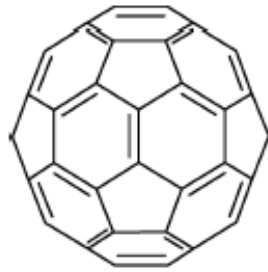


C60 proprietà biologiche e applicazioni



C₆₀

scoperto nel 1985 da Kroto, Smalley and Curl, *Nature* **1985**, 318, 162

- The C₆₀ surface contains 20 hexagons and 12 pentagons. All the rings are fused, all the double bonds are conjugated.

FULLERENES

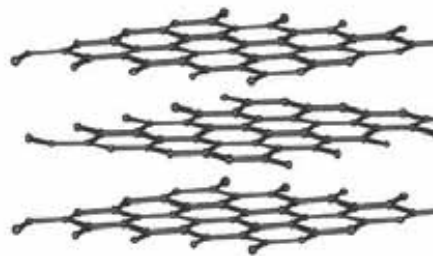
Forme allotropiche del carbonio



Diamante

materiale noto per la sua durezza

si forma a temperature comprese fra i 900°C ed i 1.200°C e pressione di circa 50 Kbar

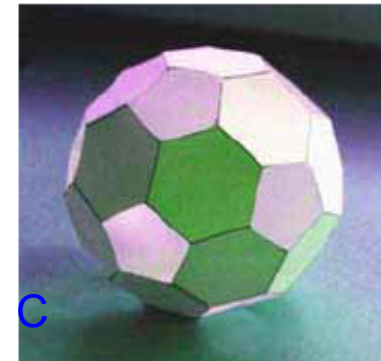
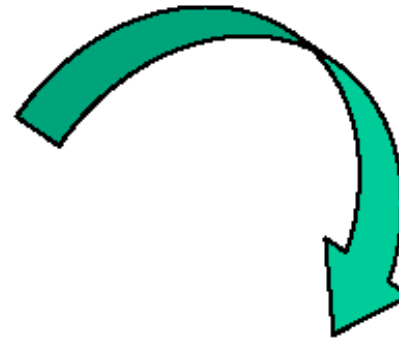


Grafite

materiale con elevata conduttività elettrica

Grafene

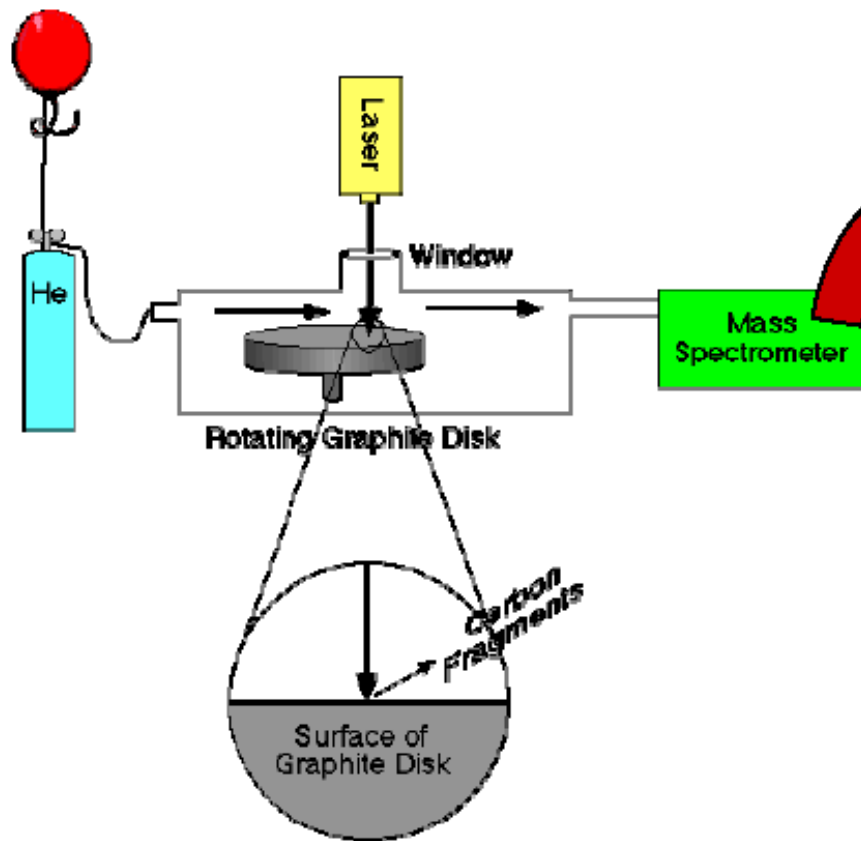
si forma alla temperatura di 1.200°C



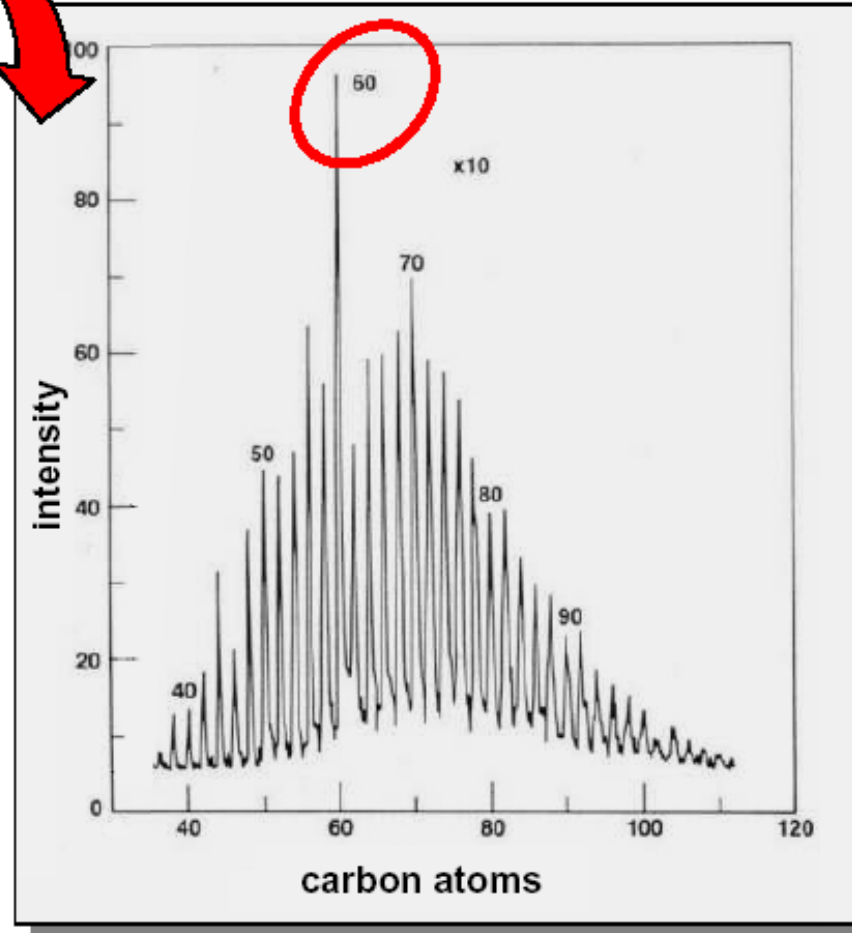
1970

{ Eiji Osawa la teorizza
R.W.Henson la propone

Fullerene: la scoperta

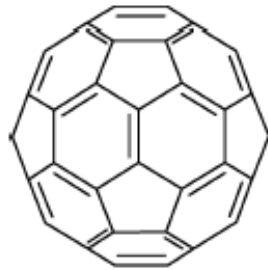


$M^+ = 720$



Nature **1985**, 318, 162

Kroto, Curl, and Smalley
Nobel, 1996



C₆₀

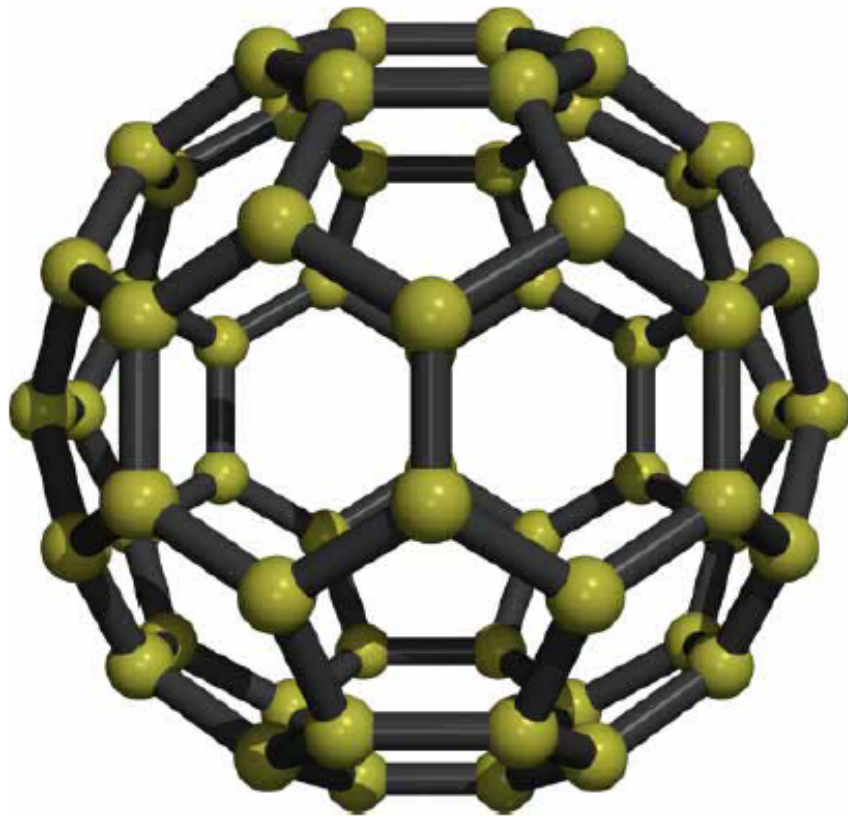
scoperto nel 1985 da Kroto, Smalley and Curl, *Nature* **1985**, 318, 162

1996 Chemistry Nobel Prize

ROBERT F. CURL, Jr. , SIR HAROLD W. KROTO , and RICHARD E. SMALLEY

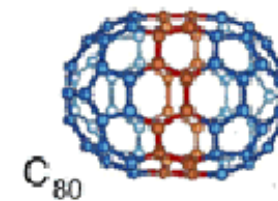
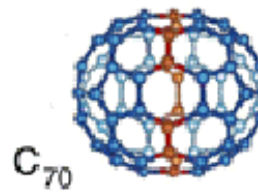
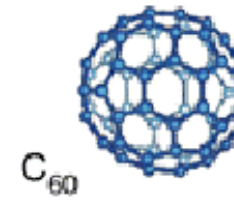
"for their discovery of fullerenes"

Fullereni

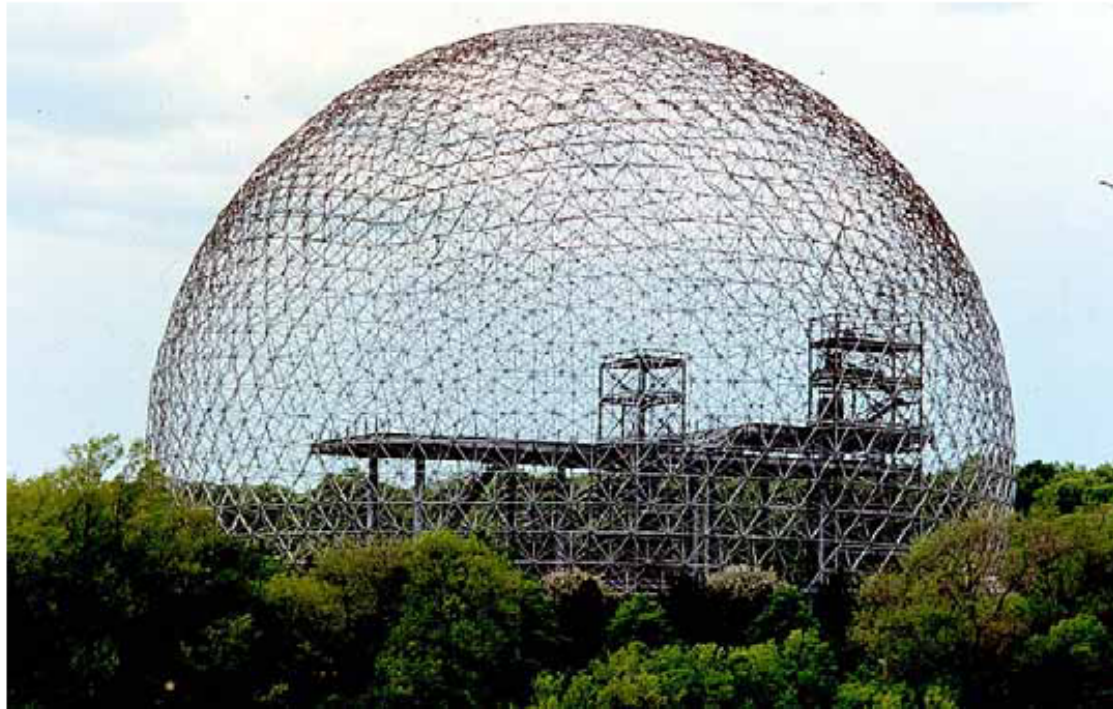


Buckminsterfullerene (C₆₀)

truncated icosahedron (I_h symmetry)

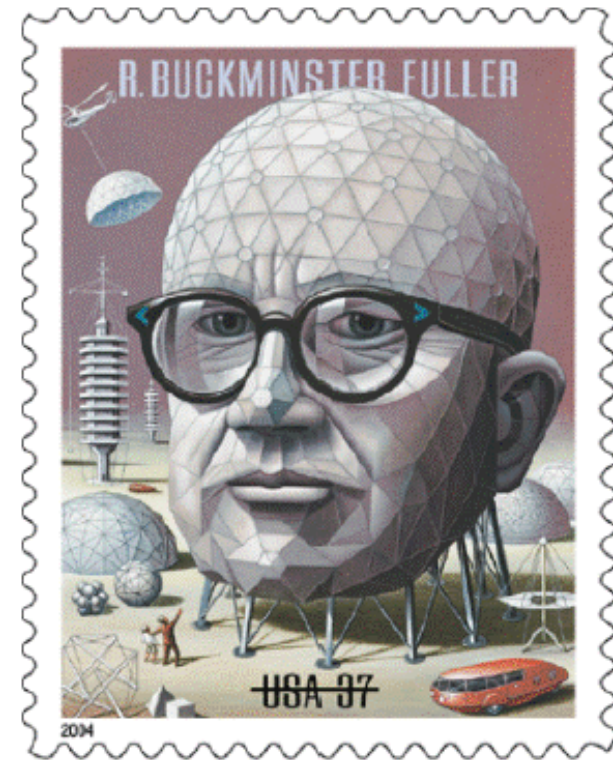


Buckminster Fuller



Geodesic Dome

Buckminster Fuller, US Pavilion for the 1967 International and Universal Exposition in Montreal



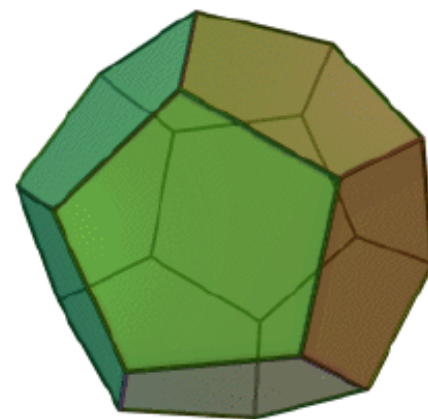
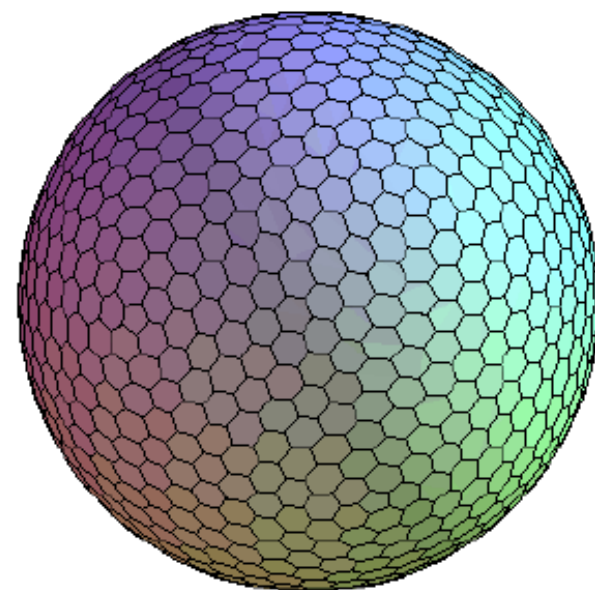
Regola di Eulero

Un fullerene è un poliedro convesso con facce esagonali e pentagonali.

$$F - S + V = 2$$

Se uso solo esagoni $F - S + V = 0$. Affinché la formula di Eulero per i poliedri sia rispettata, occorre che diventi uguale a 2. In breve, occorre sostituire **12** esagoni con altrettanti **pentagoni**

Ci sono esattamente 12 pentagoni in un fullerene. Il più piccolo fullerene è il C_{20}



Facce 12

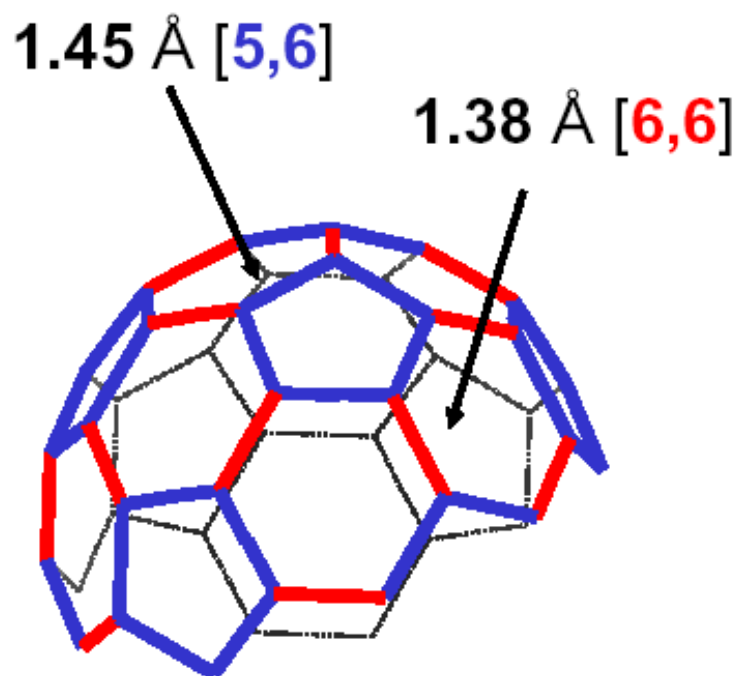
Spigoli 30

Vertici 20

C₆₀

- C₆₀ was found to become a **superconductor** in M₃C₆₀ species (M=alkali metal)
- organic soft **ferromagnet** in TDAE⁺C₆₀⁻ (TDAE=tetrakisdimethylaminoethylene) at 16.1 Kelvin
- a relatively stable **hexaanion** in cyclic voltammetry
- an interesting material with **non-linear optical properties**.
 - The C₆₀ surface contains 20 hexagons and 12 pentagons. All the rings are fused, all the double bonds are conjugated.
- X-Ray crystal structure determinations on C₆₀ and on some of its derivatives have proved the existence of two different types of bonds: 'short bonds' or 6,6 junctions shared by two adjacent hexagons (ca. 1.38 Å long) and 'long bonds', or 5,6 junctions, fusing a pentagon and a hexagon (ca. 1.45 Å long).

Proprietà strutturali del C₆₀



$\Delta H_f = 10.16$ Kcal/mol per C
(ΔH_f)graphite = 0 Kcal/mol
(ΔH_f)diamond = 0.4 Kcal/mol

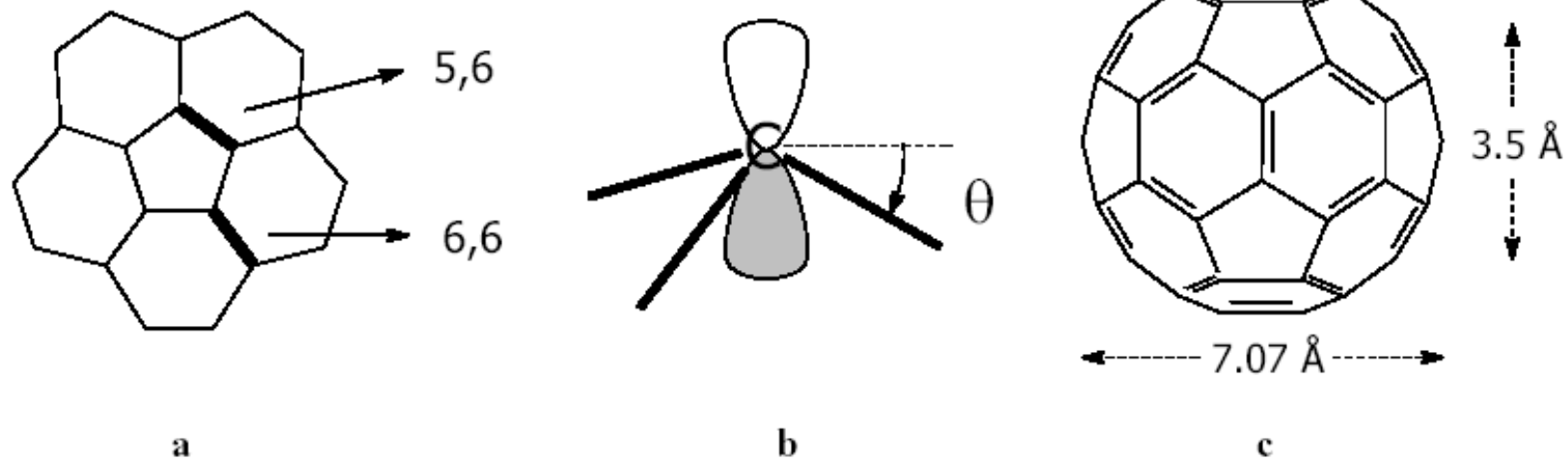
The six-membered rings are **not aromatic** in that they contain alternating single and double bonds. 6,6-bonds are shorter than 5,6-bonds.

The overall buckyball structure has to be viewed as fused **1,3,5-cyclohexatrienes** and **[5]radialenes**

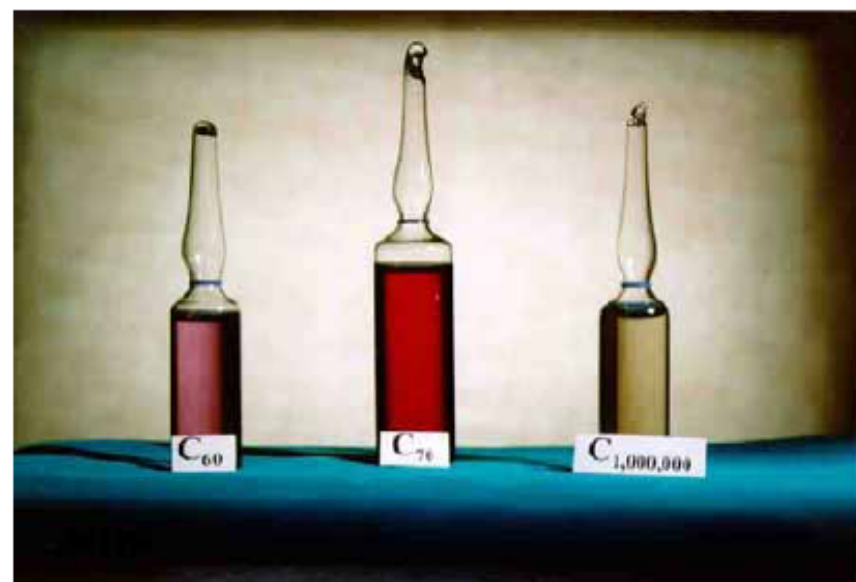
spherical geometry causes **pyramidalization** of the unsaturated C-atoms. Strain Energy $\approx 80\%$ H_f
- Haddon and Raghavachari, in *buckminsterfullerenes*, VCH, 1993
- H.D. Beckhaus et al. *Angew. Chem.* 1992, 31, 63)

- A. Hirsch, Z. Chen, H. Jiao. *Angew. Chem.* **2000**, 39, 3915.
- M. Bühl, A. Hirsch *Chem. Rev.* **2001**, 101, 1119.

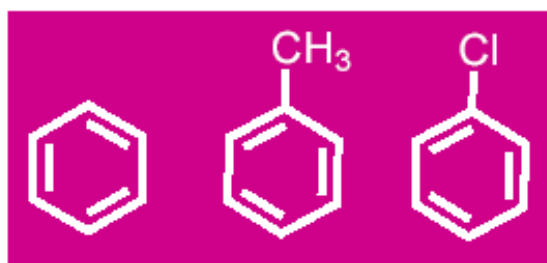
Proprietà strutturali del C_{60}



(a) legami 5,6 e 6,6 nel C_{60} ; (b) angolo di piramidizzazione θ ; (c) diametro esterno (*edge-to-edge*) e interno del C_{60} (il diametro di Wan der Waals è circa 10.4 Å)

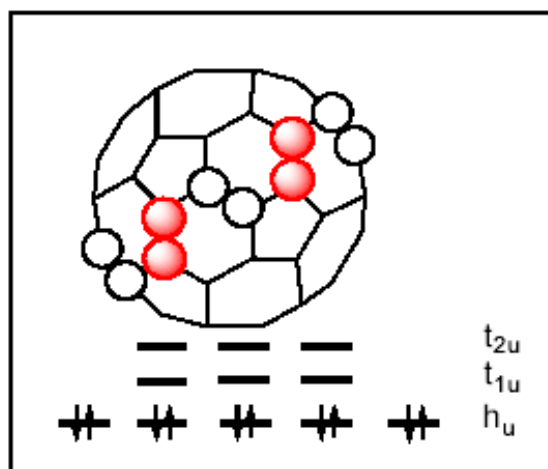


C₆₀ solution in toluene



and CS₂

Reattività



C_{60} behaves essentially as a **strained electron-poor alkene**; addition chemistry is mainly driven by strain relief

fullerenes are very difficult to oxidize but are **readily reduced** (reactivity towards electron-rich reagents)

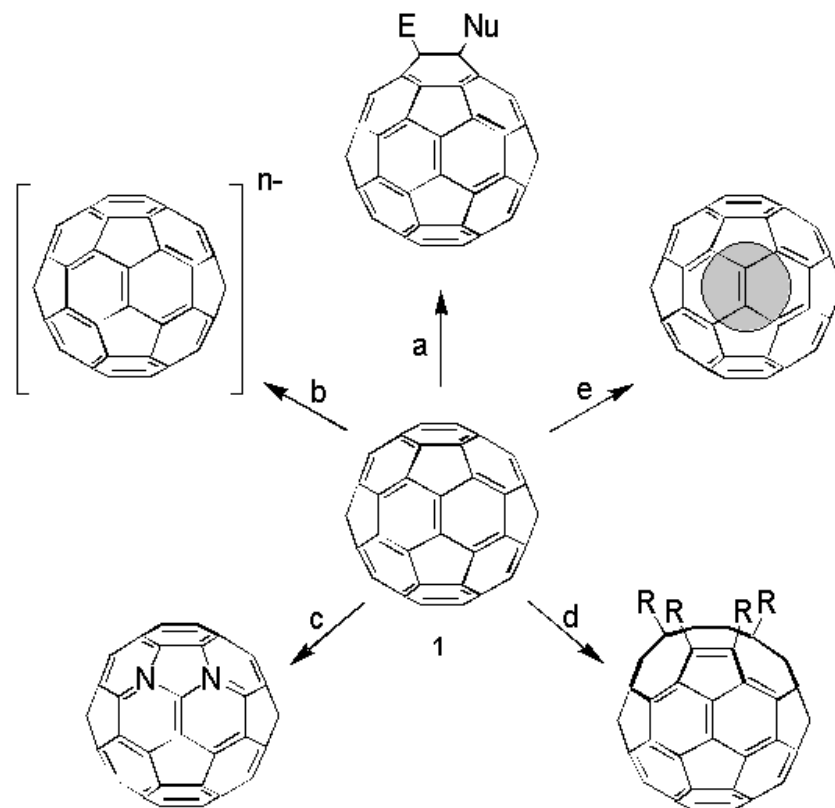
1,2-additions occur at 6,6-double bonds. In 1,2-adducts the bond-length alternation is totally preserved

the regioselectivity of addition reactions is governed by **avoidance of products with 5,6 double bonds** in the lowest energy Kekulé structure (price tag of 8.5 kcal mol⁻¹)

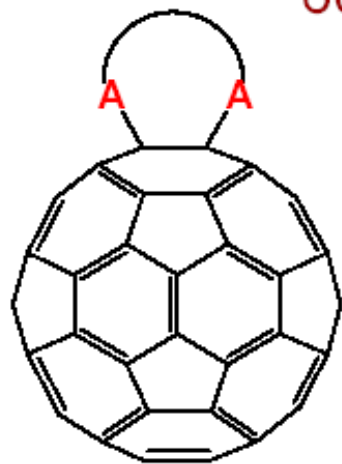
multiple addition to C_{60} is a complicated process governed by differences in bond order and LUMO coefficients at each site: many possible **regio-isomers**

The **chemical transformations** that are possible with C₆₀ could be classified in five main groups (figure 1.3):

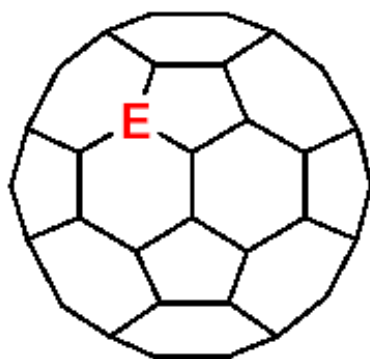
- a) *Addition reactions*. Formation of exohedral compounds by addition of nucleophiles or radicals, cycloadditions, complexations with transition metals and others.
- b) *Electron transfer reactions*. Chemical reduction of fullerenes can easily be achieved by reaction with electropositive alkali and alkaline earth metals or organic donor molecules.
- c) *Heterofullerenes*. Substitution of a carbon atom of the fullerene skeleton for a heteroatom, for example nitrogen or boron.
- d) *Ring opening reactions*. Producing a hole in the C₆₀ skeleton while breaking a discrete number of bonds.
- e) *Formation of endohedrals*. Introducing and trapping of atoms inside the spherical carbon cage.



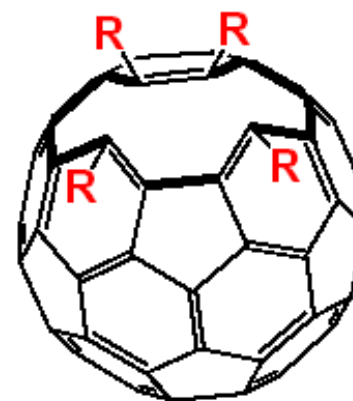
Derivati del C_{60}



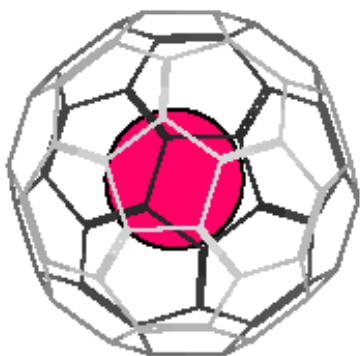
covalent exohedral
adducts



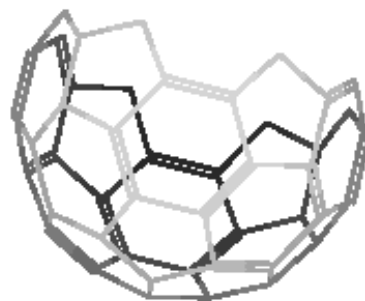
heterofullerenes



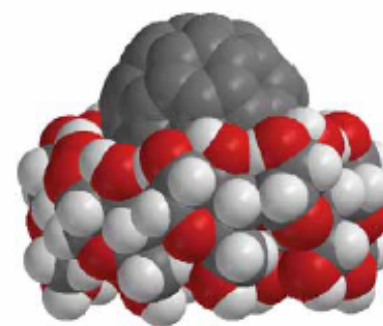
open-cage
derivatives



endohedral
fullerenes

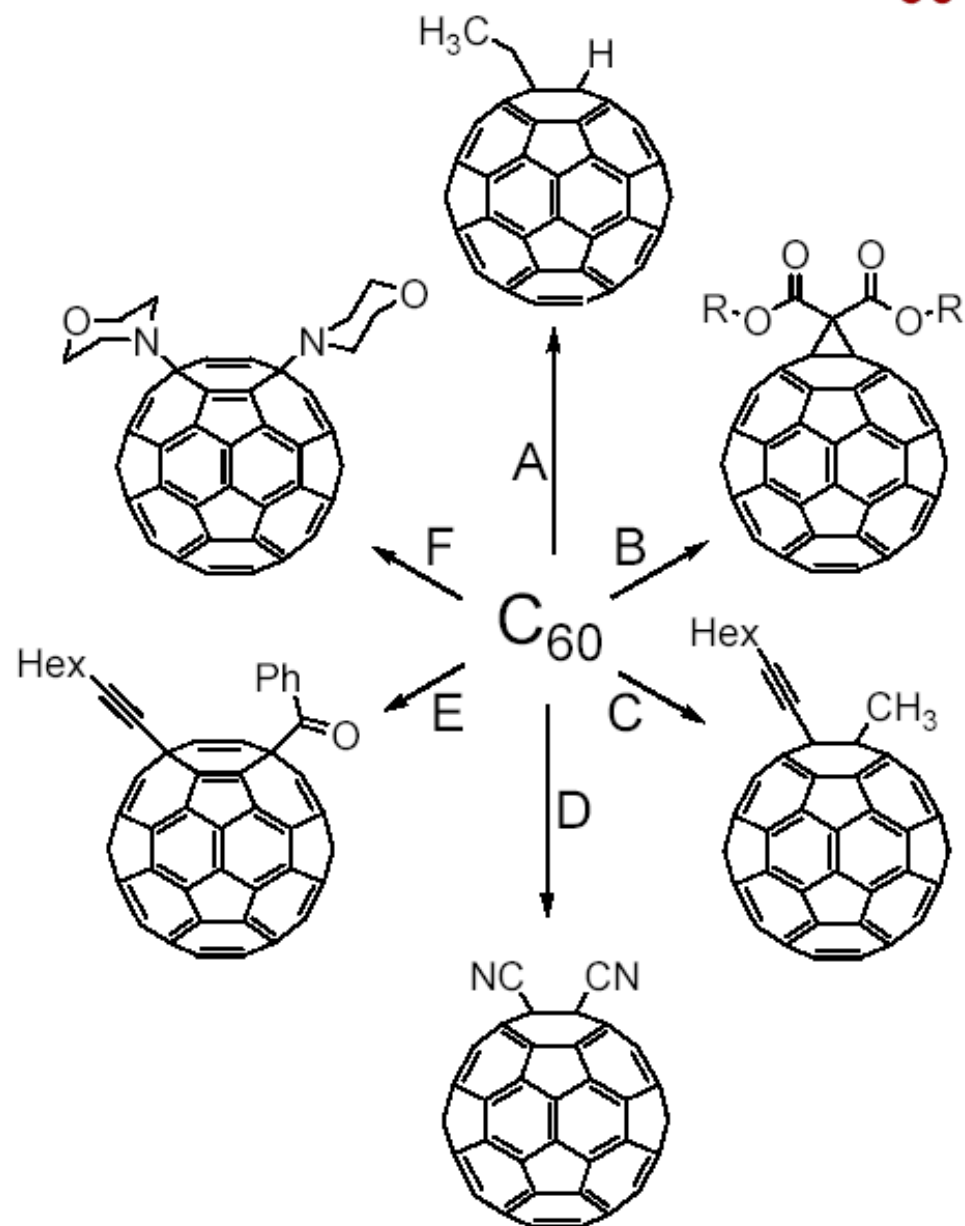


partial
structures

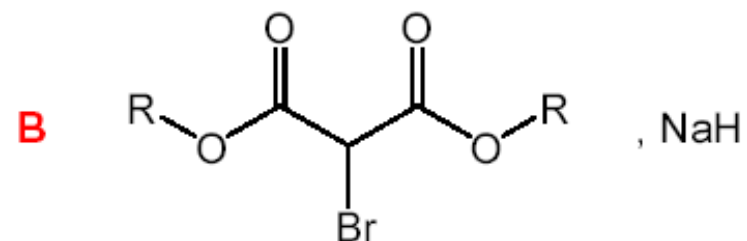


Host-guest
assemblies

Addizioni nucleofile al C₆₀



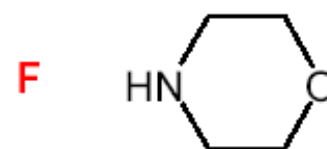
A EtMgBr, H⁺



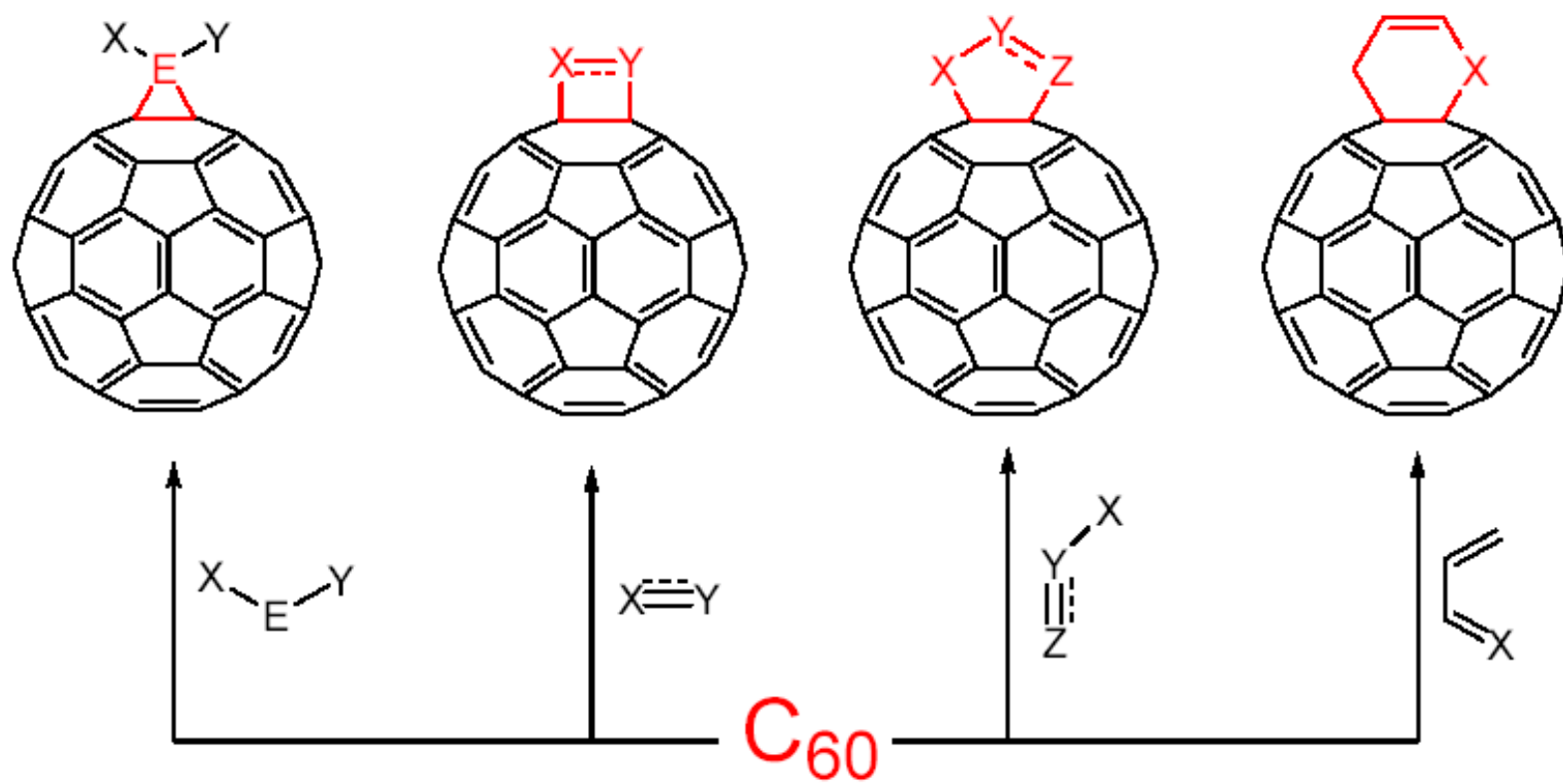
C Hex≡C-Li , MeI

D NaCN, TsCN

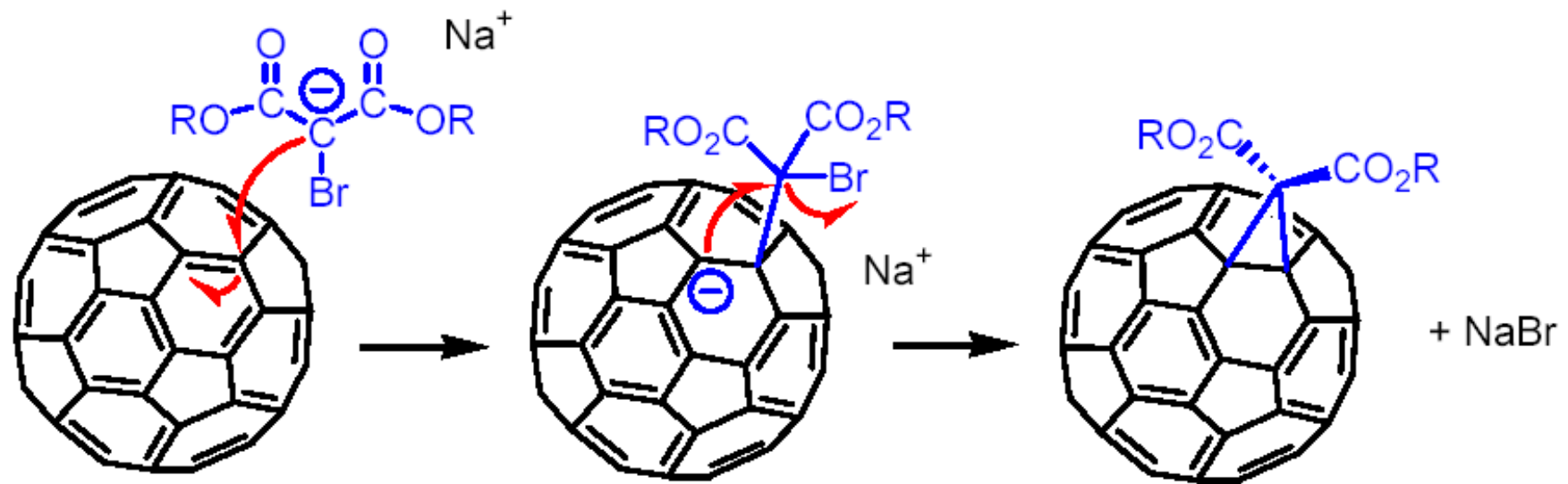
E Hex≡C-Li , PhCOCl



Cicloaddizioni al C_{60}

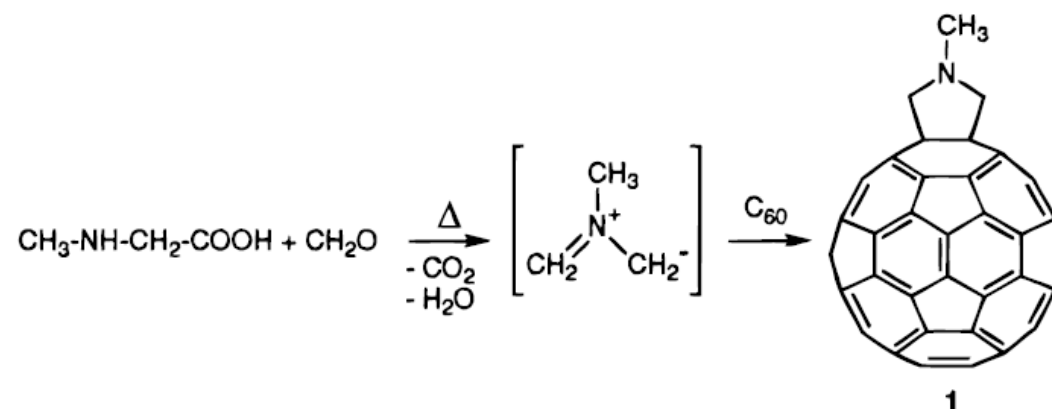


Ciclopropanazione del C_{60} (metanofullereni)



1,3-dipolar cycloaddition of azomethine ylides to C60

the Prato's reaction



41% yield

82% on the consumed C60

the reaction is site selective in that it affords exclusively the product of cycloaddition across a 6,6 ring junction of the fullerene

In the presence of large excesses of reagents, up to nine pyrrolidine rings can be introduced, as detected by MS analysis of the reaction crude.

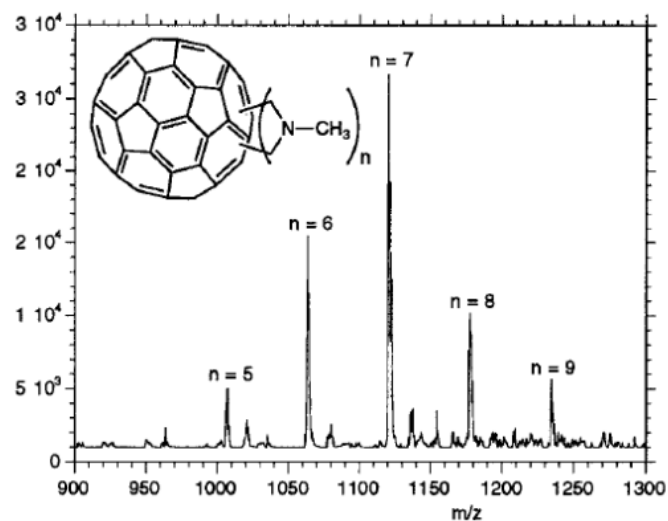
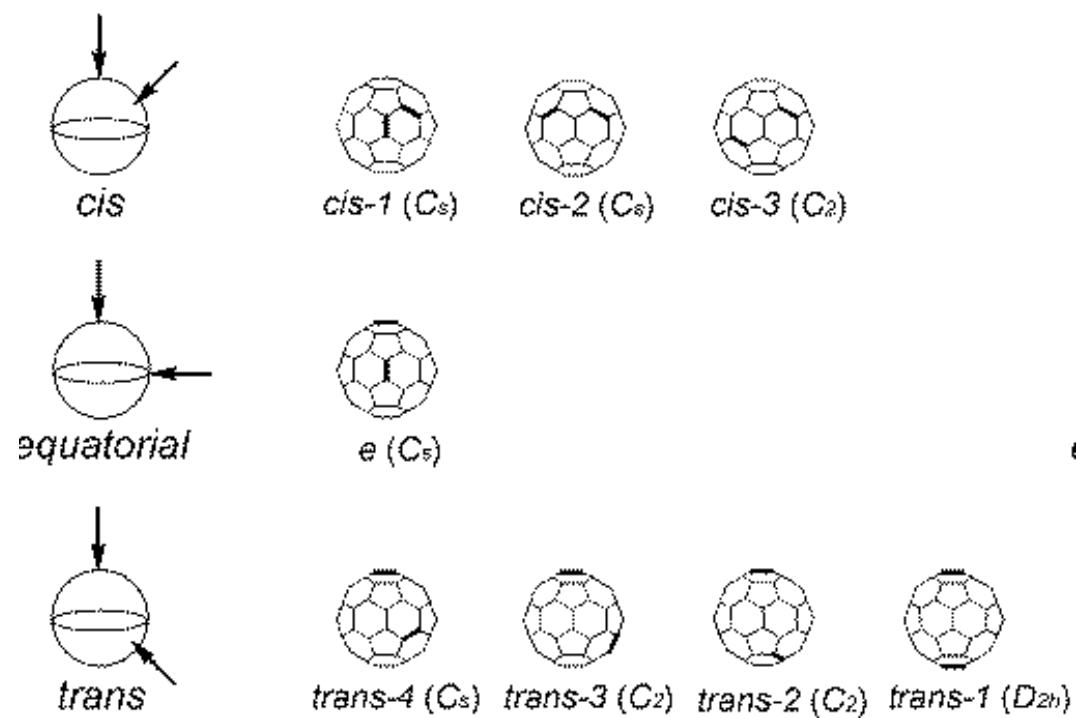


FIGURE 1. APCI-MS spectrum of the crude mixture obtained by heating a toluene solution containing C₆₀, 20 equiv of sarcosine, and 20 equiv of formaldehyde for 8 h.

Maggini, M.; Scorrano, G.; Prato, M. *J. Am. Chem. Soc.* **1993**, *115*, 9798–9799.

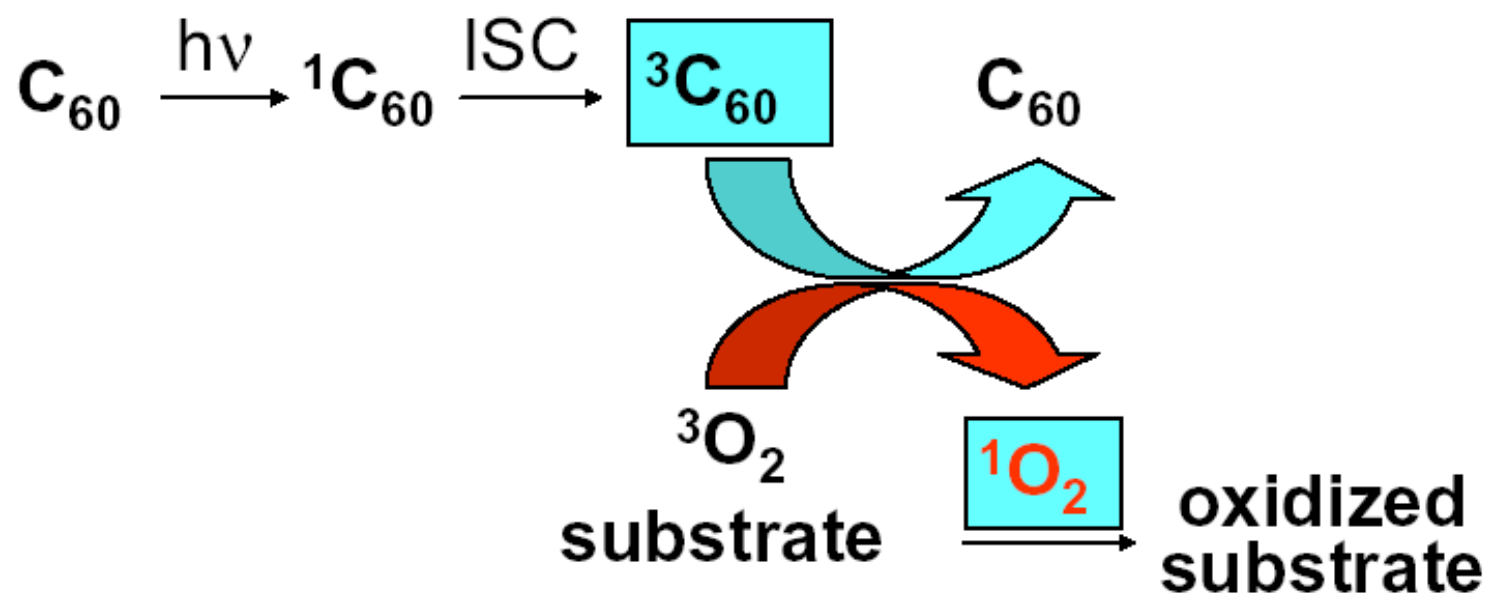
C60 bis-adducts



Some application of C₆₀ in medicine

- ◆ Fullerene is able to fit inside the hydrophobic cavity of HIV proteases, inhibiting the access of substrates to the catalytic site of enzyme.
- ◆ C₆₀ can be used as radical scavenger and antioxidant.
- ◆ If exposed to light, fullerene can produce singlet oxygen in high quantum yields. This action, together with direct electron transfer from excited state of fullerene and DNA bases, can be used to cleave DNA.
- ◆ Fullerenes have been used as a carrier for gene and drug delivery systems.
- ◆ Gd(III)@C₈₂(OH)_n for MRI

Generazione di ossigeno di singoletto



C_{60} is an excellent singlet oxygen sensitizer

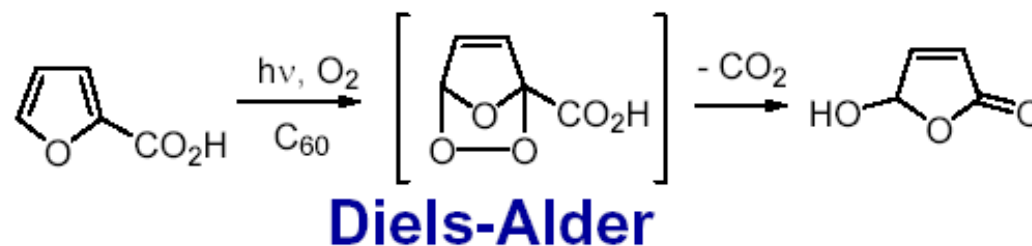
$^3\text{C}_{60}$ reacts with oxygen rapidly ($k_q = 1.9 \times 10^9 \text{ M}^{-1}\text{s}^{-1}$)

Reactivity of C_{60} with singlet oxygen is very low

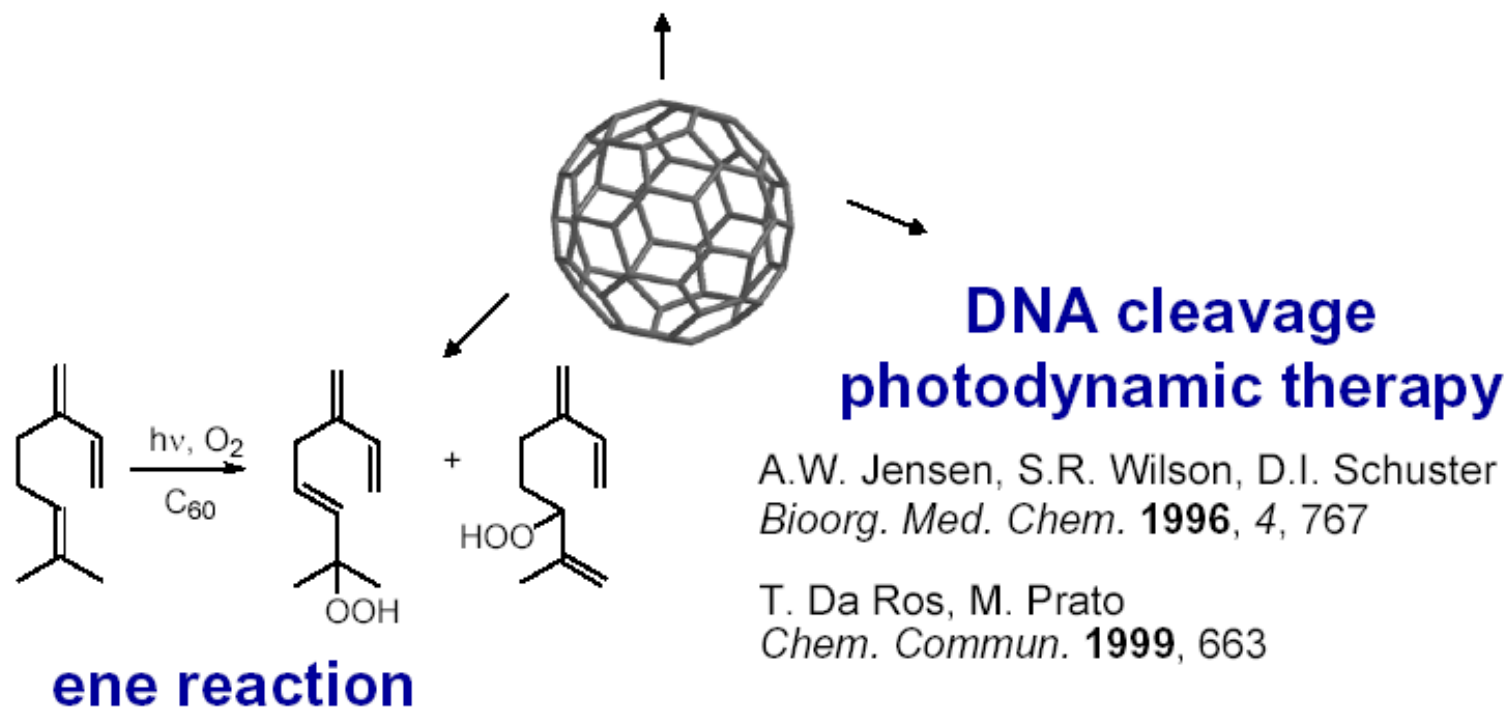
C. Foote, Y. Rubin, F. Diederich et al. *J. Phys. Chem.* **1991**, 95, 11

J. Arbogast, C. Foote *J. Am. Chem. Soc.* **1991**, 113, 8886

Generazione di ossigeno di singoletto



H. Tokuyama, E. Nakamura, JOC **1994**, 59, 1135



H. Tokuyama, E. Nakamura, JOC **1994**, 59, 1135

DNA cleavage and photodynamic therapy

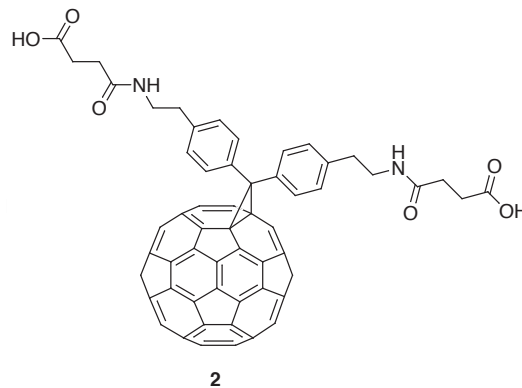
DNA cleavage: C60-derivatives are cytotoxic, they cleaves DNA only in case of irradiation. The cleavage cannot be attributed to the activity of singlet oxygen, an easily diffusing species whose action should be wider, but most probably is to be ascribed to a direct electron- transfer between guanosine and excited fullerene.

Photodynamic therapy: Upon irradiation, [60]fullerene is excited to a short-lived singlet state (lifetime ≈ 1.3 ns), which converts almost quantitatively into a longer-lived triplet state (lifetime = 50–100 ms). The triplet state transfers energy very efficiently to molecular oxygen, generating singlet oxygen with almost unitary yield.

Enzymatic inhibition and anti-HIV activity

The active site of the HIV-1 Protease (HIVP) is a quasi- spherical hydrophobic cavity, whose diameter is about 10 Å. On its surface, two amino acid residues, aspartate 25 and aspartate 125, catalyse the hydrolysis of the substrate.

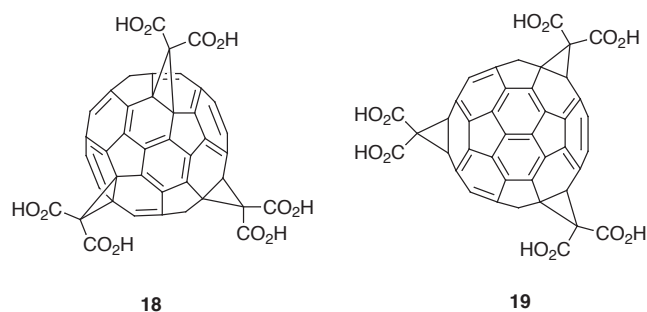
On the basis of molecular modeling, Friedman *et al.* were the first to recognise that the [60]fullerene spheroid can be almost perfectly accommodated inside the hydrophobic site if the interactions are sufficiently strong, inhibition of the catalytic activity of HIVP is to be expected. *In vitro* studies, performed using a 'first generation' water soluble fullerene derivative (**2**), confirmed that inhibition of acutely and cronically affected peripheral blood mononuclear cells (PBMC) indeed occurred with an EC₅₀ of 7 µM.



Neuroprotective properties

Many neurodegenerative diseases originate from excess production of superoxide and nitric oxide radicals, whose origin may be due to overexcitation of glutamic acid receptors. It has been shown that compounds that act as **radical sponges** reduce, though not completely, neuronal death. **[60]Fullerene, owing to its antioxidant properties** and high reactivity toward free radicals, shows promising behavior in this field.

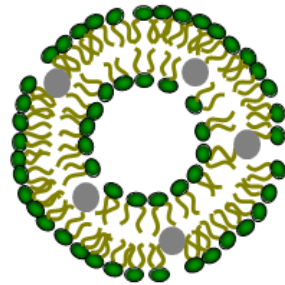
In vitro experiments using cultures of neocortical cells showed a dose-dependent decrease of neuronal death, with derivative **18** being more active than **19**.



Antiapoptotic activity

The same isomers **18** and **19** have been shown to possess antiapoptotic activity. Apoptosis due to amyloyl peptide Ab1-42 was also inhibited by the same fullerene derivatives. In a strictly connected work, the effects of trisadducts **18** and **19** on apoptosis induced by ceramide were evaluated. In this case isomer **19** is more active.

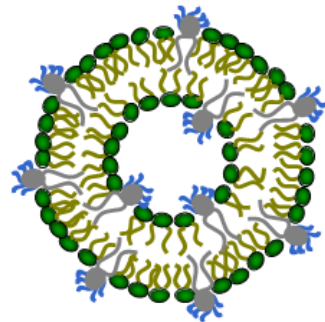
Structures and Compositions of Fullerene Liposome



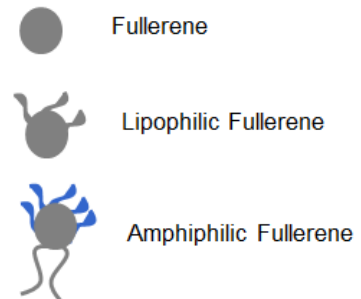
Type 1 Fullerene Liposome



Type 2 Fullerene Liposome

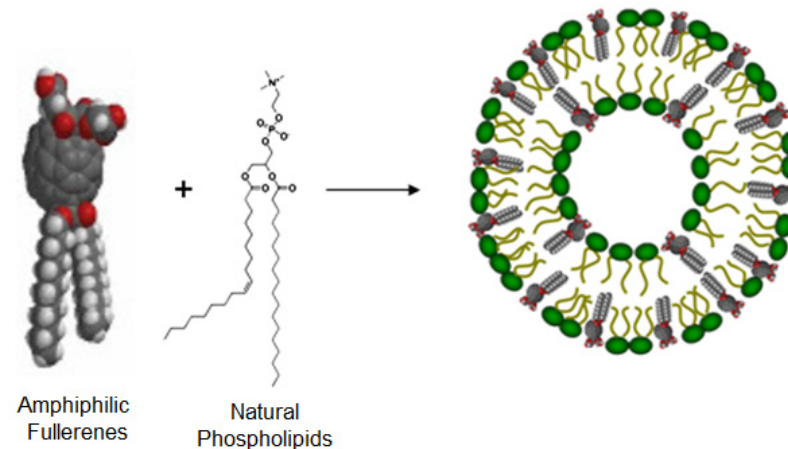


Type 3 Fullerene Liposome



Fullerene Liposome Antioxidants

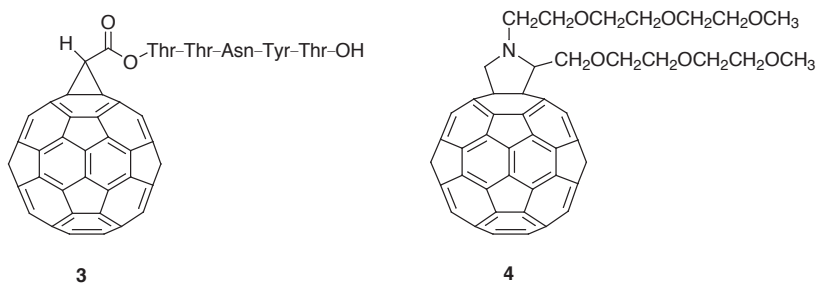
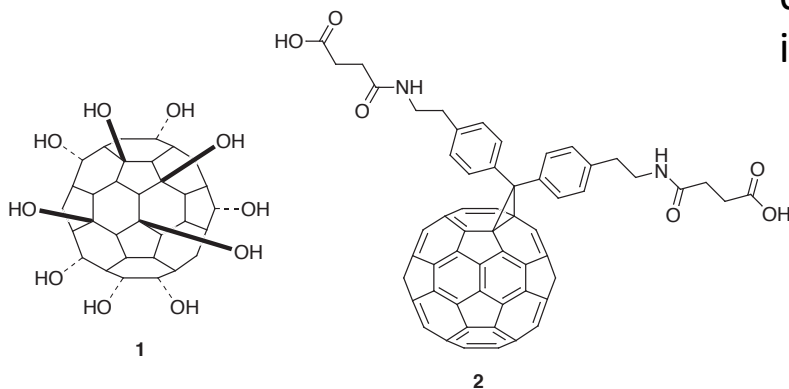
Figure 3. Vesicle formation of amphiphilic fullerene compound ALM with auxiliary phospholipids.



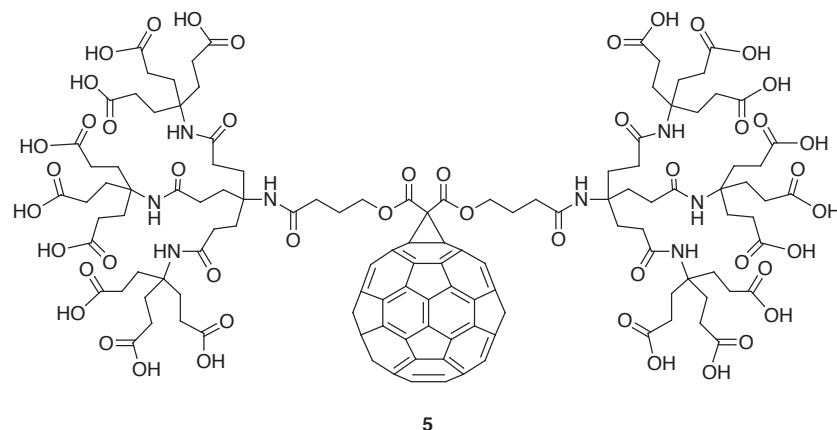
In order to increase the efficiency of delivery of fullerenes to target tissues, lipophilic fulleropyrrolidine derivatives Q-C₆₀: [*N*-methyl-(2-quinoly)fulleropyrrolidine] and I-C₆₀: [*N*-methyl-(2-indoly)fulleropyrrolidine] were also synthesized and encapsulated in multilamellar phospholipid liposomes, and the antioxidative capacity was studied using EPR spin-trapping and spin-labeling techniques [31]. Its capacity for removal of •OH (hydroxyl radical) and O₂^{•-} (superoxide radical) and for the prevention of lipid peroxidation were compared with the performance of pristine C₆₀, Q-C₆₀ and I-C₆₀ showed similar, or even better, antioxidative characteristics. Other fulleropyrrolidine derivatives were also reported for incorporation in liposomes [32].

ALM amphiphilic liposomal malonylfullerene

the radical quenching ability and the singlet oxygen production of the multiple adducts may depend on the number of addends: it decrease increasing the number of saturated bonds.



1.5×10^{-5} M in H₂O–DMSO 9:1

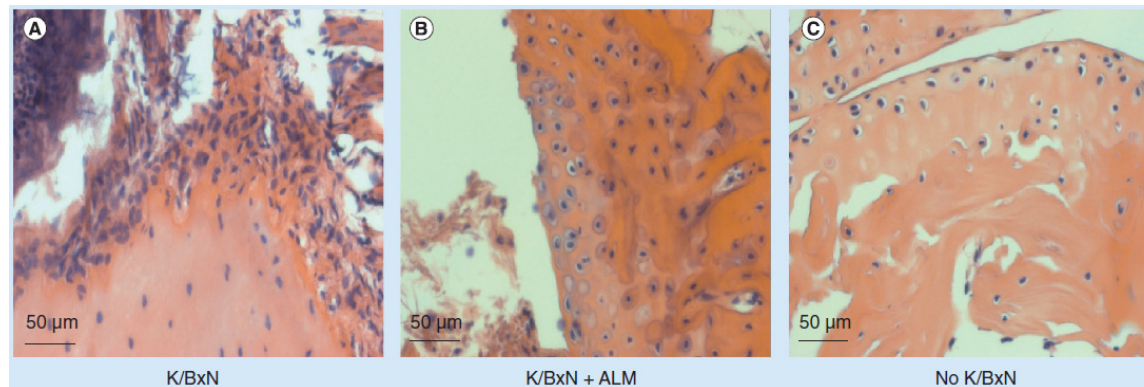


reduce aggregation
in aqueous solutions
in particular at basic pH

34 mg/ml at pH 7.4 and an
outstanding 254 mg/ml at pH 10

Fullerene Liposomes Inhibit Inflammation

Figure 4. Fullerenes attenuate inflammatory arthritis of the K/BxN-induced disease pathology. **(A)** Serum-treated mice demonstrated typical synovial hyperplasia, pannus formation and inflammatory infiltrates; **(B)** By contrast, ALM-treated animals had less evidence of clinical joint inflammation compared with **(C)** non-diseased animals. ALM: Amphiphilic liposomal malonylfullerene.



Metallofullerene Liposome for Contrast-Enhanced Molecular MR Imaging

liposome formulated gadofullerene MRI contrast agent for targeted imaging of macrophage receptors for the diagnosis of unstable atherosclerotic plaque

Figure 5. Figure: Plaque imaging of aorta arch of 23 weeks old female ApoE^{-/-} mice with 7 T imager. **Top:** ATCA (100 μ L, 4.0 mg/kg or 0.9 mg Gd/kg); **Bottom:** Non-targeted control did not enhance any contrast. Graph: Quantification of signal enhancement. The signal to noise ratio (SNR) was calculated using a reference ROI next to the plaque lesion, then SNR values were normalized to the pre-injection SNR value. The same regions were traced throughout all imaging points. ATCA: white bars, and non-targeted control: black bars. The SNR values are shown as mean for the entire aorta of five mice. * indicates significance ($p < 0.05$).

