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Theoretical study of the interaction between 5-methylcytosine and acrylamide

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Abstract The hydrogen-bonded complexes between 5-methylcytosine and acrylamide have been investigated using the density function theory (DFT) method. Five stable complexes have been found with no imaginary frequencies. Complex C3 is the most stable one with interaction energies of −69.01 kJ mol^{-1} corrected for basis set superposition error (BSSE). The charge change in the process of these complexes formation has also been examined. The atoms in molecules (AIM) theory and natural bond orbital (NBO) method have been performed to investigate the hydrogen bonds involved in all the complexes. The electron density and its corresponding Laplacian at the bond and ring critical points have been analyzed. In C3 complex, there is the largest stabilization energy (18.17 kJ mol^{-1}) between N11-H12 antibonding orbital and lone electron pair of O17. It can be seen that the hydrogen bonds play a crucial role in the stability of all the complexes between 5-methylcytosine and acrylamide. The theoretical results could provide helpful information for other researchers in further work.

Keywords Acrylamide · DFT · Hydrogen bond · Interaction energy · 5-methylcytosine

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Introduction

In recent years, researchers have paid more attention to the intermolecular interaction in two or more molecules combining through hydrogen bond [1–4], which is the chief mode of noncovalent interaction through electrostatic and charge transfer [5–8]. For many organic and biological molecules, the relationship between the weak intermolecular interactions and the activities has been extensively investigated [9]. The hydrogen bonds in biological structures, such as DNA, RNA, nucleic acids and proteins, play an important role in stabilizing and determining their structure and shape.

It is well-known that cytosine is one of the five nucleotide bases found in both DNA and RNA. Cytosine can also be methylated into 5-methylcytosine by an enzyme called DNA methyltransferase, which is involved in a wide variety of biochemical events [10–12]. 5-methylcytosine is a kind of pyrimidine base of nucleotide in many animal and plant, which has an important effect in the aspect of gene expression and regulation [13–18]. In addition, 5-methylcytosine is also a kind of important pharmaceutical intermediate in the process of drug syntheses, such as anti-AIDS drug, chronic hepatitis B drug and anti-tumor drug. Meng et al. [19] have studied the cycloaddition mechanism of 5-methylcytosine using density functional theory (DFT) method. Jin et al. [20] have theoretically investigated the structures and isomerization reactions of 5-methylcytosine-BH_3 complexes by the B3LYP and MP2 methods with 6-311+G (d) basis set. As important bioactive substances, amide is also the elementary unit of protein structure. In addition, amide group is also a kind of good model compound of polypeptide structure owing to the same skeleton structure as the peptide bond in protein molecule. It is important to investigate the mechanism of interaction between amide compounds and base.

The present study reports the results of theoretical study on the nature of 5-methylcytosine and acrylamide interactions. Detailed information has been discussed in the paper, including geometric structure, interaction, charge transfer, and bond characteristics. The calculated results are expected to provide information for understanding the interaction property between 5-methylcytosine and acrylamide.

Computational methods

In this work, all possible complexes between 5-methylcytosine and acrylamide were optimized at the B3LYP/6-31G(d) level. Each final optimized structure was checked to be a true minimum through a frequency calculation at the corresponding level. The systematic energy will decrease during the formation of new complex. The decreased energy is binding energy (ΔE), or interaction energy, which is defined as the difference between the energy of the complex and the sum of the energies of all the fragments. For this system it can be expressed as follows:

$$\Delta E = E_{5-\text{methylcytosine}-\text{acrylamide}} - \left(E_{5-\text{methylcytosine}} + E_{\text{acrylamide}}\right)$$

The counterpoise (CP) correction [21] was used to correct for the basis set superposition error (BSSE) at the B3LYP/6-31G(d) level of theory.

To analyze the degree of bond–antibond (donor–acceptor) orbital interactions within these complexes under consideration, we have performed natural bond orbital (NBO) [22] calculations using the B3LYP method and 6-31G(d) basis set. This noncovalent bonding–antibonding interaction can be quantitatively described in terms of the NBO approach, which is expressed by means of the second-order perturbation interaction energy $E^{(2)}$ [23, 24]. In addition, in order to get more detailed information on the investigated systems, AIM2000 program [25, 26] has been used to analyze the topological properties of the bond critical points (BCP) and ring critical points (RCP) in hydrogen bonds. The electron densities at BCP and RCP, along with their Laplacians, have been calculated. All calculations have been performed using Gaussian 09 program [27].

Results and discussion

Geometries and interaction energies

All possible hydrogen bonded configurations of complexes between 5-methylcytosine and acrylamide have been optimized at the B3LYP/6-31G(d) level. Five stable configurations (from C1 to C5 complex) have been obtained with no imaginary frequencies listed in Fig. 1. Selected geometrical parameters of these configurations were listed and compared in Table 1. In C1, C3 and C4, the distance of N…H (from 2.282 to 2.885 Å) is longer in contrast to that of H…O (from1.793 to 2.415 Å). It can be seen that there are hydrogen bonds NH…O and NH…N in these complexes. In addition, there are longer hydrogen bonds CH…N in C2 and C5 complexes.

As we all know, certain energy will decrease when two molecules interact with each other. The decreased energy is called interaction energy, or binding energy. Binding energy (ΔE) is the difference between the energy of the complex and the sum energy of its fragments, which reflects the interaction of 5-methylcytosine and acrylamide and relates to the stability of their complexes. The ΔE^1, interaction energies with BSSE correction of these complexes have been reported in Table 2. The BSSE correction is calculated with the counterpoise procedure method advanced by Boys and Bernardi [28]. Herein, the BSSE correction does not take into account the deformation energy and thus is a correction on the interaction energy and not on the complexation energy. As listed in Table 2, the total energy of these complexes ranges from −681.5636 to −681.5491 a.u.. The interaction energies (ΔE^1) of these complexes range from −69.01 to −31.36 kJ mol^{-1} in the order of C3>C5>C4 >C2>C1. In general, the stability is better with larger interaction energy. It can be seen that the total energy of C3 complex is smallest, and interaction energy is largest in all these complexes. In C3, there are two NH…O hydrogen bonds, the strength of hydrogen bonds H23-N20…O is strong. The stability of C1 is the weakest among these complexes owing to its smallest interaction energy. In addition, the distance between different fragments is relevant to the interaction energy. For example, the C3 has the most stable structure among these complexes, which has the shortest distance 1.793 Å of hydrogen bond H12…O17. 5-methylcytosine and acrylamide provide a proton to each other to form two strong NH…O hydrogen bonds and a weak NH…N hydrogen bond. It is obvious that hydrogen bonding interaction plays an important role in these systems. However, there are hydrogen bonds CH…N or CH…O in C1, C2 and C5. Comparing C3 with C4, the former has larger interaction energy than the latter. The reason can be explained as follows. In C3, there exists the conjugated effect from the planar structure, which has some contribution to the interaction energy as hydrogen bond. However, in C4, there is steric effect from the H atoms on C=C and the $–NH_2$ group of 5-methylcytosine, which brings out the decrease of conjugate action and interaction energy.

Atoms in molecules (AIM) analysis

The Bader's theory of atoms in molecules theory (AIM) [25] can analyze the properties of a variety of bonding

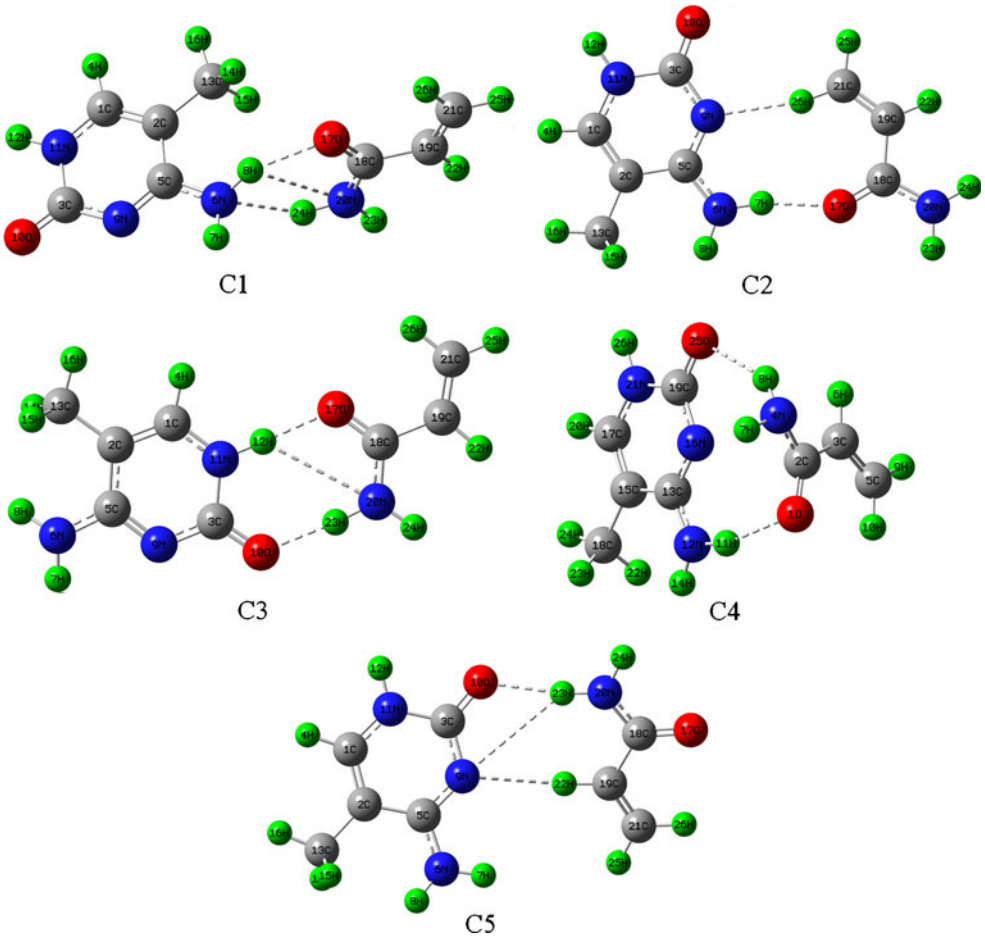

Fig. 1 Optimized structures for the five hydrogen-bonded complexes between 5-methylcytosine and acrylamide

interactions that take place in any molecular system. The properties of the electron density at bond critical points (BCP) and ring critical points (RCP) for the binding interaction between 5-methylcytosine and acrylamide were studied with the AIM2000 program. Table 3 listed the electron density (ρ_c) at BCP and RCP along with their Laplacian of electron density ($\nabla^2\rho_c$). ρ_c is used to describe the strength of a bond, with stronger bond associated with larger ρ_c value. The $\nabla^2\rho_c$ value describes the characteristic of the bond. For $\nabla^2\rho_c<0$, it corresponds to the covalent bond; for $\nabla^2\rho_c>0$, it is indicative of a closed-shell interaction, characteristic of an ionic bond, hydrogen bond or van der Waals interaction. The small and positive values of $\nabla^2\rho_c$ indicate that a small charge concentration takes place, along the bond-path linking the two nuclei. It can be observed that the behavior of $\nabla^2\rho_c$ is parallel to that exhibited by ρ_c.

For all the intermolecular BCP, there are two negative and small eigenvalues of the Hessian, λ_1 and λ_2, which

Table 1 Principal geometry parameters for complexes between 5-methylcytosine and acrylamide at B3LYP/6-31G(d) level (unit: Å)

Complex	Bond length						
C1	N20-H24	C18-O17	N6-H8	N6-H7	N20…H8	N6…H24	H8…O17
	1.016	1.236	1.022	1.014	2.762	2.282	1.981
C2	C18-O17	N6-H7	C21-H26	C5-N9	N9-C3	O17…H7	N9…H26
	1.232	1.022	1.089	1.326	1.367	1.897	2.299
C3	C3=O10	N11-H12	N20-H23	C18=O17	N20…H12	O17…H12	O10…H23
	1.237	1.035	1.032	1.243	2.885	1.793	1.806
C4	N12-H11	C19=O25	N4-H8	C2=O1	N4-H7	O25…H8	O1…H11
	1.021	1.231	1.018	1.235	1.013	2.415	2.098
C5	N20-H23	C19-H22	C3-N9	C3=O10	O10…H23	N9…H23	N9…H22
	1.019	1.088	1.364	1.229	1.970	3.108	2.613

Table 2 The total energies (E, a.u.), interaction energies without (ΔE, kJ mol^{-1}) and with the BSSE correction (ΔE^1, kJ mol^{-1}) for all five complexes calculated at the B3LYP/6-31G(d) level

Complex	E	ΔE	ΔE^1
C1	−681.5491	−43.77	−31.36
C2	−681.5503	−45.17	−34.30
C3	−681.5636	−85.45	−69.01
C4	−681.5623	−50.12	−35.86
C5	−681.5511	−46.63	−36.36

reflects the low concentration of charge density at these BCP. In addition, the positive curvature λ_3 were also very small. According to Bader's theory [25], this curvature indicates that the position of the critical point is easy to "move" along the bond path, meaning a weak interaction other than a covalent bond or ionic bond. There are a set of criteria for ρ_c and $\nabla^2\rho_c$ proposed at BCP for the conventional hydrogen bonds. Both parameters for closed-shell interactions as hydrogen bond are positive and should be within the following ranges: 0.002–0.035 a.u. for the electron density and 0.024–0.139 a.u. for its Laplacian [29]. In light of the results listed in Table 3, most electron density values do fall within the proposed typical range of the hydrogen bond, and the observed BCP are associated with Laplacian in the normal range. However, it can be noted that the ρ_c values at the BCP of the NH···O hydrogen bonds slightly exceed 0.035 a.u. To sum up, the calculated results through AIM analysis prove that there are hydrogen bonds in these complexes between 5-methylcytosine and acrylamide.

The Laplacian $\nabla^2\rho_c$ is the sum of λ_1, λ_2, and λ_3, where λ_i is the *i*th eigenvalue of Hessian matrix of the electronic density. If a critical point has two positive and one negative eigenvalues it is called (3, +1) or the ring critical point (RCP), which ρ_c is minimum in the plane defined by the axes associated with the two positive curvatures and maximum in the third direction (such ring critical points are found within rings of bonded atoms). The topological properties of the RCP may be useful to describe the intermolecular and intramolecular hydrogen bond strength [30, 31], which is a point of the minimum electron density within the ring surface and a maximum on the ring line [32]. Ring critical points have been found in C1, C3 and C5 complexes only. The electron densities at RCP and their Laplacian are also presented in Table 3. For C1, C3 and C5 complexes, it can be predicted that the stronger N…H bond is formed in order of C5<C3<C1 as the increase of ρ_c (RCP) values from 0.0031, 0.0052 to 0.0087 a.u.

Table 3 Electron densities ρ_c, eigenvalues of the Hessian matrix of density (λ_1, λ_2 and λ_3) and Laplacians $\nabla^2\rho_c$ at the bond and ring critical points of the five complexes (all values in unit: a.u.)

Complex	Bond	λ_1	λ_2	λ_3	ρ_c	$\nabla^2\rho_c$
C1	O17…H8	−0.0348	−0.0344	0.1473	0.0263	0.0780
	N20...H8	*−0.0075*	*0.0184*	*0.0308*	*0.0087*	*0.0417*
	N6…H24	−0.0179	−0.0162	0.0813	0.0160	0.0472
C2	N9…H26	−0.0177	−0.0172	0.0804	0.0161	0.0455
	O17…H7	−0.0383	−0.0379	0.1683	0.0275	0.0921
C3	O17…H12	−0.0595	−0.0585	0.2329	0.0385	0.1149
	N20...H12	*−0.0045*	*0.0104*	*0.0200*	*0.0052*	*0.0259*
	O10…H23	−0.0556	−0.0549	0.2226	0.0368	0.1121
C4	O25…H8	−0.0116	−0.0106	0.0576	0.0106	0.0354
	O1…H11	−0.0225	−0.0222	0.1020	0.0185	0.0573
C5	*N9...H23*	*−0.0020*	*0.0060*	*0.0093*	*0.0031*	*0.0133*
	O10…H23	−0.0342	−0.0337	0.1455	0.0253	0.0776
	N9…H22	−0.0083	−0.0082	0.0426	0.0089	0.0261

The italic represents the characters of the ring critical points

Natural bond orbital (NBO) analysis

In order to investigate the nature of interaction, the natural bond orbital (NBO) method has been performed to analyze these complexes between 5-methylcytosine and acrylamide. The NBO scheme is expected to present deeper insight in the intermolecular bond and lone electron pair interactions. In addition, we have examined the second-order perturbation stabilization energy, $E_{ij}^{(2)}$, of the interaction between donor orbital (i) and acceptor orbital (j) using the perturbation theory, which is defined as [23, 24]

$$E_{ij}^{(2)} = -q_i \cdot \frac{(F_{ij})^2}{E_j - E_i} \quad (1)$$

where q_i is the donor orbital occupation, E_i, E_j are the diagonal elements (orbital energies), and F_{ij} is the off-diagonal NBO Fock matrix element. The larger the $E_{ij}^{(2)}$ value is, the stronger the orbital interaction is.

The $E_{ij}^{(2)}$ mirrors the extent of charge delocalization from a Lewis- to a non-Lewis (bond–antibond) NBOs, and thus indicates the strength of bond–antibond hyperconjugative interactions between natural bond orbitals. The results of second-order perturbation theory analysis of the Fock Matrix at B3LYP/6-31G(d) level of theory are collected in Table 4.

In the NBO analysis, the Lewis σ-type (donor) NBOs are complemented by the non-Lewis σ*-type (acceptor) NBOs that are formally empty in an idealized Lewis structure picture. The donor–acceptor (bond–antibond) interactions are taken into consideration by examining all possible interactions between "filled" (donor) Lewis-type NBOs and "empty" (acceptor) non-Lewis NBOs and then estimating their energies by second-order perturbation theory. The most important interaction between "filled" (donor) Lewis-type NBOs and "empty" (acceptor) non-Lewis NBOs is reported

Table 4 The electron donor orbitals, electron acceptor orbitals, the corresponding second-order interaction energies $E_{ij}^{(2)}$ (kJ mol^{-1}), total Lewis, valence non-Lewis and Rydberg non-Lewis for the five complexes

Complex	Donor	Acceptor	$E^{(2)}$	Total Lewis	Valence non-Lewis	Rydberg non-Lewis
C1	LP (1) O17	BD*(1) N6 - H8	3.79	101.80285	2.00911	0.18805
	LP (2) O17	BD*(1) N6 - H8	8.96			
	LP (1) N6	BD*(1) N20 - H24	5.05			
C2	LP (1) O17	BD*(1) N6 - H7	9.23	101.76424	2.04830	0.18745
	LP (1) N9	BD*(1) C21 - H26	6.01			
C3	LP (1) O17	BD*(1) N11 - H12	7.25	101.65686	2.15747	0.18567
	LP (2) O17	BD*(1) N11 - H12	18.17			
	LP (2) O10	BD*(1) N20 - H23	16.16			
C4	LP (2) O25	BD*(1) N4 - H8	2.38	101.77787	2.03071	0.19142
	LP (1) O1	BD*(1) H11 - N12	2.53			
C5	LP (1) N9	BD*(1) N20 - H23	0.40	101.78056	2.02983	0.18961
	LP (2) O10	BD*(1) N20 - H23	6.43			
	LP (1) N9	BD*(1) C19 - H22	0.39			

in Table 4. It can be seen that the energy transfer occurs mainly among the lone electron pair of O or N atoms and BD*(C-H) or BD*(N-H) antibonding orbital. Of all five complexes, C3 complex has the largest stabilization energy (18.17 kJ mol^{-1}) between N11-H12 antibonding orbital and lone electron pair of O17, which indicates the strong interaction between them. Besides, in C3, the stabilization energy of N20-H23…O10 hydrogen bond is 16.16 kJ mol^{-1} and the electronic density at the hydrogen bond critical point is 0.0368 a.u. There exists charge transfer between 5-methylcytosine and acrylamide, not only from 5-methylcytosine to acrylamide but also from acrylamide to 5-methylcytosine. In C4 complexes, there are two hydrogen bonds system, i.e., O25 in the 5-methylcytosine and O1 in the acrylamide. The second-order stabilization energy of C4 is very small relative to that of C3. Besides, C5 has the lowest stabilization among the five complexes.

The charge redistribution of these complexes has been studied through NBO analysis. The formation of a hydrogen-bonded complex implies that a certain amount of charge transfers from electron donor to electron acceptor. There is a rearrangement of electron within each moiety of complex. The data in Table 5 are some of the charge increment and decrement values on these atoms around hydrogen bonds in going from the isolated moiety to the hydrogen-bonded structures, which were obtained by the comparison of the charge distribution between the original free fragments and their corresponding moieties in formed complexes. In general, positive charge change values indicate a loss of charge and negative values a gain of charge. The charge change of atoms around hydrogen bonds in these complexes has been listed in Table 5. Let us take complex C1 for example, H24 and N6, which formed hydrogen bonds between each other, the large amount of positive charge (about 0.015e) increment on atom H24. For N6, the negative charge increased with a value of 0.046e. For acrylamide moiety in C1, C2, C3 and C4 complexes, as electron donor, the total amount of charge change are 0.02e, 0.014e, 0.004e and 0.269e, respectively. In contrast, as electron acceptor, there is the charge change −0.028e in C5 complex.

Above all, these features indicate that the charge redistribution (intermolecular charger transfer) is characterized by the absolute charge and accumulates mainly on corresponding atoms that are involved in the formation of intermolecular hydrogen bonds, when going from isolated 5-methylcytosine and acrylamide to complexes. Most likely the charge redistribution contributes to the stability of the complex system.

Conclusions

The geometrical structures, interaction energies and hydrogen bonds of the five stable complexes between 5-methylcytosine

Table 5 The calculated NBO atomic charge changes (unit: e) of principal atoms in the five complexes at B3LYP/6-31G(d) level

Complex	Charge changes					
C1	N6	H8	O17	N20	H24	Total
	−0.046	0.022	0.040	0.012	0.015	0.020
C2	O17	N6	H7	N9	H26	
	−0.049	0.013	0.031	−0.032	0.022	0.014
C3	O10	H12	H23	N20	O17	
	0.054	0.023	0.029	0.025	−0.065	0.004
C4	O25	H8	H11	N12	O1	
	−0.040	0.019	0.026	0.014	0.054	0.269
C5	N9	H23	N20	H22	O10	
	0.012	0.027	0.002	0.016	−0.032	−0.028

Total means total amount of charge change of acrylamide moiety in complex, "-" means negative charge increment, "+" means positive charge increment

and acrylamide have been theoretically investigated by using quantum chemical methods. The calculation results indicate that hydrogen bonds have an important effect on the stability of these complexes. Complex C3 is the most stable one with the interaction energy of −69.01 kJ mol^{-1} (BSSE corrected). On the base of the NBO analysis, we confirmed that there is a strong interaction between the lone electron pair of O and N atoms as donor and BD*(C-H) or BD*(N-H) as acceptor. From the AIM analysis, the values of ρ_c and $\nabla^2\rho_c$ for all the observed hydrogen bonds are positive within the following ranges: 0.003 – 0.039 a.u. for the electron density and 0.013–0.115 a.u. for their Laplacian. The calculation results help us understand the mechanism of the interaction between 5-methylcytosine and acrylamide.

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