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Adsorption of Cisplatin Molecules in Nanoporous Inorganic Materials as Drug Delivery Vehicles

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Abstract: The use of nanoparticles as anticancer cargo systems for drug delivery is a promising modality, as they avoid the known toxicity of anticancer drugs on healthy cells by the delivery of multiple drugs to the target cells. Here, the adsorption behavior of cisplatin drug molecules in two different inorganic materials, silica and metallic gold, is investigated mathematically. The 6–12 Lennard-Jones potential, together with the continuum approximation, is adapted to calculate the molecular interatomic energies between molecules. For each material, the relation between the pore radius ℓ and the minimum energy is determined, and the results indicate that the minimum energy occurs when the radii are $\ell = 5.3$ and $\ell = 4.7$ Å for the silica and gold nanopores, respectively. The method is promising for applications in the design of novel nanocapsules for future targeted drug and gene delivery.

Keywords: mathematical modeling; cisplatin molecule; continuum approximation; inorganic materials; drug delivery; Lennard-Jones potential

MSC: 92-XX; 92-10

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1. Introduction

Cisplatin (Cis) is a well-known chemotherapeutic drug, $Pt(NH_3)_2Cl_2$, and it is used to treat a variety of human cancers, including testicular, lymphoma, ovarian, head and neck, bladder, lung, and ovarian cancers [1]. Cis was first synthesized in 1844 by Michele Peyrone, and in 1893, A. Werner introduced the first chemical structure of the Cis drug [1]. The discovery of anticancer cisplatin attracted tremendous attention as scientists strove to understand the mechanism of action of the drug in the body to tear down tumor cells. Due to the side effects of the cisplatin drug, such as gastrointestinal disorders, kidney issues, allergic reactions, decreased immunity to infections, considerable damage to cells, and possible oxidative DNA death, the encapsulation of the drug in nanocontainers and nanocontainers' use as drug carriers might reduce the harmful side effects and protect healthy cells by helping them reach the target cells (tumor cells). Several nanoparticles have been used in the medical field as drug-delivery carriers, such as inorganic materials, lipid particles, and nanotubes [2–5]. Inorganic materials, such as silica (SiO_2) and metallic gold (Au), have several important properties and potential applications, and they can be used in medicine for drug-delivery systems [2]. Silica nanopore has a number of properties making it one of the safest drug carriers, such as its high biocompatibility, which makes it safe to be taken up by living cells [6,7]. Furthermore, gold has good biofunctionalization properties, thus rendering its nanostructures useful in the field of medicine for drug-delivery carriers [8,9]. Gold nanomaterials can be utilized as effective agents for therapy and diagnostics of the cancers and can be easily linked to antibodies [10]. In addition, gold nanoparticles are highly biocompatible; thus, they are absorbed in the systemic circulation, which gives enough time for the absorption of the photosensitizing material into the cancer tissue. Moreover, gold nanoparticles induce radiation effects over a large cancer

area [11]. The gold nanoparticles have optical properties that can be used in imaging-based therapeutic techniques and ultrasensitive detection for the treatment of some diseases, such as cancer [11]. Nejad and Urbassek used molecular dynamics (MD) simulation to study the adsorption and diffusion behavior of the Cis drug in SiO_2 nanopores with a pore radius range of 4–10 Å. They showed that the size of the pore radius influences the diffusion and storage of Cis in the SiO_2 nanocontainer [12]. Moreover, Nejad and Urbassek investigated the adsorption and diffusivity of cisplatin in different inorganic nanopores with radii of 10 Å, including silica and metallic gold. Using MD simulations, they showed that the interactions of Cis with Au nanopores were the strongest [13]. Rejeeth et al. used aminopropyltriethoxysilane to attach the Cis drug as a linker molecule to SiO_2 nanoparticles with diameters ranging from 20 to 90 nm and characterized in terms of shape and size and the disintegration of Cis on the surface of SiO_2 [14]. Their results showed that the rate of Cis dissolution from the particle surface to the solution phase depends on the surface area of the particles. Watermann and Brieger demonstrated that the mesoporous silica nanoparticles are biocompatible and biodegradable and can be used as drug carriers to reduce the side effects and improve the efficacy of the drugs [15]. Lu et al. utilized mesoporous SiO_2 as a carrier for the camptothecin drug by setting it into the holes and delivering it to the tumor cells. They showed that during the transport of the drug, it remained in the nanoparticles and was released in the region of the cancer cells [16]. The major goal of this study was to computationally examine the energetics of the Cis drug adsorption onto two inorganic nanopore materials to obtain a favorable size of the nanopore, where SiO_2 and Au were used as nanocontainers for drug carriers to transport the antitumor to cancer tissues, which can help reduce the side effects of the drugs. The knowledge of the ideal nanomaterials and pore radius to encapsulate the anticancer drug and carry it to the target cells (using, for example, this study) might give insights on how to reduce the side effects and avoid the problem of nonspecific toxicity. In this paper, applied mathematical modeling is used to investigate the interactions between the Cis molecule and SiO_2 and Au nanocontainers. The system considered here contains large amounts of atoms; therefore, the use of molecular dynamics (MD) or atomistic modeling might be computationally expensive. Theoretical methods can look at the loading and unloading of molecular cargo and they have obtained reasonable agreement with the other modelling approaches which have been conducted through experimental and MD simulations. Furthermore, mathematical models can be used to provide overall guidelines for future related MD simulations and experimental. Ferrari states that, in order to secure the full import of nanotechnology into oncology, novel mathematical models are needed [17]. In terms of a mathematical model, the Lennard-Jones (LJ) function with continuum approximation was applied to calculate interaction energies between the Cis drug and the nanocontainers.

2. Modeling Approach

The van der Waals forces were used to determine the biophysical model of the interactions of the cisplatin molecule onto the silica and gold nanopores. The 6–12 LJ potential and a continuum approximation were applied to determine the molecular interatomic energies between the molecules (here, drug and inorganic materials). The LJ is given by:

$$W(c) = -\frac{A}{c^6} + \frac{B}{c^{12}},$$

where c is the distance between two atoms and A and B are, respectively, the attractive and repulsive parameters computed by $A = 4DR^6$ and $B = 4DR^{12}$, where D is the energy well-depth and R is the van der Waals diameter, and their values are taken from [18], as shown in Table 1.

Table 1. The values of van der Waals diameter and well-depth used in this work [18].

Atom Type	Si	O	Au	H	N	Pt	Cl
D (kcal/mol)	0.402	0.060	0.039	0.044	0.069	0.080	0.227
R (Å)	4.295	3.500	3.293	2.886	3.660	2.754	3.947

Employing a continuum approach, it was assumed that the atoms at discrete positions on the molecules were averaged over the volumes or surfaces. The interaction energies are given by computing integrals over the volume or surface of molecules, expressed as:

$$E_t = \lambda_1 \lambda_2 \int_{\Sigma_1} \int_{\Sigma_2} \left(-\frac{A}{c^6} + \frac{B}{c^{12}} \right) d\Sigma_2 d\Sigma_1, \tag{1}$$

where λ_1 and λ_2 indicate the mean volume or mean surface density of atoms on each molecule, and they can be calculated by dividing the total number of the atoms over the volume or the surface area of the molecules. With reference to Figure 1, the SiO_2 and Au were assumed to be modeled as a box with dimensions $(L \times L \times H)$ [12,13], as well as by proposing a mathematical model to configure the drug molecule in a sphere shape [19]. For convenience, the Cis-nanoparticle was assumed initially at rest, and the calculations herein are assumed to be in a vacuum to prevent improper interactions, noting that nanoparticles might be provided a means of delivery without the need to include solvents, which can cause damages to healthy cells in the drug itself, that is, because the unaltered Cis molecule might be moved through cell membranes and interact within the cell. Further, using the Cartesian coordinate system (x, y, z), the center of the box pore was assumed to be located coaxially on the z-axis with dimensions 2ℓ in height, 2ℓ in width, and H in length, where ℓ is the radius of the pore. Consequently, the coordinates of an arbitrary point on each side of the pore are (ℓ, y, z), $(-\ell, y, z)$, (x, ℓ, z), and $(x, -\ell, z)$. Next, the molecular interaction energies of the Cis molecule onto the SiO_2 and Au blocks were determined, where the energy contribution of the drugs and the cylindrical hole of the inorganic materials were assumed to arise only from the surfaces; consequently, a surface integral was applied.

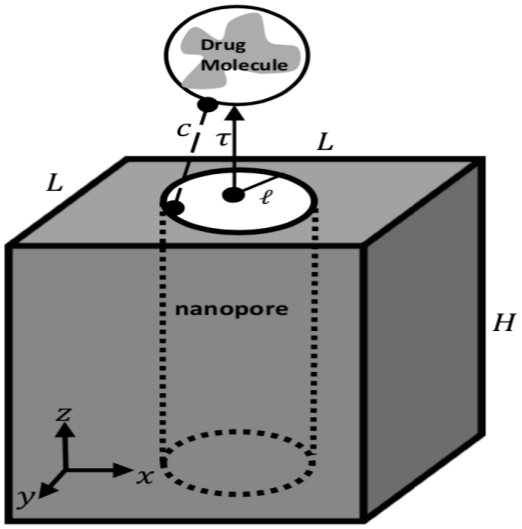


Figure 1. Optimized geometry of the adsorption of the drug molecule onto SiO_2 and Au nanopores.

Therefore, the molecular interaction energy E_{SP} was determined for a point with coordinates $(0,0,\tau)$ and a sphere that has the coordinates (a,β,γ), where a is the sphere radius, $\beta \in (0,\pi]$, and $\beta \in [-\pi,\pi]$, as depicted in Figure 2. We introduce the integral I_m as:

$$\begin{aligned} I_m &= a^2 \int_{-\pi}^{\pi}\int_{0}^{\pi} \frac{\sin\beta}{c^{2m}}\, d\beta\, d\gamma \\ &= a^2 \int_{-\pi}^{\pi}\int_{0}^{\pi} \frac{\sin\beta}{\left[a^2\sin^2\beta + (a\cos\beta-\tau)^2\right]^m}\, d\beta\, d\gamma. \end{aligned}$$

Therefore,

$$\begin{aligned} E_{SP} = -4\pi a^2\lambda_1\Bigg\{ A\left[\frac{1}{(c^2-a^2)^3} + \frac{2a^2}{(c^2-a^2)^4}\right] + \frac{B}{5}\Bigg[\frac{5}{(c^2-a^2)^6} + \frac{80a^2}{(c^2-a^2)^7} + \\ \frac{336a^4}{(c^2-a^2)^8} + \frac{512a^6}{(c^2-a^2)^9} + \frac{256a^8}{(c^2-a^2)^{10}}\Bigg]\Bigg\}, \end{aligned} \tag{2}$$

where λ_1 is the mean surface density of atoms on the sphere molecule. Thus, the total interactions E_t between the SiO_2 block and the spherical Cis were obtained:

$$E_t = -4a\pi\lambda_{Cis}\lambda_M\left[A\left(K_3 + 2a^2K_4\right) - \frac{B}{5}\left(5K_6 + 80a^2K_7 + 336a^4K_8 + 512a^6K_9 + 256a^8K_{10}\right)\right], \tag{3}$$

where $K_\alpha = \frac{1}{(c^2-a^2)^\alpha}$, $(\alpha \in \{3,4,6,7,8,9,10\})$, and λ_{Cis} is the mean surface density of the Cis molecule and λ_M is the mean surface density of the SiO_2 or Au nanopore. Now, to complete Equation (3), the integral K_n needs to be found and may be expressed as:

$$K_n = \int_R \frac{1}{(c^2-a^2)^n}\, dR, \tag{4}$$

where the positive integer n corresponds to the power of the polynomials, as shown in Figure 2.

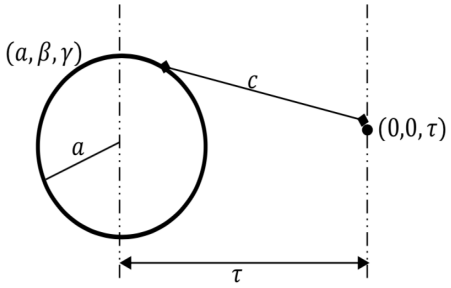


Figure 2. Schematic for a point interacting with a sphere of radius a.

The Cis molecule is centered at $(0,0,\tau)$, where τ is the perpendicular distance from the center of the drug molecule to the pore on the upper surface of the box, and H denotes the length of the box. The negative or positive sign of τ is determined as to whether the drug molecule is inside or outside the cylindrical pore. Further, a typical point on the surface of the cylindrical hole has the coordinates $(x,y,-z) \equiv (\alpha\cos\phi, \alpha\sin\phi, -z)$, where $z \in (0,H)$, H denotes the length, $\alpha \in (\ell,\infty)$, and ℓ is the radius of the pore. Thus, the distance c between the centre of the Cis drug and the surface element of the pore is given by $c = \sqrt{\alpha^2 + (\tau+z)^2}$, and the integral K_n becomes:

$$\begin{aligned} K_n &= \int_0^{2\pi}\int_\ell^\infty\int_0^H \frac{\alpha}{\left[\alpha^2 + (\tau+z)^2 - a^2\right]^n}\, dz\, d\alpha\, d\phi \\ &= \frac{1}{n-1}\int_0^H \frac{1}{\left[\ell^2 + (\tau+z)^2 - a^2\right]^{n-1}}\, dz. \end{aligned} \tag{5}$$

On making the substitution $u = \tau + z$, the integral K_n becomes:

$$K_n = \frac{1}{n-1} \int_{\tau}^{\tau+H} \frac{1}{\left[\ell^2 - a^2 + u^2\right]^{n-1}} \, du, \tag{6}$$

and again making the substitution $u = \sqrt{\ell^2 - a^2} \tan\psi$, K_n becomes:

$$K_n = \frac{\pi}{(n-1)(\ell^2 - a^2)^{n-2}} \int_{\tan^{-1}\left(\frac{\tau}{\sqrt{\ell^2-a^2}}\right)}^{\tan^{-1}\left(\frac{\tau+H}{\sqrt{\ell^2-a^2}}\right)} \cos^{2n-4}\psi \, d\psi \tag{7}$$

$$= \frac{\pi}{(n-1)(\ell^2 - a^2)^{n-2}} \int_{\tan^{-1}\left(\frac{\tau}{\sqrt{\ell^2-a^2}}\right)}^{\tan^{-1}\left(\frac{\tau+H}{\sqrt{\ell^2-a^2}}\right)} \cos^{2q}\psi \, d\psi, \tag{8}$$

where $q = n - 2$, and this integral can be found by using Formula 2.513.3 (p. 153) from [20], from which we may deduce:

$$\int \cos^{2q}\psi \, d\psi = \frac{1}{2^{2q}} \binom{2q}{q} \psi + \frac{1}{2^{2q-1}} \sum_{k=0}^{q-1} \binom{2q}{k} \frac{\sin(2q-2k)\psi}{2q-2k}, \tag{9}$$

where $\binom{p^*}{q^*}$ is the usual binomial coefficients. The results and discussion of this method are presented in the following section.

3. Results and Discussion

The interaction energies of the Cis molecule with two inorganic materials (SiO_2 and Au) were determined using Maple software, and the values of the constants are given in Tables 1 and 2. We comment that as we proposed a mathematical model, not all interactions were taken into account, such as the solvent, where the encapsulation of the drug is assumed occur within a vacuum and under isothermal conditions. We hope that the use of the nanoparticle for drug delivery might avoid the need for a solvent medium by providing a protected environment for the drug molecule. The numerical energies of the adsorption of the drug molecule onto two different materials were calculated using the analytical expressions derived in the modeling approach, and they are present in the following subsections.

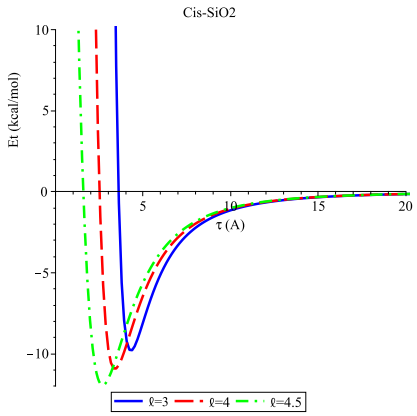
Table 2. Approximate numerical values for the constants used in this work.

Mean atomic surface density for SiO_2	$\lambda_{SiO_2} = 0.386$ Å^2[21]
Mean atomic surface density for Au	$\lambda_{Au} = 0.1065$ Å^2 [22]
Mean atomic surface density for Cis	$\lambda_{Cis} = 11/66.48 \approx 0.165$ Å^2
Radius of Cis molecule	$a = 2.3$ Å [19]

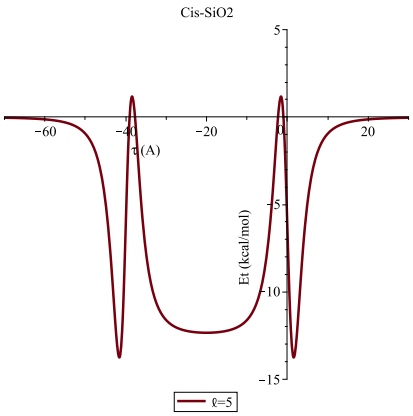
3.1. Adsorption of Cis onto SiO_2 Nanopore

Figure 3 shows the relation between the total interaction and the perpendicular distance τ for various values of the hole radius ℓ. As shown in Figure 3a,b, the Cis molecule was located above the SiO_2 surface, which corresponds to a positive value of the distance τ for the range of 3–5 Å of the pore radius. Consequently, the Cis drug did not penetrate through the SiO_2. Further, when the Cis was located closer to the SiO_2 surface, the minimum values of the energy became smaller as the radius of the hole increased, due to the lower repulsive force from the surface of the SiO_2. The center of the Cis molecule was located at the origin $\tau = 0$ Å of the silica, when $\ell = 5.2$ Å. Once $\ell > 5.2$ Å, the Cis drug penetrated through the SiO_2, and the energy profiles were as shown in Figure 3c–e.

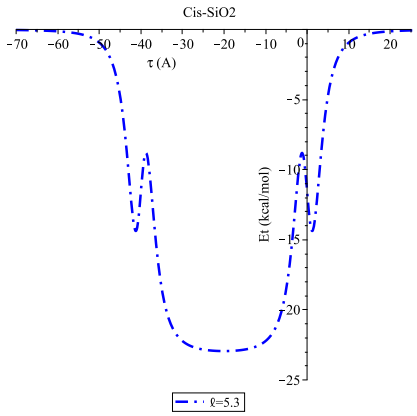
As can be seen from Figure 3c, although the Cis molecule confronted the energy barrier at the origin $\tau = 0$ Å with radius $\ell = 5.3$ Å, it penetrated the SiO_2. Moreover, the results observe that the most favorable radius of the pore that allowed the Cis to move through the SiO_2 nanopores was ≈5.5 Å when the minimum energy occurred, as shown in Figure 3d. For the pore radius $\ell = 10$ Å, the total energy was around -6 kcal/mol. By comparing it with the works by Neiad et al. [12,13], where they showed that the energy between the Cis molecule and the silica nanopores was approximately -7.5 kcal/mol, it can be seen that the results are in excellent agreement.



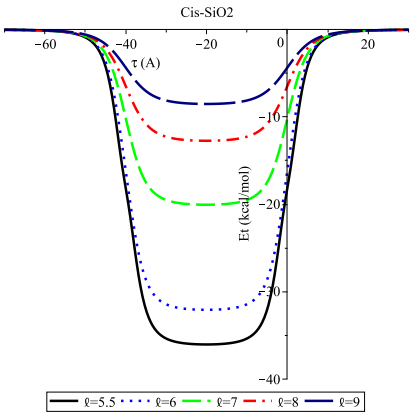
(**a**) $\ell = 3$–4.5 Å



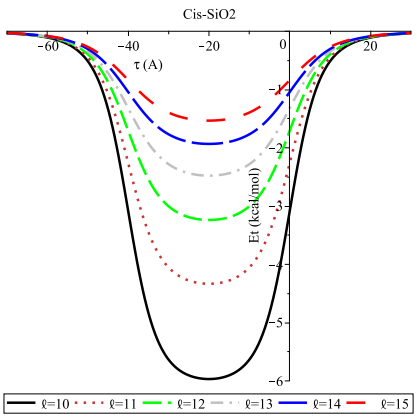
(**b**) $\ell = 5$ Å



(**c**) $\ell = 5.3$ Å



(**d**) $\ell = 5.5$–9 Å

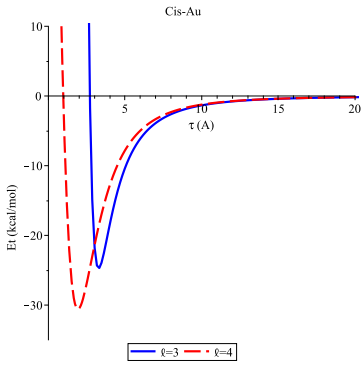


(**e**) $\ell = 10$–15 Å

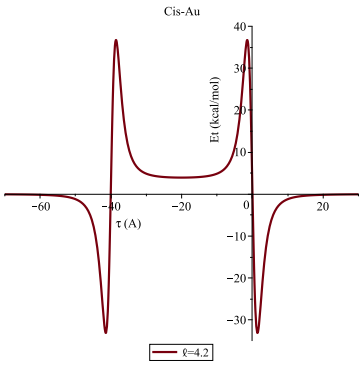
Figure 3. Energies of Cis molecule and SiO_2 nanopore of different radii ℓ with respect to the distance τ.

3.2. Adsorption of Cis onto Au Nanopore

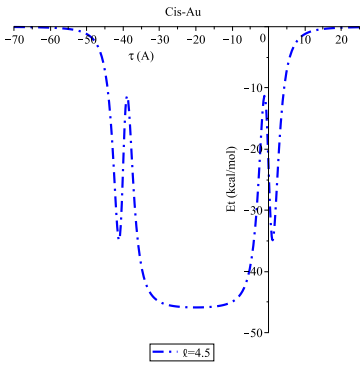
Figure 4 shows the relationship between the distance τ and the interaction energy E_t for different values of the hole radius ℓ. In addition, Figure 4a,b shows that the Cis drug did not move through the Au nanopores with radii less than ≈4.3 Å. The interaction energy changed with the distance of the Cis molecule to the wall and the size of the pore radius. Furthermore, the minimum energy position moved closer to the surface of the Au as the pore radius increased. Once the pore radius was >4.4 Å, the Cis molecule jumped into the Au, facing the energy barrier at the origin $\tau = 0$ Å, when the hole radius was equal to 4.5 Å, as shown in Figure 4c–e. In addition, the results indicate that the optimal size of the hole radius was around $\ell = 4.7$, where the minimum energy occurred. Here, for the pore radius $\ell = 10$ Å, the value of the energy was approximately -7 kcal/mol and this result was in excellent agreement with Neiad et al. [13], where it had only -6 kcal/mol adsorption energy.



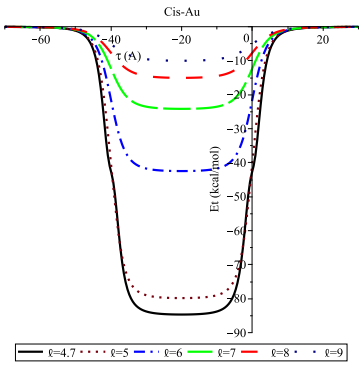
(**a**) $\ell = 3$ and 4 Å



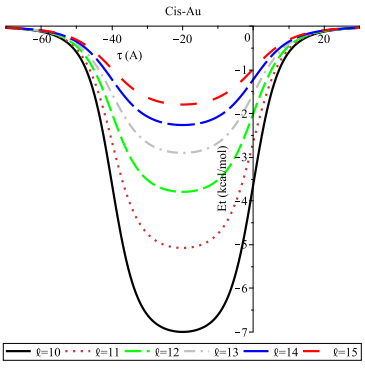
(**b**) $\ell = 4.2$ Å



(**c**) $\ell = 4.5$ Å



(**d**) $\ell = 4.7$–9 Å



(**e**) $\ell = 10$–15 Å

Figure 4. Energies of Cis molecule and Au nanopore of different radii ℓ with respect to the distance τ.

Note that the pore of the silica and gold nanoparticles was found with tunable pore diameters in the range of 20–500 Å for SiO_2 and 18–15,000 Å for Au [23,24]. Here, we comment that the interaction of both materials with Cis depends on the size of the pore radius, ℓ, and is sensitive to the LJ parameters, which are calculated by utilizing the values of the van der Waals diameter and the well depth. Moreover, the results show that the interactions of Au with Cis are stronger than that of the Cis with SiO_2, as the interaction energies between the Cis with Au gave the lowest minimum energy relative to the Cis with SiO_2, which is similar to the results in the study in [13]. In addition, as the radius of the nanopore for the SiO_2 and Au becomes larger, the energy needed to encapsulate the Cis molecule is no longer enough by interatomic forces alone, and as the nanopore radius increases, the energy approaches zero. Nevertheless, it is still energetically favorable for the Cis drug to load into the nanoparticles, and in principle, additional energy might be used for the drug molecule, but this may well involve some practical challenges. Furthermore, for both materials, SiO_2 and Au, the results show that the Cis drug molecule moves closer to the surfaces as the pore radius increases because of the lower repulsive force from the surface and the fact that Cis has more space to move through the hole. However, the presented results for the interaction of SiO_2 and Au nanoparticles with the Cis drug are not significantly different, especially in the cases of $\ell > 6$, where the SiO_2 might provide a more ideal delivery capsule than Au due to the cheaper synthesis costs. Notably, the physical parameters and geometric structure affect the interactions; therefore, in future works, we might discuss the different configurations of the Cis drug, such as a classic square planar molecule.

4. Summary

This work provides an energetic comparison for the penetration of cisplatin drug into two inorganic materials using the continuum approximation with the Lennard-Jones function to evaluate the van der Waals energy. The spacing τ between the Cis molecule and the two nanoparticles determined different values of the hole radius. The results showed that the equilibrium location of the Cis was closer to the surface of the SiO_2 and Au as the radius of the pore was larger. Moreover, the results found that the Cis molecule was located inside the SiO_2 and Au when the pore was large enough, around 5.3 Å for SiO_2 and 4.4 Å for Au (greater than the Cis radius). We conclude that silica and gold nanoparticles might be used as a container for cisplatin drugs and the optimal radii which give the minimum interaction energy are around 5.5 Å and 4.7 Å for SiO_2 and Au, respectively. Knowledge of the optimal radii may be useful to tailor the pores to adsorb the drug at the fastest rate and highest capacity. Finally, we comment that the nanocapsules can be designed in several structures for drug and gene delivery, and the model and results in this study can support other work on the loading of different drug molecules inside various type of nanoparticles and compare their results for efficiency by employing simple mathematical models rather than conducting extensive experimental tests.

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