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Computational and Theoretical Chemistry

journal homepage: www.elsevier.com/locate/comptc

Theoretical studies on hydrogen bonding in caffeine-theophylline complexes

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A R T I C L E I N F O

ABSTRACT

Article history: Received 23 August 2011 Received in revised form 15 October 2011 Accepted 16 October 2011 Available online 22 October 2011

Keywords: Density functional theory Intermolecular interactions Atoms in molecule Natural bond orbital The intermolecular interactions between caffeine and theophylline have been studied using their geometries, energies and topological features of the electron density with density functional theory (DFT) and MP2 methods implementing the 6-311G (d, p) atomic basis set. Sixteen caffeine–theophylline complexes were found on the potential energy surface involving N—H···N, N—H···O, C—H···N and C—H···O hydrogen bonds. The complex with conventional N—H···N hydrogen bond along with a strong C—H···O bond is found to be the most stable structure at MP2/6-311G (d, p) and B3LYP/6-311G (d, p) level of theories. From atoms in molecule (AIM) analysis an excellent linear correlation is shown to exist between the hydrogen bond length, electron density [$\rho(r)$] and its Laplacian [$\nabla^2 \rho(r)$] at the bond critical points. The natural bonding orbital analysis on the most stable complex in which N—H···N and C—H···O hydrogen bonding interactions are dominant, reveals that imidazole nitrogen of caffeine has offered large amount of lone pairs (0.036) to the contacting σ^* (N—H) antibond orbital of theophylline and carbonyl oxygen (amide moiety) of theophylline offers lone pair (0.004) to σ^* (C—H) antibond orbital of caffeine.

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1. Introduction

Intermolecular hydrogen bonding interaction plays an important role in determining the structures and activities of organic, organometallic and biological molecules [1–4] and is also involved in the interaction of many substrates to the active sites of enzymes. Therefore, hydrogen bonds between biomolecules, and the effects of hydrogen bonds on their properties, are of great interest. Theoretical treatments of intermolecular interactions are especially challenging, and the hydrogen bond is no exception. Several intermolecular hydrogen bondings have been observed in biological systems, such as $O-H\cdots O$, $N-H\cdots O$ and $N-H\cdots N$. Traditionally one of the most essential structures, capable of bearing hydrogen bond, is $O-H\cdots O$ unit, which has been studied extensively, but $N-H\cdots O$ and $N-H\cdots N$ units are the most frequent hydrogen bridges that exist in organic systems [5] and hence require further studies.

N-heterocyclic compounds are of considerable importance as they encompass extensive pharmaceutical significance. Caffeine and theophylline are a system of two heterocyclic rings, containing a six membered pyrimidine and a five membered imidazole rings and thus being a biologically important compound used as mild stimulants and bronchodilators for treating the symptoms of asthma. Caffeine possesses a total of three sites that can act as hydrogen-bond acceptors. One group is the imidazole nitrogen and the remaining two groups are the oxygen atoms of carbonyl groups of urea and amide moiety [6]. In addition to these acceptors, caffeine possesses three methyl groups, but has no proton-donor group; hence it cannot form complexes containing two hydrogen bonds either with other caffeine molecules or with any of the DNA bases [7]. The hydrogen bonding capability of theophylline includes three hydrogen bond acceptors similar to caffeine (two carbonyl oxygens and one basic nitrogen) and in addition, it possesses a good N—H hydrogen bond donor which has been confirmed by Trask et al. [8]. The presence of a hydrogen bond donor in theophylline is observed to play a significant role in the crystal packing of both the anhydrate and monohydrate crystal forms. Further, it has been recently shown that these purine bases can bind through C19 atom [9] which makes it ideal for studying hydrogen-bonded interactions.

A detailed theoretical study of possible caffeine dimers have been performed at MP2/6-31G (d, p) ab initio level of theory [7] and their results predicted that the deepest local minima correspond to nearly parallel arrangements of molecules (stacking) in both parallel (face-to-back) and anti-parallel (face-to-face) orientations. Theophylline is known to exist as a crystalline monohydrate [10] and there have been several studies related to its hydration behavior [11–14]. Caffeine is added to soft drinks as a flavor accompanied by its analogue theophylline which increases the serum concentrations of theophylline. In an intra individual design, the influence of a single dose of caffeine on the elimination of theophylline in six healthy subjects has been investigated [15]. The pharmacokinetic interactions of caffeine with theophylline were

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²²¹⁰⁻²⁷¹X/\$ - see front matter © 2011 Elsevier B.V. All rights reserved. doi:10.1016/j.comptc.2011.10.015

examined in two beagle dogs by administering 100 mg of aminophylline intravenously, 3 weeks before and immediately after repeated oral doses of caffeine [16]. The above studies suggest that pharmacokinetic interactions are more predominant between caffeine and theophylline and there is no direct interaction of these two drug molecules.

The aim of the present study is to explore the hydrogen bonding between caffeine-theophylline complexes and their influence on the stability of the complex with respect to chemical aspects. Investigations on the interaction between these two drug molecules may provide useful information for researchers in the field of chemistry and life science to know the hydrogen bonding nature of these drugs. In the present work, the structural and electronic properties of hydrogen bonds (N-H···N, N-H···O, C-H···N and C-H···O) in caffeine-theophylline complexes have been studied using MP2 and density functional theory methods. AIM analyses based on Bader's atoms in molecules theory [17] and NBO analyses [18] have been performed to confirm the presence of hydrogen bonding and to know the information about charge transfer, respectively.

2. Computational details

The Becke's three parameter exact exchange functional (B3) [19] combined with gradient-corrected correlation functional of Lee-Yang-Parr (LYP) [20] of DFT method has been employed to optimize the geometries of monomer and caffeine-theophylline complexes. All the possible orientations of caffeine with theophylline have been fully optimized using the above level of theory at 6-311G (d, p) basis set. Sixteen conformers corresponding to the minimum energy points have been obtained. Vibrational frequency analyses yielded no imaginary frequency, at the molecular energy hyper surface. In order to achieve rigorous energy comparison, single point energy calculation has been performed at Moller-Plesset perturbation theory (MP2) [21] for the geometries optimized at B3LYP level of theory. The interaction energies for the optimized complexes have been corrected for the basis set superposition errors (BSSE), using the counterpoise method of Boys and Bernardi [22] using 6-311G (d, p) basis set. Further, the interaction energies of the most strongly and least bound complexes have been calculated using 6-311++G (d, p) basis set. Topological analysis has been carried out using Morphy 98 software [23] for the optimized geometries. NBO analysis has been performed by using NBO 3.1 program at B3LYP level of theory. All the calculations have been carried out using the Gaussian 03 W computational package [24].

3. Results and discussion

The optimized structures of caffeine and theophylline have been computed at B3LYP/6-311G (d, p) level of theory and are presented in Fig. 1. For convenience, the optimized monomers of caffeine and theophylline are represented as CAF and THP, respectively. The geometrical parameters (bond lengths and bond angles) of CAF and THP monomers calculated with B3LYP/6-311G (d, p) basis set are presented in Table 1. All the atoms of CAF and THP except the atoms present in methyl groups are located in the same plane. The calculated bond lengths and bond angles of CAF monomer differ from experimental values [25] by 0.01-0.06 Å and 0.1-10.7° and for THP by 0.01-0.04 Å and 0.3-2.3°, respectively. The most significant difference in caffeine is related to extra-cyclic N-C bonds and angles of these bonds with intracyclic bonds. Further, the reason for this deviation may be due to that the theoretical calculations belong to isolated molecules in gaseous phase and the experimental results belong to molecule in solid state [26]. However, the calculated values are found to agree well with the previous theoretical results [27,28].

CAF and THP molecules offer several possible donor and acceptor sites to form hydrogen-bonds. Therefore, it seems reasonable to believe that there exist electrostatic and hydrogen bonding interaction between CAF and THP complex system. In contrast to merely electrostatic interactions, hydrogen bonds are directional and lead to different configurations of the complex. Therefore, to identify the actual site for hydrogen bond formation, monomers of CAF and THP have been allowed to interact with each other. The search for minimum energy structures within the potential energy surface of the interacting complexes has led to 16 structures and is presented in Fig. 2. All systems analyzed here are coupled through double hydrogen bonds. Studying all these complexes using the same level of theory allows us to analyze their relative stability in terms of properties of the binding sites. The structures are labelled with a common name CAF-THP-nn'. where CAF stands for caffeine and THP is theophylline. Here each n and n' has the values 1, 2, 3.0r 4 depending on the nature of hydrogen bonds present in the structure viz., 1 means N-H...O, 2 corresponds to N-H...N, 3 indicates C-H...N and 4 indicates C-H...O type hydrogen bonds. On surveying the structure of the complex, it is found that most of the complexes have correspondence with the other due to a similar type of hydrogen bonding. Hence, the structures with similar bonds with comparable energies have been distinguished with the letters A, B, C, D, E, F and G. The complex CAF-THP-14(A) is related to CAF-THP-14(B), both have an N-H...O and C-H...O hydrogen bonds. CAF-THP-43(A) is related to CAF-THP-43(B), CAF-THP-43(C), CAF-THP-43(D), CAF-THP-43(E), CAF-THP-43(F) and CAF-THP-43(G), all of them have a C-H···O and C-H···N hydrogen bonds. CAF-THP-33(A) is related to CAF–THP–33(B); both have two C–H···N hydrogen bonds. Further, two C—H···O type hydrogen bonds have been observed in CAF-THP-44(A), CAF-THP-44(B) and CAF-THP-44(C) and CAF-THP-44(D). CAF-THP-24 is a unique complex having an N-H···N and C-H-O hydrogen bonds. It is to be observed that most of the complexes are formed through $C-H\cdots O$ and $C-H\cdots N$ type hydrogen bonds. Further, three possible arrangements (CAF-THP-43(B), CAF-THP-43(F) and CAF-THP-44(A)) have been found to occur for the interaction of the hydrogen atom H20 in the imidazole ring of CAF with carbonyl oxygen O35 (urea moiety) in THP.

The hydrogen bonding distances and the corresponding angles can be considered as a criterion of strength of hydrogen bonding. The geometrical parameters of the intermolecular hydrogen bonds formed in CAF-THP complex are presented in Table 2. The complexes CAF-THP-14(A) and CAF-THP-14(B) possess two equivalent strong hydrogen bonds (N-H···O) of bond length 1.81 Å between N–H proton donor of THP and carbonyl oxygen of amide/urea moiety of CAF at B3LYP/6-311G (d, p) level of theory. The change in bond length $\Delta R_{N37-H45}$ is observed to be of 0.0165 and 0.0154 Å for the complexes CAF-THP-14(A) and CAF-THP-14(B), respectively. The intermolecular hydrogen bond N37-H45...N18 formed in CAF-THP-24 complex has resulted in the N_(imidazole)...H distance by 1.90 Å. The interaction has resulted in the largest elongation of bond length of the proton donor N–H ($\Delta R_{N37-H45}$) from its corresponding monomer by 0.0242 Å. However, for C-H...O type interaction the value of the bond length varies from 2.15 to 2.48 Å, while the values for the C–H…N interaction ranges between 2.35 and 2.70 Å. As the hydrogen bonding distances of C-H···O and C-H···N bonds are larger, smaller is the elongation of C-H bond (0.0001-0.0041 Å). Accordingly, C-H···O and C-H···N bonds are observed to be weaker than N-H...O and N-H...N bonds mainly because of a larger reduction in the electrostatic contribution. The analysis of the additional hydrogen bonds (C-H···O/ $C-H \cdots N$) shows that the interaction of hydrogen atom H20 in the imidazole ring of CAF with carbonyl oxygen O36 (amide



Fig. 1. The optimized structures of CAF and THP monomer.

Table 1
Geometrical parameters (bond lengths in Å, bond angles in degrees) for CAF and THP monomers calculated at B3LYP/6-311G (d, p) level of theory. For labeling of atoms see Fig. 1.

Parameters	CAF		Parameters	CAF		Parameters	THP		Parameters	THP	
	Theoretical	Expt ^a		Theoretical	Expt ^a		Theoretical	Expt ^a		Theoretical	Expt ^a
N1-C2	1.4077(1.41) ^b	1.42	N3-C17-H10	107.6(107.7) ^b		N1-C2	1.4085(1.41) ^c	1.35	N1-C2-015	121.4	
N1-C6	1.4171(1.42)	1.36	C2-N1-C6	126.9(126.9)	127.6	N1-C6	1.4165(1.42)	1.37	C6-N1-C11	117.9	
N1-C11	1.4674(1.47)	1.48	C2-N1-C11	115.2(115.1)		N1-C11	1.4675(1.47)	1.46	N1-C6-C5	110.8	112.5
N3-C2	1.3906(1.39)	1.35	N1-C2-015	121.4(121.4)	122.7	N3-C2	1.3923(1.39)	1.40	N1-C6-016	123.1	121.2
N3-C4	1.3740(1.38)	1.42	C6-N1-C11	118.0(118.0)	120.3	N3-C4	1.3736(1.37)	1.38	N1-C11-H12	110.0	
N3-C17	1.4632(1.46)	1.50	N1-C6-C5	111.1(111.0)	115.8	N3-C17	1.4635(1.46)	1.48	N1-C11-H13	110.0	
C2-015	1.2165(1.22)	1.19	N1-C6-016	122.5(122.6)	118.4	C2-015	1.2159(1.22)	1.19	N1-C11-H14	107.3	
C4–C5	1.3798(1.38)	1.32	N1-C11-H12	110.0(110.0)		C4–C5	1.3765(1.38)	1.37	C5-C4-N18	111.7	
C4-N18	1.3570(1.36)	1.31	N1-C11-H13	110.0(110.0)		C4-N18	1.3613(1.36)	1.33	C4-C5-C6	124.2	122.6
C5–C6	1.4323(1.43)	1.44	N1-C11-H14	107.3(107.3)		C5–C6	1.4318(1.43)	1.41	C4-C5-N7	104.8	
C5-N7	1.3870(1.39)	1.41	C5-C4-N18	111.7(111.8)		C5-N7	1.3816(1.38)	1.34	C4-N18-C19	104.2	
C6-016	1.2225(1.23)	1.26	C4–C5–C6	123.7(123.9)	119.9	C6-016	1.2204(1.22)	1.22	C6-C5-N7	130.9	
C17—H8	1.0907(1.09)		C4-C5-N7	105.1(105.1)		C17—H8	1.0908(1.09)		C5-C6-016	126.1	126.5
C17—H9	1.0909(1.09)		C4-N18-C19	103.8(103.6)		C17—H9	1.0908(1.09)		C5-N7-C19	106.5	
C17–H10	1.0872(1.09)		C6-C5-N7	131.2(131.0)		C17-H10	1.0867		C5-N7-H21	125.3	134.9
C11–H12	1.0905(1.09)		C5-C6-016	126.4(126.3)	126.4	C11-H12	1.0905(1.09)		H8-C17-H9	108.4	
C11–H13	1.0905(1.09)		C5-N7-C19	105.7(105.7)	103.4	C11-H13	1.0905(1.09)		H8-C17-H10	110.3	
C11–H14	1.0861(1.09)		C5-N7-C21	126.8(126.6)	128.7	C11-H14	1.0863		H9-C17-H10	110.3	
N7-C19	1.3544(1.36)	1.32	H8-C17-H9	108.4(108.4)		N7-C19	1.3559(1.36)	1.31	H12-C11-H13	108.4	
N7-C21	1.4583(1.46)	1.47	H8-C17-H10	110.3(110.3)		N7-H21	1.0085(1.01)	0.98	H12-C11-H14	110.6	
N18-C19	1.3280(1.33)	1.34	H9-C17-H10	110.3(110.3)		N18-C19	1.3254(1.33)	1.31	H13-C11-H14	110.6	
C19–H20	1.0798(1.08)	1.15	H12-C11-H13	108.3(108.3)		C19–H20	1.0790(1.08)	0.98	C19-N7-H21	128.2	
C21-H22	1.0898(1.09)		H12-C11-H14	110.6(110.6)		C2-N3-C4	119.7	119.4	N7-C19-N18	112.8	
C21-H23	1.0899(1.09)		H13-C11-H14	110.6(110.6)		C2-N3-C17	118.3		N7-C19-H20	122.5	120.6
C21-H24	1.0899(1.09)		C19-N7-C21	127.5(127.7)		N3-C2-N1	117.1	117.8	N18-C19-H20	124.7	125.1
C2-N3-C4	119.8(119.8)	122.8	N7-C19-N18	113.6(113.8)		N3-C2-015	121.5				
C2-N3-C17	118.3(118.1)	117.9	N7-C19-H20	121.8(121.6)	112.2	C4-N3-C17	122.0				
N3-C2-N1	117.1(117.2)	112.9	N7-C21-H23	110.2(110.2)		N3-C4-C5	121.3	121.8			
N3-C2-015	121.5(121.4)		N7-C21-H22	108.4(108.5)		N3-C4-N18	127.1				
C4-N3-C17	121.9(122.1)		N7-C21-H24	110.2(110.2)		N3-C17-H8	110.1				
N3-C4-C5	121.5(121.3)	121.4	N18-C19-H20	124.6(124.6)	135.3	N3-C17-H9	110.1				
N3-C4-N18	126.8(126.9)		H23-C21-H22	109.8(109.8)		N3-C17-H10	107.7				
N3-C17-H8	110.1(110.1)		H23-C21-H24	108.4(108.3)		C2-N1-C6	126.8	126.0			
N3-C17-H9	110.1(110.1)		H22-C21-H24	109.8(109.8)		C2-N1-C11	115.2				

^a Taken from Ref [25].

^b Taken from Ref [27].

^c Taken from Ref [28].

moiety) of THP in CAF-THP-24 forms the shortest bond (C–H···O) with a length of 2.13 Å producing an elongation of C–H bond by 0.0027 Å. Complex formation also results in a negative ΔR_{X-H} for C–H···O and C–H···N hydrogen bonds in few of

the complexes indicating the contraction of C–H bond from its corresponding monomer.

The calculated bond angle (Table 2) shows that the hydrogen bonds are almost linear. In general, hydrogen bond angle for strong



Fig. 2. The optimized structures of CAF-THP complexes.

hydrogen bond ranges from 170° to 180° [29]. In the present study, the intermolecular angle for N–H…N hydrogen bond (CAF–

THP-24) is observed to be 173.8° which is stronger than N–H \cdots O hydrogen bonds having a bond angle of 168° (CAF–THP–14(A))



Fig. 2 (continued)

and 169° (CAF–THP–14(B)). The interactions involving C–H \cdots O and C–H \cdots N bonds, have the intermolecular hydrogen bond angle

ranging between 138° and 179°. The deviation from linearity is larger in C31–H34 \cdots O15 hydrogen bond of CAF–THP–43(E) complex

M. Karthika et al./Computational and Theoretical Chemistry 979 (2012) 54-63

59

Geometrical parameters (bond lengths in Å, bond angles in degrees) for CAF-THP complexes calculated at B3LYP/6-311G (d, p) level of theory. For labeling of atoms see Fig. 2.

Complex	Hydrogen bond	R _{X-H}	$R_{H \cdots Y}$	ΔR_{X-H}^{a}	<x—h····y< th=""><th>Complex</th><th>Hydrogen bond</th><th>R_{X-H}</th><th>$R_{H \cdots Y}$</th><th>ΔR_{X-H}^{a}</th><th><x—h·y< th=""></x—h·y<></th></x—h····y<>	Complex	Hydrogen bond	R _{X-H}	$R_{H \cdots Y}$	ΔR_{X-H}^{a}	<x—h·y< th=""></x—h·y<>
CAF-THP-14(A)	N37—H45…016 C11—H13…036	1.0250 1.0913	1.8084 2.3453	0.0165 0.0008	168.1 171.7	CAF-THP-43(F)	C19—H20· · · O35 C41—H43· · · N18	1.0819 1.0906	2.1691 2.6858	0.0021 0.0001	163.3 154.5
CAF-THP-14(B)	N37—H45…015 C17—H10⋯036	1.0239 1.0907	1.8084 2.2892	0.0154 0.0035	169.0 173.6	CAF-THP-43(G)	C17—H8↔035 C31—H32↔N18	1.0898 1.0913	2.3907 2.5311	-0.0009 0.0005	165.5 172.3
CAF-THP-24	N37—H45…N18 C19—H20⋯036	1.0327 1.0825	1.8987 2.1309	0.0242 0.0027	173.8 151.1	CAF-THP-33(A)	C39—H40· · · N18 C17—H8· · · N38	1.0831 1.0907	2.3535 2.6916	0.0041 0.0000	166.2 145.3
CAF-THP-43(A)	C39—H40↔015 C11—H12↔N38	1.0816 1.0905	2.1509 2.6974	0.0026 0.0000	162.5 154.5	CAF-THP-33(B)	C19—H20· · · N38 C31—H33 · · · N18	1.0830 1.0907	2.4027 2.6866	0.0032 -0.0001	163.6 146.1
CAF-THP-43(B)	C19—H20↔O35 C31—H33↔N18	1.0820 1.0908	2.1674 2.6317	0.0022 0.0000	162.5 156.0	CAF-THP-44(A)	C19—H20· · · O35 C21—H22· · · O35	1.0799 1.0888	2.3046 2.4813	0.0001 -0.0010	149.6 153.4
CAF-THP-43(C)	C39—H40↔016 C21—H24↔N38	1.0819 1.0912	2.1378 2.4923	0.0029 0.0013	164.1 159.5	CAF-THP-44(B)	C21—H24…036 C41—H43…016	1.0905 1.0912	2.2640 2.4082	0.0006 0.0007	172.1 175.6
CAF-THP-43(D)	C31—H34…016 C21—H23…N38	1.0902 1.0914	2.3597 2.4835	-0.0006 0.0015	173.2 166.4	CAF-THP-44(C)	C41—H44…016 C11—H14…035	1.0898 1.0900	2.4092 2.4350	0.0035 0.0039	162.5 159.3
CAF-THP-43(E)	C31—H34…O15 C17—H9…N38	1.0879 1.0909	2.4535 2.6147	0.0006 0.0000	138.1 164.6	CAF-THP-44(D)	C17—H9…O36 C41—H43…O15	1.0900 1.0903	2.3493 2.3879	-0.0009 -0.0002	178.7 175.4

^a $\Delta R_{X-H} = R_{X-H}$ (complex) – R_{X-H} (monomer).

with an angle of 138°. This deviation is due to the weak interaction between the C—H bond (methyl group) of THP and the carbonyl oxygen (urea moiety) of CAF.

The interaction energy has been calculated after correcting the basis set superposition error (BSSE) by the full counterpoise procedure (CP) of Boys and Bernardi [22] using the equation

$$E_{\text{int}}(\text{corr}) = E_{\text{AB}}(\text{AB}) - [E_{\text{A}}(\text{AB}) + E_{\text{B}}(\text{AB})]$$

where E_{AB} (AB) is the energy of the complex, E_A (AB) and E_B (AB) are the energies of monomers A and B with the full complex basis set by setting the appropriate nuclear charge to zero, which is located at the same intermolecular configuration as in the complex. The calculated interaction energies summarized in Table 3 show that among the 16 complexes, the highest interaction energy is predicted for CAF–THP-24 with a value of 12.74 kcal/mol at MP2/6-311G (d, p) and 11.48 kcal/mol at B3LYP/6-311G (d, p) level of theories. The strong binding of N—H proton donor in THP with imidazole nitrogen of CAF and C—H (imidazole) bond in CAF with carbonyl oxygen (amide moiety) of THP has enhanced the stability of the complex. The second most stable complex is CAF–THP–14(B) with an interaction energy value of 10.60 kcal/mol at MP2 and 10.04 kcal/mol at B3LYP level of theories having N-H···O_{urea} and C-H···O type bonds in them. The complex CAF-THP-14(A) is the third most stable one with interaction energy value of 9.79 kcal/mol at MP2 and 9.22 kcal/mol at B3LYP level of theories having N-H--Oamide and C-H···O type bonds in them. It is interesting to note that the hydrogen bond distances correlate well with interaction energies. It is obvious from these data that the complex CAF-THP-24 with a hydrogen bonding distance of 1.90 Å for N-H···N bond is found to have smallest interaction energy than N-H···O bonds of CAF-THP-14(B) and CAF-THP-14(A) complexes of bond length 1.81 Å as the sum of two hydrogen bond distances in CAF-THP-24 is smaller than that in CAF-THP-14(B) and CAF-THP-14(A). Among CAF-THP-14(B) and CAF-THP-14(A) complexes which have N-H···O and C-H···O interactions in common, the complex CAF-THP-14(B) is found to have larger interaction energy due to the presence of shorter additional C-H...O bond (2.29 Å). Further, the calculated interaction energy values for other complexes that are involved in C-H...O and C—H···N interactions are comparatively low as the interactions take place through the less acidic C-H bond and the values are found to lie between 2.45-5.46 kcal/mol at MP2/6-311G (d, p) and 1.32-4.58 kcal/mol at B3LYP/6-311G (d, p) level of theories. The inclusion

Table 3

Table 2

Total energy *E*_{tot} (in Hartree) and interaction energy *E*_{int} (in kcal/mol) for CAF–THP complex calculated at MP2/6-311G (d, p) and B3LYP/6-311G (d, p) level of theories. For labeling of atoms see Fig. 2.

Complex	E _{tot}		E _{int}		Complex	E _{tot}		E _{int}		
	MP2	B3LYP	MP2	B3LYP		MP2	B3LYP	MP2	B3LYP	
CAF-THP-14(A)	-1318.1985 (-1318.2499) ^a	-1321.7992 (-1321.8219)	-9.79 (-10.29)	-9.22 (-9.41)	CAF-THP-43(F)	-1318.1895	-1321.7904	-4.64	-3.64	
CAF-THP-14(B)	-1318.2003 (-1318.2519)	-1321.8010 (-1321.8237)	-10.60 (-11.04)	-10.04 (-10.23)	CAF-THP-43(G)	-1318.1872	-1321.7874	-3.26	-1.76	
CAF-THP-24	-1318.2031 (-1318.2531)	-1321.8028 (-1321.8249)	-12.74 (-12.86)	-11.48 (-11.54)	CAF-THP-33(A)	-1318.1885	-1321.7886	-4.27	-2.76	
CAF-THP-43(A)	-1318.1894	-1321.7907	-4.64	-3.83	CAF-THP-33(B)	-1318.1882	-1321.7880	-4.14	-2.38	
CAF-THP-43(B)	-1318.1900	-1321.7909	-4.89	-3.95	CAF-THP-44(A)	-1318.1891	-1321.7904	-4.64	-3.89	
CAF-THP-43(C)	-1318.1905	-1321.7917	-5.46	-4.58	CAF-THP-44(B)	-1318.1881	-1321.7886	-4.14	-2.76	
CAF-THP-43(D)	-1318.1885	-1321.7878	-4.14	-2.13	CAF-THP-44(C)	-1318.1856 (-1318.2375)	-1321.7865 (-1321.8099)	-2.45 (-2.89)	-1.32 (-1.57)	
CAF-THP-43(E)	-1318.1863	-1321.7869	-2.82	-1.51	CAF-THP-44(D)	-1318.1862	-1321.7872	-2.89	-1.88	

^a The numbers in parenthesis indicate corresponding values calculated using 6-311++G (d, p) basis set.

of diffuse function to the basis set 6-311G (d, p) results in the interaction energy of 12.86 kcal/mol for CAF-THP-24 at MP2/6-311++G (d, p) and 11.54 kcal/mol at B3LYP/6-311++G (d, p) level of theories, which shows a difference of 0.12 and 0.06 kcal/mol in the interaction energy when compared with MP2/6-311G (d, p) and B3LYP/6-311G (d, p) level of theories, respectively. The second and third most stable complexes CAF-THP-14(B) and CAF-THP-14(A) are found to possess interaction energies of 11.04, 10.29 kcal/mol at MP2/6-311++G (d, p) and 10.23, 9.41 kcal/mol at B3LYP/6-311++G (d, p) level of theories. The difference in interaction energy is 0.44, 0.50 at MP2 and 0.19 and 0.19 kcal/mol at B3LYP level of theories, respectively. Further, the least stable CAF-THP-44(C) complex has an interaction energy of 2.89 kcal/mol at MP2/6-311++G (d, p) and 1.57 kcal/mol at B3LYP/6-311++G (d, p) level of theories which differs from MP2/6-311G (d, p) and B3LYP/6-311G (d, p) level of theories by 0.44 and 0.25 kcal/mol. The inclusion of diffuse function has increased the values of interaction energy by less than 1 kcal/mol for the most and least stable complexes. Relative stability order of complexes can be predicted from the computed interaction energies and the order is CAF-THP-24 > CAF-THP-14(B) > CAF-THP-14(A) > CAF-THP-43(C)> CAF-THP-43(B) > CAF-THP-43(F) \approx CAF-THP-43(A) \approx CAF-THP- $44(A) > CAF-THP-33(A) > CAF-THP-43(D) \approx CAF-THP-33(B) \approx CAF-$ THP-44(B) > CAF-THP-43(G) > CAF-THP-44(D) > CAF-THP-43(E) > CAF-THP-44(C) at MP2/6-311G (d, p) and CAF-THP-24 > CAF-THP-14(B) > CAF-THP-14(A) > CAF-THP-43(C) > CAF-THP-43(B) > CAF-THP-44(A) > CAF-THP-43(A) \approx CAF-THP-43(F) > CAF-THP-33(A) \approx CAF-THP-44(B) > CAF-THP-33(B) > CAF-THP-43(D) > CAF-THP-44(D) > CAF-THP-43(G) > CAF-THP-43(E) > CAF-THP-44(C) calculated at B3LYP/6-311G (d, p) level of theories. Among the various hydrogen bonding sites, the data suggest that the interaction of proton donor N-H in THP with the imidazole nitrogen of CAF is the preferred site for hydrogen bonding.

It is important to note that the relative energy (based on total energy) calculated for CAF–THP complexes shows that the most stable complex is the one in which the nitrogen atom of CAF accepts the acidic NH proton from THP while donating a proton to the carbonyl oxygen (amide moiety) of THP. The second and third most stable complexes CAF–THP–14(B) and CAF–THP–14(A) reduce by 2 to 3 kcal/mol at MP2/6-311G (d, p) and 1 to 2 kcal/mol at B3LYP/6-311G (d, p) level of theories from the most stable CAF–THP-24 complex. All other complexes differ by 8 to 11 kcal/mol at MP2 and 7 to 10 kcal/mol at B3LYP/6-311G (d, p) level of theories. The interaction energy and the relative energy order predicted at MP2 and DFT

methods agree for the first five complexes. The most stable and least stable complexes are observed to be the same at both level of theories. The relative energy values reveal the stability order for the interacting complexes as CAF-THP-24 > CAF-THP-14(B) > CAF-THP-14(A) > CAF-THP-43(C) > CAF-THP-43(B) > CAF-THP-43(F) > CAF-THP-43(A) > CAF-THP-43(A) > CAF-THP-43(A) > CAF-THP-43(A) > CAF-THP-43(G) > CAF-THP-43(E) > CAF-THP-44(D) > CAF-THP-44(B) > CAF-THP-43(G) > CAF-THP-43(E) > CAF-THP-44(D) > CAF-THP-44(C) at MP2/6-311G (d, p) and CAF-THP-43(B) > CAF-THP-44(B) > CAF-THP-43(A) > CAF-THP-43(C) > CAF-THP-43(F) > CAF-THP-43(A) > CAF-THP-43(C) > CAF-THP-43(B) > CAF-THP-44(B) > CAF-THP-44(A) > CAF-THP-43(F) > CAF-THP-43(A) > CAF-THP-44(B) > CAF-THP-44(B) > CAF-THP-44(B) > CAF-THP-43(C) > CAF-THP-43(C) > CAF-THP-44(B) > CAF-THP-43(C) > CAF-THP-44(C) = CAF-THP-44(D) > CAF-THP-44(C) = CAF-THP-44(C) = CAF-THP-44(D) > CAF-THP-44(C) = CAF-THP-44(C) = CAF-THP-44(D) > CAF-THP-44(C) = CAF-

Topological analysis of electron density for the hydrogen bonds [30.31] would be an intuitive idea to analyze the nature of bonds formed in CAF-THP complexes. The interactions are studied by considering the values of the electron density and Laplacian of the electron density at the bond critical points (BCP) of the N-H...O, N-H...N, C-H...O and C-H...N hydrogen bonds. A BCP corresponding to zero gradient of electron density is found between each pair of nuclei, which are considered to be linked by a chemical bond with two negative curvatures (λ_1 and λ_2) and one positive curvature (λ_3) denoted as (3, -1) critical point. The bond ellipticity, ε defined in terms of the two negative curvatures λ_1 and λ_2 as $\varepsilon = (\lambda_1/\lambda_2 - 1)$ shows the deviation of the charge distribution of a bond path from axial symmetry, thus providing a sensitive measure of the susceptibility of a system to undergo a structural change. The calculated values of electron density (ρ), Laplacian of electron density $(\nabla^2 \rho)$ and bond ellipticity (ε) at BCP for N-H...O, N-H...N, C-H...O and C-H...N bonds calculated at B3LYP/6-311G (d, p) level of theory for the interacting CAF-THP complexes are summarized in Table 4. Generally, for hydrogen-bonded complexes the electron density and Laplacian of electron density values are expected to be in the range 0.002-0.34 a.u. and 0.016–0.13 a.u., respectively [32,33]. In the present study, the value of ρ and $\nabla^2 \rho$ for the interacting complexes varies from 0.007 to 0.033 a.u. and 0.019 to 0.121 a.u., respectively. The above values indicate that the interacting complexes are having strong hydrogen bonds. The strong bonds are found to be associated with maximum electron density (0.033 a.u.) indicating higher structural stability, which is observed for N-H···N interactions in CAF-THP-24 complex. This type of large charge density is due to

Table 4

Electron density ρ (in a.u.), Laplacian of electron density $\nabla^2 \rho$ (in a.u.) and ellipticity ε involved in hydrogen bonds for CAF–THP complexes calculated at B3LYP/6-311G (d, p) level of theory. For labeling of atoms see Fig. 2.

Complex	Hydrogen bond	$\rho(r)$	$\nabla^2 \rho(r)$	3	Complex	Hydrogen bond	$\rho(r)$	$\nabla^2 \rho(r)$	3
CAF-THP-14(A)	H45···016 H13···036	0.032 0.013	0.120 0.044	0.036 0.040	CAF-THP-43(F)	H20·…O35 H43·…N18	0.015 0.007	0.056 0.019	0.031 0.036
CAF-THP-14(B)	H45····015 H10····036	0.031 0.012	0.121 0.036	0.043 0.026	CAF-THP-43(G)	H8·…O35 H32·…N18	0.010 0.010	0.033 0.027	0.044 0.016
CAF-THP-24	H45····N18 H20···O36	0.033 0.017	0.091 0.064	0.058 0.005	CAF-THP-33(A)	H40· · · N18 H8· · · N38	0.013 0.007	0.040 0.019	0.042 0.094
CAF-THP-43(A)	H40· · ·O15 H12· · ·N38	0.016 0.007	0.059 0.019	0.032 0.038	CAF-THP-33(B)	H20····N38 H33····N18	0.012 0.007	0.036 0.020	0.036 0.011
CAF-THP-43(B)	H20↔035 H33↔N18	0.015 0.008	0.057 0.021	0.032 0.040	CAF-THP-44(A)	H20····O35 H22····O35	0.012 0.008	0.041 0.027	0.031 0.031
CAF-THP-43(C)	H40· · ·O16 H24· · ·N38	0.016 0.010	0.060 0.028	0.042 0.048	CAF-THP-44(B)	H24···036 H43···016	0.013 0.010	0.044 0.031	0.040 0.059
CAF-THP-43(D)	H34· · · O16 H23· · · N38	0.010 0.011	0.035 0.030	0.055 0.020	CAF-THP-44(C)	H44···016 H14···035	0.010 0.009	0.031 0.030	0.038 0.037
CAF-THP-43(E)	H34↔015 H9↔N38	0.009 0.008	0.031 0.022	0.066 0.023	CAF-THP-44(D)	H9· · · O36 H43· · · O15	0.011 0.010	0.036 0.033	0.043 0.043

localization of charges. Thus the electron density value calculated at the bond critical points augment the stability predicted by the energy minimization. Further, the complexes CAF–THP–14(A) and CAF–THP–14(B) possess an electron density of 0.032 and 0.031 a.u. for N–H···O interactions representing the second and third most stable structures. However, the electron density values for C–H···O and C–H···N interactions lie in the range of 0.007–0.017 a.u. as the bond is weak compared to N–H···N and N–H···O. It is to be noted that the C–H···O interaction involved in CAF–THP-24 is associated with a larger value of electron density (0.017 a.u.) compared with other C–H···O/ C–H···N bonds resulting in the augmentation of stability of CAF–THP-24 complex.

The positive values of Laplacian of electron density in Table 4 are indicative of depletion of electronic charge along the bond path, which is a characteristic of closed shell interactions such as hydrogen bonds. It is to be noted that the Laplacian of the electron density at the BCP is found to be larger for N-H...O interactions than N–H \cdots N type interaction. While considering the C–H \cdots O and C-H...N type bonds, it is observed that the C-H...O interaction involved in CAF-THP-24 complex is found to possess a larger $\nabla^2 \rho$ value (0.064 a.u.) in comparison with other complexes. Further, a correlation between the hydrogen bond distance, electron density and Laplacian of electron density have been established, which indicate that the bond length and electron density are inverse to each other, i.e., an increase in hydrogen bond length corresponds to a decrease in the electron density which is expected, since the increase in distance results in reduced orbital overlap and hence low electron density is seen along the bond. The hydrogen bond length and Laplacian of the electron density also reveal an inverse correlation. The curves corresponding to the correlation fit are shown in Figs. 3-6. The correlation co-efficient for the electron density and its Laplacian with hydrogen bond distance are 0.945 and 0.977, respectively for the complexes containing imidazole nitrogen, carbonyl oxygen, C-H and N-H proton donor sites of CAF-THP complexes. However, for the methyl interaction the correlation co-efficient for the electron density and its Laplacian with hydrogen bond distance is observed to be 0.890 and 0.952, respectively. Another property studied here at BCP is the bond ellipticity. The magnitude of the bond ellipticity value for $C-H \cdots N_{imidazole}$ hydrogen bond in CAF-THP-33(A) complex is found to be higher



Fig. 3. The correlation between electron density at bond critical point and the hydrogen bond distance at B3LYP/6-311G (d, p) level of theory for CAF–THP complexes containing imidazole nitrogen, carbonyl oxygen, C–H and N–H proton donor sites.



Fig. 4. The correlation between electron density at bond critical point and the hydrogen bond distance at B3LYP/6-311G (d, p) level of theory for CAF-THP complexes containing methyl group.



Fig. 5. The correlation between the Laplacian of the electron density at bond critical point and the hydrogen bond distance at B3LYP/6-311G (d, p) level of theory for CAF-THP complexes containing imidazole nitrogen, carbonyl oxygen, C—H and N—H proton donor sites.

compared to other interactions, indicating the higher possibility of structural change under external perturbations.

The formation of hydrogen-bond implies that a certain amount of electronic charge is transferred from the hydrogen-acceptor to the hydrogen-donor, and a rearrangement of electron density within each part of molecule has occurred. Although AIM analysis can provide relevant information on the strength of hydrogen bonds in CAF–THP complexes, it cannot give us information on electronic charge transfer, which can be given by NBO analysis. Therefore, NBO analysis has also been performed here using DFT method to further probe the nature of hydrogen bonds. The oxygen/nitrogen atom with lone pair acts as donor and X—H (X = N, C) as acceptor in the strong intermolecular charge transfer interaction. The occupation numbers for the proton donor antibonds $\sigma^*(X-H)$ and for the proton acceptor lone pairs n(Y) calculated at B3LYP/6-311G (d, p) level of theory are summarized in Table 5. When NBO results are compared with the isolated molecules, it



Fig. 6. The correlation between the Laplacian of the electron density at bond critical point and the hydrogen bond distance at B3LYP/6-311G (d, p) level of theory for CAF–THP complexes containing methyl group.

is observed that $\sigma^*(X-H)$ occupation numbers lie in the range 0.007–0.052 for N–H···O, N–H···N, C–H···O and C–H···N bonds. The charge is transferred between the interacting orbitals and hence the X-H antibond occupation values (X = N, C) of proton donor are found to be high for all the bonds in CAF-THP complexes. Specifically, for the complex CAF-THP-24, a large amount of charge transfer (0.036) has occurred from the imidazole nitrogen N18 of CAF to the contacting $\sigma^*(N37-H45)$ antibond orbital of THP for N-H...N interaction and thereby it leads to the elongation of N37-H45 bond. Hence, the antibonding occupation values (N-H) and bond lengths of proton donor N37-H45 are found to be higher on comparing with the monomer. Further, a significant amount of charge transfer (0.027 and 0.025) to proton donor $\sigma^*(N37-H45)$ bonds from carbonyl oxygen_{amide/urea} moiety has been observed for CAF-THP-14(A) and CAF-THP-14(B) complexes resulting in the elongation of N–H bond from its corresponding monomer. Also it can be seen that the $\sigma^*(C-H)$ antibond occupation numbers does not change much in the complexes CAF-THP-43(A), CAF-THP-43(G), CAF-THP-33(A) and CAF-THP-33(B)

for a few C— $H \cdots O$ and C— $H \cdots N$ interactions which explicitly show that minimum charge transfer has occurred.

For each donor and acceptor, the stabilization energy E associated with hydrogen bonding between sites i and j is given by the following equation,

$$E(2) = q_i \frac{F^2(i,j)}{\varepsilon_i - \varepsilon_i}$$

where q_i is the *i*th donor orbital occupancy, ε_i , ε_i are diagonal elements (orbital energies) and F(i, j) are off diagonal elements associated with NBO Fock matrix. The E(2) term corresponding to hydrogen bond interactions can be considered as the total charge transfer energy. The stabilization energy between lone pair electrons of the proton acceptor and antibonding orbitals of the proton donor have been examined for various intermolecular hydrogen bonds formed among the complexes at B3LYP/6-311G (d, p) level of theory and are presented in Table 5. It is worth to note that there is a correlation between hydrogen bond length and stabilization energy E(2), i.e. shorter the bond length (strong hydrogen bond) larger is the stabilization energy. In the case of $N-H\cdots N$ and $N-H\cdots O$ type interactions in CAF-THP-24, CAF-THP-14(B) and CAF-THP-14(A) respectively, the bond is very strong and hence they are found to possess a larger value of stabilization energy. For the complex CAF-THP-24, the major interaction occurs between the lone pair N18 and the contacting $\sigma^*(N37-H45)$ antibond and this interaction has resulted in the stabilization energy of 16.77 kcal/mol. Similarly, the lone pairs of the acceptor atoms 016 and 015 in complexes CAF-THP-14(B) and CAF-THP-14(A) have offered their electrons to the $\sigma^*(N37-H45)$ antibond and thus have a stabilization energy of 9.16 and 8.71 kcal/mol, respectively. Hence it is to be observed that N-H...N interactions surpass N-H...O interactions. Further, the calculated stabilization energy values predict CAF-THP-24 to be the most stable among the 16 configurations as confirmed by the electron density values calculated at the BCP. In the case of $C-H \cdots O$ and $C-H \cdots N$ interactions, it is observed that the stabilization energies for these hydrogen bonds are found to be fairly low (0.3-3.23 kcal/mol) which implies that the minimum charge transfer has occurred. Notably, the additional C19-H20...O36 bond involved in CAF-THP-24 complex is found to possess a stabilization energy value of 2.29 kcal/mol. This can be attributed to the larger charge transfer from the lone pair oxygen atom to the antibonding orbital of C–H bond and hence it is accountable for the higher stability of the complex.

Table 5

The occupation number of lone pair in the proton acceptor n(Y) and of antibonds of proton donor n ($\sigma^*(X-H)$) involved in hydrogen bonds in CAF-THP complexes and the corresponding stabilization energies E(2) (in kcal/mol) calculated at B3LYP/6-311G (d, p) level of theory. For labeling of atoms see Fig. 2.

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Complex	Hydrogen bond	<i>n</i> (Y)	$n[\sigma^*(X-H)]$	<i>E</i> (2)	Complex	Hydrogen bond	<i>n</i> (Y)	<i>n</i> [σ*(X—H)]	<i>E</i> (2)
CAF-THP-14(A)	N37—H45…016 C11—H13…036	1.961 1.859	$0.043(0.016)^{a}$ 0.014(0.011)	8.71 1.07	CAF-THP-43(F)	C19—H20↔035 C41—H43↔N18	1.973 1.920	0.025(0.020) ^a 0.012(0.010)	2.25 0.59
CAF-THP-14(B)	N37—H45…015 C17—H10…036	1.960 1.860	0.041(0.016) 0.015(0.007)	9.16 1.23	CAF-THP-43(G)	C17—H8…O35 C31—H32…N18	1.976 1.919	0.012(0.011) 0.014(0.011)	0.73 1.64
CAF-THP-24	N37—H45…N18 C19—H20…O36	1.898 1.973	0.052(0.016) 0.024(0.020)	16.77 2.29	CAF-THP-33(A)	C39—H40· · ·N18 C17—H8· · ·N38	1.918 1.921	0.025(0.020) 0.012(0.011)	3.23 0.48
CAF-THP-43(A)	C39—H40…O15 C11—H12…N38	1.973 1.921	0.025(0.020) 0.012(0.011)	2.34 0.57	CAF-THP-33(B)	C19—H20···N38 C31—H33···N18	1.919 1.920	0.025(0.020) 0.012(0.011)	2.82 0.49
CAF-THP-43(B)	C19—H20…O35 C31—H33…N18	1.973 1.920	0.025(0.020) 0.013(0.011)	2.20 0.81	CAF-THP-44(A)	C19—H20···035 C21—H22···035	1.974 1.974	0.022(0.020) 0.007(0.005)	1.09 0.56
CAF-THP-43(C)	C39—H40…O16 C21—H24…N38	1.973 1.921	0.025(0.020) 0.014(0.011)	2.37 1.47	CAF-THP-44(B)	C21—H24…O36 C41—H43…O16	1.976 1.976	0.015(0.011) 0.013(0.010)	1.34 0.70
CAF-THP-43(D)	C31—H34…O16 C21—H23…N38	1.976 1.919	0.013(0.011) 0.015(0.011)	0.90 1.91	CAF-THP-44(C)	C41—H44…016 C11—H14…035	1.976 1.976	0.012(0.010) 0.012(0.010)	0.71 0.58
CAF-THP-43(E)	C31—H34…O15 C17—H9…N38	1.976 1.920	0.010(0.007) 0.013(0.011)	0.37 1.11	CAF-THP-44(D)	C7—H9…036 C41—H43…015	1.976 1.976	0.013(0.011) 0.012(0.010)	0.99 0.83

^a The numbers in parenthesis indicate corresponding values of monomers calculated using same basis set as in complex.

4. Conclusions

The molecular structures of monomer and CAF-THP complexes have been studied using MP2 and density functional theory methods. The results show that the stability of CAF-THP complexes has been influenced by hydrogen bonding interactions and structural deformations. The most stable complex is the one in which the nitrogen atom of CAF accepts the acidic NH proton from THP while donating a proton to the carbonyl oxygen (amide moiety) of THP as per interaction energy and relative energy values calculated at both level of theories. The additional hydrogen bond $(C-H\cdots O)$ formed in CAF-THP-24 plays a vital role in deciding the stability of the structure. The topological parameters calculated using the atoms in molecule methodology gives a proper explanation for the stability of the structure. The electron density and its Laplacian at BCPs correlate well with the hydrogen bond length. The natural bond orbital analysis shows that there is an increase in the occupancy of the σ^* antibonding orbital of the proton donor groups involved in the interaction. Notably, a large charge transfer between the proton acceptor and proton donor has been noted in N-H···N interaction of CAF-THP-24 complex and hence a larger value of stabilization energy.

Acknowledgements

One of the authors M. Karthika thanks the University Grants Commission, New Delhi, India for providing financial support to carryout this work under Minor Research Project No. F.1-2/2010-2011 (RO/SERO/MRP).

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