Synthesis and applications of amphiphilic fulleropyrrolidine derivatives

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The most successful strategies for dissolving fullerenes in polar solvents by means of 1,3-dipolar cycloaddition of azomethine ylides to C_{60} are reviewed. The preparation of the fullerene derivatives is discussed together with their properties and applications in different fields.

1. Introduction

Since 1990,[1] the applicability of fullerenes in different fields has been investigated thoroughly. In particular, C_{60} has been established as a valuable building block in the construction of novel materials and in medicinal chemistry. C_{60} is an excellent three-dimensional electron-acceptor, not only because of its high electron affinity[2–4] but also because of the high delocalization of the electrons in the three-dimensional π-system and its small reorganization energy.[5] In medicinal chemistry, C_{60} has shown activity against HIV and several microorganisms.[6] The major drawback of fullerenes is their lack of solubility in common solvents, which impairs dramatically their processability. The solvation of C_{60} requires the disruption of many solvent–solvent interactions due to its rigid geometry and lack of permanent dipole moment, which are not compensated for by the solvent–C_{60} interactions. C_{60} is completely insoluble in protic or polar aprotic solvents such as water, methanol, acetonitrile, tetrahydrofuran or dimethyl sulfoxide.[7] It is slightly soluble in alkanes, haloalkanes

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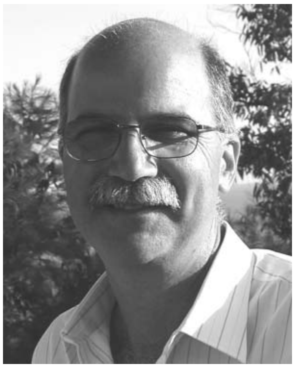

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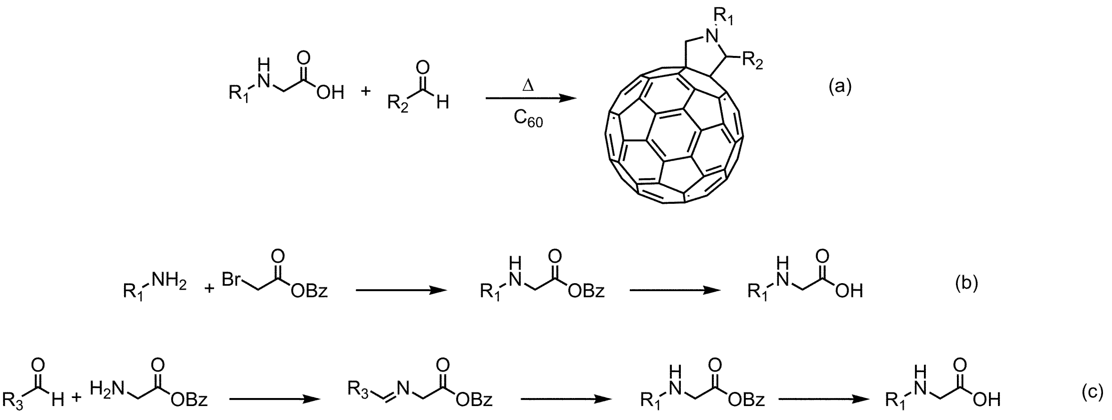


Scheme 1 (a) [3 + 2] Cycloaddition with azomethine ylides; (b) and (c) routes to *N*-functionalized glycine derivatives.

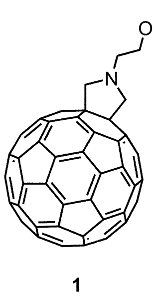
being better solvents. Aromatic hydrocarbons such as toluene and *o*-dichlorobenzene, along with CS_2, are among the best solvents for C_{60}. The lack of solubility can be overcome by functionalization. Depending on the nature of the addend, the solubility of the derivatized fullerene can be improved in certain solvents. When C_{60} is functionalized with hydrophilic residues, fullerene-based amphiphilic derivatives are obtained, making it possible to study their properties in polar organic solvents, water or physiological media. One of the most successful tools for the functionalization of fullerenes is the [3 + 2] cycloaddition with azomethine ylides.[8,9] These intermediates are generated *in situ* by decarboxylation of the imminium salts formed by condensation between *N*-substituted glycines and aldehydes [Scheme 1(a)]. The reaction is truly general and is compatible with a wide variety of functional groups, yielding fulleropyrrolidines functionalized on the nitrogen atom and on the adjacent carbon atom of the pyrrolidine ring. Another advantage of the azomethine ylide cycloaddition is its reversibility under controlled conditions, as recently the first example of the retrocycloaddition has been reported.[10]

Two general routes to *N*-functionalized glycine derivatives have been successfully adopted in our group, giving immediate access to virtually any *N*-functionalized fulleropyrrolidines. One is based on the alkylation of the desired amine with benzyl 2-bromoacetate, followed by deprotection of the acid by catalytic hydrogenation [Scheme 1(b)].[11] In the other, the corresponding aldehyde and glycine benzyl ester are condensed, followed by reduction of the resulting imine and deprotection of the acid by catalytic hydrogenation [Scheme 1(c)].[12]

In this article, the most successful strategies for dissolving fullerenes in polar solvents by means of 1,3-dipolar cycloaddition of azomethine ylides to C_{60} will be reviewed. The preparation of the fullerene derivatives will be discussed together with their properties and applications in different fields.

2. Functionalization with mTEG

Solubilizing groups can be introduced at the level of cycloaddition or a post-functionalization can serve the purpose. One example of the first approach consists in the derivatization of fullerenes with triethyleneglycol monomethyl ether chains (mTEG) due to the high solubilizing power of this class of compounds (Fig. 1).[13] The versatility of the reaction allowed the preparation of monosubstituted fulleropyrrolidines displaying the solubilizing addend in the *N*-position (**1**) by using *N*-mTEG glycine and formaldehyde,[14] or on carbon 2 (**2**) when the reaction was carried out with *N*-methyl glycine and mTEG-aldehyde.[15] A doubly-functionalized fullerene (**3**) was obtained by using both *N*-mTEG glycine and mTEG-aldehyde.[12] All compounds exhibited moderate solubility in 9 : 1 water–DMSO mixtures. Biological tests carried out with **3**,[12] revealed a wide range of activity against several microorganisms like bacteria and fungal



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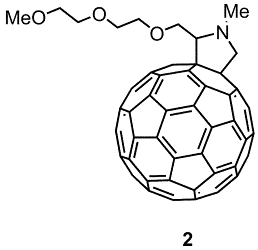

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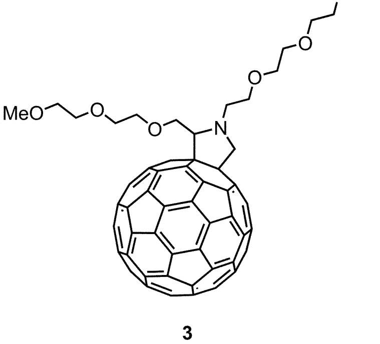

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Fig. 1 Fullerenes functionalized with mTEGs.

strains. In this regard, water–DMSO (9 : 1) soluble *N*-mTEG substituted fullerenes functionalized with biologically active molecules in position 2, including 4-aryl-1,4-dihydropyridines[16] and arylpiperazines,[17] have been successfully prepared. Their biological activity is currently under investigation.

The applicability of this family of fulleropyrrolidines has also been evaluated in materials science. Fulleropyrrolidine **1** has been shown to form 'true' Langmuir monolayers at the air–water interface that can be transferred onto hydrophilic substrates by Langmuir–Blodgett or Langmuir–Schäfer techniques.[14] Scanning Tunneling Microscopy (STM) measurements confirmed the formation of well-ordered films.

Compounds **1** and **2** were studied electrochemically in THF solutions.[18] The cyclic voltammograms exhibited only five consecutive reduction processes, shifted to more negative values when compared with C_{60}. This effect was expected on the basis that the saturation of a double bond due to functionalization caused partial loss of conjugation.[19]

The mTEG chain was also used to improve the solubility of derivatives containing other useful functionalities. A 2-mTEG-fulleropyrrolidine covalently attached to a thiophene unit was prepared to increase its solubility in polar organic solvents (Fig. 2). The solubilization in acetonitrile permitted the preparation of polymeric films containing fullerenes by electropolymerization.[18] The films retained the redox properties of the initial fullerene derivatives.

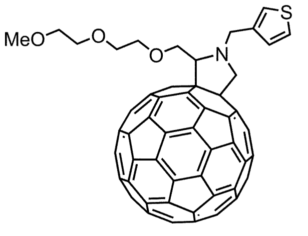


Fig. 2 Soluble 2-mTEG-fulleropyrrolidine functionalized with a thiophene unit.

When associated with an electron-donating chromophore, C_{60} becomes a very suitable candidate to construct photoactive devices. In fact, the resulting dyads typically represent useful models for artificial photosynthesis. Several fullerene–π-extended tetrathiafulvalene (exTTF) dyads have been prepared and studied by the groups of Martín and Guldi, in which mTEG functionalization was introduced to provide solubility in organic solvents. The dyads (Fig. 3) have shown charge-separated states with lifetimes between 200 and 1465 ns.[20] It was observed that by increasing the separation between the donor and acceptor through a vinylene linker, the efficiency of the dyads was improved. In this light, molecular wires in which the exTTF is connected to C_{60} through oligo (*p*-phenylenevinylene) were prepared giving long distance (up to 40 Å) charge-separated states.[21,22]

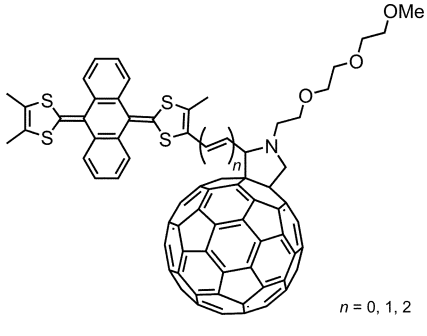


Fig. 3 Fullerene–exTTF dyads.

If a pyridyl group is introduced together with an mTEG chain, the resulting fulleropyrrolidine can complex metal porphyrins axially (Fig. 4).[23] The structure of the complex did not provide the adequate hydrophobic–hydrophilic balance to ensure the formation of stable Langmuir–Blodgett monolayers. The floating films were prepared using arachidic acid as an additive, giving reproducibility in the preparation of the film and, more importantly, the dyad molecules were separated favoring intramolecular processes. The layers were transferred onto solid substrates and studied by steady-state and transient asbsorption spectroscopy. The radical anion of C_{60} was detected with a lifetime of 2.2 μs. This approach has been successfully applied for the preparation of monolayers of non-polar fullerene derivatives, using pentadecanoic acid as the additive.[24]

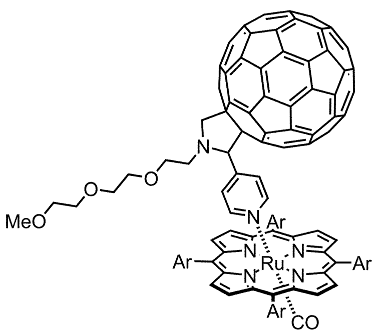
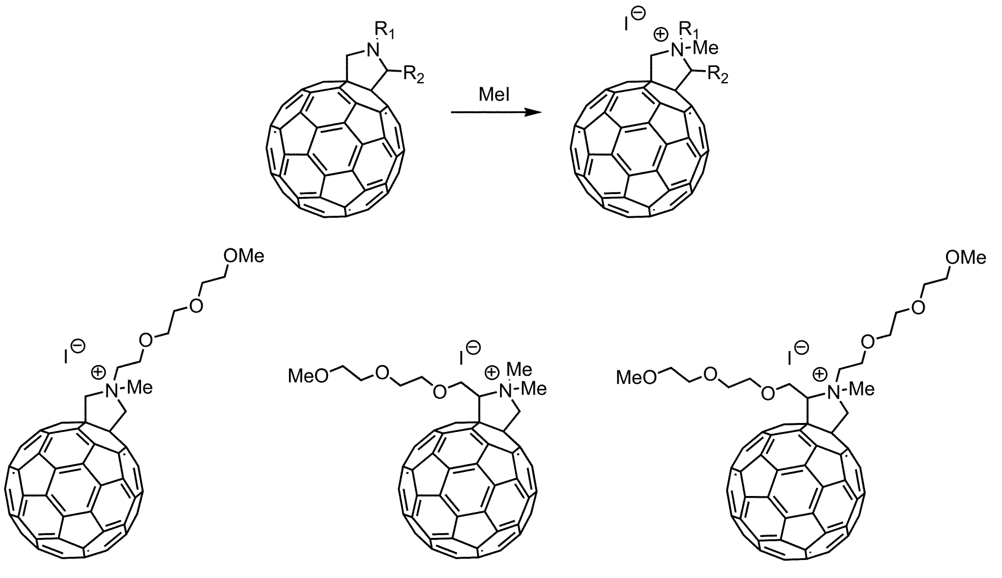


Fig. 4 Supramolecular fullerene–porphyrin dyad.

The acid–base properties and the nucleophilicity of the nitrogen atom of the fulleropyrrolidine **2** were studied in 85 : 15 [D_8]dioxane–D_2O.[25] The NMR titration experiments evidenced that the difference in basicity between fulleropyrrolidine **2** ($pK_{BD}{}^{+} = 6.6$) and the analogous model pyrrolidine ($pK_{BD}{}^{+} = 11.6$) was of six orders of magnitude. Polar effects could not be responsible for this decrease in basicity. Steric effects were not considered since the basicity differs between 1 and 2 p*K* units.[26] This effect has been attributed to through-space interactions between the nitrogen lone pair and the fullerene π-system. This effect was previously observed in spiromethanofullerenes and was called *periconjugation*.[27] In terms of nucleophicity, the fulleropyrrolidine is 1000 times less reactive when compared with the analogous model pyrrolidine in the reaction with methyl iodide.[25]

3. Introduction of positive charges in the fulleropyrrolidine ring

The advantage of fulleropyrrolidines in the preparation of hydrophilic fullerenes *versus* other functionalization patterns relies on the possibility of introducing positive charges on the nitrogen atom of the pyrrolidine ring. This can be achieved either by protonation with strong acids or by alkylation. Since complete protonation cannot be assured due to the low basicity of the fulleropyrrolidine nitrogen,[25] alkylation turned out to be the best



4 **5** **6**

Scheme 2 Preparation of fulleropyrrolidinium salts.

option to access these derivatives, not only to increase their solubility but also to study their electronic properties (Scheme 2).

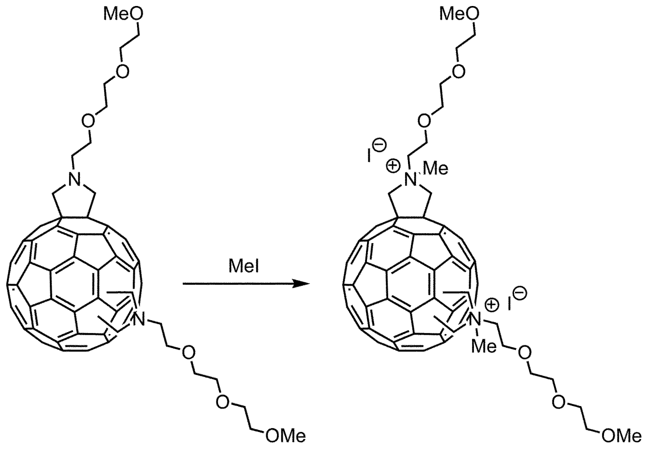
When fulleropyrrolidines **1**, **2** and **3** were methylated with methyl iodide, the corresponding fulleropyrrolidinium salts **4**, **5** and **6** were obtained (Scheme 2).[28] As expected, the solubility of the salts in 9 : 1 water–DMSO mixtures was found to be higher as compared to the neutral compounds.[29] The positively charged derivatives exhibited antimycobacterial activity[29] and were successfully used for the construction of mixed multilayer Langmuir–Blodgett films.[30]

The electrochemical properties of these positively charged derivatives[28,31] showed enhanced acceptor properties. Six reduction waves were observed. The first four reduction waves were less cathodic than those obtained for C_{60}. On the other hand, the two consecutive reduction waves were cathodically shifted, the last one being irreversible. The reason for the increased electronegativity was attributed to inductive effects.

Since the applications as electron-acceptors of **4**, **5** and **6** will require stable reduced species, the stability of the reduced species was investigated over a much longer time scale than cyclic voltammetry.[30] The first reduction species were generated and studied by bulk electrolysis and the progress was monitored by UV-Vis-NIR spectroscopy and steady-state voltammetry. The typical absorption features were in excellent agreement with the absorption spectra produced by time-resolved techniques in charge transfer species of fullerene derivatives.[32] The electrolyzed solution was stable for several hours but rapid degradation took place when further reduction was attempted. Instead, stable, two-electron reduced species were observed by chemical reduction using cobaltocene.

4. Fullerene bisadducts

Even in the presence of a solubilizing chain, the highly hydrophobic carbon spheres stick together leaving the hydrophilic chains outside of the aggregate.[33,34] Multiple functionalization can be applied to avoid aggregation of the fullerene spheres, which should give sufficiently homogeneous dispersions (Scheme 3).



Scheme 3 Methylation of bisadducts.

Stoichiometric variations of the standard procedure for the functionalization of C_{60} by *in situ* generated azomethine ylides gives bis- and tris-adducts. The preparation and isolation by HPLC of the whole series of the mTEG fulleropyrrolidine bisadducts (*trans*-1, *trans*-2, *trans*-3, *trans*-4, *equatorial*, *cis*-3, *cis*-2, and *cis*-1) was achieved.[35] Also, nine different *N*-methyl trisadducts were prepared and characterized.[36]

A series of regioisomeric bisfulleropyrrolidines obtained by cycloaddition with *N*-methyl glycine and formaldehyde were synthesized. Methylation of these by methyl iodide yielded the bisfulleropyrrolidinium salts, which were soluble enough in water without the need of mTEG solubilizing chains to study their activities against HIV-1 and HIV-2. *Trans*-2 and *trans*-3 isomers showed interesting antiviral properties, confirming the importance of the relative positions of the substituent on the C_{60} cage.[37]

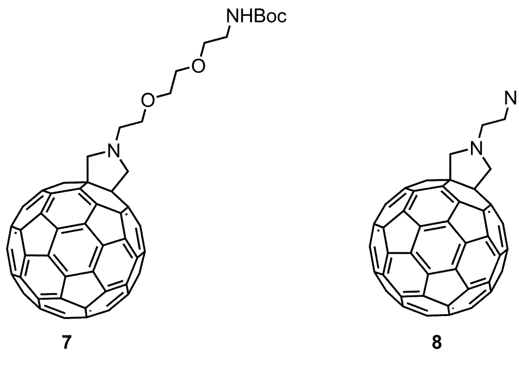
N-Methyl bisadducts have also been shown to be useful in polymer chemistry.[38] It should be noted that *trans*-2, *trans*-3 and *cis*-3 enantiomers display C_2 symmetry and are intrinsically chiral due to their addition pattern. Each couple of these enantiomers was separated by chiral HPLC. The resulting enantiomerically pure isomers were transformed into fulleropyrrolidinium salts that were soluble in water–DMSO. The enantiomerically pure *trans*-3 isomers were used to induce chiral helicity in negatively charged polymer backbones in opposite directions, depending on the absolute configuration of the bisadduct used.

The influence on the reduction potentials of the different functionalization patterns in bisfulleropyrrolidines and bisfulleropyrrolidinium salts have been studied by cyclic voltammetry.[39] The experiments confirmed an enhancement of the electronegative properties of the bisfulleropyrrolidinium salts and the opposite effect in the bisfulleropyrrolidines when compared to C_{60}. The *trans*-2 and *trans*-1 fulleropyrrolidinium salts, in which the addends are at furthest distances, resulted among the strongest reversible electron-accepting oligoadducts.

Bisfulleropyrrolidinium salts were found to be useful in nanosensing. A novel biosensor for the amperometric detection of glutathione was obtained by immobilization of a redox enzyme using the *trans*-2 *N*-methyl-*N*-mTEG bisadduct as the redox mediator,[40] improving the response range of the modified electrode.

5. Functionalization with terminal ammonium salts

Terminal amino groups can be introduced in the side chains of the fullerenes by modification of the amino acid used as precursor for the azomethine ylide cycloaddition (Fig. 5).[11]



7 **8**

Fig. 5 Fullerene building blocks with terminal amino groups.

These derivatives have shown to be useful building blocks for applications in materials science, since they can be combined with a wide variety of interesting moieties. In the presence of strong acids only the terminal amino groups are protonated efficiently giving ammonium salts in which the cation species is placed close to or far away from the fullerene sphere depending on the length of the chain. Additionally, these novel systems can be methylated on the fulleropyrrolidine nitrogen producing doubly charged species.

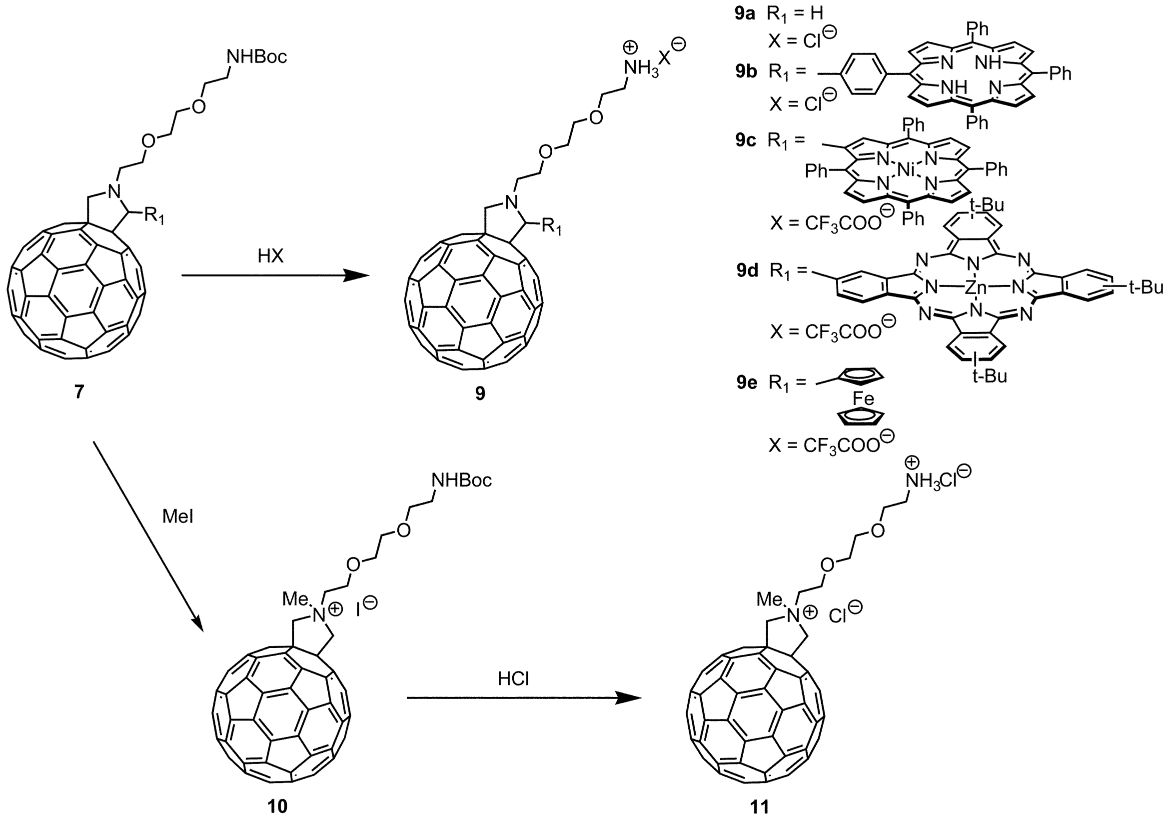
In the protonated series **9a**–**e** (Scheme 4), the combination of the strong hydrophobic character of the fullerene sphere and of the side chain, along with the hydrophilic character of the ammonium function, gives rise to amphiphilic derivatives. This leads to fullerene compounds which self-organize in solution, at the air–water interface and onto surfaces.[41]

A mixed composite thin film consisting of fulleropyrrolidine **9a** and a novel, water-soluble anionic porphyrin dissolved in the subphase was prepared using the Langmuir–Shäfer method.[42] Although the presence of the ammonium termination is not sufficient to render it adequately amphiphilic, the electrostatic interaction between the ammonium function of fulleropyrrolidine **9a** and the negatively charged porphyrin derivative induced the generation of homogeneous, high-quality photoactive films. Both Atomic Force Microscopy (AFM) studies, realized after deposition of the monolayer onto silicon substrates, and Brewster Angle Microscopy (BAM) analysis were in agreement and have shown good homogeneity of the mixed thin film.

The fabrication of high-quality and robust photoactive ITO electrodes was achieved using derivative **9b** following the layer-by-layer (LBL) technique.[43] The electrodes were built through electrostatic and van der Waals interactions between **9b** and a polyelectrolyte surface. The step-by-step deposition of poly(diallyl dimethylammonium) (PDDA) followed by poly(sodium 4-styrenesulfonate) (PSS) gave rise to surfaces sufficiently overlaid with negative charges allowing the deposition of the positively charged **9b** by immersing the substrates into an *o*-dichlorobenzene/DMSO solution of **9b**. Absorption spectra taken after each deposition showed uniform packing of the layers. The topography of each layer as well as the regularity of the surface of the modified electrode was visualized by AFM images, which showed continuous uniform films. Compound **9b** organized in an electrostatically-directed manner onto PSS. The key to this kind of assembly was the positively charged ammonium group. Indeed, the fundamental requisite of the positive charge on the active species was confirmed by the unsuccessful attempt to deposit another dyad or a porphyrin in which the positively charged side chain was missing.

Langmuir thin films have also been obtained from **9c**. Observations by BAM analysis of the floating film, revealed the existence of aggregates on the water surface. Photoactive ITO electrodes were prepared from compound **9c** by transfer of the monolayer following both the Langmuir–Schäfer and the LBL methods.[44]

This class of amphiphilic compounds has also been shown to self-organize when dispersed in water by sonication.[45,46] Depending on the hydrophobicity–hydrophilicity balance, and on the nature and length of the side chains, different nanostructures can be obtained such as nanospheres, nanorods and nanotubules. Transmission Electron Microscopy (TEM) studies have shown that **9a**, in which a long oligoethylene glycol side chain is present with one ammonium salt function, tends to aggregate in long, uniform rods with diameters of about 4 nm and lengths of several microns. Though the presence of the second positive charge on the pyrrolidine nitrogen in compound **11** increases the solubility in water, still the same rod-like linear structures were observed. Compound **9b**, bearing a porphyrin unit, forms nanotubules with a strongly improved morphology and uniformity (around 30 nm in diameter and 500 nm in length). Identical behavior was observed when the aggregation properties of the analoguous compound **9d** bearing a phthalocyanine were studied.[47] The shape improvement was attributed to the existence of extra interactions by the introduction of the macrocycle. Thus, macrocycle–macrocycle, macrocycle–C_{60} interactions add to C_{60}–C_{60} interactions,

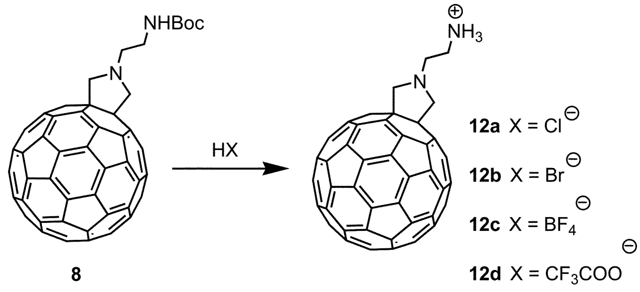


Scheme 4 Amphiphilic fullerene derivatives.

providing a better fit of the molecules within the assembly. All these interactions have been considered as the driving force of the self-assembly, allowing control over the morphology of the nanostructure, simply by changing the functionalities or by adding additional elements such as porphyrin or phthalocyanine macrocycles.

Scanning Probe Microscopy and spectroscopy studies have been carried out on fulleropyrrolidine **11**.[48] AFM measurements have shown that dendritic structures could be obtained for relatively highly concentrated solutions. The morphology of the resulting self-assembly could be controlled by fluctuations in the concentration of the sample. Thermal stability of the structure was checked by heating the sample up to 200 °C. The structures were stable but a restructuring process took place. Moreover, with more diluted solutions, cylindrical objects were obtained, ranging from 10 to 50 nm wide and up to a few microns long. This result is in agreement with the TEM studies realized at low concentration. The same heating treatment was used to study the thermal stability of the obtained nanorods, by Laser Desorption Ionization (LDI), mass spectrometry, Raman and infrared spectroscopies.

When compound **8**, which possesses a shorter aliphatic chain, was protonated by strong acids, different shapes were observed depending on the counter-ions. Fulleropyrrolidine **12a** (Scheme 5) showed spherical aggregates with diameters ranging from 500 nm to 1.2 μm. The influence of the counter-ion on the shape of the final self-assembled nanostructure was recently investigated by TEM, SEM and AFM microscopies.[49] When counter-ions such as tetrafluoroborate (**12c**) or bromide (**12b**) were evaluated, the molecules aggregated, resembling nanorods or block structures with well-defined dimensions. But when trifluoroacetate counter-ion was used (**12d**), only micellar aggregates were observed.



Scheme 5 Fullerene ammonium salts.

Nanocomposites in which polymers are reinforced with small amounts of nanoclay particles are of great interest for industry.[50] As pristine layered clays usually contain hydrated sodium or potassium ions, these inorganic clays are only miscible with hydrophilic polymers. In order to prepare the polymer nanocomposites with other kinds of organic polymer matrices, the nanoclay platelets must be organophilic. This can be achieved by an ion exchange process with charged organic species such as primary, secondary, tertiary or quaternary alkylammonium cations. Derivative **11**, although only partly soluble in water, has been successfully incorporated into the interlayer space of the smectite clays by an ion exchange process between the charge-balanced sodium ion of the clays and the ammonium functions of **11**.[51] Two other fulleropyrrolidine derivatives, **1** and **9e**, were also incorporated. The fullerene/layered aluminosilicate nanocomposites have been characterized by different techniques such as powder X-ray diffraction, Raman and ^{57}Fe-Mössbauer spectroscopies, all these analyses have proved the successful incorporation of the derivatives inside the clays.

6. Multiply charged systems

A new generation of hydrophilic fulleropyrrolidines comprises positively charged bisadducts with terminal ammonium salts displaying up to four positive charges and fulleropyrrolidines functionalized with addends that display multiple charges of different natures. By introducing one or more ammonium functions, the water solubility of the corresponding fullerene is well improved. The synthesis of multiple adducts together with multiple positive or negative charges homogeneously distributed should create a repulsive effect among the spheres, preventing aggregation and increasing the solubility in aqueous solution or physiological media. With this aim, the synthesis of four classes of novel, water-soluble fullerene bisadducts has been achieved.[52] These compounds are depicted in Fig. 6. Their solubility in water is in the range of 10^{-3}–10^{-1} M, amongst the most water-soluble fullerene derivatives ever synthesized

Activity against HIV-1 and HIV-2 strains has been evaluated.[53] The results obtained have clearly shown that the fulleropyrrolidine bisadducts **13**, bearing only two positive charges, do not show any activity, while the corresponding derivatives **14** proved to be inhibitory at low micromolar concentrations. The positive charge of the pyrrolidinium nitrogen near the C_{60} backbone, essential to increase the solubility, seems also to increase potency. *Trans*-2 isomers were the more potent, in agreement with other studies,[37] confirming that the functionalization pattern plays an active role in the activity. Most of the different bisadducts have shown significant cytotoxicity, attributed, most probably, to the amphiphilic character of these derivatives, which can lead to cell membrane disruption and subsequent cellular death. Longer solubilizing side chains seem to increase toxicity.

The cytotoxic and hemolytic properties of the series of bisadducts **14**, **15** and **16** bearing polar chains at different positions of the C_{60} sphere (Fig. 6) have been also investigated.[54] The hemolytic activity of the different derivatives was evaluated on human red blood cells. The results show that derivatives **15** and **16**, independently from their substitution pattern, had no hemolytic properties up to 80 μM. In contrast, compound **14**, bearing two cationic chains, proved to be remarkably hemolytic. Moreover, the substitution pattern on **14** seemed to confer a great influence on the hemolytic potency, since the equatorial isomer was the most efficient. The cytotoxicity of the same series of compounds was tested on different cell lines, showing that all of the derivatives possessing significant hemolytic properties were also cytotoxic while the non-hemolytic derivatives did not display any cytotoxicity. These studies allowed a correlation between structure and toxicity. It was observed that cationic chains induced toxicity while the presence of neutral or anionic moieties did not produce any response.

A different water-soluble, multi-charged, mono-functionalized fulleropyrrolidine derivative (Fig. 7), with three ethylene glycol chains and three ammonium groups, was designed and synthesized as a potential neuroprotecting agent.[55] Despite of its high solubility, it was found to be ineffective for neuroprotection and to act as a toxic agent. The toxicity was attributed to the surfactant properties of the derivative, which probably induced membrane disruption.

In a last example of the use of multi-charged systems with nanotechnological applications, the *trans*-3 adducts of **14** and **16** (Fig. 6) were used to form organic–inorganic nanoensembles with CdTe nanoparticles (NP). In solution,[56] the experients showed rapid photoinduced electron transfer between the two units due to

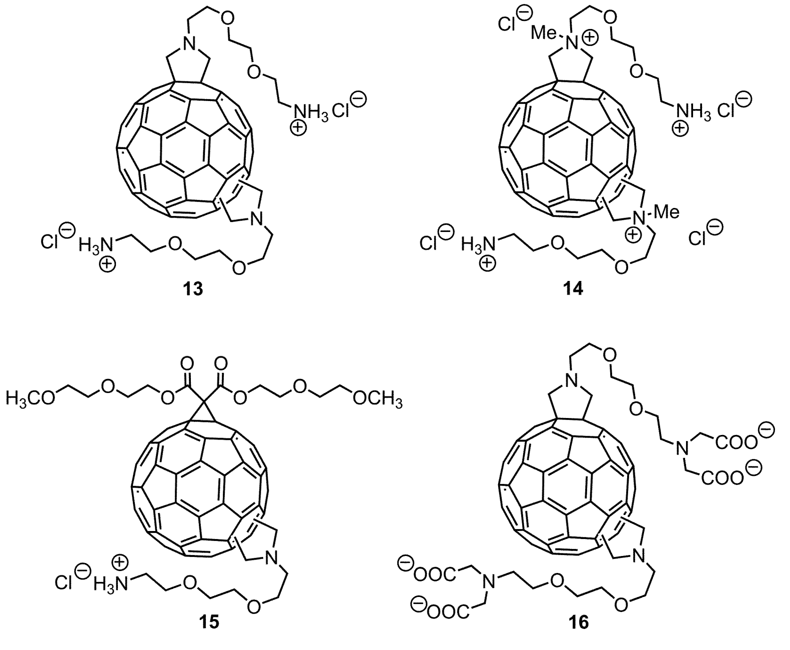


Fig. 6 Multiply charged bisadducts.

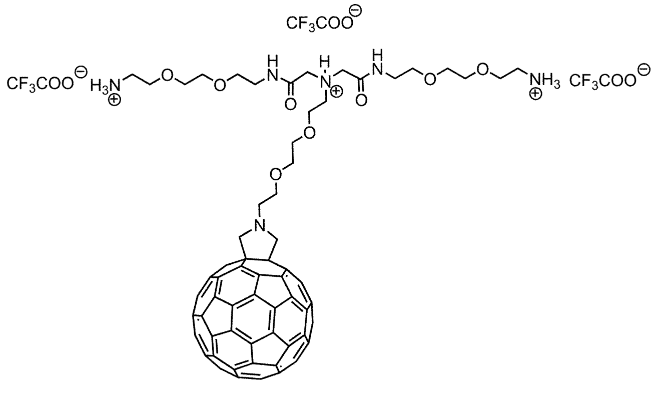


Fig. 7 Multi-charged mono-functionalized fullerene.

the electrostatic binding with lifetimes in the ms scale. The *trans*-3 bisadducts of **14** were also used to build modified ITO electrodes by the LBL technique.[57] The ITO/PDDA/NP/C_{60} photoactive thin films exhibited photon-to-current conversion efficiencies of 5.4%.

7. Conclusions

The cycloaddition of azomethine ylides leading to fulleropyrrolidines is a very powerful way to overcome low solubility of fullerenes in most organic solvents and in aqueous media, allowing the evaluation of their properties in such solvents. The design of novel amphiphilic fulleropyrrolidine derivatives, bearing suitable side chains, gives rise to a wide variety of compounds that have shown applicability in diverse fields such as materials, polymer, biological and medicinal chemistry. The mTEG fulleropyrrolidine mono- and bis-adducts have been shown to form photo- and electro-active films, as well as activity against several microorganisms. By introducing ammonium functionalities, the enhancement in the amphiphilic character of such compounds has opened the way for various applications. These include the formation of film monolayers by Langmuir techniques, the preparation of photoactive ITO electrodes, the controlled self-assembly of these derivatives in different shaped nanostructures and the preparation of organic–inorganic hybrids with smectite clays. The combination of all of these features gives fullerene multiadducts with many charges that have shown anti-HIV activity and the formation of photoactive organic–inorganic nanoensembles.

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