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Carboxyfullerenes: Nanomolecules that Work!

Sameh S. Ali*

Department of Medicine, University of California, San Diego, USA
Center for Aging and Associated Diseases, Helmy Institute for Medical Sciences, Zewail City of Science and Technology, Sheikh Zayed District, Giza 12588, Egypt

Buckminsterfullerene (C_{60}) is a fascinating spherical molecule that is composed of pure carbon atoms bonded in fused aromatic rings [1]. The discovery of fullerenes essentially expanded the number of known carbon allotropes, which were limited to graphite, diamond and amorphous carbon. Due to their unique physicochemical properties, fullerenes (Buckyballs) and carbon nanotubes (buckytubes) have been the subject of intense research yielding numerous reported applications in material science, electronics, nanotechnology and more recently, biomedicine.

Why are fullerenes unique candidates for nanotherapeutic applications?

The diameter of the C_{60} molecule is 6.973 Å in a Chem3D®-generated molecular model (Figure 1A), but derivatization can qualify the molecule as a nanoparticle! In contrast to classical planar aromatic molecules, the curvature of the spherical carbon network gives fullerenes their unique chemical reactivity profile. That is, restrained geometry imparts somewhat incomplete lateral overlaps between the bond forming p-orbitals on the outer surface while enhancing their overlap internally (Figure 1A) [2]. The result is a highly reactive surface and a completely inert interior of the C_{60} molecule, allowing derivatization and transformation through redox and many other reactions.

Early on, fullerenes were recognized as 'electron-sinks' or 'free radical sponges [3], with one molecule being capable of scavenging > 30 free radicals. However, the biomedical applications of fullerenes didn't come to fruition before water-soluble full erenol derivatives were utilized as neuroprotectants in a groundbreaking study by Dugan, Choi and their co-workers [4]. Today, the biomedical application of water-soluble fullerenes has expanded dramatically to span areas of antiviral activity, antioxidant activity and drug delivery—among many other exciting new applications; reviewed in [5,6]. For example, designed fullerene derivatives that exhibit the size and symmetry to fit inside the hydrophobic cavity of the human immunodeficiency virus (HIV) effectively inhibit the catalytic activity of the HIV proteases; reviewed in [5,6]. Moreover, fullerenes can be utilized as radical scavengers and antioxidants, despite paradoxically producing singlet oxygen and free radicals when exposed to light; reviewed in [7]. Direct electron transfers between photoexcited fullerenes and DNA bases, along with generated oxygen radicals were employed to cleave DNA [8]. Additionally, functionalized fullerenes have been used as carriers for gene and drug delivery [9].

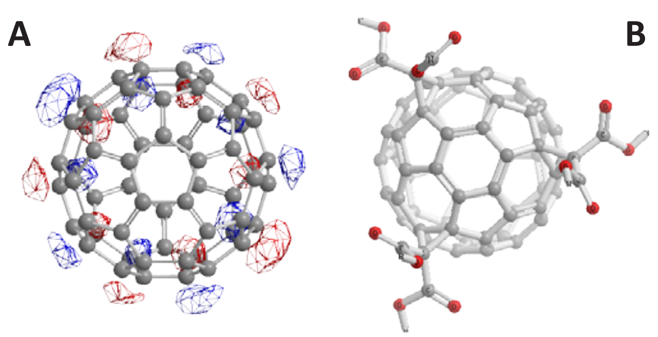

Figure 1: Chem3D generated models for Buckminsterfullerene (C_{60}) indicating the HOMO (Highest Occupied Molecular Orbital, N=120, E=-11.135 eV) as calculated by the Extended Hückel Semi Empirical Method (A) and the tris-malonic acid C_3 derivative (B).

Carboxyfullerenes: The spearhead of nanomedicinal research!

One of the most promising classes of water-soluble fullerenes is carboxyfullerenes, especially the tris-malonic acid C_3 derivative (Figure 1B). The high symmetry and partitioned lipophilic/hydrophilic characteristics of each molecule appear to enhance its ability to access various domains in the cell, to pass the blood-brain barrier and even to penetrate mitochondria thus acting as an antioxidant at the primary source of reactive oxygen species [10-12]. Interestingly, C_3 has been shown to remove superoxide radicals catalytically rather than stoicheometrically thus acting as a superoxide dismutase mimetic [10]. The extraordinary neuroprotective efficacy of this molecule has been established in several models including iron-induced oxidative injury [13], NMDA-receptor mediated neurotoxicity [12], familial amyotrophic lateral sclerosis [14] and ketamine-induced loss of interneurons implicated in schizophrenic patients [15]. Strikingly, administration of C_3 to wild-type mice starting at middle age improved their cognitive function and extended their lifespans [16]. These results provide great guidance for the development of effective fullerene-based drugs to intervene with the plethora of nervous system maladies-particularly, those involving oxidative injury.

Proceed with caution!

On the cautionary side, extensive toxicological studies are essential before fullerene-based drugs or cosmetics are made available commercially. Although several *in vitro* studies concluded a little evidence of fullerene toxicity [17], it is important to stress the fact that fullerenes are pro-oxidants when activated by light. This is particularly relevant to skin care and anti-aging products that utilize fullerene formulations. Notably, polar and non-polar fullerenes tend to aggregate in aqueous media and the variability in aggregate size, shape and surface area within the same patch makes it a challenging task to define nanotoxicological standards. It is imperative that clear safety regulations are established to control every fullerene formulation before

***Corresponding author:** Sameh S. Ali, Assistant Professor, Departments of Medicine and Anesthesiology, The University of California, USA, Tel: 858 534 7956; Fax: 858 534 0104; E-mail: ssali@ucsd.edu

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it is dispatched to the market. However, incomplete nanotoxicology research is hampering efforts to introduce such regulations [18]. This highlights the importance of the Journal of Nanomedicine & Biotherapeutics, as an open access source of data that can effectively aid decision makers to constitute nanotoxicology regulations.

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