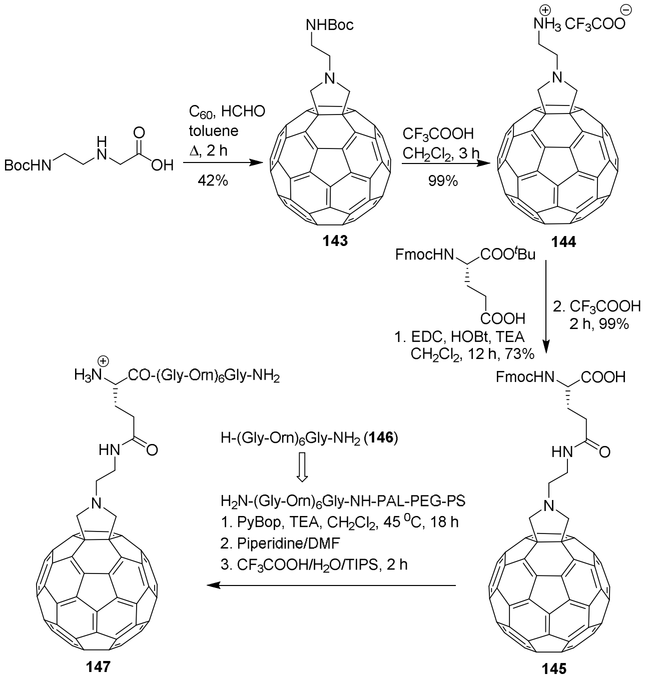
Scheme 26: Synthesis of [*60*]fullerenyl amino acid **133**.

[*60*]Fullerene pyrrolidine derivative (**139**), bearing two carboxylic acid functional groups has been reported (Scheme 27).[37] The crucial glycine precursor **137**, was synthesised from commercially available starting materials and reacted with [*60*]fullerene and formaldehyde under Prato's reaction conditions to yield the diester **138**. The *tert*-butyl groups of **138** were deprotected under acidic conditions, which efficiently provided the stable bis-acid derivative **139**. This diacid derivative was readily functionalized under solid phase conditions to yield the derivatives dipeptide **140** and PEG **141**. In addition, the reaction of **138** with TFA and TFAA provide an anhydride intermediate, which was used to synthesise [*60*]fullerene derivatives bearing two different amide moieties **142**.



Scheme 27. Synthesis of Bis-carboxylic acid group functionalized [*60*]fullerene derivatives.

The [*60*]fullerene derivative **143** was deprotected with TFA to give a free amino functional linker containing [*60*]fullerene derivative **144**. This was then reacted with *N*-Fmoc-L-glutamic acid α-*tert*-butyl ester to yield a [*60*]fullerene functionalized amino acid. The *tert*-butyl ester was deprotected under acidic conditions to give the carboxylic acid **145**, and this acid was subjected to solid-phase peptide synthesis with peptide **146**. The product **147** was cleaved from the resin support and was found to be was water soluble.[38]



Scheme 28. Solid phase synthesis of fullereno peptide **147**.

Applications of [*60*]fullerene amino acids and peptides

The potential uses of amino acid and peptide derivatives of fullerenes range from the biological to the material sciences. This section will outline the major areas of achievement.

Biological Applications

The product **110** was biologically active against sera from Mixed Connective Tissue Disease (MCTD) and Systemic Lupus Erythematosus (SLE) patients (ELISA experiments).[32]

The peptide **146** itself was not acitive against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*), whereas the analogous [*60*]fullerenopeptide **147** showed antimicrobial activity against *S. aureus* and *E. coli* (Table 1).[38]

Table 1. Antimicrobial Activity of Peptides **146** and **147**, Reported as MIC (Minimum Inhibitory Concentrations). Results are the mean of a minimum four independent evaluations run in duplicate (na = nonactive).

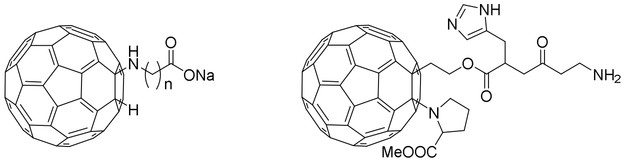
Peptide	**146**	**147**
S. aureus	na	8 µM
E. coli	na	64 µM

The antioxidant properties of the water soluble amino acid derivatives of the sodium salts of fullerenylaminobutyric acid (C_{60}-γ-ABNa, **148**) and fullerenylaminocaproic acid (C_{60}-ω-ACNa, **149**) as well as that of the hybrid structure based on a *N*-fullerenoproline and the natural oxidant carnosine (C_{60}-Pro-carnosine, **150**) (Figure 1) have been studied. Their roles in the inhibition of herpes virus infection have also been described.[39] The amino acid fullerene derivatives **148** and **149** of [*60*]fullerene were found to have significant antioxidant activities and were not cytotoxic (IC_{50} 1000 and 1200 µg mL^{-1} (mln. cells), for **149** and **148**, respectively). These derivatives were also studied as inhibitors of cytomegalovirus infection (CMVI). The introduction of C_{60}-γ-ABNa **148**, into infected human embryonic fibroblasts (HEF) reduced the concentration of virus proteins in the cells to values approaching that in non-infected cells (Table 2). The malonic dialdehyde (MDA) concentration in the infected HEF culture also decreased to the concentration in intact HEF. The drug ganciclovir also decreased the lipid peroxidation (LPO) level in the HEF culture but had significantly lower antioxidant and inhibitory effects than **148** (Table 2). These results indicated that the antioxidant activity of these fullerene derivatives played an important role in their antiviral effect against CMVI. Compound **148** was considered as a potential chemotherapeutical drug against CMVI. Its chemotherapeutical index (CTI) was found to be 5000, which fivefold exceeds that of ganciclovir.

Table 2. Contents of the protein and MDA in the HEF cultures

Sample	Protein content /mg (mln. cells)$^{-1}$	[MDA].10^{-5} /mol.L^{-1}(mln. cells)$^{-1}$
HEF	0.07±0.02	3.75±0.03
HEF-CMV	0.284±0.03	6.8±0.01
HEF-CMV- gancyclovir	0.22±0.04	5.4±0.03
HEF-CMV-C_{60}-γ-ABNa (**148**)	0.072±0.02	3.8±0.03

Note. The concentration of ganciclovir and C_{60}-γ-ABNa **148**, in the cell culture was 2.10^{-5}mol L^{-1}(mln. cells)$^{-1}$. The average values of five measurements were presented.

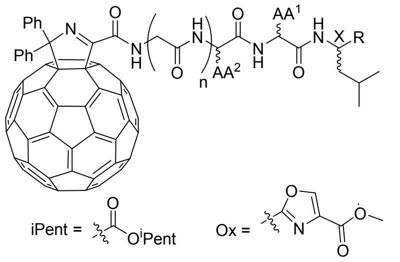


n = 3, **148** (C_{60}-γ-ABNa)
n = 5, **149** (C_{60}-ϖ-ACNa)

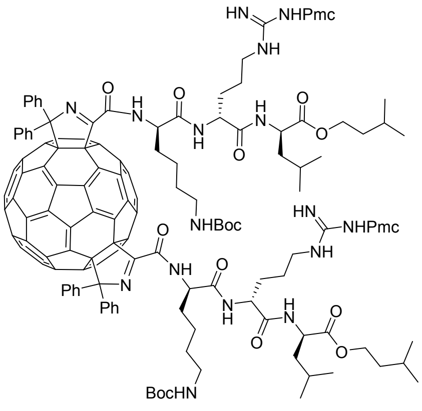
150 (C_{60}-Pro-carnosine)

Figure 1: [*60*]Fullerene based water soluble amino acids.

As part of an ongoing antibacterial drug research project a series of mono substituted and disubstituted peptide fullerene derivatives (Figure 2) were synthesised.[9] These were prepared from the acid **23** and diacid **25**, respectively. Although these derivatives did not show any substantial anti-bacterial activity, their synthesis has progressed the development of the important field of fullerenyl amino acids and peptide derivatives, in particular, their synthesis and isolation as peptide salts (**156-160**) and the high incorporation of basic amino acids with side chains. This is highlighted by the reasonable solubility of the deprotected compounds (**156-160**) in DMSO/water and the relative ease of purification of the protected fullerenyl peptides (**151-155** and **161**) by column chromatography. Further, these fullerenyl amino acids have a more rigid, and thus more defined, tethered structure than many other fullerenyl peptides reported, which traditionally employ a flexible fullerene-peptide linker. These more rigid properties could become increasingly important in the fields of medicinal chemistry or materials science.



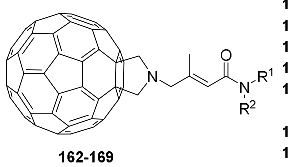
	R	X	AA^1	AA^2	n
151	iPent	D	D-Arg-Pbf	L-Lys-Boc	1
152	Ox	L	L-Arg-Pmc	D-Lys-Boc	0
153	Ox	L	L-Arg-Pmc	D-Lys-Boc	1
154	Ox	L	D-Lys-Boc	D-Lys-Boc	1
155	iPent	L	L-Lys-Fmoc	L-Lys-Fmoc	1
156	iPent	D	D-Arg.TFA	L-Lys.TFA	1
157	Ox	L	L-Arg.HCl	D-Lys.HCl	0
158	Ox	L	L-Arg.HCl	D-Lys.HCl	1
159	Ox	L	D-Lys.TFA	D-Lys.TFA	1
160	iPent	L	L-Lys.HCl	L-Lys.HCl	1



161

Figure 2: [*60*]Fullerene based novel peptides (**151**-**155** and **161**) and dicationic peptoids (**156**-**160**).

Antioxidative/anti-inflammatory activity of the fullerene-polyamine (FUL-PA) conjugates **162-169** has been described.[40] Conjugation of [*60*]fullerene with spermine (SPM) or spermidine (SPD) resulted in a large improvement of both the anti-lypoxygenase (LOX) and the anti-lipid peroxidation activity of the unconjugated molecules. An enhancement in the anti-inflammatory potency of [*60*]fullerene was observed only with the conjugate **163** (42%), which was comparable in activity to the reference compound indomethacin (47%). Most of the FUL-SPD conjugates, and especially compounds **163** and **165** were of comparable toxicity, even at the highest concentration tested (50 mM), therefore they could be potentially safely used for possible biomedical applications.[40]



162-169

162; $R^1 = (CH_2)_3NH(CH_2)_4NH(CH_2)_3NH_2$, $R^2 = H$
163; $R^1 = (CH_2)_4NH(CH_2)_3NH_2$, $R^2 = H$
164; $R^1 = (CH_2)_2$-TET-CH_2Ph, $R^2 = H$
165; $R^1 = (CH_2)_3NH_2$, $R^2 = (CH_2)_4NH_2$
166; $R^1 = (CH_2)_3NH(CH_2)_4NH(CH_2)_3NHCO$-FPB, $R^2 = H$
167; $R^1 = (CH_2)_3$-TET-$(CH_2)_4$-TET-$(CH_2)_2NHCO$-FPB
$R^2 = H$
168; $R^1 = (CH_2)_3NH(CH_2)_4NH(CH_2)_3NHCO$-ACl, $R^2 = H$
169; $R^1 = (CH_2)_3NH(CH_2)_4NH(CH_2)_3NHCO$-TRA, $R^2 = H$

TET = tetrazole
FPB = fullerenopyrrolebutenyl

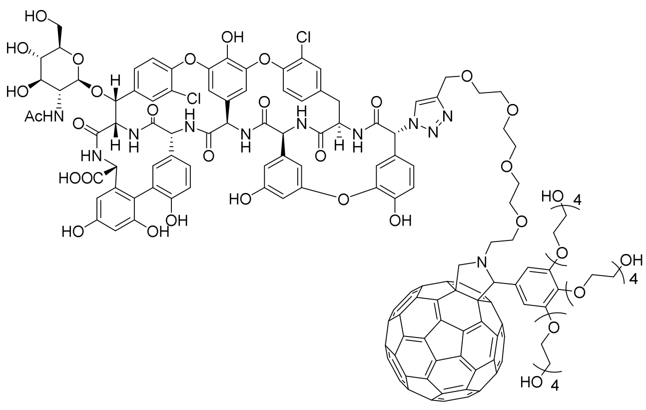
Figure 3: Biologically active novel fullerene-polyamine (FUL-PA) conjugates.

The glycopeptide antibiotic derivative teicoplanin ψ-aglycone has been covalently attached to a fullerenopyrrolidine derivative using azide-alkyne "click chemistry". The aggregation of the resulting antibiotic-fullerene conjugate **170** in aqueous solution has been studied resulting in nano-sized clusters.[41] The conjugate exhibited antibacterial activity against Enterococci resistant to teicoplanin (Table 3).

Table 3. Antibacterial activity of compound **170**.

Bacteria	Teicoplanin	Compound **170**
	MIC (μg/mL)	
B. subtilis ATCC 6633	0.5	16
S. aureus MSSA ATCC 29213	0.5	8
S. aureus MRSA ATCC 33591	0.5	4
S. epidermidis ATCC 35984 biofilm	4	2
S. epidermidis mec A	16	1
E. faecalis ATCC 29212	1	6
E. faecalis 15376 VanA	256	16
E. faecalis ATCC 51299 VanB	0.5	16

Note. MIC: Minimum Inhibition Concentration, ATCC: American Typed Culture Collection, *B. subtilis*, *Bacillus subtilis; E. faecalis, Enterococcus faecalis,* MRSA: Methicillin Resistant *Staphylococcus aureus*, vanA : vanA gene positive, vanB : vanB gene positive.



170

Figure 4: Teicoplanin ψ-aglycon-fullerene conjugate **170**.

The water-soluble dendrofulleropyrrolidine **171** (synthesised from **101**) and its bis-analogues **172** and **173** have been prepared.[42] These cationic species can efficiently complex plasmid DNA as demonstrated by gel electrophoresis studies. These molecules showed excellent DNA binding efficiencies and were therefore considered to be potential candidates for DNA binding therapies.

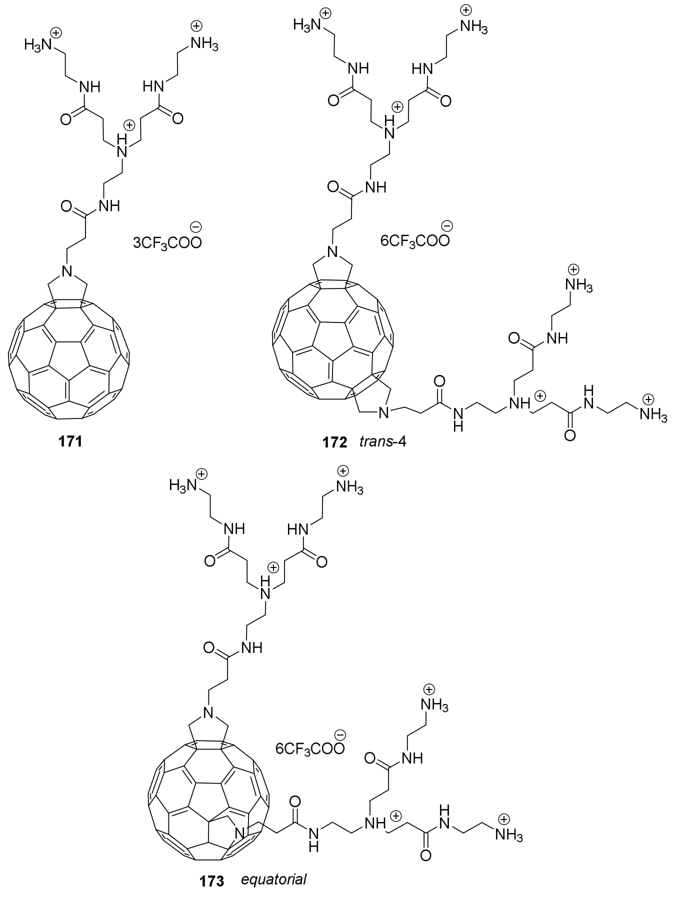


Figure 5. Monoadduct **171** and bis adducts **172** and **173** of highly water soluble polycationic [*60*]fullerenes.

The fulleropyrrolidine peptides containing only GABA (γ-aminobutyric) residues, having zero or one glycine moiety have been reported (Figure 6).[43] The authors claim that these may be used as nanobioparticles. However, no results related to these properties were reported.

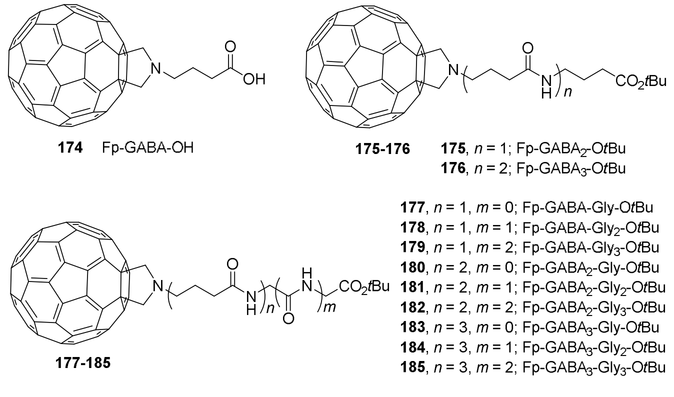


Figure 6. Fulleropeptides **175-185** synthesized from fulleropyrrolidinic acid **174**.

Mitsutoshi *et. al.* reported the inhibitory effects of [*60*]fullerene derivatives **186** ([*60*]fullerene-proline-*N*-acetic acid) and **187** ([*60*]fullerene-ethylenediamine-*N*,*N'*-diacetic acid) on acetylcholine-induced (endogenous NO) relaxation in endothelium-intact rabbit thoracic aorta precontracted by phenylephrine (10^{-6} M).[44] The [*60*]fullerene derivatives **186** (10^{-5} M) and **187** (10^{-5} M) reduced the maximum amplitude of the acetylcholine-induced relaxation without significantly changing the pD2 values obtained from the concentration response curves.

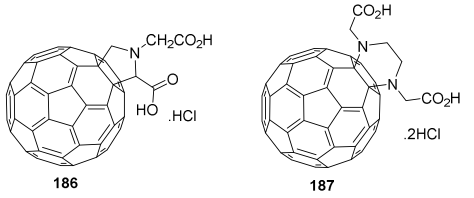


Figure 7. [*60*]Fullerene derivatives **186** ([*60*]fullerene-proline-*N*-acetic acid) and **187** ([*60*]fullerene-ethylenediamine-*N*,*N'*-diacetic acid).

Water soluble [*60*]fullerene derivatives **188-190** (WSFD), have been studied to show the potential to prevent NO-induced cytotoxicity without obvious toxicity.[45] These fullerene derivatives apply protective activities by direct interaction with NO and neutralization of O_2^-. The folacin fullerene derivative **190** (FFD) self-assembles to form spherical aggregates because of hydrogen bonding, and the aggregate ion morphology impacts on the NO-scavenging activities of the WSFD. Pretreatment of the cells with WSFD prior to the sodium nitroprusside (SNP) exposure blocks NO-induced cellular events including oxidation of membrane lipids, depolarization of mitochondrial membranes, reduction of superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidise (GSH-Px) activities and caspase-mediated apoptotic cell death. Apart from the biological studies, the authors have revealed the synthesis of novel fullerene derivatives with anti-apoptotic properties.[45, 46]

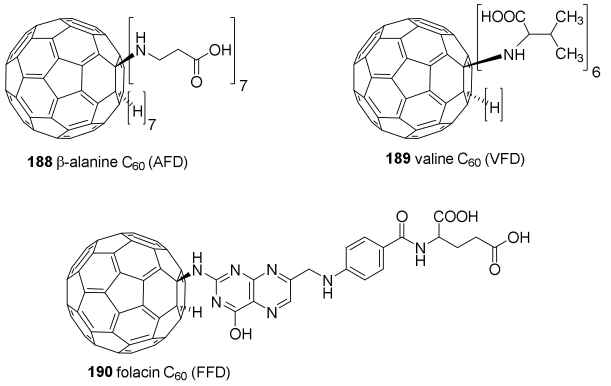
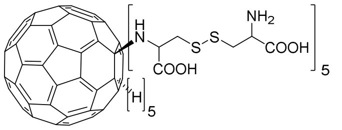
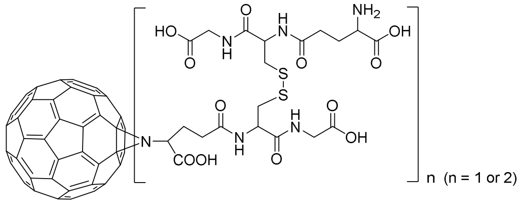


Figure 8. Chemical structures of (**188**) AFD, (**189**) VFD and (**190**) FFD.

Oxidized [*60*]fullerene glutathione derivatives have been synthesized and characterized.[46,47] The [*60*]fullerene glutathione derivative **192** was soluble in dimethylsulfoxide, dimethylformamide and dimethylacetamide. Rat pheochromocytoma (PC12) cells were treated with hydrogen peroxide, cytotoxicity and apoptotic death was estimated by the MTT assay, flow cytometry analysis, PI/Hoechst 33342 staining and glutathione assay. These results indicated that the glutathione [*60*]fullerene derivative **192** has the potential to prevent oxidative stress-induced cell death without toxicity.[46]



191, cystine C_{60}

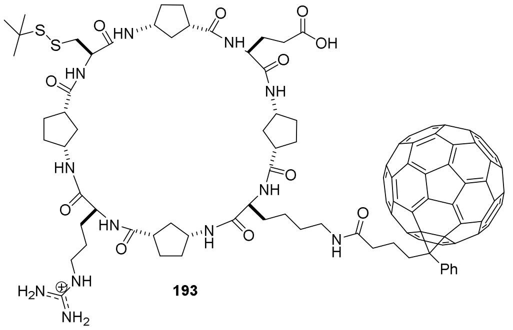


192, oxidised glutathione C_{60} derivative

Figure 9: Cystein (**191**) and oxidized glutathione (**192**) [*60*]fullerene derivatives

Materials Chemistry Applications

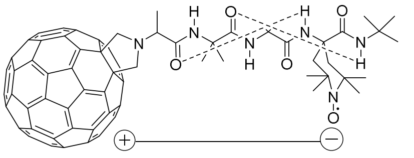
A new class of peptide nanotubes from α,γ-cyclic peptides (CPs) **193** tethered to a methanofullerene moiety have been reported.[48] These CPs are able to form nanotubes in which the fullerenes point outward from the nanotube on both sides (180° orientation). The fullerenes form two parallel wires separated by the insulating peptide nanotube. The authors suggest that these materials may have applications as nanowire components and/or in optical and electronic devices.



193

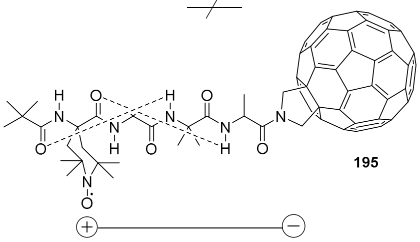
Figure 10: Structure of tethered α,γ-cyclic peptide (CP) **193**.

Two molecules having a pyrrolidino[*60*]fullerene tethered through an intramolecular hydrogen bonding peptide linker to a nitroxide radical have been synthesised.[49] These peptide moieties have rigid 3_{10}-helical structures that possess a strong molecular dipole. The direction of the molecular dipole moment can be reversed by switching the position of fullerene and nitroxide with respect to the peptide nitrogen and carbon terminus. The fullerene-peptide-radical systems **194** and **195** were compared to the behaviours of otherwise identical peptides but without either [*60*]fullerene or the free radical moiety with retaining the same number of intramolecular hydrogen bonds.



194

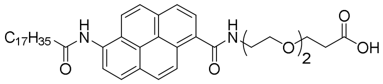
≠



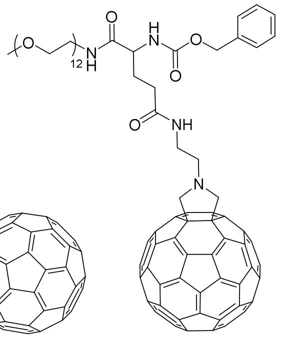
195

Figure 11: Structures of [*60*]fullerene based peptides with intramolecular hydrogen bonds and dipole moments illustrated.

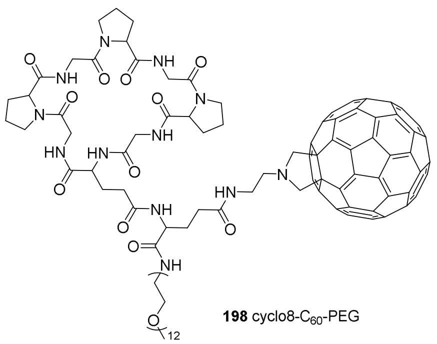
A strategy of photocurrent generation out of thin layers composed by the amphiphilic [*60*]fullerene and pyrene derivatives was investigated by Shunsaku's group.[50] Three different types of compounds namely [*60*]fullerene-cyclic peptide-PEG conjugate **198** (cyclo8-C_{60}-PEG), [*60*]fullerene-PEG conjugate **197** (C_{60}-PEG) without a cyclic peptide scaffold, and the pyrene derivative **196** (R-Pyr) having a diethylene glycol and a long alkyl chain were synthesised. The study of photoinduced electron transfer concluded that a bilayer structure with desired orientation of functional units is important for efficient photoinduced electron transfer and that cyclic peptide scaffold is useful to locate hydrophobic functional groups in a thin layer.



196 R-Pyr



197 C_{60}-PEG

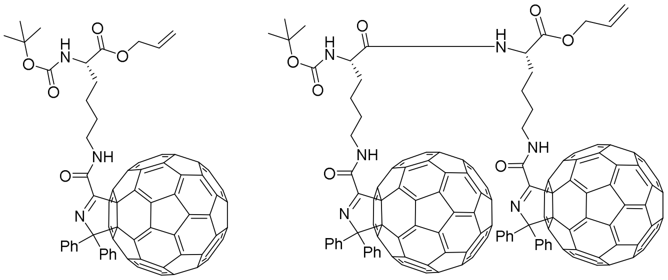


198 cyclo8-C_{60}-PEG

Figure 12: Chemical structures of R-Pyr **196**, C_{60}-PEG **197** and cyclo8-C_{60}-PEG **198**.

[*60*]Fullerene amino acid monomer **199** and the bis-fullerene **200** been studied experimentally using spectroelectrochemical measurements. The bis-fullerene-substituted peptide[51] **200** provided experimental support for density-functional theory (DFT) calculations which indicate that van der Waals fullerene dimers can form between adjacent fullerenes in semiconductor layers resulting in interstitial electron traps. The fullerenes behave like "super atoms" and the interstitial electron traps

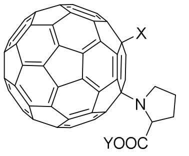
represent one-electron intermolecular σ-bonds. The proposed electron traps are relevant for all organic electronics applications in which non-covalently linked fullerenes in van der Waals contact with one another are used as n-type semiconductors.[52]



199 **200**

Figure 13: Structures [*60*]fullerene amino acid monomer **199** and bis-fullerene **200**.

The stereoselectivity of the formation of hybrid amino acid derivatives of fullerene (AADF) C_{60} was studied by Dolinina *et. al*.[53] The energies of the model addition reactions of two different reactions were calculated by the DFT method B3LYP/631G*. The most stable products of these reactions are hexamethylated fullerene derivatives in which five Me groups are arranged in the form of a regular pentagon and AADF. Among the AADF obtained by reactions, 1,4-disubstituted fullerene isomers are most stable. The molecular structures of such isomers were calculated for six biologically active hybrid AADF's **201-206** (Figure 14); the solvent contact areas of these molecules were evaluated (Table 4).



Amino Acid Derivatives of Fullerene
201-206

Figure 14: Structures of AADF **201-206**.

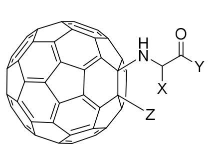
Table 4. Calculated water contact areas (S/Å2) of hybrid AADF[a]

Entry	X	Y	$S_{tot}(S_{ful})^{b}$
C_{60}	-	-	530 (530)
201	C_2H_4OH	Me	711 (443)
202	$C_2H_4ONO_2$	Me	783 (440)
203	C_2H_4OH	CH_2ONO_2	818 (437)
204	$C_2H_4ONO_2$	CH_2ONO_2	831 (412)
205	$CH_2CH(NO_3)CH_2NO_3$ (*S*)	Me	838 (423)
206	C_2H_4-carnosine	Me	968 (406)

a The equilibrium conformations were calculated at the B3LYP/631G*//B3LYP/631G* level.

b S_{tot} and S_{ful} are the contact areas of the whole molecule and the fullerene fragment, respectively. The radius of the sphere of the water molecule is 1.4 Å.

Induction of optical activity of fullerene C_{60} by covalently bound amino acid moieties and peptide fragments (**207-215**) was studied by Babievsky *et. al*.[54] using optical circular dichroism (CD) (Table 5). Significant asymmetric induction transfer was found when a stereogenic atom is adjacent to fullerene cage.[54]



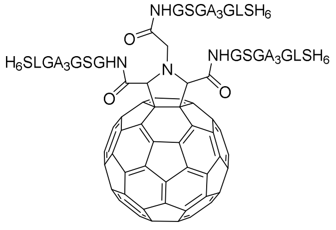
207 X = Me, Y = OK, Z = H
208 X = Me, Y = OMe
209 X = H, Y = NHCH(Me)COOK, Z = H
210 X = Me, Y = NHCH(Me)COOK, Z = H
211 X = H, Y = $NHCH_2COOK$, Z = H
212 X = Me, Y = OMe, Z = maleimide
213 X = Me, Y = OMe, Z = CH_2CH_2OH
214 X = $CHMe_2$, Y = ONa, Z = H
215 X = $CHMe_2$, Y = $NHCH(NHMe_2)COONa$

Figure 15: Structures of compounds **207-215**.

Table 5. Circular dichroism spectra of fullerene derivatives **207-215**.

Entry	*M*	$C.10^{3}$ /mol L^{-1}	$\Delta A.\ 10^{-6}$ (rel. units)	λ_{max} /nm	$\Delta\varepsilon\ 10^{-2}$ /mol L^{-1} cm^{-1}
207	847	1.77	350	530	19.7
208	823	2.43	370	540	15.2
209	918	1.04	330	556	10.1
210	904	1.77	180	550	32.0
211	874	1.80	-	-	-
212	918	0.44	150	450	34.0
213	867	0.35	78	505	22.3
214	937	1.82	123	460	6.7
215	1027	0.30	155	499	51.6

Investigation of energy transfer interactions between C_{60} fullerenes and four different quantum dots (QDs), composed of CdSe/ZnS (type I) and CdSe/CdS/ZnS (quasi type II), with emission maxima ranging from 530 to 630 nm was performed by Stewart *et. al*.[55] C_{60}-pyrrolidine tris-acid was first coupled to the *N*-terminus of a hexahistidine terminated peptide *via* carbodiimide chemistry to yield a C_{60}-labeled peptide **216** (pep-C_{60}). This peptide was studied for the ratiometric self-assembly of the QD-(pepC_{60}) nanoheterostructures by exploiting metal affinity coordination to the QD surface. Photoinitiated energy transfer and competition between electron transfer and Förster resonance energy transfer from the QD to the C_{60} were also studied with the aim of potential use in optoelectronic and biosensing applications.[55]



216

Figure 15: Structure of C_{60}-labelled peptide **216**.

Conclusions

In conclusion, fullerenyl amino acids and related derivatives have been classified into functional types for different uses: these include directly attached fullerenyl amino acids, fullerenyl N- and C-capping amino acids, and those amino acids in which the [*60*]fullerene group is attached to the amino acid side chain. These first and last mentioned derivatives have the potential to be incorporated into non-terminal positions of peptides. The applications of these substrates, by integration into different biological and materials chemistry programs, have also been highlighted.

Acknowledgements

SJ thanks the ARC Centre of Excellence for Electromaterial Science for the provision of a Scholarship.

1. (a) A. Bianco, T. Da Ros, M. Prato and C. Toniolo, *J. Pep. Sci.,* 2001, **7**, 346-347; (b) T. Da Ros and M. Prato, *Chem. Commun.,* 1999, 663-669; (c) M. Satoh and I. Takayanagi, *J. Pharmacol. Sci.,* 2006, **100**, 513-518; (d) B. C. Braden, F. A. Goldbaum, B. X. Chen, A. N. Kirschner, S. R. Wilson and B. F. Erlanger, *Proc. Natl. Acad. Sci. U. S. A.* 2000, **97**, 12193-12197; (e) N. Tagmatarchis and H. Shinohara, *Mini-Rev. Med. Chem.,* 2001, **1**, 339-348; (f) A. Bianco, T. Da Ros, M. Prato and C, Toniolo, *J. Pep. Sci.,* 2001, **7**, 208-219.
2. (a) C. S. Foote, *Top. Curr. Chem.,* 1994, **169**, 347-363; (b) E. Nakamura and H. Isobe, *Acc. Chem. Res.,* 2003, **36**, 807-815; (c) S. Bosi, T. Da Ros, G. Spalluto and M. Prato, *Eur. J. Med. Chem.,* 2003, **38**, 913-923.
3. (a) A. Bianco, M. Maggini, G. Scorrano, C. Toniolo, G. Marconi, C. Villani and M. Prato, *Am. Chem. Soc.,* 1996, **118**, 4072-4080; (b) A. Bianco, F. Gasparrini, M. Maggini, D. Misiti, A. Polese, M. Prato, G. Scorrano, C. Toniolo and C. Villani, *J. Am. Chem. Soc.,* 1997, **119**, 7550-7554; (c) Y. Z. An, L. J. Anderson and Y. Rubin, *J. Org. Chem.,* 1993, **58**, 4799-4801; (d) J. Yang and A. R. Barron, *Chem. Commun.,* 2004, 2884-2885; (e) S. Bosi, L. Feruglio, T. Da Ros, G. Spalluto, B. Gregoretti, M. Terdoslavich, G. Decorti, S. Passamonti, S. Moro and M. Prato, *J. Med. Chem.,* 2004, **47**, 6711-6715; (f) D. Pantarotto, A. Bianco, F. Pellarini, A. Tossi, A. Giangaspero, I. Zelezetsky, J. P. Briand and M. Prato, *J. Am. Chem. Soc.,* 2002, **124**, 12543-12549.
4. (a) A. Bianco, T. Bertolini, M. Crisma, G. Valle, C. Toniolo, M. Maggini, G. Scorrano and M. Prato, *J. Pept. Res.,* 1997, **50**, 159-170; (b) A. Kurz, C. M. Halliwell, J. J. Davis, H. A. O. Hill and G. W. Canters, *Chem. Commun.,* 1998, 433-434; (c) L. L. Dugan, D. M. Turetcky, C. Du, D. Lobner, M. Wheeler, C. R. Almli, C. K. Shen, T. Y. Luh, D. W. Choi and T. S. Lin, *Proc. Natl. Acad. Sci. U. S. A.* 2000, **94**, 9434-9439; (d) G. Pastorini, S. Marchesan, J. Hoebeke, T. Da Ros, L. Ehret-Sabatier, J.-P. Briand, M. Prato and A. Bianco, *Org. Biomol. Chem.,* 2006, **4**, 2556-2562; (e) D. M. Guldi, G. M. A. Rahman, V. Sgobba and C. Ehli, *Chem. Soc. Rev.,* 2006, **35**, 471-487; (f) T. Y. Zakharian, A. Seryshev, B. Sitharaman, B. E. Gilbert, V. Knight and L. J. Wilson, *J. Am. Chem. Soc.,* 2005, **127**, 12508-12509; (g) T. Da Ros, G. Spalluto and M. Prato, *Croat, Chem. Acta.,* 2001, **74**, 743-755; (h) N. Martin, *Chem. Commun.,* 2006, 2093-2104.
5. (a) L. A. Watanabe, M. P. I. Bhuiyan, B. Jose, T. Kato and N. Nishino, *Tetrahedron Lett.,* 2004, **45**, 7137-7140; (b) G. A. Burley, P. A. Keller and S. G. Pyne, *Fullerene Sci. Techn.,* 1999, **7**, 973-1001; (c) D. Pantarotto, N. Tagmatarchis, A. Bianco, M. Prato, *Mini-Rev. Med. Chem.,* 2004, **4**, 805-814.
6. (a) M. Maggini, G. Scorrano and M. Prato, *J. Am. Chem. Soc.,* 1993, **115**, 9798-9799; (b) M. Maggini, G. Scorrano, A. Bianco, C. Tiniolo, R. P. Sijbesma, F. Wudl and M. Prato, *Chem. Commun.,* 1994, 305-306; (c) M. Prato and M. Maggini, *Acc. Chem. Res.,* 1998, **31**, 519-526.
7. A. Bianco, M. Maggini, G. Scorrano, C. Toniolo, G. Marconi, C. Villana and M. Prato, *J. Am. Chem. Soc.,* 1996, **118**, 4072-4080.
8. (a) G. A. Burley, P. A. Keller, S. G. Pyne and G. E. Ball, *Chem. Commun.,* 1998, 2539-2540; (b) G. E. Ball, G. A. Burley, L. Chaker, B. C. Hawkins, J. R. Williams, P. A. Keller and S. G. Pyne, *J. Org. Chem.,* 2005, **70** (21), 8572-8574.
9. S. Jennepalli, K. A. Hammer, T. V. Riley, P. A. Keller and S. G. Pyne, *Unpublished results*.
10. R. Thayumanavan, B. C. Hawkins, P. A. Keller, S. G. Pyne and G. E. Ball, *Org. Lett.,* 2008, **10**, 1315-1317.
11. G.-W. Wang, J.-X. Li, Y.-J. Li and Y.-C. Liu, *J. Org. Chem.* 2006, **71**, 680-684.
12. M. Prato, A. Bianco, M. Maggini, G. Scorrano, C. Toniolo and F. Wudl, *J. Org. Chem.,* 1993, **58**, 5578-5580.
13. (a) L. Isaacs and F. Diederich, *Helv. Chim. Acta.,* 1993, **76**, 2454-2464; (b) C. Toniolo, A. Bianco, M. Maggini, G. Scorrano, M. Prato, M. Marastoni, R. Tomatis, S. Spisani, G. Palu and E. D. Blair, *J. Med. Chem.,* 1994, **37**, 4558-4562.
14. A. Skiebe and A. Hirsch, *Chem. Commun.,* 1994, 335-336.
15. (a) J.-F. Eckert, C. Bourgogne and J.-F. Nierengarten, *Chem. Commun.,* 2002, 712-713; (b) N. Martin, L. Sanchez and D. M. Guldi, *Chem. Commun.,* 2000, 113-114.
16. R. Pelliciari, D. Annibali, G. Constantino, M. Marinozzi and B. Natalini, *Synlett.,* 1997, 1196-1198.
17. R. Pelliciari, B. Natalini, L. Amori, M. Marinozzi and R. Seraglia, *Synlett.,* 2000, 1816-1818.
18. (a) L. Isaacs and F. Diederich, *Helv. Chim. Acta.,* 1993, **76**, 2454-2464; (b) C. Toniolo, A. Bianco, M. Maggini, G. Scorrano, M. Prato, M. Marastoni, R. Tomatis, S. Spisani, G. Palu and E. D. Blair, *J. Med. Chem.,* 1994, **37**, 4558-4562.
19. (a) X. Camps and A. Hirsch, *J. Chem. Soc., Perkin Trans. 1.,* 1997, 1595-1596; (b) J.-F. Nierengarten, V. Gramlich, F. Cardullo and F. Diederich, *Angew. Chem. Int. Ed.,* 1996, **35**, 2101-2103; (c) J.-F. Nierengarten and J.-F. Nicoud, *Tetrahedron Lett.,* 1997, **38**, 7737-7740.
20. (a) C. Thilgen, A. Herrmann and F. Diederich, *Helv. Chim. Acta.,* 1997, **80**, 183-199; (b) C. F. Richardson, D. I. Schuster and S. R. Wilson, *Org. Lett.,* 2000, **2**, 1011-1014.
21. R. F. Enes, A. C. Tome and J. A. S. Cavaleiro, *Tetrahedron.,* 2005, **61**, 1423-1431.
22. (a) M. Prato, Q. Li, F. Wudl and V. Lucchini, *J. Am. Chem. Soc.,* 1993, **115**, 1148-1150; (b) M. Yan, S.-X. Cai and J. F. W. Keana, *J. Org. Chem.,* 1994, **59**, 5951-5954.
23. E. Champeil, C. Crean, C. Larraya, G. Pescitelli, G. Proni and L. Ghosez, *Tetrahedron.,* 2008, **64**, 10319-10330.
24. (a) E. J. Corey and N. Raju, *Tetrahedron Lett.,* 1983, **24**, 5571-5574; (b) E. Keinan, S. C. Sinha and S. P. Singh, *Tetrahedron.,* 1991, **47**, 4631-4638.
25. H. Tsumoto, K. Takahashi, T. Suzuki, H. Nakagawa, K. Kohda and N. Miyata, *Bio. Org. Med. Chem. Lett.,* 2008, **18** (2), 657-660.
26. (a) Y. Wang, J. Cao, D. I. Schuster and S. R. Wilson, *Tetrahedron Lett.,* 1995, **36**, 6843-6846; (b) H. J. Bestmann, D. Hadawi, T. Roeder and C. Moll, *Tetrahedron Lett.,* 1994, **35**, 9017-9020.
27. H. Ito, T. Tada, M. Sudo, Y. Ishida, T. Hino and K. Saigo, *Org. Lett.,* 2003, **5**, 2643-2645.
28. T. Tada, Y. Ishida and K. Saigo, *Org. Lett.,* 2005, **7**, 5897-5900.

29. M. Prato, T. Suzuki, H. Foroudian, Q. Li, K. Khemani, F. Wudl, J. Leonetti, R. D. Little, T. White, B. Rickborn, S. Yamago and E. Nakamura, *Am. Chem. Soc.,* 1993, **115**, 1594-1598.
30. S. Yamago, H. Tokuyama, E. Nakamura, M. Prato and F. Wudl, *J. Org. Chem.,* 1993, **58**, 4796-4801.
31. D. Milic and M. Prato, *Eur. J. Org. Chem.,* 2010, 476-483.
32. P. Sofou, Y. Elemes, E. Panou-Pomonis, A. Stavrakoudis, V. Tsikaris, C. Sakarellos, M. Sakarellos-Daitsiotis, M. Maggini, F. Formaggio and C. Toniolo, *Tetrahedron.,* 2004, **60**, 2823-2828.
33. S. Kotha and A. K. Ghosh, *Tetrahedron. Lett.,* 2004, **45**, 2931-2934.
34. S. Kotha, K. Mandal, S. Banerjee and S. M. Mobin, *Eur. J. Org. Chem.,* 2007, 1244-1255.
35. M. Nambo, Y. Segawa, A. Wakamiya and K. Itami, *Chem. Asian. J.* 2011, **6**, 590-598.
36. L. A. Watanabe, M. P. I. Bhuiyan, B. Jose, T. Kato and N. Nishino, *Tetrahedron. Lett.,* 2004, **45**, 7137-7140.
37. S. Aroua, W. B. Schweizer and Y. Yamakoshi, *Org. Lett.,* 2014, **16**, 1688-1691.
38. F. Pellarini, D. Pantarotto, T. Da Ros, A. Giangaspero, A. Tossi and M. Prato, *Org. Lett.,* 2001, **3**, 1845-1848.
39. R. A. Kotel'nikova, I. I. Faingol'd, D. A. Poletaeva, D. V. Mishchenko, V. S. Romanova, V. N. Shtol'ko, G. N. Bogdanov, A. Y. Rybkin, E. S. Frog, A. V. Smolina, A. A. Kushch, N. E. Fedorova and A. I. Kotel'nikov, *Russ. Chem. Bull.,* 2011, **60**, 1172-1176.
40. G. E. Magoulas, T. Garnelis, C. M. Athanassopoulos, D. Papaioannou, G. Mattheolabakis, K. Avgoustakis and D. Hadjipavlou-Litina, *Tetrahedron.,* 2012, **68**, 7041-7049.
41. S. Tollas, I. Bereczki, A. Sipos, E. Rőth, G. Batta, L. Daróczi, S. Kéki, E. Ostorházi, F. Rozgonyi and P. Herczegh, *Eur. J. Med. Chem.,* 2012, **54**, 943-948.
42. A. M. López, F. Scarel, N. R. Carrero, E. Vázquez, A. Mateo-Alonso, T. Da Ros and M. Prato, *Org. Lett.,* 2012, **14**, 4450-4453.
43. M. Bjelaković, N. Todorović and D. Milić, *Eur. J. Org. Chem.,* 2012, **27**, 5291-5300.
44. M. Satoh, T. Mashino, T. Nagano, M. Hirobe, I. Takayanagi and K. Koike, *Fuller. Sci. and Techn.,* 2001, **9**, 141-151.
45. Z. Hu, Y. Huang, W. Guan, J. Zhang, F. Wang and L. Zhao, *Biomaterials.,* 2010, **31**, 8872-8881.
46. Z. Hu, W. Guan, W. Wang, L. Huang, H. Xing and Z. Zhu, *Cell Biology Int.* 2007, **31**, 798-804.
47. Z. Hu, S. Liu, Y. Wei, E. Tong, F. Cao and W. Guan, *Neuroscience Letters.,* 2007, **429**, 81-86.
48. C. Reiriz, R. J. Brea, R. Arranz, J. L. Carrascosa, A. Garibotti, B. Manning, J. M. Valpuesta, R. N. Eritja, L. Castedo and J. R. Granja, *J. Am. Chem. Soc.,* 2009, **131**, 11335-11337.
49. L. Garbuio, S. Antonello, I. Guryanov, Y. Li, M. Ruzzi, N. J. Turro and F. Maran, *J. Am. Chem. Soc.,* 2012, **134**, 10628-10637.
50. (a) S. Fujii, T. Morita and S. Kimura, *Langmuir.,* 2008, **24**, 5608-5614; (b) S. Fujii, T. Morita and S. Kimura, *Bioconjugate Chem.,* 2007, **18**, 1855-1859.
51. S. Jennepalli, P. A. Keller and S. G. Pyne, *Unpublished results*.
52. T. E. Shubina, D. I. Sharapa, C. Schubert, D. Zahn, M. Halik, P. A. Keller, S. G. Pyne, S. Jennepalli, D. Guldi and T. Clark, *J. Am. Chem. Soc.,* 2014, **136**, 10890-10893.
53. T. Y. Dolinina, V. B. Luzhkov, *Russ. Chem. Bull.,* 2012, **61**, 1631-1634.
54. K. K. Babievsky, V. S. Romanova, Y. A. Davidovich, I. A. Yamskov, *Russ. Chem. Bull.,* 2013, **62**, 2609-2611.
55. M. H. Stewart, A. L. Huston, A. M. Scott, E. Oh, W. R. Algar, J. R. Deschamps, K. Susumu, V. Jain, D. E. Prasuhn, J. Blanco-Canosa, P. E. Dawson, I. L. Medintz, *ACS Nano* 2013, **7**, 9489-9505.

[*60*]Fullerenyl Amino Acids and Peptides: A Review of their Synthesis and Applications

Sreenu Jennepalli[a,b], Stephen G. Pyne*[a] and Paul A. Keller*[a,b]