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Original scientific paper

A DFT study of the chemical reactivity of cimetidine A, C and D in the gas phase and in H_2O, MeOH and EtOH solvents

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Abstract: In the present work, the chemical reactivity of cimetidine A, C and D in different solvents was analyzed through the evaluation of global and local DFT reactivity descriptors. In the gas, MeOH and EtOH phases, cimetidine A, C and D exhibit energy differences of 3–11 kcal** mol^{-1}. However, in the aqueous phase, cimetidine A and D are approximately isoenergetic. The values of the hardness indicate that cimetidine A, C and D are more reactive in the presence of a solvent than in the gas phase. In addition, the results suggested that CimC and CimD are better nucleophiles that CimA. The values of the Fukui function suggest that the more reactive sites of CimA are not modified in the different solvents. In the case of CimC, the more reactive sites to electrophilic and free radical attack are located on the thioether sulfur. For CimD, the number and place of the electrophilic and free radical sites are independent of the solvent.

Keywords: cimetidine; reactivity; HSAB; Fukui; DFTs.

INTRODUCTION

Cimetidine, Fig. 1, is a potent histamine-H2 receptor antagonist suitable to inhibit stomach acid production because it is able to bind to an H2-receptor located

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** 1 kcal = 4184 J
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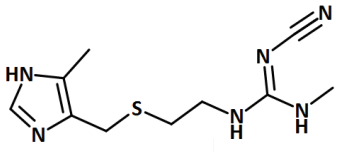

Fig. 1. General structure of *N*-cyano-*N*′-methyl-*N*″-{2--[[(5-methyl-1*H*-imidazol-4-yl)methyl]thio]ethyl}guanidine (cimetidine).

on the basolateral membrane of the astric parietal cell, blocking histamine effects.[1] This drug is one of the most used proton pump inhibitors for treating peptic ulcers in the world, by which, it is considered the first blockbuster drug.[2] Cimetidine has four anhydrous polymorphic forms A (CimA), B (CimB), C (CimC), and D (CimD) and the hydrated forms M1, M2 and M3.[3] The crystal structures of CimA, CimC and CimD are reported in the literature, but that of CimB has yet to be identified.[2] Notably, only CimA and CimB have been employed in the manufacture of pharmaceutical tablets and suspensions, respectively.[4,5] At the industrial level, CimA is the preferred form of cimetidine because it can be obtained in a pure crystallographic state and its physical properties, such as good flux and low adherence to industrial equipment, allow its easy manipulation on a large scale.[5,6] Contrarily, CimB and CimC exhibit poor flux, while CimD is not compressible and thus, they cannot be employed to fabricate tablets.[4] Interestingly, CimC has not been employed in pharmaceutical formulations, even though it might be more effective than CimA, CimB and CimD at lower dosages.[7] In the solid state, polymorphs CimA, CimC and CimD are isoenergetic,[2] but CimC is readily transformed to CimB upon minor mechanical treatment.[4,8] Furthermore, it was observed that both CimB and CimC are transformed to CimA, whereas CimA is transformed to CimD only upon nucleation.[4] On the other hand, in aqueous conditions, CimA changes completely to CimB in a short time, whereas it is transformed to D in ethanol:water 1:1.[4] Here, it is important to mention that if crystals of a pharmaceutical compound exhibit polymorphism, then their physical properties, stability, biological activity, and processability will be dependent on their crystalline form.[9–13] Furthermore, the crystal structure of cimetidine is crucial for understanding its dissolution behavior and therapeutic effectiveness.[4] Thus, an extensive characterization of this drug is necessary to establish clearly the relevance of the crystal form on the biological activity.[3–5,14,15] Here, it is interesting to mention that the presence of a solvent may modify the chemical reactivity of cimetidine, allowing the dosages of this drug and its stability to be controlled. Therefore, a good understanding of the chemical reactivity of cimetidine in different solvents may become useful to recognize how to increase the efficacy of this drug when it is employed in the fabrication of either suspensions or solutions. In this sense, the accepted theories of quantum chemistry provide adequate techniques to analyze the chemical reactivity of a molecular system. Cimetidine has been studied in the gas phase, through theoretical quantum methods in order to analyze its conformation and tautomer stability at

the AM1, HF/6-31G**, MP2/6-31G**//HF6-31G**[16] and B3LYP/6-31G(d) levels of theory.[17] In addition, the intramolecular interactions in cimetidine were analyzed by Karpinska *et al*., but it was not clarified which conformer was studied.[16] Additionally, the intramolecular interactions between cimetidine and the endothelium were analyzed employing docking studies and the obtained results suggest that cimetidine shows ability to bind to the endothelial E-selectin (E-sel) and its ligand sialyl Lewis X (sLex).[18] Olea-Roman *et al*. studied the coordination behavior of cimetidine form A with transition metal ions at the B3LYP/def2-TZVP level of theory, in the gas phase. It was found through electrostatic potential maps that the more reactive zones of CimA are in the imidazolic nitrogen and the thioether sulfur.[19] Additionally, Singh *et al*. found, at the B3LYP/6-31G*(d,p) level, that cimetidine is able to donate electrons through nitrogen and oxygen atoms to an acceptor molecule with empty and low energy orbital.[20] However, in spite of the interest dedicated to cimetidine from experimental and theoretical point of views, the chemical reactivity of cimetidine A, C and D at the molecular level in different solvents have not hitherto been analyzed. Therefore, in the present work, their reactivity was evaluated through global and local DFT reactivity descriptors to obtain a deeper understanding of the chemical behavior of this important anti-ulcer drug in the gas, H_2O, MeOH and EtOH phases.

Theory

The chemical reactivity of cimetidine was analyzed through conceptual reactivity parameters derived from density functional theory (DFT).[21] The global parameters used in the present work were the electronic chemical potential (μ), the electronegativity (χ), hardness (η)[22–24] and the global electrophilicity index (ω):[25]

$$\mu = \left(\frac{\partial E}{\partial N}\right)_{v(r)} = -\frac{1}{2}(I + A) \tag{1}$$

$$\chi = -\mu \tag{2}$$

$$\eta = \left(\frac{\partial \mu}{\partial N}\right)_{v(r)} = \left(\frac{\partial^2 E}{\partial N^2}\right)_{v(r)} = (I - A) \tag{3}$$

$$\omega = \frac{\mu^2}{2\eta} \tag{4}$$

In Eqs. (1)–(4), E, N, and $v(r)$ are the energy, number of electrons, and the external potential of the system, respectively. The vertical electronic affinity (A) is calculated as $A = E(N)–E(N+1)$, where $E(N)$ and $E(N+1)$ are the total ground-state energies in the neutral N and singly charged ($N+1$) configurations. The ion-

ization potential (I) is calculated as $I = E(N–1)–E(N)$. In addition to the global reactivity parameters, it is possible to define local reactivity descriptors that can be used to study the reactivity on different sites within a molecule.[21] This local reactivity can be evaluated through the Fukui function ($f(r)$),[26,27] which is defined as:[26]

$$f(\vec{r}) = \left(\frac{\partial \rho(\vec{r})}{\partial N} \right)_{v(\vec{r})} = \left(\frac{\partial \mu}{\partial v(\vec{r})} \right)_{N} \tag{5}$$

where $\rho(r)$ is the electronic density. $f(r)$ allows the identification of preferred regions where a chemical species will alter its electronic density when the number of electrons is modified. Thus, this function indicates the susceptibility of the electronic density to deformation at a given position upon acceptance or donation of electrons.[21–26] Moreover, it is important to highlight that sites in chemical species with the largest values of the Fukui function (FF) are those with higher reactivity.[27] The FF can be evaluated using a finite difference approximation. However, the discontinuity of the electron density with respect to the number of electrons (N) leads to three types of FFs for a system, namely $f^{+}(r)$, $f^{-}(r)$, and $f^{0}(r)$ for nucleophilic, electrophilic, and free radical attacks, respectively:[21]

$$f^{+}(\vec{r}) = \rho_{N+1}(\vec{r}) - \rho_{N}(\vec{r}) \tag{6}$$

$$f^{-}(\vec{r}) = \rho_{N}(\vec{r}) - \rho_{N-1}(\vec{r}) \tag{7}$$

$$f^{0}(\vec{r}) = \frac{1}{2}\left[\rho_{N+1}(\vec{r}) - \rho_{N-1}(\vec{r}) \right] \tag{8}$$

METHODOLOGY

The initial geometries of cimetidine A, C and D were generated from the CIF files CIMETD03, CIMETD04 and CIMETD01, respectively, obtained from the Cambridge Crystallographic Data Centre.[28] These geometries in the gas, water, methanol and ethanol phases were optimized using the dispersion-corrected density functional wB97XD.[29,30] This functional was chosen because it has proved to be an excellent method for the study of molecules with intramolecular interactions.[29,30] In addition, the def2TZVP basis set was used.[31,32] The solvent was modeled through the SMD solvation model reported by Truhlar *et al.*[33] All the calculations were realized through the Gaussian 09 packages,[34] and they were visualized with the Gausview,[35] Gabedit[36] and Arguslab packages.[37]

RESULTS AND DISCUSSION

Geometry optimization

The optimized structures of CimA, CimC and CimD in the gas phase at the wB97XD/def2TZVP level of theory are shown in Fig. 2. Note that CimA (Fig. 2a) and CimD (Fig. 2c) are folded while CimC (Fig. 2b) is extended. The total energy (electronic energy and zero-point vibrational energy correction), calculated for CimA, CimC and CimD are –1117.18590, –1117.16810 and –1117.17586

Ha, respectively. From these values, note that CimA is slightly more stable than CimC and CimD. The energy differences between CimA–CimC, CimA–CimD and CimC–CimD are –11.2, –6.3 and 4.9 kcal mol^{-1}, respectively. From these values, it is clear that in the gas phase CimA, CimC and CimD are not iso-energetic and the interconversion among the cimetidine forms is more difficult than in the solid state.

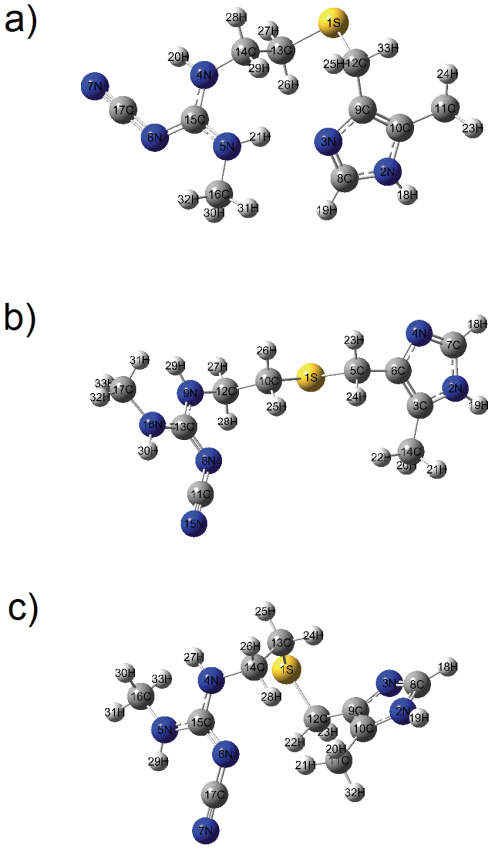

Fig. 2. Structures of: a) CimA, b) CimC and c) CimD in the gas phase, optimized at the wB97XD/def2TZVP level of theory.

A frequency analysis was applied to verify the stability criterion, and the frequency values were all positive in the optimized geometries. A summary of the main bands for CimA, CimC and CimD in the gas phase is depicted in Fig. S-1 of the Supplementary material to this paper. It is possible to identify two bands at approximately 3700 and 3640 cm^{-1} that correspond to N–H stretching vibrations. Here, it is important to mention that the N–H stretching vibrations in heterocyclic compounds are located in the region 3500–3000 cm^{-1}.[38] However, it is well

known that DFT calculations overestimate the frequency values and therefore, it is necessary to apply a vibrational scaling factor. In the present case, the scaling correction factor was obtained *via* the reduced scale factor optimization model described by Alecu *et al*. This factor is 0.950 when the wB97XD/def2TZVP level of theory is employed.[39] If this correction factor is applied, the frequency values for the N–H stretching vibrations are 3515 and 3458 cm^{-1}, which are in the range of the experimental values. Adjacent to these bands, there is a peak at 3470 cm^{-1} (corrected 3297 cm^{-1}) that was only present in the spectrum of CimA, which corresponds to an N–H stretching vibration in the guanidine group. The cyano vibration stretching band was observed at 2300 cm^{-1} (corrected 2185 cm^{-1}). A band at 1670–1620 cm^{-1} (corrected 1587–1539 cm^{-1}) is related to N–H bending vibrations. The band at 1500–1350 cm^{-1} (corrected 1425–1283 cm^{-1}) is associated with C–H bending vibrations, while a typical band for N–H bending vibrations was observed at 500–340 cm^{-1} (corrected 475–323 cm^{-1}).

In order to analyze the influence of the solvent on CimA, CimC and CimD, the structures shown in Fig. 2 were re-optimized at the wB97XD/def2TZVP level of theory and using the SMD solvation model. The electronic energy values including the zero-point vibrational energy correction for CimA, CimC and CimD in the different solvents are reported in Table S-I of the Supplementary material. The extended and folded structures of CimA, CimC and CimD remain in H_2O, MeOH and EtOH solvents and their corresponding *XYZ* coordinates are reported as Supplementary material (see Tables S-II–S-IV of the Supplementary material). Note that in all cases, CimA exhibits the lowest electronic energy value, which suggests that CimA is the most stable form of cimetidine. Furthermore, the energy differences among the cimetidine conformers are reported in Table I. Note that under aqueous conditions, the energy difference between CimA and CimD is only 0.8 kcal mol^{-1}. These results suggest a possible interconversion between these conformers. However, in all the other solvents, a possible interconversion is energetically more restricted because the energy difference among the other cimetidine conformers is larger than 2.6 kcal mol^{-1}.

TABLE I. Energy differences among the cimetidine conformers at the wB97XD/def2TZVP level of theory

Solvent	$\Delta E_{\text{CIMA-CIMC}}$ / kcal mol^{-1}	$\Delta E_{\text{CIMA-CIMD}}$ / kcal mol^{-1}
Gas	–11.2	–6.3
H_2O	–4.3	–0.8
MeOH	–5.8	–2.6
EtOH	–6.0	–2.8

The theoretical IR spectra for CimA in the different solvents are reported in Fig. S-2 of the Supplementary material. Note that there is a slight displacement of the bands in comparison to those obtained in the gas phase. In addition, obs-

erve that the peak at 3470 cm^{-1} exists even in the different solvents. The theoretical IR spectra for CimC and CimD in H_2O, MeOH and EtOH solvents are similar to those obtained in the gas phase.

Additionally, the intramolecular interactions present in the folded structures of CimA and CimD were studied. This kind of interactions may be conveniently analyzed and visualized employing the non-covalent interaction index (NCI) defined by Johnson *et al.*[40] The visualization of these intramolecular interactions in CimA and CimD was realized by plotting the isosurfaces of the reduced density gradient s (related to $|\nabla\rho|/\rho^{4/3}$), and then the isosurfaces were colored according to the values of the electron density to identify attractive and repulsive interactions. The s-colored isosurfaces for CimA, CimC and CimD are shown in Fig. 3, in which the red color represents stabilizing interactions, while the white color suggests destabilization.

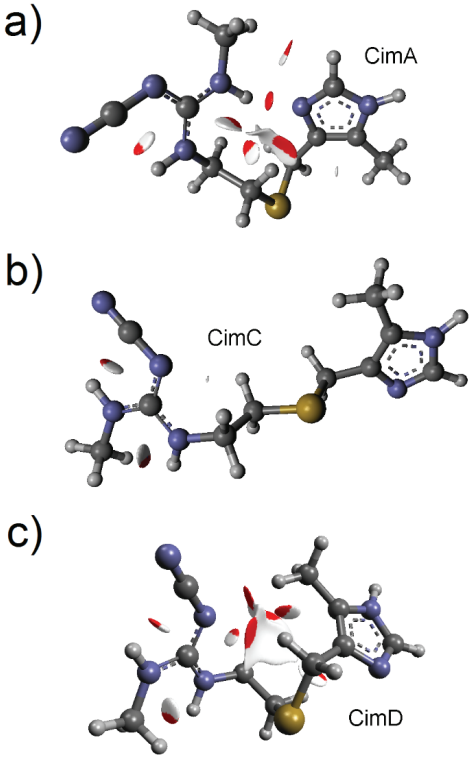

Fig. 3. NCI isosurfaces $\rho = 0.3$ for: a) CimA, b) CimC and c) CimD in the gas phase.

In Fig. 3a, note that the hydrogen bonds correspond to the stabilizing interactions, while the hydrogen–hydrogen interactions are destabilizing. Furthermore, it is possible to observe that the folded structure in CimA is caused by intramolecular interactions among imidazole nitrogen and hydrogen atoms. In the

case of CimC, the structure is extended, which is probably because there is no hydrogen bond in the center of the molecule, see Fig. 3b. The intramolecular interactions in CimD are depicted in Fig. 3c; note the presence of guanidine nitrogen–hydrogen interactions that are causing its folded structure. Similar results were obtained in the solvents H_2O, MeOH and EtOH, see Figs. S-3–S-5, respectively, in the Supplementary material.

Global reactivity parameters

To analyze the chemical behavior of CimA, CimC and CimD, their global and local reactivity descriptors. μ, η, and ω were evaluated through the Eqs. (1), (3) and (4) and the obtained values are reported in Table II. Note that CimD in the gas and aqueous phases has higher hardness values in comparison to those obtained for CimA and CimC. These results suggest greater stability of CimD in the gas and aqueous phases. However, in MeOH and EtOH, the results suggest CimC to be more stable than CimA and CimD. In addition, note that in all cases the hardness values of the cimetidine conformers were higher in the gas phase than in the other solvents, suggesting that CimA, CimC and CimD are stabilized in H_2O, MeOH, and EtOH solvents.

TABLE II Global reactivity parameters for CimA, CimC and CimD obtained at the wB97XD/ /def2TZVP level of theory according to Eqs. (1), (3) and (4)

Medium	η / eV	μ / eV	ω / eV
	CimA		
Gas	9.7	–4.8	1.2
H_2O	6.1	–3.1	0.8
MeOH	6.2	–3.1	0.8
EtOH	6.3	–3.1	0.8
	CimC		
Gas	9.8	–4.9	1.2
H_2O	6.1	–3.1	0.8
MeOH	7.0	–3.5	0.9
EtOH	7.0	–3.5	0.9
	CimD		
Gas	10.1	–5.0	1.3
H_2O	6.6	–3.3	0.8
MeOH	6.6	–3.3	0.8
EtOH	6.7	–3.3	0.8

Moreover, considering that good electrophiles are characterized by high values of μ and ω, then it could be suggested that CimA exhibits a greater electrophilic behavior in comparison to those shown by CimC and CimD, and consequently, CimC and CimD are better nucleophiles than CimA. Here, it is interesting to mention that according to the literature, the degree of nucleophilicity together with steric effects and pK_a values are important factors for predicting

antiulcer activity.[41] Thus, the obtained results suggest that either suspensions or solutions based on CimC and CimD may become more nucleophilic than those based on CimA, and thus, they might have better antiulcer drug behaviors than CimA suspensions.

Local reactivity parameters

The global reactivity trends of a molecular system can be characterized using μ, η, and ω, but it is also important to evaluate local reactivity descriptors, such as FF, to pinpoint the distribution of the reactivity in the molecule and to understand its chemical behavior. The FF was evaluated using Eqs. (6)–(8). The results for CimA in the gas phase are reported in Fig. 4.

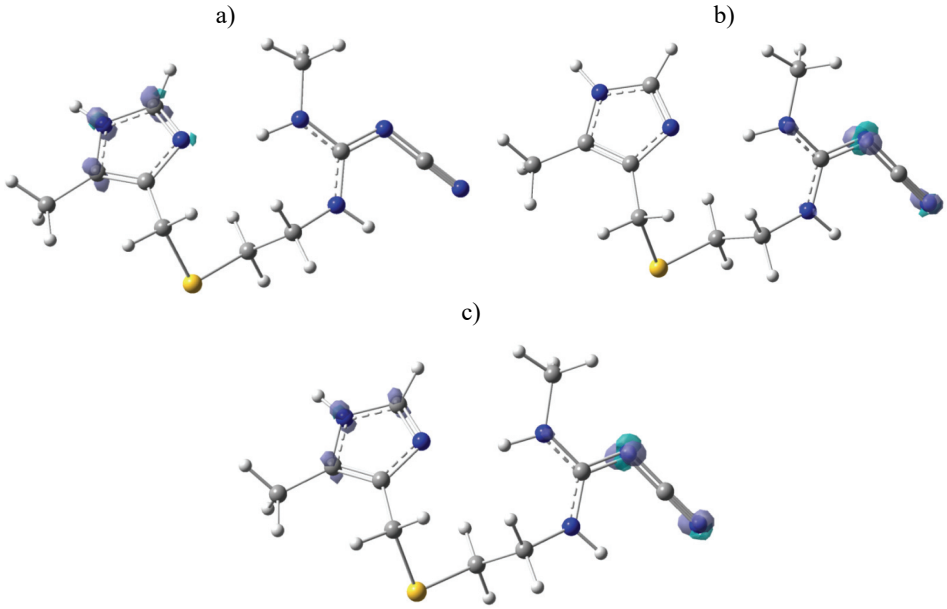

Fig. 4. Local reactivities for CimA: a) $f^{+}(\vec{r})$, b) $f^{-}(\vec{r})$ and c) $f^{0}(\vec{r})$ at the wB97XD/def2TZVP level of theory in the gas phase, according to Eqs. (6)–(8).

The isosurfaces in this Figure show that nucleophilic attacks are favored on 8C, while electrophilic and free radical attacks would be on 6N. For CimC in the gas phase, see Fig. S-6 in the Supplementary material, 9N is the most nucleophilic atom, while the results showed 3C to be the most active site for electrophilic and free radical attacks. In the case of CimD in the gas phase, see Fig. S-6, 4N is the most reactive site for nucleophilic attacks, while 10C is the most reactive site for electrophilic and free radical attacks. The FF values for CimA, CimC and CimD in H_2O, MeOH and EtOH are reported as Supplementary material in Figs, S-7–S-9, respectively. A summary of the most reactive sites for

CimA, CimC and CimD is presented in Table III. Thus, according to the obtained results, for CimA, the most active sites for nucleophilic, electrophilic and free radical attacks are located on 8C, 10C and 8C, respectively, irrespective of the solvent, *i.e.*, H_2O, MeOH or EtOH. In the case of CimC, this conformer keeps the same chemical reactivity in MeOH and EtOH, since the most reactive sites for the different kinds of attacks are on 10C, 1S and 1S, respectively. However, in aqueous conditions, 13C, 1S and 1S correspond to the most reactive sites for nucleophilic, electrophilic and free radical attacks, respectively.

TABLE III. Summary of the more reactive sites of CimA, CimC and CimD in the different solvents, according to Eqs. (6)–(8)

Medium	$f^{+}(\vec{r})$	$f^{-}(\vec{r})$	$f^{0}(\vec{r})$
	CimA		
Gas	8C	6N	6N
H_2O	8C	10C	8C
MeOH	8C	10C	8C
EtOH	8C	10C	8C
	CimC		
Gas	9N	3C	3C
H_2O	13C	1S	1S
MeOH	10C	1S	1S
EtOH	10C	1S	1S
	CimD		
Gas	4N	10C	10C
H_2O	15C	10C	10C
MeOH	15C	10C	10C
EtOH	10C	10C	10C

On the other hand, CimD retains the same reactivity in H_2O and MeOH phases, and nucleophiles, electrophiles and free radicals might attack on the atoms labeled 15C, 10C and 10C, respectively. However, in EtOH, 10C is the most susceptible site for the three kinds of attacks. These last results are coincident with those reported in the literature for cimetidine compounds.[41–47]

CONCLUSIONS

Intramolecular interactions in CimA and CimD result in their folded conformations. In the aqueous phase, cimetidine A and D are approximately isoenergetic, meaning interconversion between them is possible. The hardness values indicate that CimA, CimC and CimD are more reactive in the presence of a solvent than in the gas phase. In the phases analyzed in the present work, CimC and CimD are better nucleophiles than CimA. The values of the Fukui Function suggest that the most reactive sites of CimA are not modified in the different solvents and they are located on 8C, 10C and 8C for nucleophilic, electrophilic and free radical attacks, respectively. In all cases, the most reactive sites for elec-

trophilic and free radicals attacks for CimC are located on the thioether sulfur. However, the nucleophilic attacks on CimC are located on 13C, 10C and 10C in H_2O, MeOH and EtOH, respectively. For CimD, the most reactive sites are located on 10C atom for electrophilic and free radical attacks, independent of the solvent. The nucleophilic attacks on CimD are located on 15C, 15C and 10C in H_2O, MeOH and EtOH, respectively.

SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: http:// //www.shd.org.rs/JSCS/, or from the corresponding authors on request.

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ИЗВОД

DFT ПРОУЧАВАЊЕ ХЕМИЈСКЕ РЕАКТИВНОСТИ ЦИМЕТИДИНА A, C И D У ГАСНОМ СТАЊУ И У H_2O, MeOH И EtOH КАО РАСТВАРАЧИМА

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У овом раду је анализирана хемијска реактивност циметидина A, C и D у различитим растварачима путем процене глобалних и локалних DFT дескриптора реактивности. У гасном стању, као и у MeOH и EtOH фазама, циметидини A, C и D показују разлике у енергији од 3–11 kcal mol^{-1}. Међутим, у воденој фази, циметидини A и C су приближно изоенергетски. Вредности хемијске тврдоће указују на то да су циметидини A, C и D реактивнији у присуству растварача него у гасној фази. Такође, наши резултати сугеришу да су CimC и CimD бољи нуклеофили од CimA. Вредности Фукуијеве функције сугеришу да реактивнија места CimA нису измењена у различитим растварачима. У случају CimC, реактивнија места за напад електрофила и слободних радикала су лоцирана на тиоетарском сумпору. За CimD, број и положај места за електрофилне и слободнорадикалске нападе су независни од растварача.

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