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Stacking and hydrogen bond interactions between adenine and gallic acid

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Abstract We have performed DFT and DFT-SAPT calculations on dimers of gallic acid, the model system for plant polyphenols, and the DNA base adenine. These dimers were selected for this study as they exhibit simultaneously hydrogen bonds and stacking interactions and it allows to quantify the relative values of these interactions. We calculate the relationships between the stability of the complexes, the charge transfer between monomers and the properties of the intermolecular bonds including hydrogen bonds and other bonds that do not involve hydrogen atoms. DFT-SAPT calculations were also performed to obtain the participation of the different types of energy and so the resulting physical effects. The results show that the presence of hydrogen bonds is the main stabilizing factor for dimers: the higher number and strength, the lower the dimer energy. The contribution of stacking to the stabilization is related to the strength and number of bonds between non-hydrogen atoms and quantified by the contribution of the dispersion terms to the interaction energy. Dimers I and II are mainly stabilized due to hydrogen bonds whereas dimer III is mainly stabilized by stacking interactions.

Keywords Dimers · Hydrogen bonds · Stacking

Introduction

Aromatic π-stacking interactions play a decisive role in chemistry and biology. They are fundamental for geometry characteristics and stabilization energy of many compounds and mechanisms such as DNA molecules, tertiary structure of proteins, crystal packing of aromatic molecules, control in the interaction enzyme-nucleic acids, recognition regulating gene expression or, specifically those corresponding to the benzene dimer which is considered a model system [1–7]. The study of these interactions has been performed for years and applied for different derivatives (see, for example [8–12]). From bibliography it could be inferred that experimental and theoretical descriptions of stacking interaction of drugs into DNA are complicated. On the one hand, the experimental approximation needs the combination of different techniques in order to obtain a full description of the complexes. On the other hand, the theoretical description implies the combination of the computational levels required for obtaining an accurate description of stacking complexes.

The most important findings obtained about this topic have been reviewed by Hobza, in a themed issue of *Physical Chemistry Chemical Physics* [13], showing the experimental and theoretical advances performed including both theoretical and experimental studies in gas phase and solution.

In this paper we have performed calculations on dimers that exhibit both stacking interactions and intermolecular hydrogen bonds in order to study the relative value of the corresponding effects. Although several calculations have been performed on dimers exhibiting stacking and hydrogen bond interactions they usually are studied as separated factors [14, 15]. Our contribution in this paper is mainly based on the presence of both stacking and hydrogen bonds simultaneously, which allows us to compare the effects on the whole energy of the complex.

Pitonak et al. studied the uracil dimer in both stacked and hydrogen bonded structures and they concluded that the electrostatic interaction is the dominant interaction for the hydrogen bonded system whereas the stacked structure is mainly bonded by dispersion [16]. They also found that dispersion and induction interactions significantly contribute to the stabilization

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of the hydrogen bonded complex and that there is also an important electrostatic contribution for the stacked structure. These results agree with those obtained by Hesselmann et al. for the stacked and hydrogen bonded A….T and G….C dimers [17] that show a similar contribution of dispersion terms for both hydrogen bonded and stacked structures.

In our research group we have performed some studies about dimers and the influence of stacking and charge transfer on stabilization [18 and references therein]. So, for the benzoquinone-hydroquinone complex (quinhydrone) charge transfer (CT) was found determinant in terms of stabilization and the geometry of the complexes is obtained to maximize the overlap of the molecular orbitals (HOMO and LUMO). In-plane intermolecular hydrogen bonds provide additional stability in solution and solid state for this system [19]. However, previous computational studies using the MP2/6-31G level and NBO analysis were ineffective to confirm the determinant role of CT in the complex stabilization [20] and the reliability of Mulliken's overlap and orientation principle [21]. For catechol complexes [22], face to face and C-H/π dimers have been studied analyzing the properties of the intermolecular bonds as well as the charge transfer by using MPW1B95 as workhorse functional to obtain the best results (close to the experimental value) in non-bonded interactions. It is known that MP2 calculations often overestimate π-π interactions and as a consequence, the stacking energy is overestimated too [6]. Most common DFT methods include exchange-correlation functionals unsuitable to account dispersion energies. Several experiments have been made on MP2 calculations with CCSD(T) energy corrections [23] in order to correct this overestimation as well as to introduce non-local correlations into van der Waals functionals [24], long-range corrections in combination with van der Waals functionals [25], new functionals optimized to describe nonbonded interactions [26, 27], introduction of empirical dispersion terms in functionals [28, 29], etc. Also, the comparison with experimental data for stacking energy allows us to establish that HF and B3LYP methods give rise to very slow stacking energies (leading to unstable complexes) [5, 8, 30].

The dimer molecules we have studied are formed by two aromatic rings: gallic acid, the model system for plant polyphenols, and the DNA base adenine. Our calculations try to find the relationships between the stability of the complexes, the CT and the properties of the intermolecular bonds including hydrogen bonds and other bonds that do not involve hydrogen atoms. Also, we have performed DFT-SAPT calculations to obtain the participation of the different types of energy and so the resulting physical effects.

Computational methods

DFT calculations were performed self-consistently using Gaussian03 program package with no constraints [31]. All molecules were fully optimized using MPW1B95 Truhlar's density functional [32] and 6-311++G(2d,2p) basis set. This basis set gives good results under stacking conditions or intermolecular interactions [18]. Although it has been previously found that it is not necessary to perform counterpoise corrections when this functional is used with a triple-ζ quality or larger basis set [33], we have estimated the BSSE values for the dimers by using the method of Boys and Bernardi [34].

The wave functions obtained were used to perform the QTAIM [35, 36] charge density analysis with the AIMPAC program package [37] and AIM2000 [38], in order to build topological analysis of computed electron densities $\rho(\mathbf{r_c})$ and analyze intermolecular interactions. Several geometries for dimers were studied to find the source of the main effects responsible for the dimer stabilization.

We have performed an analysis related to bond properties at the bond critical point (bcp) such as: $\rho(\mathbf{r_c})$, the laplacian of the electron density $\nabla^2\rho(\mathbf{r_c})$ and the total electronic energy density $H(\mathbf{r_c})$. We have also calculated atomic populations, $N(\Omega)$. The atomic populations were obtained with accuracy enough to obtain $L(\Omega)$ function smaller or near to 10^{-3} au [39–41]. The calculated values of the atomic populations were used to quantify the charge transfer (CT) as a difference between charge in dimers and that in monomers.

The interaction energy was obtained as:

$$E_{bin} = E_{complex}(AB) - (E_A(AB) + E_B(AB)),$$

where the energies for the monomers were obtained using the geometries they exhibit in the complex.

Another energy term has been studied, the deformation energy:

$$E_{dim} = E_{complex}(AB) - \left(E_A^{opt} + E_B^{opt}\right),$$

where the superscript 'opt' denotes the optimized geometry of the isolated monomers.

Both E_{bin} and E_{dim} were corrected by the counterpoise method to estimate the BSSE values.

In order to illuminate the nature of the intermolecular interactions, we have used the symmetry-adapted perturbation theory (SAPT) combined with density functional theory (DFT). DFT-SAPT uses monomer properties and densities from DFT, and performs SAPT [42–46] to obtain the different components of the interaction energy. This variant of SAPT, gives accurate binding energies and good description of stacked environments [47]. The interaction energy is expressed as a combination of perturbative corrections with different physical source. The total addition is composed by energies coming from electrostatics, dispersion, induction, and exchange repulsion interactions. So DFT-SAPT energy can be given as:

$$E_{int} = E_{pol}^1 + E_{exch}^1 + E_{ind}^2 + E_{ind-exch}^2 + E_{dis}^2 + E_{dis-exch}^2.$$

Particular terms can be combined to obtain values that correspond to known physical quantities, obtaining a scheme as the following:

$$E_{es} = E_{pol}^1$$
$$E_{ind} = E_{ind}^2 + E_{ind-exch}^2$$
$$E_{dis} = E_{dis}^2 + E_{dis-exch}^2$$
$$E_{exch-rep} = E_{exch}^1$$

Finally obtaining the expression of the interaction energy as:

$$E_{int} = E_{es} + E_{exch-rep} + E_{ind} + E_{dis}.$$

In order to reduce the computational cost of calculations, a density fitting procedure was applied. The DFT-SAPT calculation was performed using the PBE0 functional [48] along with the aug-cc-pVDZ basis set, using Molpro06 [49] program package. This kind of functional obtains accurate results for electron correlation effects on dimer interaction energies [22].

Results and discussion

Several dimers were obtained due to the fact that the potential energy surface is quite flat. Three non-similar geometries were selected and the whole analysis was performed on all of them, trying to compare the different properties and the intermolecular interactions with the relative energies. Results are presented divided in four sections.

1. **Geometry and energy of the complexes**

    Figure 1 shows structures I, II, and III obtained by optimization. Energies are shown in Table 1. E_{bin}^c and E_{dim}^c values correspond to the corrected energies by using counterpoise method to estimate the BSSE values. These corrections scarcely affect the relative values of the energies as they are very similar for the three dimers (5.3, 5.1, and 5.7 kJ mol^{-1} for complexes I, II and III respectively).

    Rings in complexes are almost planar with RMS deviations from the plane lower than 10^{-3} Å. These small deviations from plane allow us to consider planar rings and to calculate mean planes and center of the rings in order to describe the geometries of the complexes. Table 1 shows the values of distances and angles between planes of the rings in each dimer and several intermolecular distances. As can be seen in Fig. 1 and Table 1 the three dimers correspond to three different arrangements of monomers in the dimers: dimer I has the closest monomers and dimer II the furthest ones. However nearest atoms are closer in dimer II as it has the higher angle between rings. Dimers I and II exhibit very similar

dimerization energies although they correspond to very different geometries with the rings in a different orientation: the distance between the O atom of the CO group of gallic acid and the N atom of the NH2 group of adenine is 3.260 Å for I and 5.912 Å for II. Dimer III has a higher energy value that does not seem related to the values of the main parameters used in this comparison and should be a consequence of the nature of the intermolecular interaction between monomers.

E_{bin} is the difference between the energy of the dimer and the energy of the monomers at the geometry that they exhibit in the complex. The differences between E_{bin} and E_{dim} reflect the deformation of the geometries upon dimerization. These differences of energy between the monomers in the dimers and the optimized monomers appear in Table 1 as E_{def}. They are higher for gallic acid than for adenine due to the flexibility of the OH groups of the acid. So, the main differences between the geometries in dimer and monomers are located in the H atoms of OH groups of the gallic acid which are oriented to establish hydrogen bonds with electronegative atoms of adenine. Thus, several of these hydrogen atoms are out of the main plane of the gallic acid ring. Also, the hydrogen atoms of the amino group of adenine go out from the plane but the effect is lower. The differences are small for the remaining atoms of the molecules.

2. **Intermolecular bonds**

    The obtained structures have different number of intermolecular bonds: two for dimer I, three for dimer II and four for dimer III. The main properties for these intermolecular bonds are listed in Table 2, where two different kinds are shown: B1, B2, B3′ and B3″ are intermolecular hydrogen bonds whereas the remaining bonds do not involve hydrogen atoms. Hydrogen bonds are shorter and stronger with higher values for the density at the bcp $\rho(\mathbf{r_c})$ and the laplacian of the electron density $\nabla^2\rho(\mathbf{r_c})$. The number of intermolecular bonds does not seem to be related to the stability, but the character and the strength of the bonds could play a role. Accordingly, although the most stable dimer I only shows two intermolecular bonds they both are hydrogen bonds. The only hydrogen bond in dimer II is the strongest. In summary, the higher number and strength of hydrogen bonds, the lower energy for the dimer. The number of non-hydrogen intermolecular bonds does not seem to be important for stability.

    Among the bonds involving non-hydrogen atoms the strongest one appears in dimer III (B1″) which exhibits the shortest distance and the highest values for $\rho(\mathbf{r_c})$ and $\nabla^2\rho(\mathbf{r_c})$.

    Although several authors have found a correlation between the summation of the $\rho(\mathbf{r_c})$ for intermolecular bonds related to stacking (those not involving hydrogen
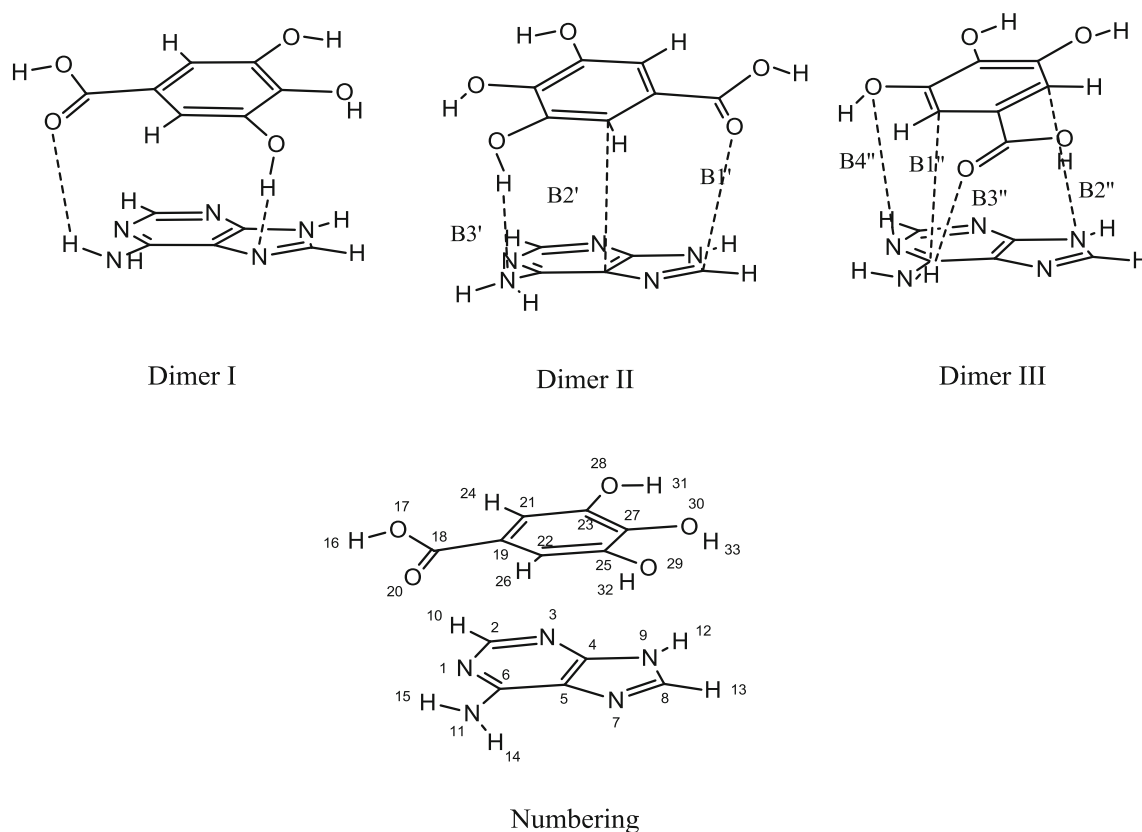
Dimer I   Dimer II   Dimer III

Numbering

Fig. 1 Geometries and numbering of the dimers

bonds) and the binding energy, this relationship is not found for the dimers in this paper [50, 51]. In fact, the most stable dimer only exhibits intermolecular hydrogen bonds. It could be related to the small magnitude of the $\rho(\mathbf{r}_c)$ values found.

Regarding $H(\mathbf{r}_c)$ values, all are positive in accordance with the closed shell character of the bonds.

3. **Charge of the complexes**

Regarding the CT (Table 1) obtained from QTAIM it is more important in dimer II, although all three values found are small and it allows us to infer that these compounds could not be considered as charge transfer dimers. The transfer takes place from adenine to gallic acid in all cases. The calculated ionization potentials (vertical ones) are

Table 1 Geometric parameters, energies and charge transfer

Parameter	I	II	III
Dist between centers (Å)	3.264	3.722	3.474
Perpendicular distance from center of gallic ring to adenine main plane(Å)	3.324	3.650	3.495
Perpendicular distance from center of adenine ring to gallic acid main plane (Å)	3.323	3.333	3.312
Dist nearest atoms (Å)	2.336	2.099	2.607
Tilt angle(degree)	11.5	15.7	12.8
Nearest atoms	H(32)-N(7)	H(32)-N(11)	O(20)-H(14)
Charge transfer (au)	0.019	0.031	0.005
Edim (kJ mol^{-1})	0	0.4	17.0
Edim^c (kJ mol^{-1})	0	0.2	17.4
Ebin (kJ mol^{-1})	0	2.9	11.5
Ebin^c (kJ mol^{-1})	0	2.7	11.9
Edef adenine (kJ mol^{-1})	2.0	4.0	1.6
Edef gallic acid (kJ mol^{-1})	10.7	6.2	16.7

Table 2 Bond properties of intermolecular bonds

Dimer	Intermolecular Bcp's	10^3 au $\rho(\mathbf{r}_c)$	10^3 au $\triangledown^2\rho(\mathbf{r}_c)$	10^3au $H(\mathbf{r}_c)$	R(Å)	Atoms	Bond
I	B1	13.0	43.6	1.5	2.336	N(7)-H(32)	N······H-O
I	B2	6.6	22.2	0.7	2.666	H(15)-O(20)	N-H······O
II	B1′	5.6	16.6	0.9	3.390	C(5)-C(22)	C·········C
II	B2′	3.6	13.1	0.8	3.428	C(8)-O(20)	C·········O
II	B3′	21.0	62.5	1.1	2.099	N(11)-H(32)	N······H-O
III	B1″	6.1	20.6	1.2	3.276	C(6)-C(22)	C·········C
III	B2″	2.8	9.1	0.4	3.797	N(9)-C(21)	N·········C
III	B3″	6.8	23.2	0.7	2.607	H(14)-O(20)	N-H······O
III	B4″	4.5	17.4	0.9	3.482	N(1)-O(29)	N·········O

8.28 eV for adenine (in accordance with the experimental value, 8.48 eV) [52] and 8.40 eV for gallic acid. The calculated electron affinities are −0.50 eV for adenine (in accordance with the experimental value, −0.54 eV [53]) and −0.48 eV for gallic acid. The differences between ionization potential and electron affinities in both molecules are small (within the error in our method) and so is the π charge flow between them. σ charge should flow through hydrogen bonds. The pattern of this transfer could be inferred from values of the charge differences between dimers and monomers shown in Table 3.

For dimer I highest differences mainly correspond to atoms involved in hydrogen bonds (N11, O29, N7 and H32) although the effect spreads to atoms bonded to them as H14. The same result is found for dimer II, where the changes in atoms involved in hydrogen bonds are higher than in dimers I and III because this dimer shows a stronger hydrogen bond. In particular in the case of N11 (−0.038) a donor lone pair effect can be observed according to Fig. 1. C06 the atom bonded to N11, exhibits the highest variation in atomic population (0.065). For dimer III the effect is not so local and the atoms in the ring of gallic acid show important differences. So, it could be inferred that dimers I and II are mainly stabilized through hydrogen bonds and the effect of the interaction in the remaining atoms is small, whereas dimer III seems to be stabilized through a different mechanism that involves the whole ring of gallic acid. Taking into account only the changes in the charges of the atoms X, H and Y in X-H….Y hydrogen bond system, the following results were obtained: (i) for dimer I adenine loses 0.019 au and gallic acid gains 0.021 au, which agrees with the calculated value for the CT in the whole molecule (0.019 au); (ii) for dimer II adenine loses 0.027 au and gallic acid gains 0.022 au, which is a higher value than that found for dimer I. Also the value for the whole molecule is higher in dimer II (0.031 au); (iii) for dimer III 0.031 au are lost by adenine and 0.012 au are gained for gallic acid. In this case a significant difference is found between values for both molecules indicating the complexity of the pattern that explains the charge flow for the complex.

Table 3 Differences (au) between atom charges in dimer and monomers (differences lower than 0.001 au are not shown)

Atom	I	II	III
C04	−0.004	−0.019	0.002
C06	0.002	0.065	0.008
C08	−0.004	−0.016	0.001
C18	−0.007	0.017	−0.001
C21	−0.006	0.004	0.014
C23	0.005	0.003	0.066
C25	−0.013	−0.019	−0.058
C27	0.011	−0.007	−0.057
H13	0.001	−0.018	0.003
H14	0.016	0.008	−0.014
H15	−0.015	0.009	0.011
H24	−0.003	0.005	0.033
H26	−0.006	−0.016	0.006
H31	0.004	0.001	0.012
H32	−0.011	−0.018	0.006
N01	−0.003	0.006	0.013
N07	0.022	−0.002	−0.004
N11	−0.027	−0.038	−0.017
O20	0.010	0.007	0.012
O28	−0.002	0.001	0.011
O29	0.021	0.033	−0.023
O30	0.012	0.008	−0.028

Table 4 Calculated energies (kJ mol^{-1}) in their different contributions

Dimer	I	II	III
Eint	−49.3	−42.7	−39.0
Ees	−38.7	−33.4	−20.1
Eexch	48.8	41.9	26.9
Eind	−6.4	−9.6	−2.3
Edisp	−53.0	−41.7	−43.4

In all three cases both σ and π charge transfers are small and so is the total one.

4. **SAPT energy analysis**

Table 4 show the components of the energy obtained for dimers I, II and III from SAPT calculations. The energies obtained by SAPT calculations are slightly different to those obtained by DFT calculations but the relative stability of dimers is correctly reproduced.

From results in Table 4 it could be inferred that both electrostatic and dispersion energies are important to explain the stability of the dimers. The electrostatic contribution is related to the hydrogen bonds and it is important in all three complexes, although it is higher in I and II. In both it represents a similar percentage of the whole energy. The dispersion contribution is often related to stacking and it is the most important contribution in percentage to the energy for the three complexes. It is higher in dimer III, where hydrogen bond is weaker and the contribution of the electrostatic term is lower. These results agree with those found by different authors for stacked dimers. For displaced stacked pyrazine dimers [54] Sütay et al. found that the dispersion energy dominates the interaction with similar contributions for induction and electrostatic terms due to the absence of hydrogen bonds. The same results were found for benzene and benzene substituted dimers for several authors [7, 55] and for uracil dimers [16]. As a summary we could conclude that all three dimers show stabilization by both hydrogen bonds and stacking effects. The effect of hydrogen bonds is more important in dimers I and II and the effect of stacking is more important in dimer III.

Conclusions

The results found in this paper show that the main stabilizing factor for dimers is the presence of hydrogen bonds: the higher number and strength, the lower the dimer energy. These bonds are the main factor of stabilization for dimers I and II. Also, the charge transfer between monomers happens mainly through hydrogen bonds because there is no π transfer between monomers due to the values of ionization potentials and electron affinities for monomers. The contribution of stacking to the stabilization is related to the strength and number of bonds between non-hydrogen atoms and quantified by the contribution of the dispersion terms to the interaction energy. Dimer III is mainly stabilized by stacking interactions because it exhibits the strongest bonds between non hydrogen atoms, the weakest hydrogen bonds and a more important contribution of the dispersion term to the total energy of the dimer.

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