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Weak C–H···O hydrogen bonds between diacylamidopyridine and thymine derivatives in solution and its influence on the binding constants

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Abstract—The presence of C–H···O hydrogen bonds in a complex composed of 2-(acrylamido)-6-(methylamido) pyridine and 1-octyl thymine is demonstrated by ^{1}H, ^{13}C NMR study and X-ray analysis. Further titration experiment shows these weak C–H···O hydrogen bonds will affect the binding constants through a geometric effect compared with other structural analogous systems.

It is now well established that the weak C–H···O hydrogen bonds exist extensively just like its strong counterparts.[1] They have been found in many kinds of systems, such as crystals,[1,2] proteins[3] and some organic samples.[1] This kind of interaction can be intermolecular or intramolecular.[4] Although it is much weaker in comparison to the usual strong hydrogen bond, X–H···Y (X, Y = O, N, F), this kind of interaction has aroused lots of interest recently among researchers worldwide. The most important reason is its potential application in crystal engineering, supramolecular chemistry, molecular recognition and drug design.[1a,c,5] Up to now, most of the work is still focused on the study of crystal structures[2] or theoretical ab initio calculations.[6] Reports concerning the occurrence of this kind of interaction in solution at ambient temperature are still scarce.[4b,7] Here we report our discovery of the presence of the weak C–H···O hydrogen bonds in a hydrogen bonded complex system including 2-(acrylamido)-6-(methylamido) pyridine (compound **2** in Table 1) and 1-alkyl thymine in chloroform at room temperature. By comparing its binding constant with other structural analogous systems, we believe this interaction will contribute to the stability of the complex.

1-Alkyl thymine was synthesized by alkylation of thymine[8] and diacyldiaminopyridine derivatives (Table 1) were synthesized by the reaction of 2,6-diaminopyridine with corresponding acid chloride.[9] The strong triple hydrogen bonding array (Fig. 1) between thymine and diaminopyridine derivatives was well studied and utilized to prepare supramolecular structures[10] or molecular imprinted polymers.[11] In this work, ^{1}H NMR spectroscopy has been used to monitor the titration of compound **2** in a concentration of 1.3×10^{-2} M with 1-octyl thymine (**OT**) at 21 °C and the spectra was shown in Figure 2. As expected, the peaks of two amido protons in diacylamidopyridine moiety moves from 7.60 and 7.70 ppm to downfield 10.28 and 10.38 ppm as **OT** concentration increased from 0 to 2.4×10^{-2} M. To our surprise, the vinyl proton *c* adjacent to carbonyl group also moved from 6.24 to 6.68 ppm, while the peak shifts of the other vinyl protons are negligible (less than 0.07 ppm). We believe that the down shift of this vinyl proton peak is caused by the formation of a weak C–H···O hydrogen bond as shown in Figure 1, in addition to the three strong hydrogen bonding interactions of N–H···O and N–H···N. One of the carbonyl oxygen atoms of **OT** formed bifurcated hydrogen bond, that is, a normal N–H···O and a weak C–H···O hydrogen

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Keywords: Diacylamidopyridine; Thymine; Weak hydrogen bond; Binding constant.

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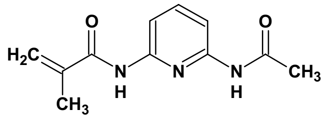
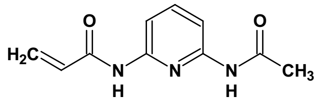
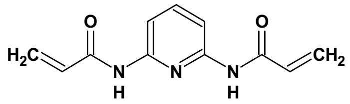
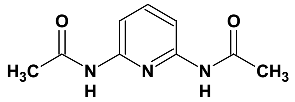
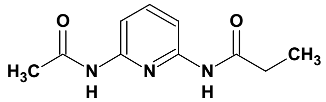
Table 1. Binding constants for complexes of receptor **1** to **5** with 1-butyl thymine in $CDCl_3$

	Receptor	K_a (M^{-1})[a,b]
1		103
2		960
3		870
4		930
5		590

[a] Estimated relative error in binding constant is 15%.

[b] K_a was obtained by standard ^1H NMR titration experiment and the data was deduced by non-linear least square fit.

bond.[4b,6b,12] This weak interaction will also help to increase the binding strength for this complex system.

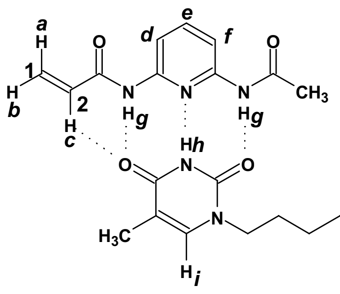


Figure 1. Proposed complex structure of compound **2** with **OT**.

Such weak C–H···O hydrogen bond is not an unusual phenomenon and our result is consistent with previous studies where this kind of weak hydrogen bond also caused a similar downfield chemical shift for the relevant protons.[4b,10a,13] In the complex system of compound **2** with **OT**, this weak C–H···O hydrogen bond was facilitated by the strong triple hydrogen bonding array, which hold the vinyl proton *c* in the deshielding cone of the carbonyl group of **OT**.[4b,14] Therefore, we believe two factors contribute to this interaction: firstly, the vinyl proton *c* in compound **2** is more acidic compared to other vinyl protons since it is adjacent to carbonyl carbon atom; secondly, an appropriated distance and angel between vinyl proton *c* in compound **2** (Fig. 1) and the carbonyl group from **OT**, which is stabilized by the triple hydrogen bonding array, is more geometrically favoured to form such weak C–H···O hydrogen bond.[1,13]

This kind of C–H···O hydrogen bond in solution is not so common compared with that in solid crystals.[2] Further evidence for the existence of this C–H···O hydrogen bonding interaction comes from the change of $^1J_{CH}$ of the vinyl carbon 2 (see Fig. 1 for the label) before and after the complex formation. As shown in Figure 3, the $^1J_{CH}$ of carbon 2 for the compound **2** in $CDCl_3$ solution (17.8×10^{-2} mol dm^{-3}, 21 °C) increased from 155.4 Hz to 163.7 Hz when **OT** (18.9×10^{-2} mol dm^{-3}) was added. For comparison, the value of $^1J_{CH}$ of carbon 1 showed almost no change before and after complex formation (158.9 vs 159.4 Hz). The increase of $^1J_{CH}$ in a value of 8.3 Hz is significant compared with other similar C–H···O hydrogen bonding systems and is consonant with the shortening of C–H bond length according to the theoretical calculation,[13,15] thus provides another evidence for the existence of this interaction.

To further confirm the existence of this C–H···O interaction and gain insight into their structure, compound **2** and ET were co-crystallized by slow evaporation of the solvents from their solution in dichloromethane and heptane[8b] and the crystal structure was analyzed by X-ray diffraction. The results (Fig. 4) confirmed the

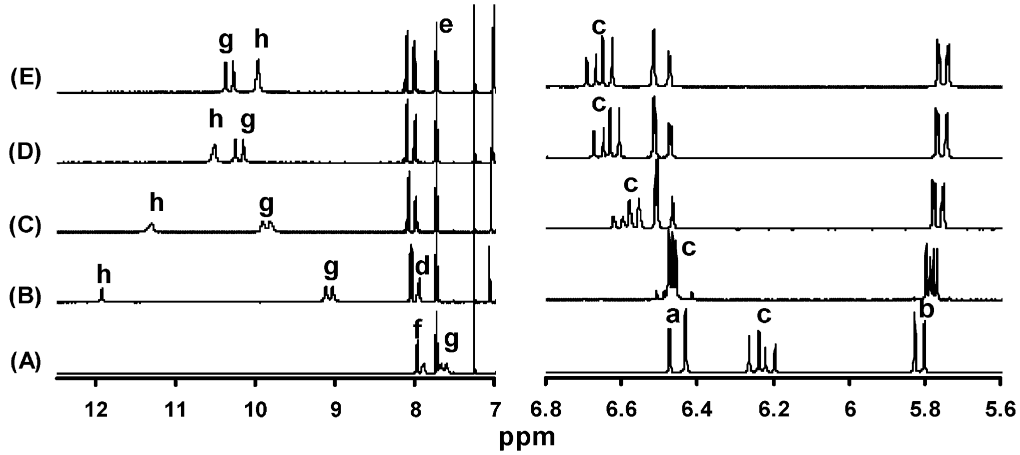


Figure 2. Partial ^1H NMR spectra of the reaction solutions of compound **2** (1.3×10^{-2} M) and **OT** in a concentration of (A) 0, (B) 3.8×10^{-3}, (C) 8.8×10^{-3}, (D) 1.5×10^{-2}, (E) 2.4×10^{-2} M in $CDCl_3$ at 21 °C. See Figure 1 for proton labels.

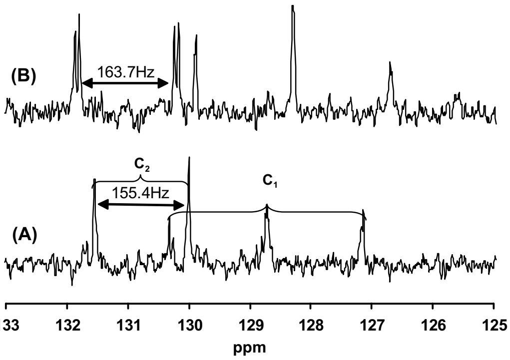


Figure 3. Partial ^{13}C NMR spectra of compound **2** (1.8×10^{-2} M) before (A) and after (B) reacting with OT (1.8×10^{-2} M) in $CDCl_3$ at 21 °C. See Figure 1 for carbon labels.

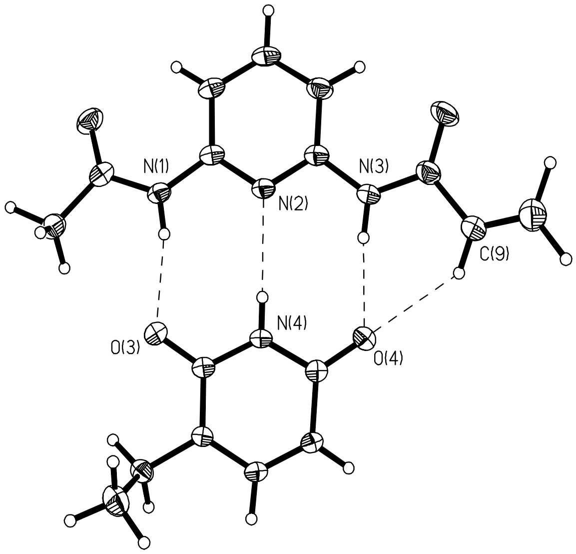


Figure 4. ORTEP representation of complex between compound 2 and ET displaying normal triple hydrogen bonds and C–H· · ·O contact. Thermal ellipsoids represent 35% probability.

assigned structure. The distance of O4· · ·H9 (2.445 Å), and C9–O4 (3.249 Å), and the angle of C9–H· · ·O4 (142.2°) are all well correlated with a typical C–H· · ·O hydrogen bond.[1a]

Binding constants between 1-butyl thymine (**BT**) and several diacylamidopyridine compounds **1–5** were then determined by standard ^{1}H NMR titration experiments in $CDCl_3$ solution at 21 °C with the results listed in Table 1. Compound **1** showed the modest binding constant of about 103 M^{-1} among all the tested compounds. This low binding capacity should be attributed to the steric hindrance of adjacent alkyl groups.[16] All these diacylamidopyridine compounds should choose *cis* conformation as demonstrated previously and the coplanar steric interaction between the amido carbonyl group and the protons *d* and *f* would cause a concave curvature in this donor–acceptor–donor array.[16a,17] Therefore, the size and rotating ability of the alkyl group adjacent to the carbonyl carbon will have a key influence on the stability of the resulted complex because of this subtle geometric interaction.

Further 2D NOESY study shows two possible conformations existed in the $CDCl_3$ solution for pure compound **1**. However, once it forms complex with **BT**, only one conformation as shown in Figure 5 has been detected. This demonstrated that the steric hindrance of the methyl group in compound **1** prevented the conversion between two conformations in the complex. This further confirmed the explanation of the low binding constant of this compound as mentioned above, and also explained the difference of binding constants between **5** (590 M^{-1}) or **4** (930 M^{-1}) with **BT**, since ethyl is more bulky compared with methyl group. Previous study shows that the strength of C–H· · ·O hydrogen bond can be counted about 2 kcal mol^{-1}, which is about 30% of the strength of a normal N–H· · ·O interaction.[4b,6a,b] For this bifurcated system as shown in the complex of compound **2** with **OT**, the C–H· · ·O hydrogen bond should not be as strong, but it will be strong enough to suppress the free rotation of the vinyl groups thus stabilize the structure of the hydrogen bonding complex. Meanwhile, a similar interaction between compound **3** and **BT** was also observed from ^{1}H NMR spectrum during the titration, where two C–H· · ·O hydrogen bonds and a binding constant of 870 M^{-1} have been found.

In conclusion, besides the strong triple normal hydrogen bonds, another weak C–H· · ·O hydrogen bond between

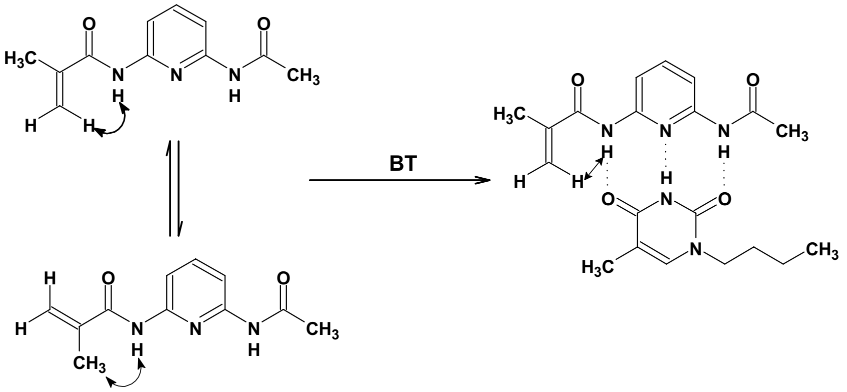


Figure 5. Preferred conformations of compound **1** in $CDCl_3$ before and after complex formation with **BT**; the observed NOE (nuclear Overhauser effect) is indicated with a double-headed arrow.

compound **2** and **OT** existed in $CDCl_3$ solution. This unusual hydrogen bond facilitates stabilizing the complex and results in a higher binding constant than that of analogous system. This result is consistent with other people's study concerning the C–H···O hydrogen bond that will affect the binding energy of the hydrogen bonded complex systems.[16b]

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