Theoretical Researches On Binding Modes and Stability of Hydrogen Bonds Between Uracil and Formic Acid

Qian Tang

Dalian University

Ting Huang

Dalian University

Ruisi Huang

Dalian University

Hongyu Cao (✉ caohongyu@foxmail.com)

Dalian University <https://orcid.org/0000-0003-3182-8866>

Lihao Wang

Dalian University

Xuefang Zheng

Dalian University

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Abstract

The hydrogen bond formation with formic acid would affect the complementary pair of bases between uracil and adenine, but the binding modes and spectral properties of hydrogen bonds are still obscure. Density functional theory and time-dependent density functional theory were applied to investigate the intermolecular hydrogen bonds between uracil and formic acid. The reduced density gradient (RDG), bond lengths and vibration absorption frequencies revealed that the most probable uracil-formic acid (U-FA) interaction mode formed in the position c of FA and the site 1 of U, that is, the mode 1c. The theoretical parameters in excited state complexes manifested that the variety of hydrogen bond configurations led to different degrees of strengthening or weakening of molecular interaction. In the implicit solvent (water), the formations of O-H...O in the uracil-formic acid complexes were promoted obviously. These theoretical studies would positively affect the researches of life science and medicinal chemistry.

Introduction

Hydrogen bonds play an important role in living organisms, participating in various life processes, such as gene and protein structure formation [1–3], enzyme reactions [4] and biomolecular interaction [5]. Hydrogen bond (X-H...Y), a non-covalent interaction, can be regarded as a kind of donor-acceptor orbital interaction from a certain perspective [6, 7]. In biological systems, hydrogen bonds are an important factor in stabilizing biologically active molecules (such as DNA and proteins). In the dynamic system, the intermolecular hydrogen bonds with the low bond energy are easily promoted to break and form continuously [8–10]. Therefore, the researches on the interaction of hydrogen bonds between molecules have received extensive attention.

Uracil, a unique nucleic acid base in RNA, can form hydrogen bond with adenine to participate in transcription and translation, and then maintain inheritance, immune and other life activities. Various studies have reported that uracil can bind to water, ketones and other small molecules through hydrogen bonds [11–17], affecting the structure and properties of uracil. Formic acid, with the least steric hindrance in fatty acids, exists in the muscles, blood and excreta of the human body. The high probability of hydrogen bond formation of formic acid would affect the complementary pair of bases between uracil and adenine, thus blocking RNA replication and destroying the reproduction of viruses, which is of great significance to life science and pharmaceutical chemistry [18–21]. However, the effect of hydrogen bonds on the binding modes, stability and spectral properties between uracil and formic acid in different states seems still ambiguous.

To solve these issues, density functional theory (DFT) and time-dependent density functional theory (TD-DFT) are used to systematically investigate the hydrogen bond binding modes between uracil and formic acid. The behaviors of hydrogen bond formation between two molecules are theoretically revealed with the mode features, electronic spectra and vibrational absorption spectra. In addition, since uracil is a strong absorber of ultraviolet rays [22], the effect of excited uracil-formic acid complexes on intermolecular hydrogen bonding is also discussed.

Computational methods

The geometry optimization of isolated uracil (U), formic acid (FA) and also the designed U-FA complexes were performed using Gaussian 16 program package [23], adapted the 6-31+G(d,p) basis set, at B3LYP exchange-correlation functional with Grimme's empirical dispersion correction [24], abbreviated as B3LYP-D3(BJ). Frequency calculations were implemented at the same computational levels to verify that all the found structures stand in the lowest point of energy.

At the level of TD-B3LYP-D3(BJ)/6-31+G(d,p), energy calculations were executed on isolated uracil, formic acid and U-FA complexes to determine their maximum absorption wavelengths.

Under the same function and basis set, the TD-DFT method was implemented to optimize the U-FA complexes in the state of maximum absorption wavelength and then calculate the frequency. GaussSum [25] was used to process data to analyze the

changes of intermolecular hydrogen bonds in different states.

The reduced density gradient (RDG) function combined with $sign(\lambda^2)\rho(r)$ was applied to distinguish hydrogen bond interactions from other weak interactions [26, 27]. The calculation formula of RDG could be expressed as:

$$RDG(r) = \frac{1}{2(3\pi^2)^{1/3}} \frac{|\nabla\rho(r)|}{\rho(r)^{4/3}}$$

1

Where ∇ , ρ and $|\nabla\rho(r)|$ are the gradient operator, the electron density and the modulus of the electron density gradient, respectively.

The calculation method of hydrogen-bond binding energy, proposed by Lu et al. [28], was based on the file containing the wave function generated after the optimization of the hydrogen bond complexes, and then using Multiwfn 3.7 [29] to obtain the electron density at the bond critical point (BCP) of the hydrogen bond to be investigated, and finally substituting it into the following formula:

$$y = -223.08x + 0.7423$$

2

Where x , y are the electron density at the bond critical point (BCP) and the hydrogen-bond binding energy, respectively.

Atoms in Molecules (AIM) analysis was performed using Multiwfn 3.7 [29] combined with VMD 1.9.4 software [30] to study the nature of the interaction between molecules.

The influence of water as implicit solvent on the intermolecular hydrogen bonds formed by the U-FA complexes was considered by using the DFT method with the same functional and basis sets in the integral equation formalism polarizable continuum model (IEFPCM).

Results And Discussion

S_0 state

For the convenience of description, the different binding sites of U as 1, 2, 3, and of FA as a, b, c (Fig S1), were marked to nine U-FA complexes. Our calculated bond length results of isolated U and FA were basically consistent with those reported by Epifanovsky et al. [31] and Buemi [32], respectively. The optimized structures of nine U-FA complexes in the S_0 state were represented in Fig. 1. The dihedral angle data (Table S1) proved that the S_0 state structure of nine U-FA complexes were plane.

In order to visually understand the non-covalent bond interactions, Fig. 2 displayed the RDG isosurface maps and RDG scatter plots of nine U-FA complexes, which could be used to distinguish hydrogen bond interactions from other weak interactions by the color of the scale bar in the lower right corner, the blue represented hydrogen-bond interaction [26], proved that all the U-FA complexes formed two hydrogen bonds. Although the RDG isosurface map corresponding to the C-H...O hydrogen bonds in all the complexes were close to green, the value of $\rho(r)$ in the RDG scatter diagram was more than 0.005, which was regarded as weak hydrogen bonds [26]. So the sites a and b of FA also formed two hydrogen bonds with uracil. Furthermore, all the O...H bond lengths in the U-FA complexes were 1.620-2.277 Å, which is smaller than the sum of the van der Waals radii of O and H atoms (2.480 Å) [33].

The hydrogen-bond binding energy of nine U-FA complexes in the S_0 state arranged by energy intensity (Fig. 3) could directly compare the strength of the intermolecular hydrogen bonds of U-FA complexes [34]. The strongest O-H...O intermolecular hydrogen bond could be observed in mode 1c.

Fig. 4 showed the comparison of the vibrational absorption spectra of isolated uracil, formic acid and mode 1c (other modes were listed in Fig. S2) in S_0 state. The calculated vibrational absorption spectra data of isolated uracil and formic acid were basically in accord with those reported by Fornaro et al. [35] and Buemi [32], respectively. The stretching vibrations of the groups involved in the formation of intermolecular hydrogen bonds in the nine U-FA complexes were all red-shifted compared with isolated uracil and formic acid as same as Zhao reported [36]. In mode 1c, due to the formation of N-H...O hydrogen bond, the stretching vibration of N-H was red-shifted by 403 cm^{-1} from 3653 cm^{-1} of isolated uracil to 3250 cm^{-1} of mode 1c, and the stretching vibration of C=O red-shifted from 1820 cm^{-1} of isolated formic acid to 1728 cm^{-1} of mode 1c. Simultaneously, the formation of O-H...O hydrogen bond led to the red-shift of O-H and C=O stretching vibration by 719 cm^{-1} and 41 cm^{-1} , respectively.

AIM (Atoms in Molecules), developed by Professor Richard F. W. Bader [37] and his coworkers, was a method based on the topological properties of the electron density scalar field to describe the bonding in molecules. The critical point (CP) of electron density, on which the gradient of a certain function was zero, usually discussed in AIM analysis. The CP could be divided into four types: (3,-3), (3,-1), (3,+1) and (3,+3), which were nuclear critical point, bond critical point, ring critical point and cage critical point, respectively [38]. The difference among them was the sign of the three eigenvalues of the Hessian matrix of the function at the CP [37].

For a better understanding of the properties of the U-FA complexes, the electron density topological analysis of the optimized modes in the S_0 state were carried out by Multiwfn 3.7 [29] and VMD 1.9.4 [30]. The topological analysis diagrams of the U-FA complexes were listed in Fig. 5. Table 1 summarized the values of the electron density (ρ), the Laplacian of electron density ($\nabla^2\rho$) and the energy density (H) at the BCP. The values of ρ at the BCP of all U-FA complexes were positive, revealing that they were all closed-shell interactions [39]. The large the value of ρ at the BCP revealed the short bond distance and the strong bonding ability [40]. The O-H...O bond in mode 1c with the largest value of ρ proved the strongest intermolecular hydrogen bond among all U-FA complexes, which was consistent with the previous observations. The $\nabla^2\rho$ and H could be used to estimate the nature of interaction. The negative value of $\nabla^2\rho$ was related to the covalent bond, while the positive value of $\nabla^2\rho$ meant non-covalent bonds [41–42]. In all the U-FA complexes, the positive $\nabla^2\rho$ and negative H at the BCP of all the O_{15/16}-H_{7/9} of the modes 1-3a and 1-2b and the O₈-H₁₇ of the modes 1-3c, indicated that the hydrogen bond had partial covalent properties [43].

Table 1

The electron density (ρ), Laplacian of electron density ($\nabla^2\rho^2$) and energy density (H) of different U-FA modes at the BCP at B3LYP-D3(BJ)/6-31+G(d,p) levels

	mode	ρ (a.u.)	$\nabla^2\rho^2$ (a.u.)	H (a.u.)
1a	H ₇ -O ₁₅	0.030832	0.088676	-0.000174
	O ₈ -H ₁₃	0.014857	0.046593	0.000458
1b	H ₇ -O ₁₆	0.021526	0.064859	-0.000060
	O ₈ -H ₁₃	0.014873	0.044758	0.000253
1c	O ₈ -H ₁₇	0.052500	0.146808	-0.002323
	H ₇ -O ₁₅	0.038215	0.112371	0.000131
2a	H ₉ -O ₁₅	0.026761	0.076662	-0.000249
	O ₈ -H ₁₃	0.014223	0.046126	0.000618
2b	H ₉ -O ₁₆	0.021523	0.065450	-0.000009
	O ₈ -H ₁₃	0.012913	0.040090	0.000458
2c	O ₈ -H ₁₇	0.047908	0.141013	-0.000707
	H ₉ -O ₁₅	0.031333	0.091797	0.000146
3a	H ₉ -O ₁₅	0.027612	0.078918	-0.000233
	O ₁₀ -H ₁₃	0.014999	0.047647	0.000525
3b	H ₉ -O ₁₆	0.021757	0.066134	0.000004
	O ₁₀ -H ₁₃	0.013548	0.041394	0.000386
3c	O ₁₀ -H ₁₇	0.052019	0.146909	-0.002071
	H ₉ -O ₁₅	0.033521	0.097924	0.000163

Electronic spectra and frontier molecular orbitals

The electron excitation energy, oscillator strength of isolated uracil and U-FA complexes were represented in Table 2 (the major orbital contributions were listed in Table S2). The calculated electronic absorption spectra result of isolated uracil and formic acid were basically in line with those reported by Improra et al. [44] and Li et al. [45], respectively. The maximum oscillator strength of isolated uracil and U-FA complexes were both at S_2 state, indicating that U-FA complexes were more likely to be in the S_2 state. In S_2 state, the absorption of complexes formed by site 2 with formic acid blue shifted, while formed by site 3 with formic acid had red shifts. The modes 1a and 1b red shifted and mode 1c blue shifted in the S_2 state. The S_2 state of the U-FA complexes were mainly contributed to HOMO→LUMO (about 90%) (Table S2).

Figure 6 showed the frontier molecular orbital diagram of the mode 1c (other modes were presented in Fig. S3). In S_2 state of the U-FA complexes, the main transition process from HOMO to LUMO was $\pi\rightarrow\pi^*$. In addition, the electrons of the HOMO and LUMO orbitals of the U-FA complexes were mainly distributed in the uracil, which symbolized the U-FA complexes were locally

excited [34]. The frontier molecular orbital diagram (Figure 6 and Fig. S3) illustrated that the charge distribution variation during the transition from HOMO orbital to LUMO orbital would affect the polar atoms of the uracil. So, we realized that the intermolecular hydrogen bond would change in the S_2 state [34], which would be discussed in the next section.

Table 2
The electron excitation energy (eV), oscillator strength of uracil and U-FA complexes at TD-B3LYP-D3(BJ)/6-31+G(d,p) levels

	U	1a	1b	1c	2a	2b	2c	3a	3b	3c
S_1	4.6539 (0.0000)	4.7080 (0.0000)	4.6759 (0.0000)	4.7313 (0.0000)	4.5902 (0.0000)	4.6347 (0.0000)	4.5781 (0.0000)	4.7071 (0.0000)	4.6776 (0.0000)	4.9007 (0.0000)
S_2	5.1771 (0.1325)	5.1474 (0.1714)	5.1734 (0.1611)	5.1871 (0.1719)	5.2180 (0.1206)	5.2040 (0.1241)	5.2670 (0.1215)	5.1114 (0.1186)	5.1336 (0.1255)	5.0124 (0.1132)
S_3	5.7538 (0.0022)	5.3147 (0.0008)	5.6647 (0.0007)	5.9053 (0.0002)	5.6766 (0.0022)	5.6909 (0.0008)	5.7121 (0.0002)	5.6567 (0.0001)	5.6562 (0.0004)	5.4331 (0.0001)
S_4	5.7636 (0.0002)	5.8223 (0.0001)	5.7685 (0.0000)	5.9265 (0.0272)	5.8058 (0.0000)	5.7227 (0.0003)	5.8287 (0.0024)	5.6951 (0.0023)	5.6977 (0.0004)	5.7338 (0.0001)
S_5	5.8857 (0.0407)	5.8863 (0.0001)	5.8231 (0.0034)	5.9539 (0.0010)	5.8179 (0.0302)	5.7576 (0.0022)	5.8391 (0.0000)	5.8169 (0.0450)	5.7634 (0.0023)	5.8416 (0.0023)
S_6	6.1398 (0.0002)	5.9471 (0.0295)	5.8300 (0.0028)	6.0841 (0.0117)	5.8447 (0.0107)	5.8600 (0.0373)	5.9043 (0.0251)	5.8638 (0.0108)	5.8579 (0.0478)	5.8675 (0.0655)
S_7	6.3620 (0.0626)	5.9766 (0.0013)	5.9318 (0.0256)	6.0924 (0.0001)	5.8789 (0.0004)	6.0230 (0.0001)	5.9177 (0.0009)	5.9158 (0.0005)	6.0088 (0.0000)	5.9356 (0.0011)
S_8	6.4941 (0.0941)	5.9858 (0.0050)	6.0981 (0.0002)	6.2743 (0.0101)	6.0522 (0.0000)	6.1883 (0.0273)	6.2493 (0.0923)	6.0389 (0.0000)	6.1748 (0.0001)	6.1244 (0.0001)
S_9	6.6572 (0.0001)	6.1736 (0.0002)	6.3638 (0.1074)	6.3502 (0.0979)	6.1339 (0.0002)	6.3230 (0.0001)	6.3268 (0.0626)	6.1295 (0.0001)	6.2344 (0.0204)	6.3954 (0.1043)

S_2 state

Based on the previous analysis, we had discovered that relatively stable U-FA complexes were formed by the position c of FA with uracil and the intermolecular hydrogen bonds would be varied in the S_2 state. Therefore, TD-B3LYP-D3(BJ)/6-31+G(d,p) was performed to optimize the structure in the S_2 state of the three complexes including modes 1c, 2c, and 3c.

The basic geometric structure of three U-FA complexes in the S_2 state was presented in Fig. 7. The dihedral angle data (Table S3) showed that the modes 1c and 2c were basically plane, while the mode 3c was distorted. From the RDG isosurface maps and RDG scatter plots (Fig. 7), it was intuitively observed that only the 3c configuration changed. In the S_0 state, the mode 3c formed two intermolecular hydrogen bonds. In the S_2 state, the mode 3c only formed one strong hydrogen bond (N-H•••O), while the another hydrogen bond O₁₆-H₁₇•••O₁₀ in S_0 had a strong tendency to become covalent in S_2 state.

Compared with the S_0 state, the bond lengths of O₁₅•••H₇ and H₁₇•••O₈ in mode 1c were elongated, indicating that both the N-H•••O and O-H•••O intermolecular hydrogen bond were weakened in excited state. In mode 2c, the bond lengths of O₁₅•••H₉ and H₁₇•••O₈ were shortened. In other words, both the hydrogen bonds of N-H•••O and O-H•••O were enhanced in the excited state. Similarly, the N-H•••O in the S_2 state of mode 3c was strengthened.

In order to visually observe the variations of the intermolecular hydrogen bonds of the U-FA complexes after being excited, the histogram of the hydrogen-bond binding energy in the S_2 and S_0 states was presented in Fig. S4. The increased hydrogen-bond binding energy absolute value of 2c', 3c and 2c revealed that the intermolecular hydrogen bond of them strengthened. The strength of hydrogen bond of 1c and 1c' reduced. These results were completely consistent with the bond length analysis.

The electronic spectrum revealed that the local excitation of the U-FA complexes occurred on uracil rather than formic acid. So, the vibration mode of the formic acid was more easily influenced by the hydrogen bond rather than the electronic excitation [34], which meant that the frequency changes of the C=O and O-H groups of formic acid in the S_0 state and the S_2 state can be compared to determine the changes in hydrogen bonds.

The vibrational absorption spectra of U-FA complexes in different electronic states were showed in Fig. 8. Compared to the vibrational absorption spectra in the S_0 state, the stretching vibration of C=O bond in formic acid of mode 1c was blue-shifted, meanwhile the stretching vibration of O-H bond in O-H...O also blue shifted in the S_2 state. In other words, the intermolecular hydrogen bonds of both the N-H...O and O-H...O were weakened in the S_2 state. For N-H...O in the mode 2c, the stretching vibration of C=O bond in the S_2 state of formic acid was red-shifted by 37 cm^{-1} compared to the S_0 state; while the excited intermolecular hydrogen bond of O-H...O, the stretching vibration of O-H bond in formic acid red shifted by 93 cm^{-1} . Both the hydrogen bonds of the N-H...O and O-H...O in mode 2c were strengthened in the excited state. A 58 cm^{-1} red-shift value of the N-H...O in the S_2 state proved strengthened intermolecular hydrogen bonds in mode 3c.

Solvent effect

The influence of water as implicit solvent on the intermolecular hydrogen bond of U-FA complexes was considered. The basic geometries in the water were not significantly different from that in the gas phase (Fig. S5). The dihedral angle data denoted that the nine geometries were basically plane (Table S4). Some phenomena were found by comparing the bond lengths in the gas phase and in the water (Fig. S5). In modes 1a, 1b, 2a, and 3a, the bond lengths of the $\text{H}_{7/9}\cdots\text{O}_{15/16}$ in N-H...O hydrogen bonds and the $\text{O}_8\cdots\text{H}_{13}$ in C-H...O hydrogen bonds were shortened and elongated, respectively, implying that the formation of N-H...O and C-H...O were promoted and interfered, respectively. When the hydrogen bond formed by the position c of FA and uracil in the water, the formation of the N-H...O and O-H...O were interfered and promoted, respectively. However, the formation of both N-H...O and C-H...O of modes 2b and 3b were interfered in the water.

The water could promote the formation of intermolecular hydrogen bonds with red-shifted wavelengths, while water could disturb the formation with the blue-shifted wavelengths (Fig. S6). In mode 1c, due to the influence of water, the formation of N-H...O hydrogen bond was disturbed, while the formation of O-H...O hydrogen bond was promoted. It could be clearly observed from the Fig. S6 that compared with the vibrational absorption spectrum of the gas phase, the stretching vibration of N-H bond in water had a blue shift, while the O-H bond had a red shift.

Conclusions

In this work, density functional theory and time-dependent density functional theory were used to calculate nine U-FA combine modes formed by hydrogen bond. It was in mode 1c that the hydrogen-bond binding energy of O-H...O was strongest, making it the lowest energy and the most stable structure. Compared with isolated uracil and formic acid, the stretching vibrations of the groups involved in the formation of intermolecular hydrogen bonds were red-shifted. In the implicit solvent (water), the formation of O-H...O in the U-FA complexes was promoted obviously. The U-FA complexes were forbidden transition in the S_1 state, and the maximum absorption peaks were in the S_2 state. In S_2 state of the U-FA complexes, the main transition process from HOMO to LUMO was $\pi\rightarrow\pi^*$. In addition, the electrons of the HOMO and LUMO orbitals of the U-FA complexes all distributed in the uracil part, which indicated that the U-FA complexes were locally excited in the U part. The theoretical parameters in excited state complexes manifested that the variety of hydrogen bond configurations led to different

degrees of strengthening or weakening of molecular interaction. The above research proved that only the position c of FA could form two strong hydrogen bonds with uracil and the intensity would be affected by excitation, which has considerable practical and far-reaching significance to the researches of life science and pharmaceutical chemical.

Declarations

Supplementary Information The online version contains supplementary material available at

Author Contributions Hongyu Cao is contributed to supervision and review & editing. Ting Huang performed formal analysis and original draft. Qian Tang, Ruisi Huang and Lihao Wang were involved in formal Analysis and validation. Xuefang Zheng is contributed to supervision and conceptualization.

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Data Availability All relevant data are given in the supporting information file.

Competing Interests The authors have no relevant financial or non-financial interests to disclose.

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Figures

Figure 1

Geometric structure and partial bond length of U-FA complexes in S_0 state

Figure 2

RDG isosurface map (isosurface: 0.5) and RDG scatter plot of U-FA complexes in S_0 state at B3LYP-D3(BJ)/6-31+G(d,p) levels

Figure 3

Histogram of hydrogen bond energies of U-FA complexes (marked O-H•••O on site c as c' and marked C-H•••O on sites a or b as a' or b')

Figure 4

The comparison of the vibrational absorption spectra of isolated U, FA and mode 1c in S_0 state at B3LYP-D3(BJ)/6-31+G(d,p) levels

Figure 5

Topological analysis of different modes in S_0 state at B3LYP-D3(BJ)/6-31+G(d,p) levels

Figure 6

The frontier molecular orbital diagram of the mode 1c

Figure 7

(Top) The basic geometric structure and partial bond length (Middle) RDG isosurface map (isosurface: 0.5) and (Bottom) RDG scatter plot of modes 1c, 2c and 3c in S_2 state at TD-B3LYP-D3(BJ)/6-31+G(d,p) levels

Figure 8

The vibrational absorption spectra of U-FA complexes in different electronic states

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