Engineering Host-Guest Interactions in Organic Framework Materials for Drug Delivery

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Abstract: Metal-organic frameworks (MOF) and covalent organic frameworks (COFs) are promising nanocarriers for targeted drug delivery. Noncovalent interactions between frameworks and drugs play a fundamental role in the therapeutic uptake and release of the latter. However, the scope of framework functionalizations and deliverable drugs remains underexplored. Using a multilevel approach combining molecular docking and density functional theory, we show for a range of drugs and frameworks that experimentally reported release metrics are in good agreement with the in silico computed host-guest interaction energies. Functional groups within the framework significantly impact the strength of these host-guest interactions, while a given framework can serve as an efficient delivery agent for drugs beyond the prototypical few. Our findings identify interaction energy as a reliable and relatively easy to compute descriptor of organic framework materials for drug delivery and facilitate their targeted design towards extended-release times.

Keywords: drug delivery, MOF, COF, host-guest interactions, DFT.

TOC Image
Introduction

Highly porous metal-organic frameworks (MOFs) and covalent organic frameworks (COFs) are emerging as attractive candidates for drug delivery. Nanoporous drug delivery systems facilitate the transport, slow the release and absorption of drugs in the body, prolong the duration of the therapeutic effect, offer response-triggered release via pH and other environmental stimuli, decrease toxicity, etc. Compared to conventional drug delivery systems such as liposomes, nanoparticles, and micelles\cite{1}, MOFs and COFs offer high loading capacity, stability in biological buffers, relatively easy customisation towards a specific drug via functionalization, desired release rate, and delivery site in the body.\cite{2,3} Horcajada el al. showed that large amounts of drugs can be incorporated in MOFs;\cite{4} since such initial pioneering studies, many drugs have been incorporated in MOFs and the systems tested \textit{in vitro}.\cite{3} The scope of incorporated drugs is not limited to small molecules and includes larger targets such as RNA\cite{5} and short single-stranded DNA, for which a much higher transfection efficiency was achieved when incorporated in IRMOF-74 as compared to conventional nanocarriers.\cite{6} More recently, COFs were also studied as promising drug delivery systems.\cite{7,8} Compared to MOFs, they offer the additional advantages of higher thermal stability and increased biocompatibility.

Rational targeted design of MOFs and COFs utilises their compositional nature, which enables customisation by replacing the metal in the nodes of a MOF, adding functional groups to the linkers or nodes, adjusting the pore size, combining the building blocks to generate alternative networks and topologies. There are no absolute criteria for the best MOF or COF drug delivery agents; rather, their optimal design strategies are tailored to specific applications. In drug delivery, the (typically noncovalent) interactions between the host framework and the guest drug are key since their strength regulates adsorption and release.\cite{9,10} \textit{In silico} modelling offers unprecedented insight into both the strength and nature of the host-guest interactions and allows facile, experiment-free design and pre-screening of candidate materials.

In this work, we employ multilevel computational modelling to engineer and characterise host-guest interactions in metal- and covalent organic frameworks with a particular focus on drug delivery. We selected several drug molecules with clinical applications for which sustained delivery is desirable and two organic frameworks for which the experimental data on drug release is available. We demonstrate a clear relationship between experimental drug release metrics and computed host-guest interaction energies. Finally, this relationship is used as a basis for testing the role of framework functionalization and expanding the scope of deliverable drug molecules.
Results and Discussion

To probe the potential of targeted *in silico* design of organic frameworks for drug delivery, we chose a zinc-based MOF-5 and two COFs, PI-COF-4 and PI-COF-5 (Figure 1a). MOF-5 was tested experimentally for the delivery of the anticancer and anti-inflammatory drug oridonin,[11] while the PI-COFs were studied for the delivery of ibuprofen, captopril, and caffeine.[12] We have considered modifications to the structures of these frameworks and examined their interactions with a range of therapeutics (Figure 1b) using a combination of molecular docking, density functional theory, and noncovalent interactions analysis.[13] The computational protocol is based on our previous studies[14,15] and its details are given in the Computational Methods section.

**MOF-5**

In the experimental study by Cai *et al.*,,[11] the phenyl linker of MOF-5 was functionalized with diverse groups (-H *(i.e., unfunctionalized)*, -Br, -CH$_3$, -CH=CH$_2$, -NH$_2$, and -OH), and the release of oridonin was measured in a liquid simulating body fluid (a commercially available standard solution with pH 7.4). The amount of oridonin released from the MOF after 24h was shown to be greatly affected by the functional group. We used two pore models of functionalized MOF-5 to perform molecular docking and subsequent partial DFT geometry optimisation of the guest to locate oridonin inside the pore (see Computational Methods and Figure S1 in the Supporting Information). Based on the obtained geometries, we computed the host-guest interaction energies at the DFT level (see Figure S3 in the Supporting Information). For each linker in MOF-5, the lowest (most stabilising) interaction energies between oridonin and MOF-5 are plotted against the amount of drug released after 24 hours (Figure 2a). These results demonstrate that, in general, the higher the host-guest interaction energy (the weaker the interaction), the less oridonin remains inside the pore, and *vice versa*. This relationship between experiment and computation is imperfect since the latter is based on a rather simplistic model and neglects the effects of temperature, solvent, guest-guest interactions, etc. Nevertheless, such a correlation enables a qualitative assessment of the drug release based on the host-guest interaction energy. As an example, functionalization of the MOF-5 linker with the carboxylic acid group, which has not been tested experimentally, results in the lowest interaction energy of -200.41 kJ mol$^{-1}$. We can thus speculate that a COOH-functionalized MOF-5 would afford an even slower release of oridonin.
Figure 1. Investigated framework hosts (a) and drug guests (b).

To examine whether oridonin release can be reliably predicted using common drug screening / qualitative structure-activity relationship (QSAR) metrics,[16] we computed the volume of each functional group in MOF-5 (Figure 2b). The apparent lack of any correlation between the steric requirements of the functional groups in MOF-5 and oridonin loading after 24h indicates that the release cannot be rationalised solely by geometric effects. Similarly, no correlation is observed between oridonin release and polarizabilities (Figure 2c) and Hammett constants (Figure 2d) of the functional groups in MOF-5. Therefore, simple geometric and electronic parameters, often employed in QSAR, are insufficient to predict the affinities of organic frameworks toward drug molecules.
Figure 2. Computed host-guest interaction energies (a), functional group volumes (b, in Bohr$^3$ mol$^{-1}$), polarizabilties (c, in Bohr$^3$), and Hammett $\sigma_{meta}$ constants (d) plotted against the experimentally determined$^{[11]}$ amount of oridonin released from functionalized MOF-5 after 24 hours.

Instead, the \textit{ab initio} framework-drug interaction energies provide a reliable qualitative estimate of the drug retention inside MOFs. The interaction energy, computed for an appropriate cluster model of the host-guest complex$^{[14]}$, captures all noncovalent interactions and thus serves as a global, rather than a local and functional group-specific metric. Among the experimentally tested MOF-5 variants, the unfunctionalized framework establishes the weakest interaction with oridonin, while adding an OH group to the phenyl linker in MOF-5 enables multiple relatively strong hydrogen bonds to form with the drug, strengthening the host-guest interaction and delaying the drug release (Figure 3). Similarly, multiple hydrogen bonds between oridonin and the COOH-functionalized MOF-5 result in the lowest computed interaction energy for this system (see Figure S7 in the Supporting Information).
Figure 3. MOF-5 (left: unfunctionalized, right: OH-functionalized) pore with oridonin at the preferred adsorption site. The inset shows the shortest hydrogen bond between oridonin and the OH-functionalized phenyl linker (in Å).

We employ the established relationship between drug release and the host-guest interaction energy to explore functionalized MOF-5 in the delivery of two other drugs, bupivacaine and methadone. Bupivacaine is a local anaesthetic whose therapeutic effect lasts several hours. However, in certain cases a more prolonged action is preferable and can be achieved by a controlled release from drug delivery systems. We computed the host-guest interaction energies in the unfunctionalized MOF-5 and its three mono-functionalized derivatives (-NH$_2$, -OH, -COOH) following the procedure used for oridonin (Figure 4). The strongest interaction is observed for the OH-functionalized phenyl linker, suggesting that this system would afford the most prolonged release.

Figure 4. Computed interaction energies between functionalized MOF-5 and bupivacaine, as well as structures of MOF-5 (left: unfunctionalized, right: OH-functionalized) hosting bupivacaine at the preferred adsorption site. The inset shows the shortest hydrogen bond (in Å) between bupivacaine and the OH-functionalized phenyl linker.

Methadone is the most frequently prescribed medication in opioid substitution treatments. Methadone is usually administered in 24-hour intervals, but patients’ reactions to the drug differ, and many face withdrawal symptoms before 24 hours. Thus, a sustained administration of methadone
could potentially alleviate this issue. The \( L \)-enantiomer (levomethadone) is the main active form of methadone\(^{[21]} \) and at biological pH it is protonated at its tertiary amine\(^{[22]} \) (Figure 5). Using this form of the drug in molecular docking, both extended and cyclic (with an intramolecular hydrogen bond) conformations of methadone were found inside MOF-5. In agreement with Bürgi \textit{et al.},\(^{[23]} \) the extended conformation forming intermolecular rather than intramolecular hydrogen bonds leads to strong host-guest interaction energies and is preferred.

\textbf{Figure 5.} \( L \)-methadone (left: base, right: protonated form).

In computing the host-guest interaction energies between methadone and MOF-5 (unfunctionalized and functionalized with -NH\(_2\), -OH, and -COOH, Figure 6), both neutral and protonated forms of methadone were considered, since its p\( K_a \) (see Table S1 in the Supporting Information) is close to the pH of PBS (phosphate-buffered saline, a liquid simulating body fluid at pH 7.4). Independent of functionalization, the protonated form interacts with the MOF-5 more strongly than neutral methadone. For the latter, the trend in the host-guest interaction energies follows that for bupivacaine (from the strongest to the weakest interaction): OH > COOH > NH\(_2\) > H. The strongest interaction overall is established between the positively charged methadone and the COOH-functionalized MOF-5 and can be ascribed to the relatively short hydrogen bond between the protonated tertiary amine and the carboxylic group of the phenyl linker (Figure 6). This system is thus a potential candidate for methadone delivery with sustained release.
**Figure 6.** Computed interaction energies between methadone (blue: unprotonated, orange: protonated) and functionalized MOF-5, as well as structures of MOF-5 (left: unfunctionalized, right: COOH-functionalized) hosting methadone at the preferred adsorption site. The inset shows the shortest hydrogen bond (in Å) between protonated methadone and the COOH-functionalized phenyl linker.

**PI-COF**

Fang *et al.* measured the release of ibuprofen, captopril, and caffeine from two COF drug delivery systems, PI-COF-4 and PI-COF-5, in simulated body fluid.[12] PI-COF-5 has an intertwined network, whereas PI-COF-4 does not. The structural models of these two COFs used in molecular docking and DFT computations with various drugs are shown in Figure S2 in the Supporting Information. The investigated drugs are subject to pH-dependent equilibria between the neutral and charged forms (see Table S1 in the Supporting Information). Percentages of the drugs remaining inside the COF after 24h were extracted from the experimental delivery curves (see Figure S13 in the Supporting Information), while the host-guest interaction energies were computed using the same methodology as before (Figure 7).

![Figure 7](image.png)

**Figure 7.** Computed host-guest interaction energy plotted against experimentally determined[12] amounts of drugs (neutral form) released from PI-COF-4 and PI-COF-5 after 24 hours.

In agreement with the trend established for oridonin in MOF-5 (Figure 2b), the drug forming the weakest interactions with the framework, caffeine, has the highest release percentage. Captopril and ibuprofen are close in both the interaction energies and the released amounts. The release of drugs from PI-COF-5 is more facile than from PI-COF-4, presumably because the former has an intertwined network (Figure 1a), leading to a sterically more obstructed release. This effect is not captured by the interaction energies computed using cluster models.

We next tested the non-intertwined PI-COF-4 as a potential delivery agent for four additional drugs (Figure 1b). Bupivacaine was chosen to have a direct comparison with MOF-5 and because sustained delivery can prolong its anaesthetic effect. Etoricoxib is a commonly used, orally administered analgesic. Sustained release could reduce its gastrointestinal toxicity and dosing frequency.[24,25] Thyroxine is used to treat hypothyroidism. Taken orally, it leads to a peak in the
production of triiodothyronine, hence encapsulation systems with slower delivery are desired.\cite{26} Valproic acid is an antiepileptic drug. It is usually administered as a slow-release formulation to control the amount of released drug and thus its serum concentration.\cite{27}

Among all tested neutral drugs, the interaction with PI-COF-4 is the strongest for thyroxine and the weakest for caffeine (Figure 8). This is likely due to multiple polar groups present in thyroxine but absent in caffeine. Bupivacaine has an interaction energy of -96.3 kJ mol$^{-1}$ with the unfunctionalized MOF-5 and -160.6 kJ mol$^{-1}$ with the OH-functionalized MOF-5, while with PI-COF-4 it is only -75.1 kJ mol$^{-1}$ since there are no possibilities to form strong hydrogen bonds with this framework (see Figure S14 in the Supporting Information). Finally, since drugs containing carboxylic acid groups are deprotonated at pH 7.0, the anionic forms of captopril, ibuprofen, and valproic acid were also studied. For thyroxine, a zwitterionic form predominant at pH 7.0 was also investigated. In all cases, the host-guest interactions are substantially stronger for charged drugs than for their uncharged analogues.

Figure 8. Computed interaction energies between PI-COF-4 and various drugs, as well as structures of PI-COF-4 hosting neutral thyroxine (left) and caffeine (right) at the preferred adsorption site. The inset shows the shortest hydrogen bond (in Å) between neutral thyroxine and PI-COF-4.
Conclusions

Delayed release is desired, and at times necessary for various therapeutic drugs. Metal- and covalent organic frameworks are attracting increasing attention as promising extended-release drug delivery systems. In this work, we demonstrated for several frameworks and a series of drugs that the experimentally measured amount of drug released from a framework carrier after 24 hours is qualitatively correlated with the respective host-guest interaction energy, computed using a multilevel approach combining molecular docking and density functional theory. The modelling approach adopted here is limited to static simulations of simple cluster models, and therefore does not take into account the effects of the environment, changes in the framework geometry, and dynamic phenomena such as diffusion. Despite this, our in silico results show good agreement with experimental literature. In contrast, no appreciable correlation was obtained between the release percentages and commonly used QSAR metrics.

Using ab initio interaction energies as promising descriptors of drug retention, we explored how functionalization of the framework can be employed to customise the host-guest noncovalent interactions and prolong drug release. We have also expanded the scope of drugs deliverable by MOF-5 and PI-COF-4 beyond those typically tested in vitro. The computed host-guest interaction energies are strongly dependent on the protonation state of the drug molecule and vary across a broad range of values. Since efficient drug delivery is a balancing act between capture and release, our findings enable facile engineering and pre-screening of MOFs and COFs for prolonged delivery of target drugs.

Computational Methods

The structure of MOF-5 was retrieved from the Cambridge Structural Database\textsuperscript{[28]} (refcode: MIBQAR\textsuperscript{[29]}) and used to construct finite models of the pore as previously described.\textsuperscript{[15]} To account for the orientation of the phenyl linkers, two pore models were created: one with the phenyl linkers pointing inwards, and one with them pointing outwards (see Figure S1 in the Supporting Information). Synthetically, MOF-5 analogues are created by replacing the terephthalic acid forming the linkers with functionalized terephthalic acid as described by Cai et al.\textsuperscript{[11]} To mimic their experiment, we modified the MOF-5 pores with one functionalization per linker using the -CH\textsubscript{3}, -NH\textsubscript{2}, -OH, -Br, -CH=CH\textsubscript{2}, and -COOH functional groups (see Figure S1c and S1d in the Supporting Information). The atoms belonging to the functional groups were optimised at the B3LYP/6-31G level of theory, while keeping the rest of the framework frozen. Cluster models of PI-COF-4 and PI-COF-5 were constructed based on structures taken from the CoRE-COF database\textsuperscript{[30]} (see Figure 1 and Figure S2 in the Supporting Information).
Adsorption sites of the studied drug molecules in the framework pore models were identified using the previously developed workflow.\textsuperscript{[15]} Briefly, molecular docking (using AutoDock 4\textsuperscript{[31]}) is followed by a partial geometry optimisation of the guest (using Gaussian16\textsuperscript{[32]}). For neutral drugs, geometry optimisations were performed at the B3LYP/6-31G level of theory. For negatively charged drugs, the DFT geometry optimisations led to notable changes in the geometry of the adsorption site. To accelerate convergence, an initial Hartree-Fock (HF) optimisation of the guest preceded subsequent DFT optimisation. For the HF optimisations of anionic drugs, a larger basis set, 6-31+G(d,p), was used. LANL2DZ basis set was used for all computations on iodine-containing molecules (thyroxine). All inputs and outputs can be found on the Materials Cloud. Based on these geometries, single-point computations at the B3LYP-D3\textsuperscript{[33]}/6-31+G(d,p) level of theory were performed to obtain host-guest interaction energies as follows:

\[
\Delta E = E_{hg} = [E_h + E_g] + E^{BSSE}
\]  
(Eq. 1),

where \(E_{hg}\) is the electronic energy of the supramolecular cluster, \(E_h\) and \(E_g\) are electronic energies of the truncated host (MOF/COF) and guest molecule (drug) in their cluster geometries, and \(E^{BSSE}\) is the counterpoise correction.

Volumes of the MOF-5 functionalized linkers (defined as the volume inside a contour of 0.001 electrons Bohr\textsuperscript{3} density) were computed at the B3LYP-D3\textsuperscript{[33]}/6-31+G(d,p) level of theory using the Monte-Carlo integration scheme implemented in Gaussian16. The software Polaber\textsuperscript{[34]} was employed to compute atomic and functional group polarizabilities. Within this approach, atomic polarizabilities \(\alpha(\Omega)\) are computed as numerical derivatives of atomic dipole moments \(\mu(\Omega)\) with respect to a (sufficiently small) external electric field \(E\):

\[
\alpha(\Omega)_{ij} = \lim_{E \to 0} \frac{\mu_{ij}(\Omega) - \mu_{ij}(\Omega)}{E_j} 
\]  
(Eq. 2).

The electric field was chosen at 0.001 a.u. and applied along the +x, -x, +y, -y, +z, and -z axes. Functional group polarizabilities were obtained as the sum of all polarizabilities of their constituent atoms. The atomic dipole moments were obtained from the partitioning of the electron density according to the quantum theory of atoms in molecules (QTAIM\textsuperscript{[35]}) using the software AIMAll.\textsuperscript{[36]}

Supplementary Material

Supporting information for this article is available on the WWW. All inputs and outputs have also been deposited on the Materials Cloud archive.
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M.E.: conceptualisation, methodology, investigation, formal analysis, visualisation, writing – original draft, writing – review & editing. G.G.: conceptualisation, supervision, funding acquisition, formal analysis, writing – review & editing.
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