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## Nanostructures of PAMAM Dendrimers in Drug Delivery System for 5-Fluorouracil

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*Abstract.* In this article, we studied five noncovalent structures for adsorption of 5 fluorouracil drug (5 FL) on poly(amidoamine) G0 generation dendrimer (PAMAMG0) carrier using M06-2X and B3LYP functionals. We investigate the quantum molecular descriptors and the binding and solvation energies in gas phase and aqueous solution. The energetic stability of non-bonded species (PAMAMG0/5-FL1-5) was shown through evaluation of binding free energies. The solvation free energies of PAMAMG0/5-FL1-5 are negative, indicating that the solvation process is spontaneous. We considered quantum molecular descriptors such as electrophilicity power and global hardness and found reduced toxicity of 5-FL drug near PAMAMG0 carrier as well as facilitated drug release. The AIM (Atoms In Molecule) analysis for all PAMAMG0/5-FL1-5 structures demonstrated that the pseudo-hydrogen and hydrogen bonds are essential in the functionalization of PAMAMG0 with 5-FL drug. We found that the structure in which 5-FL drug interacts with CO functional groups of PAMAMG0 is the most stable configuration.

*Keywords:* poly(amidoamine) dendrimer, 5-fluorouracil, nanomedicine, hydrogen bonding, DFT.

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# Наноструктуры дендримеров ПАМАМ в системе доставки лекарств для 5-фторурацила

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*Аннотация.* В этой статье мы изучили пять нековалентных структур для адсорбции лекарственного средства 5-фторурацила (5 FL) на носителе дендримеров поколения поли (амидоамина) G0 (РАМАМG0) с использованием функционалов M06-2X и B3LYP. Мы исследуем квантовые молекулярные дескрипторы и энергии связывания и сольватации в газовой фазе и водном растворе. Энергетическая стабильность несвязанных частиц (РАМАМG0 / 5-FL1-5) была показана путем оценки свободных энергий связи. РАМАМG0 / 5-FL1-5 отрицательны, что указывает на самопроизвольный процесс сольватации. Мы рассмотрели квантовые молекулярные дескрипторы, такие как мощность электрофильности и общая жесткость, и обнаружили сниженную токсичность препарата 5-FL вблизи носителя РАМАМG0, а также облегчение высвобождения лекарства. Анализ AIM (атомы в молекуле) для всех структур РАМАМG0 / 5-FL1-5 продемонстрировал, что псевдоводородные и водородные связи важны для функционализации РАМАМG0 лекарственным средством 5-FL. Мы обнаружили, что структура, в которой препарат 5-FL взаимодействует с функциональными группами CO РАМАМG0, является наиболее стабильной конфигурацией.

*Ключевые слова:* поли (амидоамин) дендример, 5-фторурацил, наномедицина, водородная связь, DFT.

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## 1. Introduction

An attempt to alleviate the side effects of anticancer medications, a bulk of experimental and theoretical research has recently concentrated on carbon-based carriers such as dendrimers [1], drug-polymer conjugates [2], liposomes [3], C60 [4, 5], carbon nanotubes [6-8] and polymeric micelles [9]. One of the method of drug delivery is the use of micro and nano sized particles [10]. Utilization of dendrimers as a host for different molecules, such as drugs, and investigation of the role of hydrogen bonding in these drug delivery systems were started in 1995 [11, 12]. With a highly symmetric structure,

dendrimers have well-defined nanostructure [13]. In fact, dendrimers describe a family of synthetic polymers that are highly branched three-dimensional structures in nature. The word dendrimer comes from the Greek word “Dendron” meaning tree; it gives a clear description of their unique structure that represents a tree-like branch [14].

Generally, a dendrimer consists of three parts; (a) a basic core that contains two or more reactive groups; (b) interior layers made up of recurring branching units that are covalently bonded to the core; and (c) terminal functional groups that are located on the outer surface [14]. The peripheral surface group is able to define the nature of dendrimer and forges bonds with branched units related to each generation. Depending on the core, 3 or 4-branched units are added to dendrimer core to create the first generation and then the two other branched units are added to each monomer of former generation to produce the second generation. Therefore, dendrimer diameters increase linearly along with an exponential growth of terminal functional groups by the addition of shells or generation [15].

Given that their physico-chemical properties are markedly different from classic polymers, they are often perceived as a distinct class of molecules. This disparity has its origin in three key properties: monodispersity, multivalency, and globular shape [16]. Based on the shape of dendrimer, it is possible to determine the specific binding of functional groups on the surface and the interior structure of dendrimer. Dendrimers are mainly found in two shapes: i) spherical shape, ii) ellipsoid shape [15]. The spherical structure together with empty spaces and a high-density functional group (like amine and carboxyle group) on the surface of dendrimer facilitates the solubility of hydrophobic drug, control the release of drug and foster the suitability of dendrimer for desired theranostic purpose [17]. The solubility of dendrimer is determined by a number of factors such as surface functional groups, repeated units, dendrimer generation, and even the core [18].

These molecules have broad applications such as drug delivery where dendrimer nanoparticles are infused with therapeutics and target specific tissues or gene delivery which is similar to drug delivery [19]. When dendrimers are used as the nanocarriers, lower dosages of anticancer drugs are needed, which in turn would alleviate the side effects of the medicine [20-22]. Dendrimers serve as carriers for various anticancer drugs such as 5-fluorouracil [23], cisplatin [24, 25], doxorubicin [26-28], famotidine [29], methotrexate [30], nifedipine [31], paclitaxel [32, 33], 10-hydroxycamptothecin [34], 7-butyl-10-aminocamptothecin [35], etoposide [36], artemisinin [37], flutamide [38], melphalan [39], gemcitabine [40], capecitabine [41] and 6-mercaptopurine [42]. Dendrimers have also been used against human immunodeficiency viruses (HIV) [43-45], Alzheimer’s disease [46, 47], prion diseases [48, 49], inflammation [50-52] and bacteria [53-55]. Quantum computing provides a powerful instrument for the analysis of drug delivery and other systems [56-63]. Fluorouracil (5-FU) that is found under the brand Adrucil, is an anticancer drug used for esophageal, colon, stomach [64] breast, pancreatic, and cervical cancers [64]. Moreover, as a cream it is utilized for basal cell carcinoma, actinic keratosis and skin warts [65]. In this paper, quantum chemical calculations were applied to investigate the host-guest interactions of PAMAMG0 generation dendrimer with 5-fluorouracil drug.

## 2. Computational method

First, we used GAUSSIAN 09 package [66, 67] for the optimization of all structures in solution and gas phases at B3LYP/6-31G(d,p) and M06-2X/6-31G(d,p). Polarized continuum model (PCM)

[68, 69] was employed the implicit solvent effects. Herein, we used the standard convergence criteria for the optimization of molecular structures. We optimized all degrees of freedom for all species. In addition, frequency calculations were performed to apply thermal corrections.

For assessing chemical reactivity and stability, the quantum molecular descriptors were used. Global hardness ( $\eta$ ) exhibits the resistance of one particle against the modification in its electronic structures:

$$\eta = \frac{(1 - A)}{2}. \quad (1)$$

In which  $A = -E_{LUMO}$  and  $I = -E_{HOMO}$  are the electron affinity and the ionization potential, respectively. Evaluating electrophilicity index ( $\omega$ ) is performed by the following formula [70]:

$$\omega = \frac{(1 + A)^2}{8\eta}. \quad (2)$$

Using the QTAIMs (Quantum Theory of Atoms in Molecules) calculations, the hydrogen bonds were studied. For performing QTAIM, we used the AIMII software [71]. QTAIM depends on topological parameters such as electron density  $\rho(r)$  [72]. We concentrate on different values of electron density such as  $V_b$  (potential energy density),  $H_b$  (total energy density),  $G_b$  (kinetic energy density), and  $\nabla^2\rho$  (Laplacian of electron density) at a critical point (BCP) to recognize the nature of the bond in various species.

### 3. Results and exchanges

Figure 1 shows the optimized structures of Poly(amidoamine) G0 generation dendrimer (PAMAMG0) and 5-fluorouracil (5-FL). We studied the interaction of 5-FL including CO and NH functional groups with PAMAMG0 nanoparticles in 5 different ways (PAMAMG0/5-FL1-5). The optimized configurations of PAMAMG0/5-FL1-5 are shown in Fig. 2 (at M06-2X / 6-31G\*\* in aqueous solution).

Binding (interaction) free energies ( $\Delta G_{binding}$ ) were calculated using the following equation:

$$\Delta G_{binding} = GPAMAMG0/5-FL1-5 - (GPAMAMG0 + G5-FL). \quad (3)$$

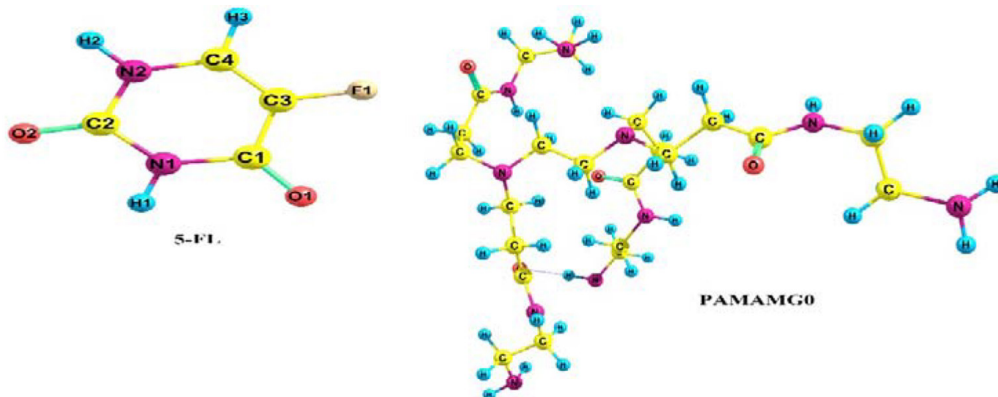


Fig. 1. Optimized structures of 5-FL and PAMAMG0

$G_{binding}$  values at M06-2X and B3LYP levels in gas phase and aqueous solution are shown in Table 1. Contrary to B3LYP, M06-2X functional considers dispersion corrections [73]. The values of  $G_{binding}$  in aqueous solution (-41.3 kJ mol<sup>-1</sup> and -49.0 kJ mol<sup>-1</sup> on average at B3LYP and M06-2X) are more positive than those of gas phase (-57.4 kJ mol<sup>-1</sup> and -51.3 kJ mol<sup>-1</sup> on average at B3LYP and M06-2X). These values are negative in both phases, therefore the adsorption of 5-FL on PAMAMG0 is spontaneous and the dispersion corrections in aqueous solution emerge as attractive forces. Comparing these values with the values obtained from other sources that examined the interaction of PAMAM nanocarrier with other molecules, shows that the values of  $G_{binding}$  are in the same range [74-77]. The values of the binding free energies indicate that the 5-FL drug is loading well on the PAMAMG0 carrier because  $G_{binding}$  is an indicator of drug loading [78, 79].

It is observed that  $G_{binding}$  depends on the orientation of 5-FL relative to PAMAMG0. As shown by both B3LYP and M06-2X levels and both phases, among 5 structures, PAMAMG0/5-FL1 is the most stable ones where the NH functional group of 5-FL interacts with the CO functional groups of PAMAMG0 (Fig. 2). According to our research, PAMAMG0/5-FL4 and PAMAMG0/5-FL3

Table 1. Binding ( $\Delta G_{binding}$ ) and solvation ( $\Delta G_{solv}$ ) free energies in kJ mol<sup>-1</sup> for optimized geometries

Species	$\Delta G_{binding}^{B3LYP}$ gas	$\Delta G_{binding}^{B3LYP}$ H <sub>2</sub> O	$\Delta G_{binding}^{M062X}$ gas	$\Delta G_{binding}^{M062X}$ H <sub>2</sub> O	$\Delta G_{solv}^{B3LYP}$	$\Delta G_{solv}^{M062x}$
PAMAMG0/5-FL1	-82.53	-44.91	-77.68	-71.57	-120.70	-124.08
PAMAMG0/5-FL2	-12.83	-9.05	-23.32	-17.95	-154.54	-124.82
PAMAMG0/5-FL3	-71.25	-83.93	-25.14	-24.25	-122.73	-129.29
PAMAMG0/5-FL4	-51.88	-32.40	-59.74	-61.46	-138.83	-131.91
PAMAMG0/5-FL5	-68.38	-36.01	-70.84	-69.62	-125.94	-128.97

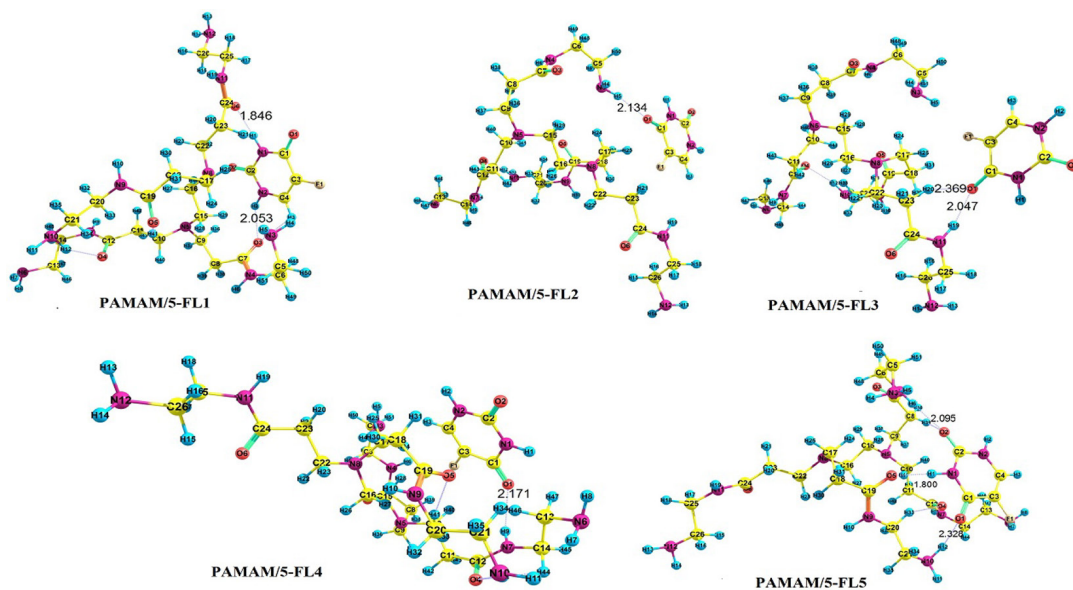


Fig. 2. Optimized structures of PAMAMG0/5-FL1-5

configurations in terms of stability and in the aqueous solution are located in the second and third positions, respectively.

Using the following equation, the solvation free energies ( $\Delta G_{solv}$ ) have been assessed (Table 1):

$$\Delta G_{solv} = G_{ag} - G_{gas}. \quad (4)$$

In which  $G_{ag}$  and  $G_{gas}$  demonstrate the free energies in the aqueous solution and gas phase, respectively. The large negative values of solvation free energies of PAMAMG0/5-FL1-5 demonstrate that the solvation process is spontaneous and it signifies the solubility of PAMAMG0/5-FL1-5 configuration in solution phase.

Table 2 depicts the quantum molecular descriptors including global hardness ( $\eta$ ), electrophilicity power ( $\omega$ ) and  $E_g$  (energy gap between LUMO and HOMO) for 5-FL, PAMAMG0 and PAMAMG0/5-FL1-5 in aqueous solution and gas phase at M06-2X and B3LYP levels.

As shown in the Table 2,  $E_g$  and  $\eta$  values of 5-FL and PAMAMG0 are almost the same. They were decreased in PAMAMG0/5-FL1-5 structures. In other words, there may be an insignificant charge transfer between the carrier and the drug. This may be perfect for a drug delivery system, because 5-FL drug can be easily released from the exterior surface of the PAMAMG0 carrier.  $E_g$  and  $\eta$  values of PAMAMG0/5-FL1 is more than other structures, showing that it is more stable than other structures. Toxicity prediction using  $\omega$  showed that the toxicity of 5-FL drug is decreased near the PAMAMG0 carrier. The  $\omega$  values of PAMAMG0/5-FL1-5 are higher than those of 5-FL, indicating that 5-FL is the electron acceptor in these configurations.

Table 2. Quantum molecular descriptors (eV) for optimized geometries

Species	$E_{HOMO}$	$E_{LUMO}$	$E_g$	$\eta$	$\omega$	Species	$E_{HOMO}$	$E_{LUMO}$	$E_g$	$\eta$	$\omega$
	B3LYP-H2O						M06-2X-H2O				
PAMAMG0	-5.44	-4.48	6.04	3.02	0.97	PAMAMG0	-7.09	1.79	8.88	4.44	0.79
5-FL	-6.61	-1.23	5.38	2.69	2.86	5-FL	-8.07	-0.12	7.95	3.98	2.11
PAMAMG0/5-FL1	-5.40	-0.99	4.41	2.20	2.31	PAMAMG0/5-FL1	-7.0.9	0.05	7.14	3.57	1.74
PAMAMG0/5-FL2	-5.40	-1.37	4.04	2.02	2.84	PAMAMG0/5-FL2	-7.04	-0.28	6.76	3.38	1.99
PAMAMG0/5-FL3	-5.33	-1.33	4.00	2.00	2.77	PAMAMG0/5-FL3	-7.11	-0.43	6.68	3.34	2.13
PAMAMG0/5-FL4	-5.55	-1.32	4.23	2.11	2.79	PAMAMG0/5-FL4	-7.32	-0.21	7.11	3.56	1.99
PAMAMG0/5-FL5	-5.45	-1.26	4.19	2.10	2.68	PAMAMG0/5-FL5	-7.11	0.02	7.13	3.57	1.76
	B3LYP-GAS						M06-2X-GAS				
PAMAMG0	-5.04	0.75	5.79	2.90	0.79	PAMAMG0	-6.91	1.45	8.36	4.18	0.89
5-FL	-6.79	-1.39	5.40	2.70	3.10	5-FL	-8.25	-0.26	7.99	4.00	2.26
PAMAMG0/5-FL1	-5.31	-0.40	4.73	2.37	1.62	PAMAMG0/5-FL1	-6.89	0.23	7.13	3.56	1.56
PAMAMG0/5-FL2	-4.86	-1.78	3.08	1.54	3.58	PAMAMG0/5-FL2	-6.77	-0.65	6.12	3.06	2.25
PAMAMG0/5-FL3	-5.37	-1.01	4.36	2.18	2.33	PAMAMG0/5-FL3	-6.98	-0.93	6.05	3.02	2.59
PAMAMG0/5-FL4	-5.14	-1.37	3.78	1.89	2.81	PAMAMG0/5-FL4	-6.71	-0.64	6.07	3.04	2.22
PAMAMG0/5-FL5	-5.09	-1.16	3.93	1.97	2.48	PAMAMG0/5-FL5	-6.73	-0.24	6.49	3.24	1.87



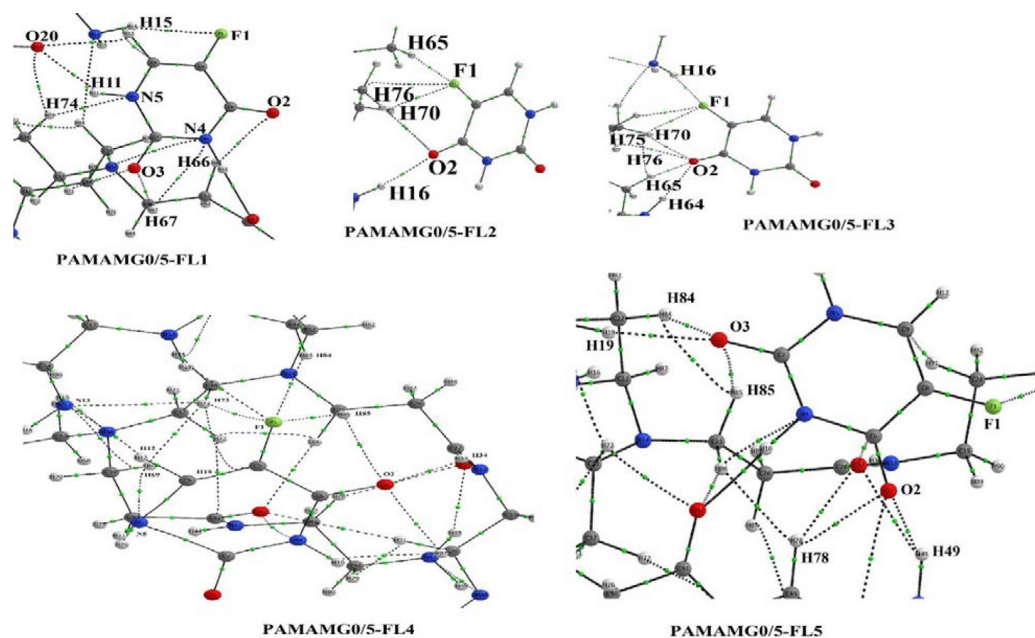


Fig. 3. Molecular graph of PAMAMG0/ 5-FL1-5. Small green spheres and lines related to the bond critical points (BCP) and the bond paths, respectively

For exploring the intermolecular hydrogen bonds in detail, we used the charge density properties. In addition, we utilized QTAIM analysis to study the interactions. The strength and characteristic of an interaction can be determined by  $\rho(r)$  and  $\nabla^2\rho(r)$ , respectively [80]. In other words, it is possible to show the interactions by the signs of  $\nabla^2\rho$  and  $H_b$ . If, ( $\nabla^2\rho > 0, H_b > 0$ ), ( $\nabla^2\rho > 0, H_b < 0$ ) and ( $\nabla^2\rho < 0, H_b < 0$ ), weak, medium and strong interactions are expected, respectively.

In addition,  $-G_b/V_b$  demonstrates the characteristics of an interaction. Moreover  $-G_b/V_b > 1$  and  $0.5 < -G_b/V_b < 1$  explain noncovalent and partially covalent characters, respectively. Figure 4 shows the molecular graphs of PAMAMG0/5-FL1-5 in aqueous solution at M06-2X/6-31G(d,p). In these Figures, the atoms included in the interaction of the drug with the carrier are marked. Table 3 shows the values of  $\nabla^2\rho(r)$ ,  $\rho(r)$ ,  $-G_b/V_b$  and  $H_b$ ,  $G_b$  and  $V_b$  for these interactions at M06-2X level in aqueous solution. The following equation was used to assess the hydrogen bond energies ( $E_{HB}$ ).

$$E_{HB} = \frac{1}{2V_b}. \quad (5)$$

We observed three major types of hydrogen bonds (O-H, N-H, F-H) in PAMAMG0/5-FL1-5 structures. First, the most stable structure (PAMAMG0/5-FL1) was evaluated for this purpose, where the NH functional group of 5-FL approaches CO functional groups of PAMAMG0. The H10...O57 ( $E_{HB} = -33 \text{ kJ mol}^{-1}$ ) interactions with, and  $0.5 < -G_b/V_b < 1$  lead to medium hydrogen bonds and the (H95...N35) with  $-G_b/V_b = 0.9824$  may be close to strong hydrogen bonds. Furthermore, the N5...H74, F1...H15, H11...O20, O3...H71, N4...H67, O3...H67 and O2...H66 interactions ( $E_{HB(\text{average})} = -10.57 \text{ kJ mol}^{-1}$ ) with  $\nabla^2\rho > 0, H_b > 0$  and  $-G_b/V_b > 1$  result in weak hydrogen bonds.

We found that PAMAMG0/5FL4-5 structures have similar stability. In these configurations CO functional group of 5-FL interacts with NH functional groups of PAMAMG0. PAMAMG0/5FL4

Table 3. Topological parameters in a.u. and the hydrogen bond energy ( $E_{HB}$ ) in  $\text{kJ mol}^{-1}$  for PAMAMG0/5-FL1-5 at M06-2X in aqueous solution

Atoms	$\rho(r)$	$\nabla_p^2(r)$	$G_b$	$V_b$	$H_b$	$-G_b/V_b$	$E_{HB}$
PAMAMG0/5-FL1							
N5 – H74	0.0108	0.0342	0.0077	-0.0068	0.0009	1.1258	-8.9666
F1 – H15	0.0076	0.0346	0.0074	-0.0062	0.0012	1.1917	-8.1888
H11 – O20	0.0205	0.0716	0.0177	-0.0174	0.0002	1.0140	-22.8302
O3 – H71	0.0100	0.0333	0.0076	-0.0070	0.0007	1.0981	-9.1200
N4 – H67	0.0077	0.0307	0.0063	-0.0049	0.0014	1.2888	-6.3711
H10 – O57	0.0324	0.0969	0.0247	-0.0251	-0.0004	0.9824	-32.9193
O3 – H67	0.0084	0.0284	0.0064	-0.0058	0.0007	1.1176	-7.5502
O2 – H66	0.0116	0.0385	0.0090	-0.0084	0.0006	1.0746	-10.9705
PAMAMG0/5-FL2							
O2 – H76	0.0085	0.0299	0.0066	-0.0057	0.0009	1.1516	-7.5331
O2 – H16	0.0156	0.0527	0.0130	-0.0128	0.0002	1.0133	-16.8302
F1 – H70	0.0071	0.0330	0.0068	-0.0054	0.0014	1.2682	-7.0518
O2 – H70	0.0083	0.0306	0.0066	-0.0055	0.0011	1.1926	-7.2433
F1 – H65	0.0096	0.0391	0.0089	-0.0081	0.0008	1.1045	-10.6085
PAMAMG0/5-FL3							
O2 – H70	0.0066	0.0248	0.0053	-0.0043	0.0009	1.2206	-5.6420
F1 – H70	0.0077	0.0355	0.0074	-0.0058	0.0015	1.2603	-7.6538
F1 – H16	0.0097	0.0394	0.0091	-0.0084	0.0007	1.0879	-10.9849
F1 – H76	0.0078	0.0354	0.0075	-0.0061	0.0014	1.2283	-7.9738
O2 – H75	0.0080	0.0309	0.0065	-0.0053	0.0012	1.2276	-6.9666
O2 – H65	0.0122	0.0390	0.0094	-0.0090	0.0004	1.0393	-11.8531
O2 – H64	0.0197	0.0610	0.0156	-0.0160	-0.0004	0.9758	-21.0006
PAMAMG0/5-FL4							
N5 – H69	0.0149	0.0561	0.0122	-0.0104	0.0018	1.1765	-13.6066
H12 – N13	0.0200	0.0508	0.0134	-0.0141	-0.0007	0.9497	-18.5010
F1 – H19	0.0094	0.0389	0.0089	-0.0081	0.0008	1.1024	-10.5915
F1 – H84	0.0119	0.0466	0.0110	-0.0103	0.0007	1.0649	-13.5161
F1 – H85	0.0088	0.0358	0.0079	-0.0068	0.0011	1.1552	-8.9639
O2 – H85	0.0069	0.0229	0.0050	-0.0043	0.0007	1.1731	-5.5843
O2 – H92	0.0096	0.0327	0.0073	-0.0065	0.0008	1.1283	-8.5233
O2 – H34	0.0152	0.0548	0.0131	-0.0124	0.0006	1.0498	-16.3239
N5 – H76	0.0115	0.0379	0.0083	-0.0071	0.0012	1.1674	-9.2970
F1 – H73	0.0048	0.0216	0.0043	-0.0032	0.0011	1.3544	-4.1377
PAMAMG0/5-FL5							
O3 – H19	0.0161	0.0558	0.0137	-0.0134	0.0003	1.0203	-17.5725
O3 – H84	0.0127	0.0403	0.0098	-0.0095	0.0003	1.0308	-12.4446
O3 – H85	0.0090	0.0327	0.0070	-0.0059	0.0011	1.1909	-7.7574
F1 – H30	0.0107	0.0432	0.0101	-0.0094	0.0007	1.0734	-12.3580
H10 – O42	0.0320	0.1123	0.0266	-0.0251	0.0015	1.0584	-32.9823
O2 – H79	0.0094	0.0372	0.0080	-0.0067	0.0013	1.1901	-8.8433
O2 – H78	0.0077	0.0285	0.0061	-0.0052	0.0010	1.1891	-6.7816
O2 – H49	0.0127	0.0435	0.0104	-0.0099	0.0005	1.0497	-12.9639



has 1 medium hydrogen bond with  $E_{\text{HB}} = -18.5 \text{ kJ mol}^{-1}$  and  $-G_b/V_b = 0.9497$ , the attributes of which are similar to strong hydrogen bonds. Other structures (N5...H69, F1...H19, F1...H84, F1...H85, O2...H92, O2...H85, O2...H34, N5...H76, and F1...H73) are arranged as weak hydrogen bonds. PAMAMG0/5FL5 has two interactions whose characteristics are close to the medium hydrogen bonds (H10...O42, H19...O3) and the other six interactions are weak.

The third most stable configuration is PAMAMG0/5-FL3. The O2...H64 ( $E_{\text{HB}} = -21 \text{ kJ mol}^{-1}$ ) interaction with,  $0.5 < -G_b/V_b < 1$  is medium hydrogen bonds and six other including O2...H70, F1...H70, F1...H16, F1...H76, O2...H75, O2...H65 are weak. PAMAMG0/5-FL2 has the most unstable structure with  $E_{\text{HB}}(\text{average}) = -9.28 \text{ kJ mol}^{-1}$ .

### Conclusions

This work explored five structures of noncovalent adsorption of 5-fluorouracil (5-FL) drug on poly(amidoamine) G0 generation dendrimer (PAMAMG0) at B3LYP and M06-2X density functional levels in gas and aqueous solution phase (PAMAMG0/5-FL1-5). By interaction of two CO functional groups of PAMAMG0 with NH functional group of 5-FL simultaneously, it leads to the most stable structure (PAMAMG0/5-FL1).

Given the values of solvation and binding free energies, the functionalization of PAMAMG0 with 5-fluorouracil drug would be suitable in energies. The average value of  $\Delta G_{\text{binding}}$  calculated at M06-2X functional is more negative than those of B3LYP in solution phase. Unlike B3LYP, dispersion corrections are considered by M06-2X functional. Considering  $\Delta G_{\text{solv}}$  of PAMAMG0/5-FL1-5, it is observed that the solvation process is spontaneous. The HOMO-LUMO energy gap indicated that the global hardness and the toxicity of 5-FL in PAMAMG0/5-FL1-5 decreased. Furthermore, considering the AIM studies, 5-FL can be non-covalently functionalized on PAMAMG0/5-FL through hydrogen and pseudo-hydrogen bonds. The outcomes demonstrated that the most stable structures leads to stronger and more hydrogen bonds (PAMAMG0/5-FL1).

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