

ACCOUNTS of CHEMICAL RESEARCH[®]

SEPTEMBER 1998

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Fulleropyrrolidines: A Family of Full-Fledged Fullerene Derivatives

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Received November 14, 1997

Introduction

Since their first discovery¹ and isolation,² the fullerenes have attracted the attention of an increasing number of scientists. Besides their unique geometrical shapes, in fact, C₆₀ and its caged relatives exhibit a wide variety of uncommon properties, ranging from the superconductivity of alkali-metal intercalated fullerenes³ to the ferromagnetism of some charge-transfer salts of C₆₀.⁴ Cyclic voltammetry experiments in solution have shown that C₆₀ can accept, reversibly, up to six electrons.^{5–7} Among the

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Michele Maggini was born in Padova in 1959 where he received his Laurea degree in Chemistry in 1984. His interest in strained caged molecules began in 1986 with cubane, during postdoctoral research at The University of Chicago. After spending 1 year working on structural modification of glycopeptide antibiotics at Dow in Gerenzano (Italy), he returned to Padova where he is currently a research staff member of the National Council of Research (CNR). His main research interests concern the organic chemistry of strained molecules, including the fullerenes.

most notable features of C₆₀ are its optical properties, which make this molecule interesting from the point of view of nonlinear optical materials,⁸ as shown, for example, in optical limiting experiments.⁹ Also, efficient photoconducting devices have been produced by heterogeneously mixing C₆₀ to a number of conducting polymers.¹⁰ With the help of computer modeling, Wudl, Friedman, and collaborators were able to show that the C₆₀ sphere can fit the hydrophobic cleft that characterizes the active site of the HIV-1 protease, thus inhibiting the activity of this enzyme,¹¹ and paving the way to the investigations of the biological properties of the fullerenes.^{12,13}

C₆₀ and the higher fullerenes display also a remarkable chemical reactivity, and this latter feature has generated an entirely new research field: the organic functionalization of fullerenes,^{14–17} driven by the possibility of combining some of the outstanding properties of the fullerenes with those of other interesting materials, such as photoactive and/or electroactive units. Another useful task of the organic modification of the fullerenes is the increased solubilization of the fullerene derivatives in polar solvents or aqueous media where C₆₀ and the other fullerenes are not soluble or only sparingly soluble.

The reactivity of C₆₀ is typical of an electron-deficient olefin. C₆₀, in fact, reacts readily with nucleophiles and is a reactive 2 π component in cycloadditions.^{14,18} Most reactants add to junctions between two six-membered rings of C₆₀ (6,6 junctions), where the electron density is higher. Insertions into 5,6 bonds have been reported only as rearrangements that follow a 6,6 junction attack.^{15,19,20}

Synthesis

The production of well-defined, stable and characterized derivatives, which retain the original properties of the pristine fullerene, is highly desirable and is currently being pursued by several research groups. Among the several successful functionalization methodologies reported in the past 4–5 years, the 1,3-dipolar cycloaddition of azomethine ylides to C₆₀ has met a broad acceptance, probably

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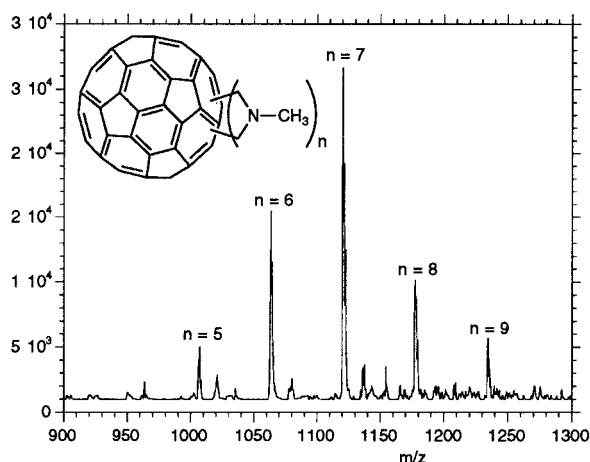
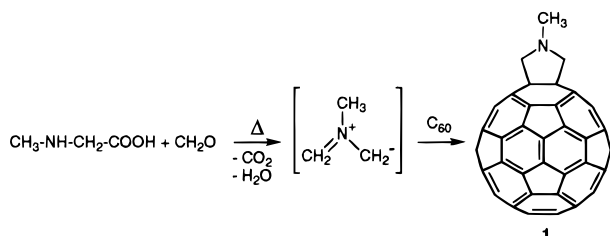


FIGURE 1. APCI-MS spectrum of the crude mixture obtained by heating a toluene solution containing C_{60} , 20 equiv of sarcosine, and 20 equiv of formaldehyde for 8 h.

due to the many ways available to generate the reactive intermediates from a wide variety of easily accessible starting materials.²¹ The most successful approach has been the decarboxylation of immonium salts derived from condensation of α -amino acids with aldehydes. In its simplest version, the reaction between *N*-methylglycine (sarcosine), formaldehyde, and C_{60} in toluene at reflux leads to the formation of the *N*-methylpyrrolidine derivative (**1**) in 41% isolated yield, which becomes 82% when considering the amount of C_{60} recovered (eq 1).^{21,22}

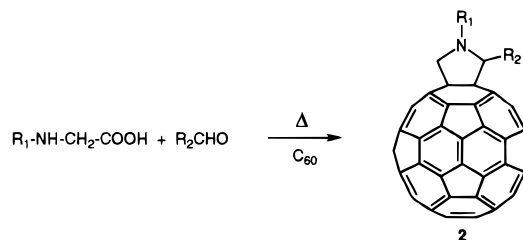


The reaction of azomethine ylides to C_{60} is site selective, in that it affords exclusively the product of cycloaddition across a 6,6 ring junction of the fullerene.²¹ This is easily seen in the proton and carbon NMR spectra of compound **1**, where the number of signals corresponds to that of a molecule with C_{2v} symmetry. The correct structural assignment to fulleropyrrolidines has been recently confirmed by X-ray crystallographic analysis.²³ When the reaction is carried out in the presence of large excesses of reagents, up to nine pyrrolidine rings can be introduced, as detected by mass spectrometric analysis of the reaction crude (Figure 1).

During any addition to C_{60} , careful attention must be paid to the formation of multiple adducts. In fact, multiple adducts are usually complex mixtures of isomers. The bisaddition of a symmetrical reagent to C_{60} can form up to 8 positional isomers, whereas the trisaddition can generate up to 46 isomers.¹⁴ Unless there is a specific interest in multiple adducts, for the isolation of pure single addition products, the reaction is typically carried out until about 50–60% of C_{60} is consumed. At this stage, about

40–50% of the monoadduct is formed, along with 10–20% of bisadducts. We usually recover the unreacted fullerene, discard the multiple adducts, and concentrate on the monoaddition products.²⁴

The scope of the reaction is very broad. The use of a different starting aldehyde (ketones can also be used) allows the preparation of 2-substituted *N*-methyl-3,4-fulleropyrrolidines. On the other hand, condensation of *N*-functionalized glycines with aldehydes will lead to *N*-substituted fulleropyrrolidines. As a matter of fact, the addition of azomethine ylides to C_{60} via the decarboxylation route is a powerful methodology for obtaining functionalized fullerene derivatives. The main advantages are as follows: (1) the reaction leads to a single monoaddition compound; (2) a wide variety of α -amino acids and aldehydes are commercially available or readily available from commercial sources; (3) two functional chains can be introduced simultaneously (eq 2). This latter offers the possibility of incorporating both the functionality we wish to combine with C_{60} and a solubilizing appendage in one single step (vide infra).

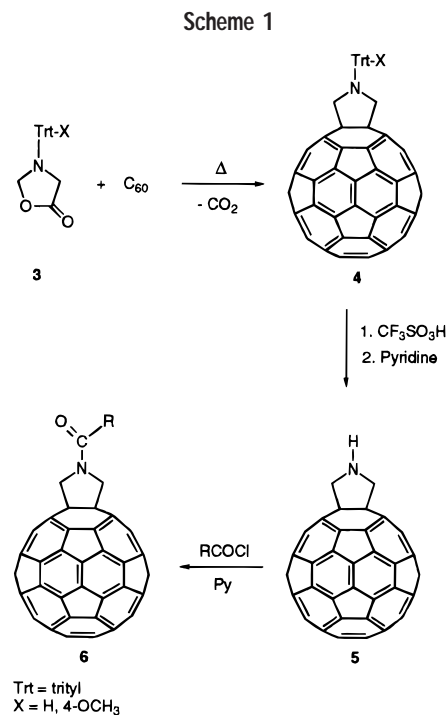


A minor drawback of this methodology is the generation of a racemic center at carbon 2 of the pyrrolidine ring when $R_2 \neq H$. This can produce mixtures of diastereomers when either R_1 or R_2 chain contains a chiral group.

Other methods for generating azomethine ylides have been successfully employed in the preparation of substituted fulleropyrrolidines, such as the thermal ring-opening of aziridines,^{21,25} and the acid-catalyzed²⁶ or thermal²⁷ desilylation of trimethylsilyl amino derivatives. Photochemical treatment of triethylamine with C_{60} has also led to fulleropyrrolidines.^{28,29}

Functionalization at nitrogen in fulleropyrrolidines can be achieved by using a nitrogen-protected amino acid.^{21,30} The *N*-tritylfulleropyrrolidines **4** were easily prepared by heating to reflux a toluene solution of *N*-trityloxazolidinones **3** and C_{60} (Scheme 1). When treated with trifluoromethanesulfonic acid, compounds **4** give a precipitate, which, upon treatment with pyridine, generates the parent *N*-H fulleropyrrolidine **5**. Reaction with acylating agents affords the corresponding amides **6**, which were studied in Langmuir–Blodgett film formation and deposition.^{30,31}

Substituted *N*-H fulleropyrrolidines can be isolated when either position 2 or 5 in the pyrrolidine ring is occupied by alkyl or aryl groups, which probably create some steric hindrance around the nitrogen atom.^{27,32–39}



Properties

The physicochemical properties of the fulleropyrrolidines are expected to arise from the combination of the two molecular fragments, the fullerene and the pyrrolidine moiety. For any applications, it is of fundamental importance to verify the extent to which the main fullerene properties are retained in the derivatives, in particular the electrochemical and the photophysical properties. As shown in cyclic voltammetry experiments, C₆₀ is an excellent electroactive unit, as it can accept, reversibly, up to six electrons.^{5–7} The same type of behavior was observed for the fulleropyrrolidines, whose cyclic voltammograms are typically characterized by small shifts of the reduction potentials to more negative values.⁴⁰ This is expected if we consider that saturation of a double bond causes a partial loss of conjugation in the extended π -system of C₆₀. Due to this effect, at most five reduction peaks for the C₆₀ moiety in fulleropyrrolidines have been detected so far in the accessible potential range.^{40,41} As a typical example, Figure 2 shows the cyclic voltammetry of C₆₀ (a), together with that of *N*-methyl-fulleropyrrolidine **1** (b).

The electronic properties of the fulleropyrrolidines are typical of most C₆₀ monoadducts.⁴² Analogously to C₆₀, the electronic spectra of the pyrrolidine derivatives are dominated by strong absorptions in the UV region,²¹ which in C₆₀ correspond to the electronic transitions with high oscillator strength from the ground state to the ³1T_{1u} and to the ⁶1T_{1u} excited states, observed at 328.4 and 256.6 nm, respectively, in *n*-hexane solution.⁴³

In the visible region, fulleropyrrolidines show a broader range of absorption up to almost 800 nm, with a sharp peak at 430 nm and a broader band at around 700 nm (Figure 3). The fluorescence spectrum of **1** is in excellent agreement with its UV-vis spectrum, indicating photo-

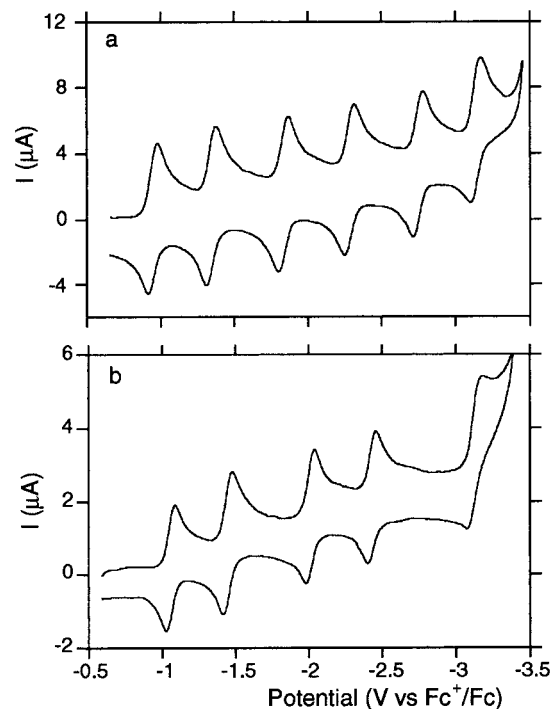


FIGURE 2. Cyclic voltammograms (sweep rate 0.1 V s⁻¹) of C₆₀ (a) and **1** (b) on a glassy carbon electrode in 3:1 toluene/acetonitrile solutions (0.1 M TBAP), at -45 °C.

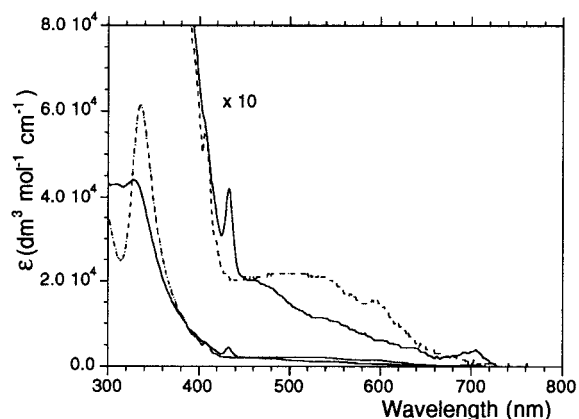


FIGURE 3. UV-visible absorption spectrum of **1** (solid line) and C₆₀ (dotted line) in toluene ($\approx 1.2 \times 10^{-5}$ M).

physical behavior similar to C₆₀.⁴⁴ The first excited singlet of compound **1** has an absorption maximum at 886 nm, remarkably blue-shifted relative to C₆₀ (920 nm),⁴⁵ with a half-life of 1.2 ns⁴⁵ or a lifetime of 1.3 ns.⁴⁶ The triplet-triplet absorption of **1**, broader than C₆₀, is centered at 692 nm, with a shoulder at 800 nm.⁴⁴ Its absorption coefficient, assuming quantitative triplet formation, was calculated to 16 700 M⁻¹ cm⁻¹ in methylcyclohexane⁴⁴ (for C₆₀, $\epsilon = 14\,500$ M⁻¹ cm⁻¹ at 750 nm⁴⁷).

An interesting question to be addressed is if and how the fullerene spheroid influences the acid-base properties of the pyrrolidine nitrogen. Indeed, we have found that in 85:15 dioxane/water, fulleropyrrolidine **7** is almost 6 orders of magnitude less basic than its model **8** (Chart 1). Whereas **8** has a p*K*_{BH⁺} = 11.1, a typical value for a tertiary amine, fulleropyrrolidine **7**, has a p*K*_{BH⁺} = 5.6.⁴⁸ This result can be tentatively attributed to some kind of

Chart 1

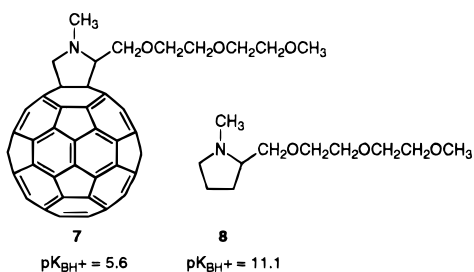
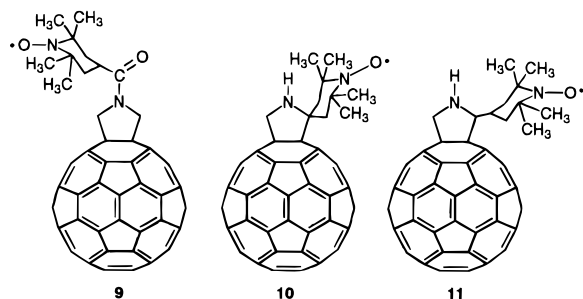


Chart 2



through-space interactions of the nitrogen lone pair with the fullerene π -system.⁴⁹ A confirmation of this hypothesis comes from a second experiment, the methylation of the pyrrolidine nitrogen by excess methyl iodide. Again, the reaction rate is much slower in the case of fulleropyrrolidine **7**, confirming the diminished availability of the nitrogen lone pair in **7**.⁴⁸

A series of fulleropyrrolidines bearing a nitroxide group (2,2,6,6-tetramethylpiperidine-1-oxyl) has been synthesized; see Chart 2.^{32–34} These compounds possess a paramagnetic probe useful for investigating the electronic properties of the fullerenes. As a matter of fact, they were successfully employed for the study of the anions³⁴ and the excited triplet states^{32,33} of the C₆₀ moiety. In particular, the properties of the reduced fulleropyrrolidines become relevant since these compounds are being extensively used as electron-accepting units in photoactive dyads.^{17,50} When compounds **9–11** were reduced by contact with sodium metal, the anion radical of the C₆₀ moiety was generated, whose unpaired electron experiences a strong exchange coupling with the nitroxide unpaired electron. Frozen solution EPR spectra of the anionic species allowed the determination of the electron–electron dipolar interaction parameters, which were compared with theoretical MO calculations. The experimental values are in good agreement with a spin distribution of one unpaired electron located around the equatorial belt of the fullerene.³⁴ The unpaired electron in **1**-radical anion on the fullerene moiety was also detected with the help of ¹H and ¹³C NMR spectroscopies.²³

Optically pure fulleropyrrolidine derivatives have been synthesized.^{51,52} The chiroptical properties of the adducts have been studied by means of circular dichroism (CD) spectra. The CD spectrum of each compound shows a wide range of optically active bands due to the large window of absorptions of the fullerene moiety coupled with the dissymmetric perturbation induced by the chiral

pyrrolidine ring. The most distinctive feature is a sharp maximum at $\lambda \approx 428$ nm. The sign of this Cotton effect is indicative of the absolute configuration of the newly generated asymmetric center (carbon 2 of the pyrrolidine ring).^{51,52}

Applications

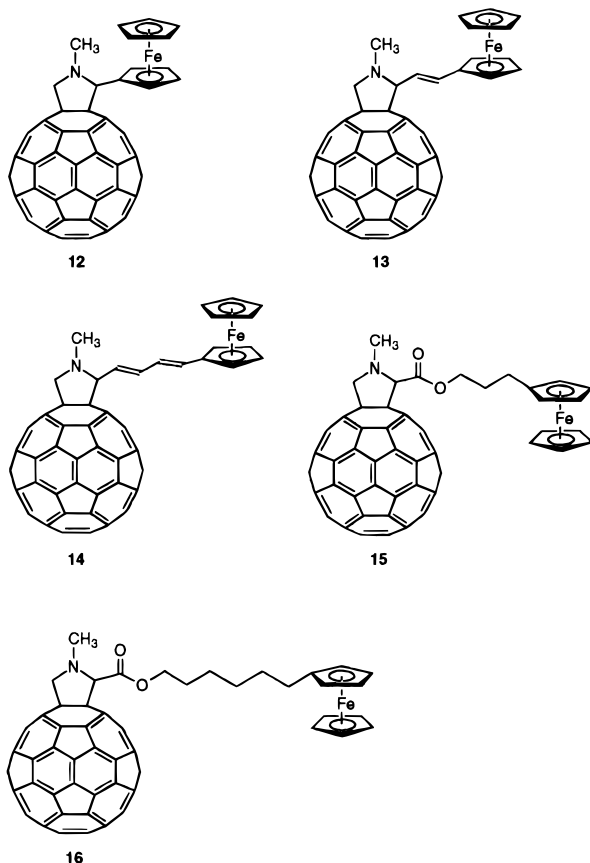
The high degree of functionalization achievable with the addition of azomethine ylides to C₆₀ has stimulated the synthesis of quite a number of fulleropyrrolidines specifically designed for applications in materials science and medicinal chemistry. For example, the facile introduction of covalently linked electro- or photoactive units has been utilized by several groups in the construction of donor–bridge–acceptor diads, where C₆₀ is the acceptor unit.^{17,50} C₆₀, in fact, combines the low reduction potential typical of small acceptors such as quinones together with low excited-state energies typical of large π systems and has a small reorganization energy.⁵⁰ Donor units covalently attached to C₆₀ via azomethine ylide cycloaddition include ferrocene,^{40,41,45} electron-rich aromatics,^{44,53} ruthenium-(II) trisbipyridine complexes,^{54,55} tetrathiafulvalene,^{41,56,57} porphyrins.^{46,58–60} The synthesis and the photophysical behavior of an interesting fulleropyrrolidine–porphyrin–carotene triad has also been reported.⁶¹

A systematic steady-state fluorescence and time-resolved flash photolytic investigation was carried out on the fulleropyrrolidine–bridge–ferrocene diads **12–16** (Chart 3).⁴⁵ It was found that the nature of the spacer has important consequences on the lifetime of the charge-separated states. In all cases electron transfer occurs from the ferrocene donor to the fullerene acceptor upon irradiation at 532 nm. However, two different quenching mechanisms were observed, through bond electron transfer for **12–14** and formation of a transient intramolecular exciplex for **15–16**. Nanosecond-resolved photolysis of **15–16** in degassed benzonitrile revealed long-lived charge-separated species with characteristic fullerene radical anion bands at $\lambda_{\text{max}} = 1055$ nm.⁴⁵

Thin films containing fulleropyrrolidines have been prepared using different techniques. Mirkin and collaborators have used a thiol-functionalized fulleropyrrolidine to achieve adsorption onto a gold surface, obtaining a well-defined, surface-confinable fullerene.⁶² A methylthio group, attached to a porphyrin-linked fulleropyrrolidine, allowed the formation of a self-assembled monolayer onto a gold electrode. This multicomponent system generates photocurrent upon irradiation.⁶⁰

The introduction of a polar head onto the pyrrolidine nitrogen was essential for the deposition of robust monomolecular layers via Langmuir technique. Either an amide group^{30,31} or a hydrophilic triethylene glycol chain⁶³ has been successfully employed to anchor the fulleropyrrolidine to the water surface. In particular, the amphiphilic derivative **2a** (eq 2, R₁ = CH₂CH₂OCH₂CH₂OCH₂CH₂OCH₃, R₂ = H) forms a stable monolayer at the air–water interface when dropped from a deuteriochloroform solution, with an area per molecule of 105 Å² at zero pressure.

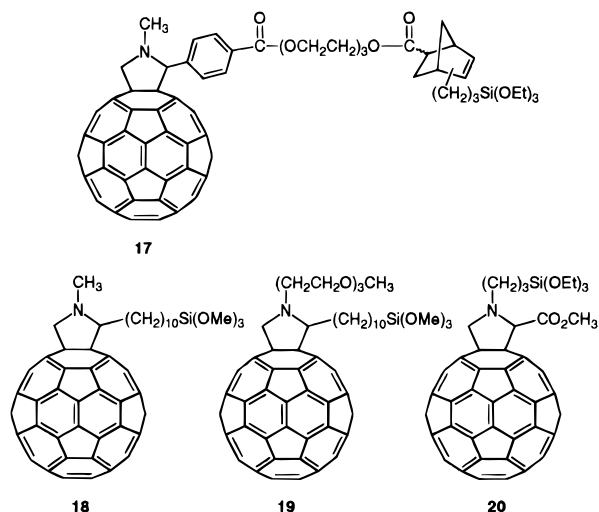
Chart 3



This monolayer could be transferred onto a glass microscope slide or quartz slide by the Langmuir–Blodgett method or onto highly oriented pyrolytic graphite by the Langmuir–Schaefer (quasi-horizontal transfer) technique. The same derivative **2a** has a very strong interaction with a KCl/water surface. Instead, the hydrophobic fulleropyrrolidine **2b** (eq 2, $R_1 = n\text{-C}_{12}\text{H}_{25}$, $R_2 = \text{H}$) used for comparison, did not form a true monolayer film at the air–water interface.⁶³

A most promising field of application of the fullerenes is related to the optical limiting (OL) behavior exhibited by C_{60} (and C_{70}) solutions via the reverse saturable absorption mechanism.⁹ In C_{60} , in fact, both the first singlet excited state and the lowest energy triplet state show cross-sections larger than the ground state in the visible and the near-infrared spectral regions.⁴⁷ In solution, the nonlinear properties of C_{60} compare well with those of other materials currently under consideration for OL purposes.⁹ However, for practical uses, such as fabrication of goggles, windows, shields, etc., C_{60} must be incorporated in solid matrices. For this purpose, the ideal substrate would be a glassy matrix, more specifically a glassy film obtained via the sol–gel technique. C_{60} itself cannot be used, due to its exceedingly low solubility in ethanol or tetrahydrofuran, the solvents commonly used in sol–gel processing.⁶⁴ We reasoned that if a soluble fullerene derivative with an attached alkoxy silane chain is used during the glass preparation, in the end, the C_{60} spheroid should be covalently attached to the silicon matrix and then homogeneously dispersed. Accordingly,

Chart 4



the ideal molecule should possess both a solubilizing appendage and a silicon alkoxide moiety. The molecules synthesized for this purpose (see Chart 4) have in fact given excellent results in terms of solubility and the quality of the films.⁶⁵ As compared to C_{60} , fullerene derivatives show a lower singlet–triplet quantum yield,⁴² so that **17–20** are expected to exhibit a lower OL efficiency in the nanosecond time scale. However, it was demonstrated that the optical limiting properties of C_{60} and its derivatives depend on the excitation wavelength.^{66,67} When the latter is closer to the triplet–triplet absorption maximum of the fullerene derivative ($\lambda_{\text{max}} \approx 700 \text{ nm}$), the OL performance of the organofullerene becomes more efficient.

Fulleropyrrolidine **20** (Chart 4) is a very useful compound. It can be prepared on a large scale by thermal ring-opening of *N*-(3-propyltriethoxysilyl)-2-(carbomethoxy)aziridine in the presence of C_{60} .⁶⁸ Compound **20** was profitably used in the preparation of a fullerene-modified HPLC stationary phase. The silicon alkoxide group, in fact, guarantees the chemical grafting to silica. Attachment to HPLC spherical silica particles can be achieved under mild conditions such that a new chromatographic phase is easily prepared. Standard chromatographic tests with simple aromatic compounds revealed that the new phase works with high efficiency both in organic- and water-rich media. However, with respect to more conventional types of silica, different interactions are expected toward more complex solutes capable of establishing multipoint contacts with the spheroidal shape of the fullerene. Accordingly, exceptionally high size-selectivities were obtained for cyclic oligomeric compounds such as calixarenes and cyclodextrins in organic- and water-rich media, respectively. A number of helical-shaped peptides, containing hydrophobic cavities complementary in size to C_{60} , bind selectively to the grafted fullerene (Figure 4).⁶⁸

The synthesis of derivatives of the unnatural amino acid fulleroproline (termed Fpr, using the three-letter code for amino acids) can be achieved by means of 1,3-dipolar cycloadditions of azomethine ylides to C_{60} .^{51,69} Compound **2c** (eq 2, $R_1 = \text{H}$, $R_2 = \text{COOH}$) contains a proline

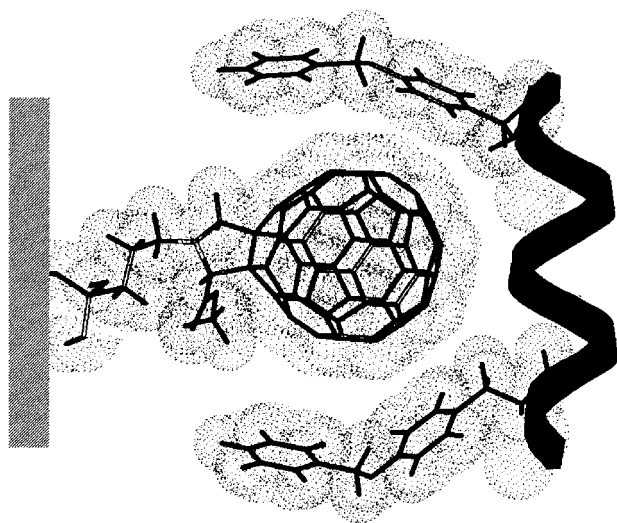


FIGURE 4. Schematic representation of the supramolecular complex between the nonapeptide *p*-BrBz-Aib-L-Tyr(Bn)-Aib₂-Gly-Aib₂-L-Tyr(Bn)-Aib-OMe and fulleropyrrolidine **20** anchored to HPLC silica particles, obtained with the help of Insight II program running on a Silicon Graphics workstation (Bz = benzoyl, Bn = benzyl, Aib = 2-aminoisobutyric acid). The helical ribbon is an exact geometrical reproduction of the ₃-helical peptide backbone. The two Tyr residues, separated by five intervening amino acids, are located on the same side of the ternary, right-handed helix after two complete turns. This scaffold generates a cavity characterized by a distance between the two Tyr C^β atoms of 11.5 Å, ideal for acting as a fullerene receptor. We thank Dr. Roberto Battistutta and Dr. Alberto Bianco for their help in generating this image.

ring fused to C₆₀ and probably represents the biggest unnatural amino acid. This class of compounds has acquired considerable interest after the recent discovery that C₆₀ derivatives are potentially active against the HIV-1 protease and reverse transcriptase.^{11,70,71} Furthermore, it was also reported that C₆₀ derivatives possess good properties for photodynamic therapy.^{13,72} These exciting results have prompted many research groups to prepare water-soluble C₆₀ derivatives potentially endowed with biological activity.^{12,13} In this context, fulleroproline can be considered a valuable building block for the preparation of fullerene-based peptides. Among others, a fully protected Fpr was easily prepared as a starting material for peptide synthesis.⁵¹ In fact, under standard conditions of peptide synthesis, dipeptides that include Fpr have been prepared.⁵¹ The preparation of optically active fulleroprolines, fundamental in avoiding stereoisomer formations during peptide synthesis, relies on asymmetric azomethine ylide cycloadditions or chiral chromatography. Both ways have been pursued with positive results.⁵¹ The CD spectra of all isomers show, as a common feature, a sharp maximum centered at 428 nm. The sign of this Cotton effect offers a strong clue to the determination of the absolute configuration of the chiral C^α atom generated during the cycloaddition: a positive maximum is associated with R configuration, whereas the S isomer gives a negative maximum.^{51,73} The conformational analysis of Fpr peptides has also been investigated.⁷⁴

A few water-soluble fulleropyrrolidines have been synthesized.⁷⁵ The new compounds exhibit moderate

solubility in 9:1 water–DMSO (up to 3×10^{-5} M), and their biological activity could be tested against different microorganisms.⁷⁵

Conclusions and Perspectives

The cycloaddition of azomethine ylides can be considered a very useful way for the structural modification of C₆₀. Many commercially or readily available starting materials can be successfully employed in the preparation of highly functionalized fullerenes. The reaction products, colloquially termed fulleropyrrolidines, retain the basic physicochemical properties of C₆₀, having acquired those of the newly added groups. Nowadays, we can confidently say that the functionalization of fullerenes is routinely carried out in many laboratories and that, at least in principle, any type of molecular fragment can be covalently attached to C₆₀. In this context, the addition of azomethine ylides shares the privilege, together with other cycloadditions, of having provided the fullerene community with a preferred means for solving practical problems, such as the exceedingly low solubility of the caged carbon clusters and the coupling of the fullerene spheroid with photo- and/or electroactive units with new perspectives in molecular recognition, redox chemistry, and photoinduced electron transfers. Accordingly, diads and triads containing C₆₀ have already been synthesized, and their photophysical behavior appears very promising in terms of the lifetime of the charge-separated species. Fulleropyrrolidine-modified HPLC stationary phases have been prepared, and their peculiar chromatographic behavior has been analyzed. Highly soluble fulleropyrrolidines have been incorporated in sol–gel glasses, giving rise to optical-limiting materials. Water-soluble fulleropyrrolidines have been prepared, which could be used for biological tests against several microorganisms.

More and more complex architectures are going to be built on the fullerene surface. C₆₀ is becoming a relatively common building block in organic synthesis, and its chemical reactivity is now well-established. There is, however, plenty of room for novelty. Part of the fascination of working with C₆₀ and its cousin higher fullerenes is that it is often impossible to fully envisage the properties of the new derivatives. In a way, each new compound can unveil surprises and generate excitement. This is probably the reason the number of scientists attracted by this field is still increasing.

We are deeply indebted to all our collaborators, whose names appear in the references. These colleagues have played the fundamental role of making our compounds useful in practical applications, while allowing us to work in a very friendly and stimulating atmosphere. Our profound gratitude goes to Professor Gianfranco Scorrano, who has always closely followed our work and very keenly discussed every matter since its very beginning. We also thank Professor Fred Wudl, who has given us the great opportunity to start our work on fullerenes in the best way. We dedicate this paper to the memory of our friend and colleague Ugo Quintily (1942–90), who taught us the first steps in the laboratory and suggested to us the best shortcuts for succeeding in organic synthesis.

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AR970210P