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COMPOSITIONS FOR MEDICINAL CHEMISTRY OF FULLERENES

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The paper presents a quantum-chemical approach to two aspects of fullerene nanomedicine related to the oxidative and antioxidant actions of fullerene. The first topic is concerned in regards photodynamic therapeutic effect of fullerene solutions. A new mechanism of the effect is proposed. The second aspect is exemplified by the consideration of two fullerene-silica complexes, namely, fullerosil and fullerosilica gel.

Статья посвящается памяти талантливого ученого,
креативного лидера и большого человека,
любившего науку и считавшего ее делом своей жизни,
умевшего одинаково искренне радоваться своим и чужим успехам,
Алексея Алексеевича Чуйко.
Автору дороги все встречи и беседы с этим неординарным человеком,
стимулировавшие, в частности, и это исследование.

INTRODUCTION

Nanomedicine of fullerene seems to be a beautiful platform to illustrate the synergetic of chemistry, biology and physics in fullerene science. The modern medicinal fullerenics is a largely explored field, actively developing and enlarging. We are not going to go into the depth of the topic and address readers to some exhausted reviews just recently appeared [1–3]. Our purpose is to show the basic grounds that lay the foundation of biological and medicinal applications of fullerenes to be tightly connected with distinguished properties of fullerenes. This concerns first of all the mechanism of their therapeutic action.

For today a large number of efficient biomedical actions of fullerenes have been found among which there are antiviral, anticancer, neuroprotective, enzymatic, antiapoptopic and many others [4–6]. The list is worthwhile to supplement by the latest sensational news on a fullerene-based gene delivery in mice [7]. Expert judgments suggest that this work opens a large way to test efficacy of fullerenes for *in vivo* applications such as insulin gene delivery to reduce blood glucose levels for diabetes treatment and so forth.

Empirically estimated, fullerenes fulfill therapeutic functions acting as either antioxidant or oxidative agent thus revealing seemingly two contradictory behaviors. However, this two-mode behavior is just the manifestation of two appearances of fullerenes that are, on one hand, radicals due to the availability of a considerable number of effectively unpaired electrons N_D and an efficient donor-acceptor (D-A) agent, on the other. Actually, the consideration of chemical behavior of fullerenes discussed in [8] clearly show that they must willingly interact with other radicals forming tightly bound compositions thus providing an efficient radical scavenging. In full consistence with this statement, the first exhibited therapeutic function of fullerene C_{60} was its action as a radical scavenger [9]. Later on this laid the foundation of the antioxidant administrating of fullerenes in medical practice [10–12]. Establishing the preservation of antioxidant properties in C_{60} derivatives in general as well as its dependence on the chemical structure and, mainly, on the number of attached chemical groups with a clear preference towards monoderivatives, are in a complete accordance with expected behavior of molecular chemical susceptibility and can be quantitatively described in terms of N_D. It is enough to remain a clearly justified working out this pull of effectively unpaired electrons under successive fluorination [13] and hydrogenation

[14]. Therefore, the antioxidant therapeutic function of fullerenes is intimately connected with electronic structure of the molecule itself.

Oppositely to individual-molecule character of the antioxidant action, the oxidative action of fullerenes occurs under photoexcitation of their solutions in both molecular and polar solvents in the presence of molecular oxygen. The action consists mainly in the oxidation of targets by singlet oxygen $^1O_2$ produced in due course of photoexcitation of fullerene solutions. The difference in the behavior of singlet and triplet oxygen is obviously connected with the difference in the pairing of the molecule electrons caused by different spin multiplicity. A quantitative characteristic of the pairing can be expressed in terms of the total number of unpaired electrons N_D. Calculations performed within the framework of the UBS HF approach [15] expose $N_D = 2$ for both spin states. But, if for the triplet state this finding just naturally reflects two electrons that are responsible for maintaining the molecule spin multiplicity, in the singlet state the availability of two effectively unpaired electrons evidences a biradical character of the molecule which explains $^1O_2$ high oxidative activity. Therefore, the photostimulated $^3O_2 \to {}^1O_2$ transformation in the presence of fullerene molecule just means exempting the molecule two electrons from the spin multiplicity service thus transforming chemically inactive molecule into a biradical.

The presence of fullerene for the photostimulated $^3O_2 \to {}^1O_2$ transformation is absolutely mandatory, so that the treatment was called as photodynamic fullerene therapy [16, 17]. For the reason alone that the action is provided by a complex involving fullerene and solvent molecules as well as molecular oxygen, it becomes clear that it is resulted from a particular intermolecular interaction. However, until now, the mechanism of the photodynamic therapy has been hidden behind a slogan "triplet state photochemical mechanism" that implies the excitation transfer over a chain of molecules according to a widely accepted scheme [16–18]

$$^1C_{60} \xrightarrow{\hbar\nu} {}^1C_{60}^* \to {}^3C_{60}^* \xrightarrow{^3O_2 \to {}^1O_2} {}^1C_{60}\,.$$

Scheme 1

The scheme implies the energy transfer from the singlet photoexcited fullerene to the triplet one that further transfers the energy to convenient triplet oxygen thus transforming the latter into singlet oxygen. The first two stages of this "single-fullerene-molecule" mechanism are quite evident while the third one, the most important for the final output, is quite obscure in spite of a lot of speculations available [18]. Obviously, the stage efficacy depends on the strength of the intermolecular interaction between fullerene and oxygen molecules. Numerous quantum chemical calculations show that pairwise interaction in the C_{60}–O_2 dyad in both singlet and triplet state is practically absent. The AM1 UBS HF computations [15] fully support the previous data disclosing the coupling energy of the dyad E_{cpl}^{f-o} equal to zero in both cases. This puts a serious problem for the explanation of the third stage of the above scheme forcing to suggest the origination of a peculiar intermolecular interaction between C_{60} and O_2 molecules in the excited state, once absent in the ground state.

However, exclusive D-A ability of fullerenes strongly influences intermolecular interaction (IMI) [8] and cannot be omitted when considering intermolecular events, particularly under photoexcitation. Let us look at oxidative fullerene-based solutions from this viewpoint.

SPIN-FLIP IN THE OXYGEN MOLECULE IN FULLERENE SOLUTIONS

The system under consideration consists of fullerene C_{60}, solvent, both polar (water, etc.) and nonpolar (benzene, etc.), and oxygen. Molecules of fullerene and solvent are in singlet ground state while the ground state of oxygen molecule is triplet. Let us call this system as photodynamic (PD) solutions. There are a few types of IMI in the solutions, among which we will be interested in the IMI between fullerene molecules (*f–f*), between fullerene and solvent molecules (*f–s*) and between fullerene and oxygen (*f–o*). So far, we have pointed aside the *f–s* IMI which might be important in some cases (see the influence of this interaction on nanophotonics of fullerene solutions in [8]). In the case of such solvents as benzene and water it is very weak and can be neglected.

In contrast, interaction between fullerene molecules is rather significant and causes the fullerene clusterization that is experimentally proven in many cases (see for example [19–22]). Consequently, instead of an ideal solution, the PD one presents a conglomerate of clusterized C_{60} molecules as shown schematically in Fig. 1.

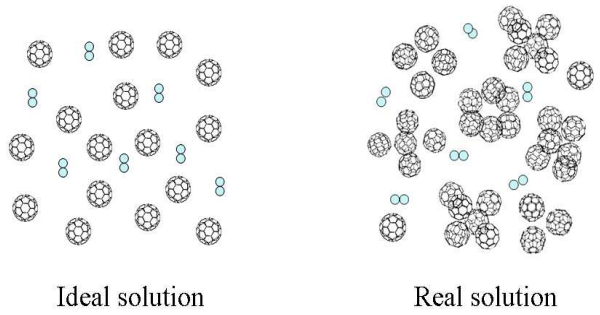


Fig. 1. Schematic presentation of an ideal (*a*) and real (*b*) fullerene solution in the presence of molecular oxygen

As shown in [8], clusters of any composition of C_{60} molecules have properties of charge transfer complexes. Excitation by the UV visible light of any of them provides the formation of a pair of molecular ions that quickly relax into the ground state of neutral molecule after the light is switched off. In contrast to neutral C_{60}, both molecular ions C_{60}^- and C_{60}^+ efficiently interact with oxygen molecule giving coupling energy E_{cpl} of -10.03 and -10.05 kcal/mol, respectively, referring to $^3O_2$ molecule and -0.097 and -0.115 kcal/mol in regards to $^1O_2$. Therefore, oxygen molecule is quite strongly held in the vicinity of both molecular ions forming $[C_{60}+O_2]^-$ and $[C_{60}+O_2]^+$ complexes as schematically shown in Fig. 2.

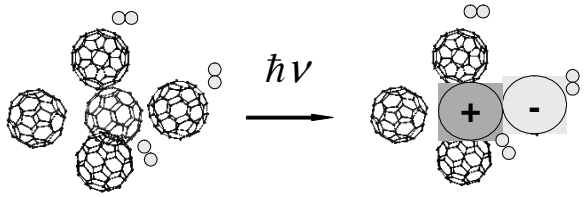


Fig. 2. The formation of $^2[C_{60}^- + O_2]$ and $^2[C_{60}^+ + O_2]$ complexes under photoexcitation of $(C_{60})_5$ cluster

UBS HF AM1 calculations for the corresponding pairs show [15] that the complexes are of $^2[C_{60}^- + O_2]$ and $^2[C_{60}^+ + O_2]$compositions of the doublet spin multiplicity. Since both fullerene ions take the responsibility over the complex spin state, so that two electrons of the oxygen molecule that were on the service of triplet spin multiplicity of $^3[(C_{60})_n + O_2]$ dyads in the ground state are not more needed for the job and become effectively unpaired thus adding two electrons to the N_D pool of unpaired electrons of complexes $^2[C_{60}^- + O_2]$ and $^2[C_{60}^+ + O_2]$. The distribution of effectively unpaired electrons of both complexes over their atoms, which displays the distribution of the atomic chemical susceptibility of the complexes, is shown in Fig. 3. A dominant contribution of electrons located on oxygen atoms 61 and 62 is clearly seen thus revealing the most active sites of the complexes. It should be noted that these distributions are intimate characteristics of both complexes so that not oxygen itself but both complexes as a whole provide the oxidative effect. The effect is lasted until the complexes exist and is practically immediately terminated if the latter disappear when the light is switched off.

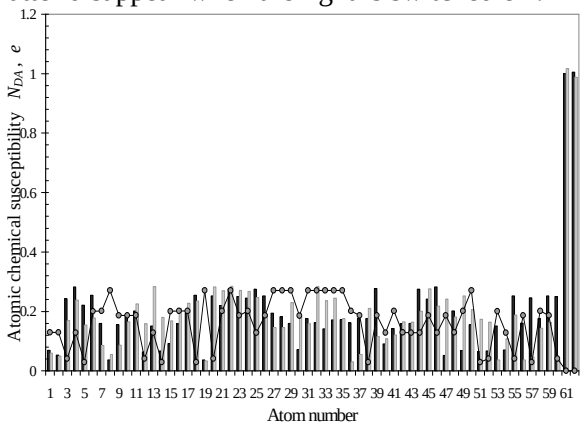


Fig. 3. Distribution of atomic chemical susceptibility N_{DA} over atoms of $^2[C_{60}^- + O_2]$ (black bars) and $^2[C_{60}^+ + O_2]$ (light gray bars) complexes [15]. Curve with black dots plots distribution over atoms of C_{60}. UBS HF AM1 doublet and singlet states

The obtained results make it possible to suggest the following mechanism that lays the foundation of the photodynamic effect of fullerene solutions schematically presented as

$$^3[(C_{60})_n + O_2] \xrightarrow{\hbar\nu} \begin{cases} ^2[(C_{60})_{n-2}C_{60}^+ + O_2] \\ ^2[(C_{60})_{n-2}C_{60}^- + O_2]. \end{cases}$$

Scheme 2

Here $(C_{60})_{n-2}C_{60}^+$ and $(C_{60})_{n-2}C_{60}^-$ present fullerene clusters incorporating molecular ions. The transformation of the triplet ground state complex into two doublet ones under photoexcitation is accompanied with a spin flip of the oxygen molecule electrons in the presence of fullerene molecule which is shown scematically in Fig. 4. This approach allows attributing photodynamical effect of fullerene solutions to a new type of chemical reactions in the modern spin chemistry.

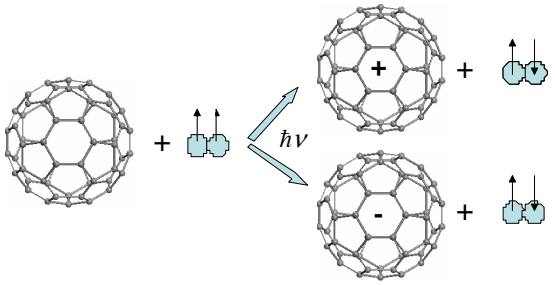


Fig. 4. Schematic presentation of the spin-flip in oxygen molecule under photoexcitation

Since fullerene derivatives preserve D-A properties of pristine fullerene, Scheme 2 is fully applied in this case as well. So that not only C_{60} or C_{70} themselves but their derivatives can be used in PD solutions. However, parameters of the photodynamic therapy occur therewith to be different depending on the fullerene derivative structure [23]. Changing solute molecules it is possible to influence the efficacy of their clusterization that, in its turn, may either enhance or press the therapeutic effect [2, 18]. The situation appears to be similar to that occurred in nanophotonics of fullerene solution. In more details this similarity is discussed in [8].

FULLERENE–SILICA COMPLEXES FOR MEDICINAL CHEMISTRY

If photodynamical therapy is mainly administered by using aqueous solution, the delivery of fullerene-based antioxidant in a living body presents a serious problem. A few types of techniques have been suggested for medical practice until now among them there are the following mostly used [2]:

1. films or fullerene-coated surfaces containing immobilized fullerene [24]
2. aqueous suspensions of micronized crystalline fullerene [25, 26]
3. stable colloidal fullerene solutions in water [27]
4. water soluble fullerene-based complexes [28]
5. water soluble fullerene derivatives [29].

Each of these techniques covers a large field of investigations and has own advantages and disadvantages. The author previous experience in amorphous silica study [30], complemented by knowledge about high medicinal activity of nanosize silica (NSS) [31], forced to think about a possibility of conjugation of silica and fullerene to provide an easy delivery of the medicament in the body just using NSS as a carrier of immobilized fullerene molecules as well as about strengthening therapeutic effects of each components in a synergetic manner [32].

As known, there are a few technological polymorphs of NSS [30, 33], among which the most popular are pyrogenic nanosized silica (PNSS, or Aerosil), silica gel (SCG), and aerogel. Either component of a possible NSS–C_{60} complex exhibits an appreciable medico-biological effect; for example, SCG-based enterosorbents are widely used in medicine. More versatile, the medicinal chemistry of PNSS has made even more impressive progress [31]. One result of these studies is SILICS [34], a wide-spectrum-effect drug, which proved to be not only a highly efficient enterosorbent, superior to all known sorbents, but also an effective medicinal agent for monotherapy of various diseases [31]. The biomedical activity of fullerenes has been discussed earlier. The main factors that make them biologically active are summarized in Table. In this connection, it is seems natural to find out what effect these two component would produce when combined.

Table 1. Main factors underlying the biomedical activity of pyrogenic nanosized silica (PNSS) and C_{60} fullerene

SILICS [34]	**C_{60} fullerene [2]**
high hydrophobicity of the PNSS surface	antioxidant activity
high efficiency in the sorption of proteins	neuroprotective activity
agglutination of a large number of microorganisms and microbial toxins	antivirus and antimicrobial effect
adsorption of low-molecular-weight compounds	inhibition of enzymatic activity
enhancement of the action of immunoactive drugs	gene delivery
inhibition of the aggregation of thrombocyte, etc.	

The idea of creating complex drugs on the basis of NSS is not new. For example, experiments with PNSS covered with various medicinal agents, such as amphotericin and highly dispersed medicinal plants, demonstrated [35] that the use of such composite systems with a prolonged action of the drug may decrease its dose and enhance its bioaccessibility, features indicative of a synergistic action of the ingredients. Moreover, composite system on the basis of fullerene and highly dispersed silica were also used [36–39]. The carrier was a highly porous SCG. It was

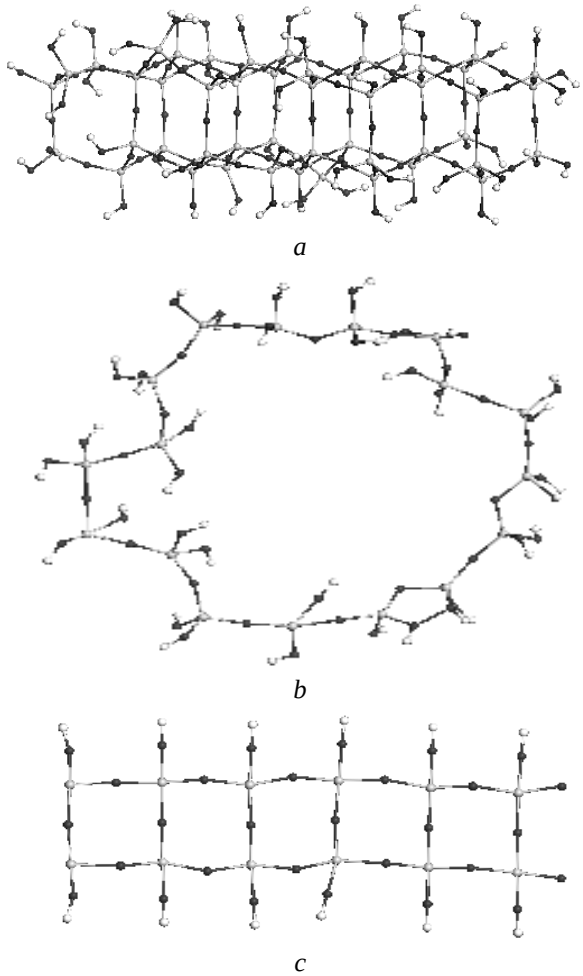
demonstrated that appreciable amounts of fullerene are adsorbed and/or retained in the SCG pores. Fullerene–SCG composites (fullerenized SCG, in the terminology of [36]) selectively adsorb low-density lipoproteins (LDLP), a property that makes them effective immunosorbents for treating atherosclerosis. But it remains unknown how C_{60} fullerene is bound to the carrier and how its properties change because of this binding.

Empirically is known that C_{60} is a poor adsorbate in regards to NSS substrates. Thus, the specific amount of C_{60} fullerene (a hydrophobic substance) adsorbed on unmodified PNSS, a hydrophilic carrier, proved extremely low. When the surface of PNSS was modified, for example, with amines, the amount of fullerene adsorbed increased substantially [40]. The specific amount of fullerene on aerogel was also very low [41]. And only SCG, according to [36–39] investigations, seemed to be promising. Let us look what is going on the PNSS surface or inside SCG pore in the presence of fullerene C_{60}.

C_{60} FULLERENE–HIGHLY DISPERSED SILICA COMPOSITE

NSSs are formed during the condensation or polymerization that accompanies the hydrolysis of silicon tetrahalides, their organic orthoesters, and silicic acid salts [33]. The commercial products manufactured in these ways are known as Aerosil, aerogel, and SCG. A special series of experiments aimed at examining the vibrational spectra of these products (summarized in the review [30]) showed that the spectra of the frameworks and surface zones of these three types of silicas differ so radically that they should be considered as different structural formations. The finding has led to exhibiting new structural phenomenon called technological polymorphism of NSS. A comprehensive understanding of the motivation leading to the formation of different polymorphs gave rise to a new algorithmic approach to modeling NSSs [30]. Let us briefly consider the main point of the approach.

Aerosil (PNSS). Aerosil is prepared by the hydrolysis of silicon tetrachloride in an oxygen–hydrogen flame with the subsequent polycondensation of orthosilic acid formed at the first stage. Agglomerated solid-phase nuclei look like virtually ideal particles. The particles are composed of closely packed silicon-oxygen tetrahedra (SOT) with Si–O lengths lying in a narrow interval (Fig. 5*a*). That the frequencies of bending (Si–O–Si and O–Si–O) and torsional vibrations are small allows the corresponding angles vary within wide limits, leading to the amorphization of the substance. The most abundant functional group on the surface of the particle is the isolated silanol group. Silanediol groups are located at structural defects of the surface, but their concentration is below 10–15% [42]. Later, based on the principles underlying the modeling of structures, the authors of [43–45] developed models of the interfaces between PNSS particles and polysiloxane polymers, models that made it possible, in particular, to understand why the polymer becomes stiffer upon being filled with PNSS.



a

b

c

Fig. 5. Cluster models of nanosized silica: (*a*) a fragment of an Aerosil particle comprised of 48 SOT (Si48), (*b)* siloxane cycle of silica gel composed of 17 SOT (Si17sg), and (*c*) polymer chain of aerogel composed of 12SOT (Si12ag)

Silica gel (SCG). Silica gel is normally prepared in aqueous solutions of silicates of alkali metals in the presence of an acid [33]. The hy-

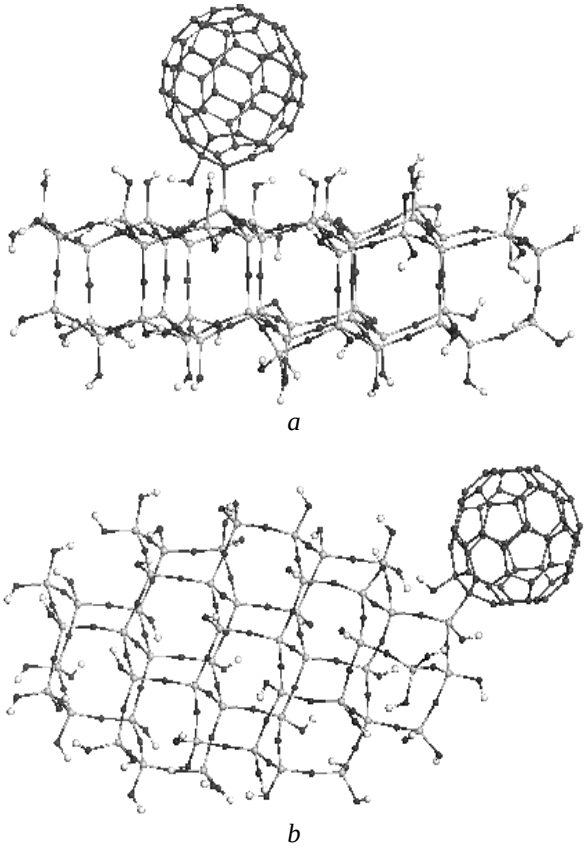
drolysis of a metal silicate in an aqueous medium produces SOT chains of varying length, such that each silicon atom is bonded to two hydroxyl groups (Fig. 5*b*). At a high concentration, chains close to form cycles composed of different numbers of silicon atoms. Brought in contact, such cycles form a silica gel pore in the form of a deflated football with faces of different sizes.

Aerogel. The industrial technology for manufacturing this product is the hydrolysis of tetraethylorthosilicate catalyzed by an acid or alkali [46]. The hydrolysis is accompanied by the formation of a silicate polymer in which each atom is bonded to a hydroxyl group (Fig. 5*c*). Intertwining and bonding to each other, such chains form a gel.

As can be seen in Fig. 5, distinctions in silicon–oxygen structures give rise to the diversity in the structure of hydroxyl covering of these products, a feature that manifests itself through vibrational spectra recorded by means of inelastic neutron scattering [30]. NSS models presented in Fig. 5 allow for examining the interaction of a C_{60} molecule with PNSS modeled by a Si48 cluster (Fig. 5*a*) and with SCG modeled by one or two Si17sg linear cycles. The main focus is therewith on the possibility of formation of *fullerosil* and *fullerosilica gel.*

FULLEROSIL

Given that the hydroxyl covering of the cluster is heterogeneous, let us examine how a fullerene molecule is adsorbed at two areas of its surface with different compositions of hydroxyl groups. In the first case, the molecule position is characterized by the shortest distance, C_f –O_{siln}, between one of its atoms and the oxygen atom of a silanol group. In the second case, the initial distance from C_f to the oxygen atom of a silanediol group, O_{sild}, was determined. The attacking carbon atom was selected among those characterized by the highest atomic chemical susceptibility N_{DA} [32]. It turns out that the parameters of the equilibrium structures of the complex obtained by full optimization of the initial structures depend on the initial distances C_f–O_{siln} and C_f–O_{sild}. At C_f–$O_{siln} \le 1.2$ Å and C_f–$O_{sild} \le 1.6$ Å, the fullerene molecule is bonded to the particle surface in the configurations displayed in Fig. 6. At larger initial distances, it is not bonded to the particle surface.



a

b

Fig. 6. Equilibrium configurations of the Si48–C_{60} complex, with the fullerene molecule located near (*a*) silanol and (*b*) silanediol groups [32]. UBS HF AM1 singlet state

As seen in Fig. 6, in both cases the binding of the C_{60} molecule to the surface occurs via the formation of Si–C_f bond. The carbon atom substitutes previously bound hydroxyl that after releasing is coupled to another carbon atom that is a partner by a short bond to the first one. The final configuration shown in Fig. 6*b* differs from that shown in Fig. 6*a* in that the silicon atom has a second hydroxyl attached, a factor that produces a substantial effect on the coupling energy of the C_{60} molecule to the surface, +10.38 and –6.42 kcal/mol for the structures shown in Fig. 6*a* and Fig. 6*b*, respectively. Since silanediol groups reside predominantly in defective areas of the particle hydroxyl covering, their characteristics vary, which is manifested as a ±1.32 kcal/mol variation in the energy of coupling the fullerene molecule to the model cluster.

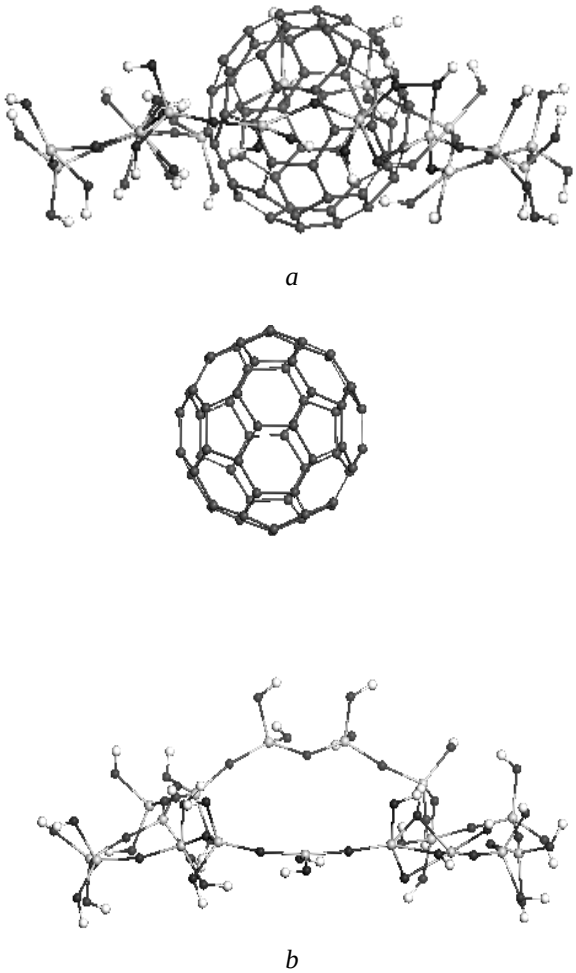
Thus, for the configuration shown in Fig. 6*a*, the attachment a fullerene molecule to a PNSS particle is an endothermic process and, therefore, cannot occur under normal conditions. Exothermic, as it is, the formation of the second

configuration (Fig. 6*b*) is feasible. We believe that this process is responsible for the adsorption of small amounts of C_{60} on PNSS observed in [40]. According to these experimental data, the coupling energy of C_{60} with this substrate is on the order of a few kcal/mol. The product formed can be termed *fullerosil*. The sharp dependence of whether the addition occurs or not on the initial distance between the molecule and the particle surface is suggestive of the existence of a substantial barrier. The reaction is accompanied by 0.42 a.u. charge transfer from the particle to the fullerene. Owing to the presence of C_{60} molecules, fullerosil exhibits high donor-acceptor properties with the ionization potential and electron affinity being 9.58 and 2.35 eV, respectively.

The obtained characteristics of fullerosil suggest that it may prove to be a highly efficient medicinal agent. A relatively low energy of binding of the C_{60} molecule to the surface signifies that it can be readily detached in a biological medium from the particle on which it was transported. Thus, the pharmacological activity of either component can reveal itself in the best way. At the same time, limited by the concentration of silanediol groups, the concentration of C_{60} molecules is low, a characteristic that may prove favorable for the possible pharmacological uses of the complex in light of the specificity of the action of medicinal agents administered in extremely small concentrations [47].

FULLEROSILICA GEL

As discussed above, the surface covering of nanosized pores in silica gels is largely formed by silanediols. Since the presence of silanediols was demonstrated to be the necessary prerequisite for the formation fullerosil, we assumed that C_{60} fullerene would readily attach to siloxane rings; nevertheless, quantum-chemical calculations did not support this assumption. Fig. 7 shows the initial and equilibrium configurations of the NSS–C_{60} complex imitated by a C_{60} molecule bonded to the Si17sg ring. At all reasonable values of the initial C_f–O_{sild} distances, the C_{60} molecule was ejected out of the ring irrespective of whether the atoms comprising the Si–O–Si chain were allowed to optimize their positions or not. This means that, if silica gel were composed of individual rings, it could have not retained C_{60} fullerene.



a

b

Fig. 7. Initial (*a*) and equilibrium (*b*) configurations of the Si17sg–C_{60} complex [32]

However, SCG has a porous structure and Fig. 8 displays calculation results for an element of an SCG pore modeled by two Si17sg siloxane rings. During the optimization of the geometry of the complex the structures of the siloxane chains were fixed to reproduce the properties of the actual SCG silica gel framework while the positions of the hydroxyl groups were optimized. As can be seen in Fig. 8*a*, the fullerene molecule remains inside the pore. No chemical contacts with the pore body via Si–C bonds as in the PNSS case are formed. To within 0.0004 a.u., no charge transfer occurs between the C_{60} molecule and the surrounding siloxane rings. Nevertheless, the coupling energy of this complex is quite noticeable and constitutes -4.13 kcal/mol.

To make the fullerene molecule chemically interact with one of the siloxane rings comprising the pore, the rings were made approach each other, as shown in Fig. 8*b*.

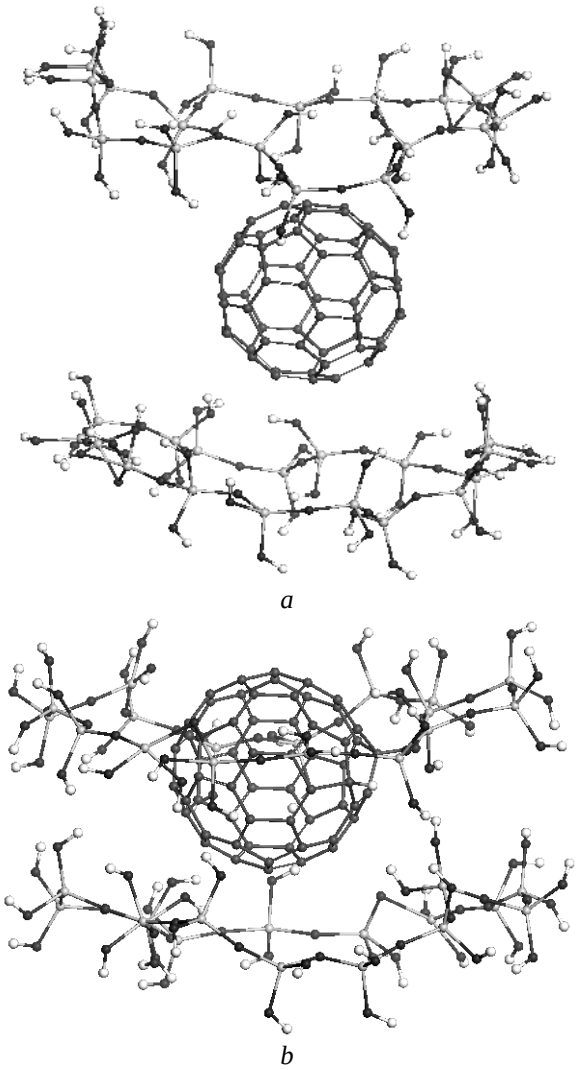


Fig. 8. Equilibrium configurations of the Si17sg–C_{60}–Si17sg complex at normal (*a*) and compresed (*b*) configuration of siloxane rings [32]

Under these conditions, the fullerene molecule remains inside one of the rings borrowing a hydroxyl group and a hydrogen atom from its silanediol covering. However, the coupling energy of such a complex has a large positive quantity (41.64 kcal/mol), rendering this configuration energetically unfavorable. Therefore, when examining the retention of fullerene molecules in SCG pore, such in ring configurations should be excluded from consideration. Thus, the retention of a C_{60} molecule in a SCG is a result of the balanced forcing out of the molecule from each of the rings comprising the pore without the formation of new chemical bonds. There is good reason to believe that such a situation will be realized in an SCG pore of arbitrary shape. Clearly, in some pores the resultant force acts so as to eject the molecule while in others, the molecule is retained, with the coupling energy being dependent on the characteristics of the pore.

Based on these results, a generalized model of fullerosilica gel is presented in Fig. 9. Let us look how this construction makes it possible to explain the main experimental observations for fullerized SCG.

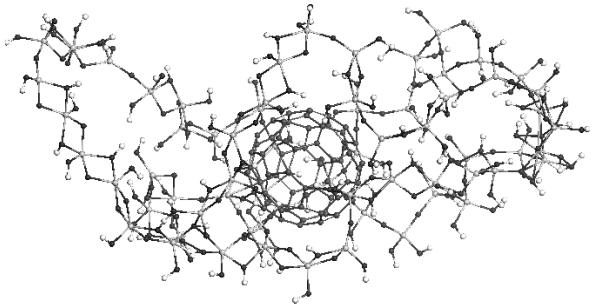


Fig. 9. A model of fullerosilica gel. The pore in silica gel was built of three cycles: Si34sg, Si28sg, and Si17sg

(1) The two-step adsorption isotherms for LDLP on fullerosilica gel, in contrast to single-step ones for SCG modified by aromatic molecules, was explained in [36, 38] by the existence of a 3D adsorption element. This explanation is in full agreement with our concept that a 3D SCG pore with a fullerene molecule retained in it can be considered as a single whole.

(2) The adsorption of LDLP linearly increasing with the fullerene concentration points to the fullerene molecule being incorporated into the composition of a complex adsorption element in the monomeric form. This finding is fully coherent with the suggested general view on fullerene molecule incorporating inside the SCG pores. Consequently, the number of elements increases with the concentration of molecules introduced being limited only by the number of pores suitable for accommodating fullerene.

(3) The LDLP is adsorbed by fullerosilica gel more effectively than lipoproteins with other structures can also be explained by the spatial structure of the adsorption element. As discussed in [33], the size of linear siloxane cycles only rarely exceeds 20–30 units. As can be seen in Fig. 9, the internal size of a pore composed of cycles comprised of 17, 28, and 34 SOT is commensurate with the diameter of the fullerene molecule, so that the latter occupies a significant fraction of the pore, a configuration that prevents high-molecular-weight lipoproteins from penetrating into the pore.

(4) Another feature favorable for the selective adsorption of LDLP on fullerosilica gel is the donor-acceptor interaction between LDLP and C_{60}. The observed electron-exchange adsorption of LDLP [37, 38] is a direct result of this interaction in which LDLP and C_{60} act as a donor and an acceptor, respectively. According to calculations, the high donor-acceptor characteristics of the C_{60} molecule experience virtually no change upon its inclusion into the composition of fullerosilica gel. For example, the ionization potential and electron affinity for the adsorption element shown in Fig. 8*a* were found to be 9.60 and 2.41 eV, respectively, as compared to 9.86 and 2.66 eV for the free molecule. It is its high electron affinity that makes the fullerene molecule so effective in donor-acceptor interactions with both LDLP and simple amines.

CONCLUDING REMARKS ON NATURE OF BIOLOGICAL ACTIVITY OF FULLERENE

To imagine the character of medicinal efficiency of drugs based on NSS-fullerene compositions let us come back to basics of chemical activity of fullerenes. It is known that reactive oxygen-containing species, such as singlet oxygen ($^1O_2$) and superoxide ($O_2^{\bullet -}$), hydroxy (HO•), and hydroperoxy (HOO•) radicals play an important role in regulating a predominant majority of biological processes in a living body. Normal or pathological conditions of the vital activity of biosystems are characterized by the corresponding levels of these species [47]. As other vitally important human being characteristics, such as temperature, blood pressure, glucose level in blood, and so forth, a normal level of the reactive oxygen-containing species must be kept within a rather narrow interval. Thus, many pathological conditions are associated with an anomalously high level of overoxidation of biomolecules [47], specially, lipids in cellular membranes. At the same time, it is known that a decrease in the overoxidation level is accompanied by the attenuation of inflammatory processes. That is why the antioxidant therapy is the most effective if it can support a normal overoxidation level and thus treat a wide spectrum of pathological conditions.

To analyze the therapeutic activity of compositions based on NSS-fullerene it is necessary to compare their characteristics at atomic level with those related to fullerene-based drugs experienced in practice. Molecular-colloid solutions containing hydrated C_{60} molecules (C_{60}HyFn=C_{60}{H_2O}n) [27, 48–51] seem to be a proper analog. A wide spectrum of positive therapeutic effects of C_{60}HyFn administered in small doses, sometimes comparable with homeopathic ones, led the authors of [50] to assume that "…the C_{60}HyFn show "wise" and long-term anti-oxidative activity, maybe due to the universal mechanism of the level regulation of free radicals (FR) in aqueous medium that is determined by properties of ordered water structures".

The above peculiarities of the antioxidant action of C_{60}HyFn are undoubtedly associated with the C_{60} molecule being virtually free within the hydrate complex. Fullerosil and fullerosilica gel are expected to exhibit a similar antioxidant activity due to the weak binding between the fullerene molecules and solid carrier. As to the specific and "wise" action of C_{60} fullerene, it is clearly associated with the radical-type properties of the C_{60} molecule so that the mechanism of the scavenging action of the C_{60} molecule and its hydrate complex is obvious. Given that each C_{60} molecule is capable of trapping tens of radicals, it becomes self-evident why its antioxidant ability increases with the concentration of reactive oxygen-containing species.

What remains unclear is the regulatory function of the fullerene. In the case of C_{60}HyFn hydrates, the feature is connected with a particular role of the ordered water structure that influences a recombination of free radicals. As for NSS compositions, some clues as to how this function is realized can be obtained by examining the interaction of a fullerene molecule with a PNSS particle. As can be seen in Fig. 6, the fullerene molecule tears the hydroxyl group away from the surface silicon atom while interacting with either a silanol or a silanediols group. Note, however, that the energies of these reactions differ significantly, even in sign. Thus, while in the former case, it is energetically more favorable for the fullerene molecule to return the hydroxy group back to the surface, in the latter one, it is more profitable to retain it. Since the electronic characteristics of the radical on the surface (the charges on the atoms, bond lengths, and valence indices) are similar in both cases, the distinctions in the character of the intermolecular interaction are probably associated with a cooperative effect, the characteristics of which are determined by the

configuration of the atoms surrounding the attacked hydroxyl radical. In our opinion, it does not seem farfetched to assume that similar cooperative effects in a biological medium will accompany the absorptive and regulatory functions of a fullerene molecule as an antioxidant.

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Структури фулеренів в медичній хімії

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Стаття присвячена квантово-хімічному розгляду двох аспектів наномедицини фулерену, які стосуються його оксидативної та антиоксидативної функцій. Перший аспект розглянуто по відношенню до фотодинамічного терапевтичного ефекту розчинів фулерену. Запропоновано новий механізм цього ефекту. Другий аспект обговорюється на прикладі двох комплексів фулерену з кремнеземом: фулеросилу та фулеросилікагелю.

Структуры фуллеренов в медицинской химии

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Статья посвящена квантово-химическому рассмотрению двух аспектов наномедицины фуллерена, относящихся к его оксидативной и антиоксидантной функциям. Первый аспект рассмотрен применительно к фотодинамическому терапевтическому эффекту растворов фуллерена. Предложен новый механизм этого эффекта. Второй аспект обсуждается на примере двух комплексов фуллерена с кремнеземом: фуллеросила и фуллеросиликагеля.