ORIGINAL PAPER

A DFT study of the interaction of aspirin, paracetamol and caffeine with one water molecule

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Abstract

We have studied the interaction of water with three important analgesics, aspirin, paracetamol and caffeine using DFT calculations and FTIR-ATR spectroscopy. In our study, water is used as a probe molecule to reveal the various H-bonding sites on the electrostatic potential energy surface of the analgesics. We find that water forms a strong double H-bond with the COOH group of aspirin and that the oxygen of the ester group can become H-bond acceptors. Paracetamol forms the strongest H-bond with water at the hydroxyl group and weaker H-bonds with the $C=O$ group and the N–H group. Caffeine forms the strongest H-bond with water at the top $C=O$ group and can form additional H-bonds with the bottom $C=O$ group and the nitrogen of the imidazole ring. These studies may help to better understand the solvation of these analgesics in water.

Keywords Aspirin · Paracetamol · Caffeine · H-bonding · Water

Introduction

Many analgesics are poorly soluble and therefore have low bioavailability. This necessitates the intervenous injection of these drugs in order to increase their absorbance by the human body. Aspirin (acetylsalicylic acid), paracetamol (acetaminophen) and caffeine (1,3,7-trimethylxanthine) are important non-steroidal anti-inflammatory analgesics for the treatment of acute headaches as they can alleviate pain [1]. It is therefore important to obtain a more fundamental understanding of their interaction with water at the molecular level and explain how water interacts with these molecules as these analgesics have low solubility in water Here we have used a single water molecule to probe the electrostatic potential energy surface of three analgesics in order to identify the strongest H-bonding adsorption site. This approach gives a rigorous identification of the possible sites that water interact with when these analgesics are dissolved in it.

Aspirin shown in Fig. 1 is a pharmaceutical product by Bayer and it was first synthesised in 1897 [2]. Aspirin has proven to be an important drug during the 1918 flu pandemic

[2]. There are thousands of papers about aspirin and there are more than 21 papers dealing with the infrared and Raman spectrum of aspirin [3, 4]. There are a few computational studies of aspirin which have calculated the various conformer of aspirin, carried out assignments of its IR spectrum and studied its intramolecular H-bond [5, 6]. The adsorption and desorption of aspirin from zeolite HY was studied by thermogravimetric analysis, HF and DFT calculations [7]. There are only a few computational studies that study the interaction of aspirin with water. For example, Esrafili and Behzadi studied the interaction of one, two and three water molecules around aspirin and found that they form cyclic structures around the carboxylate group [8]. Also, the phase/form I of aspirin was calculated via DFT which showed that the structure is stabilised by the reciprocal intermolecular O–H⋯O hydrogen bond [9].

Paracetamol is a drug that is used to treat mild fever and pain [10]. It is used in the treatment of many conditions such as arthritis, backache, colds, menstruation pain and toothache [10, 11]. The mechanism of its action within the human body is not well understood [12]. It is known to be extremely toxic to cats [13] that lack an enzyme that detoxifies it named UDP-glucuronosyltransferase 1–6 (UGT1A6); however, it is used to treat musculoskeletal pain in dogs [14]. The infrared and Raman spectra of paracetamol have been widely studied [15, 16]. Resonant 2-photon ionisation spectrum of jet-cooled paracetamol has been studied between 33,400 and

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Fig. 1 Lewis structures of aspirin, paracetamol and caffeine
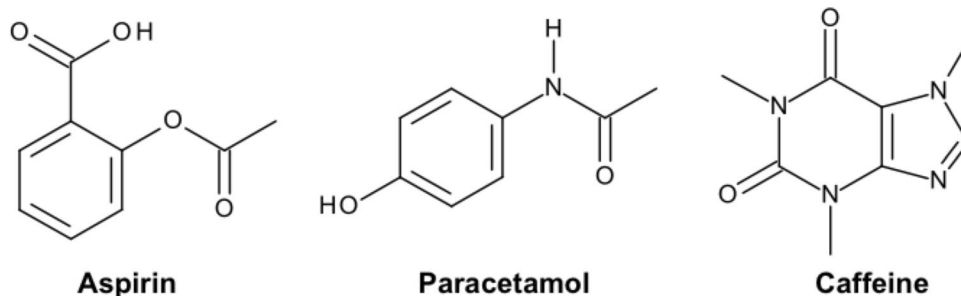
45,500 cm^{-1} [17]. The geometry, dipole moment and vibrational frequencies of paracetamol have been studied using the B3LYP/6-31G(d) method and compared to aspirin [18]. There is only one other computational study that tries to understand the interaction of paracetamol with water [19]. Paracetamol-water (PA-H$_2$O) complexes have been studied computationally using the MP2/6–311 + + G(d,p) method and found that 6 PA-H$_2$O complexes exist [19].

Caffeine belongs to the family of methyl xathines and is the worlds most consumed psychoactive stimulant [20]. It has been suggested that caffeine is an analgesic based on studies that found that 800 mg of aspirin with 64 mg of caffeine where more effective than aspirin alone in treating pain from a sore throat [21]. The mixture had also better antipyretic properties [21]. Caffeine flat structure and weakly hydrating non-polar molecular rings make it to have only weak solubility in water [22]. Calorimetric measurements have shown that it therefore self-aggregates, in water [22]. Callahan et al. studied the gas phase structure of various methylated xanthine derivatives including caffeine by resonant two-photon ionisation and IR–UV double resonance spectroscopy and through assignment of the peaks with DFT calculations found evidence of a stacked structure [23]. Molecular dynamic simulations with TIP3P and TIP4P water models have shown that caffeine associates only weakly with water molecules which cause it to aggregate [24]. This self-aggregation has been confirmed by nuclear magnetic resonance (NMR) in combination with molecular dynamics studies [25]. B3LYP/CBSB7 calculations have shown that water molecules act as bridges between the aggregated caffeine molecules and that they increase the interplanar distance [26]. There has also been a molecular dynamics study of the binding of caffeine with the human adenosine A$_{2A}$ receptor [27]. A study of the interaction of single caffeine molecule with water is not available to the best of our knowledge.

In this experimental and computational study, we have evaluated the interaction of aspirin, paracetamol and caffeine with water using density functional theory (DFT) and Fourier-transform infrared—attenuated total reflectance (FTIR-ATR) spectroscopy. We first present the minimum energy conformers of each analgesic, then we study the interaction of water with the analgesic and finally we study

the FTIR-ATR spectra of each analgesic. For the aspirin-water complex, we also perform IR simulations to provide a method of identifying the intramolecular H-bond.

Methods

Computational methods

All molecular structures where designed in Avogadro and optimised using various starting structure using the MMFF94 force field [28]. The starting structure was found by visually seeing how a water molecule interact with the analgesics while it was moved at a distance of about 1–2 Å from the molecular surface of these molecules which ensured that the potential energy surface was sampled exhaustively. The optimisation algorithm used was a steepest descent algorithm molecular mechanics calculations with a convergence criterion of 10^{-7} kJ/mol. The optimised structures from the MMFF94 calculations where then used as starting structures for DFT full optimisations within Gaussian 16 W with the use of Becke's three-parameter hybrid exchange functional [29] (XC) combined with the Lee–Yang–Parr non-local correlation functional [30], abbreviated as B3LYP. The basis set that was used was Pople's 6-31G basis set with one set of diffuse functions denoted as 6-31G(d) [31, 32]. Linear dependencies of the basis functions were removed by using the spherical version (5d and 7f) of this basis set. Single-point energy calculations have also been performed with the 6-311G(p,d) basis set. This method/basis set yields good adsorption energies for water to clusters and is considered as a good compromise between computational accuracy and computer time needed for the calculation. The self-consistent field (SCF) convergence criteria for the root mean square (rms) density matrix and the total energy were set to 10^{-8} Hartree/bohr and 10^{-6} Hartrees, respectively. Infrared spectra simulations were performed within the harmonic oscillator approximation. The infrared intensity of each vibrational mode i was taken to be proportional to the square of the derivative of the molecular dipole field with respect to the vibrational coordinate, q$_i$:

$$\left[\int \Psi_{v=0} \frac{\partial \mu}{\partial q_i} \Psi_{v=1} dq_i \right]^2 \qquad (1)$$

where the harmonic oscillator wave functions are used for $\Psi_{v=0}$ and $\Psi_{v=1}$. The dipole derivatives are calculated analytically, together with the force constants from the DFT wave function [33]. The optimised geometries at B3LYP/6-311G(d,p)// B3LYP/6-31G(d) are given in the supporting information file.

Experimental methods

Aspirin was purchased from Acros Organics (158,185,000) and was 99.0% pure. Paracetamol was purchased from Sigma-Aldrich (A7085) which was 99.0% pure. Caffeine was purchased from Sigma-Aldrich (C0750) and used as is.

The Fourier-transform-infrared (FTIR) spectra where obtained on a Alpha Platinum Diamond ATR spectrometer by Bruker. All spectra had 4 cm^{-1} resolution and where a result of signal-averaging of 24 spectra (sample scan = 24, background scan = 24). The beamsplitter was made out of KBr and the source was a Mid-IR source. The samples were placed on the ATR crystal with the use of a spatula and compressed with the clamp provided by the ATR cell. A small portion of deionised water was added to the sample while it was in this compressed state and the spectrum was recorded after 30 s.

Results and discussion

Computational section

Energy optimisations of aspirin

We have first optimised the various conformations of aspirin using the MMFF94 force field and found that there are 4 stable conformations for aspirin (see Fig. 2). These

optimised geometries where then used as starting structures for B3LYP/6-31G(d) optimisations. We note that although the MMFF94 calculations could obtain with good accuracy the structures of the various conformers, it could not predict with good accuracy the relative energies of the various conformers (see Fig. 2) where it swaps the energy ranking of conformer **C** and **D**. We therefore report the B3LYP/6-31G(d) results in the following sections.

The lowest energy conformer of aspirin is **A** in which the O–H of the carboxylic group is pointing away from the ester group. This is not anticipated based on the Lewis structure of this molecule that suggests that it may stabilise by forming an intramolecular H-bond with the ester group -O-. In conformer **B**, the O–H group is rotated by almost 180° pointing again away from the ester group. This conformer is 2.5 kJ mol^{-1} higher in energy than conformer **A**. In conformer **C**, the relative energy increases to 16.1 kJ mol^{-1}, although it forms an intramolecular H-bond with the C=O group of the ester shown in Fig. 2. This is perhaps due to strain caused to the acetoxy (AcO) group. This observation is in agreement with the B3LYP/6-31G(d) study of Sandra Cotes et al. who found that the conformers of aspirin that have an intramolecular H-bond are less stable, which was interpreted as a repulsive interaction between the O–H group and the ester group [34]. This strain is even larger in conformer **D** which has a relative Gibbs free energy of 12.0 kJ mol^{-1}. In conformer **D**, the intramolecular H-bond is to the -O- atom of the AcO group and forms a 6-membered ring. The intramolecular H-bond in **D** is stronger than in **C** which can be seen by comparison of the bond length, r(O–H…O), the bond angle, a(O–H…O), of the H-bond and the O-to-O separation, r(O…O), in the H-bond. These are given in Table 1 and show that the intramolecular H-bond of conformer **D** is stronger as it has a shorter r(O–H…O) = 1.806 Å compared to conformer **C** which has a H-bond length of r(O–H…O) = 1.849 Å. In very strong H-bonds, the angle of the H-bond is 180 Å. However, for
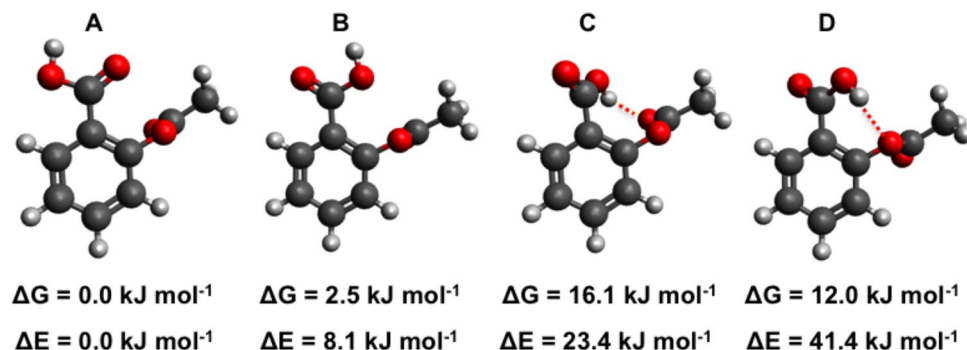

Fig. 2 Various conformers of aspirin and their relative energies using the MMFF94 (ΔE) force field and the B3LYP/6–31G(d) (ΔG) methods. The red dotted line indicates the intramolecular H-bond. Note that conformer **C** forms a 8-membered ring and conformer **D** forms a 6-membered ring for the intramolecular H-bond which can be seen in this figure and have previously been identified by Rainer Glaser [5]

these intramolecular H-bonds, the angles are much smaller, being a(O–H…O) = 154.3° and 146.1° for conformer **C** and **D**, respectively. Another factor that shows that the intramolecular H-bond of conformer **D** is stronger that conformer **C** is the O-to-O separation, r(O…O), which is 2.767 Å and 2.672 Å for conformer **C** and **D**, respectively.

Our calculations are in general agreement with the computational study of Rainer Glaser at the B3LYP/6-311G**//B3LYP/6-31G* level of theory [5]. We note here that B3LYP/6-311G**//B3LYP/6-31G* is equivalent to the B3LYP/6-311G(d,p)//B3LYP/6-31G(d) method. He finds that the conformer **C** and **D** are somewhat higher in energy due to an ortho repulsion [5]. However, he finds more isomers for aspirin which is a result of exploring the potential energy surface using the B3LYP/6–31* method. In the method that we employ, here some of the similar in energy conformations are missed because the potential energy surface was explored using MMFF94 force field. This simplifies the potential energy surface of this molecule and just finds structures that have completely

different features. This has some practical advantages in the study of the interaction of this molecule with water as it reduces the possible conformations. Furthermore, for the H-bonded conformers, our study is in agreement with the results Jose Cotuá and co-workers who finds that the 8-membered H-bonded conformation is more stable than the 6-membered H-bonded conformation [34].

Infrared spectra simulations of aspirin

In Fig. 3, we have simulated the infrared spectrum of gas phase aspirin from 400 to 4000 cm^{-1}. There are generally three areas where peaks of high intensity appear. There is a double peak in the range 1815 to 1870 cm^{-1} which corresponds to the C = O stretching frequency of both the carboxylic group and the ester group. The carboxylic group C = O vibration is 55 cm^{-1} lower in wavenumber than the ester C = O vibration. There is a peak in the range 3630 to 3696 cm^{-1} which corresponds to the O–H stretching frequency. This peak in an experimental FTIR spectrum of aspirin is a broad peak due to H-bonding with the aqueous phase. The peak that undergoes the largest perturbation upon formation of the intramolecular H-bond is the bending vibration of the O–H group. In Fig. 3, it can be seen that this peak shifts from 1229 to 1421 cm^{-1} when the intramolecular H-bond is present. These spectral shifts can be interpreted if we consider that the bending vibration of a H-bonded O–H is more restricted due to the electrostatic interaction with the oxygen atom of the ester group. A

Table 1 Tabulating geometric parameters of the intramolecular H-bond in conformer C and D of aspirin from B3LYP/6-31G(d) calculations

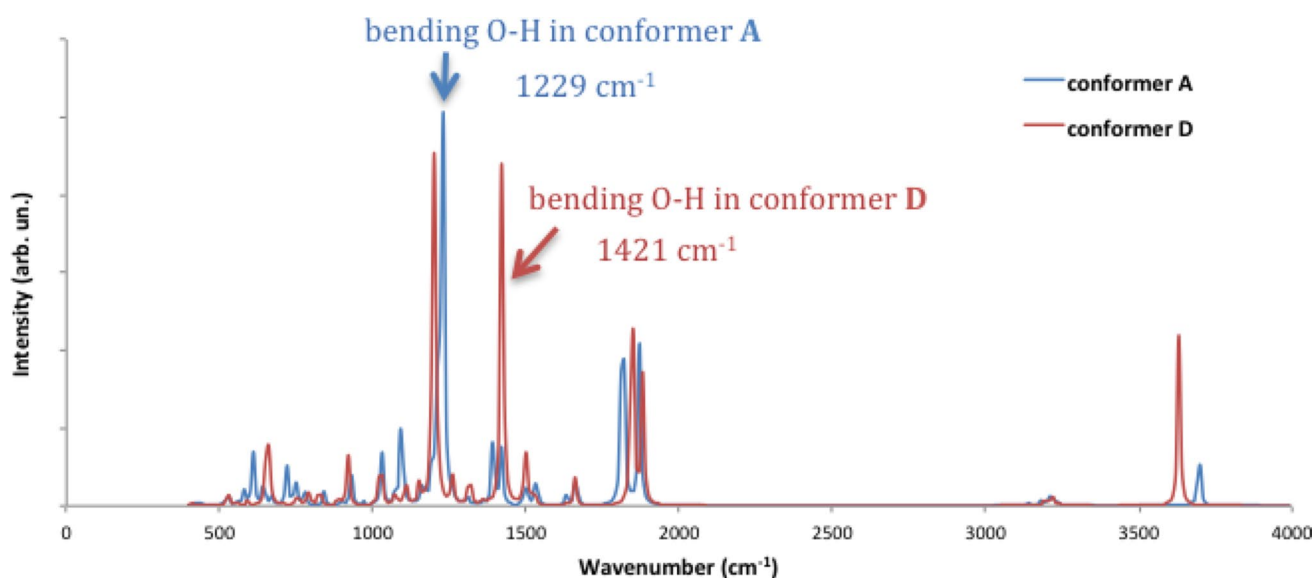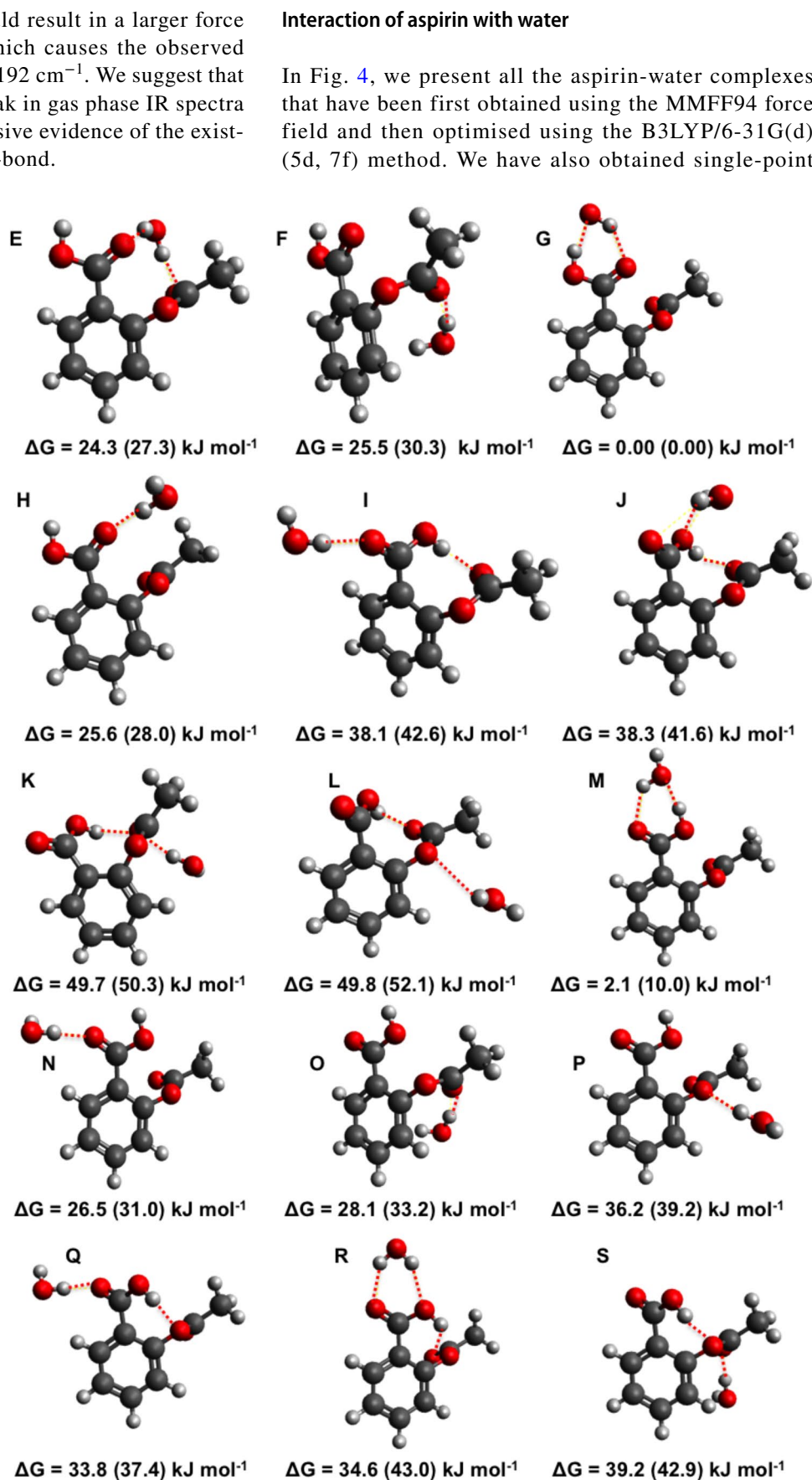| Geometric parameter	Conformer C	Conformer D
r(O–H…O)	1.849 Å	1.806 Å
r(O…O)	2.767 Å	2.672 Å
a(O–H…O)	154.3°	146.1°

Fig. 3 Simulated IR spectrum (400–4000 cm^{-1}) of aspirin that has an intramolecular H-bond (conformer **D**) and that is lacking the H-bond (conformer **A**). Peak in the range 1815 to 1870 cm^{-1} is the C = O stretching frequency. Peak in the range 3630 to 3696 cm^{-1} is the O–H stretching frequency

more restricted vibration would result in a larger force constant for the vibration which causes the observed blue-shift of this vibration by 192 cm^{-1}. We suggest that careful observation of this peak in gas phase IR spectra of aspirin will provide conclusive evidence of the existence of this intramolecular H-bond.

Interaction of aspirin with water

In Fig. 4, we present all the aspirin-water complexes that have been first obtained using the MMFF94 force field and then optimised using the B3LYP/6-31G(d) (5d, 7f) method. We have also obtained single-point

Fig. 4 Optimised geometries of aspirin-water complexes using the B3LYP/6-311G(d,p)// B3LYP/6-31G(d) method. Values in parenthesis are given by comparison of the energies from a frequency calculation using the B3LYP/6-311G(d,p) at the fully optimised geometry using B3LYP/6-31G(d). Red dotted lines indicate the H-bonds formed
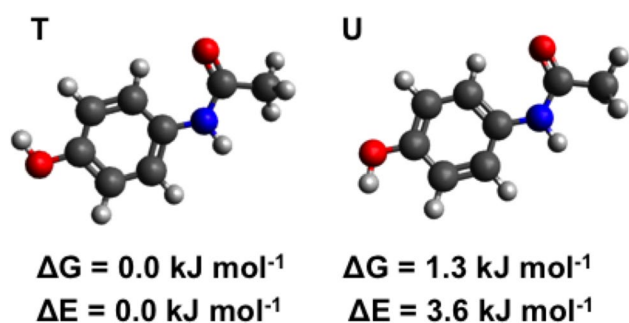

E $\Delta G = 24.3 \ (27.3) \ \text{kJ mol}^{-1}$

F $\Delta G = 25.5 \ (30.3) \ \text{kJ mol}^{-1}$

G $\Delta G = 0.00 \ (0.00) \ \text{kJ mol}^{-1}$

H $\Delta G = 25.6 \ (28.0) \ \text{kJ mol}^{-1}$

I $\Delta G = 38.1 \ (42.6) \ \text{kJ mol}^{-1}$

J $\Delta G = 38.3 \ (41.6) \ \text{kJ mol}^{-1}$

K $\Delta G = 49.7 \ (50.3) \ \text{kJ mol}^{-1}$

L $\Delta G = 49.8 \ (52.1) \ \text{kJ mol}^{-1}$

M $\Delta G = 2.1 \ (10.0) \ \text{kJ mol}^{-1}$

N $\Delta G = 26.5 \ (31.0) \ \text{kJ mol}^{-1}$

O $\Delta G = 28.1 \ (33.2) \ \text{kJ mol}^{-1}$

P $\Delta G = 36.2 \ (39.2) \ \text{kJ mol}^{-1}$

Q $\Delta G = 33.8 \ (37.4) \ \text{kJ mol}^{-1}$

R $\Delta G = 34.6 \ (43.0) \ \text{kJ mol}^{-1}$

S $\Delta G = 39.2 \ (42.9) \ \text{kJ mol}^{-1}$

Fig. 5 Various conformers of paracetamol and their relative energies using the MMFF94 (ΔE) force field and the B3LYP/6–31(d) (ΔG) methods

energy calculations with the 6-311G(d,p)(5d,7f) basis set. The Gibbs free energies of the various conformers are listed and the ordering found with the smaller basis (i.e. 6-31G(d)) set roughly agrees with what has been found for the larger basis (i.e. 6-311G(d,p)) set. It is interesting to observe that the Gibbs free energy differences (ΔG) of the various conformers can be as large as 52.1 kJ mol^{-1}. This suggests that conformational changes in aspirin are very important in determining its relative stability which may also be important in the biological action of aspirin. The data here suggest that aspirin will form up to two intramolecular H-bonds of the COOH group with the -O- and the C = O group of

Fig. 6 Optimised geometries of paracetamol-water complexes using the B3LYP/6-311G(d,p)//B3LYP/6-31G(d) level of theory. Values in parenthesis are given by comparison of the energies from a frequency calculation using the B3LYP/6-311G(d,p) at the fully optimised geometry using B3LYP/6-31G(d). Red dotted lines indicate the H-bonds formed
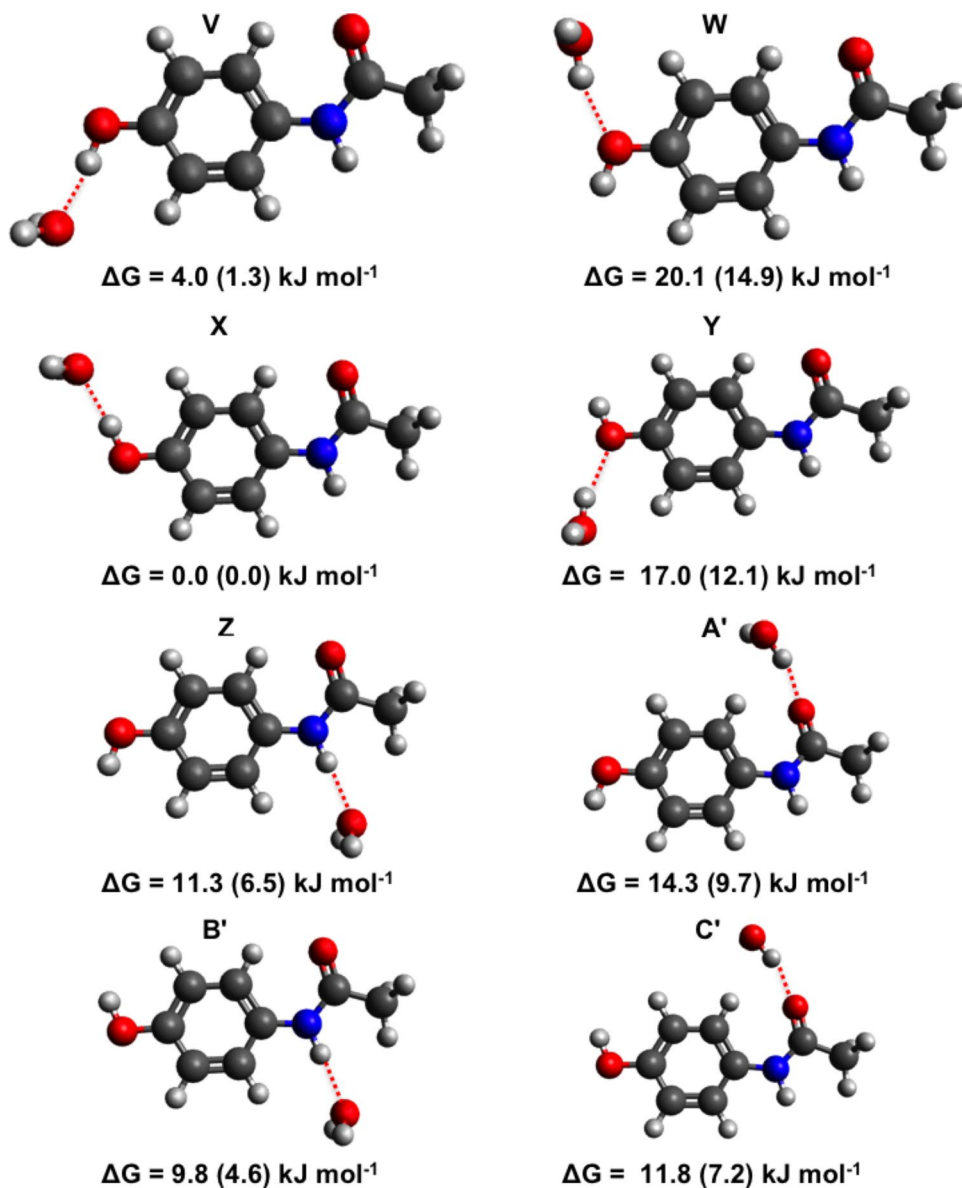
the ester that correspond to six-membered and eight-membered ring structures, respectively.

It will also form various intermolecular H-bonds with the water molecule that generally binds at the following sites (a) the COOH group (e.g. **G** and **M**) which are the most stable binding site for water forming simultaneously 2 hydrogen bonds, (b) simultaneously the $C=O$ of the COOH group and the $C=O$ of the ester group forming 2 H-bonds (e.g. **E**), (c) the $C=O$ group of the ester forming one H-bond (e.g. **F**, **K**, **O** and **S**), (d) the $C=O$ group of the COOH forming one H-bond (e.g. **E**, **H**, **I**, **N** and **Q**) and (e) the -O- group of the ester forming 1 H-bond (e.g. **L** and **P**).

It is also interesting to compare the relative energies of the various conformers at the B3LYP/6-311G(d,p)//B3LYP/6-31G(d) level of theory. The lowest Gibbs free energy conformer is **G** followed by **M** which is 10 kJ mol^{-1} higher in energy. In these structures, water forms simultaneously 2 H-bonds with the COOH group and this appears to be the most stable conformation of the aspirin-water complex.

Energy optimisations of paracetamol

B3LYP/6-311G(d,p)//B3LYP/6-31G(d) level of theory calculations show that there are two stable conformations for paracetamol in gas phase. These differ only by the rotation of the O–H bond with respect to benzene ring. In Fig. 5, the stable conformations of paracetamol are presented as well as their relative Gibbs free energies (ΔG).

The small Gibbs free energy difference of 1.3 kJ mol^{-1} could be a result of the dipoles of O–H and N–H being parallel and therefore slightly higher in energy. However, this statement cannot be made with great certainly as the limitation of the accuracy of the DFT method is about 1 kJ mol^{-1}.

Interaction of paracetamol with water

Water binds to paracetamol in eight different conformations (i.e. **V-C′**) shown in Fig. 6. These conformations

have relative energy differences at B3LYP/6-311G(d,p)//B3LYP/6-31G(d) level of theory that are as large 14.9 kJ mol^{-1}, which is significantly lower than the energy differences seen for the aspirin-water complexes. The lowest Gibbs free energy conformation of the paracetamol-water complex has water H-bonded to the O–H group as a H-bond acceptor shown in conformation **X**.

The second lowest in Gibbs free energy conformation of the paracetamol-water complex is similar to **X** but the O–H group is pointing in the opposite direction, which can be seen in conformation **V**. This conformation is only 1.3 kJ mol^{-1} higher in energy, which is a result of the Gibbs free energy difference of the two conformers of paracetamol, **T** and **U**. So water binds more strongly to the O–H group of paracetamol as a H-bond acceptor, then to the N–H group as a H-bond acceptor, then to the $C=O$ group as a H-bond acceptor and finally to O–H group as a H-bond donor.

Meifang Xu et al. has studied the complexes of paracetamol and water using MP2/6-311G(d,p) and found six conformers most of which are reproduced in this study [19]. In addition, we find to more conformations which are conformations **X**, **B′** and **Y**. In their study, they identify an intramolecular H–bond formed between the methylene and carbonyl oxygen atom of paracetamol [19]. This H-bond has an angle of about 120° and a bond length between the H…O in the range of 2.192 to 2.401 Å indicative of a weak H-bonding intramolecular interaction. In all paracetamol-water complexes studied, there is the formation of a strong intermolecular H-bond with the water molecule and the O–H group, the N–H group or the $C=O$ group. The lengths of these H-bonds is 1.825 to 1.819 Å with the O–H group when the water is a H-bond acceptor, 1.997 to 1.996 Å when the water is the H-bond donor. The H-bonds with the N–H group are 1.986 to 1.989 Å which is in the same range as those found for the water H-bonded when it is a H-bond donor. The H-bond length with the $C=O$ group is 1.892 to 1.907 Å, which are indicative of a moderate strength H-bond.

D′   **E′**   **F′**

ΔG = 2.1 (4.2) kJ mol^{-1} ΔG = 0.0 (0.0) kJ mol^{-1} ΔG = 1.6 (1.6) kJ mol^{-1}
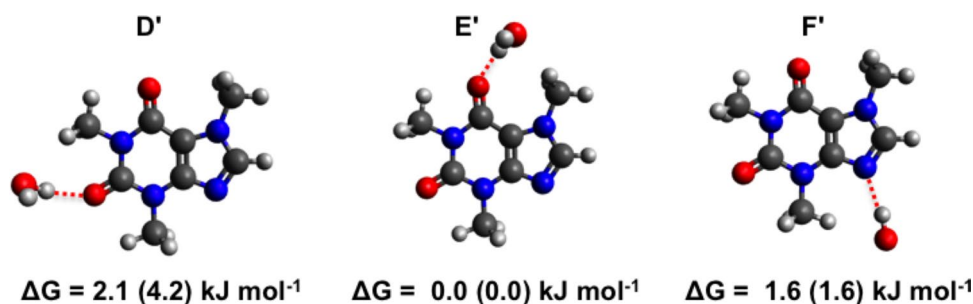
Fig. 7 Optimised geometries of caffeine-water complexes using the B3LYP/6-311G(d,p)//B3LYP/6-31G(d) level of theory. Values in parenthesis are given by comparison of the energies from a fre-quency calculation using the B3LYP/6-311G(d,p) at the fully opti-mised geometry using B3LYP/6-31G(d). Red dotted lines indicate the H-bonds formed

Fig. 8 FTIR-ATR spectra of **a** aspirin and aspirin-water mixtures, **b** paracetamol and paracetamol-water mixtures and **c** caffeine and caffeine-water mixtures
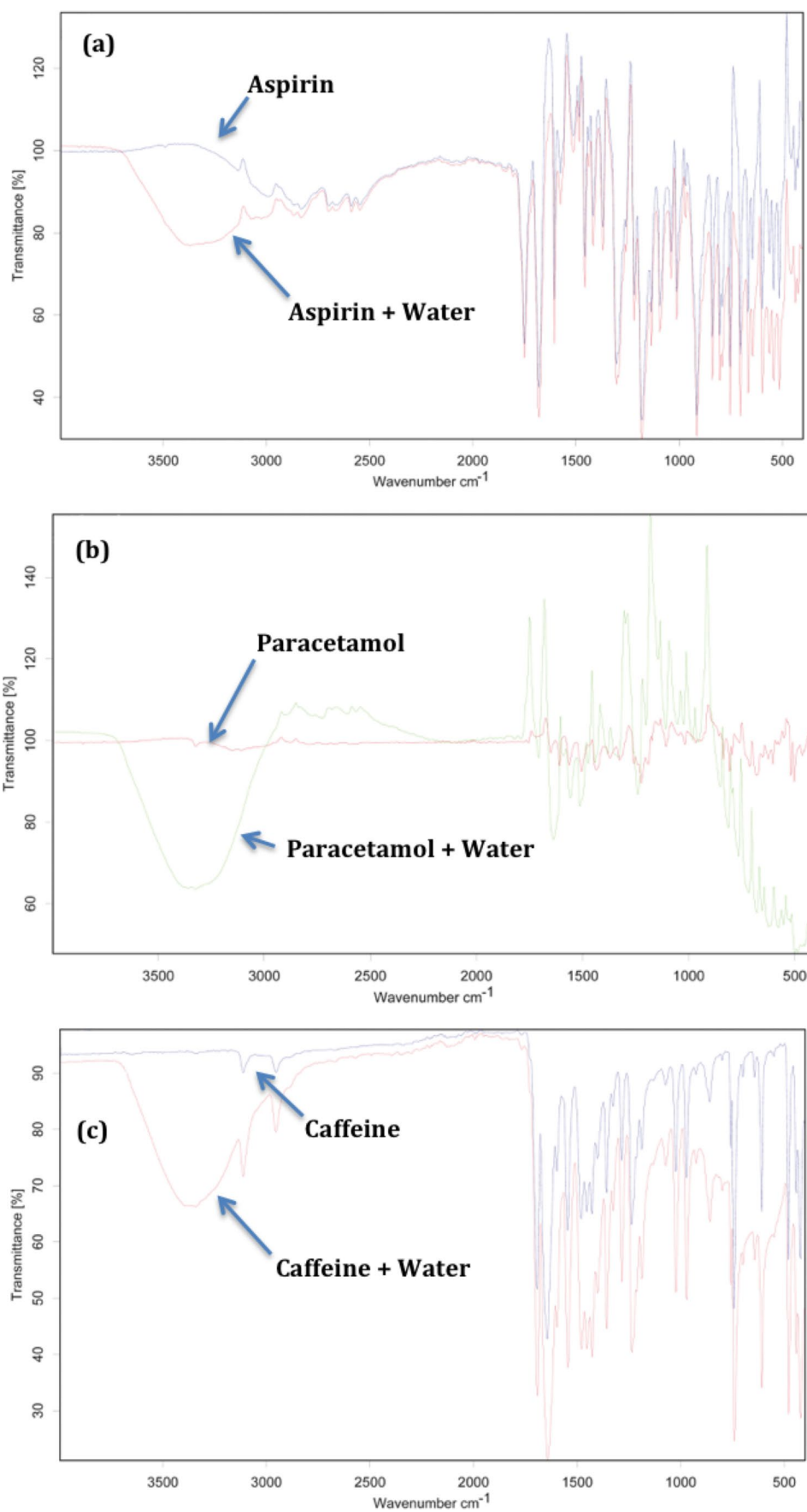
Interaction of caffeine with water

The study of caffeine interaction with water was easier than aspirin and paracetamol, as caffeine only has one low energy conformer. Furthermore, it has three H-bonding sites so its forms three caffeine-water complexes which are shown in Fig. 7. In the conformation **E′** water is bound to the top C=O bond and this is the lowest in energy conformation. Higher in Gibbs free energy by 1.6 kJ mol^{-1} is conformation **F′** in which water is bound to the N of the imidazole ring. The highest in Gibbs free energy conformation is one where the water molecule is bound to the bottom C=O group as shown in structure **D′**.

Experimental section

FTIR-ATR spectra of aspirin, paracetamol, caffeine and water mixtures

In Fig. 8, we present the FTIR-ATR spectra of aspirin, paracetamol and caffeine mixtures with water. The spectra where obtained for the dry powder of the analgesic and for the powder to which two droplets of deionised water have been added. All the spectra that also contain water in the mixture show the characteristic peak of O–H stretching in water from 3600 to 3000 cm^{-1} and a broad band in the fingerprint region of the spectrum. We were not able to observe any shift of peaks associated to the functional groups of the molecules that form H-bonds in the presence of water. It is clear from these spectra that only gas phase matrix isolated IR spectra of these analgesics with a single water molecule can provide further evidence of the preference of water in binding to the carboxylate group in aspirin and to the hydroxyl group in paracetamol. It is nice to observe that FTIR spectra of the analgesic dissolved in water can be taken without using sophisticated instrumentation just by adding a small portion of water to the solid as this is compressed in the ATR cell. More clearly seen for aspirin (see Fig. 8a) and caffeine (see Fig. 8c), addition of the water causes all the peaks in the fingerprint region to become more pronounced. This clearly suggests that addition of a thin aqueous layer can significantly enhance the signal-to-noise ratio in FTIR-ATR spectra fingerprint region. This maybe a result of decrease in the surface roughness of the solid sample and a better progression of the evanescent wave which extends into the sample.

Judging from the intensity of the water broad peak in the region 3600 to 3000 cm^{-1} if it can be clearly seen that aspirin has a lower solubility in water than caffeine and paracetamol which both have a much stronger intensity in their FTIR-ATR spectra of this band. This is in agreement with the measured solubility of caffeine in water 22 mg/mL [35] and the solubility of paracetamol is 17.39 ± 0.02 mg/mL at 30 °C [36] compared to the solubility of aspirin which is only 2–4 mg/mL.

Conclusions

Aspirin (acetylsalicylic acid), paracetamol (acetaminophen) and caffeine (1,3,7-trimethylxanthine) are important non-steroidal anti-inflammatory substances for the treatment of acute headaches as the can alleviate pain. In this computational study, we have studied the interaction of them with a water molecule in order to try to explain their different H-bonds these molecules form with water.

We find that aspirin forms the strongest H-bonding interaction with the COOH group in which it simulateneously forms 2 hydrogen bonds. It can also form a bridging interaction between the C=O of the COOH group and the C=O of the ester group forming 2 H-bonds. It also forms a H-bond with the C=O group of the ester, the C=O group of the COOH forming one H-bond and the -O- group of the ester forming 1 H-bond. In all paracetamol-water complexes studied, there is the formation of a strong intermolecular H-bond with the water molecule and the O–H group followed by a moderate in strength H-bond with the C=O group and a weaker in strength H-bond with the N–H group. Caffeine-water complexes have three H-bonding sites two of which are with the C=O group and one with the the N of the imidazole ring.

In our FTIR-ATR spectra of mixtures, these molecules with water show that there is an increase of the signal-to-noise ratio in the fingerprint region of the spectrum when water is added to these analgesics which could be used to improve the resolution of peaks in the fingerprint region of IR spectra.

Author contribution This computational study was conceived, designed by Dr. Constantinos Zeinalipour-Yazdi. C. D. Z. also collected the data; did the computational analysis and wrote the paper.

Declarations

Conflict of interest The author has no relevant financial or non-financial interests to disclose.

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