Specific Hydration Effects on Oxo−Thio Triazepine Derivatives

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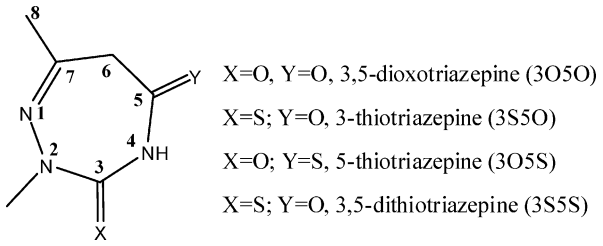
The specific hydration of 2,7-dimethyl-1,2,4-triazepine oxo−thio derivatives by one water molecule has been investigated at the B3LYP/6-311++G(3df,2p)//B3LYP/6-311+G(d,p) level of theory. The existence of different hydrogen bond (HB) donor and acceptor centers in these molecules led to different kinds of hydrogen bonds (CH−O, OH−S, NH−O, OH−N, and OH−O) and different kinds of complexes. Among them, the most stable structures correspond to complexes where the heteroatom X or Y at positions 3 and 5 behaves as HB acceptor and the hydrogen atom associated with the nitrogen atom at position 4 as HB donor. In accordance with previous studies, it has been shown that the thiocarbonyl group forms stronger HBs than the carbonyl group because the sulfur atom is a better HB acceptor than the oxygen one. With the help of the AIM (atoms in molecules) theory and ELF (electron localization function) analysis, it has been shown that, in the case of **3O5O**, **3S5O**, and **3S5S**, the most basic site is the heteroatom at position 3, while in **3O5S** species the most basic center is the sulfur atom.

Introduction

Heterocyclic chemistry as a part of organic chemistry has received much attention in the past decade. As useful reaction intermediates, the heterocyclic compounds have found widespread application in organic synthesis,[1,2] and some of them are active drugs with important application in pharmacology.[3−7] In particular, seven-membered rings exhibit important biochemical activity.[4−6] For this reason, the different oxo and thio derivatives of diazepines and triazepines have attracted a great deal of attention as starting materials in the synthesis of fused heterocyclic systems with potential pharmacological activities.[8−12]

Moreover, as uracil and its thio derivatives,[13−20] these compounds exhibit several basic centers, such as oxygen, nitrogen, and sulfur atoms. The ring environment brings important changes in the electronic reorganization that affect the intrinsic reactivity of the molecular groups such as thiocarbonyl and carbonyl ones. Recently, we have studied the basicity of uracil and its thio derivatives toward H^+, Cu^+, and Cu^{2+} in order to illustrate the behavior of these basic centers when the bond type changes from covalent to ionic.[16,21−23] In the present work, we will explore the variation of basicity in the case of weak interactions. Nguyen et al. have published recently a paper on the interaction of the thiouracil derivatives with water where hydrogen-bonding had been largely discussed.[15,24] The first question that we should address is how the thiocarbonyl and carbonyl groups react when we pass from six-membered rings to seven-membered rings. The second question that should be addressed concerns the activity of the most basic center of these compounds toward a water molecule; in other words, in spite of the weakness of the interaction, can we differentiate between the basicity of the different sites? In fact, our study of the protonation and the isomerization of 3-thio-5-oxo (**3S5O**), 5-thio-3-oxo (**3O5S**), and 3,5-dithio (**3S5S**) derivatives of 2,7-dimethyl[1,2,4]triazepine[25−27] (**3O5O**) (see Scheme 1) showed that, in systems were both carbonyl and thiocarbonyl groups

SCHEME 1



are present, the thicarbonyl group is the most favorable site for protonation. When only one of these groups is present, due to the resonance effect issued by the neighboring nitrogen atom at position 4, the electron density of the heteroatom at position 3 is increased, enhancing the interaction of this center with the proton. This behavior has been related to the contribution of a zwitterionic configuration, $-{}^{+}N4{=}C3(X3^{-})-$, which accumulates negative charge on the heteroatom at position 3. Similar conclusions have been obtained for the interaction of these compounds with Cu^+.[28]

It is well-known that the elimination of water in synthetic processes is a difficult task, and in many cases, it cannot be discarded that some traces of water may still influenced the reactivity of the synthesized compound. This is the reason why we have focused the aim of the present work in discussing the intrinsic electronic changes of the triazepine thio derivatives upon hydration. The present objective is to discuss the nature of the hydrogen bond formed when the water interacts with the different basic centers present in these compounds, to illustrate the different behavior carbonyl, thiocarbonyl, and amino groups of triazepines may have when interacting with a single water molecule.

Computational Details

Standard DFT calculations, in the framework of the B3LYP approach, have been carried out using the Gaussian 03 suite of

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programs.[29] The B3LYP method combines Becke's three-parameter nonlocal hybrid exchange potential[30,31] with the nonlocal correlation functional of Lee, Yang, and Parr.[32] This approach has been shown to yield results consistent with high-level ab initio studies for strong hydrogen bonds.[33,34] In fact, as presented by McAllister et al.[33,34] and Garza et al.,[35,36] B3LYP functional gave a good description of the structural parameter changes issued from the hydrogen bond interactions of the type O−H, C−H, or N−H. These changes have been proved to be closed to that obtained at the MP2 level of theory. More importantly, several assessments[37−40] have shown that this hybrid functional, when combined with a flexible enough basis set, provides descriptions of hydrogen-bonded system of a similar quality as MP2 or even high-level ab initio calculations. More recently, a similar assessment, with analogous conclusions, has been reported for the particular case of intramolecular hydrogen bonds.[41] Nevertheless, since the energy difference between some of the complexes included in this study is as small as 2 kJ mol^{-1}, which is the precision limit of the calculations, the reliability of the B3LYP energy ordering was assessed by comparing it with that obtained in single-point CCSD(T)/6-31+G(d,p) calculations carried out on MP2/6-31+G(d,p)-optimized geometries, for the different structures of 3,5-dioxotriazepine−H_2O complex, as suitable model systems. The results obtained show a perfect agreement between DFT and ab initio relative stabilities (see Table 1S of the Supporting Information). Nevertheless, it should be mentioned that CCSD(T)/6-31+G(d,p) hydration energies are ca. 8 kJ mol^{-1} lower than B3LYP values. In order to assess whether this is an actual limitation of B3LYP values, it would be necessary to carry out CCSD(T) calculations with a basis set expansion larger than the one used here. Unfortunately, such calculations are too demanding for systems of this size.

The different complexes studied were fully optimized using the 6-311+G(d,p) basis set. The harmonic vibrational frequencies, zero-point vibrational energies (ZPE), and the thermal corrections to enthalpy (TCE) were calculated at the same level of theory. All structures found correspond to local minima of the PES using the default convergence criteria of the Gaussian 03 program package.[29] Taking into account that quite often when dealing with weak interactions the potential energy curves associated with the interaction coordinate may be remarkably flat,[42] a tight optimization convergence criterion has been used for some specific complexes. However, in all the cases considered, no significant changes were found for the relevant parameters involved in the hydrogen bonds. Hydration enthalpies, at 298 K, has been evaluated at the B3LYP/6-311+G(3df,2p)//B3LYP/6-311+G(d,p) level of theory after including the ZPE scaled by factor 0.9806[43] and TCE corrections. It was also found, for some suitable examples, that the effect of adding a diffuse function on the hydrogen atoms in the geometry optimization has an almost negligible effect on the results, while the increase in the computational effort is significantly higher.

With the aim of further exploring the nature of the hydrogen bonds in these complexes, we turn here to the usefulness of the topological analysis of the electron localization function (ELF), a direct measure of the local Pauli principle. The reader is referred to different reviews on this powerful technique of bonding analysis.[44−46] In our survey, the ability of the ELF qualitative analysis[44,47] to describe the hydrogen bonding was used to classify the different bonds. In fact, as the ELF is a scalar function, the analysis of its gradient field can be carried out in order to locate its attractors (the local maxima) and the corresponding basins. The picture of the molecule provided by the ELF analysis is consistent with the Lewis valence theory,[48] and therefore, it is possible to assign a chemical meaning to the attractors and to their basins. In the formation of a hydrogen bond, the topology of this function is essentially the addition of those of the constituent moieties. In the localization process, the first bifurcation creates two molecular reducible domains, one for the donor and the other for the acceptor (see Figure 1), for an ELF value defining the bounding isosurface, which may be used to classify the different hydrogen bonds present in the interaction. To carry out these calculations the TopMod suite of programs has been used.[49] The bonding characteristics were also analyzed by means of the atoms in molecules (AIM) theory of Bader.[50] For this purpose, we have located the relevant bond critical points (BCP) and evaluated the electron density at each of these points. To perform the AIM analysis, we have used the AIMPAC series of programs.[51]

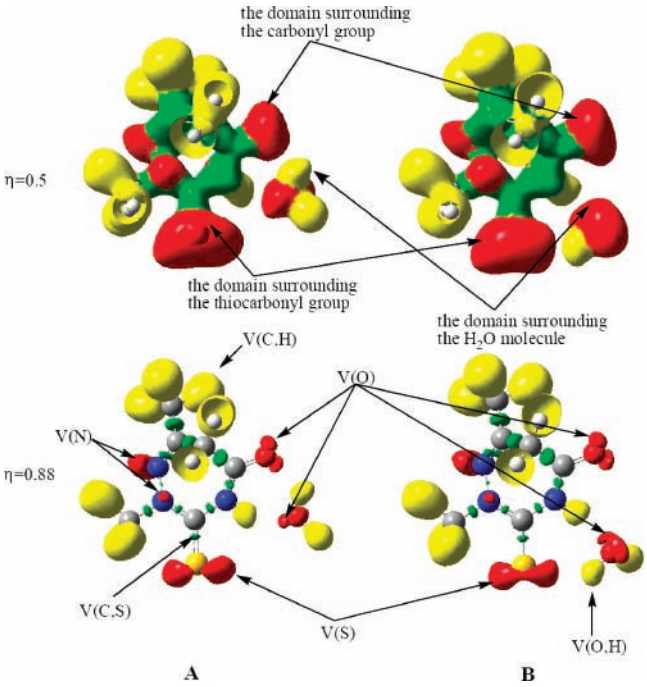

Figure 1. Schematic representation of attractors localized in structures **A** and **B** in the case of 3-thiotriazepine−H_2O complex. Two values of ELF ($\eta = 0.5$ and $\eta = 0.88$) are considered.

Results and Discussion

The interaction of triazepine and its thio derivatives with one water molecule is guided by the possibility of the water molecule behaving as a hydrogen-bond donor or as a hydrogen-bond acceptor when respectively interacting with the basic centers and the acidic groups existing in these compounds. So, as shown in Figure 2, five possible water−triazepine structures may exist in which water behaves simultaneously as hydrogen-bond acceptor and donor (**A**−**E**). For **3S5O** and **3S5S**, another structure, **F**, is found as a result of the participation of the thiocarobonyl group at position 3 as HB acceptor and the hydrogen atom attached to the methylene at position 6 as HB donor. A similar complex could not be optimized for **3O5O** and **3O5S** compounds, because it collapses to structure **D**. The total energy of each structure is listed in Table 2S of the Supporting Information. Hydration enthalpies are reported in Table 1.

The first conspicuous fact is the weakness of the interaction between water and these compounds. The calculated values are in the range 9.1−23.7 kJ mol^{-1}, which allows classification of

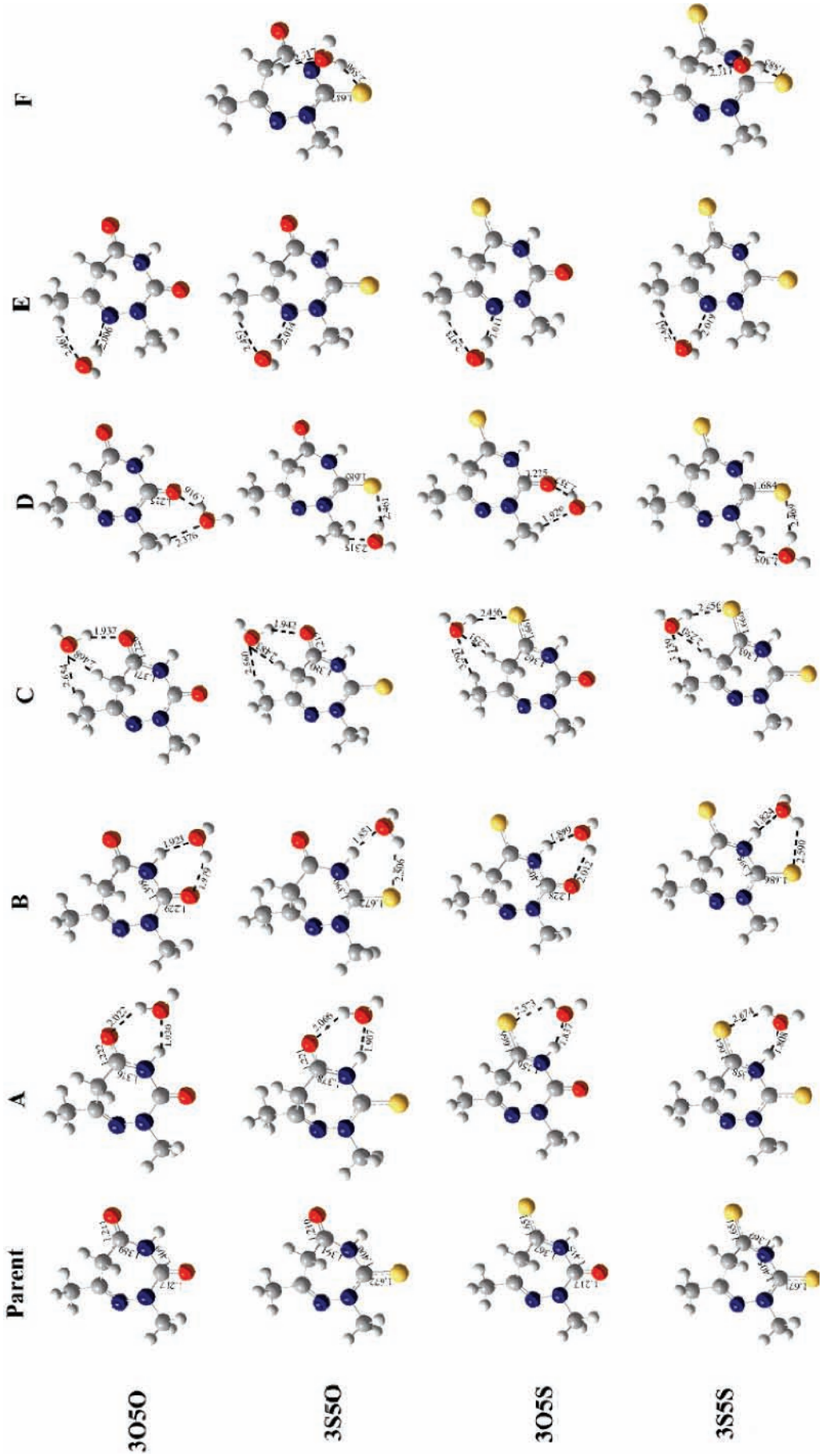

Figure 2. Optimized geometries of thiotriazepines and thiotriazepine−H_2O complexes. Bond lengths are in Å and bond angles in degrees.

TABLE 1: Hydration Enthalpies [$\Delta H = [H_{complex} - (H_{parent} + H_{water})]$, kJ mol^{-1}] at 298 K of the Different Triazepine$-H_2O$ Complexes

	3O5O	3S5O	3O5S	3S5S
A	−22.40	−20.70	−21.42	−19.82
B	−23.72	−20.05	−22.29	−17.88
C	−19.46	−20.04	−14.77	−15.37
D	−15.53	−9.72	−14.97	−9.13
E	−13.36	−12.63	−12.75	−12.20
F	−	−14.68	−	−13.16

the corresponding hydrogen bonds as moderate. Structures **A** and **B** are predicted to be the most stable ones, with similar hydration enthalpies. It is worth noting, however, that in the case of **3O5O** and **3S5O** species, quite unexpectedly, complex **C** competes in stability with these structures. In order to make this discussion more systematic, complexes **A** and **B** will be discussed in the same section, because they constitute a subset in which water interacts with heteroatoms X and Y as a hydrogen-bond donor and with the same NH group as a hydrogen-bond acceptor, while in the other complexes the group acting as hydrogen-bond donor is always a CH bond. In the latter case, three subgroups may be identified: (a) complexes **C** and **D**, where the heteroatoms X and Y are involved as HB acceptors; (b) complex **E**, where the HB acceptor is the nitrogen atom at position 1; and (c) complex **F**, which involves an out-of-plane HB interaction.

Complexes A and B. In complexes **A**, the thiocarbonyl (or carbonyl) group at position 5 acts as a hydrogen-bond acceptor with respect to water. In complexes **B**, this role is played by the thiocarbonyl (or carbonyl) group at position 3. Both kinds of complexes have in common the NH group at position 4 acting as a HB donor. The fact that water behaves simultaneously as a HB donor and as a HB acceptor by forming a five-membered ring with triazepine will result in some kind of cooperativity effects, as shall be discussed later. The results show that for all the triazepines considered, namely, **3O5O**, **3S5S**, **3O5S**, and **3S5O**, the hydration enthalpy for complexes **A** and **B**, which are in the range 20−24 kJ mol^{-1}, differ very little from one another, the greatest difference being 2 kJ mol^{-1} for the case of **3S5S**. Nevertheless, and in spite of this apparent similarity, complexes **A** and **B** exhibit significantly different hydrogen-bonding patterns.

Let us analyze in detail the case of 3,5-dioxotriazepine **3O5O**. The hydration enthalpy is estimated to be −22.7 kJ mol^{-1} when the interaction occurs in position 5 (complex **A**) and −23.4 kJ mol^{-1} when the interaction occurs in position 3 (complex **B**). There are significant differences, however, as far as the interaction with the NH group is concerned, although there are not dramatic differences as far as the NH$-O_w$ is concerned (see Figure 2). Significant differences are observed as far as the hydrogen bond with carbonyl groups is concerned, where the O$-H_w$ distance is much shorter for complex **B** (1.979 Å) than for structure **A** (2.022 Å). This seems to indicate that the carbonyl group at position 5 is a weaker HB acceptor than the carbonyl group at position 3. This is in accordance with our recent findings showing that the carbonyl group at position 3 has a larger intrinsic basicity than the one at position 5. In fact, in both protonation[27] and copper association[28] reactions, the heteroatom at position 3 of triazepine was the most basic center. These findings are also supported by the topology of the electron density of the complexes and reflected in the value of the electron density at the BCP of the corresponding bonds. In fact, the electron density in the H_w-O BCP is higher in complex **B** (0.026 e au^{-3}) than in complex **A** (0.023 e au^{-3}) (see Figure 3). Also the changes in the electronic population of the valence basins V(O3) and V(O5) triggered by the hydrogen-bond interaction, obtained through an ELF analysis, are in line with the previous discussion. In fact, the stronger interaction of water with the carbonyl oxygen at position 3 to form complex **B** is reflected in an increase of the population of basin V(O3) (0.34 e$^-$) which is much larger than that calculated for basin V(O5) (0.07 e$^-$) when complex **A** is formed (see Table 4S).

When we move to the dithiotriazepine compound, **3S5S**, the hydration enthalpy is approximately 4 kJ mol^{-1} smaller than that calculated for **3O5O**$-H_2O$ complex. Similar trends have been also observed in thioguanine$-H_2O$ in comparison to guanine$-H_2O$ complex[52] and in dithiouracil$-H_2O$ versus uracil$-H_2O$ complex.[15] As for **3O5O**$-H_2O$ complexes, structures **A** and **B** are very close in energy (about 2 kJ mol^{-1}). Here again, the S$-H_w$ distance involving the sulfur atom attached to position 3 (2.590 Å) (complex **B**) is shorter than that (2.674 Å) involving the S atom at position 5 (complex **A**), in agreement with the values of the electron densities at the corresponding BCPs. The larger intrinsic basicity of the thiocarbonyl group with respect to the carbonyl group[53] and the higher acidity of the NH group of **3S5S** are reflected in a stronger NH$-O_w$ HB in **3S5S**$-H_2O$ than in **3O5O**$-H_2O$. Therefore, in **3S5S** complexes, cooperative effects should be stronger than in **3O5O** complexes, because, as has been shown before in the literature,[54] an enhancement of the HB-donor ability of a water molecule leads to an enhancement of its HB-acceptor ability.

The greater acidity of the N4H group of **3S5S** can be easily understood by looking at the population of the valence basin of N4 obtained through an ELF analysis of the isolated (nonhydrated) molecules (see Figure 4). For **3O5O**, this basin exhibits a population of 1.8 e$^-$ (close to a typical lone pair), while in the case of **3S5S** it reduces to 1 e$^-$, indicating that in this latter compound one electron of the nitrogen lone pair is engaged in the delocalization within the system. This would result in an enhancement of the effective electronegativity of N4 and therefore in the acidity of the hydrogen attached to it.

The simultaneous existence of carbonyl and thiocarbonyl groups (**3S5O** and **3O5S**) in the same molecule has a small effect on the hydration enthalpies, which, as cited above, are slightly smaller than that found for **3O5O**. Again, the relative stability of structures **A** and **B** is similar in both cases. However, for both molecules, water association when the carbonyl group acts as HB acceptor seems to be weaker than in the **3O5O** species. In fact, in the case of 3-thiotriazepine (**3S5O**), the O$-H_w$ bond length in complex **A** (2.066 Å) is larger than that calculated (2.022 Å) for the same structure of compound **3O5O**. The contrary is observed for the NH$-O_w$ bond when we go from the structure **A** of **3O5O** to **3S5O** (see Figure 2). The same behavior is observed for the **B** complexes of compound **3O5S**, where the carbonyl group is at position 5, where the NH$-O_w$ distance decreases significantly (from 1.899 to 1.851 Å) while the length of the O$-H_w$ distance increases (from 1.979 to 2.012 Å).

These changes in the strength of the NH$-O_w$ HBs in structures **A** and **B** of thiotriazepines are nicely reflected in the shifts of the NH stretching frequencies. As a matter of fact, there exists a good linear relationship between NH$-O_w$ bond lengths and ν_{N-H} frequency shifts (see Figure 5), but more importantly, the NH$-O_w$ interaction depends on the nature and the position of the acceptor group to which the water molecule donates the proton. In fact, two subgroups may be distinguished in the plot: complexes in which the acceptor is a thiocarbonyl group and those in which the acceptor is a carbonyl one. In the

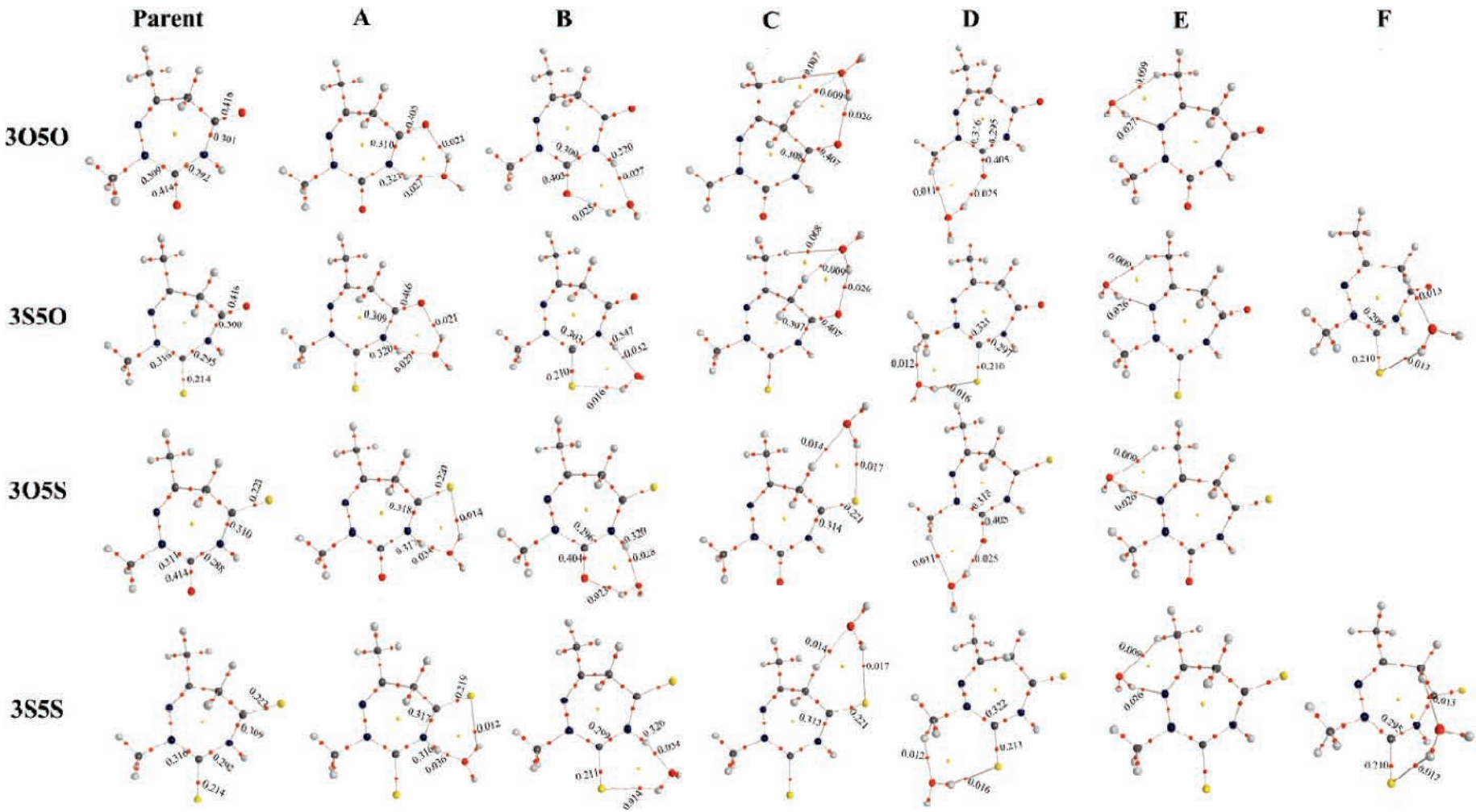

Figure 3. Molecular graphs of the different thiotriazepine−H_2O complexes. Red dots represent bond critical points and yellow dots ring critical points. Electron densities are in au.

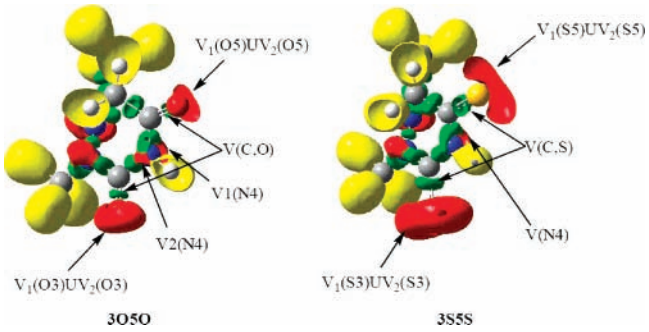

Figure 4. ELF (at $\eta = 0.8$) plot of isolated (nonhydrated) dioxotriazepine and dithiotriazepine.

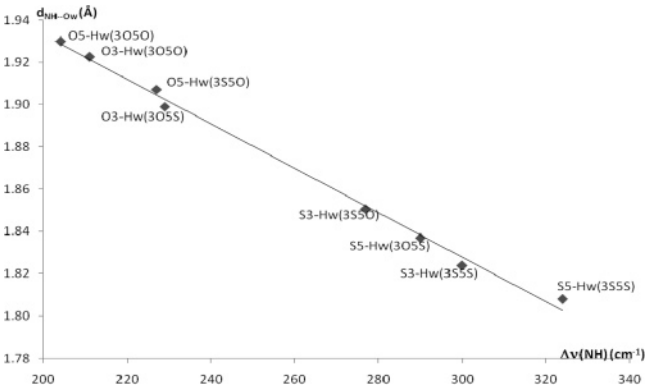

Figure 5. Correlation between N4H$-$O$_w$ bond lengths and ν_{N4-H} frequency shifts in the monohydrated thiotriazepines.

former, the $\Delta\nu_{N-H}$ shift is greater and the NH$-$O$_w$ hydrogen bond length shorter than in the latter. It worth noting that, as mentioned above, the strength of the NH$-$O$_w$ is also modulated by the position of the acceptor. So, the strongest hydrogen bond is observed in the dithiotriazepine when the interaction involves the thiocarbonyl group at position 5, whereas the weakest one is found in dioxotriazepine when the interaction involves the carbonyl group at position 3.

Complexes C and D. In these structures the group acting as HB donor is a CH group rather than a NH group. In complexes **C**, in principle, the hydrogen atoms attached to positions 6 and 8 may be involved in the HB interaction, while in complexes **D** only the methyl group attached to N2 may behave as HB donor. It is worth noting that while for compounds **3O5O** and **3S5O** the hydration enthalpy is around 20 kJ mol^{-1}, for **3O5S** and **3S5S** species this energy is 15 kJ mol^{-1} smaller, likely reflecting that, in the former two cases, the water molecule behaves as HB acceptor of both the CH at position 6 and the CH of the methyl group (see Figure 2), whereas in the latter water is not hydrogen bonded to the methyl group.

Complexes E. In this structure the HB acceptor of the triazepine molecule is the nitrogen atom at position 1. In principle, the methyl groups near to this basic site may also participate in the interaction as hydrogen-bond donors. However, all attempts to locate a local minimum in which the methyl group attached to the nitrogen atom at position 2 behaves as HB donor failed, and the optimization collapses always to the structure **E**. The hydration enthalpy when structures **E** are formed is approximately 13 kJ mol^{-1} and therefore smaller than for complexes **A**$-$**D**. There is practically no difference in the complex formation energy between the species under consideration. Also the N$-$H$_w$ hydrogen bond distance changes within narrow limits (2.006$-$2.019 Å), which indicates that the presence of a carbonyl or a thiocarbonyl in the system has an almost negligible effect on the interaction. This is also reflected in the very small changes in the electron density at the O$_w-$HC and at the N$-$H$_w$ BCPs.

Structure F. The nonplanar nature of the molecules under investigation permits a water out-of-plane interaction mainly when the hydrogen-bond acceptor has a voluminous electronic cloud, like the thiocarbonyl group. Hence, this situation was found to be possible only for **3S5O** and **3S5S** compounds. As shown in Figure 2, the water molecule is located in such a way that it may simultaneously act as a HB acceptor with respect to the CH group at position 6 and as a hydrogen-bond donor to the sulfur at position 3. The hydration enthalpy of the structure **F** is approximately 15 kJ mol^{-1} for **3S5O**$-$H$_2$O complex and 13 kJ mol^{-1} for **3S5S**$-$H$_2$O complex, which is less stable than the corresponding complex **B** by approximately 5 kJ mol^{-1}. This difference is a good illustration of cooperative effects. In complex **B**, water behaves as a HB acceptor of N4H group, which is a better HB donor than the C6H group of complex **F**. This would imply, following the model of Mó et al.,[54] that water should be a better HB donor in complexes **B** than in complexes **F**, which is indeed the case. Consistently, as shown in Figure 2, the S$-$H$_w$ distances are slightly larger for complexes **F** (by 0.09 Å for **3S5O** and by 0.02 for **3S5S**) than for complexes **B** and the electron density of the corresponding BCPs is smaller (see Figure 3).

Conclusion

The triazepine and its thio derivatives may be considered suitable model systems to investigate specific water solvatation effects on organic compounds, because of the possibility of having different hydrogen-bond interactions. The electronic donor ability of a thiocarbonyl group, considered more basic than a carbonyl group, depends on its relative position within the molecule. Indeed, a preference for solvation of the heteroatom at position 3 has been shown, in agreement with the fact that protonation[27] and the Cu$^+$ association[28] take place preferentially at this site. Even though the hydrogen bonds formed are of moderate strength, the AIM and the ELF analysis put in evidence significant dissimilarities between the different reactive centers. When the two heteroatoms are identical (case of **3S5S** and **3O5O** molecules), the results indicate that the most stable complex corresponds to that in which the water molecule acts as hydrogen-bond donor with respect to the heteroatom at position 3 and as hydrogen-bond acceptor with respect to the NH group at position 4. When sulfur atom is involved in the interaction, the acidity of the NH group is enhanced, which results in a stronger hydrogen bond between water and this group. It has been shown that the NH$-$O$_w$ bond depends on the nature and the position of the heteroatom acting as HB acceptor. In fact, two sets of complexes have been observed: complexes in which the acceptor is the thiocarbonyl group and those in which the acceptor is the carbonyl one. In the former, the NH$-$O$_w$ hydrogen bond is stronger than the latter.

On the other hand, when the interaction involves a hydrogen bond issued from the CH group, these results indicate that the methyl groups are not good HB donors. Also, the interaction of the nitrogen atom at position 1 has been explored; in the case of structures **E**, it acts as a hydrogen-bond acceptor and the nearest methyl at position 8 behaves as a hydrogen-bond donor. The change from carbonyl to thiocarbonyl group has no effect on this interaction. The N$-$H$_w$ bond presents a negligible variation when going from dioxotriazepine to dithiotriazepine. Another interaction of importance, which is only observed in **3S5O** and **3S5S** molecules, is the out-of-plane association of water. These complexes illustrate the importance of cooperative effects in the solvatation of thio derivatives of triazepine.

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Supporting Information Available: Tables containing the total energy, zero-point energy, and thermal correction of enthalpy of the different triazepines and thiotriazepine−H_2O complexes; some selected structural parameters; and the basin population in the ELF analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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