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Controlling Keto–Enol Tautomerism of Ureidopyrimidinone to Generate a Single-Quadruple AADD-DDAA Dimeric Array

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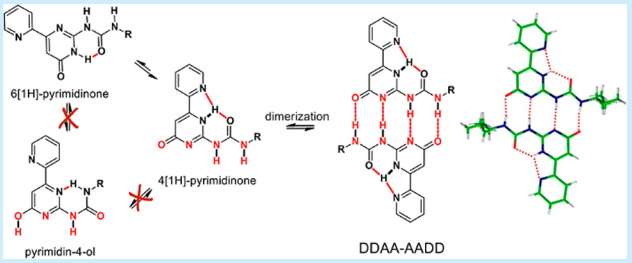
ABSTRACT: Units of ureidopyrimidinone (UPy) which dimerize via strong quadruple hydrogen bonding are widely used for the construction of supramolecular systems. This self-complementary system exists in the tautomerism equilibrium of 4[1*H*]-pyrimidinone dimer and pyrimidin-4-ol dimer, making generated supramolecular assembly systems essentially complicated. In this contribution, a rational but simple design concept is described for preorganizing the self-complementary quadruple hydrogen bonding of UPy via supramolecular strategy into a single-quadruple DDAA-AADD dimeric array. With this concept, the designed UPy derivatives form only 4[1*H*]-pyrimidinone dimer with a ketone configuration via intermolecular hydrogen-bonding interactions, both in the solid state as well as in solution, as is evident from single-crystal X-ray diffraction and ^{1}H NMR spectroscopy. The single DDAA-AADD dimeric array provides defined noncovalent driving forces that can be used to generate constitutionally clear supramolecular structures that are vitally important in the fields of supramolecular chemistry and materials.



Prototropic tautomerism, intramolecular transfer of hydrogen from one atom to another, is a common phenomenon in living systems.[1−4] Keto−enol tautomerism is a typical paradigm of intramolecular proton transfer, and it is of great significance in biochemistry.[5−9] The canonical keto form and its corresponding rare tautomeric enol form of the bases guanine and thymine exist in cells, and the tautomerism of base pairs which have different base-pairing properties increases the uncertainty of genetic information, resulting in an imprecision of the recognition, replication, and transfer of genetic information.[10] Essentially, an intrinsic genetic instability arisen by keto−enol tautomerism in cells possibly facilitates mutation and even cancer development.[10−12] Therefore, it is extraordinarily important to study how to control keto−enol tautomerism.

Inspired by the DNA base pairing of natural genetic materials, and with an eye toward building supramolecular polymers with a higher degree of polymerization, chemists have sought to develop multiple hydrogen-bonded systems with stronger binding capacity. The UPy-based self-assembly system, a famous quadruple hydrogen bonding self-complementary array, was developed by the Meijer group in 1997.[13−15] This system has been extensively used in the fields of supramolecular chemistry and materials science owing to its excellent features such as cheap raw materials, readily accessible synthesis, easy derivatization, and strong noncovalent driving force. Meanwhile, an important feature that cannot be ignored of this system is that there are three kinds of equilibriums of proton tautomers, which are solvent dependent.[14,16] In polar solvents such as DMSO, because the hydrogen bonding between molecules is destroyed, it is mainly in the form of the monomeric 6[1*H*]-pyrimidinone tautomer. However, in weak polar solvents such as chloroform and toluene, the 4[1*H*]-pyrimidinone tautomer and the pyrimidin-4-ol form self-complementary dimeric array respectively via quadruple intermolecular hydrogen bonds. According to Jorgensen's secondary electrostatic interactions theory, dimer of ADAD (acceptor−donor−acceptor−donor) array which has sextuple repulsive secondary interactions is predicted to be less stable than DDAA (donor−donor−acceptor−acceptor) dimer, both are self-complementary quadruple hydrogen-bonded systems with compact hydrogen-bonding sites.[17,18] In addition, because of the existence of the inherent tautomerization of this heterocyclic ring-based system, there are various isomers in supramolecular assemblies based on this building block, which makes supramolecular structures very complicated essentially.

Structure control of intramolecular proton tautomerism is the basis for the functionality of biomacromolecules such as DNA and proteins and has inspired a fruitful research area of supramolecular chemistry.[19−32] Meijer and co-workers studied

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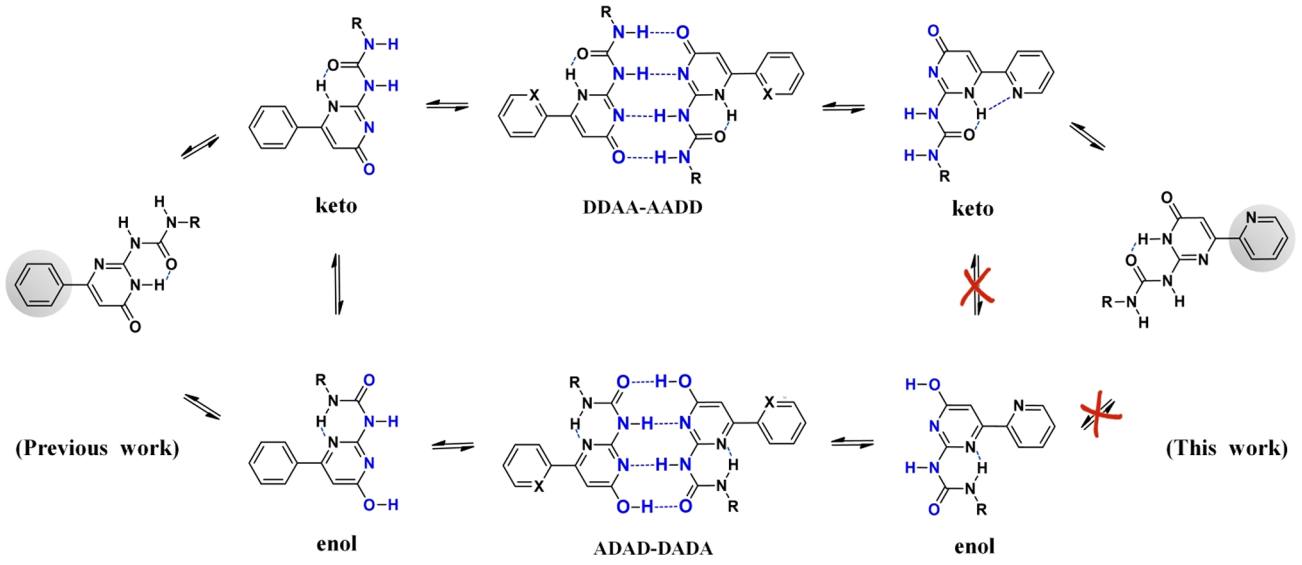


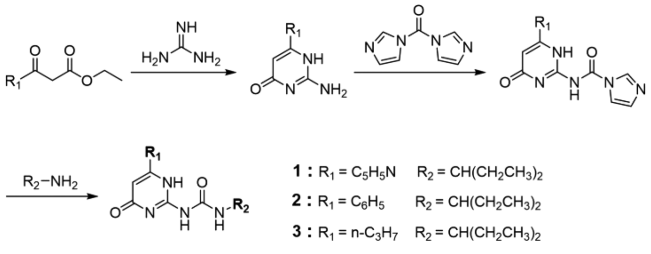
Figure 1. Representative diagram of tautomerism and dimerization of ureidopyrimidinone (UPy) derivatives (X = CH or N).

in detail the effect of substituents on the equilibrium of tautomers.[14] The change of the electronic properties of substituents on the monomers can significantly influence the stability of complex. The enol form is favored in ureidopyrimidinone derivatives with electron-withdrawing substituents at the 6-position of these heterocycles.[22] Sanjayan et al. used a degeneracy strategy to restrain intramolecular proton transfer of tautomers.[23] Hailes et al. have developed a ureidocytosine-based quadruple hydrogen-bonded dimer via an N alkylation strategy to inhibit proton tautomers.[24] In addition, an intramolecular hydrogen bond from the pyrimidine NH group to the urea oxygen atom preorganizes the UPy molecule for dimerization (Figure 1, left), and further control over the configuration of UPy to realize a single DDAA-AADD dimer can in principle be achieved by employing additional noncovalent interaction.

We here use a supramolecular strategy to restrict intramolecular proton transfer and then control the configuration of keto−enol tautomers and eventually realize a single DDAA-AADD dimeric array. Accordingly, we designed a simple ureidopyrimidinone derivative **1** that has a pyridine group at the 6-position of the heterocycle to provide additional intramolecular H-bonds between the NH group of pyrimidine and N atom of pyridine, which can exclusively generate a DDAA-AADD dimer with a keto configuration (Figure 1, right).

UPy derivatives **1**−**3** were synthesized, and the difference among them is the substituent at the 6-position of pyrimidinone heterocycle (R1) (Scheme 1). In order to observe the exact structure of compound **1**, we carried out a single-crystal X-ray diffraction study. The X-ray single-crystal structure was obtained by the slow evaporation of solvent from a concentrated solution of **1** in chloroform. The crystal structure of **1** demonstrates that the dimers are formed via four intermolecular hydrogen bonds in the solid state, in which the molecular structures are in the form of 4[1*H*]-pyrimidinone (Figure 2a). The outer N−H···O hydrogen bonds are shorter than the inner N−H···N hydrogen bonds. An intramolecular six-membered conjugated H-bonded network is formed between the urea carbonyl group and N−H of heterocyclic ring. The pyridine unit at the 6-position of heterocycle appears to undergo a significant intramolecular interaction, meanwhile, forming an intramolecular five-membered hydrogen bond ring with the N−H of heterocycle. These two factors make the whole molecule present a near plane structure (Figure 2b). From the crystal structure, we demonstrate that compound **1** indeed generates a quadruple hydrogen-bonded DDAA-AADD dimer with ketone configuration in the solid state. Single quadruple DDAA-AADD dimeric array from **1** with keto form also exists in solution, as confirmed by the correlations between H_4 and H_5 in two-dimensional NOESY spectrum (Figure S2). The formation of intramolecular hydrogen bonds can essentially control the configuration of keto−enol tautomers.

Scheme 1. Synthetic Route of Compounds 1−3



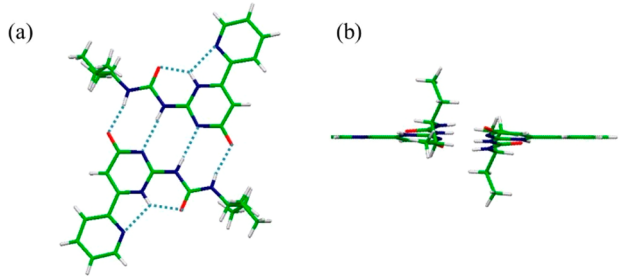


Figure 2. (a) Single-crystal X-ray structure of compound **1**, showing the formation of quadruple hydrogen bonded dimer via a DDAA-AADD dimeric array resulting from the 4[1*H*]-pyrimidinone (keto) form of the heterocycle. (b) Side view of crystal structure of **1**.

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In order to investigate the influence of additional intramolecular hydrogen-bonding interactions on the tautomerism, we synthesized compounds **2** and **3** for comparison. Different from **1**, compounds **2** and **3** were obtained by introducing a phenyl moiety and an alkyl chain at the 6-position of the heterocycle, respectively. Then NMR experiments of these three were carried out under identical experimental conditions. The ^{1}H NMR spectrum of **1** clearly reveals the presence of only a single tautomer in solution (Figure 3a). The three NH proton signals at 14.21, 11.80, and 9.75 ppm in the downfield area are the characteristic peaks of strong hydrogen-bonding interactions, indicating the formation of a definite 4[1*H*]-pyrimidinone dimer via an exclusive DDAA-AADD array. Similar to that reported previously,[14] the ^{1}H NMR spectrum of **3** in $CDCl_3$ also indicates that only 4[1*H*]-pyrimidinone exists as the DDAA dimers in solution (Figure 3c). However, compound **2** with a phenyl moiety at the 6-position of the heterocycle, which is a very similar structure to **1** but lacks other additive driving forces to preorganize the self-complementary quadruple hydrogen bonding of UPy, shows more complex dimerization behavior in solution than **1**. It is obvious that two sets of signals can be seen from the ^{1}H NMR spectrum (Figure 3b) of **2**, illustrating that the existence of tautomeric equilibrium between the 4[1*H*]-pyrimidinone (keto) dimer and the pyrimidin-4-ol (enol) form in solution. The latter tautomer dimerizes via four intermolecular hydrogen bonds in a DADA-ADAD dimeric array. One set of three NH proton signals at 14.00, 12.05, and 9.92 ppm corresponds to the keto form of tautomers. Another set of signals at 13.72, 11.32, and 9.92 ppm is assigned to the enol configuration of tautomers. The proportion of dimers formed by 4[1*H*]-pyrimidinone tautomer and pyrimidin-4-ol tautomer in solution is 87.7% (DDAA-AADD) and 12.3% (DADA-ADAD), respectively. The presence of two tautomeric forms of dimers is also confirmed by two-dimensional NMR (NOESY) studies on **2** in $CDCl_3$ (Figure S3). As shown, NOEs were observed between protons *a* and *b*, which correspond to the intermolecular contacts between two molecules constituting the DADA-ADAD dimer. The results of NMR experiments indicate that intramolecular proton transfer during the tautomerism of keto−enol can be effectively controlled by supramolecular interactions to generate single DDAA-AADD dimeric array.

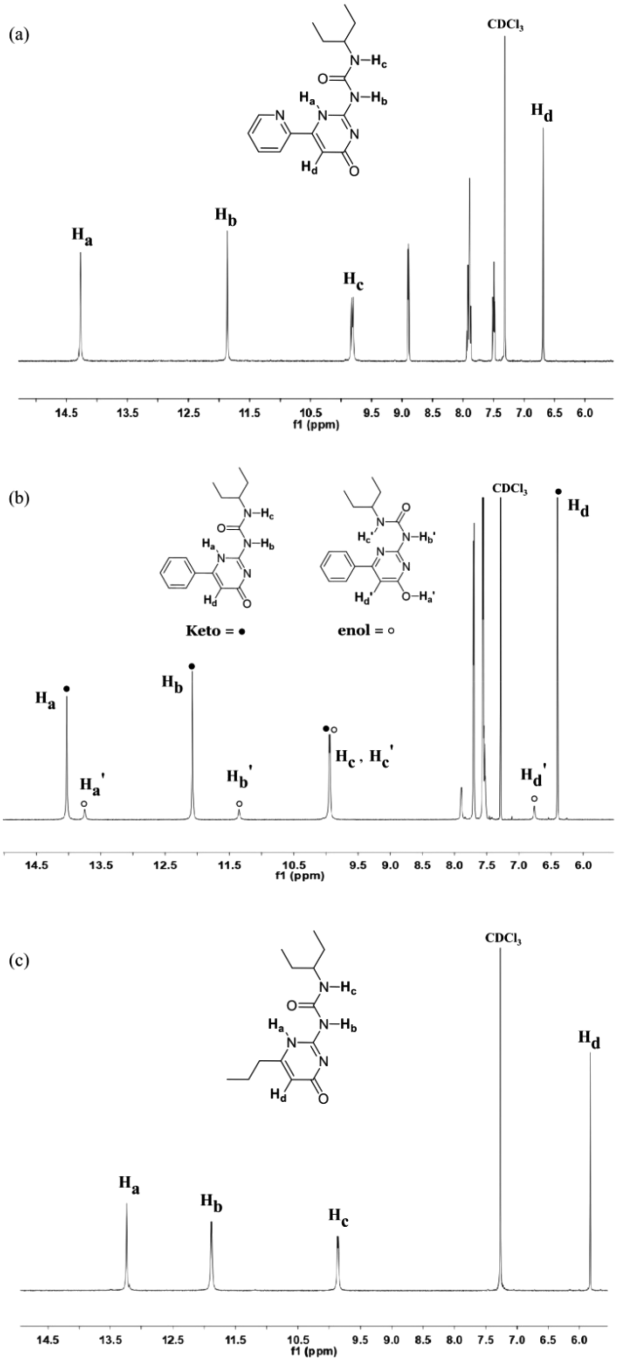

Figure 3. ^{1}H NMR spectra of compounds (a) **1**, (b) **2** and (c) **3** in $CDCl_3$.

Next, we wonder if a well-defined supramolecular structure can be noncovalently synthesized by controlling the tautomerism of UPy. In order to clearly prove this, compounds **4** and **5** containing bis-2-ureido-4-pyrimidinone connected by a *m*-xylylene spacer were prepared, which can self-assemble into extraordinarily stable dimeric structures based on eight intermolecular hydrogen bonds (Figure 4a). Three sets of signals with different structures can be observed from the ^{1}H NMR spectrum of **4**, signifying that there is an equilibration of three supramolecular structures formed by different isomers in pyridine-d_5 (Figure 4c). The interconversion of dimeric arrays formed by the keto and enol form, respectively, exists in solution and is in a fast equilibrium. According to previous reports,[33,34] we conclude that the interconversion of three isomeric cyclic supramolecular structures **I**, **II**, and **III** exists in solution (Figure 4b). The first supramolecular isomer **I** is a syn conformation, and the two 4[1*H*]-pyrimidinone units are located on the same sides of the plane of phenyl ring. The second supramolecular isomer **II** exists in anticonformation, with the two 4[1*H*]-pyrimidinone units located on the opposite sides of the benzene ring plane. In the process of self-assembly into supramolecular structures, the tautomeric form changes from keto to enol spontaneously. The third supramolecular isomer **III** is the keto−enol configuration, with two asymmetric molecules around the plane of benzene ring, half of which is a 4[1*H*]-pyrimidinone unit and the other half is a pyrimidin-4-ol unit. Due to the existence of a dimeric array of DDAA in the supramolecular structure, the whole molecule of **III** is also in a relatively stable thermodynamic environment. The proportion of supramolecular structures formed by these three isomers in pyridine-d_5 is 7.2% (**I**), 21.4% (**II**), 71.4% (**III**). In addition, the ratio of different supramolecular isomers

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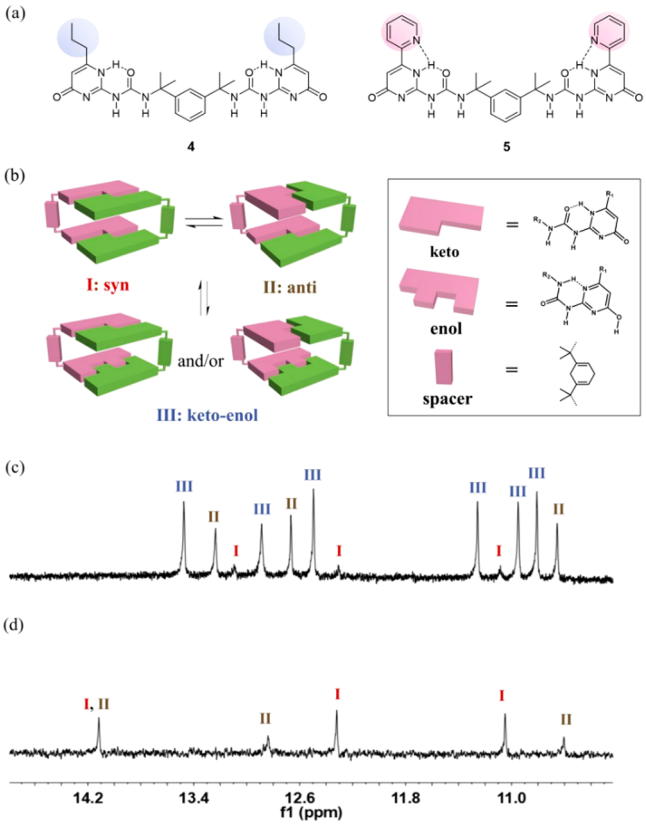

Figure 4. (a) Molecular structures of bifunctional UPy derivatives **4** and **5**. (b) Schematical representation of the interconversion of three isomeric cyclic dimers **I**, **II**, and **III**. (c) ^{1}H NMR spectrum of compounds **4** and (d) **5** in pyridine-d_5. The signal peaks of three isomers **I**, **II**, and **III** have been assigned.

is related to the solvent to some extent, and slight changes in the isomer ratio of 4.1% (**I**), 17.3% (**II**), and 78.6% (**III**) are observed in $CDCl_3$ (Figure S26). It is noteworthy that compound **3** that constitutes the molecular structure of **4** only exists as a DDAA-AADD dimer from the 4[1*H*]-pyrimidinone form in $CDCl_3$ as observed by an NMR study (Figure 3c). By using compound **4** as a building block, however, the DADA-ADAD dimeric array unexpectedly dominates the supramolecular structure.[34] Strikingly, only two sets of signals can be observed in the ^{1}H NMR spectrum of compound **5**, which correspond to the syn (**I**) and the anti (**II**) conformations, respectively (Figure 4d). Compared to **4**, the absence of supramolecular isomer **III** of **5** indicates that there is no DADA-ADAD dimeric array from pyrimidin-4-ol tautomer in solution. These results clearly illustrate that controlling keto−enol tautomerism of UPy can generate a single DDAA-AADD dimeric array that makes the supramolecular structure constitutionally clear.

In conclusion, we have significantly improved this noncovalent driving force of well-known UPy-based quadruple hydrogen-bonding dimerization by controlling the keto−enol tautomerism of UPy. Our findings indicate that the formation of intramolecular hydrogen bonds is able to essentially control the configuration of keto−enol tautomers. The change of UPy tautomers from the enol to keto form has been realized by introducing a pyridine unit at the 6-position of heterocycle. The designed molecule **1** exists as only a 4[1*H*]-pyrimidinone tautomer in solution and in the solid state, which gives rise to the generation of a single DDAA-AADD dimeric array. In the construction of supramolecular systems, building block **5** composed of **1** self-assembles into supramolecular structures with exclusive DDAA-AADD dimeric arrays, whereas the DADA-ADAD dimeric arrays unexpectedly dominate in supramolecular structures by using extensively studied building blocks, such as **4**. This study represents successful control of keto−enol tautomerism of UPy by supramolecular strategy, which will not only make it clear that the supramolecular structure is essentially important in supramolecular chemistry and materials but also provide the possibility of controlling disease-related prototropic tautomerism in biological systems in the future.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02644.

Experimental procedure and characterization of compounds (^{1}H and ^{13}C NMR spectra) (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**, **1a**, **1b**, **2**, **2a**, **2b**, **3**, **3a**, **3b**, **4**, and **5** (ZIP)

Accession Codes

CCDC 2021875 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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