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Density functional theory investigation of cocaine water complexes

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Abstract Twenty cocaine–water complexes were studied using density functional theory (DFT) B3LYP/6-311++G** level to understand their geometries, energies, vibrational frequencies, charge transfer and topological parameters. Among the 20 complexes, 12 are neutral and eight are protonated in the cocaine-water complexes. Based on the interaction energy, the protonated complexes are more stable than the neutral complexes. In both complexes, the most stable structure involves the hydrogen bond with water at nitrogen atom in the tropane ring and C=O groups in methyl ester. Carbonyl groups in benzoyl and methyl ester is the most reactive site in both forms and it is responsible for the stability order. The calculated topological results show that the interactions involved in the hydrogen bond are electrostatic dominant. Natural bond orbital (NBO) analysis confirms the presence of hydrogen bond and it supports the stability order. Atoms in molecules (AIM) and NBO analysis confirms the C-H···O hydrogen bonds formed between the cocaine-water complexes are blue shifted in nature.

Keyword Blue shift · Cocaine · Density difference plot · DFT · NBO analysis · Red shift

Introduction

Hydrogen bonding plays an important role in determining the structures and activities of organic, organometallic and biological molecules [1–7]. The hydrogen bond (H-bond) plays a vital role in molecular recognition [8] and the bonds formed between biomolecules, are of great interest. It presents interesting properties such as cooperativity and directionality, which are relevant for determining wide range structural properties, like the aggregation states of molecule [9, 10] and the stability of bio molecules [11]. H-bond has the form of X–H···Y, where X is an electronegative atom and Y is either an electronegative atom or π-electrons of aromatic systems. The essence of physical interactions that contribute hydrogen bonding has been the subject of interest. Because the nature of interactions involved in an O-H···O hydrogen bond has sometimes been considered to be controversial [12, 13]. The formation of a H-bond generally results in elongation of the X–H bond and a broadening of the X–H stretching potential, which then causes red-shift of the X–H stretching frequencies [14, 15]. In the last few years, the concept of hydrogen bond has been extended to C-H···Y bonding types, where Y is an electronegative atom [16–18]. These hydrogen bonds exhibit peculiar phenomenon of C-H bond shortening and lengthening, which are referred to as blue shifting and red shifting, respectively. The blue-shifted H-bond formation leads to increase of X–H vibrational frequency and usually to X–H bond length contraction [14, 15].

Cocaine (Benzoylmethylecgonine) the major alkaloid of Erythroxylum coca, has a long history of human use and abuse. Cocaine is one of the most reinforcing and addictive compounds ever studied [19]. Cocaine abuse is a major medical and public health problem that continues to defy treatment [20–23]. Research work based on pharmacodynamic and pharmacokinetic approach is being carried out to develop molecules as antagonizers of cocaine. In addition to the above an alternative pharmacokinetic approach using an enzyme or catalytic antibodies with the capacity to bind and degrade cocaine has been the subject of interest in the recent past [24–27]. Cocaine is used therapeutically as a topical

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and local anesthetic. The phenomenological binding affinity of cocaine is dependent not only on the microscopic binding affinities of the protonated and deprotonated molecular species but also on the pKa values of the amine compound and the PH solution. In chemistry, cocaine can have two enantiomers, one is synthetic and biologically inactive (+) cocaine, and the other is toxic and naturally occurring (−) cocaine [28]. Cocaine structure consists of two rings one is benzoyl and the other one is tropane ring. Cocaine is protonated via nitrogen atom of the tropane ring of cocaine. Further the tropane ring of cocaine molecule can itself exist in four conformations. The classifications of the conformation are as follows; N-methyl group can be either syn (or) anti to the ethano bridge and in addition, the piperidine ring (without C_2H_4 in tropane) adopt either chair or boat conformation. Examinations of the ^{1}H NMR spectra of cocaine have led Beyerman and Coworkers [29] to conclude that the chair form was the preferred conformation of the piperidine ring of all the cocaine conformers [30]. Cocaine and three of its derivatives are cation while the other three are neutral species, although one of them (Benzoylecogonine) is usually described as a zwitterion with a negative charge on the carboxylate group and a positive one on the protonated N [31]. In order to properly relate the conformational properties of cocaine to its biological function, both the neutral and protonated forms need to be studied. Due to the importance of cocaine, several other groups have determined the conformational properties of cocaine and its analogues.

Conformational analysis of cocaine was performed using molecular mechanics (MM2P) and comparing the attained results with ^{1}H-NMR data [32]. Another conformational study was performed by Villar and Loew on cocaine and its three diastereisomers, pseudococaine, allococaine, and allopseudococaine, using molecular mechanics and the semi empirical method AM1 [33]. Also, Froimowitz carried out a conformational analysis by using the MM2-87 program and parameter set on cocaine, an analogue like 2-carbomethoxy-3-(4-fluorophenyl)tropane (CFT, 2), and a group of dopamine reuptake blockers, which includes LU 19–005, 1-amino-4-phenyltetralin,hexahydropyrrolo [2,1-a] isoquinoline, diclofensine and hexahydro[1,2-b] pyridine [34]. Finally, Zhu et al. carried out a conformational partial study for cocaine-HCl and an analog of cocaine with the MMX molecular mechanics method [35]. The conformational information about cocaine and ecgonine methyl ester in gas and aqueous solution was studied by Rincon et al. The arrangement of the benzoyloxy group in cocaine is mainly determined by its repulsions with the methyl ester group [36].

Earlier theoretical calculations of cocaine hydrolysis focused on the hydrolysis of the Benzoyl-ester [37, 38]. Zhan et al. [39] carried out the reaction pathways for the hydrolysis of both benzoyl- ester and methyl-ester groups of neutral cocaine with the corresponding energy barriers by using the first-principles calculations. There are two competing pathways for the cocaine hydrolysis: one associated with the direct proton transfer from the hydroxide/hydroxyl oxygen to the ester oxygen, and the other associated with a water-assisted proton transfer. For the water-assisted proton transfer pathway, the water molecule hydrogen-bonding with the ester oxygen in the tetrahedral intermediate gradually transfers a proton to the ester oxygen through the hydrogen bond, while the hydroxide/hydroxyl proton gradually transfers to the water oxygen. Zhan and co-workers carried out the reaction pathways and the corresponding energy barriers for the ester hydrolysis of protonated cocaine in its chair and boat conformation [40]. The conformational landscape of cocaine can form hydrogen bonds with solvent through carbonyl (C=O) and protonated nitrogen.

All the studies related to the hydrolysis of cocaine mentioned above instigate the need for understanding the hydrogen bonding ability of cocaine with water as well as effect of water on the cocaine structure. It is also important to mention that, water is known to participate actively in molecular recognition processes both in chemical and especially in biological systems, by mediating the interactions between binding partners and contribute to either enthalpic or entropic stabilization. Also, several works have reported on the occurrence of illicit drugs and its metabolites constitute substances in environmental waters in various countries all over the world [41]. So in the present work as a simple case single water molecule has been interacted with both the chair and boat conformation of both protonated and neutral cocaine, at various binding sites namely methyl ester group, phenyl group, protonated nitrogen, carbonyl group and tropane ring [42]. We believe that the results of this study would elucidate the binding nature of cocaine molecule.

Computational details

The electronic structure of the chair and boat conformations of both protonated and neutral cocaine are interacted with water, at various binding sites. These structures are computed at the density functional theory, using the B3LYP functional, [43–46] and 6-311++G** basis sets. To obtain the zero point corrected interaction energy (ΔE), the basis set super-position error (BSSE) approach is incorporated into the calculations via the counterpoise (CP) method proposed by Boys and Bernardi [47]. To examine the topological properties of hydrogen bonds in the cocaine water complexes, the electron density and Laplacian electron density was calculated using Bader's atom in molecular

theory, by using Morphy 98 software package [48]. NBO has been carried out to study the charge transfer property in the interacting orbitals of the proton donor and acceptor. Optimization, frequencies and single point calculations reported here have been carried out with the Gaussian 09 package [49]. The neutral and protonated cocaine complexes starting geometries were taken from Yang et al.[50].

Results and discussion

The structure of the neutral, protonated and most stable (Pccme, Nccn) cocaine are shown in Fig. 1. The geometry of the 18 cocaine–water complexes are shown in supplementary Fig. S1. The structures are labeled, according to the charge of the cocaine system, conformations and site of the hydrogen bonding with water. For example, P indicates protonated, N-neutral, bc-boat conformations, cc-chair conformations, be-carbonyl group which is attached to the benzoyl ring, me-methyl ester group, n-nitrogen, tro-tropane, metn-methyl group (nitrogen). In this way the structures are labeled as Pccme, Pccbe, Pbcme, Pbcbe, Pmetn, Pccmetn, Ptro, Pbcmet, Nccn, Nccbe, Nccme, Nphe, Nbcme, Nbcbe, Nbe, Nme, Nbcmetn, Ntro, Nbctro, and Nmetn. In these complexes both the intramolecular and intermolecular hydrogen bonds are formed. The intramolecular hydrogen bond (N-H···O) is formed between the protonated nitrogen and carbonyl group (C=O) of the methyl ester group in the tropane ring. The intermolecular hydrogen bond is formed between the OH of the water and carbonyl (C=O) of the benzoyl, methyl ester group, protonated and deprotonated nitrogen, methyl group of the tropane ring. It is found that in all complexes, intermolecular hydrogen bonds are formed as either conventional (N-H···O, O-H···O) or non conventional (C-H···O) hydrogen bond and in

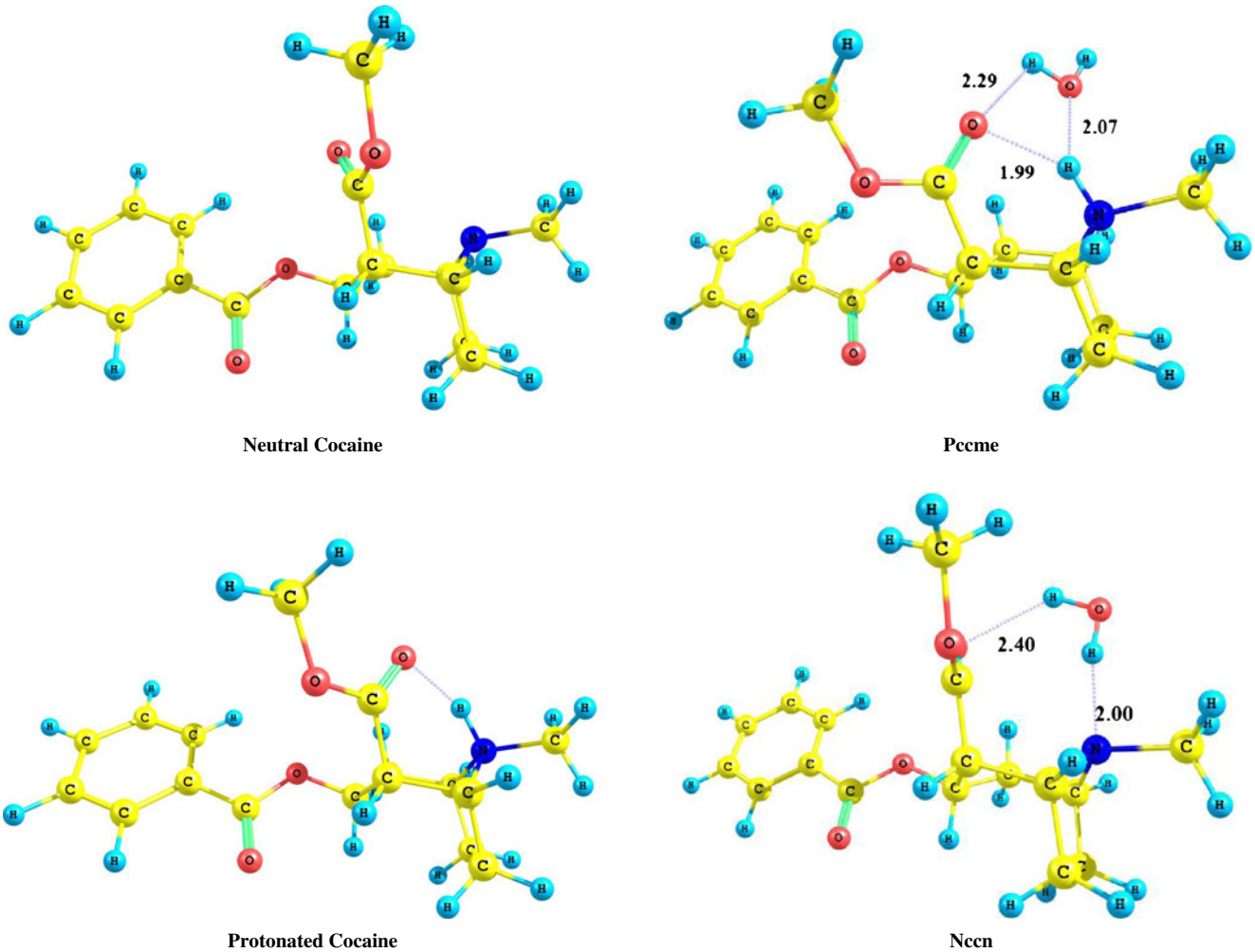

Fig. 1 The optimized neutral and protonated cocaine complexes along with the most stable (Pccme, Nccn) cocine water complexes

Table 1 Optimized structural and topological parameters for protonated and neutral cocaine-water complexes calculated using B3LYP level at 6–311++G** basis set. Bond length in (Å), bond angle in degrees, interaction energy in ΔE (kcal mol^{-1}), electron density (ρ), Laplacian of electron density ($\nabla^2\rho$) and ellipticity (ε), potential energy density V(r), kinetic electron energy density G(r) and total electron energy density H(r) all values in (*a.u*)

System	Bond type	Bond length	Bond angle	ΔE kcal mol^{-1}	ρ	$\nabla^2\rho$	ε	V(r)	G(r)	H(r)
Pccme	N-H···O	2.07	138. 6	−8.62	0.018	0.072	0.012	−0.013	0.01561	0.002
	O-H···O	2.29	113.7		0.012	0.053	0.601	−0.009	0.01129	0.002
	N-H···O	1.99	133.6		0.025	0.088	0.070	−0.018	0.0202	0.002
Pccbe	O-H···O	1.94	153.7	−8.52	0.023	0.094	0.012	−0.017	0.02049	0.003
	C-H···O	2.28	155.1		0.013	0.045	0.102	−0.008	0.00978	0.002
	C-H···O	2.42	132.0		0.010	0.034	0.105	−0.006	0.00744	0.001
	N-H···O	1.80	142.6		0.040	0.123	0.024	−0.033	0.03179	−0.001
Pbcme	O-H···O	2.01	148.0	−7.66	0.019	0.079	0.006	−0.046	0.04069	−0.005
	C-H···O	2.36	141.4		0.011	0.038	0.045	−0.014	0.01695	0.003
	C-H···O	2.25	147.4		0.014	0.049	0.09	−0.007	0.00806	0.001
	N-H···O	1.63	168.6		0.055	0.152	0.014	0.017	0.01041	0.03
Pbcmet	C-H···O	2.30	170.9	−7.62	0.012	0.041	0.114	−0.033	0.03193	−0.001
	N-H···O	1.60	169.2		0.059	0.155	0.016	−0.007	0.00875	0.001
Pccmetn	C-H···O	2.38	152.1	−7.03	0.011	0.035	0.108	−0.032	0.03129	−0.001
	C-H···O	2.36	149.8		0.011	0.037	0.099	−0.006	0.00764	0.001
	N-H···O	1.81	142.6		0.037	0.121	0.021	−0.007	0.0081	0.001
Pmetn	C-H···O	2.37	150.1	−6.97	0.011	0.037	0.104	−0.084	0.04645	−0.037
	C-H···O	2.40	152.1		0.011	0.034	0.107	−0.007	0.00795	0.001
	N-H···O	1.81	142.3		0.038	0.122	0.024	−0.006	0.00744	0.001
Pbcbe	C-H···O	2.41	134.5	−6.62	0.011	0.039	0.07	−0.054	0.03179	−0.02
	O-H···O	2.14	130.5		0.015	0.062	0.09	−0.007	0.00802	0.001
	C-H···O	2.53	121.3		0.009	0.030	0.05	−0.011	0.01315	0.002
	N-H···O	1.68	165.8		0.048	0.142	0.019	−0.006	0.00656	0.001
Ptro	C-H···O	2.31	169.3	−6.50	0.012	0.042	0.092	−0.031	0.03078	−0.001
	C-H···O	2.57	142.8		0.008	0.024	0.114	−0.01	0.0089	0.002
	N-H···O	1.80	142.9		0.039	0.124	0.023	−0.005	0.00544	0.001
Nccn	O-H···N	2.00	170.0	−5.44	0.027	0.079	0.014	0.010	0.00481	0.015
	O-H···O	2.40	121.8		0.010	0.036	0.194	−0.002	0.00561	0.004
Nccbe	O···H-O	1.87	168.7	−5.29	0.026	0.106	0.025	−0.019	0.01926	0.0004
	C-H···O	2.43	160.2		0.011	0.031	0.096	−0.007	0.00811	0.001
Nccme	O-H···O	1.92	173.6	−4.97	0.023	0.096	0.025	−0.021	0.02384	0.003
	C-H···O	2.35	166.3		0.011	0.036	0.066	−0.006	0.00677	0.001
Nphe	C-H···O	2.63	149.9	−4.68	0.007	0.020	0.031	−0.018	0.02099	0.003
	O···H-O	1.91	165.6		0.024	0.100	0.064	−0.006	0.00772	0.001
Nbcme	O-H···O	1.93	177.5	−4.83	0.023	0.092	0.046	−0.004	0.0045	0.001
	C-H···O	2.52	150.3		0.008	0.025	0.098	−0.019	0.02197	0.003
Nbcbe	O-H···O	1.89	169.1	−4.63	0.025	0.100	0.026	−0.017	0.02027	0.003
Nbe	O-H···O	1.90	169.5	−4.29	0.025	0.099	0.026	−0.005	0.00556	0.001
Nme	O-H···O	1.96	165.0	−4.19	0.022	0.086	0.025	−0.023	0.02239	−0.001
Nbcmetn	O-H···O	1.95	172.1	−4.33	0.021	0.088	0.075	−0.022	0.02219	−0.0002
	C-H···O	2.56	139.4		0.007	0.024	0.111	−0.031	0.01872	−0.013
Ntro	C-H···O	2.60	154.1	−0.75	0.007	0.022	0.102	−0.061	0.04987	−0.01
Nbctro	C-H···O	2.61	152.7	−0.82	0.007	0.022	0.114	−0.094	0.04987	−0.044
Nmetn	C-H···O	2.51	170.7	−0.54	0.008	0.026	0.095	−0.003	0.00486	0.002

some complexes involve both. In total there are 13 O-H···O hydrogen bonds, eight N-H···O hydrogen bonds, and one O-H···N bond formed between the cocaine and water complexes. The O-H···O bonds occur when cocaine acts as a proton acceptor, water acts as a proton donor while in case of N-H···O hydrogen bonds water as proton acceptor and cocaine acts as proton donor respectively. In O-H···N hydrogen bond, cocaine act as a proton acceptor in Nccn complex. Further 21 C-H···O hydrogen bonds are found in complexes, in which cocaine acts as proton donor and water acts as proton acceptor. All the hydrogen bond lengths are found to be in the range of 1.60 to 2.63 Å and are shown in Table 1. Among them, the O-H···O bonds length vary in the range 1.87 to 2.40 Å and are the strongest bond. In protonated complexes intramolecular hydrogen bond (N-H···O) is found between the nitrogen of the tropane ring and carbonyl in the methyl ester group, in the range of 1.60 to 2.07 Å. The C-H···O hydrogen bond length formed between the water and cocaine complexes are in the range of 2.31 to 2.63 Å. In Table 2, both protonated and neutral complexes bond length are compared with monomers; the bond length of the binding sites in cocaine gets elongated for all the O-H···O bonds while for N-H···O bonds in the complex they are contracted by 0.01 Å. The intramolecular hydrogen bond N-H···O gets weakened by an amount 0.012 to 0.207 Å after water interaction. In the case of C-H···O bond, the bond length deviation is meager by an amount 0.001 Å due to interaction of water. The bond length of C=O (in methyl ester), C-H (in entire cocaine), N-C (in tropane ring) are elongated about 0.01 Å. In Pccme, the bond length value for the N-H bond is 1.03 Å, which when compared with the monomer is found to be contracted by 0.01 Å (1.04 Å). The bond angles of N-H···O, C-H···O, O-H···O and O-H···N hydrogen bonds vary in the range of 113.7 to 177.4° which are shown in Table 1. In neutral complexes, the hydrogen bond angles are linear around 170° and in protonated the bond angles are not linear except for Pbcmet structure. The O-H···O bonds in neutral complexes are found to be the strong hydrogen bonds since their bond angles are linear. Comparing both cocaine-water complexes with monomer, the angle (H19-N1-C7 and N1-C7-C6) gets deviated from 0.036 to 4.244°. In general, for the stronger hydrogen bonds, the bond angles are mostly linear. The structural deformation due to hydrogen bond formation when analyzed indicates that in the most stable structure Pccme, the angle (H19-N1-C7) in the tropane ring has been elongated from monomer about 4.244° along with changes in the structural parameters of methyl ester group. The intermolecular hydrogen bond also weakened by the amount 0.207 Å. The complexes like Pccbe, Pccmetn, Pmetn, Pbcbe, Ptro, Nccn, Nphe, Nbe, Nme, Nbcmetn, Nbctro and Nmetn are elongated from monomers in tropane ring structure. In contrast, the bond angle (H19-N1-C7) in the complexes Pbcme, Pbcmet, Nccbe, Nccme, Nbcme, Nbcbe, Ntro gets contracted in the range of 0.01 to 0.358°.

The zero point corrected interaction energies were calculated by using the procedure developed by Boys and Bernardi [47] and are shown in Table 1. From Table 1, it is evident that protonated cocaine–water complexes are the more stable forms than the neutral cocaine-water complexes. The difference in interaction energy between the two systems is approximately 3.18 kcal mol^{-1}. The most stable complex among protonated cocaine-water complexes is Pccme (ΔE=8.62 kcal mol^{-1}) and has three hydrogen bonds, in which water is bonded with both the protonated nitrogen atom (N-H···O) and also with oxygen in the carbonyl group which is present in tropane ring (O-H···O). Both these hydrogen bonds are strong with bond length values 2.07 to 2.29 Å. Along with these bonds, there is an intramolecular hydrogen bond (N-H···O) which is formed between the protonated nitrogen and oxygen in the carbonyl group of the methyl ester group. The second most stable complex is Pccbe with energy difference of about 0.1 kcal mol^{-1} with respect to Pccme. In Pccbe complex water is bonded through three hydrogen bonds, one is O-H···O, other two is C-H···O. Similar to Pccme, intramolecular hydrogen bond (N-H···O) is also formed. The bond O-H···O is formed due to interactions of water with carbonyl group of phenyl ring and C-H bond in the tropane ring. The above three hydrogen bonds, one conventional and two nonconventional bonds, explain the reason for such small difference in interaction energy, which has increased the stability of the complex, as we know the increase in number of hydrogen bond increases stability [51]. The third most stable structure Pbcme has similar types of hydrogen bonds as of Pccbe with interaction energy 7.66 kcal mol^{-1}. There are three protonated complexes (Pccmetn, Pmetn and Ptro) with two C-H···O bonds having higher interaction energies (7.03, 6.97, and 6.50 kcal mol^{-1} respectively) than neutral cocaine-water complexes, but the difference in the interaction energy is on the order of 0.5 to 2 kcal mol^{-1}. Among the neutral complex structures, Nccn is the most stable complex, and has two conventional hydrogen bonds O-H···N and O-H···O; both these bonds are formed with nitrogen and carbonyl group respectively in tropane ring. The least stable complex in neutral cocaine-water complex Nmetn has one C-H···O bond, and its interaction energy is 0.54 kcal mol^{-1}. While comparing the results of stable neutral complex with Pccme structure, it indicates that protonation of Pccme has enhanced the stability of the complexes. In general interaction of water with protonated cocaine-water complexes is stronger than neutral cocaine-water complexes.

Table 2 The occupation number of lone pair in the proton acceptor Y=O, N and antibonding orbital of proton donor X-H involved in hydrogen bonds in cocaine complexes and the corresponding stabilization energies $E^{(2)}$ (kcal mol^{-1}), and *X*=*O*, *N*, *C* all values were calculated using B3LYP theory at 6-311++G** basis set

Complex	Bond type	Bond length (Å)	X-H (Å)	*N*(*Y*)	$\sigma^*(X\text{-}H)$	$E^{(2)}$
Pccme	N-H···O	2.07	1.033 (1.040)[a]	1.982	0.054 (0.061)[a]	6.54
	O-H···O	2.29	0.965(0.962)	1.970	0.001(0.000)	0.16
	N-H···O	1.99	1.033(1.040)	1.970	0.055(0.061)	3.03
Pccbe	O-H···O	1.94	0.970(0.96)	1.971	0.011 (0.000)	3.31
	C-H···O	2.42	1.090(1.090)	1.993	0.016 (0.014)	0.96
	C-H···O	2.28	1.090(1.089)	1.989	0.014 (0.009)	2.93
	N-H···O	1.80	1.039(1.04)	1.968	0.058(0.061)	3.90
Pbcme	O-H···O	2.01	0.968(0.96)	1.973	0.007 (0.000)	1.90
	C-H···O	2.36	1.087(1.088)	1.989	0.018 (0.016)	0.78
	C-H···O	2.25	1.089(1.089)	1.989	0.008 (0.004)	2.31
	N-H···O	1.63	1.047(1.053)	1.950	0.086(0.0935)	11.89
Pbcmet	C-H···O	2.30	1.086(1.086)	1.992	0.010(0.007)	2.49
	N-H···O	1.60	1.053(1.053)	1.950	0.094(0. 0935)	12.05
Pccmetn	C-H···O	2.38	1.089(1.090)	1.991	0.018(0.016)	1.10
	C-H···O	2.36	1.089(1.089)	1.991	0.008(0.004)	1.60
	N-H···O	1.81	1038(1.040)	1.968	0.056(0.061)	12.42
Pmetn	C-H···O	2.37	1.089(1.089)	1.991	0.007(0.004)	1.52
	C-H···O	2.40	1.089(1.09)	1.991	0.018(0.016)	1.04
	N-H···O	1.81	1.038(1.04)	1.968	0.057(0.0568)	12.58
Pbcbe	C-H···O	2.41	1.087(1.089)	1.992	0.006(0.004)	1.43
	O-H···O	2.14	0.966(0.961)	1.953	0.004(0.0)	0.59
	C-H···O	2.53	1.088(1.089)	1.994	0.015(0.015)	0.37
	N-H···O	1.60	1.043(1.053)	1.953	0.077(0.935)	0.56
Ptro	C-H···O	2.31	1.088(1.087)	1.990	0.010 (0.004)	2.84
	C-H···O	2.57	1.089((1.09)	1.994	0.011(0.010)	0.66
	N-H···O	1.80	1.038(1.040)	1.968	0.058(0.0605)	3.90
Nccn	O-H···N	2.00	0.976(0.962)	1.886	0.024(0.000)	7.62
	O-H···O	2.40	0.963(0.962)	1.976	0.0014(0.000)	0.06
Nccbe	O···H-O	1.87	0.972(0.962)	1.969	0.017(0.0)	4.48
	C-H···O	2.43	1.090(1.091)	1.992	0.012(0.010)	1.70
Nccme	O-H···O	1.92	0.971(0.962)	1.970	0.013 (0.000)	3.73
	C-H···O	2.35	1.082(1.082)	1.990	0.016 (0.013)	2.23
Nphe	C-H···O	2.63	1.082(1.082)	1.992	0.015(0.013)	0.87
	O-H···O	1.91	0.971(0.962)	1.969	0.015 (0.000)	3.44
Nbcme	O-H···O	1.93	0.970(0.962)	1.970	0.013 (0.000)	3.04
	C-H···O	2.52	1.091(1.092)	1.993	0.009(0.008)	0.86
Nbcbe	O-H···O	1.91	0.971(0.962)	1.859	0.016(0.000)	3.97
Nbe	O-H···O	1.90	0.971(0.962)	1.859	0.015 (0.000)	3.94
Nme	O-H···O	1.96	0.969(0.962)	1.971	0.012(0.000)	2.24
Nbcmetn	O-H···O	1.95	0.969(0.962)	1.971	0.010 (0.000)	2.79
	C-H···O	2.56	1.081(1.082)	1.993	0.014 (0.013)	0.73
Ntro	C-H···O	2.60	1.090(1.092)	1.994	0.012(0.011)	0.84
Nbctro	C-H···O	2.60	1.090(1.092)	1.994	0.011(0.010)	0.73
Nmetn	C-H···O	2.51	1.091(1.092)	1.994	0.008 (0.008)	1.10

[a]Indicates monomer value

The similar trend was observed in nicotine with ethanol [52]. The order of stability predicted for the cocaine complex structures is as follows,

Pccme>Pccbe>Pbcme>Pbcmet>Pccmetn>Pmetn>Pbcbe>Ptro>Nccn>Nccbe>Nccme>Nphe>Nbcme>Nbcbe>Nbe>Nme>Nbcmetn>Ntro>Nbctro>Nmetn.

Electron density difference plot, HOMO and molecular electrostatic potential

Hydrogen bonding can be characterized by the change of electron density for the bonded moiety. The shifts of electron density that results from the formation of the classic hydrogen bond in the cocaine-water complexes are plotted for the most stable and least stable complexes, i.e., protonated (Pccme and Ptro), neutral (Nccn, and Nmetn) shown in Fig. 2. The orange region represents the accumulation of the electron density and violet region represents the loss of the electron density in the plot. In both complexes, the most obvious effects of the hydrogen bond formation include the orange region that surrounds the water molecule. The lost density is shifted to the lone pair of the proton accepting atoms such as (oxygen and nitrogen) which is indicated by the violet region. In the most stable structure in both (protonated and neutral) cases, the electron density is lost in the tropane ring and in phenyl ring there is no change. In the least stable structure (Nmetn), the structure losses the electron density in both tropane and phenyl ring. The density plot of highest occupied molecular orbital (HOMO) for most and least stable cocaine-water complexes are shown in Fig. 3. Colors denote the bonding and antibonding combinations between different orbitals. Orange color represents the positive region (bonding) and blue color (antibonding) represents the negative region. For the most (Pccme) and least stable (Ptro) complex in protonated cocaine-water complexes, indicates that the HOMO is largely localized on the benzoyl ester ring. In neutral complexes, the HOMO is largely localized on the tropane ring and OH of the water molecule.

The molecular electrostatic potential (MEP) serves as a useful quantity to explain hydrogen bonding, reactivity and structure–activity relationship of molecules including biomolecules and drugs [53]. In order to predict the reactive sites for electrophilic and nucleophilic attacks of the cocaine water complexes, electrostatic potential surfaces were plotted for neutral, protonated, most and least stable complexes which are shown in Fig. 4. There are three important colors to represent the MEP such as blue, red and green used to indicate the value of the electrostatic potential. The surfaces with blue and red colors show the positive and negative values of the potential respectively. The surfaces with green colors indicate zero potential. In neutral and protonated cocaine, the carbonyl groups have nucleophilic recognition whereas the hydrogen in these structures has electrophilic recognition. The presence of green region in the map shows that the molecule is soluble in water. In the most stable complexes (Pccme and Nccn) after the interaction of cocaine with water, the electrostatic potentials get shifted toward the water molecule. The Pccme complex when compared with protonated cocaine monomer, it is found that the nucleophilic site is shifted toward the carbonyl group in the benzoyl ester. Further in the Pccme complex, nucleophilic potential of the carbonyl group (in methyl ester) of the tropane ring has shifted toward water molecule. In least stable complex (Ptro) there is no significant change in the potentials. In the most stable neutral complex (Nccn), major regions are surrounded by the intermediate potentials. On comparing the neutral cocaine with least stable complex, there are no significant changes observed in the potential distribution. Among all the complexes considered for MEP plot, the negative regions are found distributed on the hydrogen atom while the positive regions are localized over the C=O and nitrogen in the tropane ring.

Atoms in molecules (AIM) study

The study of a hydrogen bond through an intuitive picture can be accomplished through the electron density based topological parameters, such as the value of the electron density (ρ) and its Laplacian at the bond critical path (BCP). A BCP (point corresponding to $\nabla\rho=0$) is found between each pair of nuclei, which is considered to be linked by a chemical bond with two negative curvature (λ_1 and λ_2) and one positive curvature (λ_3) denoted as the critical point. The bond ellipticity defined in terms of the two negative curvatures as $\varepsilon = \left(\frac{\lambda_1}{\lambda_2} - 1\right)$ reflects the deviation of the charge distribution of a bond path from axial symmetry. In terms of the orbital model of electronic structure, the ellipticity provides a quantitative measure of the π-bond character and of the delocalization electronic charge. Also, ellipticity is a measure of bond stability; high ellipticity values indicate instability of the bond [54–57]. The Laplacian of electron density indicates whether the electron density is locally concentrated ($\nabla^2\rho < 0$) or depleted ($\nabla^2\rho > 0$) and it provides a detailed map of the basic and acidic regions of the molecule. If $\nabla^2\rho < 0$ at BCP means it is related to the covalent character of the bond indicating a sharing of electrons, while $\nabla^2\rho > 0$ implies a closed shell type interaction, which is found in noble gas repulsive stats, ionic bonds, hydrogen bonds and van der Waals molecules. It is expected that the strong bonds are usually associated with higher electron density, indicating higher structural stability. Atoms in molecular theory have been applied to characterize the hydrogen bonds of different strengths in a variety of molecular systems and complexes [55, 58–68]. In general, for hydrogen bond complexes, the ρ and $\nabla^2\rho$ values are in the range of 0.002 – 0.34 and 0.016- 0.13 a.u respectively. This is possible to describe the inter atomic interaction by

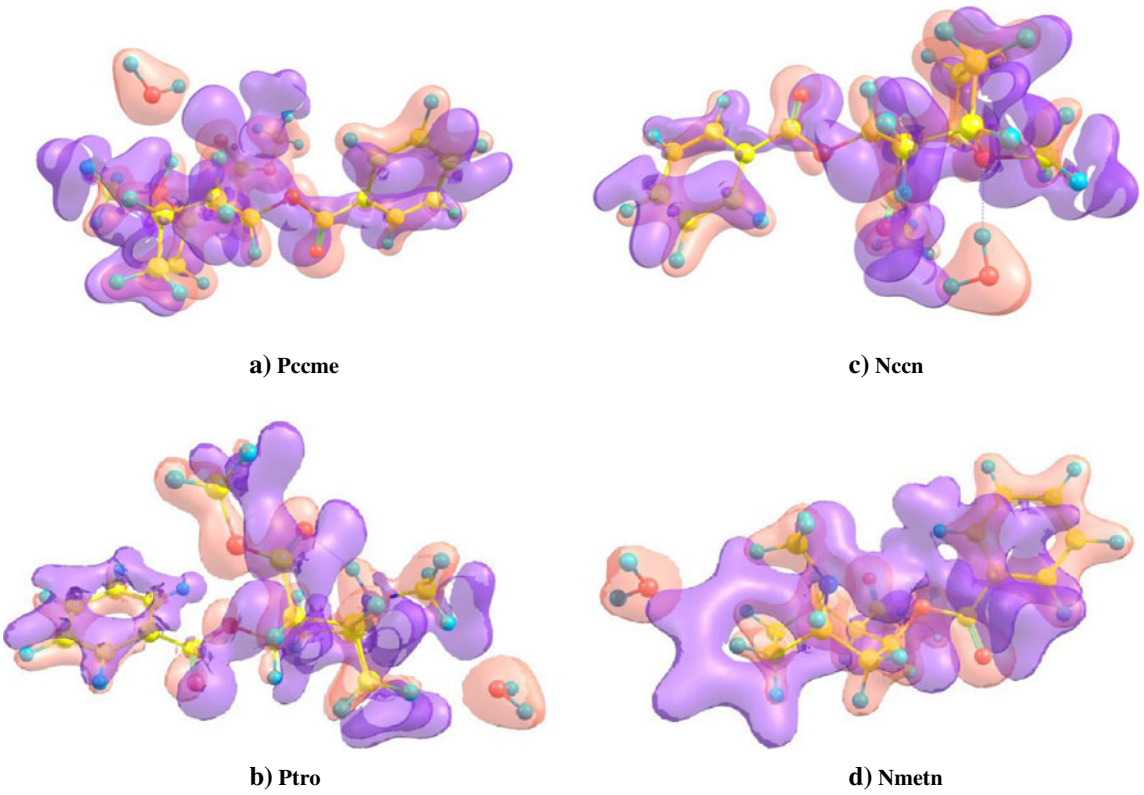

Fig. 2 Electron density difference maps for protonated cocaine water and neutral cocaine complexes. Here violet region represents the gain of an electron density and pale orange represents the loss of electron density

topological properties of the electron density ρ(r). The energetic topological parameters and the Laplacian at BCP can be given as:

$$\frac{1}{4}\nabla^2\rho(r_{BCP}) = 2G(r_{BCP}) + V(r_{BCP}), \quad (1)$$

additionally,

$$H_{BCP} = G(r_{BCP}) + V(r_{BCP}), \quad (2)$$

where H, G and V correspond to the total electron energy density, the kinetic electron energy density and the potential electron energy density at BCP, respectively. The electronic energy density (H) is an appropriate index to understand non covalent interactions, and its sign at the BCP determines whether the interaction is electrostatic dominant (H>0) or covalent dominant (H<0) [69, 70]. The total electron energy density at BCP and the Laplacian $\nabla^2\rho$ are two topological parameters often applied to classify and characterize hydrogen bonds. Rozas et al. [68] proposed the following classification of these interactions:

- weak H-bonds (E_{HB}<12.0 kcal mol^{-1}) reveal ($\nabla^2\rho$>0 and H_{BCP}>0)
- medium H-bonds (12.0 kcal mol^{-1}<E_{HB}<24.0 kcal mol^{-1}) for which ($\nabla^2\rho$>0 and H_{BCP}<0) and
- Strong H-bonds (E_{HB}>24.0 kcal mol^{-1}) are characterized by ($\nabla^2\rho$<0 and H_{BCP}<0).

Based on the electronic energy density H_{BCP} at BCP, the character of hydrogen bonds according to the approach presented above [70]. It should be mentioned that for the strong H-bonds (HBCP<0 and $\nabla^2\rho$<0) the covalent character of interactions is claimed, for medium (HBCP<0 and $\nabla^2\rho$>0) the partially covalent character is established and for weak ones mainly electrostatic [71].

The calculated values of topological parameter are presented in Table 1. The electron density $\rho(r)$ values of the intermolecular hydrogen bond (N-H···O, O···H-O, N···H-O, and C-H···O) range from 0.007 to 0.027 a.u., and Laplacian of electron density ($\nabla^2\rho$) ranges from 0.020 to 0.155 a.u., which is in good agreement with the values reported for hydrogen bonded complexes. All the values indicate the presence of hydrogen bond as per Popelier criteria [63–65]. The electron density $\rho(r)$ and Laplacian of electron density ($\nabla^2\rho$) of intramolecular hydrogen bonds (N-H···O) are in the range 0.025–0.059 a.u and 0.088–0.155 a.u respectively, while the values of the electron density and its Laplacian for N-H···O are away from the range of the criteria of a hydrogen-bonded system. Strong hydrogen bonds are found to have large electron density values. The Nccbe structure associated with strong hydrogen bond (O-

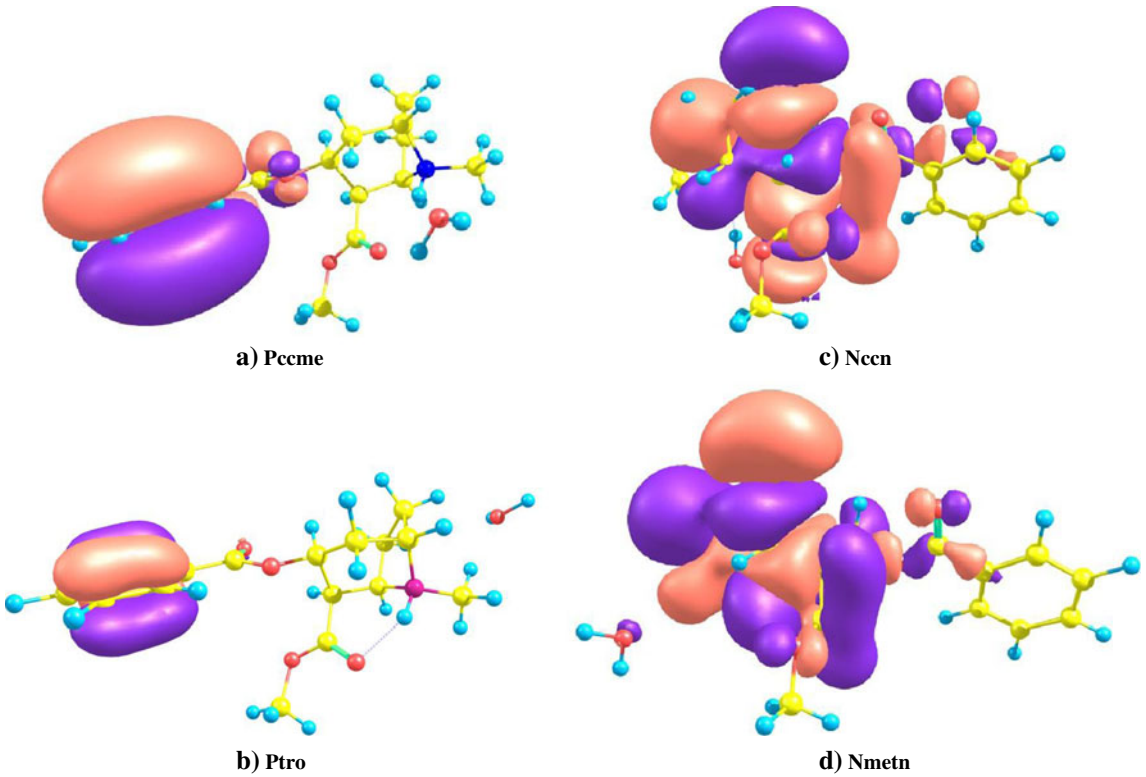

Fig. 3 Highest occupied molecular orbital (HOMO) for the most stable and least stable forms of protonated (Pccme, Ptro) and neutral (Nccn, Nmetn) cocaine water complexes. Colors denote the bonding and antibonding combinations between different orbitals. Orange color represents the positive region and blue color represents the negative region

H···O), the bond length is 1.87 Å, has maximum electron density value of 0.027 a.u. The Laplacian of electron density for the O-H···O bond is 0.106 a.u. Similarly in protonated complexes, O-H···O bond in Pccbe has the strong hydrogen bond length (1.94 Å), its BCP electron density value is found to be 0.023 a.u. and laplacian of electron density is 0.094 a.u. The most stable complex Pccme has the electron density value 0.018 and 0.012 a.u for its N-H···O and O-H···O bonds respectively. The Laplacian of electron density value is found to be 0.072 and 0.053 a.u. The ellipticity values of the cocaine-water complexes lies between 0.006 to 0.601 a.u. In the complex Pbcme, the bond O-H···O has the minimum ellipticity value and this bond is the most stable bond among the all. Further, the correlation between the hydrogen bond distances, 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 decrease in electron density, since the increase in distance results in reduced orbital overlap and hence low electron density. 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 Fig. 5(a) and (b). The correlation coefficients obtained for electron density and Laplacian of electron density with respect to hydrogen bond is 0.9720 and 0.9842 a.u respectively. In addition to the bond critical point properties, the calculated electron density distributions provide important information about the local energy density properties for the bonded interactions. The potential electron energy density V(r), kinetic electron energy density G(r), and the total energy density H(r) values are tabulated in Table 1. The total energy density is positive for most of the complexes and it indicates that interactions involved are electrostatic dominant. Few complexes, the C-H···O, O-H···O and N-H···O in which the values are negative involve the methyl group, carbonyl and protonated nitrogen of the tropane ring respectively. The negative values indicate that they are covalent dominant. Figure 6(a) and (b) show the plot between the local electronic energy density H(r) and the hydrogen bond length in Å for the protonated and the neutral complexes. From the protonated and neutral complex plot, increase in hydrogen bond does not affect the total energy density, it is around 0.002–0.003 a.u. For the weak hydrogen bond length, the value of H(r) is more negative −0.044.

NBO analysis

The NBO analysis has been performed to substantiate the nature of bonding and to study the factors that are responsible for the changes in the internal geometry of the cocaine

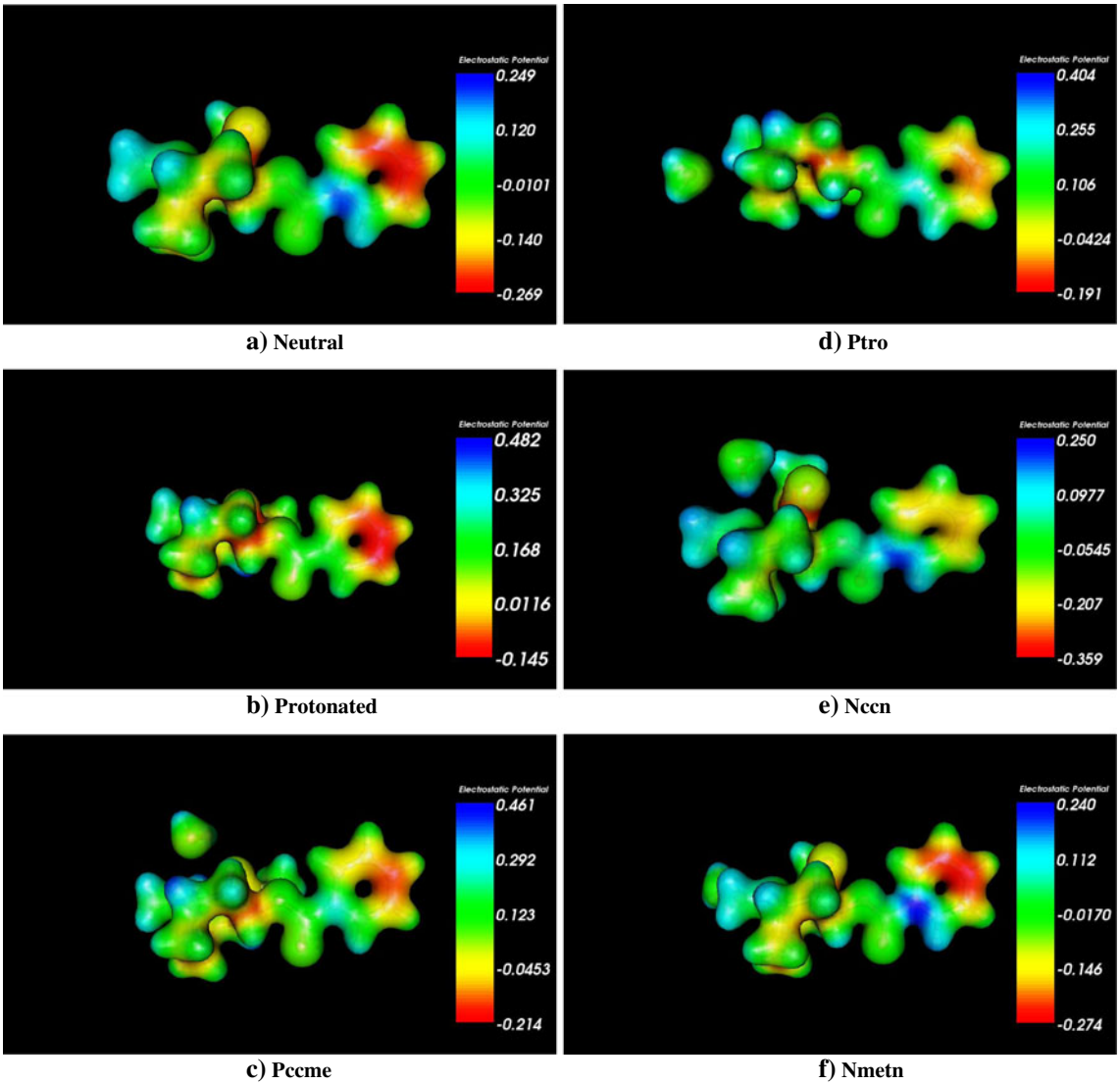

Fig. 4 Molecular electrostatic potential (MEP) maps on the isodensity surface calculated at the B3LYP/6-311G(d,p) level of theory for the neutral and protonated cocaine, along with most and least stable forms of protonated (Pccme, Ptro) as well as neutral (Nccn, Nmetn) cocaine water complexes. The values displayed are in atomic units

molecule due to the presence of water. The NBO occupation number of lone pair electrons involved in hydrogen bond N(x), and occupation number of the antibonding orbitals of the X-H bonds is $N\left[\sigma^{*}(H-Y)\right]$ for all the complex structures given in Table 2. The monomer value of the antibonding orbital $N\left[\sigma^{*}(H-Y)\right]$ is also given in Table 2. The NBO model has been very useful in explaining the hydrogen bonded (X-H···Y) system, as the donor–acceptor charge delocalization takes place between the lone pair of the hydrogen bond acceptor (Y) and the proximal antibonding σ*(X-H) orbital of the donor [72–74]. The strength of the charge transfer between donor and acceptor in the intermolecular interaction is closely related to the hyper conjugation interaction energy obtained through the NBO second-order perturbation theory. In general, the larger the hyper conjugation interaction energy, the stronger the charge transfer from the electron donor to the acceptor. The second order stabilization energy $E^{(2)}$ (donor/acceptor) that involves the lone pairs of the oxygen atom and the X-H antibonding orbitals is also given in Table 2. The O-H···O bond in Nccbe complex has the strong hydrogen bond length of 1.87 Å. The occupancy of the Nccbe complex is 1.969, comparing with corresponding monomer the occupancy decreased by 0.009 a.u. The occupancy of weak hydrogen bond (C-H···O) in Nphe is 1.992 and its monomer value is 1.997. The interaction of water with cocaine leads to decrease in occupancy of lone pair and antibonding orbitals, and results in charge transfer in complexes. The occupancy of the (N-H) antibonding orbital in Pccme is 0.054 which is 0.0007e less than the monomer. For O-H···O hydrogen bond in Pccme complex the occupancy of (O-H)

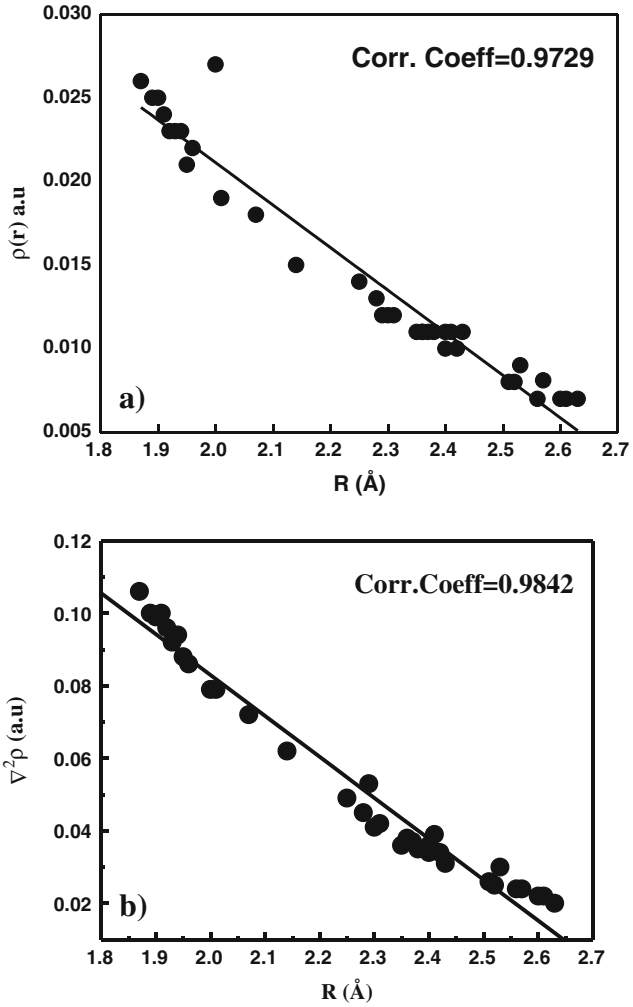

Fig. 5 **a** The correlation between the electron density at bond critical point and the hydrogen bond distance at B3LYP level for all the cocaine complexes. **b** The correlation between the Laplacian electron density at bond critical point and the hydrogen bond distance at B3LYP level for all the cocaine complexes

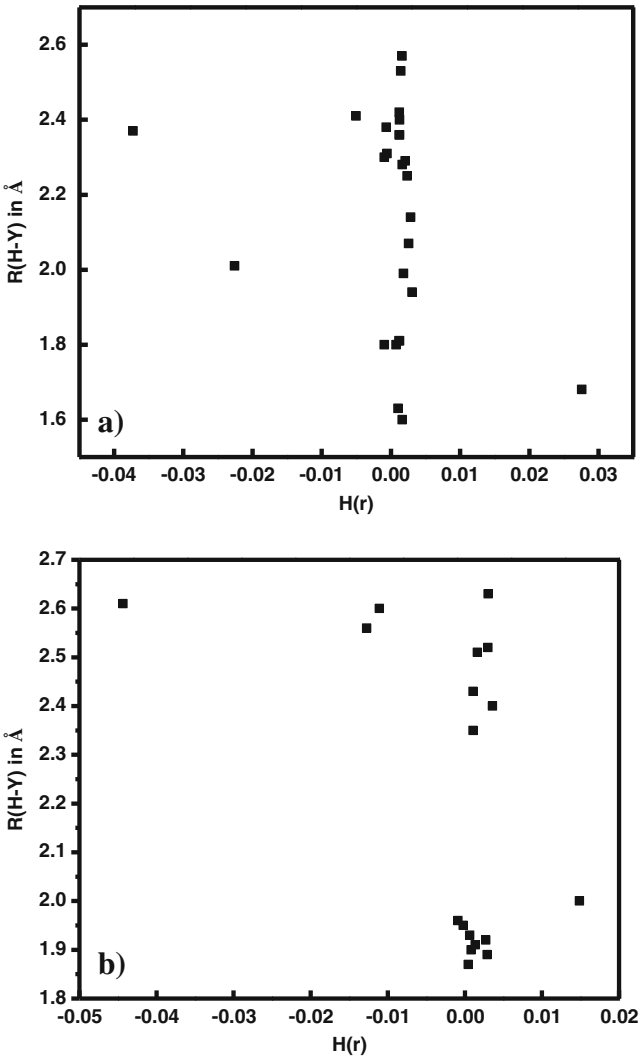

Fig. 6 **a** Scatter diagrams of the observed bond lengths, R(H-Y) Å, plotted against the total electron energy density for the protonated complexes. **b** Scatter diagrams of the observed bond lengths, R(H-Y) Å, plotted against the total electron energy density for the neutral complexes

antibonding orbital increased by 0.001e. In Nccn, the occupancy of the antibonding orbital value for the N-H···O, O-H···O is 0.024 and 0.0014 respectively. The antibonding orbital bond length (N-H, C-H and O-H) of the complex is compared with corresponding monomer, bond length gets contracted. The O-H bond is elongated by the amount 0.002 to 0.008 Å and the values are tabulated in Table 2. Generally the occupancy in antibonding orbitals of all proton donors have increased from their corresponding monomer values but for (N-H···O) bond in Pccme and C-H···O hydrogen bond in Pbcbe complex, where the charge transfer has decreased when compared with the monomer by 0.007e and 0.00009e respectively. For all the intramolecular hydrogen bonds present in the protonated complexes, occupancy of antibonding orbital is decreased when compared with the monomer. The stabilization energy $E^{(2)}$ of hydrogen bond in the complex Pccme (6.54 kcal mol^{-1}) is higher and therefore the strength of the hydrogen bond formed in this complex structure is high, compared to other complex structures. The charge transfer from proton acceptor to proton donor in Pccme complex is about 0.005e. Similarly the $E^{(2)}$ stabilization energy is 6.54 kcal mol^{-1}, but it does not directly correlate with stability because neutral structures Nccn which has N···H-O hydrogen bond has $E^{(2)}$ stabilization energy as 7.62 kcal mol^{-1}. In overall stability order Nccn is not the most stable complex whereas among neutral cocaine-water complexes it is the most stable. Therefore stabilization energy is not a real indicator of stability, but indicates the strength of interaction between the two monomers.

Red and blue shift frequency analysis

The frequency analysis of the C-H···O hydrogen bond is important to characterize their nature, to know whether the C-H bonds are proper or improper, red shifted or blue shifted. In the cocaine-water complexes there are about 21 C-H···O hydrogen bonds. The bond length, frequency, electron density, occupancy of $\sigma^*(Z\text{-}C)$ (Z=H, C, N), for both C-H and Z-C bonds are tabulated in Tables 3 and 4. It is found that in the majority of the complexes of C-H•••O interaction involves sp^3 hybridization of C, shows a contracted C-H bond compared to the monomer. The C-H stretching frequency of the complex is found to be higher than that of the monomer whose C-H bond in most of the complexes are blue shift in nature. The C-H bond frequency has increased in the range of 6 cm^{-1} to 82 cm^{-1} more than the monomer. The stretching frequency of the C-H bond in the complex is decreased in relation to the monomer in Pccbe (H-C-H···O), Pbcme (H-C-H···O), Pmetn (H-C-H···O), Ptro (H-C-H···O) Pbcmet (H-C-H···O) and Nccme (C-C-H···O) complexes, in the range 3 cm^{-1} to 90 cm^{-1}, resulting in red shift nature. In Pbcme complex the C-H (C-C-H···O, H-C-H···O) bond length is decreased by the amount 0.01 Å, which results in the increase of monomer frequency. Similarly in the complexes Pbcbe (N- C-H···O), bond length of the complex is shorter than the monomer by 0.01 Å and the corresponding increase in the frequency has resulted in blue shift. Further when the occupancy of $\sigma^*(C\text{-}H)$ orbital in C-H bond is analyzed, using NBO data it is found that occupancy of C-H antibonding orbitals has increased from the corresponding monomer except for the complex Nccbe. The occupancy of the C-H bond in most stable and least stable in protonated cocaine-water complexes, [Pccbe (C-C-H···O), (H-C-H···O) and Ptro (H-C-H···O), (H-C-H···O)] has increased from the corresponding monomer by 0.00165e, 0.005e, 0.00511e and 0.00127e respectively. Among neutral complex, the most stable Nccbe complex (H-C-H···O) has a decreased antibonding occupancy in relation to the monomer. In the least stable Nmetn complex (N-C-H···O) the occupancy of the antibonding orbital has increased from the monomer by 0.0006e. In

Table 3 The bond length (in Å), frequency (in cm^{-1}) calculated at B3LYP/6-311++G** level, of the Z-C (Z=C, H), C-H bonds of the proton donor of the complex to that of the corresponding monomer

Complex	Bond type (Z-C-H···O)	Bond length (Å)				Frequency in cm^{-1}			
		Z-C		C-H		Z-C		C-H	
		comp	Mono	comp	mono	comp	Mono	Comp	mono
Pccbe	C-C-H···O	1.5243	1.5249	1.09001	1.09011	1082.36	1140.36	3113.72	3102.93
	H-C-H···O	1.0907	1.0903	1.09024	1.08966	3126.14	3083.57	3126.14	3129.80
Pbcme	C-C-H···O	1.5548	1.55162	1.08768	1.08826	1131.04	1131.75	3135.71	3128.73
	H-C-H···O	1.0895	1.08934	1.08928	1.08926	3166.65	3155.96	3065.65	3155.96
Pbcmet	H-C-H···O	1.0897	1.0931	1.08655	1.08626	3142.02	3147.24	3142.02	3179.89
Pccmetn	C-C-H···O	1.5460	1.54	1.08933	1.09005	1022.98	1076.27	3119.92	3105.58
	H-C-H···O	1.0878	1.08	1.08922	1.08933	3161.33	3170.58	3155.92	3073.18
Pmetn	H-C-H···O	1.0879	1.08	1.08900	1.08928	3179.42	3170.56	3155.10	3170.56
	C-C-H···O	1.5346	1.53	1.08931	1.08981	1013.02	1012.64	3122.95	3113.29
Pbcbe	H-C-H···O	1.0896	1.08	1.08754	1.08944	3159.54	3166.08	3170.67	3155.96
	N-C-H···O	1.5165	1.51	1.08845	1.08934	1053.31	1128.21	3139.39	3106.65
Ptro	H-C-H···O	1.0896	1.09	1.08890	1.08769	3148.84	3155.56	3158.51	3170.56
	H-C-H···O	1.5562	1.09	1.08960	1.09043	3118.09	3129.67	3132.40	3129.67
Nccbe	H-C-H···O	1.0922	1.09	1.09088	1.09182	3058.01	3080.71	3109.21	3080.71
Nccme	C-C-H···O	1.4008	1.39 (1.4)	1.08299	1.08204	1103.53	1098.07	3202.77	3209.95
Nphe	C-C-H···O	1.3926	1.39 (1.38)	1.08172	1.08205	1126.04	1129.72	3220.72	3209.92
Nbcme	H-C-H···O	1.0928	1.10	1.09154	1.09245	2934.06	2936.40	3109.36	3055.89
Nbcmetn	C-C-H···O	1.3926	1.39	1.08155	1.08211	1042.97	1097.78	3219.65	3208.93
Ntro	H-C-H···O	1.0930	1.09	1.09069	1.09197	3048.91	3049.62	3105.46	3049.62
Nbctro	H-C-H···O	1.0927	1.09	1.09097	1.09225	3055.89	3057.97	3104.03	3048.39
Nmetn	N-C-H···O	1.4623	1.46 (1.46)	1.09137	1.09258	3055.61	3056.94	3112.11	3056.94

The values in the bracket are the compared experimental values of the monomers [75]

Table 4 The electron density (ρ in a.u) and occupation number of antibonding orbitals (σ^*) and the bonding orbital (σ) the C-H, Z-C bonds of protonated and neutral cocaine-water complexes where Z=H, C, N of the complex to that of the corresponding monomer is calculated at B3LYP/6-311++G** level

Complex molecules	Bond type	ρ				σ^*			
		Z-C		C-H		Z-C		C-H	
		comp	mono	comp	mono	comp	mono	comp	mono
Pccbe	C-C-H···O	0.25169	0.25150	0.28410	0.28292	0.06019	0.06098	0.01618	0.01453
	H-C-H···O	0.27819	0.27922	0.28181	0.27903	0.01007	0.01013	0.01412	0.00912
Pbcme	C-C-H···O	0.23425	0.23598	0.28931	0.28773	0.02448	0.02417	0.01806	0.01647
	H-C-H···O	0.28153	0.28230	0.28540	0.28261	0.00384	0.00389	0.00884	0.00404
Pbcmet	H-C-H···O	0.28379	0.28471	0.28959	0.28710	0.01035	0.01065	0.01065	0.00731
Pccmetn	C-C-H···O	0.23747	0.23755	0.28828	0.28541	0.01616	0.01625	0.01842	0.01663
	H-C-H···O	0.28281	0.28346	0.28469	0.28241	0.00494	0.00497	0.00782	0.00389
Pmetn	H-C-H···O	0.28271	0.28346	0.28459	0.28238	0.00495	0.00497	0.00773	0.00396
	C-C-H···O	0.24248	0.24260	0.28814	0.28525	0.01598	0.01607	0.01812	0.01637
Pbcbe	H-C-H···O	0.2819	0.28261	0.28509	0.28230	0.003981	0.00404	0.00677	0.00389
	N-C-H···O	0.23206	0.23396	0.28869	0.28560	0.03858	0.03863	0.01511	0.01520
Ptro	H-C-H···O	0.28158	0.28241	0.28522	0.28346	0.00394	0.00389	0.01008	0.00497
	H-C-H···O	0.22878	0.22856	0.28141	0.27913	0.00933	0.00932	0.01170	0.01043
Nccbe	H-C-H···O	0.27543	0.27621	0.27915	0.27569	0.01110	0.01116	0.01031	0.01036
Nccme	C-C-H···O	0.30512	0.30574	0.28726	0.28570	0.02260	0.02267	0.01669	0.01313
Nphe	C-C-H···O	0.31002	0.31003	0.28686	0.28570	0.01495	0.01547	0.01495	0.01312
Nbcme	H-C-H···O	0.27700	0.27747	0.28104	0.27793	0.00778	0.00831	0.00898	0.00793
Nbcmetn	C-C-H···O	0.30987	0.30991	0.28566	0.28558	0.01548	0.01574	0.01455	0.01345
Ntro	H-C-H···O	0.27407	0.27497	0.27897	0.27607	0.01053	0.01046	0.01192	0.01133
Nbctro	H-C-H···O	0.27416	0.27510	0.27858	0.27569	0.01056	0.01049	0.01074	0.01022
Nmetn	N-C-H···O	0.26290	0.26483	0.28068	0.27763	0.01311	0.01332	0.00850	0.00790

few structures, frequency of C-H bond has decreased by amount $5\,cm^{-1}$ to $37\,cm^{-1}$. This suggests that these bonds (Pccbe, Nccme, Pbcmet, Ptro) are red shifted. The $\sigma^*(C\text{-}H)$ orbital in C-H bond when analyzed using NBO data indicates that occupancy of these antibonding orbitals has increased from the corresponding monomer, supporting that the bonds are proper and red shifting in nature. The complexes (Pccbe, Pbcme, Pmetn, Ptro, Pbcmet, Nccme) have both proper red shift and improper blue shift hydrogen bonds. From the NBO analysis it is found that the charge transfer in the majority of bonds has taken place at $\sigma^*(C\text{-}H)$ orbital.

The topological parameter $\rho(r)$ when analyzed for the C-H bond, indicates that the electron density has significantly increased (0.002 to 0.003 a.u) from monomer to complex in all blue shift bonds, while the electron density value of Z-C has decreased by a good amount (−0.00046 to −0.00210 a.u) except for the Pccbe (C-C-H···O) where the electron density of C-C bond has increased meagerly. So due to the increase in electron density in C-H bond, the bond strength has increased subsequently decreasing bond length, which has resulted in blue shift.

Conclusions

Protonated cocaine-water complexes are in general more stable than neutral cocaine-water complexes [76]. Among the protonated complexes, water interacted at protonated nitrogen atom and carbonyl group of chair conformation of cocaine (Pccme) is the most stable complex. In neutral complexes, Nccn is the most stable structure, in which water is interacted at the nitrogen of the tropane ring. The favorable binding site of the cocaine is carbonyl group (C=O) in the phenyl ring and the methyl ester, which form the strong hydrogen bond with water. The zero point corrected interaction energy predicts higher stability for the protonated cocaine form Pccme with strong hydrogen bonds. The density difference map reveals that water molecule in the complex gains the electron density, and the lone pair electrons which are involved in hydrogen bond (tropane and phenyl ring) have depleted electron density. The distribution of molecular orbital in protonated complexes reveals that the contribution of HOMO is on the phenyl ring. In neutral complexes, distributions of HOMO is

around the tropane ring. MEP plots reveal that the carbonyl group and hydrogen atoms in both neutral and protonated cocaine complexes are susceptible to electrophilic and nucleophilic attack respectively. The topological parameters of electron density and laplacian of electron density correlate well with the hydrogen bond length and augment the stability order. The NBO analysis indicates the presence of blue shift C-H···O hydrogen bonds. Topological analysis justifies the existence of proper blue shifted C-H···O hydrogen bond, where in the electron density in the C-H bond has increased from monomer to complex.

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