Conformational Analysis of Protonated cyclo-[(S)-Phenylalanyl-(S)-Histidyl] and its Complex with Benzaldehyde Within Metal-Organic Frameworks (MOFs)

Claudia F. Braga and Ricardo L. Longo*

*Departamento de Química, CCEN, Universidade Federal da Paraíba, 58036-300 João Pessoa-PB, Brazil
bDepartamento de Química Fundamental, Universidade Federal de Pernambuco, Cidade Universitária, 50740-540 Recife-PE, Brazil

The conformational analysis of protonated cyclo-[(S)-phenylalanyl-(S)-histidyl], denoted as cyclo-[(S)-Phe-(S)-His-H⁺], within a cavity of a new IRMOFs-phen (isoreticular metal-organic frameworks with a 2,7-dicarboxylate phenanthrene substituted bridges) porous material was performed with the AM1 quantum chemical method. Two forms of cyclo-[(S)-Phe-(S)-His-H⁺] were considered: the bound-form, where the peptide is chemically linked to the phenanthrene moiety and the unbound-form where the peptide is free within the cavity: The most probable conformers of cyclo-[(S)-Phe-(S)-His-H⁺] within the cavity have been compared to the conformers in gas phase and in water, simulated by the implicit solvent SM5.4 model. The preferred conformations within the IRMOF-phen cavity are the (g–, g+) and (t, g+) in contrast to the gas and aqueous phases. The environment within the cavity is also relevant, since the substitution of a hydrogen atom by CH₃ (IRMOF-phen-CH₃) or Br (IRMOF-phen-Br) lead to new IRMOFs-phen that changes drastically the conformer populations, as well as the adsorption site of the dipeptide. These results have important implications in controlling the stereoselectivity of reactions in the presence of chiral inductors. Indeed, this is the first time that a folded conformation of cyclo-[(S)-Phe-(S)-His-H⁺] was found, as well as an stable cyclo-[(S)-Phe-(S)-His-H⁺]-benzaldehyde complex was obtained using the ONIOM(PBE1:AM1) method. This complex is compatible with the proposed structure for the transition state of the hydrocyanation of benzaldehyde that explains the observed enantioselectivity.

Keywords: enantioselectivity conformation, quantum chemistry, confined species

Introduction

Chirality and more specifically the origin of the homochirality in our biota has been a life long interest of Prof. Ricardo Ferreira. It is thus with great honor that we present this contribution showing that the selectivity of enantiomeric reactions can be increased within the confined spaces of cavities, such as, zeolites and isoreticular metal-organic frameworks. Indeed, porous solids are important for technological applications because they can interact

*e-mail: longo@ufpe.br
with atoms, ions and molecules not only on their surfaces, but throughout the bulk of the material. Open metal-organic frameworks are widely regarded as promising materials for applications in catalysis, separations, gas storage and molecular recognition. Compared to conventionally used microporous inorganic materials such as zeolites, these metal-organic structures have the potential for more flexible rational design, by controlling the size and functionalization of the organic bridges as well as the architecture of the pores via secondary building units. The successful design of isoreticular metal-organic frameworks (IRMOFs) with rigid dicarboxylate rings connecting Zn₄(μ₃-O) clusters has provided highly porous and thermally stable crystalline materials. In addition to their immediate application in gas storage, these materials can be used as confining systems for improving stereoselectivity in reactions with chiral inductors or auxiliaries as already explored for zeolites, as well as for enantioselective separation and catalysis.

The cyclic dipeptide cyclo-[(S)-phenylalanyl-(S)-histidyl] is an excellent catalyst for the hydrocyanation reaction of aldehydes with high enantioselectivity. Due to its importance in mimicking the role of enzymes active sites via its histidine-imidazole moiety this dipeptide was studied in detail by NMR and IR spectroscopy. This study aimed at the elucidation of the hydrocyanation reaction mechanism, where the conformation of the dipeptide and the interactions between the histidine-imidazole moiety with the aldehyde and the cyanide are the most important aspects. The cyanide addition to carbonyl yielding cyano hydrin has a first order kinetics are the most important aspects. The cyanide addition to imidazole moiety with the aldehyde and the cyanide dipeptide and the interactions between the histidine-imidazole moiety (bound-form), with the phenanthrene mimicking the phenyl ring of the phenylalanyl residue. As a result, the unbound-form of cyclo-[(S)-Phe-(S)-His-H⁺] leads to a chiral auxiliary within the confined space of the IRMOF-phen cavities that can induce chirality in asymmetric reactions, while the new bound-form of IRMOF-phen has a chiral cavity. Indeed, the present results are the first ones to corroborate the folded conformation of the dipeptide suggested for its complexation with benzaldehyde. In addition, the hydrogen bonded and π-stacking complex between cyclo-[(S)-Phe-(S)-His-H⁺] and benzaldehyde has been obtained within the IRMOF-phen cavity, which suggests that hydrocyanation of this benzaldehyde should be highly enantioselective.

Methodology and Computational Procedures

The molecular structures of the IRMOF-phen with the bound and unbound forms of the peptide, the IRMOF-phen-Br and the IRMOF-phen-CH₃ with the free dipeptide within their cavities were obtained with the MOPAC2000 program using the AM1 (Austin Model 1) method. These structures were fully optimized with methyl groups saturating the dangling bonds of the cubic model. These optimized IRMOF capped-CH₃ models were kept fixed when the conformational analysis of cyclo-[(S)-Phe-(S)-His-H⁺] was performed without any constraints. Also, the molecular mechanics correction for the HNCO barrier was not used, since it does not make any difference in the conformational analysis. The aqueous medium was simulated with the SM5.4 solvation continuum model. All geometry optimizations were performed using the default program parameters and an energy gradient smaller than 4 kJ mol⁻¹ nm⁻¹.

The ONIOM(PBE1/6-31G(d,p):AM1) method has been used to obtain the molecular structure of the cyclo-[(S)-Phe-(S)-His-H⁺]-benzaldehyde complex within the IRMOF-phen cavity. The complex has been treated as...
the high level layer (PBE1) and the IRMOF-phen as the low level one (AM1), which has been kept fixed during the geometry optimization.

**Results**

The AM1 method\(^{12}\) was used to calculate the standard enthalpy of formation \((\Delta H_f)\) and the relative enthalpy \((\Delta A_H)\) at 298 K for the most probable conformers of the dipeptide \(\text{cyclo}-(\text{S}-\text{Phe}-\text{S}-\text{His-H}^+)\) via a systematic and a stochastic conformational search procedure. The solvent effects (water) were considered in the calculations via the SM5.4 implicit hydration model.\(^{13}\) The systematic search involved the rotation around the \(\chi_1 = N(4)-C(3)-C(7)-C(4')\) and \(\chi_2 = N(1)-C(6)-C(8)-C(1'')\) dihedral angles (for the atomic numbering see Figure 1). It should be notice that only the conformation where \(\chi_3 = C(6)-C(8)-C(1'')-C(2'') = 270^\circ\) has been considered since the other non-equivalent conformation, \(\chi_3 = 90^\circ\), is very unstable.\(^{16}\) The notation \(g^+, g^-\) and \(t\) is related to conformers for the \(C_A-C_B\) bonds and specify the relative position of the NH group at \(C_A\) and the C (phenyl or imidazole) group at \(C_B\) as illustrated in Figure 2.

The result of this systematic search yielded nine conformers that were energetically accessible. In addition, a stochastic search consisting of generating more than 40,000 conformations via the Monte Carlo method at 5000 K was performed. From this stochastic search, two new conformers were found and selected, since they presented compatible structures with the proposed transition state for the hydrocyanation. All the selected conformers are illustrated in Figure 3.

Considering that specific interactions are similar in all conformers, the SM5.4 approach can fairly represent the solvent effects on the conformational equilibrium.\(^{13}\) The enthalpy of formation and hydration of all nine conformers with their optimized \(\chi_1\) and \(\chi_2\) dihedral angles are presented in Table 1.

Also these conformers were confined in the IRMOF-phen cavity (unbound-form) and had their geometry re-optimized, keeping the IRMOF-phen structure rigid. The \(\text{cyclo}-(\text{S}-\text{Phe}-\text{S}-\text{His-H}^+)\) has also being chemically linked to the position 4 of the phenanthrene ring (bound-form) in the IRMOF-phen, as illustrated in Figure 4, and the same conformations of the unbound-form were explored in this bound-form.

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\(\Delta H_f\) and \(\Delta A_H\) at 298 K for the most probable conformers of the dipeptide \(\text{cyclo}-(\text{S}-\text{Phe}-\text{S}-\text{His-H}^+)\).
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The relative enthalpies of the most stable conformers for the unbound- and bound-forms are presented in Table 2 with their respective $\text{C}_1$ and $\text{C}_2$ dihedral angles.

The same analysis was performed for the unbound-form of the cyclo-[(S)-Phe-(S)-His-H$^+$] within the cavity of the IRMOF-phen-CH$_3$ (IRMOF with a 2,7-dicarboxylate-1-methyl-phenanthrene bridge) and IRMOF-phen-Br (IRMOF with a 2,7-dicarboxylate-9-bromo-phenanthrene bridge). The results for the relative enthalpies and optimized dihedral angles the most stable conformers are presented in Table 3.

### Discussion

Due to some known shortcomings of the AM1 method$^{17}$ for performing conformational analysis, its choice deserves some comments. Firstly, several molecular mechanics force-field were tested, but none have performed satisfactorily in reproducing a stable structure for the model.

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**Figure 4.** The structure of IRMOF-phen with the bound-form of cyclo-[(S)-Phe-(S)-His-H$^+$]. The hydrogen atoms were omitted. The atoms are coded by the following colors: carbon (cyan), oxygen (red), nitrogen (blue) and zinc (gray).

**Table 1.** Optimized dihedral angles (°) enthalpies (in kJ mol$^{-1}$) of hydration, $\Delta H_f$ of formation in gas phase, $\Delta H_f$(g), and of formation in aqueous solution, $\Delta H_f$(aq), for the stochastic conformational search of cyclo-[(S)-Phe-(S)-His-H$^+$]. The numbers in parenthesis are relative enthalpies (in kJ mol$^{-1}$)

<table>
<thead>
<tr>
<th>Conformer</th>
<th>$\text{C}_1$</th>
<th>$\text{C}_2$</th>
<th>$\Delta H$</th>
<th>$\Delta H_f$(g)</th>
<th>$\Delta H_f$(aq)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conf-1</td>
<td>$-139.9$</td>
<td>$-61.5$</td>
<td>$-243.5$</td>
<td>$587.9 (0.00)$</td>
<td>$344.4 (0.00)$</td>
</tr>
<tr>
<td>Conf-2</td>
<td>$60.8$</td>
<td>$-60.5$</td>
<td>$-238.1$</td>
<td>$590.7 (2.80)$</td>
<td>$352.6 (8.21)$</td>
</tr>
<tr>
<td>Conf-3</td>
<td>$-143.1$</td>
<td>$63.3$</td>
<td>$-243.5$</td>
<td>$591.9 (4.01)$</td>
<td>$348.4 (4.07)$</td>
</tr>
<tr>
<td>Conf-4</td>
<td>$60.2$</td>
<td>$51.5$</td>
<td>$-238.5$</td>
<td>$593.0 (5.13)$</td>
<td>$354.5 (10.1)$</td>
</tr>
<tr>
<td>Conf-5</td>
<td>$60.5$</td>
<td>$-123.8$</td>
<td>$-241.4$</td>
<td>$601.6 (13.7)$</td>
<td>$360.2 (15.8)$</td>
</tr>
<tr>
<td>Conf-6</td>
<td>$-142.9$</td>
<td>$-150.0$</td>
<td>$-253.1$</td>
<td>$602.7 (14.8)$</td>
<td>$349.6 (5.23)$</td>
</tr>
<tr>
<td>Conf-7</td>
<td>$65.7$</td>
<td>$57.6$</td>
<td>$-227.6$</td>
<td>$604.7 (16.8)$</td>
<td>$377.1 (32.7)$</td>
</tr>
<tr>
<td>Conf-8</td>
<td>$63.1$</td>
<td>$-61.3$</td>
<td>$-243.5$</td>
<td>$604.8 (16.9)$</td>
<td>$361.3 (16.9)$</td>
</tr>
<tr>
<td>Conf-9</td>
<td>$-122.6$</td>
<td>$58.4$</td>
<td>$-237.2$</td>
<td>$607.1 (19.2)$</td>
<td>$369.9$</td>
</tr>
</tbody>
</table>

*See Figure 1 for the definition of dihedrals angles, $\text{C}_1$ and $\text{C}_2$.

**Table 2.** Relative enthalpy of formation, $\Delta\Delta H_f$ (kJ mol$^{-1}$), and optimized dihedral angles (°) for the most probable conformers of cyclo-[(S)-Phe-(S)-His-H$^+$] within the IRMOF-phen cavity (unbound-form) and chemically linked to the phenanthrene ring of IRMOF-phen

<table>
<thead>
<tr>
<th>Conformer</th>
<th>$\Delta\Delta H_f$</th>
<th>Bound-form</th>
<th>$\text{C}_1$</th>
<th>$\text{C}_2$</th>
<th>Unbound-form</th>
<th>$\text{C}_1$</th>
<th>$\text{C}_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(g',t)</td>
<td>$172.6$</td>
<td>$-62.5$</td>
<td>$-159.8$</td>
<td>$17.8$</td>
<td>$-138.3$</td>
<td>$-115.4$</td>
<td></td>
</tr>
<tr>
<td>(l,t)</td>
<td>$146.9$</td>
<td>$120.6$</td>
<td>$-154.7$</td>
<td>$16.9$</td>
<td>$-154.6$</td>
<td>$177.6$</td>
<td></td>
</tr>
<tr>
<td>(g',g')</td>
<td>$32.5$</td>
<td>$73.5$</td>
<td>$-71.7$</td>
<td>$0.0$</td>
<td>$-142.2$</td>
<td>$62.6$</td>
<td></td>
</tr>
<tr>
<td>(g',g')</td>
<td>$121.2$</td>
<td>$67.0$</td>
<td>$-74.4$</td>
<td>$21.4$</td>
<td>$56.4$</td>
<td>$75.9$</td>
<td></td>
</tr>
<tr>
<td>(g',l)</td>
<td>$117.9$</td>
<td>$-144.6$</td>
<td>$-71.8$</td>
<td>$20.5$</td>
<td>$-141.6$</td>
<td>$-58.8$</td>
<td></td>
</tr>
<tr>
<td>(g',g')</td>
<td>$5.8$</td>
<td>$-64.3$</td>
<td>$-72.6$</td>
<td>$38.9$</td>
<td>$-80.9$</td>
<td>$-37.8$</td>
<td></td>
</tr>
<tr>
<td>(g',l)</td>
<td>$132.3$</td>
<td>$72.1$</td>
<td>$-154.6$</td>
<td>$424.7$</td>
<td>$16.6$</td>
<td>$-77.8$</td>
<td></td>
</tr>
<tr>
<td>(l,g')</td>
<td>$5.3$</td>
<td>$139.1$</td>
<td>$61.6$</td>
<td>$0.7$</td>
<td>$-143.4$</td>
<td>$-21.3$</td>
<td></td>
</tr>
<tr>
<td>(g',g')</td>
<td>$5.3$</td>
<td>$138.2$</td>
<td>$60.8$</td>
<td>$24.4$</td>
<td>$54.8$</td>
<td>$42.8$</td>
<td></td>
</tr>
<tr>
<td>(g',50)</td>
<td>$138.9$</td>
<td>$-144.1$</td>
<td>$-72.5$</td>
<td>$50.3$</td>
<td>$-144.6$</td>
<td>$-60.9$</td>
<td></td>
</tr>
</tbody>
</table>

*See Figure 1 for the definition of the dihedrals angles $\text{C}_1$ and $\text{C}_2$. 

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IRMOF-1 (IRMOF with a 1,4-dicarboxylate benzene bridge), probably due to the unusual bonding in the Zn(4-O) cluster. Secondly, due to the size of the system, for instance, the model system IRMOF-phen-Br + cyclo-[((S)-Phe-(S)-His-H⁺) has the following empirical formula: C_{255}H_{174}O_{106}N_{4}Zn_{32}Br_{12}, so that ab initio or DFT methods are impractical to perform extensive conformational searches. However, since the AM1 method has yielded very good results for reproducing the structure of the IRMOF-1 and we are interested in comparing trends and relative sequences of conformations, we believe that the main conclusions about the confining effects of the IRMOF cavities are reliable. In addition, previous conformation analysis of the neutral cyclo-[(S)-Phe-(S)-His] by semi-empirical methods have yielded results compatible with NMR measurements in benzene and DMSO solutions.

Regarding the proposed new IRMOF-phen it is simpler, from a computational point of view, than the IRMOF-14, which has a 2,7-dicarboxylate pyrene (PDC) bridge. However, despite the phen bridge being less symmetric than the PDC bridge, it is very likely that the phen would form an isoreticular structure. In addition, cavity size and free volume of the IRMOF-phen should be slightly larger than the IRMOF-14, so that it could accommodate the protonated dipeptide cyclo-[(S)-Phe-(S)-His-H⁺] and aldehydes, like benzaldehyde, and HCN within the cavity, in order to promote the stereoselective hydrocyanation reaction.

Also, the modeling of the crystalline IRMOF deserves some comments. It was simulated by one unit cell capped with methyl groups, which enclosed one cavity, as shown in Figure 4. This model has been successfully tested and validated by comparing with crystallographic results, which provided very good agreement when the AM1 method was used. In addition to this structural agreement, the vibrational spectrum of the [Zn₄(4-O)(CH₃OO)₆] complex has been adequately simulated by the AM1 method. Since the model simulates the crystal by a cluster-type approach, it seems reasonable to keep the cluster structure rigid at its optimized structure upon loading with dipeptide and other molecules, because in the case of the crystal it would be expected that the lattice would impose this rigidity for this kind of loading.

From Table 1 it can be observed that the stability of the cyclo-[(S)-Phe-(S)-His-H⁺] conformers in gas phase has the following sequence: (t,g⁻) > (g⁺,g⁻) > (t,g⁺), whereas in solution: (t,g⁻) > (t,g⁺) > (g⁺,g⁻) > (g⁺,50°). In addition to some reordering of the stability sequence of the conformers, the solvent effects have strong influence in the energy differences, causing an increase from 19.2 to 32.7 kJ mol⁻¹ in the energy difference between the most stable and unstable conformers in gas phase and solution, respectively. In gas phase there is a clear separation between Confs-4 and Confs-5 (8.6 kJ mol⁻¹), which is lost in solution. Note also the strong solvent effects in the energy of Conf-6, which becomes the third most stable conformer. Also, pairs of conformers (Confs-2 and Confs-8) and (Confs-4 and Confs-7) have very similar dihedral angles (1 and 2), but their energies are quite different due to the orientation of the histidyl ring. Conformers Confs-4 and Confs-9 have the most probable structure for the proposed structure for the transition state of the cyanide addition to the carbonyl of benzaldehyde. The hydrogen bonded complex would be formed between the carbonyl of benzaldehyde and either hydrogen in the HN(1) or HN(4) groups, and an additional stabilization could be provided by the π-stacking interaction between the phenyl rings of the phenylalanyl residue and the benzaldehyde molecule, as well as with the π-electrons of the histidyl residue.

### Table 3. Relative enthalpy of formation, ΔH (kJ mol⁻¹), and optimized dihedral angles (°) for the most probable conformers of cyclo-[(S)-Phe-(S)-His-H⁺] within the IRMOF-phen-CH₃ and IRMOF-phen-Br cavity

<table>
<thead>
<tr>
<th>Conformer² (His,Phe)</th>
<th>IRMOF-phen-CH₃</th>
<th>IRMOF-phen-Br</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ΔH</td>
<td>¹</td>
</tr>
<tr>
<td>(g⁺,t)</td>
<td>14.0</td>
<td>-113.6</td>
</tr>
<tr>
<td>(t,g⁺)</td>
<td>38.1</td>
<td>-154.5</td>
</tr>
<tr>
<td>(g⁺,g⁻)</td>
<td>41.6</td>
<td>-70.5</td>
</tr>
<tr>
<td>(g⁺,g⁺)</td>
<td>7.3</td>
<td>-54.4</td>
</tr>
<tr>
<td>(t,g⁻)</td>
<td>11.0</td>
<td>-139.8</td>
</tr>
<tr>
<td>(g⁺,g⁻)</td>
<td>5.8</td>
<td>-156.2</td>
</tr>
<tr>
<td>(t,g⁺)</td>
<td>12.0</td>
<td>-138.6</td>
</tr>
<tr>
<td>(g⁺,g⁻)</td>
<td>55.2</td>
<td>40.7</td>
</tr>
<tr>
<td>(g⁺,g⁻)</td>
<td>65.9</td>
<td>66.1</td>
</tr>
<tr>
<td>(g⁺,g⁻)</td>
<td>0.0</td>
<td>-139.9</td>
</tr>
<tr>
<td>(g⁺,g⁻)</td>
<td>57.7</td>
<td>62.0</td>
</tr>
</tbody>
</table>

² See Figure 1 for the definition of the dihedrals angles ¹ 1 and ² 2.
The confining effects of the IRMOF cavity on the conformation of cyclo-[(S)-Phe-(S)-His-H+] can be observed in Table 2, which clearly shows that the bound-form has a very distinct conformational behavior when compared to the unbound-form. Namely, the bound-form has essentially two conformers (61.5, –54.8) and (139.0, 61.0) for the optimized dihedral angles, which are not the same for the unbound-form, that has the (–142.2, 62.6) and (–143.4, –21.3) thermally accessible conformers at room temperature. In addition, for the unbound-form, the chemical environment of the cavity induces significant changes in the conformational behavior of the dipeptide as can be ascertain by comparing Tables 2 and 3. Upon substitution by –CH₃ and –Br groups, the conformer populations change from (–142.2, 62.6) and (–143.4, 21.3) for IRMOF-phen to (–138.9, –61.8) and (–139.5, –50.9) for IRMOF-phen-CH₃ and to (–139.2, –125.0) for IRMOF-phen-Br, where in this last environment there is only one accessible conformation.

Some representative conformers of cyclo-[(S)-Phe-(S)-His-H+] within the IRMOF-phen, IRMOF-phen-CH₃ and IRMOF-phen-Br are presented in Figures 5 e 6.

In addition to the effects in the conformer populations, the substitution of H by CH₃ and Br in the IRMOF-phen...
affects significantly the relative position of the cyclo-
[(S)-Phe-(S)-His-H⁺] within the cavity. Despite the initial
relative position of the dipeptide being the center of the
cavity, during its geometry optimization it migrates to the
top of the IRMOF-phen-CH₃ and IRMOF-phen-Br in
concert with the hydrogen bond between the carboxylic
oxygen and the hydrogen at the protonated histidyl ring.
Thus the adsorption of the dipeptide changes remarkably
with cavity environment.

These results show the importance of confined spaces in
selecting a specific conformation as well as the adsorption
site, thus determining the selectivity of reactions catalyzed
by the dipeptide. Regarding the hydrocyanation of
benzaldehyde, a dipeptide-benzaldehyde complex has been
found which could explain the observed enantioselectivity
in solution and also indicates that this selectivity can be
increased within the cavity of IRMOF-phen. The molecular
structure of the complex is illustrated in Figure 7.

The ONIOM(PBE1:AM1) calculated molecular structure of the
cyclo-[(S)-Phe-(S)-His-H⁺]-benzaldehyde complex within the IRMOF-phen.
On the right, an amplified view of the complex.

The use of the ONIOM(PBE1:AM1) method is quite
important, since the PBE1 hybrid functional₁⁵ improves
the description of hydrogen bonds and intermolecular
interactions quite significantly.₂² Other functionals as well as
HF/6-31G(d,p) and AM1 methods were inadequate
for the study of the cyclo-[(S)-Phe-(S)-His-H⁺]-benzaldehyde
complex either in gas phase or within the IRMOF-phen. In
the ONIOM(PBE1:AM1) calculated structure the complex
is stabilized by a hydrogen bond between the HN(1) and
the carbonyl oxygen as well as π-stacking-type interactions
between the aromatic rings. In addition, considering the
positive charge on the histidyl ring, the anion CN⁻ should
approach the carbonyl group preferably from the side of
this ring, thus inducing enantioselectivity as observed in
solution. However, in solution, this selectivity should be
lower since the conformer (g⁺,50) or conf-9 should have
a very small population, whereas within the IRMOF-phen
it has a significantly population. Indeed, the bound-
form of the cyclo-[(S)-Phe-(S)-His-H⁺] to the IRMOF-
phen, this conformer is the most stable one, and thus the
enantioselectivity predicted within this material should
be even higher. Studies are underway to determine the
structure of the peptide-benzaldehyde complex in this new
IRMOF as well as the transition states related to the addition
of cyanide into the carbonyl.

Conclusions

The confining space of the IRMOFs cavity has
significant effects upon the thermal conformational
populations of the dipeptide cyclo-[(S)-Phe-(S)-His-H⁺],
when compared to conformers in gas or aqueous phases.
In addition, the chemical environment of the cavity can
influence these populations, where an –CH₃ substituent in
the phenanthrene ring of the IRMOF-phen leads to several
distinct thermally accessible conformers, whereas an –Br
substituent leads essentially to one only conformer, at room
temperature. Also, these substituents affect remarkably the
adsorption sites of the dipeptide. We have successfully
determined a stable structure of the cyclo-[(S)-Phe-(S)-His-
H⁺]-benzaldehyde complex within the IRMOF-phen. As
a result, the cavities of the IRMOFs can not only change
the conformer populations, but also stabilize intermediate
structures and complexes by a proper designed environment
of the cavity, thus improving the enantioselectivity of organo-
catalyzed reactions.
Acknowledgment

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