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ARTICLE TYPE

# Crystallographic and *ab initio* Study of Pyridine CH/O Interactions. Linearity of the interactions and influence of pyridine classical hydrogen bonds

Jovan Lj. Dragelj,<sup>a</sup> Goran V. Janjić,<sup>b</sup> Dušan Ž. Veljković,<sup>a</sup> and Snežana D. Zarić<sup>\*a,c</sup><sup>5</sup> Received (in XXX, XXX) XthXXXXXXXXXX 20XX, Accepted Xth XXXXXXXXXXXX 20XX

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The CH/O interactions of pyridine with water molecule were studied by analysing data in the Cambridge Structural Database (CSD) and by *ab initio* calculations. The analysis of the CH/O interactions in the crystal structures from the CSD indicate that pyridine C-H donors do not show preference for linear contacts. The results of the *ab initio* calculations are in accord with the CSD data and show that stabilization energy is larger for bifurcated than for linear interactions. The calculated interaction energies at MP2/cc-pVQZ level for linear CH/O interactions between water and pyridine *ortho*, *meta*, and *para* C-H group are -1.24, -1.94 and -1.97 kcal/mol respectively. The calculated energies for bifurcated *ortho/meta* and *meta/para* interactions are -1.96 and -2.16 kcal/mol. The data in crystal structures from the CSD and *ab initio* calculation show strong influence of simultaneous classical hydrogen bonds of pyridine on CH/O interactions. The results show that simultaneous hydrogen bond strengthens CH/O interaction for about 20%. The calculated interaction energies for linear CH/O interactions between water and pyridine, with simultaneous hydrogen bond, for *ortho*, *meta*, and *para* C-H group are -1.64, -2.34, -2.33 kcal/mol respectively, while for *ortho/meta* and *meta/para* bifurcated interactions are -2.44 and -2.58 kcal/mol. The energies of *meta/para* bifurcated interactions calculated at CCSD(T)(limit) level for pyridine without and with hydrogen bond are -2.30 and -2.69 kcal/mol respectively. The result that nonlinear interactions are energetically favoured can be very important for recognizing CH/O interaction of heteroaromatic rings in crystal structures and biomolecules.

## 25 Introduction

The CH/O interactions are very important in many molecular systems, like biomolecules, crystals and host-guest systems. The CH/O interactions play very important role in stabilizing structures of proteins, 20–25% of the total number of hydrogen bonds in proteins are CH/O interactions.<sup>1–6</sup> These interactions are of particular importance in the interactions of proteins with ligands and for structure of  $\beta$ -sheets.<sup>1,3,7</sup> The CH/O interactions are very important in the crystal engineering<sup>8</sup> and it was shown that they play important role in the recognition of host-guest systems.<sup>9</sup> In numerous studies CH/O interactions were examined by different spectroscopic methods,<sup>10–13</sup> theoretical calculations<sup>2,4,13–17</sup> and using data in the Cambridge Structural Database (CSD)<sup>20,21</sup> and in the Protein Data Bank (PDB).<sup>3,5,6,22</sup>

The CH/O interaction energies can vary from very weak, -0.3 kcal/mol, to very strong, over -4 kcal/mol.<sup>1</sup> Recent studies revealed strong CH/O interaction between fucose and water (-2.55 kcal/mol)<sup>23</sup> and very strong interaction in caffeine-theophylline complexes (-4.64 kcal/mol).<sup>24</sup> Interaction energy of CH/O interactions of aromatic C-H donors depends on substituents on aromatic ring and on acceptor.<sup>16, 25, 26</sup>

Hydrogen bonds with linear or close to linear geometries are energetically more stable than bent ones. Based on directionality it was shown that the CH/O interactions, although can be weak, are hydrogen bonds and not the van der Waals interaction.<sup>21</sup> Namely, the main structural difference between the hydrogen bonds and the van der Waals interactions is preference of hydrogen bonds for linearity.<sup>21</sup> In our recent work, by analyzing crystal structures from the CSD we showed that the CH/O interactions of the C<sub>6</sub>-aromatic molecules do not show preference for the linear contacts.<sup>27</sup> This is caused by the possibility for the simultaneous CH/O interactions with two adjacent C-H groups in C<sub>6</sub> aromatic ring. Bifurcated interactions were observed in substantial number of structures. Moreover, in the structures with the substituent in the o-position there is probability of bifurcated interactions with the substituent. The results of *ab initio* calculations at MP2/cc-pVTZ level showed that stabilization energy is larger for bifurcated interaction than for linear. The energies of linear interactions of benzene with water, methanol, and acetone are -1.28, -1.47, and -1.45 kcal/mol, while of bifurcated are -1.38, -1.63, and -1.70 kcal/mol respectively.

The study of noncovalent interactions of six-membered

nitrogenated aromatic rings is of particular importance since they are commonly found in proteins, nucleotides and many other compounds.<sup>28</sup> Pyridine CH/O interactions were studied on few systems.<sup>29,30</sup> The calculated interaction energy between pyridine *para* C-H group and Me<sub>2</sub>O was -1.3 kcal/mol,<sup>29</sup> while the calculated energy for charge assisted simultaneous interaction between (MeO)<sub>2</sub>PO<sub>2</sub><sup>-</sup> and *meta* and *para* C-H groups of pyridine was -7.2 kcal/mol.<sup>29</sup>

Nitrogen in pyridine molecule is a good acceptor of hydrogen bonds. Numerous studies have been performed to understand the impact of hydrogen bonding on properties of heteroaromatic molecules.<sup>28,31</sup> Our recent results show that hydrogen bonds of pyridine nitrogen remarkably influence pyridine stacking interactions.<sup>32</sup> The calculated energies of the stacking interactions are substantially stronger for pyridines with hydrogen bonds; the energy of the stacking interaction between pyridine/water complexes is -6.86 kcal/mol, while the energy of pyridine-pyridine interaction is -4.08 kcal/mol. Interestingly it was shown that in the energy of the most stable stacking pyridine/water complex, the contribution of the local parallel-alignment water/pyridine interactions (-2.98 kcal/mol) is somewhat larger than the contribution of stacking interaction between two pyridine molecules (-2.67 kcal/mol).<sup>33</sup>

Here we present the systematic study of CH/O interactions between pyridine and water molecule. The pyridine/water CH/O interactions were studied by analyzing the data in the CSD and by *ab initio* calculations on model systems. Influence of simultaneous pyridine hydrogen bonding on CH/O interactions was also studied. To the best of our knowledge this is the first study of CH/O interactions of heteroaromatic ring indicating the importance of nonlinear interactions.

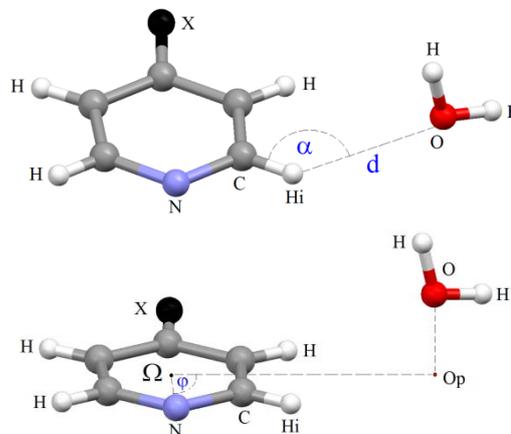
## Methodology

### CSD search

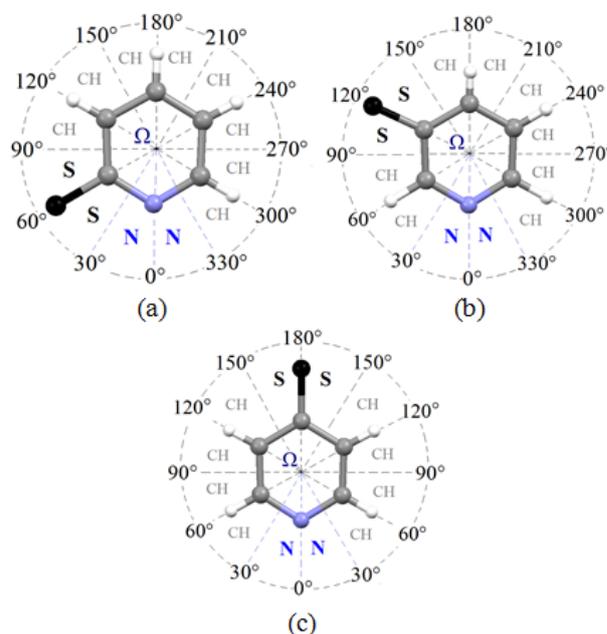
It was shown that analysing the data in the crystal structures from the Cambridge Structural Database gives important information about noncovalent interactions.<sup>33,34,35</sup> The crystallographic analysis is based on the crystal structures archived in the CSD (November 2011 release, version 5.33<sup>36</sup>). To study CH/O interactions between pyridine and water molecule we searched for crystal structures containing non-coordinated, non-substituted pyridine and water molecules. We found small number of structures with non-substituted pyridines. Therefore, we based the study of CH/O interactions on monosubstituted non-coordinated pyridine molecules. We had three sets of structures with pyridine molecule substituted in *ortho*, *meta* or *para* position.

The geometric parameters used for search the CSD and description of CH/O interactions are shown in Fig.1 and 2. The geometric criteria for CH/O interactions were the same as in study of CH/O interactions with benzene molecule.<sup>27</sup> A contact was considered a CH/O interaction if the distance between a C-H group of pyridine molecule and a water oxygen atom (*d*) was less than 2.9 Å and angle  $\alpha \geq 110^\circ$  (Fig.1). To avoid the parallel alignment interactions of the O-H group<sup>33</sup> and short H-H contacts, additional criterion was used; *d* distance was shorter than distances between interacting hydrogen and any hydrogen atom of water.

The influence of simultaneous classical hydrogen bonds of pyridine nitrogen on pyridine/water CH/O interactions was also studied. We searched for pyridine/water CH/O interactions where pyridine nitrogen has a classical hydrogen bond. The contacts between pyridine molecules and X-H species (X is O, N, F or S), where X...N distance was shorter than 4.0 Å and X-H...N angle is larger than 110°,<sup>37</sup> were considered as hydrogen bonds.



**Fig. 1** The geometric parameters used for search the CSD and analysis of CH/O interactions between water molecule and substituted pyridine molecule: the distance between pyridine C-H group and water oxygen atom is *d*. Angle  $\alpha$  is the C-H...O angle. The distance between the centre of the aromatic ring ( $\Omega$ ) and oxygen atom projection to the plane of that ring ( $O_p$ ) represents the horizontal displacement (offset)  $r_o$ . The angle in the plane of the aromatic ring formed by N atom, the centre of the aromatic ring ( $\Omega$ ) and water oxygen projection to the plane of the ring ( $O_p$ ) is angle  $\phi$ .



**Fig. 2** The distribution of N (region of nitrogen atom), S (region of substituent), and CH (the rest of the space) regions, defined by  $\phi$  parameter, in (a) *ortho*, (b) *meta* and (c) *para* substituted pyridine molecules.

The CSD search program ConQuest1.14<sup>38</sup> was used to retrieve structures satisfying the following criteria: (a) the

crystallographic R factor <10%; (b) the error-free coordinates according to the criteria used in the CSD; (c) the H-atom positions were normalized using the CSD default X-H bond lengths; (d) no polymer structures.

The preference for linear geometry can be observed by the distributions of angle  $\alpha$  (Fig. 1). To obtain more reliable data, cone correction should be used.<sup>21b</sup> In crystal structures, the distribution of bond angle ( $\alpha$ ) suggests that hydrogen bonds in crystals are non-linear for purely geometrical reasons. Namely, the number of hydrogen bonds increases with bond angle  $\alpha$  and distribution is proportional to  $\sin \alpha$ , because there is a greater probability of finding such interactions on the rims of cones of increasing angle  $\alpha$ . To obtain the more relevant frequencies per angle  $\alpha$ , histograms of  $N$  (where  $N$  is the number of interactions in the range  $\alpha$  and  $\alpha+\Delta\alpha$ ) must be replaced by  $N/\sin\alpha$ .<sup>21b</sup> This is called cone correction.

The space around pyridine ring can be divided in three regions (Fig. 2): N region (region of nitrogen atom), S region (region of substituent), and CH region (the rest of the space). Regions are defined by angle  $\varphi$ : N region has angle  $\varphi$  values from 0-30° and 330-360° (in case of *para* substituted pyridines only in range 0-30° as it is symmetric), S region is the region around substituent, while CH region can be in a range 30-330° (in case of *para* substituted pyridines only in range 30-180° as it is symmetric), depending on the position of substituent. We did not search for CH/O interactions in the N and S regions. Namely, interactions in N region are governed by strong tendency of nitrogen atom for hydrogen bonds, while interactions in S region are strongly influenced by the nature of the substituent.

### Ab initio calculations

*Ab initio* calculations were performed on pyridine/water complexes with water in perpendicular orientation, since preliminary calculations on CH/O interactions in pyridine/water complexes and our previous results benzene/water<sup>27</sup> showed that interactions with perpendicular orientations are more stable. The geometries of isolated molecules, the pyridine and the water molecule, were optimized by gradient optimization using the cc-pVTZ basis set and the Møller–Plesset second-order perturbation method (MP2).<sup>39</sup> The optimized geometries were used for the calculation of the interaction energies. The interaction energies were calculated at MP2/cc-pVQZ level, as it is in good agreement with CCSD(T) limit interaction energies,  $\Delta E_{\text{CCSD(T)}(\text{limit})}$ . To estimate the influence of diffuse functions in the basis set, we performed additional single point calculations with cc-pVTZ basis set and including diffuse functions (aug-cc-pVTZ basis set) (Supplementary Information). The results show that diffuse functions influence calculated energies less than 0.1 kcal/mol.

Within each pyridine/water complex geometries of the monomers were kept rigid while the distance  $d$  (Fig. 1) was systematically varied. The interaction energies were corrected for the basis set superposition error (BSSE) using the standard Boys-Bernardi counterpoise procedure.<sup>40</sup> The Helgaker et al. method of extrapolation<sup>41</sup> was used to estimate the CCSD(T) interaction energies at the basis set limit,  $\Delta E_{\text{CCSD(T)}(\text{limit})}$ , of the most stable CH/O bifurcated interaction. All *ab initio* calculations were performed using Gaussian03<sup>42</sup> series of programs.

The interaction energy between water and pyridine molecules

( $\Delta E_{\text{W/Pyr}}$ ) was determined as difference between the energy of water/pyridine complex and the sum of monomer energies. The interaction energy was corrected for basis-set superposition error (BSSE) using the full counterpoise procedure. The interaction energy, corrected for BSSE error, was calculated using the expression (1):

$$\Delta E_{\text{W/Pyr}} = E_{\text{W/Pyr}}^{\text{W/Pyr}} - E_{\text{W}}^{\text{W/Pyr}^*} - E_{\text{Pyr}}^{\text{W/Pyr}^*} \quad (1)$$

where the symbol in parentheses denotes the chemical system considered, the symbols W and Pyr in superscripts and subscripts of energy denote water and pyridine molecules respectively, while molecules with \* (W\* and Pyr\*) denote the molecules with ghost orbitals

The energy of CH/O interaction between water and pyridine molecules, where pyridine forms hydrogen bond (PyrW<sub>H-bond</sub>), was determined for binary systems, as difference between energy of the complex (W/PyrW<sub>H-bond</sub>) and the sum of energy for water molecule, included in CH/O interaction ( $E_{\text{W}}$ ), and energy of pyridine with hydrogen bonded water ( $E_{\text{PyrWH-bond}}$ ). The interaction energy was corrected for basis-set superposition error (BSSE) using the full counterpoise procedure. The interaction energy, corrected for BSSE error, was calculated using the expression (2):

$$\Delta E_{\text{W/PyrWH-bond}} = E_{\text{W/PyrWH-bond}}^{\text{W/PyrWH-bond}} - E_{\text{W}}^{\text{W/Pyr}^*\text{WH-bond}^*} - E_{\text{PyrWH-bond}}^{\text{W/Pyr}^*\text{WH-bond}^*} \quad (2)$$

The influence of hydrogen bond on the energy of water/pyridine interaction is calculated by  $\Delta\Delta E$  (expression (3)):

$$\Delta\Delta E = \Delta E_{\text{W/PyrWH-bond}} - \Delta E_{\text{W/Pyr}} \quad (3)$$

The geometries of pyridine/water structures with bifurcated interactions were optimized using MP2/cc-pVTZ level of theory. In the geometry with hydrogen bond optimization was done keeping coordinates of hydrogen bonded water frozen.

## Results and discussion

By searching the Cambridge Structural Database (CSD) using criteria described in the Methodology section, 9 CH/O interactions of nonsubstituted pyridine and water were found. Because of relatively small number of CH/O interactions with nonsubstituted pyridines statistical analysis of the geometries was not very reliable and the analysis was presented in Supplementary Information. The search of the CH/O interactions of water with monosubstituted pyridines gave large number of contacts and enabled the analysis.

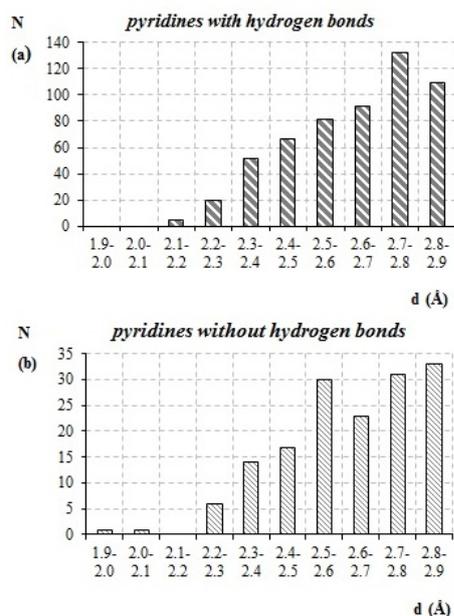
By searching the CSD 717 CH/O interactions between monosubstituted pyridine and water molecule were found. In some of the structures, simultaneously with CH/O interaction, pyridine molecule forms classical hydrogen bond. It was shown that hydrogen bond can influence significantly stacking interactions of pyridines.<sup>32</sup> Our preliminary results show that hydrogen bonds can also influence CH/O interactions of pyridine. Therefore, we separately analyzed the CH/O interactions of pyridines with and without hydrogen bonds. In the crystal

structures we found 561 CH/O interactions of pyridines with hydrogen bonds and 156 interactions of pyridines without hydrogen bonds. The number of the CH/O interactions of pyridines without and with hydrogen bonds for three positions of substituents (*ortho*, *meta*, and *para*) is given in Table 1.

**Table 1.** Number CH/O interactions of monosubstituted pyridines with water molecule in crystal structures from the CSD.

Position of substituent	Total	Pyridines with hydrogen bonds	Pyridines without hydrogen bonds
<i>Ortho</i>	271	180	91
<i>Meta</i>	113	95	18
<i>Para</i>	333	266	47
$\Sigma$	717	561	156

The distribution of distance  $d$  for CH/O interactions of pyridines with and without hydrogen bonds is given in Fig. 3. The peak of the distribution of distance  $d$  for pyridines with hydrogen bonds is in range 2.7–2.8 Å, while for pyridines without hydrogen bonds the peak is in range 2.8–2.9 Å (Fig.3).



**Fig. 3** The distribution of distances  $d$  (Fig. 1) of intermolecular pyridine/water CH/O interactions in crystal structures for pyridines with hydrogen bonds and (b) without hydrogen bonds.

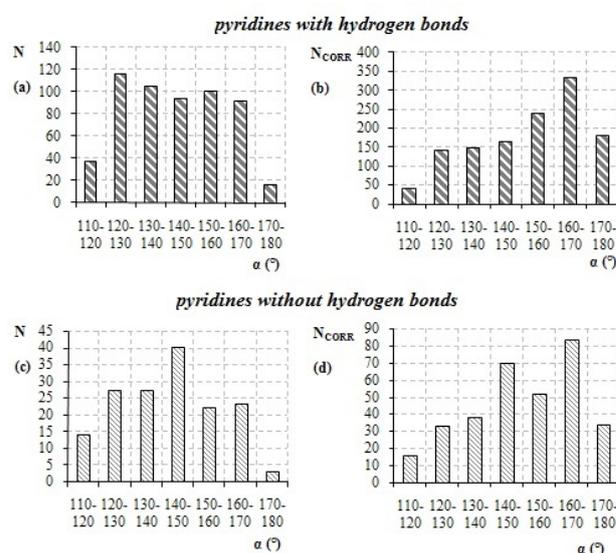
The noncorrected and corrected distributions of angle  $\alpha$  for pyridine/water CH/O interactions are shown in Fig. 4. The noncorrected distributions of angle  $\alpha$  for both groups, pyridines with and without hydrogen bonds, do not show clear preference for any value and show very small number of linear interactions with angle  $\alpha$  close to 180° (Fig. 4). These distributions are similar to the distribution obtained for CH/O interactions with aryl groups<sup>27</sup> and quite different than the distribution for strong hydrogen bonds of alcohols.<sup>43</sup> Namely, analysis of hydrogen bonds of alcohols based on CSD data show clear preference for linear geometries with small number of contacts with the angle  $\alpha$

below 150°.<sup>43</sup>

The correct angular preference for the hydrogen bonds can be considered after cone correction, that is very important for the weak hydrogen bonds.<sup>21</sup> The correction is described in Methodology section. The diagrams for the CH/O interactions with the cone-correction are shown in Fig. 4b (for pyridines with simultaneous hydrogen bonds) and Fig. 4d (for pyridines without hydrogen bonds). The corrected diagrams indicate that CH/O interactions have slight preference for the linear arrangements, similar to CH/O interaction of aryl group and water molecule.<sup>27</sup>

Although both corrected diagrams show similar preference for linearity, there is a slight difference. The CH/O interactions of pyridines with hydrogen bonds, have somewhat larger tendency towards linear orientations.

The distributions of angle  $\phi$  (Fig. 2) for CH/O interactions of pyridines with and without hydrogen bonds are shown in Fig. 5-7. The diagrams were shown separately for *ortho*, *meta* or *para* substituted pyridines. The N region is not shown, while the gaps in diagrams correspond to the region of the substituent (Fig. 2). Structures of *para* substituted pyridines are symmetric and range of angle  $\phi$  from 30° to 180° is shown (Fig. 7).



**Fig. 4** Distributions of angle  $\alpha$ : Noncorrected (a) and cone-corrected (b) for pyridine/water CH/O interactions of pyridines with hydrogen bond and noncorrected (c) and cone-corrected (d) for pyridine/water CH/O interactions of pyridines without hydrogen bonds.

The diagrams of distributions of angle  $\phi$  for pyridines with hydrogen bonds are shown in Fig. 5a, 6 and 7a. The dominant peaks for set of *ortho* substituted pyridines (Fig. 5a) are in regions 110-120°, 150-160°, 190-200°, 270-280°, 300-320° and not so pronounced in the region 220-230°. These peaks, except peak at 110-120°, correspond to the areas between pyridine C-H groups (Fig.2) and it indicates preference for regions between pyridines C-H groups. In case of *meta* substituted pyridines (Fig. 6), one very pronounced peak is present in the region 170-180°, and less pronounced in the region 60-70°, indicating the preference for CH/O interaction with *para* and *ortho* C-H group respectively. In *para* substituted pyridines (Fig. 7a) there is pronounced peak in region 120-130° indicating preference for interaction with *meta* C-H group.

In case of pyridines without hydrogen bonds for *ortho* substituted (Fig. 5b) the most dominant peak is in region 190-200° and not so pronounced in 110-120°, 160-170° and 300-310° regions, indicating the preference for interactions in between *para/meta*, proximity of *meta*, between *meta/para*, and proximity of *ortho* C-H groups respectively. For the set of *meta* substituted pyridines the number of interactions is too small preventing analysis (Table 1). Finally, in case of *para* substituted pyridines (Fig. 7b) one peak is in region 120-130° and not so pronounced one in region 90-100° showing the preference for proximity of *meta* C-H group and in between *meta* and *ortho* C-H groups.

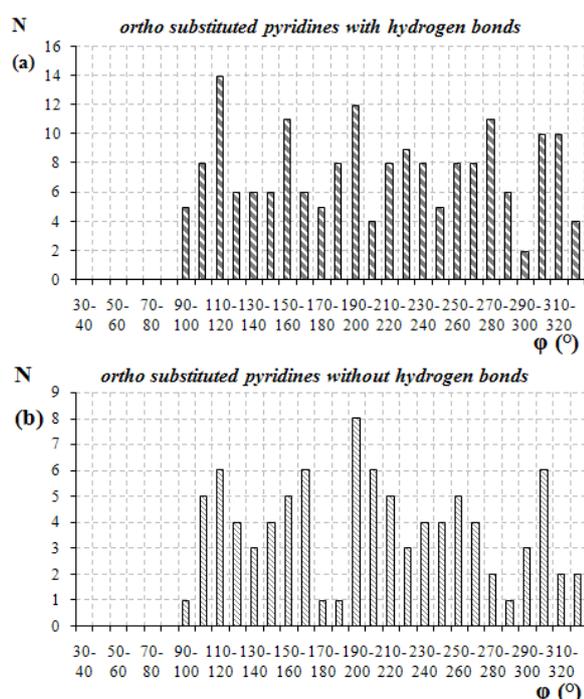


Fig. 5 Distributions of angle  $\phi$  for: *ortho* substituted pyridines with (a) and without (b) hydrogen bonds.

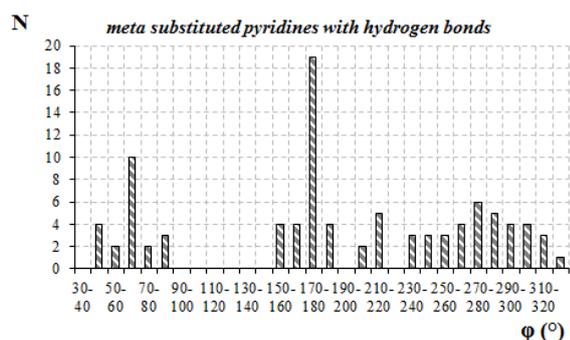


Fig. 6 Distributions of angle  $\phi$  for *meta* substituted pyridines with hydrogen bonds. The distribution for pyridines without hydrogen bonds is not shown because of small number of interactions.

The data in Fig. 5-7 indicate strong influence of substituents on the distributions of angle  $\phi$ . All distributions have peaks at angle  $\phi$  corresponding to position of C-H group in vicinity of the substituents (at the position of the substituent there are gaps on the diagrams). In all distributions, except for *ortho* substituted without hydrogen bond (Fig. 5b), these peaks are the most

pronounced. Visual analysis of the crystal structures showed that in majority of cases water oxygen forms simultaneous interactions with pyridine C-H group and substituent. An example is shown in Fig. S4 (Supplementary Information).

Almost all peaks that are not in vicinity of substituent are between two pyridine C-H groups. Moreover, data on nonsubstituted pyridines also indicate preference for the interactions between two C-H groups (Supplementary Information). As was mentioned above, we found quite small number of interactions between nonsubstituted pyridines and water, however, the data on angle  $\phi$  indicate preference for the interactions between two C-H groups. The contacts with  $\phi$  values close to 90°, 150°, 210° and 270° probably are consequence of the bifurcated CH/O interactions with two pyridine C-H groups. In our previous study on CH/O interactions between benzene and water we observed substantial number of bifurcated interactions, 33% of contacts, using geometrical criteria  $d < 2.9 \text{ \AA}$  and  $\alpha < 110^\circ$ .<sup>27</sup> In this work using less restricted criteria for bifurcated CH/O interaction ( $d < 3.2 \text{ \AA}$  and  $\alpha < 110^\circ$ )<sup>41</sup> 122 (94 with hydrogen bonds, 28 without hydrogen bonds) bifurcated interactions were found. It is 10% of all CH/O interactions with pyridines. These results show a lower tendency of pyridine molecules for bifurcated interaction, than benzene molecules.<sup>27</sup> This is in agreement with our observation that substituents have strong influence on  $\phi$  values for substituted pyridines; in Fig. 5-7, the most pronounced peaks are in vicinity of substituents, and, as was mentioned, in large number of CH/O interactions water molecule forms simultaneous interactions with substituent.

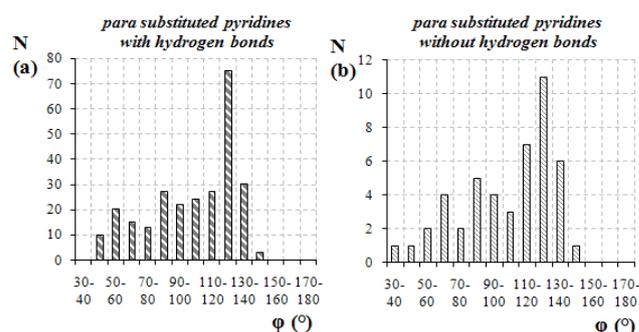
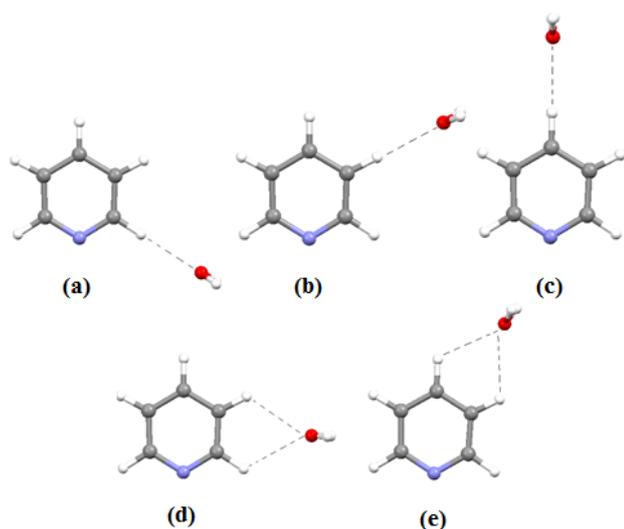


Fig. 7 Distributions of angle  $\phi$  for: *para* substituted pyridines with (a) and without (b) hydrogen bonds

### Ab initio calculations

**CH/O interactions of pyridine without hydrogen bond.** To estimate the interaction energies in the linear and bifurcated CH/O interactions of pyridine as CH donor the calculations were performed on pyridine/water model system. Five orientations of the water molecule were considered (Fig. 8). In all cases the O atom is in the plane of the pyridine ring. In the bifurcated geometries the oxygen atoms were on the bisector of the C<sup>-</sup>O-C angle of pyridine. In these five orientations H-O-H plane of water was perpendicular to the pyridine ring plane, since previous results on CH/O interactions with benzene ring<sup>27</sup> and our preliminary results on pyridine/water complex showed that perpendicular orientations are more stable than coplanar orientation. The results of the calculations are shown at Table 2.

The calculated energies for the CH/O interactions show that the strongest interaction energy is -2.16 kcal/mol (Table 2). It is bifurcated interaction with water interacting with *meta* and *para* C-H groups. The energy for the bifurcated interaction with *ortho* and *meta* C-H groups is -1.96 kcal/mol. In general, energy of CH/O interactions of pyridine with water tends to increase in order *ortho*, *meta*, *para*. The calculated energy for the linear interaction with C-H group in *ortho* position is -1.24 kcal/mol, while energies for C-H groups in *meta* and *para* positions are stronger -1.94 and -1.97 kcal/mol respectively.

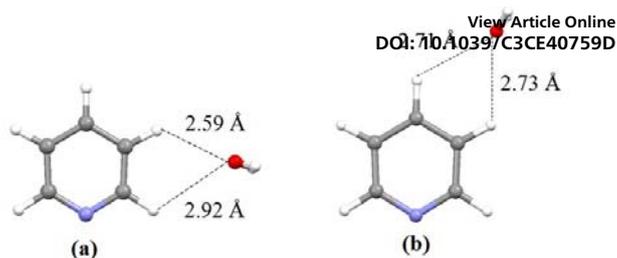


**Fig. 8** Different geometries of the pyridine/water (W/Pyr) model system. In linear CH/O interactions water interacts with C-H group in (a) *ortho*, (b) *meta*, (c) *para* position. In bifurcated CH/O interactions water interacts with C-H groups in (d) *ortho* and *meta* and (e) *meta* and *para* positions.

The energy for bifurcated interaction between *meta* and *para* C-H groups of pyridine was also estimated at the CCSD(T) level at the basis set limit,  $\Delta E_{\text{CCSD(T)}(\text{limit})} = -2.30$  kcal/mol (Table 2). The interaction energy calculated at MP2/cc-pVQZ level, -2.16 kcal/mol, is in good agreement with  $\Delta E_{\text{CCSD(T)}(\text{limit})}$ .

Geometries of *ortho/meta* and *meta/para* pyridine/water complexes were optimized. The optimized geometries are shown in Fig. 9. Calculated interaction energy on optimized geometries are -2.05 and -2.21 kcal/mol respectively (Fig. 9). In both *ortho/meta* and *meta/para* pyridine/water complexes distances between water oxygen atom and pyridine C-H groups are not the same (Fig. 9), since C-H groups do not have the same tendencies for the interactions, however, the difference is larger for

*ortho/meta*-complex.



**Fig. 9** Optimized geometries of pyridine/water structures with water interacting with a) *ortho* and *meta* C-H group and b) *meta* and *para* C-H groups.

In comparison to previous results on CH/O interactions between benzene and water molecules,<sup>27</sup> pyridine/water interactions are substantially stronger (except the interaction with C-H group in *ortho* position). The calculated energies of CH/O interactions of benzene with water are -1.28 kcal/mol for linear and -1.38 kcal/mol for bifurcated interaction.<sup>27</sup> In terms of geometry, the optimal O...H distance for linear CH/O interactions with C-H groups in *meta* or *para* position (2.4 Å) is equal to those of water-benzene linear CH/O interactions (2.4 Å), but distance is somewhat larger with C-H group in *ortho* position (2.5 Å). The bifurcated water/pyridine CH/O interactions have the same optimal O...H distance (2.7 Å) (Table 2) as the bifurcated water-benzene interaction.<sup>27</sup>

The calculations on CH/O interactions in pyridine/water systems are in agreement with the results obtained by the crystal structure data analysis from the CSD. Distribution of distance  $d$  (Fig. 1) for intermolecular CH/O interactions without hydrogen bonds in crystal structures shows peaks in the range 2.7–2.9 Å (Fig. 3) which is in agreement with the calculated distance for most stable pyridine/water model system (Table 2). The distribution of angle  $\phi$  in crystal structures (Fig. s 5-7) indicate that water molecules that are not in vicinity of substituents have tendency to be positioned somewhere in between two pyridine C-H groups which is in agreement with calculated larger interaction energies for bifurcated interactions.

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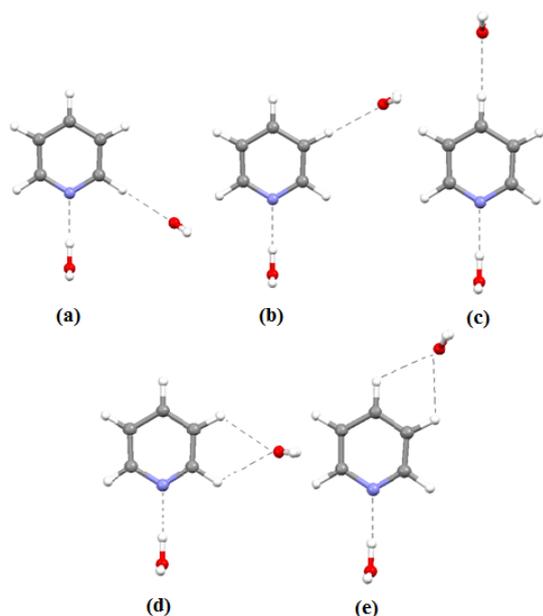
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**Table 2.** Calculated interaction energies (in kcal/mol) and the optimal distances  $d^a$  (in Å) of pyridine/water CH/O interactions in model systems without (Fig. 8) and with hydrogen bond (Fig. 10).

Model system	W/Pyr		W/PyrW <sub>H-bond</sub>		$\Delta\Delta E$
	d (H $\cdots$ O)	$\Delta E$	d (H $\cdots$ O)	$\Delta E$	
	<i>MP2/cc-pVQZ level</i>				
<i>Ortho</i>	2.5	-1.24	2.4	-1.64	-0.40
<i>Meta</i>	2.4	-1.94	2.4	-2.34	-0.40
<i>Para</i>	2.4	-1.97	2.4	-2.33	-0.36
<i>Ortho/Meta</i>	2.7	-1.96	2.7	-2.44	-0.48
<i>Meta/Para</i>	2.7	-2.16	2.7	-2.58	-0.42
	<i>CCSD(T) level at the basis set limit</i>				
<i>Meta/Para</i>	2.7	-2.30	2.7	-2.69	-0.39

<sup>a</sup> Fig. 1.**CH/O interactions of pyridine with simultaneous hydrogen bond.**

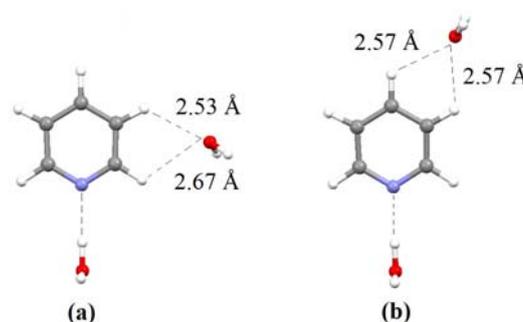
The results of the CSD search presented in this paper showed that most of pyridine/water CH/O interactions are interactions of pyridines with hydrogen bonds. The data from crystal structures indicated that the hydrogen bond influences CH/O interactions (Fig.s 3-7). To study the influence of pyridine hydrogen bond on pyridine/water CH/O interactions by *ab initio* calculations, model systems with water molecule as hydrogen donor were used. All model systems had a perpendicular water molecule with H $\cdots$ N distance of 2.0 Å, as it was shown to be the most stable geometry for pyridine/water hydrogen bond.<sup>32</sup> The model systems for linear and bifurcated CH/O interactions are shown in Fig. 10.

**Fig. 10** Model systems for pyridine/water interactions of pyridine with hydrogen bond, W/PyrW<sub>H-bond</sub>. In linear CH/O interactions water interacts with CH groups in (a) *ortho*, (b) *meta*, (c) *para* position. In bifurcated CH/O interactions water interacts with CH groups in (d) *ortho* and *meta* and (e) *meta* and *para* positions.

All interaction energies in systems with hydrogen bonds are stronger than -2.0 kcal/mol (except for *ortho* CH group) and bifurcated interactions are stronger than linear. The strongest interaction is *meta/para* bifurcated interaction with the energy of -2.58 kcal/mol at the MP2/cc-pVQZ level. The energy of this interaction was also estimated at the CCSD(T) level at the basis set limit,  $\Delta E_{\text{CCSD(T)}(\text{limit})} = -2.69$  kcal/mol (Table 2).

The difference in the energy of the CH/O interactions of pyridines without and with hydrogen bonds,  $\Delta\Delta E$ , (Table 2) shows the influence of hydrogen bond on CH/O interactions. The difference in energy is between -0.36 kcal/mol and -0.48 kcal/mol; the CH/O interactions of pyridine with hydrogen bond are around 20% stronger. The smallest influence was observed on CH/O interaction in *para* position which is in accord with NPA analysis presented in Supplementary Information.

Geometries of bifurcated *meta/para* and *ortho/meta* CH/O interactions of pyridine with hydrogen bond were optimized. In case of *ortho/meta* CH/O interaction, optimized geometry shows slight preference for *meta* C-H group, as the H $\cdots$ O distances between water oxygen and *ortho* and *meta* C-H group are 2.67 Å and 2.53 Å respectively (Fig. 11a). In optimized geometry for *meta/para* CH/O interaction H $\cdots$ O distances are the same and relatively short (2.57 Å) (Fig. 11b). The calculated energies of CH/O interactions in the optimized structures are -2.50 kcal/mol for *ortho/meta* and -2.61 kcal/mol for *meta/para* CH/O interactions.

**Fig. 11** Optimized geometry of water/pyridine/water structure with water interacting a) *ortho* and *meta* C-H group and b) *meta* and *para* C-H groups.

The calculated CH/O interaction energies in this work, between pyridine and water, indicate that these interactions are relatively strong among CH/O interactions. Energies of CH/O interaction of aromatic ring in amino acid side chains were previously calculated only for linear CH/O interaction. The calculated energy between *ortho* positioned CH donor group of phenyl ring (as tyrosine model) was -1.3 kcal/mol, while interactions of indole and imidazole rings, presenting side chains of tryptophan and histidine, were -2.1 kcal/mol and -2.3 kcal/mol, respectively.<sup>16</sup> Our calculated energies for linear interactions of pyridine with hydrogen bonds are quite similar. However, we calculated also bifurcated interactions and showed that they are stronger (Table 2).

Strength of CH/O interactions of aromatic C–H donors depends on the substituents on the aromatic ring and on the acceptor<sup>16,25,26</sup> and some of the interactions are stronger than interactions calculated in this work. For example, there are very strong CH/O interactions in 1,2,4,5-tetrafluorobenzene–acetone complex estimated to be -3.2 kcal/mol<sup>26</sup> and bifurcated interactions between caffeine and theophylline estimated to be even -4.64 kcal/mol.<sup>24</sup>

## Conclusions

The analysis of data from the crystal structures in the Cambridge Structural Database indicate that angular distribution of pyridine/water CH/O interactions do not show strong preference for linear contacts and that pyridine ring substituents have strong influence on CH/O interactions. Visual analysis showed that very often water oxygen forms simultaneous interactions with pyridine C-H group and substituent. Water molecules that are not in vicinity of the substituent have tendency to form bifurcated CH/O interactions with two adjacent CH groups of pyridine.

The calculated energies of pyridine/water CH/O interactions are in agreement with the data in the crystal structures; bifurcated interactions are stronger than the linear ones.

Calculated energies show that classical hydrogen bonds of the pyridine nitrogen have strong influence on CH/O interactions. Pyridines with hydrogen bond have around 20 % stronger CH/O interactions than the pyridines without hydrogen bonds. The strongest calculated CH/O interaction is bifurcated *meta/para* interaction of pyridine with hydrogen bond, the energy at CCSD(T) level at the basis set limit is -2.69 kcal/mol.

These results can be very important for recognizing CH/O interactions of heteroaromatic rings, since the results show that nonlinear interactions are energetically favoured.

## Notes and references

<sup>a</sup>Department of Chemistry, University of Belgrade, Studentski trg 12-16, 11000 Belgrade, Serbia. E-mail: [szaric@chem.bg.ac.rs](mailto:szaric@chem.bg.ac.rs)

<sup>b</sup>ICTM, University of Belgrade, Njegoševa 12, 11 000 Belgrade, Serbia.

<sup>50</sup>Department of Chemistry, Texas A & M University at Qatar P.O. Box 23874 Doha, Qatar

†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See

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# Crystallographic and *ab initio* Study of Pyridine CH/O Interactions. Linearity of the interactions and influence of pyridine classical hydrogen bonds

Jovan Lj. Dragelj, Goran V. Janjić, Dušan Ž. Veljković, and Snežana D. Zarić

The study of pyridine/water CH/O interactions showed that nonlinear interactions are energetically favoured.

