Metal-Organic-Frameworks as potential nanocariers of anticancer drugs: Designing a bottom-up computational approach

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***Abstract*—**As a fundamental step for the controlled drug delivery of well-known anticancer drugs through Metals Organic Frameworks (MOFs), we have studied by ab initio Density Functional Theory (DFT), the biochemical interaction of a well-known anticancer drug, tamoxifen (TAM), with representative MOFs and amino acids, such as glycine (GLY), for various sites and ways of approach, using the hybrid PBE0 functional. We have located several active sites and we have calculated the interaction energy, which is of the order of 14-17 Kcal/mole, depending on site and orientation, indicating a rather strong primary hydrogen bonding, which is practically of the same order of magnitude with the GLY-MOFs interaction energy. It is concluded that MOFs should be considered as very promising drug delivery vehicles.

***Keywords*—**Anticancer drugs, Density Functional Theory, Drug Delivery, Metal Organic Frameworks.

I. Introduction

BESIDES surgery, which can remove cancer focuses (but cannot eliminate free cancer cells, which often lead to relapse), chemotherapy with anticancer drugs is the main auxiliary treatment for cancers. However, although chemotherapy can be successful in several cases, it often fails due to toxic and other side effects largely related to the lack of selectivity for cancerous and healthy tissues and cells. In addition, poor bioavailability (i.e. big doses only give low levels of drug in the body) and biostability or in vivo drug metabolism (it is readily metabolized) have severely limited the usefulness of existing key chemotherapy drugs. To face these problems, recent research efforts have been focused on the idea that (novel) nanomaterials can be used as drug delivery agents1. The potential advantages of this approach include the possibility of tailoring the materials to achieve delivery-site-specificity and assistance in achieving long-term sustained drug release at low dosages. Clearly there should be a strict set of criteria, including non-toxicity and consistent and controlled release of the drug, which must be met by any new nanomaterial drug delivery candidate. Ideally the drug delivery nanomaterial besides biocompatibility and non-toxicity should be characterized by:

1) High loading and protection of the desired guest molecule
2) Non premature release before reaching its target
3) Efficient cellular uptake
4) Efficient endosomal escape
5) Controllable rate of release to achieve an effective local concentration

and 6) Cell and tissue targeting.

Yet, it is not possible to fully and successfully meet all of these requirements, together at the same time and to the same (high) degree, especially high selectivity and zero side effects. This is why despite many astonishing advances in fundamental cancer biology; these results have not been translated into comparable clinical advances2. Initially organic nanoparticles such as liposomes and polymer drug conjugates were considered as drug delivering systems. Lately however, a large amount of research is focused in novel inorganic nanocarriers consisting of hollow nanoparticles or porous nanosystems. Such nanocarriers, which are schematically shown in Fig.1, have the added advantage of increased functionalization and properties tailoring by controlling, besides composition, the size and porocity of the nano-vehicle include (among others): (a) Carbon nanotubes [1]-[4] ; (b)Fullerenes [5]; (c) Magic core/shell CdSe/ZnS nanoparticles [6-7]; (d) Silver nanoparticles [8]; (e) Silicon nanoparticles and/or porous silica [9]; (f) Silicon nanowires [10] (g) Boron cages and carboranes [11], sometimes combined with other nanocarriers [12]; and more recently: (h)

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Graphene and graphene derivatives [13] (carbon fullerenes and nanotubes can be considered in the broad sense as graphene derivatives); as well as (i) Metal-organic-frameworks (MOFs) [14]-[16], which are our current interest [15]-[16]. The reason is that many of these proposed agents (a)-(g) have failed in one way or another, namely by not meeting satisfactorily one or more of the criteria mentioned above, one of which is the non-zero toxicity [3]-[4], [7]. However, it has recently been shown that hybrid Metal Organic Frameworks (MOFs) offer exciting potential in the drug delivery field by virtue of their low toxicity, high payloads and controlled drug release [14]-[15], [17]. MOFs are a novel family of hybrid inorganic–organic nanoporous materials with a three-dimensional periodic structure, consisting of inorganic primary building units (pbu) which are linked via secondary organic building units (sbu), commonly referred to as the organic linkers. MOFs have demonstrated regular tunable porosity with high loading capacities. Furthermore, the organic linker (sbu) is also highly tunable to the needs of both the drug and its delivery site. In addition, the physical characteristics of the MOFs are also highly adaptable and well-suited to the role of drug delivery agent (for example, simultaneous hydrophilic and hydrophobic character can be engineered to suit the aqueous environment of the body alongside those of a lipophilic drug candidate).

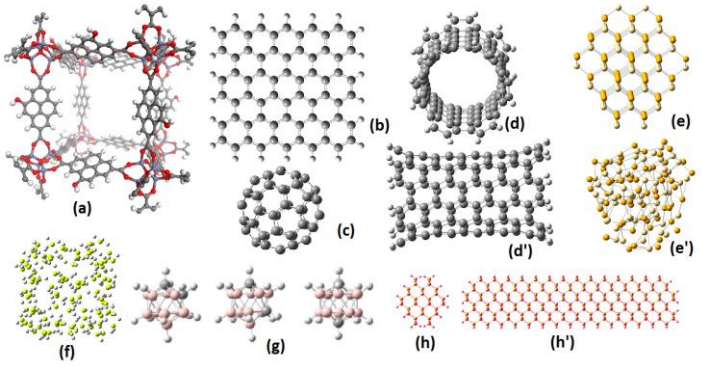

Fig. 1 Representative nanocarriers for drug delivery: (a) MOF, (b) graphene, (c) fullerene, (d) and (d') carbon nanotube (angle and side views), (e) and (e') CdSe nanoparticles, (f) silver nanoparticles, (g) carboranes, and (h) and (h') silicon nanowires (top and side views).

The present study constitutes a fundamental step towards the very ambitious "bottom up" ab initio approach of the general problem of drug delivery at the molecular if possible, not just the cellular, level. This problem at the fundamental level involves the study of three key characteristics: (a) the study of the interaction of the drug with the appropriate nanoparticle carrier, MOF in this case; (b) the understanding of the binding of the drug with the cell; and (c) the investigation of the direct interaction of the drug with the cell. Although the first problem (a) is relatively tractable (but not at all trivial) due to the small size of the drugs and the corresponding nanoparticles, the second and third problems are rather impossible and intractable, not only at the ab initio molecular level but also at the cellular or microscopic empirical regime, due the large size and complexity of the cell (and even more so of the tissue). In these cases, the theoretical description of the process is modeled by molecular dynamics (MD) and Monte-Carlo (MC) techniques, which often dramatically depend on several (many) empirical adjustable parameters, the choice of which can be obscure and/or biased. In the ab initio description, based in molecular Quantum Mechanics (QM), there are not any adjustable parameters. The only parameters entering the calculations (solution of the Schrödinger's equation) are the mass and charge of the electron, the atomic numbers, and some other fundamental physical constants such as Planks constant (h), the velocity of light(c), Boltzmann's constant (k), etc. In this approach the fundamental ingredients, at the zero level of complexity involve the interactions of the drug with the nanoparticle(s), and with representative amino acids, as the building blocks of the proteins, as well as the interaction of the nanoparticles with these amino acids. Obviously, to gradually build up the full complexity in the theoretical ab initio description we have to (and we plan to) use a multiscale approach in which any parameter entering the higher scale description (MD, MC) would be selfconsistently determined from the lower (more fundamental) level. Even so, this is still a very ambitious project, even a partial fulfillment of which, would be very important. Moreover, the fundamental interactions between amino acids and potential drugs or amino acids and potential nanocarriers are very important on their own merit in biochemistry. We have already performed preliminary studies of the interaction between Glycin and MOFs16, and between Tamoxifen and MOFs15. In the present work we study by ab initio density functional theory (DFT) the direct interaction of Glycin with Tamoxifen, as the third (but not final) fundamental step, towards the remote end of a (as much as possible) complete theoretical description and/or understanding of the delivery of Tamoxifen (and other potential drugs) by MOFs (and other potential nanocarriers) to the cell, even at ideal conditions. At the same time, we "renormalize" the GLY-MOFs and TAM-MOFs interactions to a uniform (and less expensive numerically) DFT/PBE0 framework with identical technical details (such as choice of basis sets, convergence criteria, etc.)

The key results of our calculations are presented and discussed in section 3, after a short description of the technical details in section 2.

II. Methods and Techniques

We have performed all-electron calculations within the framework of density function theory (DFT) and the generalized gradient approximation (GGA) in real space, using the hybrid functional PBE0 [18], using the program Package GAUSSIAN [19] The interaction energies of glycin with tamoxifen at various sites were computed by performing a potential energy surface (PES) scan with respect to various distances and orientations. All of the geometry optimizations

were performed using the "rich" 6-311G(2p,d) basis set and the Ahlrichs method [20] in Cartesian space without imposing symmetry constraints (C1). Initially, we performed an exhaustive search of GLY–TAM relative orientations in order to locate the maximum interaction site, using coarse scan meshes and (6-31G(d)) basis sets. After locating the maximum interaction region, the calculations were refined and the high quality 6-311G(2p,d). At each stage of the PES scan both GLY and TAM were allowed to relax and optimize. For the GLY-MOFs and TAM-MOFs interactions, only the final stages of the calculations were repeated at the PBE0/SVP level. The interaction energy, E_{Int}, at each point was determined, as usual, by the relation:

$$E_{Int} = E_{TAM+GLY} - \left(E_{\mathrm{TAM}} + E_{\mathrm{GLY}}\right) \quad (1)$$

III. Results and Discussion

The optimized structures of TAM and GLY are shown in Fig. 2 (a) and (b) respectively.

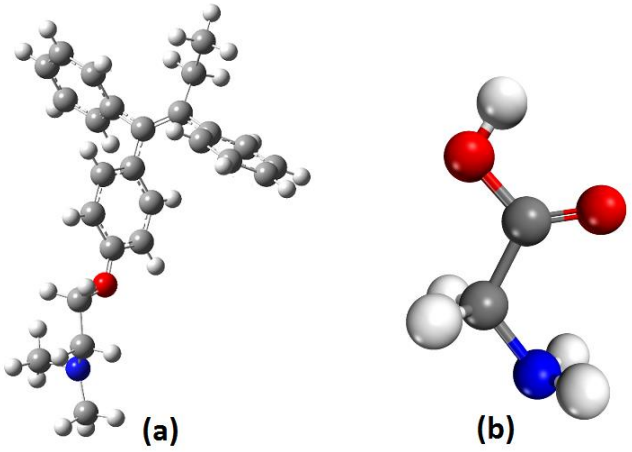

Fig. 2 The (optimized) geometries of TAM (a) and GLY (b) in a ball-and-stick diagram. Carbon atoms are denoted by grey spheres and hydrogen with white. Red (on line) balls indicate oxygen atoms and blue (on line) nitrogen atoms. The scale is not the same for TAM and GLY.

The final geometry optimization was performed with the same basis sets (6-311G(2p,d)) [20], and the same functional (PBE0)18. In Fig. 3 we show the results of the recalculated (with the PBE0 functional and the 6-311G(2p,d) basis set) PES scans of TAM-MOF and GLY-MOF maximum interaction sites. The corresponding maximum interaction energies were found at 21.0 kcal/mol and 12.5 kcal/mol respectively, which are slightly smaller than the results we have obtained earlier (with different functional and basis sets). These values do not include possible basis set superposition errors which are expected to slightly lower these values, but practically leaving the same relative magnitude. These results were obtained by modeling the IRMOF-14 [14]-[16] MOF through its organic linker, which is strategically functionalized with an –OH unit, as was described in ref. 15.

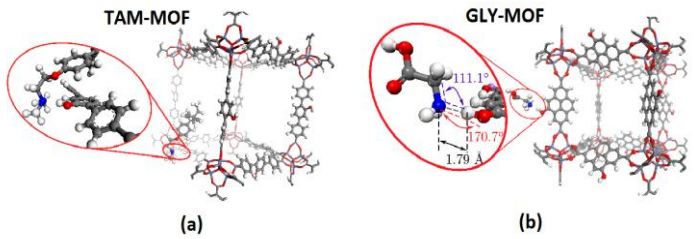

Fig. 3 The maximum interaction sites of TAM-MOF (a) and GLY-MOF (b).

This linker and its calculated charge distribution, obtained by population analysis (which includes multicenter corrections) of the calculated ground state wave function) is shown in Fig. 4.

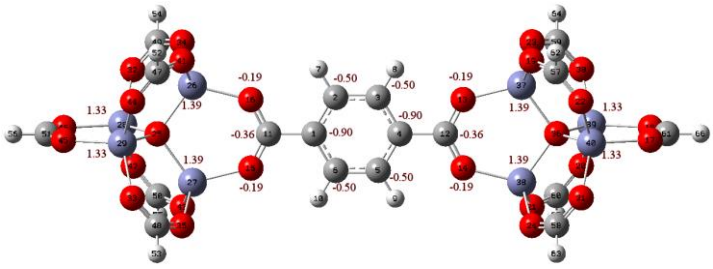

Fig. 4 The IRMOF-14 organic linker with the linked metallic edges, and the corresponding calculated charge distribution.

However, to make the calculations tractable this linker was truncated and the metallic edges were replaced by Li atoms, without seriously affecting the interaction site and energy15-16. The resulting charge density at the maximum interaction site of the GLY-TAM interaction is shown in Fig. 5. As is

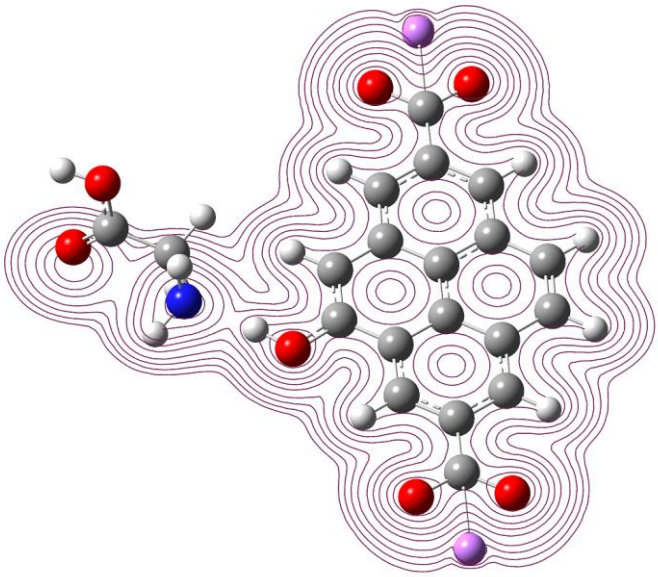

Fig. 5 The electronic charge distribution at the maximum interaction arrangement of the GLY amino acid with the –OH functionalized organic linker of IRMOF-14.

shown in Fig. 5, this interaction is mainly due to a rather strong hydrogen bond between the GLY nitrogen and the –OH unit of the modified linker.

For the GLY-TAM interaction we have initially considered two regions of approach for GLY on TAM, one around the TAM Nitrogen region as is shown in Fig. 6 (a), and the other one around the TAM oxygen vicinity, as shown in Fig. 6 (b). As it turns out, this second region is non-binding, at least at the level of PBE0/6-31g(d) and therefore the PES scan was restricted in the first region (around the TAM- Nitrogen).

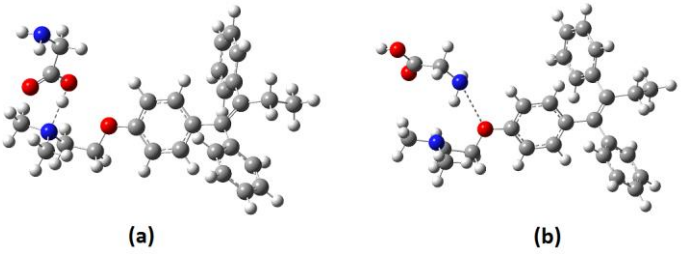

Fig. 6 Two initial ways of GLY-TAM approach.

In this region we have found two very "nearby" energy minima, as shown in Fig. 7.

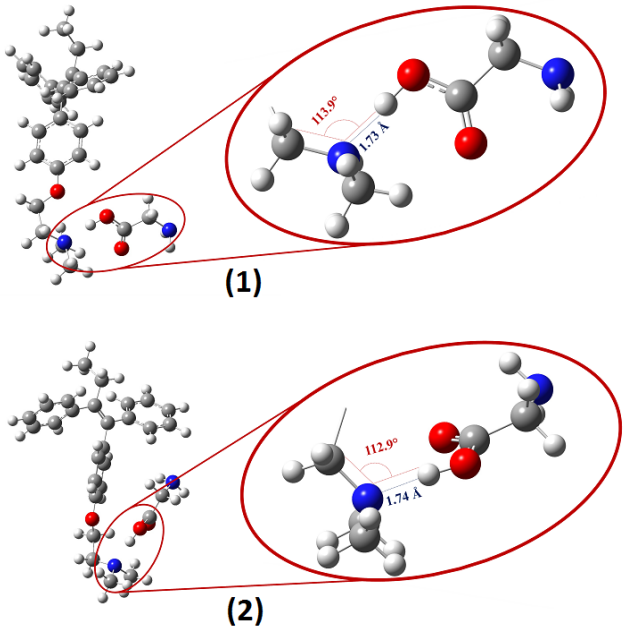

Fig. 7 The two "nearby sites of the maximum interaction energy.

Table. 1 Maximum Interaction Energies in "Kcal/mole".

GLY-MOF	TAM-MOF	GLY-TAM (1)	GLY-TAM (2)
12.5	21.0	16.1	17.30
Hydrogen bond	Hydrogen+(π-π)	Hydrogen bond	Hydrogen bond

As we can see in Table 1, the interaction energy at site 2 is slightly larger, by about 1kcal/mol.

The interaction energy curve for site 2 is shown in Fig. 8.

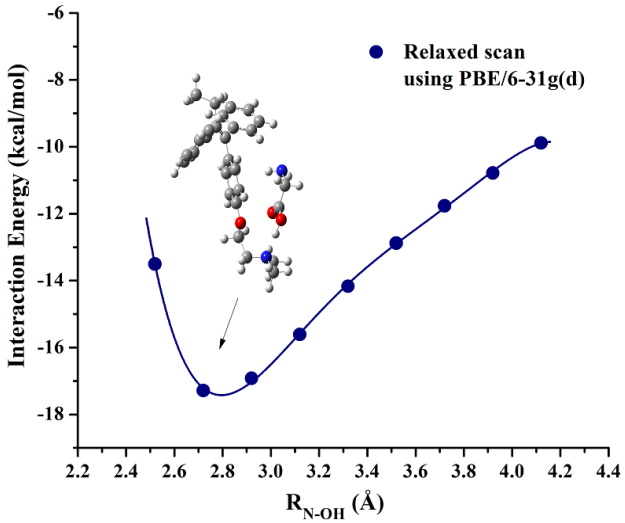

Fig. 8 Interaction energy for site (2) as a function of distance.

In Fig. 9 we can see the frontier molecular orbitals at the maximum interaction site.

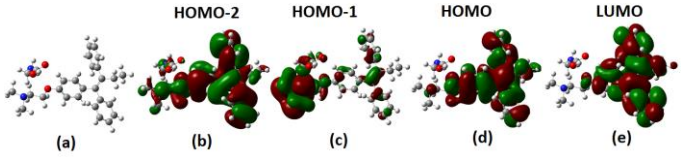

Fig. 9 The Frontier molecular orbitals (b)-(e) at the maximum interaction geometry (a).

As we can see in Fig. 9, both HOMO and LUMO orbitals are well localized on Tamoxifen, but the lower occupied molecular orbitals HOMO-1 and HOMO-2 are well distributed over both molecules. Apparently the HOMO-LUMO gap of TAM remains practically the same before and after the interaction, and therefore it could be in principle used for molecular labeling. And furthermore, it is concluded that the GLY-TAM interaction, compared to the GLY-MOF and TAM-MOF is of the practically the right magnitude for drug delivering purposes. Yet, realistically speaking, this theoretical description cannot be directly compared with experiment safely, since we have ignored in this comparative description the solvation effects which are very important for a realistic description of the process. This would be a subject of future work.

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