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ARTICLE

Conformational change in association of heterocyclic urea derivative forming two intramolecular hydrogen bonds in polar solvent

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Association of a model, heterocyclic compound capable to form two intramolecular hydrogen bonds was studied with the use of various anionic and neutral species in highly polar solvent but also, for some of them, in chloroform. The hydrogen bonding of anions was tuned by the substituent present in their strucutre. This approach was used in distinguishing which part of the bisurea heterocyclic derivative is preferred during complex formation. Neutral counterparts capable to form three or five hydrogen bonds were also used. Moreover, the triple association was probed suggesting formation of the complex only in chloroform. DFT computations were helpful in interpretation of experimental data related to relatively complicated equilibrium. These are based on the energy of rotation about single bonds, energy of interaction and QTAIM-based energies of hydrogen bonds.

Introduction

Hydrogen bond is one of the most often studied non-covalent interactions and plays an important role in design of self-organizing complexes in solid state and in solution. Generally, the existence of this attractive force falls into two categories: intra- and intermolecular hydrogen bonding. The first one is present in the plethora of compounds and stabilizes specific conformation by decrease of rotational freedom in molecule.[1-3] The second one is present in a number of supramolecular complexes that may be designed rationally based on the current knowledge. These complexes are dimers[4, 5], trimers[6], polymers[7, 8] present in solution and in solid.[9-15] Inspiration of our current study is the general competition between intra- and intermolecular bonding.[6, 16-25] It is worth to mention that multiple intramolecular hydrogen bonding that breaks upon association is not often studied to date[26-28] and is still under discussion.[29, 30] One of classical examples of intra- and intermolecular hydrogen bonding (and breaking of this interaction) is *o*-hydroxybenzamide. In this molecule a competition between basic centres for labile proton takes place.[31] Taking into account that multiple hydrogen bonding in biomolecules plays a crucial role in life processes, it is correct to tell that study on these effects is important.

In general, according to Etter's rules[32], the intramolecular hydrogen bonding is stronger and more probable than the intermolecular one and has a major influence on shape (conformation) of molecules. However, the association with another, complementary compound by multiple hydrogen-bonding could change relative arrangement of groups yielding conformational equilibrium. The said competition is common in urea derivatives.[33,34] In our previous study[2] we investigated pyridine-2-yl urea derivatives (Fig. 1) and showed that the efficient association is possible even if intramolecular hydrogen bond exists.[2] Zimmerman et al. previously described similar effects.[24,34]

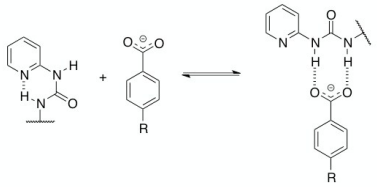

Figure 1. Isomerization in N-(piridin-2-yl)urea derivative upon association

The stability of supramolecular assemblies depends on many factors such the strength and the number of intermolecular hydrogen bonds[35], their character and hydrogen bonding pattern (the order of hydrogen bond donors (D) and acceptors (A))[4, 32, 36], secondary interactions[37] as well as the character of substituent (electronic[38, 39] or steric[5, 40, 41]). All these factors give rise to competition between intra- and intermolecular interactions giving conformational change. It is worth mentioning that solvation, which might be competitive to association, may also influence the relative ratio of conformations including ones with intramolecular hydrogen bonding.

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Electronic Supplementary Information (ESI) available: Cartesian coordinates and figures of the optimized geometries, QTAIM-based graphs, NMR spectra, titration curves, correlation charts and additional discussion are available. See DOI: 10.1039/x0xx00000x

In the current study we have focused on electronic effect in anions on conformational equilibrium in compounds stabilized by multiple intermolecular hydrogen bonding. Additionally we have used neutral counterparts with variable number of hydrogen bonding sites that can make the title molecule to isomerize. We have recently shown that variation in substituent changes properties of a base (guest) and may be a method of choice to study properties of the host molecule. This approach was used in pyrinin-2-yl urea derivatives[2] but also in polyimide (triuret) case.[26] There are several publications describing how hydrogen bonding[16,42] influences the stability of specific rotameric form and thus association of molecules, but only a couple of papers have focused on the significance of conformational equlibrium.[43, 44] Based on this we designed and synthesized 1-(2-(3-isopropylureido)pyrimidin-4-yl)-3-phenylurea (**1**) that is able to exist in several forms (rotamers). Some of them are stabilized by intramolecular hydrogen bonding. The similar amino-derivatives were described and studied in the solid state and solution.[45] The previous studies, however, were focused on acyl[46] and urea derivatives of pyrimidine[45] (Fig. 2 *a* and *b*), while in the current manuscript we have focused on bisurea derivative (Fig. 2*c*) as a host and its forms (Fig. 3).

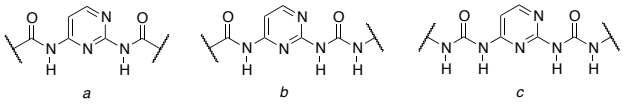

Figure 2. The acyl- (*a*)[46], urea (*b*)[45] and bis-urea (*c*) derivatives of pyrimidine

In conformations shown in Fig. 3 each form carry different array of hydrogen bond donors and acceptors. Black dot denotes the intramolecular electronic repulsion (destabilizing force).

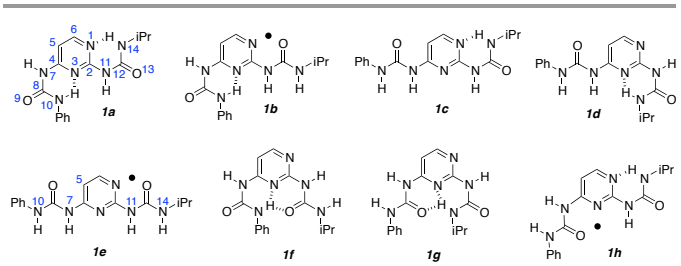

Figure 3. Possible forms of **1** and atom numbering

Recently we have shown that some conformations of model compound (carrying DDDD hydrogen bonding pattern) are preferred over other ones. These may coexist as temperature, for example, changes and some conformations are visible by NMR only when the temperature is low enough.[26] In the current study the similar is realized but the hydrogen-bonding pattern is extended to the DDADD one (Fig. 3, **1e**). For comparison purposes the triuret studied by us previously is shown in Fig. 4. The currently studied molecule differs from triuret by separation of two urea moieties by heterocyclic ring. Still, **1** can form two intramolecular hydrogen bonds.

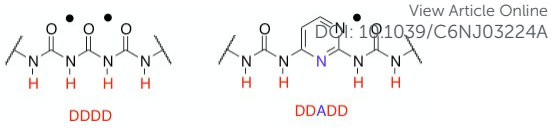

Figure 4. The hydrogen bonding patterns in triuret and bis(urea)pyrimidine derivative

Taking into account single "urea arm" in subjected molecule its conformation changes from *ZEZ* to *EZZ* (bonds C4-N10, N10-C11, C11-N12) during quasi-ring (the one with intramolecular hydrogen bond) "opening". Among forms of **1** these in *EEZ* conformation (**1b**-**1g**) fit geometrically to the hydrogen-bonding pattern of carboxylate anion.[2,26] The interaction of **1e** with two anions is possible because the urea moieties are separated by heterocyclic ring. This is opposite to the triuret derivative[26], in which two anions would be much too close with each-other to stabilize its linear form (Fig. 4). We have used substituted benzoates (**D**-**K**) to probe the interaction of the urea moieties in **1** and its association preferences. Moreover, to probe the existence of some conformations of **1** another molecules were used. Those were: 2,6-bis(acylamino)pyridine[41] (**A**), 3,3-dimethylglutarimide (**B**) and, previously unknown, bis(1,8-naphthyridine-2-yl)amine (**C**). All compounds used in current study are shown in Fig. 5.

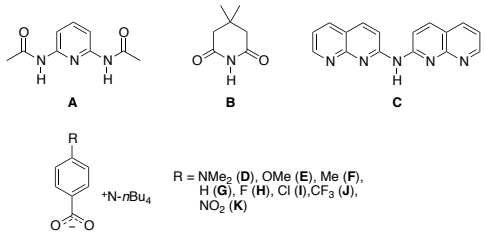

Figure 5. Structures of compounds **A**-**K** used as counterparts for **1**

The interaction of **1** with benzoate is tuned by the substituent present in anion while the interaction with remaining counterparts is dependent on the number of hydrogen bonds and hydrogen bonding pattern. Thus, for example, form **1e** should be able to interact by five hydrogen bonds with **C** (Fig. 6) and by three hydrogen bonds with **B**, while forms **1c**, **1d** or **1g** should interact with DAD hydrogen bonding pattern of **A** forming three hydrogen bonds (two NH···N and one NH···O interaction). On the other hand in the **1c:A** complex the methyl-to-H7 steric effect (Fig. 6), most probably, would hinder such complexation. Also, form **1e:B** would be less stable than **1c:B** (the *i*Pr-carrying part would exists in a form with intramolecular NH···N hydrogen bond). Association of molecules that equlibriate by rotamerism may be complicated. Above examples show that. However, some of mentioned interactions are possible if two requirements are fulfilled *a*) at least one intramolecular hydrogen bond is broken and *b*) the solvation of respective counterparts would not prohibit association.

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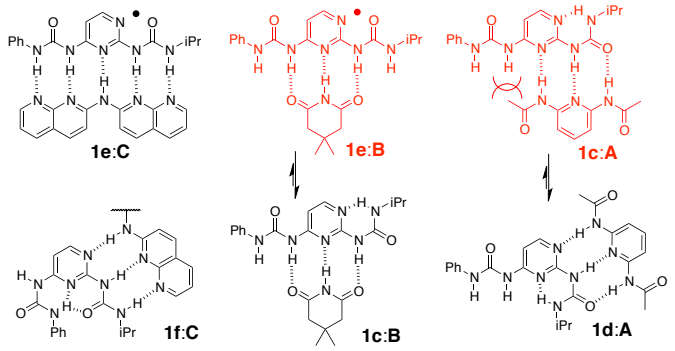

Figure 6. The complexes of **1** with various counterparts

This study is aimed to find how two urea arms fit the counterparts and to check how un-equivalent urea moieties compete during complexation. Additionally, the computations performed for all studied structures would allow better understanding of experimental results.

Experimental

Synthetic procedures

2-Amino-1,8-naphthyridine and 2-hydroxy-1,8-naphthyridine

2,6-Diaminopyridine (12.0 g, 0.11 mol) and 1,1,3,3-tetramethoxypropane (18.2 g, 0.11 mol) were heated (120 °C) in phosphoric acid (110 ml) for 48h. After cooling the mixture was poured on ice and basicified to pH=12 (50% KOH). The mixture was extracted with ethyl acetate (3 x 250ml), organic fraction dried with Na_2CO_3 and solvent evaporated under vacuum. Crystalization from methanol gave 1.6g of 2-hydroxy-1,8-naphthyridine as dark yellow needles (yield 10%) m.p. 199-202 °C (lit. 198-199 °C[47]). The filtrate was evaporated and purified by column chromatography (CH_2Cl_2:MeOH, 10:1, SiO_2) giving 1.3g (8 %) of pure 2-amino-1,8-naphthyridine (dark yellow powder), m.p. 138-141 °C (lit. 130-132 °C).[48]

2-Amino-1,8-naphthyridine: ^{1}H NMR (TMS, $CDCl_3$) δ: 8.85 (d, $^3J_{HH}$ = 2.48 Hz, 1H), 7.93 (d, $^3J_{HH}$ = 5.88 Hz, 1H), 7.86 (d, $^3J_{HH}$= 8.72 Hz, 1H), 7.19 (m,1H), 6.78 (d, $^3J_{HH}$ = 8.72 Hz, 1H), 5.27 (bs, 2H). ^{13}C NMR (TMS, $CDCl_3$) δ: 161.23, 157.26, 152.21 138.09, 136.75, 117.62, 117.23, 113.86. Anal. Calc. for $C_8H_7N_3$: C 66.19, H 4.86, N 28.95. Found: C 66.28, H 4.99, N 28.56.

2-Hydroxy-1,8-naphthyridine: ^{1}H NMR (TMS, DMSO) δ: 12.15 (bs, 1H), 8.51 (dd, $^3J_{HH}$ = 2.96 Hz, 1H), 8.12 (dd, $^3J_{HH}$ = 5.96 Hz, 1H), 7.93 (d, $^3J_{HH}$ = 9.52 Hz, 1H), 7.24 (m, 2H), 6.57 (d, $^3J_{HH}$ = 9.52 Hz, 1H), ^{13}C NMR (TMS, DMSO) δ: 163.37, 150.91, 150.28, 139.57, 136.90, 123.57, 118.76, 114.72. Anal. Calc. for $C_8H_6N_2O$: C 65.76, H 4.14, N 19.17. Found: C 65.88, H 4.27, N 19.02.

2-Bromo-1,8-naphthyridine

2-Hydroxy-1,8-naphthyridine (1.0 g, 7 mmol) and phosphoryl bromide (5.0 g, 52 mmol) were dissolved in DMF and heated up (120 ^{O}C, 24h). Then mixture was poured onto ice and basified with aqueous ammonia solution to pH=10. Residue was filtrated and crystallised from water and gave 0.99g (69%) of analytically pure compound as white powder, m.p: 154.5-156.7 °C (lit. 152-153 °C[47]). ^{1}H NMR (TMS, $CDCl_3$) δ: 9.12 (dd, $^3J_{HH}$ = 2.32 Hz, 1H), 8.22 (d, $^3J_{HH}$ = 6.16 Hz, 1H), 8.04 (d, $^3J_{HH}$ = 8.44 Hz, 1H), 7.65 (d, $^3J_{HH}$ = 8.44 Hz, 1H), 7.55 (m,2H). ^{13}C NMR (TMS, $CDCl_3$) δ: 155.59, 155.03, 144.78, 141.17, 138.49, 127.46, 123.60, 122.38. Anal. Calc. for $C_8H_5BrN_2$: C 45.96, H 2.41, N 13.40. Found: C 46.10, H 2.53, N 13.27.

Bis(1,8-naphthyridin-2-yl)amine

Synthesis was performed as described for similar amines.[49] The reaction flask was dried in oven (120 °C, 24h) and purged with argon (10 min.). After that, toluene was added, followed by 2-bromo-1,8-naphthyridine (0.8 g 3.8 mmol), 2-amino-1,8-naphthyridine (0.55 g, 3.8 mmol), $Pd_2(DBA)_3$ (57 mg, 0.06 mmol, 4mol % Pd,), 1,3-bis(diphenylphosphino)propane (dppp, 0.126 mmol, 50 mg) and tBuONa (423 mg, 4.4 mmol). The reaction mixture was then heated to the boiling point under argon for 48h and then cooled to room temperature. After adding diethyl ether (20 mL) sediment was filtrated and the filtrate was evaporated under vacuum. Purification by flash column chromatography afforded the pure product; 0.44g (42%) yellow powder, m.p: 262 °C (dec). ^{1}H NMR (TMS, DMSO) δ: 11.04 (bs, 1H), 8.93 (d, $^3J_{HH}$ = 2.32 Hz, 2H), 8.39 (s, 4H), 8.33 (dd $^3J_{HH}$ = 5.88 Hz, 2H), 7.46 (dd $^3J_{HH}$ = 3.56 Hz, 2H). ^{13}C NMR (TMS, DMSO) δ: 155.99, 155.46, 153.46, 139.37, 137.39, 120.32, 119.47, 115.89. Anal. Calc. for $C_{16}H_{11}N_5$: C 70.32, H 4.06, N 25.63. Found: C 70.45, H 4.21, N 25.47.

1-(4-aminopyrimidin-2-yl)-3-isopropylurea

Compound was obtained by heating 2,4-diaminopyrimidine (1.1g , 10 mmol) and *i*-Pr isocyanate (1.7g, 20 mmol, 1:2 molar ratio) for 24 h under reflux in pyridine (15 ml). Then pyridine was removed under vacuum and the residual was recrystallized twice from methanol giving white powder 1.63 g product (yield 83%), m.p. 263.2-265.3. ^{1}H NMR (TMS, DMSO) δ: 9.27 (d, $^3J_{HH}$ = 7.52 Hz, 1H), 8.85 (bs, 1H), 7.85 (d, $^3J_{HH}$ = 5.84 Hz, 1H), 7.00 (bs, 2H), 6.01 (d, $^3J_{HH}$ = 5.84 Hz, 1H), 3.84 (m, 1H), 1.15 (d, $^3J_{HH}$ = 6.56 Hz, 6H). ^{13}C NMR (TMS, DMSO) δ: 164.02, 158.58, 155.15, 154.19, 99.29, 41.44, 23.38. Anal. Calc. for $C_8H_{13}N_5O$: C 49.22, H 6.71, N 35.87. Found: C 49.34, H 6.84, N 35.95.

1-(2-(3-isopropylureido)pyrimidin-4-yl)-3-phenylurea

The 1-(4-aminopyrimidin-2-yl)-3-isopropylurea (1g, 5.1 mmol) and 10 ml of phenyl isocyanate was heated for 7 days at 120 °C. After that, the mixture was cooled to room temperature, precipitate was filtered off and washed twice with absolute ethanol (2x50 ml) giving 1.1g (68%) of product as a white powder, m.p. 266.0 (dec). ^{1}H NMR (TMS, DMSO) δ: 10.48 (bs, 1H, H10), 9.92 (s, 1H), 9.80 (s, 1H), 8.60 (d, $^3J_{HH}$ = 6.52 Hz, 1H), 8.25 (d, $^3J_{HH}$ = 5.80 Hz, 1H), 7.67 (d, $^3J_{HH}$ = 7.72 Hz, 2H), 7.32 (t, 2H), 7.06 (t, 1H), 6.78 (d, $^3J_{HH}$ = 5.80 Hz, 1H), 3.87 (m, 1H), 1.17 (d, $^3J_{HH}$ = 6.52 Hz, 6H). ^{13}C NMR (TMS, DMSO) δ: 159.45, 157.54, 157.36, 153.61, 152.04, 138.85, 128.95, 123.8, 121.28, 101.82, 41.62, 23.29. Anal. Calc. for $C_{15}H_{18}N_6O_2$: C 57.31, H 5.77, N 26.74. Found: C 57.48, H 5.89, N 26.61.

Salts **D**-**K** were prepared as described elsewhere.2

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Samples preparation

Most experiments were conducted in DMSO-d_6, a polar and competitive solvent. Although the solubility of **1** in $CDCl_3$ was low it was still possible to carry out some ^{1}H NMR experiments. These spectra were measured but it is fair to mention that the signal to noise ratio was low. Nevertheless it was still possible to observe broad NH signals. The low solubility of **1** did not allow making the dilution experiment and calculation of its dimerization constant. To minimize the effect of water that may be present in any solvent or that could be added to the solution with organic compounds molecular sieves were used. All ^{1}H NMR titrations were conducted adding the solution of **1**:titrant with the use of microliter syringe to the solution of **1** of the same concentration of **1** as in mentioned mixture placed in NMR tube. Compounds used in titrations were kept in desiccator for 48h before use. The CIS (*Complexation Induced Shift*) values are calculated as a difference between chemical shift of the nucleus under question in free **1** and in its associated form with the guest:host ratio extrapolated to infinite concentration of guest molecule. The Benesi-Hildebrand[50] equation was used to fit the experimental data and calculate association constants (K_{assoc}) as before.[2, 6, 46]

DFT calculations

All optimizations have been carried out in Gaussian 09 with the use of M05 functional (to have the methodology comparable with previous data[2, 26]) and 6-311+G(2d,2p) basis set. The solvent was included in calculations based on PCM[51] model of solvation. For all structures frequency calculations were ran in order to characterize obtained geometry. To simplify computations we have used methyl groups instead of Ph and *i*Pr in **1** (obtaining **1'**) and acetate anion (AcO^-) as counterpart. Except transition states (TSs), for all structures (complexes and forms of **1'**) only real frequencies were obtained while for transition states there was one imaginary frequency present (pictures with imaginary frequency are collected in SI). Also, for **1'a**-**1'h** forms optimizations with DMSO molecule were carried out assuming the urea···OS double, bifurcated hydrogen bonding is preferred over singular NH···OS. The energy of intermolecular interactions ($E_{int.}$) was corrected to ZPE (zero-point energy) and BSSE (basis set superposition error) using counterpoise method implemented in Gaussian with default settings. This energy is defined as $E_{int.} = E_{(A,B)} - (E_{(A)}+E_{(B)})$ where $E_{(A,B)}$ is the energy of complex, $E_{(A)}$ – energy of counterpart A, $E_{(B)}$ – energy of counterpart B. The relative energies collected in tables below are corrected to ZPE. For calculation of hydrogen bond energy QTAIM (*Quantum Theory of Atoms In Molecules*)[52, 53] software was used. The computations-based CIS values (CIS_{theo}) were obtained as the difference between shielding of the nucleus in question in associated and in free form. It is worth to keep in mind that these numbers are related to model compound and the real solvent-solute interactions were not taken into account during optimization. Energy of hydrogen bonds (E_{HB}) was based on Espinosa approach.[54, 55]

Results and discussion

Association in solution

Table 1 collects the chemical shift data for **1** and its mixtures with chosen counterparts ($CDCl_3$). It is seen that **1** do not associate with **A**-**C** but the complex is formed with **G**. The triple mixture (**1**:**G**:**A**) was also recorded in $CDCl_3$. We have assumed (based on previous data[2]) that in chloroform solution **1** exist in **1a** form. This experiment was aimed to check if the geometrical preorganization (**1c**→**1d** isomerization upon complexation with **G**, Fig. 7) would allow binding **A** by triple hydrogen bonding.

Table 1. The chemical shifts of NH protons observed in mixtures[a] of **1** with **A-C** and **G**

1 or its complex	δ [ppm]	δ [ppm]	δ [ppm]
1	11.45	9.78	9.05
1:G	12.55	11.99	9.25
1:A	11.45	9.77	9.04
1:B	11.45	9.78	9.05
1:C	11.44	9.77	9.04
1:G:A	not observed	9.62	9.00

[a] - In all experiments [**1**]:[guest] ratio was from ca. 1 to ca. 2.

In fact, small changes of the chemical shifts were observed for triple mixture **1:G:A**. It is fair to note that the given chemical shifts (Table 1) are not assigned to specific protons in **1**. That shows how the solubility issues complicate full interpretation.

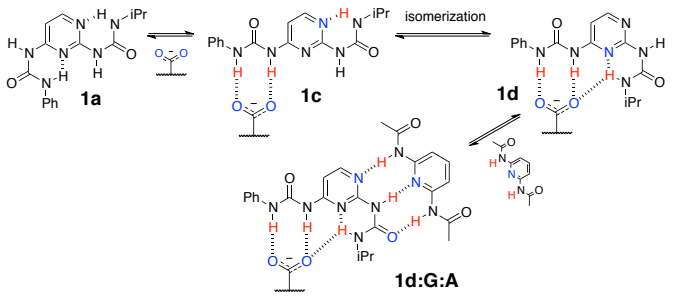

Figure 7. Triple complexation of **1** in chloroform

The fact that one NH signals is not observed in **1:G:A** mixture suggest fast in NMR timescale equilibrium that may be caused by association/dissociation of **1d**:**G**:**A** complex together with rotational equilibrium in **1** (**1c** vs. **1d**). Most probably, the association with **G** takes place in NHCONHPh part of **1** and the fast equilibrium between forms **1c** and **1d** exists. The binding of **A** to **1** already hydrogen bonded to **G** is seen in chemical shift change from 9.78 in pure **1** to 9.62 in **1:G:A** mixture (compare δ=11.99 for **1**:**G**). The results show that investigated compound is stabilized by intramolecular hydrogen bonding in $CDCl_3$. The fact that NHCONHPh part of **1** bind anion more effectively may come from formation of H14···N1 and H14···N3 hydrogen bonds by NHCONHiPr moiety. The NHCONHPh moiety may form only one intramolecular hydrogen bond.

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Thus independently form the rotameric state of NHCONHPh moiety the NHCONHiPr one is always able to form intramolecular hydrogen bond that prevents anion association by this part of molecule. It is worth to mention that association in $CDCl_3$ may also be lowered by dimerization of **1**.

Since the solubility of **1** in chloroform is very low we used DMSO to further study the electronic effect of substituent and influence of the number of hydrogen bonds on association. The dilution experiments showed that **1** does not dimerize in DMSO solution due to high competitive character of that solvent. This is reasonable since dimerization of **1** could only be possible by formation of two or three intermolecular hydrogen bonds (Fig. 8) and under condition that two various rotamers coexist in solution simultaneously.

The association of **1** with chosen counterparts was performed as before[2, 41] by ^{1}H NMR titrations (see ESI for example spectra and *Experimental* section for details). Table 2 collects the association constants (K_{assoc} [M^{-1}]) for complexes (Fig. 9) of **1** and values of CISs. The same table contains the correlation coefficient (*R*) between Hammett substituent constant (σ_{para}) and K_{assoc}/CIS values.

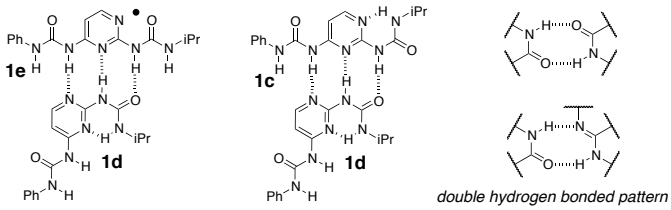

Figure 8. The examples of dimers of **1** and double hydrogen bonding patterns

Table 2. The association constants (K_{assoc}) and CIS values based on various protons

R	σ_{para} [a]	K_{assoc}, CIS H10	K_{assoc}, CIS H7	K_{assoc}, CIS H11	K_{assoc}, CIS H14	K_{assoc}, CIS H5
NMe_2	-0.83	400, 2.10	470, 3.18	420, -0.65	420, 0.71	450, 0.36
OMe	-0.27	250, 2.03	270, 3.11	250, -0.70	250, 0.69	200, 0.34
Me	-0.17	220, 2.00	230, 3.06	220, -0.63	220, 0.72	180,[b]
H	0	220, 1.75	220, 2.67	230, -0,55	230, 0.60	210, 0.36
F	0.06	220, 1.92	220, 2.19	210, -0.54	220, 0.59	220, 0.35
Cl	0.23	180, 1.49	180, 2.31	180, -0.51	160, 0.55	180, 0.34
CF_3	0.54	90, 1.34	90, 2.12	100, -0.41	85, 0.50	110, 0.30
NO_2	0.78	78, 1.03	75, 1.61	75, -0.38	70, 0.40	78, 0.27
R[c]		*0.98, 0.92*	*0.97, 0.91*	*0.98, 0.90*	*0.98, 0.92*	*0.91, 0.82*

[a] – substituent constant taken from ref. [56], [b] - overlapped with other peaks, [c] - correlation coefficient

It is worth noting that association of **1** with substituted benzoates in DMSO is an order of magnitude higher that association of similar heterocyclic urea with the same anions in $CDCl_3$.[2] This shows the solvent is an important factor influencing intramolecular hydrogen bonding and thus association. Comparison of the current data with the $CDCl_3$-derived suggests that polar solvent, albeit competitive, may act as a medium that shifts the conformational equilibrium towards forms without strong intramolecular hydrogen bonds. The data in Table 2 show the association constants of **1** with benzoates are dependent on the character of substituent. Since titrations were prepared in separate experiments and salts used may be hygroscopic to variable extent high correlation coefficients (*R*) suggest that water does not influence association significantly. However, it is worth to keep in mind that this is not a general rule. Here a minimized water influence may be explained by solvation of water molecules by basic DMSO-d_6 much better than anions forming hydrogen bonds with urea moiety.

Regarding, the values of CIS, those are much higher for H7/H10 than that for H11/H14. The absolute value of the averaged ratios of CIS(H10)/CIS(H14) and CIS(H7)/CIS(H11) are equal to 2.85 and 4.09, respectively. This clearly shows that association is much preferred by interaction with H7/H10 protons. This is further confirmed by the CIS value for H5 (aromatic CH) comparable to the values reported previously for N-(pyridin-2-yl)-N'-alkyl ureas[2] (molecular anisotropy of C=O group, Fig. 9). Anyway, the changes of chemical shift of H5 prove the conformational change depicted in Fig. 9 is present in DMSO.

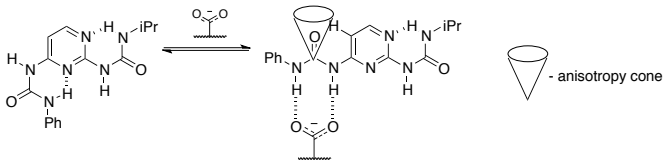

Figure 9. The magnetic anisotropy of C=O group and its influence on the chemical shift of H5

The isomerization preferably takes place in the urea moiety attached in 4 position (major interaction) of the pyrimidine core. To verify this and to probe for simultaneous isomerization at 2- and 4- positions we have used another compounds that fit hydrogen-bonding pattern of **1** (Fig. 6).

Unfortunately compounds **A**-**C** did not associate with **1** in DMSO. Repeating the triple complexation (Fig. 7) in DMSO also gave negative results. Thus, only anionic counterparts associate with **1** in highly polar solvent.

To have a deeper insight into the nature of urea moieties in **1** in various environments another experiments were conducted. Thus the first one was recording VT (variable temperature) ^{1}H NMR spectra in $CDCl_3$. It was concluded that the molecule exist in form **1a**. This can be seen in splitting NH signals into doublets (temperature decrease) due to slowed rotation about single bonds in **1**. At the same time NH signals did not change chemical shifts much ($\Delta\delta_{max}$ = 0.2 ppm for the most deshielded proton). This means that the structure of **1** is rigidified by intramolecular hydrogen bonding in $CDCl_3$. Next, to check what is the influence of competitive solvent (DMSO-d_6) on **1** the titration of subjected compound using this solvent was performed in $CDCl_3$ reaching the ratio of 1:1 ([**1**]:[DMSO-d_6]). At this point salt **G** was added gradually to check if DMSO competes effectively with **G** for association with **1**. The addition of DMSO-d_6 to the $CDCl_3$ solution of **1** caused chemical shifts of NH protons to decrease (Fig. 10). This was caused by breakage of the intramolecular hydrogen bonding or dissociation of $\mathbf{1}_2$. The presence of DMSO-d_6 in chloroform solution confirmed the influence of basic solvent molecules on conformational/dimeric state of **1**. The interaction of **1** with **G** is evident in chloroform solution also in the presence of DMSO. The chemical shift of H7 proton increased during titration of the **1**:DMSO mixture in $CDCl_3$ with **G**. Overall effect is as follows: proton H7 changes chemical shift from 11.4 to 9.8 ppm (DMSO-d_6 addition) and then to 11.1 ppm (addition of **G**), while H10 changes from 9.0 to 8.7 and then to 9.2 ppm. The changes of chemical shifts for these two protons are different by size because for H7 the hydrogen bonding changes from *inter*molecular-neutral (within the $\mathbf{1}_2$) to *inter*molecular-anion (complex with **G**), while for H10 *intra*molecular-neutral hydrogen bond changes to *inter*molecular-anionic. The chemical shift of the latter proton does not change much taking into account the data from 1:1 [**1**]:[DMSO-d_6] ratio to 1:1:1 [**1**]:[DMSO-d_6]:[**G**]. For remaining NH protons the decrease of chemical shift during sequential DMSO-d_6 and **G** titration was observed. Moreover, change in conformational state (rotation around N11-C12 bond) of NHCONHiPr moiety causes the electronic repulsion (**1b** form, for example, Fig. 3) between O13 and N1 or N3. This, for sure, destabilize such structure shifting the equilibrium towards form stabilized by intramolecular hydrogen bonding (H14···N1 or H14···N3).

Fig. 10 presents the change in NH chemical shifts during addition of DMSO-d_6 and then **G** (H7, H10 and H14) showing DMSO is a solvent that causes dissociation of $\mathbf{1}_2$ and, most probably, weakens intramolecular hydrogen bonding *preparing* the molecule of **1** for anion binding.

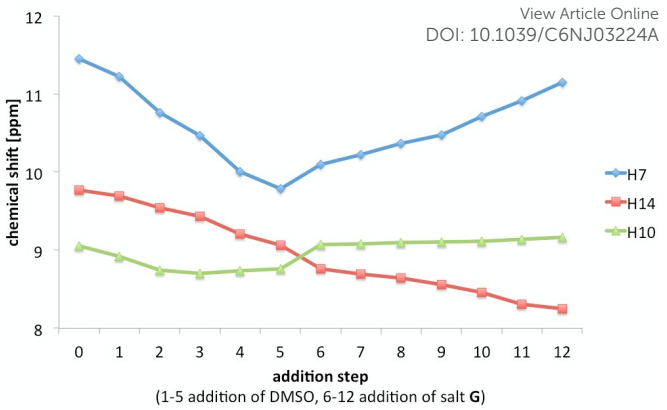

Figure 10. The chemical shifts observed during addition of DMSO-d_6 and next salt **G** to chloroform solution of **1**

Modelling structure of complexes by DFT calculations

Since experimental data deliver information on averaged picture of equilibria in solution a series of computations were carried out to understand said processes. Thus, first of all, to evaluate the ^{1}H NMR data we calculated the shielding of nuclei in **1'** in its various forms (Fig. 3) and respective complexes. In case of **1'e** two associated structures were used, i.e. the acetate anion hydrogen bonded to urea moiety attached in 4 position (**1'e**-left) and in 2 position (**1'e**-right). The shielding of the nuclei involved in hydrogen bonded (NHs) and aromatic proton (H5) were used to calculate CIS_{theo} (Table 3).

Table 3. The calculated CIS_{theo} values for complexes of rotamers of **1'** with AcO^-

	H10	H7	H11	H14	H5
1'b	0.45	-0.31	5.34	5.33	-0.23
1'c	5.73	5.26	-0.17	-0.02	0.15
1'd[a]	5.46	5.99	-0.23	0.51	0.11
	1.75	*2.67*	*-0.55*	*0.60*	*0.36*
1'e-left	5.63	5.46	-0.01	-0.02	0.11
1'e-right	0.00	-0.01	4.91	5.64	-0.22
1'f	0.37	-0.08	4.97	5.47	0.05
1'g	5.47	5.93	-0.09	0.34	0.49

[a] – in *italics* the experimental values are given for comparison

From the data above it is easy to see that in two cases (**1'd** and **1'g** forms) only one negative CIS_{theo} value is present (H11). The same was observed in experiment. That may be caused by de-solvation of **1** upon complexation or may suggest the NHCONHiPr part of **1** does not change its conformation. The last possibility may explain the negative CIS value for H11. This is because the magnetic anisotropy of the phenyl ring that is in proximity of H11 in form **1a** do not influence its shielding in form **1c/1d**. At the same time the order of the CIS_{theo} values for **1d** resembles that coming from experiment (Table 2 and shape of bars in Fig. 11).

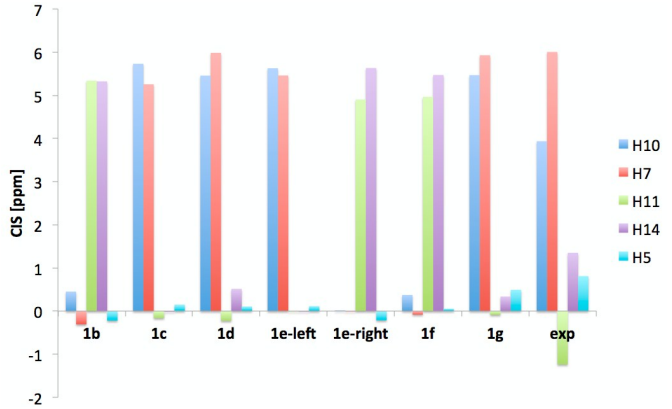

Figure 11. Experimental (exp) values of CIS normalized and compared to CIS_{theo} for rotamers

The said similarities in CIS values suggest compound **1** exist in **1d** form in complex with anions. As mentioned above the chemical shift of H5 changes upon complexation due to proximity of CO group (Fig. 9) and the same is observed in CIS_{theo} data.

Thus, the energy of forms was calculated and the same was done for interaction energy (Table 4) together with the geometrical transition states (vide infra) related to rotation about single bonds.

Table 4. The relative energy (E_{rel}, kJ/mol) for model associates of **1'** with acetate anion and the energy of intermolecular interaction (E_{int}, kJ/mol)

Form	E_{rel}	E_{int}
1'b	18.6	-53.8
1'c	6.0	-49.2
1'd	0.0	-56.9
1'e-left	32.5	-46.9
1'e-right	11.9	-67.5
1'f	14.1	-46.6
1'g	6.1	-56.4
1'h	16.8	-53.2

The energies of interaction collected in Table 4 are comparable to those reported in our previous publication.[2]

The next step was to evaluate the data related to hydrogen bonding preferences based on QTAIM. This methodology[54, 55] was used to study the energy of individual intra- and intermolecular interactions (Table 5). The labels "bif" and "intra" refer to protons that form *bifurcated* hydrogen bond interaction with acetate oxygen and *intramolecular* hydrogen bond with nitrogen atom of heterocycle (see example in Fig. 7 - form **1d**). The ΣE_{HB} is the summarized energy of all intermolecular hydrogen bonds that stabilize complexes. For all hydrogen bond critical points the positive Laplacian was found proving the interaction is of closed-shell hydrogen bond nature.[52, 57]

Table 5. The energy (E_{HB}, kJ/mol) of hydrogen bonds in **1'** and its associates with acetate anion

Form	E_{HB} H11/H7	E_{HB} H14/H10	E_{HB} H10/H14^{bif}	E_{HB} H10/H14^{intra}	ΣE_{HB} intermol.
1'b	-33.6	-33.0	-7.5	-24.7	-74.1
1'c	-33.0	-34.4	-	-28.8	-67.5
1'd	-36.1	-34.1	-6.9	-24.9	-77.1
1'e-left	-33.7	-33.6	-	-	-67.3
1'e-right	-31.2	-33.5	-	-	-64.7
1'f	-32.5	-33.0	-	-30.4	-65.5
1'g	-37.9	-34.1	-	-30.9	-72.0
1'h	-37.2	-33.4	-	-28.1	-70.5

The data in Table 5 show that the highest ΣE_{HB} is obtained for **1'd** but this is still very close to that of **1'b** and **1'g** complexes with AcO^- suggesting coexistence of these forms. It is worth mentioning that ΣE_{HB} for **1'b** and **1'd** are higher than other values due to presence of relatively weak, bifurcated hydrogen bonding (vide supra).

There are number of rotameric paths joining respective forms of **1**. Each step in these paths is represented by rotation about single bonds. To study these the rotational transition states were optimized for **1'** and **1':AcO$^-$** complexes. First, to have an insight into the stability of forms **1'a**-**1'h**, the relative energy was calculated (Table 6).

Table 6. The relative energy [kJ/mol] for forms **1'a**-**1'h**

Form	E_{rel}
1'a	0.0
1'b	25.2
1'c	8.0
1'd	9.7
1'e	32.3
1'f	13.5
1'g	15.4
1'h	22.9

Then, forms that are on the path from **1'a** to the structure **1'd** in the complex (the most probable taking into account experimental data) were considered taking into account the least number of rotations about single bonds. The following reactions were assumed: **1'a** → **1'h**, **1'h** → **1'g**, **1'h** → **1'c**, **1'c** → **1'd**, **1'a**→**1'b**. It is worth mentioning that: *a*) in **1'h** and **1'b** forms a strong N/O repulsion exists, *b*) form **1'h** is necessary to reach **1'c** before **1'd** can be stabilized by bifurcated hydrogen bonding (Fig. 12).

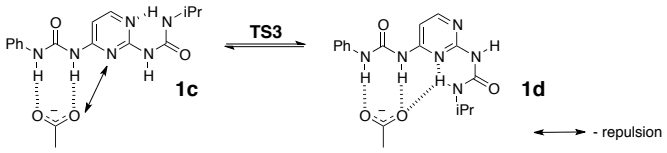

Figure 12. The final reaction with the repulsion replaced by hydrogen bonding showing conformational "lock" by bifurcated hydrogen bond

Form **1'e** was excluded as the one with the highest energy. The **1'h** form as a complex with anion was excluded from part of computations since the barrier between **1'h**:AcO^- complex and its TS was very low. Also **1'g** was not taken into account as a

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complex with AcO^- because in this rotamer the experimentally observed deshielding of H5 would not be possible (see Fig. 9). Tables 7 and 8 collect data related to the energy of respective transition states, while Fig. 13 is a graphical representation of rotational equilibriums. The more negative the number in Table 7 the higher barrier of transition is (more stable respective forms are).

Table 7. The energy of rotamers of **1** in relation to respective transition state [kJ/mol]

Reaction	TS	Substrate	Product
1'a[a] → **1'b**[b]	**TS1**	-37.1	-11.9
1'a → **1'h**	[c]	-1.4	-21.6
1'h → **1'g**	[d]	-56.2	-48.7
1'h → **1'c**	**TS2**	-22.8	-37.7
1'c → **1'd**	**TS3**	-47.9	-46.2

[a] - substrate, [b] – product, [c] – very small barrier - may be considered as spontaneous process, [d] – the highest barrier not considered further

The **1'd:AcO**$^-$ complex has the lowest energy, while the fast in NMR time-scale equilibrium is related to forms and associates within some energy barrier ca. 60 kJ/mol (the values close to $E_{int.}$ presented in Table 4).

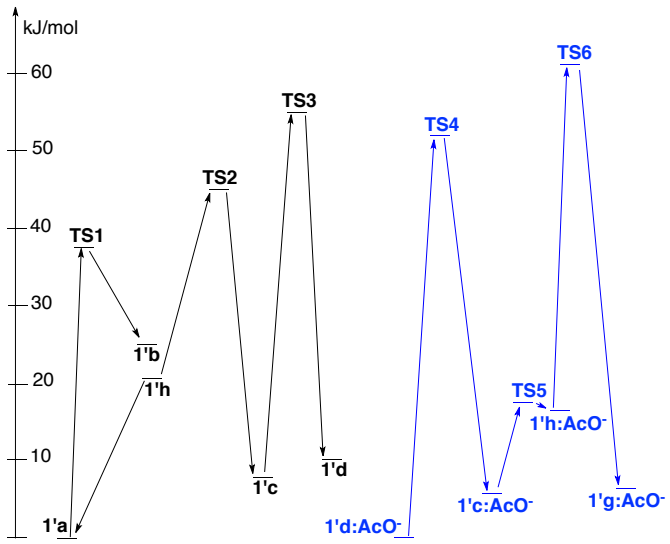

Figure 13. The energy diagram for rotameric equilibriums in **1'** and its complex with acetate (in blue)

Table 8. The energy of complexes of rotamers of **1'** with AcO^- in relation to respective transition states [kJ/mol]

Reaction	TS	Substrate	Product
1'd:AcO$^-$[a] → **1'c:AcO**$^-$[b]	**TS4**	-52.8	-46.9
1'c:AcO$^-$ → **1'h:AcO**$^-$	**TS5**	-11.6	-0.8
1'h:AcO$^-$ → **1'g:AcO**$^-$	**TS6**	-45.8	-56.5

[a] - substrate, [b] – product

Except for **1'h:AcO**$^-$-to-**TS** reaction the barrier between forms associated with acetate is ca. 45 to 56 kJ/mol. The very low barrier for **1'h:AcO**$^-$-to-**TS** is caused by the electronic repulsion between lone electron pairs located at N3 and O9 of the carbonyl group. Since value of the energy of this transition state is low it is very probable that process is spontaneous, but from the geometrical point of view form **1'h** is needed to consider path between other forms with **1'h** as a mid-product.

Calculations for complexation of AcO^-, in general, support the experimental findings. We have also optimized other complexes that were tested for association experimentally. These are: **1'e:C**, **1'f:C**, **1'c:B**, **1'd:A** (Fig. 6) and also **1'd:AcO**$^-$**:A** (Fig. 7). The other ones (**1'e:B** and **1'c:A**) were not taken into account due to the steric and electronic repulsion. Some additional discussion on triple complex was placed in ESI.

To have a fuller view on hydrogen bonding preferences conformers were optimized with DMSO molecule as a hydrogen-bonding counterpart. Table 9 shows the interaction energy for those and QTAIM-based hydrogen bond energies.

The data in Table 9, when compared to those in Table 5 suggest the energy of interaction between rotamers of **1'** and acetate anion or DMSO molecule is comparable. This may be explained by the fact that DMSO molecule has a highly dipolar character and the sulphur-oxygen bond is polarized with partial negative charge located at the oxygen atom. On the other hand the sum of the hydrogen bond energies for these two types of complexes is much higher in case of complexes with acetate. This shows the hydrogen bonding with anions is stronger than with neutral molecules and is in agreement with the common knowledge about hydrogen bonding. Moreover the acetate carrying two oxygen atoms fits much better to the geometry of the NHCONH moiety than DMSO molecule. It is worth remembering that in case of DMSO two hydrogen bonds points towards one oxygen atom. That interaction is not favored by entropy. On the other hand, in experiment the number of DMSO molecules in the solvation shell of **1** is large as opposite to the number of anionic species coming form salts. However, several factors influence the association of **1** *a*) effect of the solvent that dissociate dimers of **1**, *b*) solvent assisted weakening of intramolecular hydrogen bonds, *c*) better solvation of compounds carrying hydrogen bond donors than anionic species leading to prohibition of complex formation between neutral molecules.

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Table 9. The $E_{int.}$ (kJ/mol) between rotamers of **1** and DMSO molecule and E_{HB} (kJ/mol) for these complexes

Complex	$E_{int.}$	E_{HB} H7/H11	E_{HB} H10/H14	ΣE_{HB} [a]
1'b:DMSO	-61.0	-24.4	-19.0	-43.4
1'c:DMSO	-36.1	-24.6	-19.0	-43.6
1'd:DMSO	-45.0	-24.4	-20.1	-44.5
1'e:DMSO (left)	-60.6	-23.7	-19.5	-43.2
1'e:DMSO (right)	-70.4	-21.8	-20.0	-41.8
1'e:DMSO (left and *right*)	-75.1	-23.6	-19.9	-43.5
		-22.8	*-19.6*	*-42.4*
1'f:DMSO	-33.8	-26.9	-17.0	-43.9
1'g:DMSO	-50.1	-25.6	-19.0	-44.5

[a] – sum of the hydrogen bond energy per one DMSO molecule

Conclusions

The molecular *flexibility* and the tendency to form intramolecular hydrogen bonds is a main driving force in stabilization of one conformation over another in equilibrium state. Other molecules, however, may perturb this equilibrium by intermolecular hydrogen bonding. This was observed for the current system where two intramolecular hydrogen bonds are present in the most stable form of 1-(2-(3-isopropylureido)pyrimidin-4-yl)-3-phenylurea. The rotational equilibrium of two urea arms may be influenced by variety of counterparts but in polar solution only anions are able to act like that. Even bis(1,8-naphthyridin-2-yl)amine that should be able to form five intermolecular hydrogen bonds did not associate with **1**. This is, most probably, due to the fact that *a*) two intramolecular hydrogen bonds should be broken and *b*) solvation of counterparts in polar DMSO solution. This shows that interaction with anions is preferred over interaction with neutral compounds even if much more hydrogen bonds would stabilize neutral complex. Based on the titration data, complexation induced shift and computations we concluded that benzoates changes the conformation of urea moiety attached in 4 position of pyrimidine preferably over one at 2 position. This, in turn, suggests that if the molecular probe is going to be designed the sensing/interacting part of the pyrimidine should be placed in 4 position.

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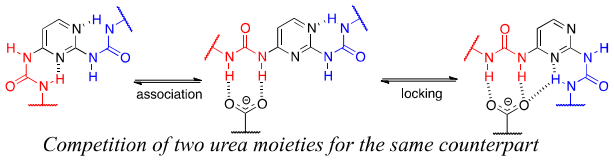

Competition of two urea moieties for the same counterpart including change of conformation upon binding in polar solvent.