

## ENDOHEDRAL COMPLEXES OF FULLERENE C<sub>60</sub> WITH SMALL CONVALENT MOLECULES (H<sub>2</sub>O, NH<sub>3</sub>, H<sub>2</sub>, 2H<sub>2</sub>, 3H<sub>2</sub>, 4H<sub>2</sub>, O<sub>2</sub>, O<sub>3</sub>) IN THE CONTEXT OF POTENTIAL DRUG TRANSPORTER SYSTEM

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**Abstract:** The fullerene C<sub>60</sub> has chemical properties which seem to predestinate it to be effective transporter of drugs in biological system. To prove this, the DFT/B3LYP (6-31G\*) calculations were performed especially in order to determine the structures and energies of the inclusion complexes of C<sub>60</sub> with small molecules. It was found that the small molecule is more compact when it is located in the centre of the C<sub>60</sub> cage than as isolated molecule. The calculated inclusion energies in case of: H<sub>2</sub>O, NH<sub>3</sub>, O<sub>2</sub>, O<sub>3</sub>, H<sub>2</sub>, 2H<sub>2</sub>, 3H<sub>2</sub>, 4H<sub>2</sub> are: 1.84, 3.81, 3.75, 21.07, 1.97, 20.10, 47.78 and 77.54 kcal/mol, respectively. The charge transfer and the influence of the complexed small molecules on the electrostatic potential distribution inside and outside of the C<sub>60</sub> cavity are discussed.

**Keywords:** endohedral fullerene, drug transporter, charge transfer

Cisłowski found that C<sub>60</sub> cage could act as a polarizable sphere that stabilizes the polar molecules and destabilizes the non-polar (or weakly polar) ones. These results indicate that formation of the endohedral complexes, from nonpolar or slightly polar molecules such as H<sub>2</sub>, N<sub>2</sub> and CO separated molecules is an endothermic process. The C<sub>60</sub> can stabilize molecules such as HF and LiH, encased inside its skeleton (1).

Pupysheva et al. studied the possible structure and stability of nH<sub>2</sub>O@C<sub>60</sub> where n represents the number of H<sub>2</sub>O molecules encapsulated in C<sub>60</sub> (2).

Ren and Liu (3) investigated the endohedral complex of fullerene C<sub>60</sub> with N<sub>4</sub> using hybrid DFT-B3LYP functional in conjunction with 6-31G (d) basis sets. Their results prove that formation of the endohedral complexes consisting of N<sub>4</sub> and C<sub>60</sub> is an endothermic process with destabilization energies of 37.92 kcal/mol (3). Shameema et al. studied the encapsulation of molecule NH<sub>3</sub> inside the C<sub>60</sub> cage (4). Ganji et al. studied the possibility of formation of endohedral complexes of NH<sub>3</sub> and C<sub>60</sub>. The DFT calculations showed that maximum of 7 ammonia molecules inside the C<sub>60</sub> cage have metastable structures (5). Their observations are in contrast with the semi-empirical results of Erkoç and Türker (6) that

have demonstrated that (NH<sub>3</sub>)<sub>n</sub>@C<sub>60</sub>, where n = 1 - 6 are thermodynamically unstable but kinetically stable.

Türker and Erkoç studied the possible structure and stability of n H<sub>2</sub>@C<sub>60</sub> where n represents the number of H<sub>2</sub> molecules encapsulated in C<sub>60</sub>. Their calculations at the level of AM1 (RHF) level show that the structures of n H<sub>2</sub>@C<sub>60</sub> (n: 9, 12, 15, 19, 21, 24) are stable but highly endothermic (7).

One of the most important challenges for today's medicinal chemistry seems to be development of effective transporter of drug molecules on the whole their pathway to the therapeutic target. Taking into account the desirable structural properties one expects that just fullerenes may be effective transporter of many drugs. Drug placed inside fullerene cage could be isolated from external environment and due to that protected from inactivation during transport. Additionally, such transport of drug might significantly reduce its toxicity and, at the same time, the relatively strong intermolecular interaction may extra activated transported molecules by increasing their energy (8). It is also worthy to notice the important property of such transporter system, from toxicological point of view, that the endohedral fullerenes can

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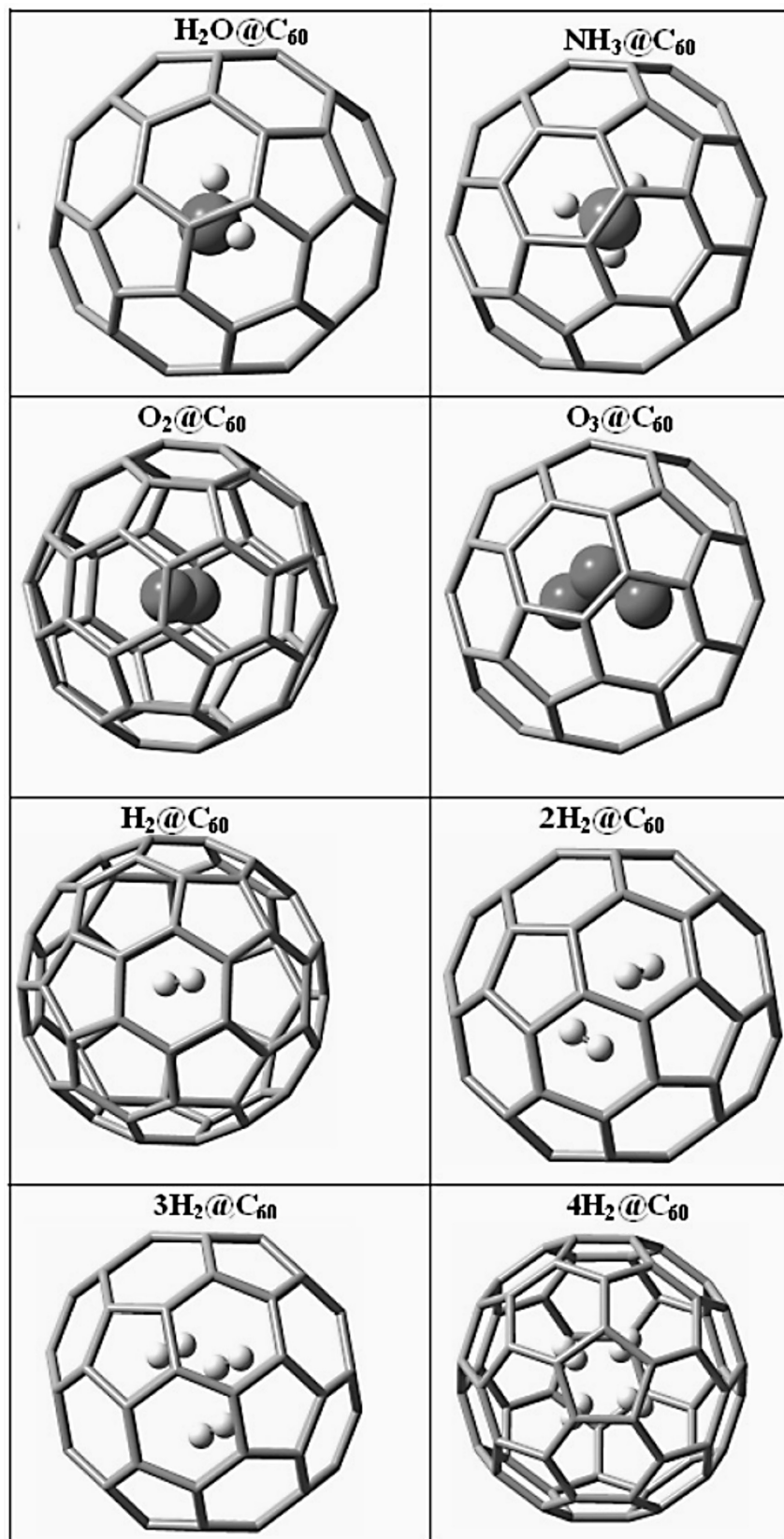


Figure 1. The B3LYP/6-31G(d) optimized geometries of endohedral complexes

be removed from organism after the drug has been released (9, 10).

Here, we studied the endohedral complexes of fullerene C<sub>60</sub> with small molecules. The molecular characteristics like stabilization energy, electrostatic potential of C<sub>60</sub> cage and the charge-transfer mechanism are studied and discussed here.

## METHODOLOGY

Calculations of energies of the inclusion complexes of C<sub>60</sub> with small molecules were carried out with the GAUSSIAN 03W (11) and the Spartan 08 (12) program packages. Quantum mechanics provides an efficient theory to describe and understand the structures of endohedral complexes. The success of a computational study depends on the careful selection of the methodology. Here the geometries

of endohedral complexes were optimized with the hybrid functional B3LYP in 6-31G\* basis set. The minimum of total potential energy of endohedral complexes we determined by full geometry optimization with B3LYP/6-31G\* method.

## RESULTS AND DISCUSSION

### Optimized equilibrium parameters

The B3LYP/6-31G (d) optimized equilibrium structures of endohedral complexes are shown in Figure 1.

The equilibrium parameters of isolated small molecules and encaged small molecules are listed in Table 1.

The fullerene cage and the encaged small molecules undergo small structural changes what is an indication of the weak interaction.

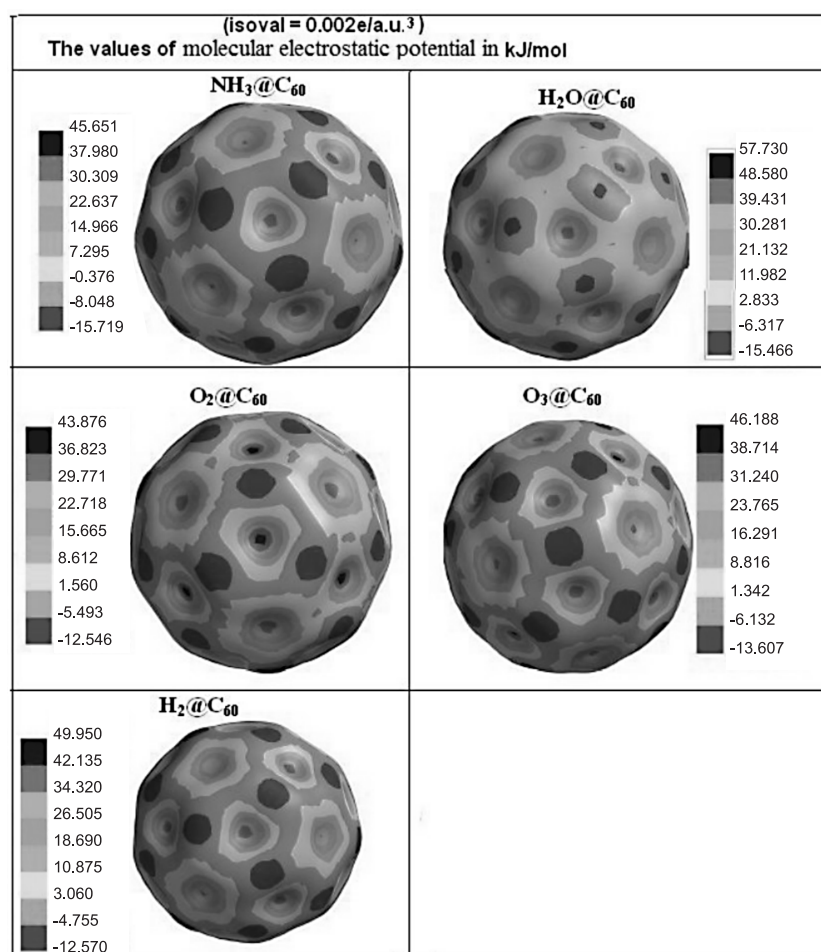


Figure 2. Electron density from total density (mapped with electrostatic potential) for endohedral fullerenes.

Table 1. The B3LYP/6-31G(d) optimized geometry parameters (length of bond in Å and bond angles in degrees).

	H <sub>2</sub> O	H <sub>2</sub> O@C <sub>60</sub>		NH <sub>3</sub>	NH <sub>3</sub> @C <sub>60</sub>
r H-O	0.969	0.968	r N-H	1.020	1.017
$\alpha$	103.659	104.395	$\alpha$	105.751	105.277
	O <sub>3</sub>	O <sub>3</sub> @C <sub>60</sub>		O <sub>2</sub>	O <sub>2</sub> @C <sub>60</sub>
r O-O	1.264	1.264	r O-O	1.216	1.216
$\alpha$	117.939	115.241			
	H <sub>2</sub>	H <sub>2</sub> @C <sub>60</sub>			
r H-H	0.743	0.741			

Table 2. Total energies ( $E_{\text{tot}}$  in a.u.) and distortion energies in kcal/mol of covalent molecules at the B3LYP/6-31G (d) level.

	$E_{\text{tot}}$ of covalent molecule calculated in optimized geometry ( $E_{\text{tot}}$ in a.u.)	$E_{\text{tot}}$ of covalent molecule calculated in distorted geometry of the complex ( $E_{\text{tot}}$ in a.u.)	Distortion energies of covalent molecule (in kcal/mol)
H <sub>2</sub> O	-76.408946	-76.408932	0.01
H <sub>2</sub>	-1.175484	-1.175482	0.00
O <sub>2</sub>	-150.257426	-150.257426	0.00
NH <sub>3</sub>	-56.547941	-56.547903	0.02
O <sub>3</sub>	-225.406422	-225.405847	0.36
2H <sub>2</sub>	-2.350931	-2.342239	5.45
3H <sub>2</sub>	-3.526445	-3.501990	15.34
4H <sub>2</sub>	-4.701916	-4.658330	27.35

Table 3. Total energies ( $E_{\text{tot}}$  in a.u.) of C<sub>60</sub> and distortion energies of C<sub>60</sub> in kcal/mol at the B3LYP /6-31G (d) level.

	$E_{\text{tot}}$ of C <sub>60</sub> calculated in optimized geometry ( $E_{\text{tot}}$ in a.u.)	$E_{\text{tot}}$ of C <sub>60</sub> calculated in distorted geometry of the complex ( $E_{\text{tot}}$ in a.u.)	Distortion energies of C <sub>60</sub> (in kcal/mol)
H <sub>2</sub> O@C <sub>60</sub>	-2286.174363	-2286.174171	0.12
H <sub>2</sub> @C <sub>60</sub>		-2286.173993	0.23
2H <sub>2</sub> @C <sub>60</sub>		-2286.173681	0.43
3H <sub>2</sub> @C <sub>60</sub>		-2286.172554	1.14
4H <sub>2</sub> @C <sub>60</sub>		-2286.171609	1.73
O <sub>2</sub> @C <sub>60</sub>		-2286.174334	0.02
NH <sub>3</sub> @C <sub>60</sub>		-2286.174312	0.03
O <sub>3</sub> @C <sub>60</sub>		-2286.173708	0.81

Table 4. Distortion energies in kcal/mol at the B3LYP /6-31G (d) level.

	Distortion energies of encapsulated molecules in kcal/mol)	Distortion energies of C <sub>60</sub> (in kcal/mol)	Sum of distortion energies of encapsulated molecules and distortion energies of C <sub>60</sub> ( in kcal/mol)
<b>H<sub>2</sub>O@C<sub>60</sub></b>	0.01	0.12	0.13
<b>H<sub>2</sub>@C<sub>60</sub></b>	0.00	0.23	0.23
<b>O<sub>2</sub>@C<sub>60</sub></b>	0.00	0.02	0.02
<b>NH<sub>3</sub>@C<sub>60</sub></b>	0.02	0.03	0.05
<b>O<sub>3</sub>@C<sub>60</sub></b>	0.36	0.81	1.17
<b>2H<sub>2</sub>@C<sub>60</sub></b>	5.45	0.43	5.88
<b>3H<sub>2</sub>@C<sub>60</sub></b>	15.34	1.14	16.48
<b>4H<sub>2</sub>@C<sub>60</sub></b>	27.35	1.73	29.08

Table 5. Total energies (E<sub>tot</sub> in a.u.), inclusion energies (E<sub>inclu</sub> in kcal/mol) and interaction energies in kcal/mol of the endohedral fullerenes at the B3LYP /6-31G (d) level.

Complex	E <sub>tot</sub> in a.u	E <sub>inclu</sub> in kcal/mol	Interaction energy in kcal/mol
<b>H<sub>2</sub>O@C<sub>60</sub></b>	-2362.586250	-1.84	-1.97
<b>H<sub>2</sub>@C<sub>60</sub></b>	-2287.346706	1.97	1.74
<b>2H<sub>2</sub>@C<sub>60</sub></b>	-2288.493259	20.10	14.22
<b>3H<sub>2</sub>@C<sub>60</sub></b>	-2289.624663	47.78	31.30
<b>4H<sub>2</sub>@C<sub>60</sub></b>	-2290.752704	77.54	48.46
<b>O<sub>2</sub>@C<sub>60</sub></b>	-2436.425818	3.75	3.73
<b>NH<sub>3</sub>@C<sub>60</sub></b>	-2342.716229	3.81	3.76
<b>O<sub>3</sub>@C<sub>60</sub></b>	-2511.547214	21.07	19.90

Table 6. Natural charge populations of separated and encapsulated small molecules at the B3LYP /6-31G (d) level.

	Charge			Total charge
<b>H<sub>2</sub>O</b>	<b>O</b> - 0.774		<b>H</b> 0.387	<b>H<sub>2</sub>O</b> 0.000
<b>H<sub>2</sub>O @C<sub>60</sub></b>	<b>O</b> - 0.808		<b>H</b> 0.409	<b>H<sub>2</sub>O</b> 0.010
<b>H<sub>2</sub></b>			<b>H</b> 0.000	<b>H<sub>2</sub></b> 0.000
<b>H<sub>2</sub>@C<sub>60</sub></b>			<b>H</b> -0.002	<b>H<sub>2</sub></b> -0.004
<b>NH<sub>3</sub></b>	<b>N</b> -0.888		<b>H</b> 0.296	<b>NH<sub>3</sub></b> 0.000
<b>NH<sub>3</sub>@C<sub>60</sub></b>	<b>N</b> -0.958		<b>H</b> 0.320	<b>NH<sub>3</sub></b> 0.002
<b>O<sub>3</sub></b>	<b>O</b> -0.116	<b>O</b> -0.116	<b>O</b> 0.232	<b>O<sub>3</sub></b> 0.000
<b>O<sub>3</sub>@C<sub>60</sub></b>	<b>O</b> -0.171	<b>O</b> -0.171	<b>O</b> 0.202	<b>O<sub>3</sub></b> -0.140
<b>O<sub>2</sub></b>			<b>O</b> 0.000	<b>O<sub>2</sub></b> 0.000
<b>O<sub>2</sub>@C<sub>60</sub></b>			<b>O</b> 0.001	<b>O<sub>2</sub></b> 0.002

Our observations confirm that small molecules are more compact when placed inside a fullerene cavity than when they are separated (3, 5). Ren and Liu (3) demonstrated that the shortened N-N bond length in  $N_4@C_{60}$  may suggest that the N-N bonds in  $N_4$  are strengthened by the fullerene cage or that the fullerene cage may stabilize the highly labile tetrahedral  $N_4$  molecule.

Son and Sung (13) calculated the exohedral and endohedral complexation energies of complexes of  $X@C_{60}$  between fullerene and rare gas atoms. They found that there exist two minima energies in potential surface; exohedral complexation energy ( $E_{exo}$ ) which is located in the outside of the  $C_{60}$  molecule between 6.5 and 7.5 Å and endohedral complexation energy ( $E_{endo}$ ) which is located in the centre of the  $C_{60}$  molecule (13).

Encapsulated molecule is stabilized in the centre of the carbon cage and is unbound to  $C_{60}$ .

### Stability

Here we use the following notation: Inclusion energy ( $E_{inclu}$ ) of the  $A@C_{60}$  endohedral fullerenes were calculated as a difference:

$$E_{inclu} = E(A@C_{60}) - [E(A) + E(C_{60})].$$

where:  $E(A@C_{60})$  is the total energy of the complex  $A@C_{60}$ ,  $E(A)$  is the total energy of the isolated molecule  $H_2O$ ,  $NH_3$ ,  $H_2$ ,  $2H_2$ ,  $3H_2$ ,  $4H_2$ ,  $O_2$ ,  $O_3$ ,  $E(C_{60})$  is the total energy of the isolated molecule  $C_{60}$ .

The thermodynamical stability is expected to produce negative  $E_{inclu}$  value. The more negative value of  $E_{inclu}$ , the more stable the endohedral derivative is expected. In contrast, a positive  $E_{inclu}$  defines an unstable endohedral derivative. The calculated energies of endohedral complexes,  $C_{60}$  and small molecules are presented in Tables 2-5.

Formation of the endohedral complexes from the small molecule and  $C_{60}$  separated molecules is the process with the inclusion energies of -1.84 kcal/mol for  $H_2O$ , 3.81 kcal/mol for  $NH_3$ , 3.75 kcal/mol for  $O_2$ , 21.07 kcal/mol for  $O_3$ , 1.97 kcal/mol for  $H_2$ , 20.10 kcal/mol for  $2H_2$ , 47.78 kcal/mol for  $3H_2$  and 77.54 kcal/mol for  $4H_2$ .

### Electron density from total density (mapped with electrostatic potential)

The negative electrostatic potential corresponds to an area of concentrated electron density in the molecules. The positive electrostatic potential corresponds to an area of the low electron density in the molecules.

Electron density from total density (mapped with electrostatic potential) for endohedral fullerenes are presented in Figure 2.

The minimum values of molecular electrostatic potential in case of:  $NH_3@C_{60}$ ,  $H_2O@C_{60}$ ,  $O_3@C_{60}$ ,  $H_2@C_{60}$ ,  $O_2@C_{60}$  are: -15.719, -15.466, -13.607, -12.570, -12.546 kJ/mol, respectively. The maximum values of molecular electrostatic potential in case of:  $O_2@C_{60}$ ,  $NH_3@C_{60}$ ,  $O_3@C_{60}$ ,  $H_2@C_{60}$ ,  $H_2O@C_{60}$  are: 43.876, 45.651, 46.188, 49.950, 57.730 kJ/mol, respectively. The value of molecular electrostatic potential of  $C_{60}$  correlates with partial charges. The changes in the value of molecular electrostatic potential of endohedral fullerenes result from the value of molecular electrostatic potential around encapsulated molecule.

Ren and Liu studied the molecular electrostatic potential of  $N_4@C_{60}$ . Their results indicate that each N atom in encapsulated  $N_4$  molecule gains (-0.012) of charge units from the  $C_{60}$  skeleton (3).

Table 6 summarizes the natural charge population of small molecules (isolated and encapsulated into the  $C_{60}$  cage).

Natural population analysis of endohedral fullerenes proves that the negative charge is transferred from fullerene  $C_{60}$  cage to the encapsulated molecules ( $O_3@C_{60}$ ,  $H_2@C_{60}$ ) and from encapsulated molecules to the fullerene  $C_{60}$  cage ( $NH_3@C_{60}$ ,  $O_2@C_{60}$ ,  $H_2O@C_{60}$ ).

The values of natural charge population on the guest species inside the  $C_{60}$  skeleton decrease in the series as follows:  $O_3$  (-0.140),  $H_2$  (-0.004),  $NH_3$  (0.002),  $O_2$  (0.002),  $H_2O$  (0.010) (cf. Table 6).

### CONCLUSIONS

From analysis of the obtained results the following can be concluded: (i) among the all studied complexes only  $H_2O@C_{60}$  complex has negative inclusion energy; (ii) the remained studied complexes have only slightly positive inclusive energies which, above all, do not mean that these complexes are unstable on account of the expected high energetic barrier of transfer of even small molecules through the wall of fullerene cage; (iii) all complexes are stabilized by universal interactions and all molecules forming complex are deformed in comparison with their structures in unbound state.

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