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Fullerenes: Properties and therapeutic applications

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ABSTRACT

Ever since their discovery in 1985, fullerenes have captured the imagination of pharmaceutical researchers for their unique properties and medical applications. They are compounds composed solely of an even number of carbon atoms which form a cage-like fused-ring polycyclic system with twelve five-membered rings and the rest six-membered rings. Fullerenes have unique chemical, physical, and biological properties which make them ideal candidates in the field of medicine. This review focuses on the chemical and biological properties of fullerenes giving detailed descriptions of their various medical applications such as anti-oxidant activity, anti-HIV activity, antimicrobial action, anti-cancer/tumor activity, and as photodynamic and diagnostic agents.

KEYWORDS

Fullerene;
Therapeutic applications;
Endohedral fullerene;
C_{60} molecule;
Anti-oxidant properties.

INTRODUCTION

In 1985[1], a group of scientists led by Harold Kroto, Richard Smalley and Robert Curl at the Rice University were trying to understand the absorption spectra of interstellar dust, which they suspected to be related to some kind of long-chained carbon molecules. However, in the course of their experiments, they discovered a unique form of carbon called fullerene[2]. These fullerenes are a family of carbon allotropes named after Richard Buckminster Fuller, designer of the geodesic dome[3]. However, unlike diamond and graphite, whose molecules go on and on, fullerenes are spherical molecules that are attached to each other by Van der Waal's forces in the solid[4].

Fullerenes are compounds composed solely of an even number of carbon atoms which form a cage-like fused-ring polycyclic system with twelve five-membered rings and the rest six-membered rings; the archetypal example is the sixty atom structure, where the atoms and bonds delineate a truncated icosahedron[5]. However, over the years, other fullerenes have been discovered as well: C_{70} is elongated, like a rugby ball; another molecule called the "Russian doll" can be obtained by

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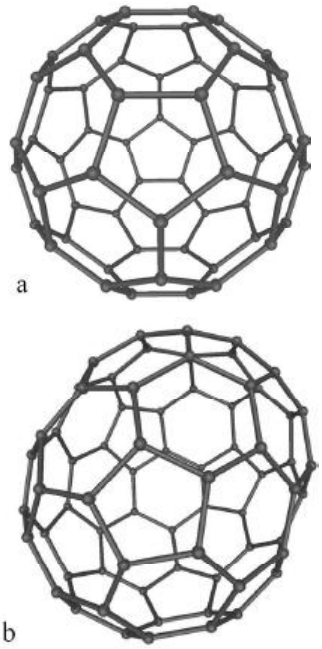

Figure 1 : Computer representation of fullerenes. (a) 3D model of a C_{60} fullerene; (b) 3D model of a C_{70} fullerene (Image courtesy of Michael Ströck; Source: Wikipedia)

TABLE 1: Color of the solutions of fullerenes[9,11]

Fullerenes	Color of the solution
C_{60}	Purple/Violet
C_{70}	Brick-red
C_{76}	Light Yellow-green
C_{84}	Brown
C_{86}	Olive-green

trapping the C_{60} molecule inside a very large (C_{240}) fullerene[1](Figure 1).

Fullerenes have also been found to exist in the natural environment; in geological formations, but only in the ppm-range. Some of these places include Shunga/Russia[6], New Zealand[7], and Sudbury/Canada[8].

2. Chemical and physical properties

Fullerenes fulfill the Euler's theorem, i.e., if a polyeder is to build a closed structure from pentagons and hexagons; it has to contain exactly 12 pentagons. Following this rule, the smallest stable fullerene is C_{60}, which has no two pentagons side by side, making it the most stable structure. The diameter of a C_{60} molecule is about 7Å in diameter[9]. The C_{60} molecule has two bond lengths. The 6:6 ring bonds (between two hexagons; 1.45±0.015Å) can be considered "double bonds" and are shorter than the 6:5 bonds (between a hexagon and a pentagon; 1.40±0.015Å)[10].

The carbon atoms in fullerene are in the sp^2 and sp^3 hybridized state[11]. The sp^2-hybridized carbon atoms, which are at their energy minimum in planar graphite, must be bent to form the closed sphere or tube, which produces angle strain. The characteristic reaction of fullerenes is electrophilic addition at 6,6-double bonds, which reduces angle strain by changing sp^2-hybridized carbons into sp^3-hybridized ones[12]. The change in hybridized orbitals causes the bond angles to decrease from about 120 degrees in the sp^2 orbitals to about 109.5 degrees in the sp^3 orbitals. This decrease in bond angles allows for the bonds to bend less when closing the sphere or tube, and thus, the molecule becomes more stable[13]. The free electrons on the cage build a strong delocalized π-electron system. This π-electron system influences the chemical reactions of the fullerenes[11]. These molecules do not exhibit 'superar omaticity', instead, they show aliphatic behavior[13].

Fullerenes are insoluble in water however, they are soluble in other solvents like carbon disulphide, toluene, o-dichlorobenzene, and xylene[14-16]. Solutions of pure C_{60} have a deep purple color. Solutions of C_{70} are of reddish brown whereas, the higher fullerenes C_{76} to C_{84} have a variety of colors (TABLE 1). The color of the fullerene is attributed to the pi-pi electron transitions[11,12].

3. Synthesis of fullerenes

Synthesis of fullerenes was first accomplished by laser sublimation of graphite in an inert gas atmosphere. In this method, a surface of solid graphite was vaporized by irradiation with the laser into plasma containing atoms and free ions. The free atoms and ions were chilled down due to collision with the helium atoms. Through the collision, clusters containing various numbers of carbon atoms were formed. The clusters were examined in a mass spectrometer, and it was found that clusters that had 60 and 70 carbon atoms had dominated, and that most clusters had 60 carbon atoms[17]. However, this technique did not provide for the production of gram quantities of C_{60}. Efforts to scale-up this approach were unsuccessful and other methods were later developed. These included resistive heating method[18], electron beam evaporation[19], diffusion flame[20], and ion beam sputtering[21]. In 1990, Krats chmer and Huffman[4] for the first time produced isolable

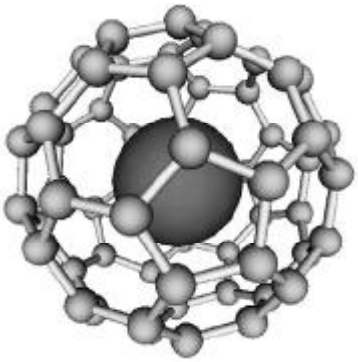

Figure 2: 3D representation of an endohedral C_{60} Fullerene. (Source: http://www.chm.bris.ac.uk/webprojects 2001/ tweedale/fullerene_derivatives.htm

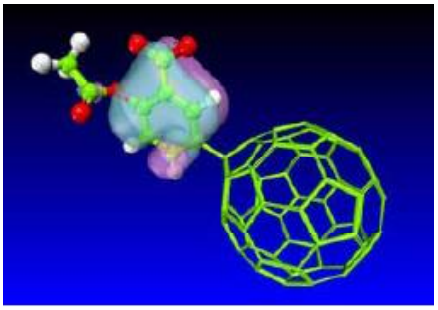

Figure 3: A 3D illustration of an exohedral C_{60} Fullerene. (Image courtesy of Accelrys, www.accelrys.com)

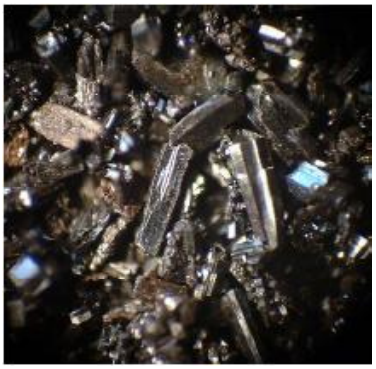

Figure 4: The C_{60} fullerene in crystalline form (Fullerite). (Source: Wikipedia)

quantities of C_{60} by causing an arc between two graphite rods to burn in a helium atmosphere and extracting the carbon condensate so formed using an organic solvent. The C_{60} could be conveniently extracted using benzene as solvent. This is one of the best methods for maximum production rate, cost and ease of implementation.

4. Types of fullerenes

Since the discovery of fullerenes in 1985, many chemical modifications of fullerenes have been discovered. Some of the important fullerene species are as follows:

Endohedral fullerene

Since fullerenes are hollow with a closed shell of carbon atoms, it is possible to enclose another atom inside. This class of fullerene derivatives is termed as "Endohedral" fullerenes (Figure 2)[9]. When the atoms trapped inside are metallic, they are also called Metallofullerenes. Even though C_{60} is the most common fullerene, few endohedral materials have a C_{60} cage because it is fairly small inside. Most of these materials are made out of C_{82}, C_{84}, or even higher fullerenes[22]. Atoms that are known to form stable endohedral compounds include transition metals like lanthanum, yttrium, scandium, and some of the noble gases[23-25]. Doping fullerenes with electropositive metal takes place in an arc reactor or via laser evaporation. The first C_{60} endohedral complex was synthesized in 1985 where lanthanum was the atom enclosed in the fullerene molecule. The accepted notation for endohedral material is to use the '@' symbol to show that a small molecule is trapped inside a shell e.g. $La@C_{60}$[13].

Endohedral metallofullerenes are characterized by the fact that electrons will transfer from the metal atom to the fullerene cage and that the metal atom takes a position off-center in the cage. The size of the charge transfer is not always simple to determine. In most cases it is between 2 and 3 charge units, like in $La_2@C_{80}$, however it can even be about 6 charge units such as in $Sc_3N@C_{80}$ which is better described as $[Sc_3N]^{+6}@[C_{80}]^{-6}$. These anionic fullerene cages are very stable molecules and do not have the reactivity associated with ordinary empty fullerenes. They are stable in air up to very high temperatures(600 to 850°C)[13].

Noble gases like helium, neon, argon, krypton, and xenon are also capable of forming stable endohedral fullerene molecules[26]. In fact, Saunders in 1993[27], proved the existence of endohedral complexes $He@C_{60}$ and $Ne@C_{60}$ which form when C_{60} is exposed to a pressure of around 3 bar of the noble gases[13].

Exohedral fullerene

Exohedral fullerenes (Figure 3) are the most im-

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portant and versatile of all species of fullerenes. These derivatives are formed by a chemical reaction between fullerenes and other chemical groups. Unlike Endohedral fullerenes, where a molecule is trapped inside the fullerene shell, Exohedral fullerenes are derivatives for which the reactions take place on the surface of the fullerene shell. As fullerenes possess the conjugated π-system of electron, two main types of primary chemical transformations are possible on fullerene surface: addition reactions and redox reactions, which lead to covalent exohedral adducts and salts respectively[9].

Heterofullerenes

Heterofullerenes are derivatives of fullerenes in which one or more carbon atoms of the cage are substituted by a heteroatom e.g. Nitrogen (N) or Boron (B)[28,29]. An example of this species is the nitrogen fullerene called aza (60) fullerene $C_{59}N$ which forms the dimer $(C_{59}N)_2$ in the solid state[28].

Fullerites

C_{60} molecules condense to form a solid of weakly bound molecules. This crystalline state is called fullerite (Figure 4). At room temperature, this solid has a face centered cubic crystal structure. It is weakly bound with a lattice constant a=14.71Å and electrically insulating[9]. Their hardness is comparable to that of diamonds. Ultrahard fullerite (C_{60}) is a type of fullerite which has been found to be harder than diamond and can be used to create even harder materials, such as aggregated diamond nanorods[13]. It is a unique version of the fullerene with three-dimensional polymer bonds. Ultrahard fullerite has a hardness value of about 290±30 and 310±40 GPa (gigapascals) depending on the synthesis conditions[13,30].

Fullerides

As fullerene molecule is highly electronegative, it readily forms compounds with electron donating atoms like alkali metals. This reaction leads to the formation of a class of compounds called fullerides, wherein alkali metal atoms fill in the space between Buckyballs[9,31] and donate valence electron to the neighboring C_{60} molecule e.g. K_3C_{60}[9].

Carbon nanotubes

Carbon nanotubes[32,33] (Figure 5) are cylindrical fullerenes. They are often described as a graphene sheet rolled up into the shape of a cylinder[34]. To be precise, they are graphene cylinders about 12nm in diameter and capped with end-containing pentagonal rings. A single walled carbon nanotube (SWNT) is one such cylinder, while a multiple walled carbon nanotube (MWNT) consists of many nested cylinders whose successive radii differ by roughly the interlayer spacing of graphite[35]. Carbon nanotubes have novel properties that make them potentially useful in a wide variety of applications in nanotechnology, electronics, optics, medicine and other fields of material science. They are gifted with unique properties with include remarkable strength, high elasticity, and large thermal conductivity and current density[34].

5. Applications

Fullerenes have potential applications as drug delivery devices. They have captured the imagination of pharmaceutical researchers for their unique properties as drug candidates. Fullerenes can undergo a wide number of reactions such as hydrogenation, halogenation, epoxidation, formation of exohedral transition metal complexes, cycloadditions, carbene additions, alkylation and arylation. Fullerene derivatives of sugars, amino acids, polypeptides, estrogen, cholesterol and large proteins are also known[36]. However, fullerenes have a major drawback, i.e., their natural repulsion to water. To overcome this limitation, a number of methodologies are being developed; these include synthesis of fullerene derivatives having modified solubility profile, encapsulation of C_{60} in cyclodextrins[37] or in calixarenes or water suspension preparations[9].

Anti -oxidant properties

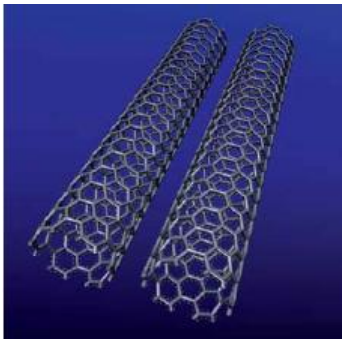

Figure 5: 3D representation of single walled carbon nanotubes. (Image courtesy of Accelrys, www.accelrys.com)

Fullerenes have been known to act as strong anti-oxidants. Because of the large number of conjugated double bonds that are readily attacked by radical species, C_{60} has been referred to as a "radical sponge"[38], and facile addition of up to 34 methyl radicals to C_{60} has been reported. Often reactive oxygen species, free radicals use their unpaired electrons to break chemical bonds in critical molecules, such as nucleic acids, thereby triggering cell damage and possible apoptosis. Fullerenes may be interrupting this process by acting as a "radical sponge," essentially absorbing the potentially damaging electrons[39].

Many fullerene derivatives have shown their ability as potent free-radical scavengers; these include fullerenols[40], carboxyfullerene[41], polyalkylsulfonated C_{60}, hexa(sulphobutyl)fullerene[42], C_{60}-dimalonic acid, C_{60}-trimalonic acid, and C_{62} bis(malonate)[43]. These fullerenes have shown potent anti-oxidant properties about hundred more times potent than Vitamin E[44].

Anti-oxidant properties of fullerenes were demonstrated in the following example in which fullerene derivatives were shown to have promising neuroprotective effects. Glutamate receptor-mediated excitotoxicity has been implicated in the pathogenesis of neuronal loss in the central nervous system in several disease states, including hypoxia-ischemia, epilepsy, and trauma. Oxygen or nitric oxide radicals are produced as a consequence of glutamate receptor overstimulation, and free radical scavengers have been shown to attenuate, but not to block, excitotoxic neuronal death. Malonic acid derivatives of fullerenes were experimented *in-vitro* on cortical neuronal cultures and were able to reduce the neuronal death resulting from exposure to the glutamate receptor agonists, N-methyl-D-aspartate (NMDA) or α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA). These compounds had the ability to completely block intense, rapidly triggered, NMDA receptor-mediated excitotoxicity[45]. Another experiment also demonstrated similar decreased excitotoxic neuronal death following brief exposure to NMDA(by 80%), AMPA(by 65%), or kainate (by 50%)[44].

As a "radical sponge", the protective effect of full erene derivatives has been demonstrated in various systems, including reduced injury on ischemia reperfusion intestine, protecting cell types from undergoing apoptosis, reduced free radical level in organ perfusate, and having neuroprotective effect[9]. These compounds are suggested to have attractive therapeutic properties in several acute or chronic degenerative diseases such as amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease), Parkinson's disease and Alzheimer's disease[43].

Anti-HIV properties

An especially promising target for treatment and prevention of AIDS is the HIV Protease (HIV-P). HIV produces a small, dimeric aspartyl protease which specifically cleaves the polyprotein precursors encoding the structural proteins and enzymes of the virus. This proteolytic activity is absolutely required for the production of mature, infectious virions and is therefore an attractive target for therapeutic intervention. The active site of this enzyme can be roughly described as an open-ended cylinder which is lined almost exclusively by hydrophobic amino acids except for two catalytic aspartic acids (Asp25, Asp125)[46]. It has been hypothesized that the main driving force behind the association of the HIV-P and fullerene derivatives is a presumably hydrophobic interaction between the non-polar active site surface of HIV-P and the C_{60} surface[46]. The preferred substitutions on the fullerene ring include organic moieties comprising from 1-20 carbon atoms and optionally further comprising polar heteroatoms, such as oxygen and nitrogen. Inhibition of HIV-P in presence of C60 was demonstrated through molecular modeling studies and experimental observations[9,46,47].

Activity of fullerenes against HIV can be confirmed by the experiment in which a fullerene derivative (the bis(monosuccinimide) derivative of p,p'-bis(2-amino ethyl)diphenyl-C_{60}) showed activity against HIV Type 1 (HIV-1) and HIV-2 in acutely or chronically infected human lymphocytes as well as in *in-vitro* experiments against 3'-azido-3'-deoxythymidine (AZT)-resistant HIV-1[48].

Photodynamic properties

In recent years interesting attempts have been made to develop alternative methods for virus inactivation. By the late 1990s, photodynamic reactions induced by singlet oxygen ($^1O_2$) -generating agents were known to inactivate enveloped viruses[49]. Among these agents, dyes like phthalocyanines[50], merocyanines[51], and rose

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bengal[52] have been widely used. However, a disadvantage of these dyes is there water solubility, which makes them difficult to remove[53]. Pure water-insoluble photosensitizer C_{60} could be used to mediate the inactivation of enveloped viruses[43]. Their use as photosensitizers is due to their ability to convert triplet oxygen($^3O_2$) to, a highly reactive and tissue-killing singlet oxygen ($^1O_2$)[36,54].

The use of fullerenes as photosensitizers was demonstrated by the following experiment in which buffered solutions containing Semliki Forest virus (SFV, Togaviridae) or vesicular stomatitis virus (VSV, Rhabdoviridae) were illuminated at 0°C in the presence of C_{60} and oxygen for up to 5 hours. It resulted in significant loss of infectivity. The inactivation was found to be clearly dependent on the presence of oxygen and changing the oxygen with argon resulted in a dramatic reduction of the inactivation capacity. Also, inclusion of free radical scavengers like glutathione in the assay had no effect on virus inactivation by C_{60} which suggested that no radical mechanism is involved in the inactivation process[43,53].

DNA photocleavage

Water-soluble fullerene derivatives are able to cleave DNA on exposure to light via a $^1O_2$ independent mechanism[55]. However, the DNA cleavage was found to occur at the guanidine residues by an electron transfer mechanism[55,56]. An experiment suggested that fullerene-oligonucleotide can bind to single or double-stranded DNA and cleaves the strands upon exposure to light[57]. Another experiment with a fullerene carboxylic acid derivative was also found to be cytotoxic when exposed to visible light. The cytotoxicity of this derivative was attributed to its ability to cleave DNA[55].

Anti-microbial properties

Fullerene derivatives have been shown to be active against a wide number of bacterial agents[43]. Experiments conducted by Tsao et. al. showed that water-soluble malonic acid derivative of carboxyfullerenes (C_{60}) were protective in mice against *Escherichia coli*-induced meningitis death in a dose-dependent manner, even when administered intraperitoneally as late as 9 hours after *E.coli* injection[58]. Fullerene-treated mice were found to have less tumor necrosis factor alpha and less interleukin-1beta production compared to the production levels for non-treated mice. *E.coli*-induced increases in blood-brain barrier permeability and inflammatory neutrophilic infiltration were also inhibited, suggesting that C_{60} compounds could be useful therapeutic agents in some cases of bacterial meningitis[58]. Positively-charged water-soluble fullerene derivatives have also been found to inhibit the growth of Mycobacterium tuberculosis at ~0.005 mg/cm^3 concentrations[59].

Carboxyfullerenes can directly inhibit the in vitro growth of *Streptococcus pyogenes* and also enhance the bactericidal activity of neutrophils in mice *in vivo*, suggesting that fullerene derivative can be considered as antimicrobial agent for 'group A streptococcus' infections[60]. Further studies have found that the antibacterial action of carboxyfullerenes on gram-positive bacteria is achieved by insertion into the cell wall and destruction of membrane integrity[43,61].

Anti-cancer/tumor properties

Photodynamic properties of fullerenes have made these compounds excellent candidates for photodynamic tumor therapy. These compounds when irradiated with light cause tumor necrosis without affecting the underlying normal tissue. In fact, photodynamic activity of Polyethylene Glycol (PEG)-modified fullerene molecules has been reported against fibrosarcoma tumors in mice and on erythrocyte membrane[43]. Water-soluble $C_{60}(OH)_{24}$ has shown to strongly block microtubule assembly, inhibit cell growth via inhibition of mitotic spindle formation, and also affect the growth kinetics of human lymphocyte cultures and HEP-2 epidermal carcinoma cell cultures[62].

Chemotherapeutic agents can also be attached to fullerene molecules for effective treatment against cancer. Studies have shown that C_{60}-paclitaxel conjugates, when delivered as a liposome formulation, have shown to possess significant anticancer activity in tissue culture[63].

Diagnostic applications

Endohedral metallofullerenes have shown potential applications as diagnostic agents. Current radiopharmaceuticals employ small quantities (nanograms or milligrams) of drugs containing specially-chelated radioisotopes of metals for imaging or therapeutic applications. The chelating ligands prevent direct binding of the toxic

metal ions with serum components and tissue by providing a thermodynamically stable molecular environment. However, a major concern with these drugs is their *in vivo* kinetic instability, which can allow the release of small amounts of toxic radioactive metal ions. In comparison, metallofullerenes provide a unique alternative to chelating compounds because of their resistance to metabolism and their high kinetic stability. Thus, metallofullerenes may be useful as a new, more stable alternative for transporting radiometals *in vivo*[36]. An example of this is the $_{166}Ho^{3+}@C_{82}(OH)_{30}$ which has been extensively studied as a radioactive tracer for imaging of diseased organs and for killing cancerous tumors[9,36].

Fullerenes have also found use as contrast enhancement agents in the Magnetic Resonance Imaging (MRI) and X-Ray diagnostic processes. Examples include water solubilized forms like $M@C_{82}(OH)_{30}$ where 'M=Gd^{3+}' for MRI contrast agents and 'M=Ho^{3+}' for X-Ray contrast agents[9]. Paramagnetic malonodiamide C_{60} derivatives may also be useful in making MRI contrast agents[64].

Other applications

Fullerene compounds have effects on nitric oxide and acetylcholine signaling pathways[43,65,66]. Fullerene derivatives like polyhydroxylated fullerenes (Fullerenols) can significantly attenuate non-cholinergic airway constriction in guinea pigs[67]. They can also produce slight bronchial constricting action at high doses (2mg/kg) when applied via intratracheal instillation[67,68].

Fullerenes are also now being investigated as alternative agents for treatment of osteoporosis. Biphos phonate compounds and fluoride anions, which are the drugs currently used in the treatment of osteoporosis and other bone disorders have limitations, such as, they are not absorbed orally and are fairly toxic. Advantage is being taken of the preferential localization of fullerene derivatives in bones[9]. Hence polyfluoro biphospho nated fullerene derivatives are being developed as bimodal drugs for osteoporosis therapy[69].

Fullerenes can also be used as adsorbents for harmful gases. Studies by Hayashi et al. showed that $C_{60}Pd_n$ polymer-like materials can be used to successfully adsorb toluene at ambient temperature without any energy source. This adsorptivity was retained even at concentrations of 100ppb, which is close to the actual toluene concentration in the environment. The pi-electrons of toluene were believed to adsorb on the partially positive Pd atoms of $C_{60}Pd_n$[70].

CONCLUSION

Fullerenes have brought to medicine, novel 3-dimensional carbon structures that can be made tissue selective as well as act as potential therapeutic agents. Forthcoming breakthroughs in their synthesis and manipulation promise lower cost, and more sophisticated analogs, which are capable of challenging present market-place technologies.

As quoted by Smalley, the fullerenes are still being discovered. But already, it seems clear, their discovery and what it revealed about the fundamental properties of carbon will be benefiting humanity for many, many years to come.

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