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Theoretical Study of Amino Acid Interaction with Metal Organic Frameworks§

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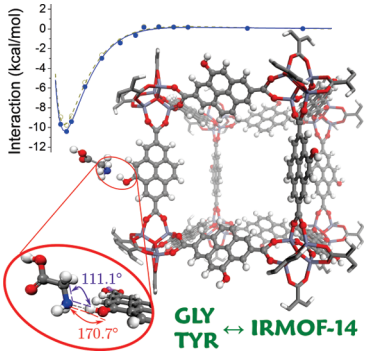
ABSTRACT We have investigated by density functional theory the interaction of representative amino acids such as glycine and tyrosine with a suitably functionalized organic linker of the IRMOF-14 metal−organic framework for various sites and ways of approach. It was found that the only active site with nonmarginal interaction energy is the one introduced by the strategic replacement of a linker hydrogen by a hydroxyl unit. Such replacement, which is experimentally tested and implemented, is capable of producing intermediate magnitude hydrogen bonds with interaction energies of 9.8 kcal/mol for glycine and 10.8 kcal/mol for tyrosine. The type and magnitude of these interactions, which have been also verified by second-order Møller−Plesset perturbation theory, allow appreciable binding without overbinding. This is very promising for possible pharmaceutical applications of MOFs.

SECTION Molecular Structure, Quantum Chemistry, General Theory



One of the major directions of nanobiotechnology research is currently focused on the interactions between biomolecules and nanoporous materials.[1,2] The fabrication of structures with functional surfaces on which proteins will be immobilized without losing their biological activity remains a major goal.

Initially, carbon nanotubes (CNTs) were studied for drug delivery. Both theoretical[3] and experimental[4−6] investigations have proved that nanomaterials are good candidates for the encapsulation of proteins, taking into account the fact that functionalized CNTs exhibit low toxicity and are not immunogenic.[5,6] Nevertheless the axial porosity of CNTs together with their graphitic surface places limits on the variety of biological reactants and potential applications.

Lately, a novel family of framework hybrid inorganic−organic nanoporous materials was synthesized, the metal−organic frameworks (MOFs).[7] The 3D periodic structure of MOFs consists of inorganic primary building units (pbu), which are linked via secondary organic building units (sbu), commonly referred to as the organic linker. The almost unlimited variety of organic linkers that can be used for their skeleton provides them with a large range of pore dimensions along with a great diversity of interaction sites. It is worth noting that the recently manufactured MOF-177 and MOF-210[8,9] exhibit ultrahigh values of (Brunauer−Emmett−Teller) surface areas, in the range of 4500 and 6240 $m^2\ g^{-1}$, respectively. This flexibility, combined with a large variety of pore volumes, permits for the methodical and targeted design of storage materials for molecules within a wide range of sizes.

These advantages of MOFs, compared with other nanoporous materials, lead to the consideration of MOFs as drug vehicles for improving drug delivery by increasing their bioavailability and biostability, ensuring progressive drug release under physiological conditions. In their recent work,[10,11] Férey et al., using iron(III) carboxylate MOFs, demonstrated and verified for the first time the remarkable capacity for drug encapsulation and controlled delivery of such MOFs and their biocompatibility. By examining the adsorption and delivery capabilities of MOFs with different porosities (specifically MIL-100 and MIL-101), they showed that the combination of high and regular porosity with the presence of organic groups within the framework may cumulate the advantages to achieve both a high drug loading and a controlled release. Equally significant are the results of their in vitro and in vivo studies, which reveal low to no cytotoxicity and toxicity, respectively, of the (iron carboxylate) MOFs MIL-88A, MIL-100, and MIL-88Bt.

In this work, we examine the "direct" interaction of two very important amino acids, glycine (GLY) and tyrosine (TYR), with the organic part of a strategically modified pyrenol-based IRMOF-14 framework (Figure 1a−c, respectively). Our approach is based on the separation of the two major factors that control the encapsulation: the pore size and the interaction sites. In this way, we are trying to shed some light on the reaction mechanism and understand the nature of the encapsulation phenomenon.

The sbu of IRMOF-14, pyrene-2,7-dicarboxylate (PDC), was modified by replacing a hydrogen atom with a hydroxyl unit in the main body of the structure and thus introducing a strong interaction site, leading to 3-pyrenol-2,7-dicarboxylate

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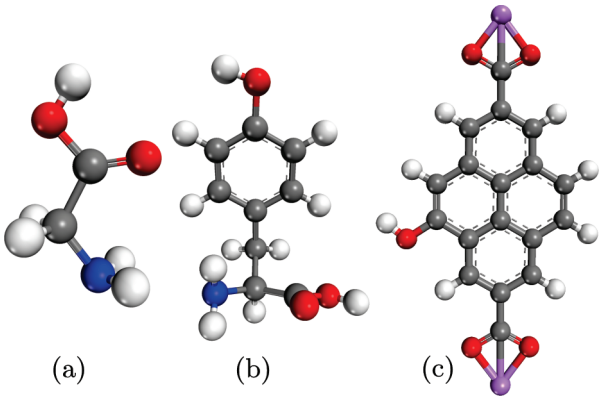

Figure 1. Optimized structures of the (a) glycine (GLY) and (b) tyrosine (TYR) amino acids as well as the (c) dilithium 3-pyrenol-2,7-dicarboxylate organic linker (sbu). (These structures are not under scale. The reduction is increased from left to right.)

(hPDC) (Figure 1c). This methodology was previously proposed by our group to enhance the interaction of the organic linker of MOFs[12] and verified experimentally by two groups working in the field.[13,14] The functionalization of the ligand with −OH groups is a straightforward synthetic procedure and can be applied in a very large category of MOFs. It could be perhaps possible to attempt to modify the sbu of the IRMOF-14 (and/or other MOFs) by exploring alternative synthetic procedures, employing other conceivable groups beside hydroxyl, if one wishes to do so; however, this is not a primary concern of our present work.

We have performed all-electron calculations within the framework of density functional theory (DFT)and the generalized gradient approximation (GGA) in real space. The interaction energies of the amino acid molecules with the organic linker of the modified IRMOF-14 were computed by performing a PES scan with respect to various distances and orientations. All of the geometry optimizations were performed using the Ahlrichs method[15] in Cartesian space without imposing symmetry constraints (C_1), employing the gradient-corrected PBE exchange−correlation functional.[16] Initially, we performed an extensive search for a large variety of sites and amino acid−sbu relative orientations (including perpendicular and parallel orientations) to locate the maximum interaction site, using coarse scan meshes and basis sets. After locating the maximum interaction region, we refined the calculations and used the high quality triple-ζ def2-TZVPP[17] basis set. These results were further tested by additional ab initio calculations using second-order Møller−Plesset perturbation theory (MP2), with the same high quality basis set. The average difference in interaction energy between the two methods was ∼3%, which shows very good agreement between them and verifies the validity of the results obtained. In every step, we have calculated and removed the basis set superposition errors (BSSEs) using the counterpoise correction method (CP). Tight convergence criteria were enforced on the SCF energy (10^{-7} au), the one electron density (rms of the density matrix up to 10^{-7}), as well as the norm of the Cartesian gradient (10^{-4} au). We have checked that the correct electronic configuration has been obtained by

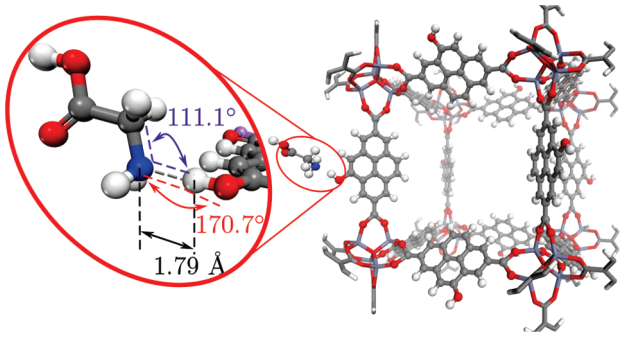

Figure 2. Maximum interaction configuration of the GLY amino acid with the dilithium 3-pyrenol-2,7-dicarboxylate organic linker (sbu).

performing multiple calculations on different fixed spin states (singlet, triplet, etc.) and in some cases by additionally employing an occupation number optimization procedure using (pseudo-Fermi) thermal smearing. All calculations were performed using the Turbomole program package.[18]

To reduce the computational cost, which could end up prohibitively large, a truncated model system was used that provides a good representation[19−22] of the effect of the metal unit (pbu) on the organic linker by terminating the linker trough saturating the carboxylate groups with Li^+ cations. This is not expected to alter the present results in any significant way, as has been illustrated elsewhere.[19−22] The interactions of the glycine and tyrosine amino acids with the sbu (organic linker) of the modified IRMOF-14 were determined by potential energy surface (PES) scans with the amino acids approaching the sbu in various ways at different sites. The maximum distance for the scan was set at 14 Å to account for any energy barriers that might exist.

In Figure 1, we give the fully optimized structures of the lithium-terminated hPDC sbu as well as those of the glycine (GLY) and tyrosine (TYR) amino acids. These structures were used in the detailed PES scan, which was performed by approaching the amino acids toward the strongest interaction site of the sbu. At each point of the scan for a selected (constant) distance, the structures of both the amino acids and the organic linker were allowed to relax and optimize. The interaction energy, E_{int}, at each point was determined, as usual, by the relation

$$E_{int} = E_{linker+aminoacid} - (E_{linker} + E_{aminoacid})$$

It should be emphasized that the values of the interaction energies include BSSE corrections, calculated at every point of the relaxed PES scan by the counterpoise (CP) method.

After identifying the maximum interaction energy sites on the structure of the sbu, with each of the GLY and TYR amino acids, we performed a series of partial geometry optimizations with each of the amino acids located on various sites of the sbu structure and in various relative orientations. In both cases, as could be expected, the strongest interaction site lies on the hydroxyl unit with which we have modified the initial PDC structure, whereas the amino acid's orientation is such that the nitrogen atom is nearest to the hydrogen of the sbu hydroxyl group (Figures 2 and 3). On the contrary, the

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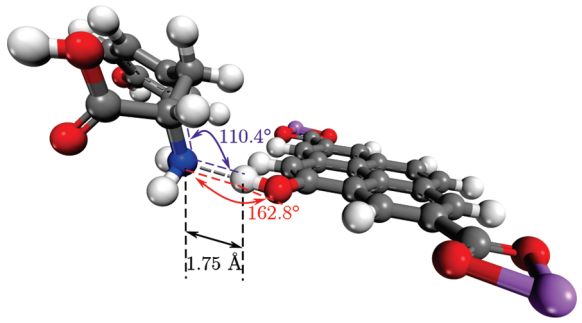

Figure 3. Maximum interaction configuration of the TYR amino acid with the dilithium 3-pyrenol-2,7-dicarboxylate organic linker (sbu).

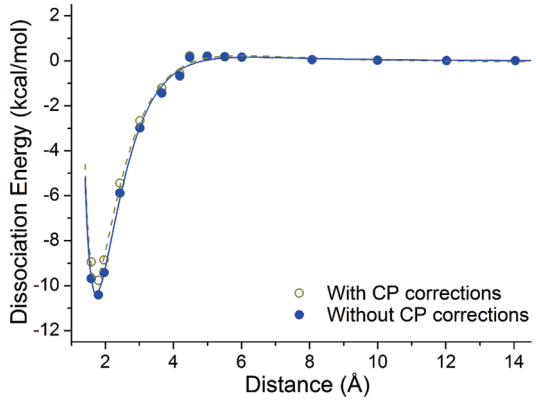

Figure 4. Interaction energy at the maximum interaction configuration of the GLY amino acid with the dilithium 3-pyrenol-2,7-dicarboxylate organic linker (sbu).

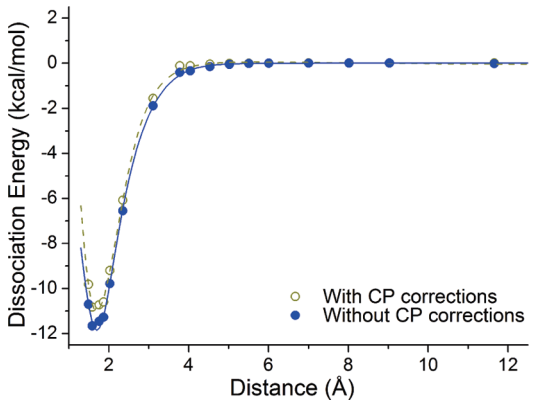

Figure 5. Interaction energy at the maximum interaction configuration of the TYR amino acid with the dilithium 3-pyrenol-2,7-dicarboxylate organic linker (sbu).

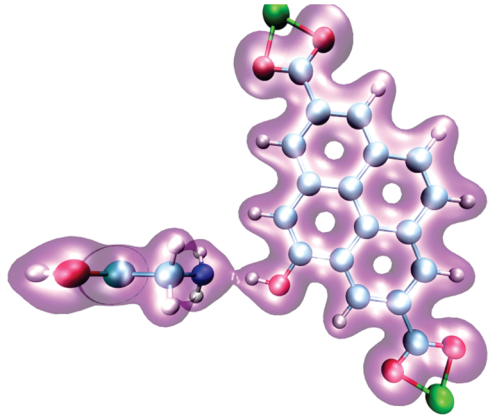

Figure 6. Electronic charge distribution at the maximum interaction arrangement of the GLY amino acid with the −OH functionalized organic linker of IRMOF-14.

interaction of glycine (N-approach) with the carbon atoms in the central region of hPDC was marginal or repulsive. It should be stressed that many diverse sites and ways of approach were examined before and after the introduction of hydroxyl, including ways that the amino acids were lying flat onto the IRMOF-14 linker. Without the OH unit, the interaction, as in the rest of the cases, was marginal. Even after the introduction of the active OH site, the interaction in this "flat" case was at least 5 to 6 kcal/mol less than the maximum interaction energy reported here below, depending on the precise orientation. As a consequence, we have restricted the refined PES scans at the region of the maximum interaction.

Figures 2 and 3 show the equilibrium positions (maximum interaction configuration) for the cases of GLY (in which we also show the MOF framework) and TYR, respectively; while in Figures 4 and 5, we plot the interaction energy diagrams (for GLY and TY, respectively). The equilibrium distance of the nitrogen atom of the GLY (Figure 2) amino acid from the hydrogen atom of the hydroxyl group of the organic linker is found to be 1.79 Å, whereas in the case of TYR (Figure 3), this distance is 1.75 Å. Both of these bond distances are in full agreement with what would be expected for a typical hydrogen bond (∼1.6 to 2.0 Å), which is also verified by the O−N distance of 2.79 Å for glycine and 2.73 Å for tyrosine and the O−Ĥ···N angle (where OH is the hydroxyl group of the organic linker and N is the nitrogen atom of the amino acid) of 170.7° for GLY and 162.8° for TYR. These are characteristic values for a typical hydrogen bond (with O as a hydrogen bond donor and N as a hydrogen bond acceptor). However, the magnitude of the interaction (9.8 kcal/mol and 10.8 for GLY and TYR, respectively) is relatively larger compared with what would be expected (∼5 to ∼7 kcal/mol) for a normal hydrogen bond. We can rationalize this difference by examining the C−N̂···H angle (where C is directly bonded to the N atom of the amino acid and H is the hydrogen of the hydroxyl group of the organic linker). As we can see in Figures 2 and 3, this angle is 111.1° for GLY and 110.4° for TYR, very close to the theoretical optimum angle of an sp^3 hybrid bond. Finally, Figure 6 shows the electronic charge distribution at the maximum interaction arrangement (given in Figure 2), which clearly illustrates the GLY−linker interaction.

In conclusion, we have examined the interaction of a strategically modified organic linker of a (pyrenol-based) IRMOF-14 with two important amino acids, glycine and tyrosine, using a properly selected cluster model. We have found that although the interaction of glycine at the N-approach (where N is the nitrogen atom of the amino acids) to

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the central carbons of the linker is marginal; the interaction energy at the equilibrium distance above the hydroxyl group of the organic linker has a maximum value of 9.8 kcal/mol for GLY and 10.8 kcal/mol for TYR, implying a rather strong hydrogen bond. Without the introduction of the active OH− site, there would have been no interaction in this case, which fully justifies the strategy followed in the present work. These results (the type and magnitude of bonding) look promising for a detailed modeling of possible pharmaceutical applications because the −OH functionalization can be applied in a very large category of MOFs.

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Dedication

§ Dedicated to our collaborator, Elpiniki Zdetsis (deceased November 16, 2010).

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