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Research Article

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Research of hydrogen bonding between shikonin and thymine

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ABSTRACT

*Density function M06 method has been used to optimize the geometries of shikonin -thymine at 6-311++G** basis. Finally, fourteen stabilized complexes have been obtained. Theories of atoms in molecules (AIM) and natural bond orbital (NBO) have been utilized to investigate the hydrogen bonds involved in all the systems. The interaction energies of all the complexes were corrected by basis set superposition error (BSSE). By the analysis interaction energy, charge density and second-order interaction energies E(2) of the complexes, it is found that complex 2 is the most stable structure.*

Key words: Shikonin, DNA base, Thymine, DFT; Hydrogen bond

INTRODUCTION

It is generally appreciated that thymine in nature are the basic unit of DNA which plays an important role in biotechnology and genetic variation and plays a crucial role in the courses of the skin cancer causing by UV damage to DNA and other diseases[1]. The interactions between anti-cancer drugs and DNA or RNA, inhibiting DNA replication or transcription and other forms, are the usual function of anti-cancer drugs [2]. Hence, studying on the function of anticancer drug molecules and cytosine is conductive to understand the mechanism of action of anti-tumor drugs and its carcinogen, by which valuable information can be provided for the design of new anticancer drug [3-5]. Theoretical researches of the interaction between some anticancer drugs and DNA have been reported previously [6-9]. Siavash[6] had a study of the mechanism of interaction between the anticancer drug gatifloxacin and DNA base by employing B3LYP method of density functional theory. Lv and co-workers studied the mechanism of interaction between the ethocaine and DNA base by the same way [9]. The interactions between the natural anticancer drugs and DNA base, such as catechin, luteolin and camptothecin have been researched by us [10-12].

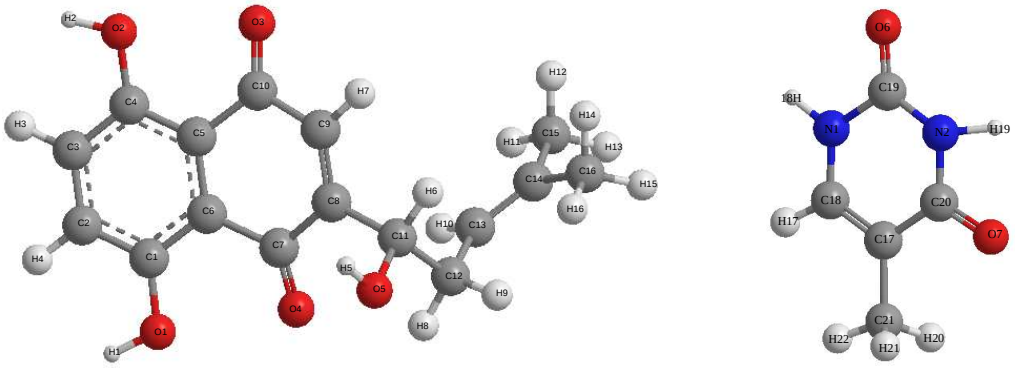
Alkanna tinctoria, a traditional Chinese prescription in clinic, has activating blood, detoxification and outthrust papules effects. Alkannin naphthoquinones, phenolic acid, alkaloids etc were isolated from alkanna tinctoria[13]. One of the most compelling but also the kind of alkannin naphthoquinones, showing many physiological functions, has two stereo isomers in nature, one is the R-isomer called shikonin, and the other is the S-isomer called alkannin[14]. According to research, shikonin can inhibit topoisomerase Ⅰ activity of DNA, and then prevents the growth of tumor cell[15]. The research of hydrogen bonds between shikonin and thymine is vitally important for the formulation of new anticancer drugs. Therefore, studying the complexes formed by shikonin and DNA base by using quantum chemistry method will be beneficial to the understanding of the interaction law of these active small molecules and biological molecules, and have a better clarification of its biological effect mechanism. Our team has worked on the investigation of interaction between shikonin and cytosine, and result shows that the hydroxyl group of shikonin plays the major role in promoting shikonin and cytosine to form complexes [16]. This paper will study shikonin-thymine complexes to know the microcosmic mechanisms of the interaction of shikonin with thymine at the molecular level, which can provide a useful theoretical basis for the design, modification, synthesis and screening of shikonin.

EXPERIMENTAL SECTION

The geometries of shikonin, thymine and shikonin-thymine have been optimized at the M06/6-311++G**, and the computational results of the vibrational frequency show that there is no imaginary frequency, which indicates that all vibrational frequencies are attributed to possibly existent structures. To acquire deeper insight into the nature of shikonin-thymine interactions, atoms in molecules (AIM) analysis is performed by using AIM2000 [17]. In addition, analyses of the charge distribution and charge-transfer processes are performed by using natural bond orbital (NBO) partitioning scheme [18]. The interaction energies are corrected for the basis set superposition errors (BSSE). The BSSE has been evaluated by using the counterpoise (CP) method proposed by Boys and Bernardi [19]. The uncorrected (De) and corrected (De BSSE) interaction energies can be evaluated as follow:

$$\Delta E = E_{AB} - E_A(B) - E_B(A)$$

where the $E_A(B)$ stands for the energy of complex AB; $E_A(B)$ is the energy of monomer A acquiring from the calculation of complexes when all the nucleus B are set as puppet atoms carrying virtual orbit; in a similar way, $E_B(A)$ is the energy of monomer B acquiring from the calculation of complexes when all the nucleus A are set as puppet atoms carrying virtual orbit. All calculations are carried out by using the Gaussian 09 program [20].



a **b**

Figure 1 the optimized geometrics of a) shikonin and b) thymine

RESULTS AND DISCUSSION

1. Raman spectra analysis of thymine

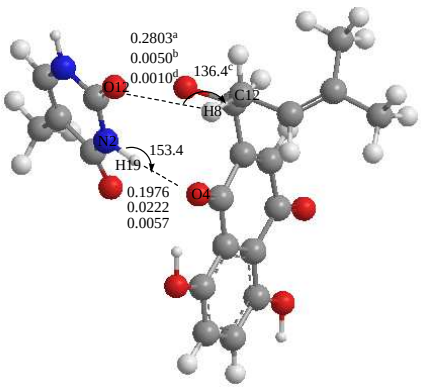
Firstly, Gaussian 09 program were used to optimize the structure of thymine. And the frequency calculation was performed by the same way basing on optimized structure. Two methods have been adopted; they are B3LYP and M06, at the same level 6-311++G**. Table 1 is listing theoretical and experimental vibrational frequencies of thymine. These results indicated that the Raman spectrum by using B3LYP and M06 methods of quantum chemistry calculation agrees with the experimental spectrum, there still are minute differences between them. It is generally thought that the difference mainly caused by without any consideration for the relativity between the molecules as doing theoretical calculation. However, the molecular interactions have been considered during experimental testing. It is generally known that thymine molecular might be linked by hydrogen bonds in its natural state, but this factor has never been contemplated during theoretical calculations, which may result in a negligible difference between results of theoretical and experimental. A comparison between Raman spectrum result of B3LYP method and that of M06 shows the latter is more desirable, which is more reasonable comparing to the experimental result and it reveals the method presented in this paper is feasible.

2. Conformation analysis of shikonin–thymine complexes

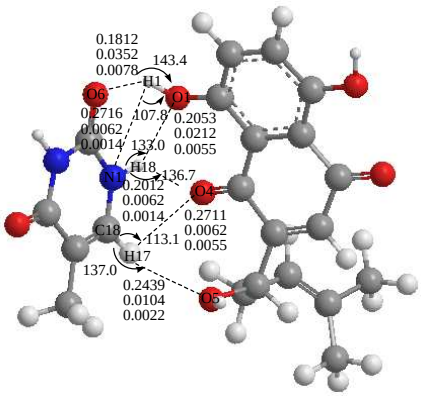
Table 1 Theoretical and experimental vibrational frequencies (cm^{-1}) of thymine

Assignment	B3LYP(cal)	M06(cal)	NRS(exp)[21]
Ring deformation, C18—H17 wag	398	427	426
Ring torsion, C19—O6, C17—CH_3, C20—O7 wag	657	605	614
Ring deformation, N1—H18 wag	595	558	558
Ring deformation, N1—C19—N2	841	741	745
Ring deformation, C18—H17, N2—H19 asym bend	968	1052	982
Ring deformation, C18—H17, N1—H18 scissor	1203	1252	1243
C18—H17, N1—H18 asym bend, CH_3 bend	1506	1376	1367
Ring deformation, C20—O7 stretch, N2—H19 bend	3194	3045	2932

The geometries of shikonin –thymine complexes and frequency calculations have been fully optimized at the M06/6-311++G** level, fourteen stabilized complexes no with no imaginary frequency, which indicates that all of them are possibly existent structures have been obtained at last. The molecular structures of shikonin and thymine are shown in Figure 1. The fully optimized geometry parameters of complexes are also shown in Figure 2 and the interaction energies of complexes have been observed in Table 2 accordingly. From Figure 2, it is evidently to see that there are various types of these hydrogen bonds, including six-hydrogen, four-hydrogen, three-hydrogen and double-hydrogen. Fourteen complexes cover following types of hydrogen bonds: O⋯H—C, O⋯H—N, N⋯H—O, O⋯H—O, N⋯H—C. The bond distance and bond angle for each hydrogen bond were analyzed within the range of 0.1727～0.2935nm and 105.6°～171.6°. In order to deeply understand the bonding character of complexes, electron density at the bond critical point (BCP) is used to analyze the bonding situation. Among those criteria to establish hydrogen bond proposed by Koch and Popelier [22, 23], "there is a BCP for the H…Y contact", "the value of (r) at BCP of H…Y lies within the range of 0.002-0.040 au" and the value of Laplacian($\nabla^2\rho$) is in the range of 0.0240～0.1390a.u.. Large ρ(r) values represent shared interactions, characteristic of covalent bonds. In contrast, low ρ(r) values are indicative of closed-shell interactions typically found in ionic bonds and hydrogen bonds as well as in van der Waals interactions. The values of charge density ρ in the bond critical point (BCP) for each complex are shown in Figure 2, and all of those are within the value limit of hydrogen bonds. It is well known that BCP is used to describe bond strength, and the value of that is in proportion to bond strength. Furthermore, Laplacian at the hydrogen bond critical point are shown in Figure 2 as well, all of them are greater than zero, being characteristic of the intermolecular weak interactions [24].



1



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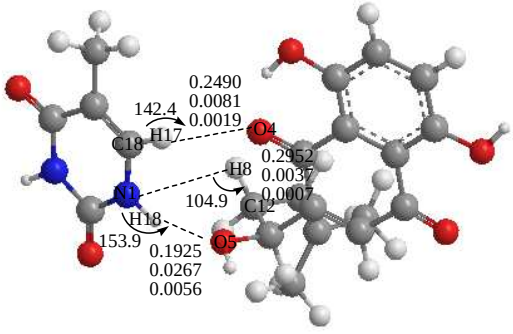

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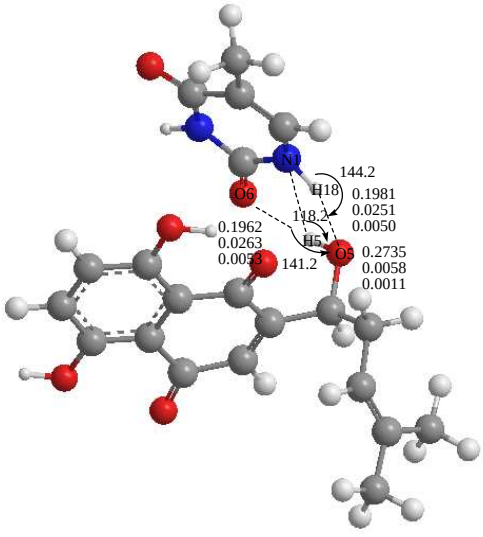

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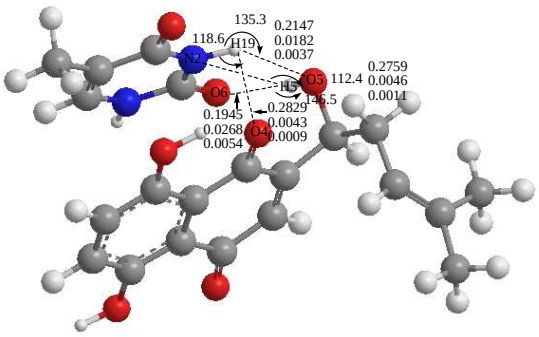
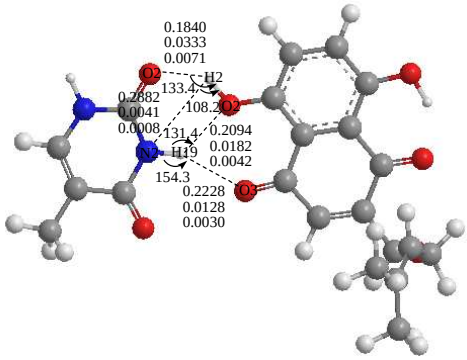
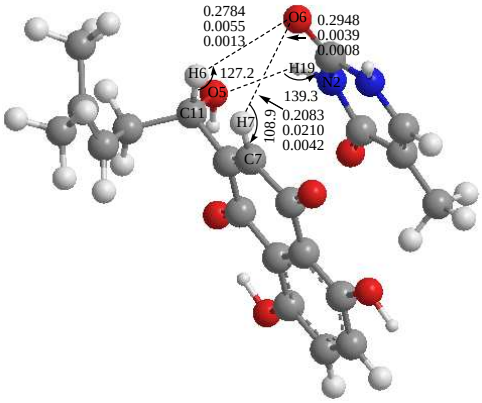

135.3
0.2147
0.0182
0.0037
118.6
H19
N2
O5
112.4
0.2759
0.0046
0.0011
O6
H5
146.5
0.1945
0.0268
0.0054
0.2829
0.0043
0.0009
O4

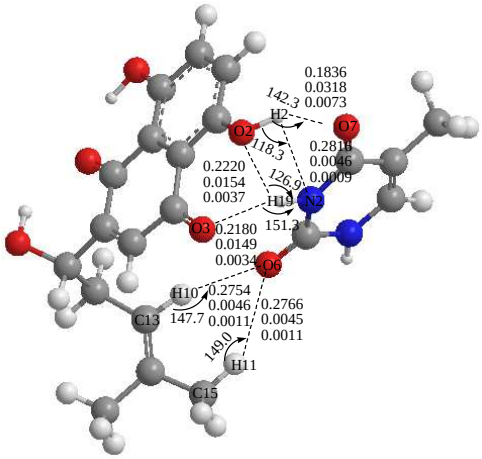
5


0.1840
0.0333
0.0071
O2
H2
133.4
0.2882
0.0041
0.0008
108.2
O2
131.4
0.2094
0.0182
0.0042
O12
H19
154.3
O5
0.2228
0.0128
0.0030

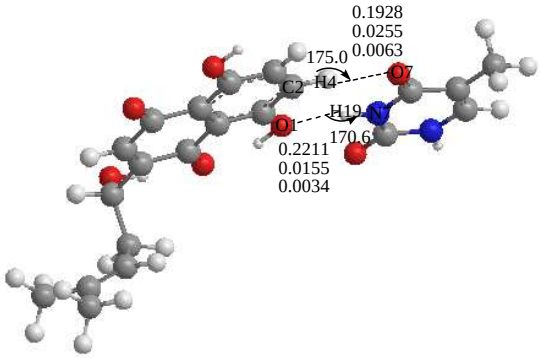
6


0.2784
0.0055
0.0013
O6
0.2948
0.0039
0.0008
H6
127.2
H19
O5
N2
139.3
C11
H7
0.2083
0.0210
0.0042
108.9
C7

7


0.1836
0.0318
0.0073
142.3
H2
O7
O2
118.3
0.2818
0.0046
0.0009
0.2220
0.0154
0.0037
126.9
H19
N2
O3
0.2180
0.0149
0.0034
151.3
O6
H10
0.2754
0.0046
0.0011
0.2766
0.0045
0.0011
C13
147.7
149.0
H11
C15

8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0.0255
0.0063
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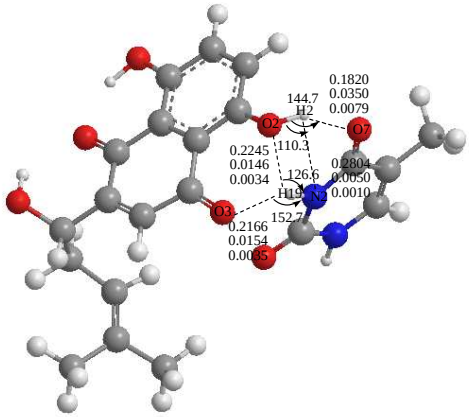
C2
H4
O7
H19
N1
O1
170.6
0.2211
0.0155
0.0034

9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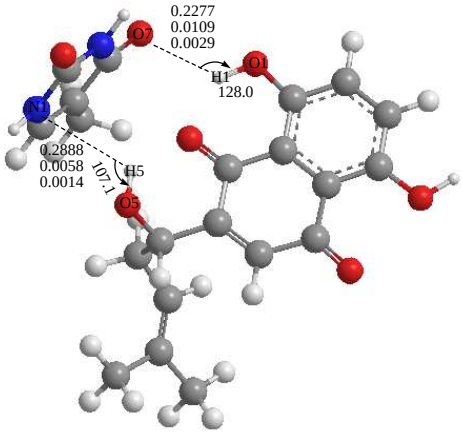
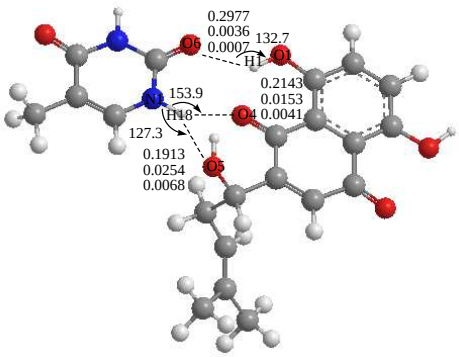
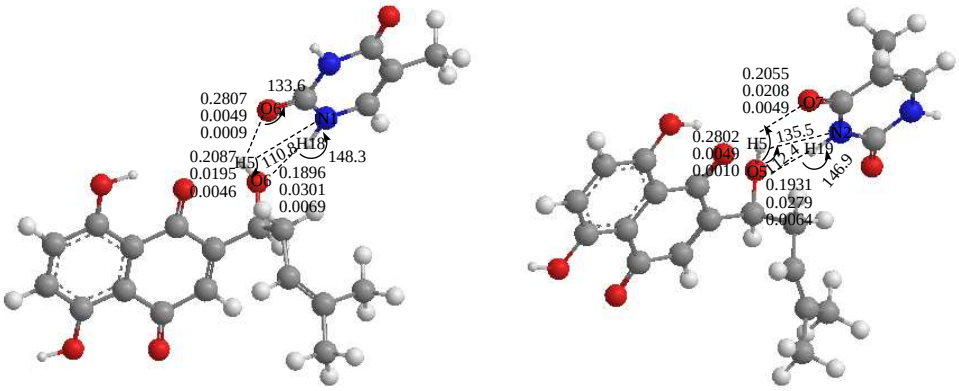
H2
O2
O7
110.3
0.2245
0.0146
0.0034
0.2804
0.0050
0.0010
126.6
H19
N2
O3
152.7
0.2166
0.0154
0.0035

10


0.2277
0.0109
0.0029
O7
O1
H1
128.0
N1
0.2888
0.0058
0.0014
107.1
H5
O5


0.2977
0.0036
0.0007
O6
132.7
H1
O1
0.2143
0.0153
0.0041
N1
153.9
H18
O4
127.3
0.1913
0.0254
0.0068
O5

11 **12**



13 **14**

Figure 2 the optimized geometrics of complexes at M06/6-311++G level**

a. bond length(nm); b. charge density ρ in the bond critical point(a.u.); c. bond angle(°)d. Laplacian value(a.u.)

Table 2 Interaction energies without (△*E*) and with the BSSE correction (△*E'*,kJ/mol) for all the complexes, calculated at the M06/6-311++G level**

Species	E(a.u.)	BSSE(a.u.)	△*E*(kJ/mol)	△*E'*(kJ/mol)
2	-1448.7721754	-1448.765970	-129.31	-113.02
9	-1448.7632297	-1448.755488	-105.82	-85.50
11	-1448.7486033	-1448.747727	-67.42	-65.12
7	-1448.7479933	-1448.743834	-65.82	-54.90
4	-1448.7448543	-1448.743188	-57.58	-53.20
5	-1448.7434612	-1448.742748	-53.92	-52.05
14	-1448.7418267	-1448.739902	-49.63	-44.58
8	-1448.7402551	-1448.738370	-45.50	-40.55
15	-1448.7397947	-1448.738008	-44.29	-39.60
6	-1448.7389161	-1448.737226	-41.99	-37.55
13	-1448.7371258	-1448.736287	-37.29	-35.09
3	-1448.7357719	-1448.734260	-33.73	-29.76
12	-1448.7354519	-1448.734073	-32.89	-29.27
10	-1448.7352785	-1448.733975	-32.44	-29.01

3. Energy analysis of shikonin –thymine complexes

The energy analysis of all the complexes as shown in Table 2, the total energies of complexes are in the range of -1448.772175～-1448.734926 a.u.. Which are lower than that of shikonin -cytosine complexes [16], indicating that the new complexes are more stable than previous types and with larger interaction energies. The interaction energies of them are listing in Table 2 and range from -129.31kJ/mol to -31.51 kJ/mol. The interaction energies are in the order: 2>9>11>7>4>5>13>14>6>12>11>3>9>1, after being corrected by the basis set superposition errors. There are two hydrogen bonds at least in the complexes, and up to six. The interaction energies of complex 2 including six hydrogen bonds is the largest, thus it is the most stable in those complexes, in this complex 6, the major contribution dues to O(6)⋯H(1)—O(1) among six hydrogen bonds, which distance (0.1812 nm) is relatively short, the bond angle (143.4°) and charge density in the bond critical point (0.0352a.u.) are larger than five others, thus, this bond is the most stable in the complex 2. In interaction energy, it is known that the complex 2 of shikonin –thymine(△*E*=-129.31 kJ/mol) is larger than that of the complex 1 of shikonin–cytosine(△*E*=-93.20 kJ/mol)which is the most stable one among those complexes. Causes the above phenomenon, is more hydrogen bonds in the complex 2 of shikonin –thymine. From the order of the interaction energy, it shows that the top two, both of complexes 2 and 8 are six-hydrogen bond complexes. The next seven orders are four-hydrogen bond complexes and three-hydrogen bond complexes appearing in turn, and then followed three three-hydrogen bond complexes, the final two are double-hydrogen bond complexes, they are complex 10 and 1 respectively. There is no five-hydrogen bond complex in the whole experiment. The four-hydrogen bond complexes and three-hydrogen bond complexes, which are in the middle of the order and the energy gap between them, is less than 25.83 kJ/mol. The alternative phenomenon of interaction energy, appearing in the two types complexes, indicates that the conclusion of the number of hydrogen bonds being in proportion to the amount of the interaction may not apply to all the hydrogen-bond complexes. There are so many important factors in stability of complexes, such as steric hindrance, the properties of bonded atom and binding site. There are two hydrogen bonds in complex 1, with the lowest interaction energy, which is the most unstable one among all the shikonin–thymine complexes, the bond distance of O(6)⋯H(19)—N(2) is 0.1976 nm and charge density in the bond critical point is 0.0222 a.u.; while the bond distance of O(6)⋯H(8)—C(12) is 0.2803nm , and charge density in the bond critical point is 0.0050 a.u., showing

that the latter one is of smaller BCP and longer bond distance, so it is unstable.

Table 3 Electron donor orbitals, electron acceptor orbitals and their corresponding second-order interaction energies *E* (2) :(kJ/mol)

Species	Bond	Donor *i*	Acceptor *j*	*E*(2)
1	O(6)-H(8)	LP(2)O(6)	BD*(1)C(12)-H(8)	21.88
	O(4)-H(19)	LP(1)O(4)	BD*(1)N(2)-H(19)	81.71
2	O(5)-H(17)	LP(1)O(5)	BD*(1)C(18)-H(17)	42.30
	O(4)-H(17)	LP(1)O(4)	BD*(1)C(18)-H(17)	33.01
	O(4)-H(18)	LP(1)O(4)	BD*(1)N(1)-H(18)	72.59
	O(1)-H(18)	LP(1)O(4)	BD*(1)N(1)-H(18)	71.46
	N(1)-H(1)	LP(1)N(1)	BD*(1)O(1)-H(1)	31.63
	O(6)-H(1)	LP(1)O(6)	BD*(1)O(1)-H(1)	113.34
3	N(1)-H(8)	LP(1)N(1)	BD*(1)C(12)-H(8)	9.54
	O(5)-H(18)	LP(1)O(5)	BD*(1)N(1)-H(18)	95.06
	O(4)-H(17)	LP(2)O(4)	BD*(1)C(18)-H(17)	41.88
4	N(1)-H(5)	LP(2)N(1)	BD*(1)O(5)-H(5)	29.92
	O(6)-H(5)	LP(1)O(6)	BD*(1)O(5)-H(5)	82.80
	O(5)-H(18)	LP(1)O(5)	BD*(1)N(1)-H(18)	79.20
5	O(6)-H(5)	LP(1)O(6)	BD*(1)O(5)-H(5)	82.97
	O(5)-H(19)	LP(1)O(5)	BD*(1)N(2)-H(19)	59.16
	N(2)-H(5)	LP(2)N(2)	BD*(1)O(5)-H(5)	26.90
	O(4)-H(19)	LP(1)O(4)	BD*(1)N(2)-H(19)	14.90
6	O(3)-H(19)	LP(1)O(3)	BD*(1)N(2)-H(19)	52.59
	O(2)-H(19)	LP(1)O(2)	BD*(1)N(2)-H(19)	65.14
	N(2)-H(2)	LP(1)N(2)	BD*(1)O(2)-H(2)	13.51
	O(2)-H(2)	LP(1)O(6)	BD*(1)O(2)-H(2)	106.78
7	O(5)-H(19)	LP(1)O(5)	BD*(1)N(2)-H(19)	68.28
	O(6)-H(6)	LP(1)O(6)	BD*(1)C(11)-H(6)	24.60
	O(6)-H(7)	LP(1)O(6)	BD*(1)C(9)-H(7)	11.17
8	O(6)-H(11)	LP(1)O(6)	BD*(1)C(15)-H(11)	25.56
	O(6)-H(10)	LP(1)O(6)	BD*(1)C(13)-H(10)	29.00
	O(3)-H(19)	LP(1)O(3)	BD*(1)N(2)-H(19)	56.23
	O(2)-H(19)	LP(1)O(2)	BD*(1)N(2)-H(19)	53.26
	N(2)-H(2)	LP(1)N(2)	BD*(1)O(2)-H(2)	15.15
	O(7)-H(2)	LP(1)O(7)	BD*(1)O(2)-H(2)	109.50
9	O(1)-H(19)	LP(1)O(1)	BD*(1)N(2)-H(19)	90.21
	O(7)-H(4)	LP(2)O(7)	BD*(1)C(2)-H(4)	53.81
10	O(7)-H(2)	LP(1)O(7)	BD*(1)O(2)-H(2)	112.84
	N(2)-H(2)	LP(1)N(2)	BD*(1)O(2)-H(2)	20.17
	O(1)-H(19)	LP(2)O(2)	BD*(1)N(2)-H(19)	50.84
	O(3)-H(19)	LP(1)O(3)	BD*(1)N(2)-H(19)	57.91
11	O(7)-H(1)	LP(1)O(7)	BD*(1)O(1)-H(1)	49.45
	N(1)-H(5)	LP(1)N(1)	BD*(1)O(5)-H(5)	13.01
12	O(5)-H(18)	LP(2)O(5)	BD*(1)N(1)-H(18)	7.74
	O(4)-H(18)	LP(1)O(4)	BD*(1)N(1)-H(18)	95.27
	O(6)-H(1)	LP(1)O(6)	BD*(1)O(4)-H(1)	62.13
13	O(5)-H(18)	LP(2)O(5)	BD*(1)N(1)-H(18)	99.37
	N(1)-H(5)	LP(1)N(1)	BD*(1)O(6)-H(5)	17.28
	O(6)-H(5)	LP(1)O(6)	BD*(1)O(6)-H(5)	66.99
14	O(7)-H(5)	LP(1)O(7)	BD*(1)O(5)-H(5)	70.08
	N(2)-H(5)	LP(1)N(2)	BD*(1)O(5)-H(5)	16.07
	O(5)-H(19)	LP(1)O(5)	BD*(1)N(1)-H(19)	87.11

4. NBO analysis of shikonin–thymine complexes

NBO analysis is performed at the same level M06/6-311++G**, in order to reveal the nature of the interaction. The role of hydrogen-bonding is to exert external electric field on shikonin–thymine complexes, which cause the separation of charge within molecules and led to changes in the structure of molecules. Electron donor orbital (i), electron acceptor orbital (j) and their corresponding second-order interaction energies *E* (2) of the shikonin–thymine are listed at Table 3. The higher the *E* (2) is, the stronger the interaction between i and j that is, i is easier to provide electron to j, the hydrogen-bonding interaction is stronger. In addition, the order of sum *E* (2) is the same as that of the interaction. In this study, most of electron transfer occurs in lone pair electrons of atom O or N, and among the anti-bonding orbital, including BD*(N—H), BD*(O—H) or BD*(C—H). The complex 2, six- hydrogen bond complex, has the largest *E* (2) of all, which formed by the anti-bonding orbital BD*(1) O (1)—H (1) and the lone pair electrons of O6, *E* (2) of which is 113.34kJ/mol, and the total *E* (2) of complex 2 is 364.34kJ/mol, it is larger than the others. The results further demonstrate that complex 2 has the best stability. Followed by O(2)⋯H(2)—O(2) , and its *E* (2) is 112.84kJ/mol; the third and fourth stable hydrogen-bonding appear in complexes 8 and 6, they are O(7)⋯H(2)—O(2) and O(6)⋯H(2)—O(2), and *E* (2) of which are 109.50kJ/mol and 106.78kJ/mol respectively. The hydrogen-bonding N(1)⋯C(12)— H(7) of complex 3, and *E* (2) is 9.54kJ/mol , having the worst stability. Furthermore, O(6)⋯C(12)—H(7) of complex 7 is unstable either. From such an analysis, we can conclude that the

interaction between the one pair electrons of O(6) and O(7) in the cytosine and the contacting O—H anti-bond orbital of the shikonin are stronger, and atoms N(4) and O(5) are electron donor of the excellent stability; however, the one pair electrons of N(1) and O(6) in the thymine as the electron donor are difficult to donate electron to the other anti-bond orbital, such as C—H and N—H, indicating that the hydroxyl group of shikonin plays an important part in the interaction between shikonin and thymine.

CONCLUSION

Shikonin, thymine and shikonin-thymine complexes have been studied by using quantum chemistry ab initio and density function theory (DFT) calculations at M06/6-311++G** level and fourthteen stable complexes are obtained along the potential energy surface. It shows that the total energies of this kind system are lower than other similar complexes, indicating shikonin-thymine complexes are more stable than others we studied before. There are at least two hydrogen-bonds in each complex, furthermore, six hydrogen-bond complex 2 has the lowest energy and largest total *E*(2) is 364.34kJ/mol, with the strongest interaction, which is more stable than the best stable complex of shikonin-cytosine complexes, so it is the most stable complex in shikonin and basic group complexes we have worked out at present.

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