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Studies on Interactions between Sulfadiazine and Peptide Amides

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ABSTRACT

In this study, the optimal structures and binding energies of 14 hydrogen bonded complexes, which contained the sulfadiazine, N-methylacetamide, a glycine dipeptide and an alanine dipeptide, were obtained. The sites preference of sulfadiazine hydrogen bonding to peptide amides were explored. The interaction energies of all the complexes were corrected by Basis Set Superposition Error (BSSE). By the analysis interaction energy, charge density and second-order interaction energies E(2) of the complexes, it is found that N-methylacetamide can use three binding sites (site NMA1, NMA2 and NMA3) to form N—H…O=C or N—H…N hydrogen-bonded complexes with sulfadiazine, the N—H…O=C hydrogen-bonded complexes formed at site NMA1 of N-methylacetamide are more stable. The calculation results also show that the glycine dipeptide can use either site Gly1 or Gly2 and the alanine dipeptide can use either site Ala1 or Ala2 to form hydrogen-bonded complexes with sulfadiazine, the hydrogen-bonded complexes formed at site Gly2 of the glycine dipeptide and at site Ala2 of the alanine dipeptide are more stable. The interaction between sulfadiazine and the peptide is preferred to that between sulfadiazine and N-methylacetamide.

Key words: DFT, sulfadiazine, N-methylacetamide, glycine dipeptide, alanine dipeptide, hydrogen bond

INTRODUCTION

The Magnetic Resonance Imaging (MRI) contrast agents are one group which can be used in enhancing image contrast between the normal tissue and the location of diseases (Lauffer, 1987). A pattern of micromolecule, gadolinium-containing contrast agent (Gd-DTPA) is widely used in clinic at present, which could shorten longitudinal relaxation time (T_1) and increase contrast and image sharpness, however, such contrast agent remains in the body is so short time that it fails to be of the effect of targeting in the organs or the tissues, especially in tumor tissues image effect of Gd-DTPA is poor (Laurent *et al*., 2007; Villaraza *et al*., 2010; Dirksen *et al*., 2004). Thus, it is important to study a new targeted macromolecular MRI contrast agent for early detection of tumor, which can increase the relaxation rate as well as the length of time contrast agent remains in patients' body.

The sulfonamide has shown a broad range of bioactivity, which can be very good selectivity to the site of the tumor in animal models, furthermore, it may inhibit the growth of cancer cells (Yan *et al*., 2005). In order to prepare a new kind of targeting anticancer nanometer prodrug Yan *et al*. (2010) and his co-workers had added 5-fluorouracil and sulfadiazine (SD) as a tumor-targeting group to amphiphilic carbonic ester copolymer. This smart nano-anti-cancer drug has superior performance in targeting tumor and controlling its releasing ability when compared with 5-fluorouracil. The study also proved that such new nano-anti-cancer drug be able to kill human cervical HeLa cells effectively and induce tumor cells apoptosis, but without toxic effect on normal cells. Bartulin *et al*. (1974) and Abel *et al*. (1973) reported that the concentrations of sulfonamide and its derivatives in Walke cancer or Yoshida cancer were two to three times higher than that of liver. The sulfadiazine can selectively be taken in by

human tumor tissues and cell lines, so it has the great potentia to use as a tumor-targeting group for anti-cancer-drug. It is generally known that the effect of the drugs can work after reaching the acceptor, by means of the transportation of blood. Most of drugs fail to be transported any further because they are difficult to penetrate capillaries after combining with plasma proteins (It is mainly the albumin) more or less in plasma. Meanwhile, as more drug-albumin complexes generate the intensity of effects of almost all drugs weakens and the action time prolongs (Oravcova *et al*., 1996). Therefore, to explore binding features between small drug molecules and proteins has attracted considerable research interest in recent years. Intermolecular binding is determined by noncovalent interactions. Among various noncovalent interactions hydrogen bondings are the most important ones and studying on them is intensive (Zhang *et al*., 2010; Liu and Wang, 2012; Dong *et al*., 2007; Li and Wang, 2011; Wang and Xu, 2011). Theoretical chemical computation methods, such as density functional theory method and Møller-Plesset second-order perturbation theory method, have become powerful tools in studying on hydrogen bonding (Cai *et al*., 2011; Zheng *et al*., 2011; Wang *et al*., 2013a, 2014). In this study, N-methylacetamide (NMA), a glycine dipeptide and an alanine dipeptide were chosen as the simplest models of protein molecules. We carried out the density functional theory calculations on the hydrogen bonding interactions of sulfadiazine with these molecules. We hope the results obtained would be helpful for deeply understanding the interactions between sulfadiazine and the polypeptides and therefore provide useful insight on rationally designing and screening new medical molecules.

MATERIALS AND METHODS

Constriction of mode system: The structures and label schemes of sulfadiazine, N-methylacetamide, a glycine dipeptide and an alanine dipeptide are depicted in Fig. 1. Figure 1 shows a sulfadiazine (SD) which contains one benzene ring and one heterocyclic ring, possesses one imino group, two amino groups and two sulfinyl groups which can hydrogen bond to a peptide. A sulfadiazine can hydrogen bond to a N-methylacetamide or a glycine dipeptide or an alanine dipeptide through two binding sites which herein we refer to as site SD1 and SD2. A N-methylacetamide (NMA) (Fig. 1b) can hydrogen bond to a sulfadiazine through three binding sites herein we refer to as site NMA1, NMA2 and NMA3. The other two dipeptides, a Glycine dipeptide (Gly) and an Alanine dipeptide (Ala) can respectively hydrogen bond to a sulfadiazine through two binding sites (Fig. 1c site Gly1 and Gly2, Fig. 1d site Ala 1 and Ala 2). When a sulfadiazine and a N-methylacetamide form a hydrogen-bonded complex in which the sulfadiazine uses site SD1 and the N-methylacetamide uses site NMA1, we denote the complex as NMA1-SD1 and so on.

Method of calculation: The density functional theory M06 method has been widely used to study the structures and properties for biomolecules (Tian *et al*., 2014; Zhang *et al*., 2013). All geometries are fully optimized at the M06/6-31+G (d,p) level of theory using the Gaussian 09 package (Frisch *et al*., 2010). The frequency calculations are carried out to confirm that all the structures obtained are geometrically stable. The binding energies are then evaluated
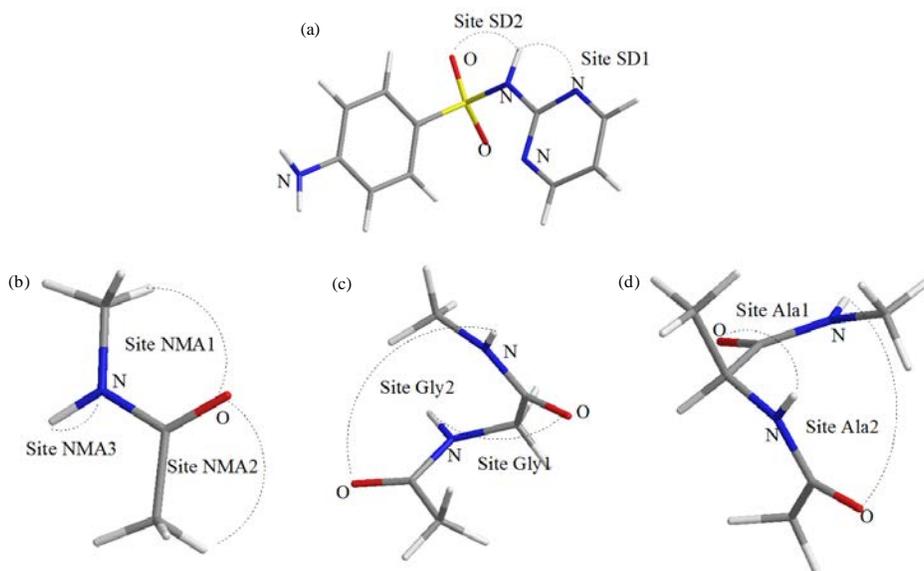

Fig. 1(a-d): Hydrogen bonding sites of sulfadiazine, N-methylacetamide, glycine and alanine dipeptides (a) Sulfadiazine, (b) N-methylacetamide, (c) Glycine and (d) Alanine dipeptides

using the B3LYP method combined with the 6-311++G (3df, 2p) basis set including the Basis Set Superposition Error (BSSE) correction and the solvent effect is discussed by the SMD model. To acquire deeper insight into the nature of complexes system interactions, Atoms In Molecules (AIM) analysis is performed by using AIM 2000 (Bader, 1990). In addition, analyses of the charge distribution and charge transfer processes are performed by using Natural Bond Orbital (NBO) partitioning scheme (Reed *et al.*, 1986).

RESULTS AND DISCUSSION

Structural optimization of sulfadiazine: To ensure the reliability of this method that we selected, two methods have been adopted to optimize sulfadiazine (Fig. 2), they are B3LYP and M06, at the same level 6-31+G (d,p). Table 1 is listing theoretical and experimental geometrical parameters of the sulfadiazine. With two methods, the results of calculation are essentially consistent with experimental values, there still are minute differences between them, which arose in the past research (Wang *et al.*, 2013b). It is generally thought that the difference mainly caused by without any consideration for the relativity between the molecules as doing theoretical calculation. However, the molecular interactions have been considered during experimental testing. It is generally known that sulfadiazine molecular might be linked each other by hydrogen bonds in its natural state, but this factor has never been contemplated during theoretical calculations, which may result in a negligible difference between results of theoretical and experimental. A comparison between geometrical parameters of the sulfadiazine result of B3LYP method and that of M06 shows the latter is more desirable, which is

Table 1: Main optimized geometrical parameters of the sulfadiazine

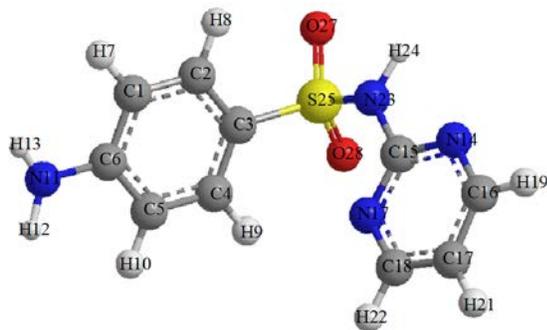| Bond	B3LYP/6-31+G (d,p)	M06/6-31+G (d,p)	Exp (Pan *et al.*, 2013)
N11—H12	0.1009	0.1009	0.1010
S25—O26	0.1462	0.1451	0.1448
S25—C3	0.1777	0.1759	0.1758
S25—N23	0.1717	0.1701	0.1712
C15—N23	0.1387	0.1380	0.1383
N23—H24	0.1016	0.1016	0.1013
C15—N17	0.1339	0.1334	0.1335

Fig. 2: Structure of sulfadiazine

more reasonable comparing to the experimental result and it reveals the method presented in this study is feasible.

N—H…O=C hydrogen-bonded complexes: The sulfadiazine can respectively unite with N-methylacetamide, a glycine dipeptide and an alanine dipeptide to form fourteen stabilized complexes which could be divided into three types as follows: the first type is N—H…O=C hydrogen-bonded complexes are shown in Fig. 3 displays such complexes from one to nine, another type we call N—H…N hydrogen-bonded complexes are shown in Fig. 4, 5 presents the last type including two hydrogen-bonded complexes, which contain not only N—H…O=C hydrogen bond but also N—H…N hydrogen bond, hence, we call them traditional double-hydrogen-bonded complexes.

Figure 3 presents the optimal structures and the key structural para1. Which meters of nine N—H…O=C hydrogen-bonded complexes. In these complexes, we find that in addition to N—H…O=C hydrogen bond, each one has the other weak interaction, which is C H…O=S or N H…O=S or C H…N C. The C H…N C hydrogen bond distance is 0.2100 nm for the complex NMA1-SD1 and 0.2310 nm for NMA2-SD1. The N—H…O=C hydrogen bond distance is 0.1914 nm for NMA1-SD1 and 0.1966 nm for NMA2-SD1. Compared with both of them, N—H…O=C hydrogen bond of NMA1-SD1 is shorter, indicating that the H-bonding interactions of complex NMA1-SD1 is stronger than that of NMA2-SD means that a N-methylacetamide tends to use site NMA1 to interact with a sulfadiazine to form a more stable hydrogen-bonded complex through the traditional N—H…O=C hydrogen bond. The binding energies in gas phase of NMA1-SD1 and NMA2-SD1 are calculated to be -38.8 and -36.6 kJ mol^{-1}, respectively. These results also indicate that a N-methylacetamide hydrogen bonds to the site SD1 of a sulfadiazine to form a hydrogen-bonded complex most likely through site NMA1 and least likely through site NMA1.

The hydrogen bond lengths (nm) are beside dotted lines. The electron densities at the hydrogen bond critical points (a.u.) are in parentheses and the second-order stabilization energies (kJ mol^{-1}) in square brackets. The BE (gas) are bonding energies in gas phase and BE (water) are the binding energies in water solvent.

Moreover, Fig. 3 shows the electron densities at the hydrogen bond critical points in parentheses and the second-order stabilization energies in square brackets. The results of electron density at the hydrogen bond critical point and the second-order stabilization energy in the nine complexes, indicating that the N—H…O=C interaction is stronger than that of the others weaker interaction (C H…O=S or N H…O=S or C H…N C) as well as the second-order stabilization energy. From such an analysis, we can conclude that the N—H…O=C interaction is the most stable hydrogen bond for the entire N—H…O=C hydrogen-bonded

BE (gas) = -38.8 kJ mol^{-1}, BE (gas) = -36.8 kJ mol^{-1}, BE (gas) = -36.6 kJ mol^{-1}
BE (water) = -17.9 kJ mol^{-1}, BE (water) = -17.1 kJ mol^{-1}, BE (water) = -16.8 kJ mol^{-1}

BE (gas) = -31.1 kJ mol^{-1}, BE (gas) = -52.1 kJ mol^{-1}, BE (gas) = -54.5 kJ mol^{-1}
BE (water) = -16.5 kJ mol^{-1}, BE (water) = -38.2 kJ mol^{-1}, BE (water) = -42.3 kJ mol^{-1}

BE (gas) = -40.8 kJ mol^{-1}, BE (gas) = -46.0 kJ mol^{-1}, BE (gas) = -43.1 kJ mol^{-1}
BE (water) = -26.3 kJ mol^{-1}, BE (water) = -31.7 kJ mol^{-1}, BE (water) = -28.0 kJ mol^{-1}

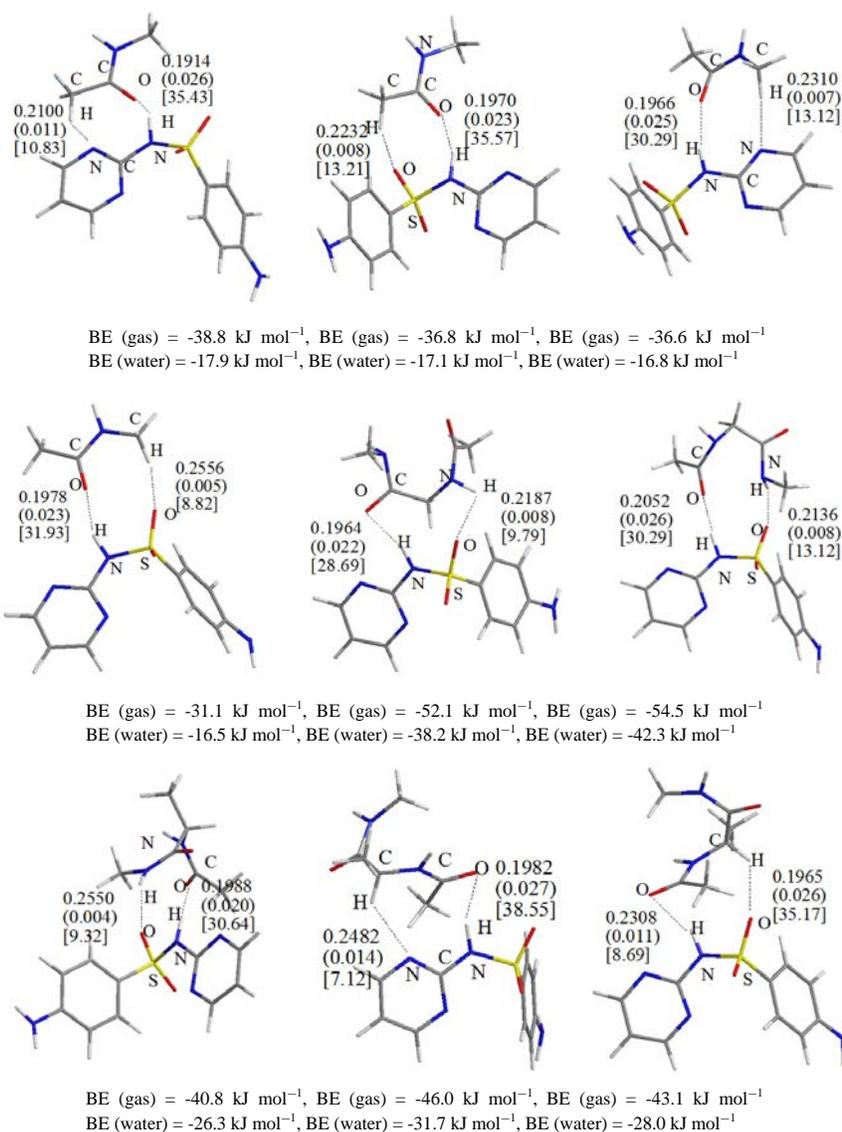Fig. 3(a-c): Optimal structures and relative properties of the N—H…O=C hydrogen-bonded complexes (a) 1 NMA1-SD1 2 NMA1-SD2 3 NMA2-SD1, (b) 4 NMA2-SD2 5 Gly1-SD2 6 Gly2-SD2 and (c) 7 Ala1-SD2 8 Ala2-SD1 9 Ala2-SD2

complexes. This result is same as that of Wang's (Wang *et al*., 2013a) research which discussed the hydrogen bonding between small biological molecules. From Fig. 3, it is obtained the results that the charge density ρ in the bond critical point are consistent with the total second-order stabilization energy. For example, the total second-order stabilization energy of NMA1-SD2 is as large as 48.79 and only 40.75 kJ mol^{-1} for that of NMA2-SD2, in accordance with that the total electron density at the hydrogen bond Σρ is 0.031 a.u. for NMA1-SD2 and 0.028 a.u. for NMA2-SD2, the total second-order stabilization energy is 46.36 kJ mol^{-1} for NMA1-SD1 and 41.01 kJ mol^{-1} for NMA2-SD1, the total electron density at the hydrogen bond critical point of the complex NMA1-SD1 (Σρ = 0.037 a.u.) is larger than that

of NMA2-SD1 (Σρ = 0.032 a.u.). The order of interaction energies of N—H…O=C hydrogen-bonded complexes in gas phase are: Gly2-SD2>Gly1-SD2>Ala2-SD1>Ala2-SD2>Ala1-SD2>NMA1-SD1>NMA1-SD2>NMA2-SD1>NMA2-SD2, indicating that the Gly2-SD2 hydrogen-bonded complex is the most stable in those complexes. Next is Gly1-SD2, it shows that site Gly2 of the glycine dipeptide is the most favored site for a sulfadiazine hydrogen bonding to site SD2 to form the N—H…O=C hydrogen-bonded complexes, far behind are three hydrogen-bonded complexes which are formed by the alanine dipeptide and the sulfadiazine, there are four NMA-SD complexes in the final. In general, the hydrogen-bonded complexes formed between the dipeptide and the sulfadiazine are more stable than NMA-SD complexes.
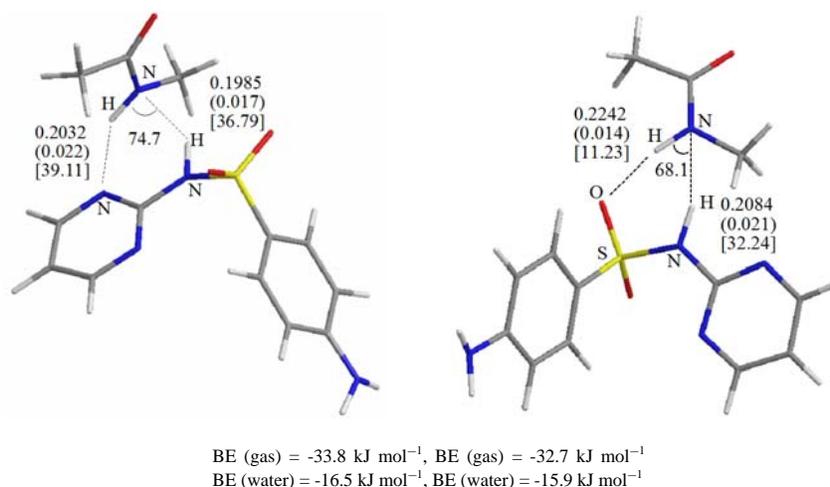
BE (gas) = -33.8 kJ mol^{-1}, BE (gas) = -32.7 kJ mol^{-1}
BE (water) = -16.5 kJ mol^{-1}, BE (water) = -15.9 kJ mol^{-1}

Fig. 4: Optimal structures and relative properties of the N—H…N hydrogen-bonded complexes, 10 NMA3-SD1 11 NMA3-SD2

BE (gas) = -45.83 kJ mol^{-1}, BE (gas) = -59.91 kJ mol^{-1}, BE (gas) = -56.92 kJ mol^{-1}
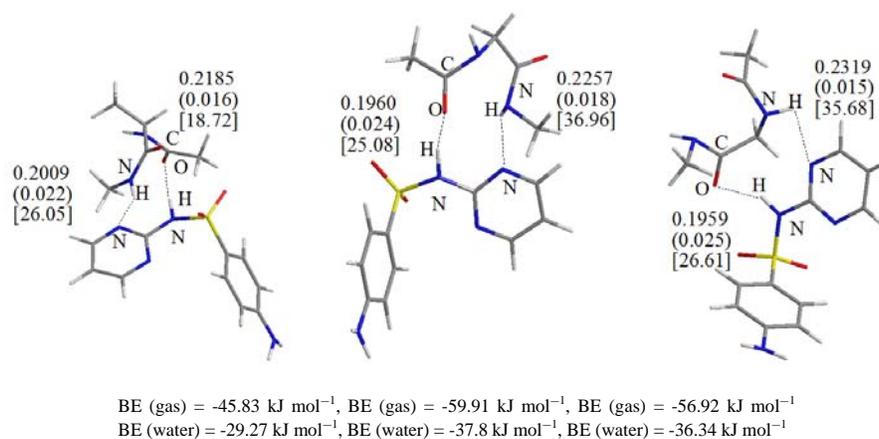BE (water) = -29.27 kJ mol^{-1}, BE (water) = -37.8 kJ mol^{-1}, BE (water) = -36.34 kJ mol^{-1}

Fig. 5: Optimal structures and relative properties of the hydrogen-bonded complexes containing both N—H…O=C and N—H…N hydrogen bonds, 12 Ala1-SD1 13 Gly2-SD1 14 Gly1-SD1

N—H…N hydrogen-bonded complexes: The binding energies for these two N—H…N hydrogen-bonded complexes are given in Fig. 4. There are two N—H…N hydrogen bond in NMA3-SD1, we find that N—H bond of NMA3-SD1 acts as proton donor of hydrogen bond as well as receptor, meanwhile the N—H bond of the sulfadiazine is proton donor and N atom of the six-membered ring which has lone pair electrons is proton receptor. In the Fig. 4, it is also clear that the N—H…N hydrogen bond containing N—H bond of the sulfadiazine which acts as proton donor, is more stable than another N—H…N hydrogen bond in which the N—H bond of the sulfadiazine acting as proton receptor, since the distance of the former N—H…N hydrogen bond is much shorter than the latter one. Except the N H…N hydrogen bond, there is the other C H…O=S interaction in NMA3-SD1 complex. The study found that in this NMA3-SD1 complex, N—H bond of

the N-methylacetamide is not only the proton donor of hydrogen bond but also the proton receptor, besides that, the sulfur atom of sulfadiazine acts as proton donor and the proton receptor is N—H bond. Any of the two distance of N—H…N hydrogen bonds in NMA3-SD1 complex is shorter than that of NMA3-SD2 complex when comparing the distance of N—H…N hydrogen bonds between NMA3-SD1 and NMA3-SD2 complexes. This result indicates that, a sulfadiazine hydrogen bonds to a NMA to form a N—H…N hydrogen-bonded complex most likely through site SD1. The binding energies in gas phase of NMA3-SD1 and NMA3-SD2 are calculated to be -33.8 and -32.7 kJ mol^{-1}, respectively and Fig. 4 also shows the electron densities at the hydrogen bond critical points and the second-order stabilization energies of NMA3-SD1 and NMA3-SD2, revealing that the atomic orbital has made a great role in N—H…N hydrogen bonds. As a

result, the same conclusion can be deduced from these studies. The hydrogen-bond interaction between adenine and NMA have been explored by Liu *et al*. (2013), showing that N—H…N hydrogen-bonded complexes were prefer to form by comparing the bonding energies in gas phase of N—H…N and N—H…O=C hydrogen-bonded complexes respectively. However, the conclusion of this study is different from that one, N—H…O=C hydrogen-bonded complexes are easier to get when sulfadiazine interacts with NMA. Figure 3, 4 shows SD-NMA complexes, all the N—H…O=C hydrogen-bonded complexes are more stable than NMA3-SD1 and NMA3-SD except NMA2-SD2 (bonding energies in gas phase is -31.1 kJ mol^{-1}).

Further analysis of the results shows that ∠H—N…H in NMA3-SD2 complex is 68.1°, whereas that of NMA3-SD1 is 74.7°. The strongest hydrogen bond can be gotten when the bond angle of N—H…N gets close to 90°, the reason is that the *p* orbital including lone pair electrons which belong to the nitrogen atoms of the amide in N-methylacetamide molecule may generate the maximum overlap with the antibonding orbital σ* of N—H bond in the sulfadiazine.

Traditional double-hydrogen-bonded complexes: Traditional double-hydrogen-bonded complexes in Fig. 5 containing both N—H…O=C and N—H…N hydrogen bonds are obtained through interacting between dipeptides and the sulfadiazines. In these fourteen hydrogen-bonded complexes that we got, Gly2-SD1 complex has the lowest bonding energies in gas phase as well as in water phase, indicating that this complex is the most stable one. The N—H…O C hydrogen bond distance is 0.1960 nm for the complex Gly2-SD1 and 0.2050 nm for Gly2-SD2. The total second-order stabilization energy of Gly2-SD1 and Gly2-SD2 are calculated to be 43.41 and 74.04 kJ mol^{-1}, respectively. Furthermore, the total electron density at the hydrogen bond critical point of the complex Gly2-SD1 ($\Sigma\rho$ = 0.044 a.u.) is larger than that of Gly2-SD2 ($\Sigma\rho$ = 0.034 a.u.). All these results indicate that site SD1 is the most favored site for a sulfadiazine hydrogen bonding to the site Gly2 of a glycine dipeptide. The N—H…O C hydrogen bond distance is 0.1959 nm for the complex Gly1-SD1 and 0.1964 nm for Gly1-SD2. The total second-order stabilization energy of Gly1-SD1 and Gly1-SD2 are calculated to be 62.29 and 38.48 kJ mol^{-1}, respectively, the total electron density at the hydrogen bond critical point of the complex Gly1-SD1 ($\Sigma\rho$ = 0.040 a.u.) is larger than that of Gly1-SD2 ($\Sigma\rho$ = 0.030 a.u.). The same conclusion can be obtained when a sulfadiazine interacts with a glycine dipeptide. The conclusion is that the traditional double-hydrogen-bonded complexes seem more likely to form when a sulfadiazine interacts with a glycine dipeptide and site SD1 is the most favored site for a sulfadiazine hydrogen bonding to the site Gly2 of a glycine dipeptide.

All the four hydrogen-bonded complexes which interact between a sulfadiazine and an alanine dipeptide, except Ala1-SD1 complex including two traditional intermolecular hydrogen bonds in Fig. 5. The other three complexes (Ala1-SD2, Ala2-SD and Ala2-SD2) possesses only one N—H…O=C hydrogen bond and their order of bonding energies in gas phase: Ala2-SD1>Ala1-SD1>Ala2-SD2> Ala1-SD2, the same order can be obtained when the total second-order stabilization energies of these four complexes are compared, suggesting that a sulfadiazine hydrogen bonds to an alanine dipeptide most likely through site SD1 and least likely through site SD2. Moreover, the N—H…O=C hydrogen bond is 0.2009 nm for Ala1-SD1 and 0.1982nm for Ala2-SD1, the total second-order stabilization energies of Ala1-SD1 and Ala2-SD1 are 44.77 and 45.67 kJ mol^{-1}, respectively, the total electron density at the hydrogen bond critical point of the complex Ala1-SD1 ($\Sigma\rho$ = 0.038 a.u.) is smaller than that of Ala2-SD1 ($\Sigma\rho$ = 0.041 a.u.). These results indicate that Ala2-SD1 is more stable than Ala1-SD1 and site SD1 is the most favored site for a sulfadiazine hydrogen bonding to the site Ala2 of an alanine dipeptide. The same conclusion can be deduced when dipeptide interacted with adenine to form traditional double-hydrogen-bonded complexes (Liu *et al*., 2013), indicating that the hydrogen-bonded complexes formed at site Ala2 of the alanine dipeptide are more stable.

Influence on binding energy from the solvation effect: Furthermore, the solvent effect is discussed by the SMD model at the M06/6-31+G (d,p) level of theory for all the fourteen complexes. Figure 3-5 show that the binding energies of all the complexes in water solvent. It can be seen from these pictures that the water solvent makes an important role in the binding energies of the hydrogen-bonded complexes. The binding energies of all the complexes in water solvent are far weaker than those of complexes in gas phase, however, the decreasing degree is different for different complex. For N—H…O=C hydrogen-bonded complexes, the binding energies of these complexes reduces by 12-21 kJ mol^{-1} in water solvent and the order of the interaction energy even changes a little. For example, in gas phase, the binding energy of NMA1-SD1 is 1.9 kJ mol^{-1}, more negative than that of NMA1-SD2, whereas in water solvent, the binding energy of NMA1-SD2 is 0.7 kJ mol^{-1}, more negative than that of NMA1-SD1. For N—H…N hydrogen-bonded complexes, though the water solvent makes the binding energies of these complexes reduce by about 17 kJ mol^{-1} as well, in accordance with the order the interaction energy in gas phase. Now the same thing is happening to the traditional double-hydrogen-bonded complexes, the binding energies of these complexes reduces by 14-20 kJ mol^{-1} in water solvent. It can be concluded from the foregoing discussion that when a sulfadiazine uses site SD2 to interact with a glycine dipeptide, two hydrogen-bonded complexes Gly1-SD2 and

Gly2-SD2 are formed, in gas phase, Gly2-SD2 is more stable than Gly1-SD2 only 2.4 kJ mol^{-1}, but at the same time, in water solvent, Gly2-SD2 is more stable than Gly1-SD2 at least 4.1 kJ mol^{-1}, namely Gly2-SD2 more frequently presents in water solvent because of the solvation effect. Traditional N—H…O=C hydrogen bond and N—H…N hydrogen bond are obtained through interacting between dipeptides and the sulfadiazines. The watery environment could make the binding energies of all the complexes weaker, when site preferences of adenine hydrogen bonding to peptide amides are studied by Liu *et al*. (2013), which is certainly consistent with this research.

CONCLUSION

This study discovers that N-methylacetamide can use three binding sites to form N—H…O=C or N—H…N hydrogen-bonded complexes with sulfadiazine. It shows that once the binding site of the sulfadiazine is fixed, the N—H…O=C hydrogen-bonded complexes can form through the N-methylacetamide site NMA1 or through site NMA2 and the N—H…N hydrogen-bonded complexes formed through the N-methylacetamide site NMA3 are the strongest. The interaction between the sulfadiazine and the dipeptide is much stronger than that of sulfadiazine-N-methylacetamide complexes. The more stable sulfadiazine-dipeptide complexes are formed when a sulfadiazine uses site SD1 to interact with dipeptide (site Gly2 and Ala2). In addition, we find that the aqueous solution actually has a larger impact on the binding energies of all the complexes. The results obtained should be very helpful for understanding the interactions between drug molecules and biomolecules and for reasonable designing new drug molecule.

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