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Association of *N*-(Pyridin-2-yl),*N*′-substituted Ureas with 2-Amino-1,8-naphthyridines and Benzoates: NMR and Quantum Chemical Studies of the Substituent Effect on Complexation

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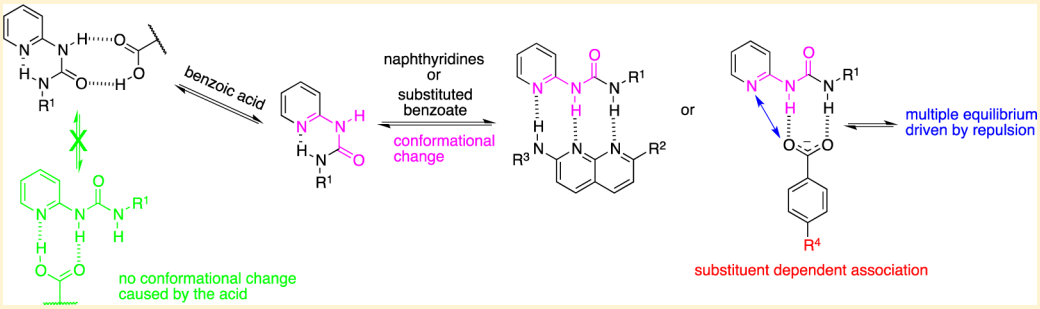
Supporting Information



ABSTRACT: Association of four *N*-(pyridin-2-yl),*N*′-R[1]-ureas (R[1] = ethyl, *n*-butyl, phenyl, and *tert*-butyl) with substituted 2-amino-1,8-naphthyridines and benzoates were studied by ^{1}H NMR spectroscopic titrations and quantum chemical calculations. The benzoates and 2-amino-1,8-naphthyridines were selected as representatives of double and triple hydrogen bonding counterparts, respectively. The classical substituent effect on the association was studied. A prerequisite and a crucial step for the complex formation was the breaking of the intramolecular hydrogen bond in urea derivatives. The QTAIM calculation method was employed to explain the hydrogen bonding within complexes. In the case of benzoates carrying an electron-donating substituent the experimental findings were explained by the formation of two complexes. These observations were rationalized by the electronic repulsions between atoms in a close proximity and further verified by calculations. Single-crystal X-ray diffraction was used to confirm the structure of studied ureas in the crystalline state. These results are in line with the solution studies of self-association of ureas.

INTRODUCTION

Hydrogen bonding is one of the most often studied noncovalent interactions. Its existence is essential to many reactions and the self-organization of molecules in solution and solid state. Generally, it is possible to apply known intermolecular interactions[1−3] in a predictable way to tailor molecular sensors/receptors,[4−17] control the organocatalysts inside molecular capsules,[18−21] cause reactions driven by hydrogen bonding in cases such as thioureas,[22−24] and design crystal structures[25−32] and noncovalent polymers.[33,34] Further, hydrogen bonding as an attractive interaction is responsible for the secondary structure of proteins and is crucial for the formation of the DNA double helix. It also affects tautomerism.[35,36] The conformational preference of a molecule can change due to the competition between intra- and intermolecular interactions. Examples are compounds that possess intramolecular hydrogen bonding[37−47] (Scheme 1). On the other hand, molecules that are not able to form such stabilizing interactions are potent in forming variable complexes depending on their rotameric state.[48] According to Etter's rules[49] intramolecular hydrogen bonding is generally stronger than the intermolecular one. Such a competition between intra- and intermolecular hydrogen bonding is common in urea derivatives.[50,51]

The stability of hydrogen-bonded complexes depends on many factors such as the strength and the number of intermolecular hydrogen bonds,[1] the character of the hydrogen bond donor (D) and acceptor (A),[49] secondary interactions (SIs, as introduced by Jorgensen and Pranata[52]), steric effects,[53−57] and competition with solvent molecules. Recently we have demonstrated that even the relatively small methyl group is able to influence interactions in the solution[57] and to determine the crystal structure.[53] Also the size of the cycloalkyl ring plays a role in association.[56] Since our group has studied the steric effects that drive the association, we decided to focus

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Scheme 1. Association after the Breaking of Intramolecular Hydrogen Bonds

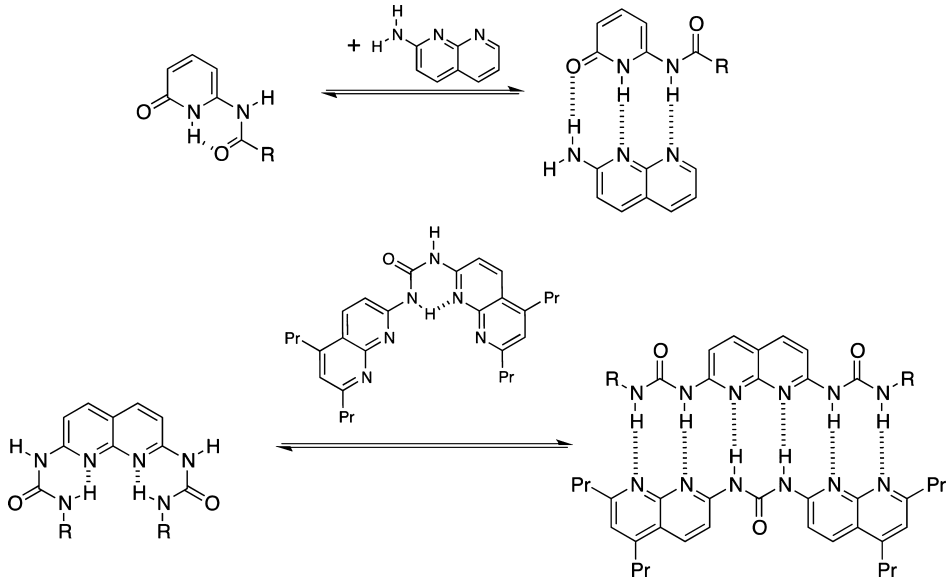
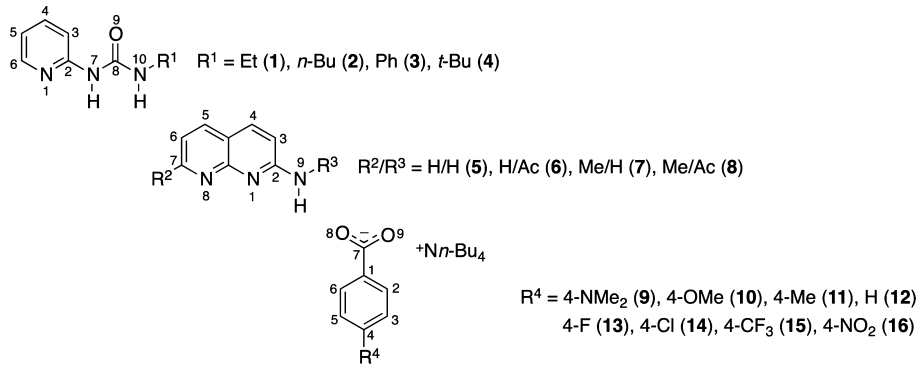


Chart 1. Structure of Compounds and Their Atom Numbering



also on the electronic effects. To the best of our knowledge, these have not yet been extensively studied. Although some attempts to study the effect of the substituent on intermolecular interactions have been made, none of these were systematic with more than five various substituents,[58−60] especially when one considers conformationally free substituted urea derivatives. Some reports on the functionalization of urea derivatives[16,61−64] or phenolates[65] and phenols[66−68] and its influence on the association are known. However, benzoates are less used, and in a parent benzoate among other anions[69] the interaction was supposed to be due to π-stacking.[70] The high quality review by Cooke and Rotello[71] covers generally the modification of molecules to tune their noncovalent interactions. The current work is focused on the conformational changes of heterocyclic urea derivatives and their influence on the association with substituted 1,8-naphthyridines and benzoates. In Chart 1 are depicted the studied compounds with their atom numbering.

There are publications on R-CO_2^- anion binding; however, none of these treat in a systematic way the effect of a substitution of the carboxylate on the association.[58,69,72]

The aim of the current study is to answer the question whether changes in the substituent size (Me and Ac groups in 1,8-naphthyridines) can influence the association and if the electronic properties of the urea counterparts (benzoates) influence its conformational preferences and the association of these compounds.

RESULTS AND DISCUSSION

Dimerization. All heterocyclic urea derivatives **1**−**4** form intramolecular hydrogen bonds resulting in a *Z*,*E*,*Z* conformation (bonds C2−N7, N7−C8, and C8−N10, respectively), which is confirmed by single crystal XRD for **1**−**3**. Figure 1 shows as an example the X-ray structure of the dimer of **2**, in which the *Z*,*E*,*Z* conformation with intramolecular hydrogen bonding the S(6) graph set[73] motif is clearly observed.

The ^{1}H NMR-monitored sample dilutions suggest that the same structures are present in solutions also. For **1**−**4** the chemical shift of H7 (NH) changes with concentration more than $\Delta\delta$ = 2.0 ppm, while the chemical shift change for H10 is below 0.1 ppm. Thus, the dimers of **1**−**4** are held together by two NH···O hydrogen bonds as depicted in Chart 2, which is in agreement with Etter's rules. Similar dimers have been described before in the solid state[44,46,47,50,74−78] and have been studied as compounds capable of interaction by four hydrogen bonds.[46,79] The single-crystal structure also shows the existence of two intermolecular NH···O interactions and an overall $R_2^2(8)$ motif (Figure 1). The $R_2^2(8)$ refers[73] to an eight-

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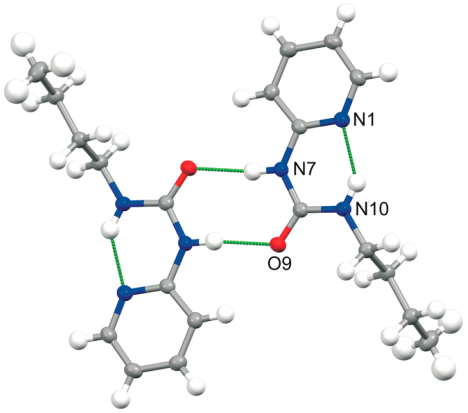
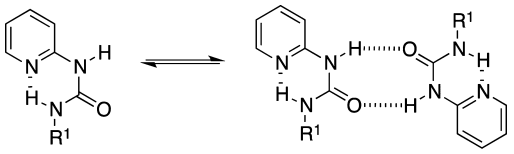


Figure 1. A hydrogen-bonded dimeric crystal structure of **2**. Hydrogen bonds are shown as dotted lines.

Chart 2. Dimerization of 1−4



membered (8) ring (*R*) stabilized by two hydrogen bond acceptors (^{2}) and two donors ($_2$) as shown in Chart 2.

Dilutions were also performed for **5**−**8**. Table 1 collects the dimerization constants (K_{dim} [M^{-1}]) and complexation-induced shift values (CIS [ppm]) for compounds **1**−**8**.

Table 1. K_{dim} [M^{-1}] and CIS[a] [ppm] for 1−8

	K_{dim}	CIS
1	23	2.08
2	24	2.07
3	50	2.06
4	26	2.13
5	2.50	0.62
6	5	1.51
7	1.50	0.22
8	5.50	0.97

[a]Values based on the chemical shift at the initial concentration and at a concentration 40 times higher.

The data in Table 1 show that the dimerization is weak for **1**−**4** and very weak (nearly undetectable by ^{1}H NMR) for **5**−**8**. However, it is worth mentioning that compounds carrying the acetyl group (**6**, **8**) may form various dimers (Chart 3).

The dimer $\mathbf{6}_2$−**2** is stabilized by the same interactions as in dimers of **1**−**4** (NH···O hydrogen bonds). This dimer is formed via easy rotations around the C2−N9 and N9−C(O) bonds.[48] Thus it is assumed that dimers $\mathbf{6}_2$−**2** and $\mathbf{6}_2$−**3** are slightly more stable (Etter's rules) than $\mathbf{6}_2$−**1** (see later) but need amide moieties to adopt the *E* conformation. Higher CIS values and slightly higher association constants for dimerization of **6**/**8** compared with that for **5**/**7** may be caused by (a) increased acidity of the NH proton due to acylation and (b) the tendency to form dimers $\mathbf{6}_2$−**2** or $\mathbf{6}_2$−**3**. This is further confirmed by the fact that in compounds **5** and **6** very similar changes of the chemical shift of H3 are observed upon dimerization. This means that the C═O group is most probably in a rotameric state similar to dimer $\mathbf{6}_2$−**2** (*Z*,*E*). If the dimer preferred were $\mathbf{6}_2$−**1** (*E*,*Z*) the association would cause significant changes in the H3 chemical shift. For the effect of the close proximity of H3 of the pyridine ring and the C═O group, the reader is referred to the NMR data in our previous publications.[80,81]

Heterocomplexation. Some papers report analogous conformational changes in urea derivatives driven by the association with proper counterparts.[42,44−46,79,82,83] The association of **2** with 2-amino-1,8-naphthyridine derivatives by three hydrogen bonds is depicted in Chart 4.

Chart 4. Conformational Change of *N*-(Pyridin-2-yl),*N*′-*n*-butylurea by Association with 2-Amino-1,8-naphthyridine Derivatives

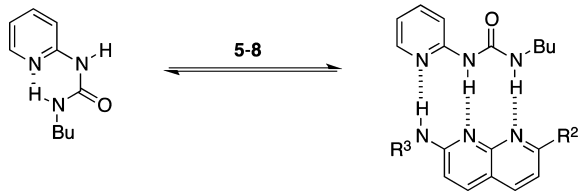


Table 2 collects the association constants (K_{assoc} [M^{-1}]) and CIS values [ppm] for proton H9 of **5**−**8** (titration curves are collected in Supporting Information).

Table 2. K_{assoc} [M^{-1}] and CIS [ppm] for Complexes of 1−4 with 5−8

	1		**2**		**3**		**4**	
	K_{assoc}	CIS	K_{assoc}	CIS	K_{assoc}	CIS	K_{assoc}	CIS
5	11.5	0.50	12	0.47	20	0.79	11	0.23
6	14	0.88	12	0.85	18	1.01	12	0.88
7	11	0.36	11	0.35	20	0.43	8	0.13
8	15	1.09	14	1.04	19	1.13	14	1.04

Chart 3. Possible Dimers of 6 and 8

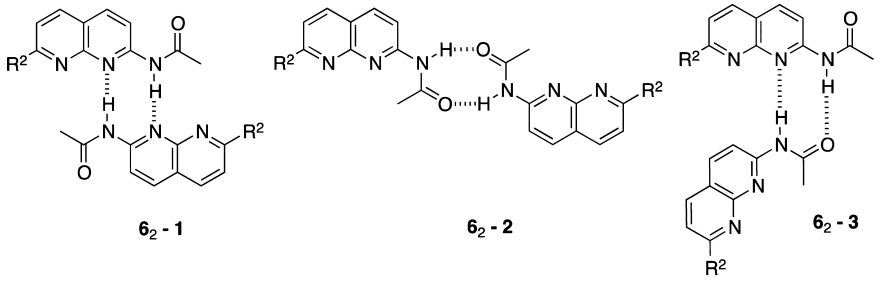


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Chart 5. Conformational Change in 1−4 Induced by Carboxylic Acids and Their Anions

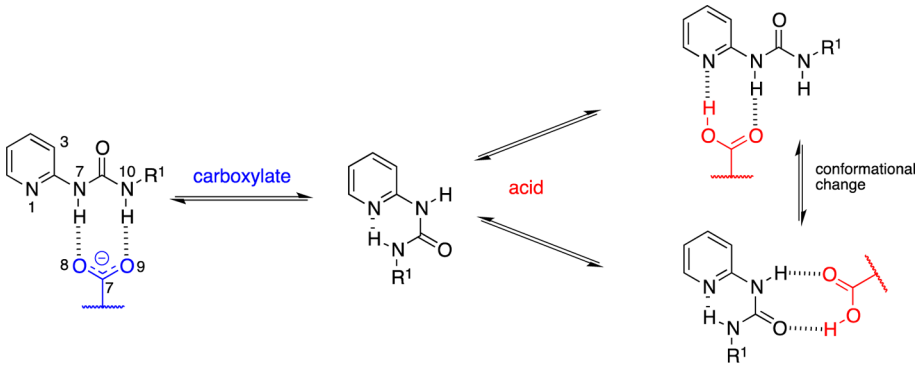


Chart 6. δ(H7), δ(H10), and δ(H3) of 2 as a Function of [Guest (12/12′)]/[Host (2)] Molar Ratio

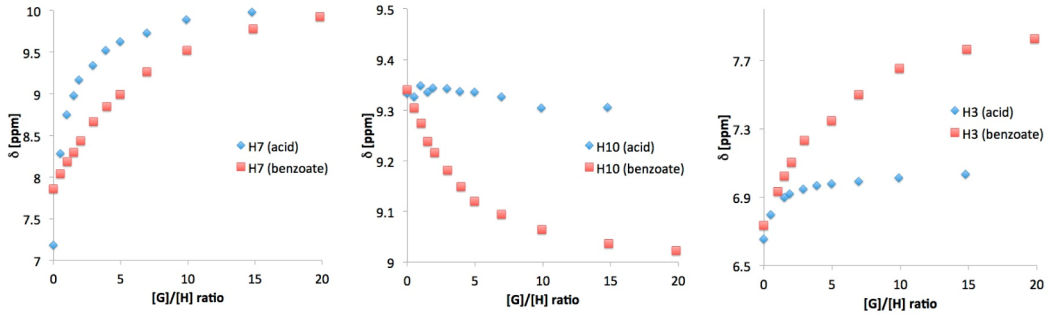
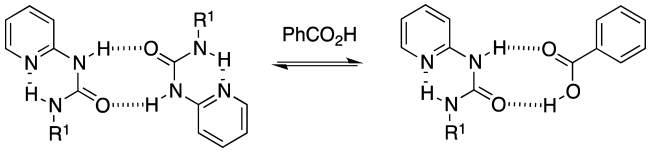


Table 2 reveals that the K_{assoc} values are similar for all **1**−**4**/**5**−**8** pairs and in agreement with the previous data,[37,44,53,57,84,85] while the CIS values vary from one compound to another. In general, CIS values are higher for amides than for amines. The association constants are lower than in other triply hydrogen-bonded complexes[42,79,85] due to the stabilization of the *Z*,*E*,*Z* isomer of ureas **1**−**4** by intramolecular hydrogen bonds. The conformational change in ureas caused by triple intermolecular hydrogen bonding (Chart 4) is realized almost independently from R^2 and R^3, showing that all ureas studied fit the triple AAD hydrogen bonding motif of 2-amino-1,8-naphthyridines.

An interesting question is whether double hydrogen bonding is strong enough to cause the conformational change in urea derivatives as shown in Chart 5.

Compound **2** was chosen and titrated with benzoic acid (**12′**), showing a clear influence on δ(H7), but δ(H10) remained practically unchanged, whereas with benzoate titration both δ(H7) and δ(H10) changed significantly (Chart 6a/b). δ(H3) of **2** behaves similarly in a titration with **12′** and in dilution experiments for **2** ($\Delta\delta$ = 0.30 ppm and $\Delta\delta$ = 0.38 ppm, respectively), while in the case of benzoate the effect was larger ($\Delta\delta$ = 1.1 ppm, Chart 6c). The changes of δ(H3) upon titration with an acid may be driven by two effects: (a) the change in the rotameric state and the magnetic anisotropy of C═O of **2** resulting in a deshielding of H3 (Chart 8 later in text) or (b) the higher fraction of **2** that is associated by hydrogen bonding with **12′** than in **2** as a neat compound (dimerization). The lack of change of δ(H10) in **2** upon titration with **12′** suggests that the conformation of **2** is not changed by benzoic acid (Chart 7). This conclusion is further supported by the higher value of K_{assoc} for **2**/**12′** than the K_{dim} for **2**. It is clearly seen (Chart 6a) that the

Chart 7. Complex of 2 with 12′ (K_{assoc} = 190 M^{-1})



conformational change that must precede association with carboxylate makes the titration curve for H7 less steep than in the titration by acid.

Because of the different behavior between anion and acid, it is reasonable to study whether the basicity of anions has an influence on the association. Thus eight benzoates possessing different substituents were used in further experiments. In Table 3 are collected the K_{assoc} and CIS values for **2**/**9**−**16** pairs. In the case of benzoates carrying electron-donating substituents, sigmoidal curves were observed. For that reason two K_{assoc} values are given (see table footnotes).

As can be seen, both H7 and H10 and aryl H3 used as probes show chemical shift changes. The change in δ(H3) is caused by the conformational change in **2** and is induced by the close proximity of H3 and C═O group[46] (magnetic anisotropy[86] of the C═O bond, Chart 8).

However, the NH chemical shift is much more sensitive than that of the CH proton in ^{1}H NMR titrations. In the case of δ(H10) it first decreases and then increases. This is due to the opposing effects during titrations (multiple equilibrium evidently seen in electron-donating substituents and the character of hydrogen bond, i.e., intra- and intermolecular) reducing the CIS(H10) values (see Experimental Section).

The data clearly show that in the case of benzoate anions the tendency for conformational change depends on the character

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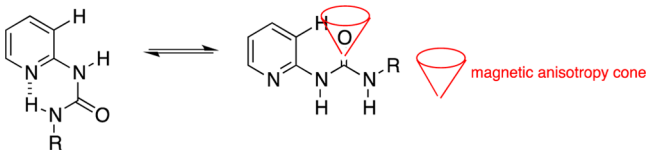
Table 3. K_{assoc} [M^{-1}] and CIS [ppm] for 2 with Benzoates 9–16 using δ(H7), δ(H10), and δ(H3) as Probes

		H7		H10		H3	
R^4 (substituent)	σ_p	K_{assoc}	CIS	K_{assoc}	CIS	K_{assoc}	CIS
4-NMe_2 (**9**)	−0.83	12	0.50	30[a]	−0.06	12	0.29
4-OMe (**10**)	−0.27	10	0.36	25[b]	−0.07	13	0.23
4-Me (**11**)	−0.17	10	0.43	25[c]	−0.07	13	0.26
H (**12**)	0	8	0.24	11	−0.07	9	0.20
4-F (**13**)	0.06	6[d]	0.28	11[d]	−0.07	9	0.19[e]
4-Cl (**14**)	0.23	6	0.25	18	−0.08	9	0.19
4-CF_3 (**15**)	0.54	4	0.22	10	−0.08	7	0.16
4-NO_2 (**16**)	0.78	3	0.16	6	−0.05	5	0.09

[a]For the increasing part of the curve the K_{assoc} = 2 M^{-1} has been found (see text for explanations) [b]For the increasing part of the curve the K_{assoc} < 2 M^{-1} has been found (the quality of the fit is low most probably due to hygroscopicity of the **10** salt or competitive interaction by the OMe group; see later in text) [c]For the increasing part of the curve the K_{assoc} = 3 M^{-1} has been found. [d]Association constant is approximate only because it is based on 7 points only due to low solubility of **13** in $CDCl_3$. [e]CIS value based on fitted curve instead of raw data due to signal overlap.

Chart 8. Conformational Change Leading to Close Proximity of H3 and O9



of the *para* substituent. Table 4 collects the correlation coefficients between K_{assoc}/CIS and σ_p of the substituent[87] (charts collected in Supporting Information).

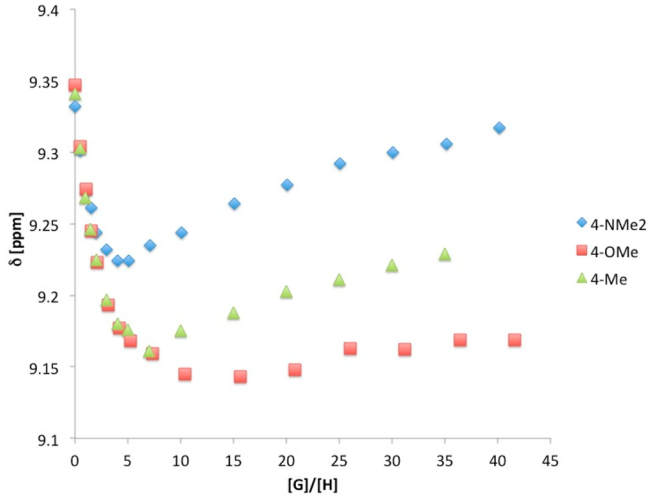
Table 4. Correlation Coefficients between K_{assoc}/CIS and σ_p (Table 3) for Complexes 2/9–16

	H7	H10	H3
K_{assoc}	0.966	0.877	0.865
CIS	0.928	0.006	0.960

The low correlation coefficient for H10 and the odd shape of the titration curves urged us to use even higher concentrations of the titrants than usual (see Experimental Section). Thus three benzoates carrying electron donors were used up to their solubility limit (ca. 35–42 molar excess, Chart 9). The sigmoidal shape of the titration curves observed has already been described[88] and was reported also by us using other compounds.[37,48] The titration charts showing their dependence on the character of the substituent are collected in Supporting Information.

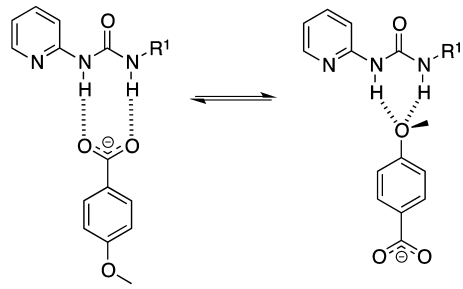
For H7 and H3 only deshielding is observed so that the conformation of **2** remains (*E,Z,Z*). In the case of the 4-OMe derivative the titration curve does not fall between those for 4-NMe_2 and 4-Me (as the value of substituent constant does). Two effects may cause this: (a) Tetrabutylammonium 4-methoxybenzoate is highly hygroscopic and an increased amount of water may be the cause. This may be only a part of the reasoning since it was shown that the effect of water on the association during titration in a chloroform solution should not be larger than 20%.[85] (b) The 4-OMe group may be

Chart 9. Titration of 2 (Host) by Benzoates Carrying Electron-Donating Substituents (Guests)



involved in bifurcated hydrogen bonding as in organocatalysis[89] (Chart 10).

Chart 10. Two Forms of the 2/10 Complex



Calculations. For a deeper insight into the studied complexes, calculations at the M05/6-311+G(2d,2p) level in chloroform (PCM) were conducted. The *n*-butyl group in **2** was replaced by methyl (**2′**) to shorten the time-consuming calculations.

In the formation of complexes shown in Charts 4 or 5 two steps must take place. The first is breaking the H10···N hydrogen bond, which can be achieved by *quasi*-ring-opening. The second step is the rotation around the C2–N7 and N7–C8 bonds. There are two possible ways for rotation about single bonds, as shown in Chart 11. The same chart shows the structures and numerical data for the energy of transition states (TSs) and the energy of the *E,Z,Z* conformer. The conformational change in question is driven by attractive or repulsive intramolecular interactions and π-electron resonance. The relevant interactions are intramolecular hydrogen bonding of the NH···N and weak CH···O (in blue) type and H/H repulsion and N/O lone-pair repulsion[44] (in red). In general the intramolecular repulsions are not preferred. Instead, after an initial rotation about the C2–N7 or N7–C8 bond, another rotation takes place about N7–C8 and C2–N7 bonds leading to an *E,Z,Z* conformer capable of triple hydrogen bonding.

The easier rotation about the C2–N7 (**TS1**) bond compared with that for the N7–C8 one (**TS2**) is most probably caused by the higher partial double bond character of the N7–C8 bond due to the mesomerism in the -NH-C=O fragment. Since

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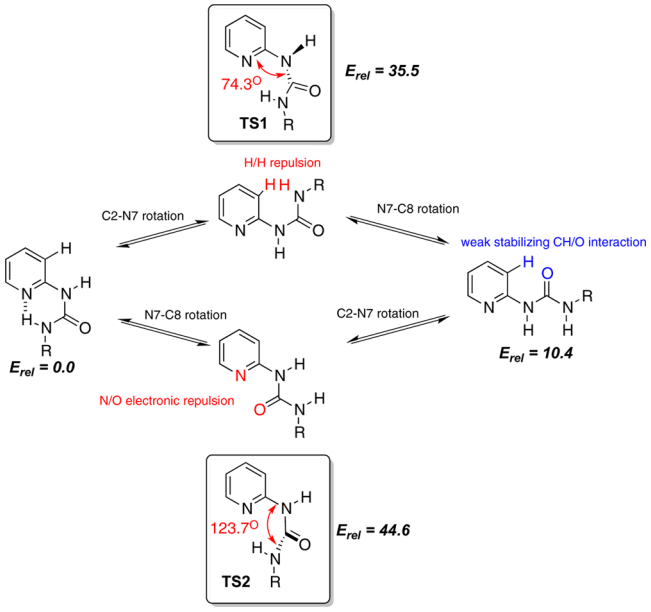
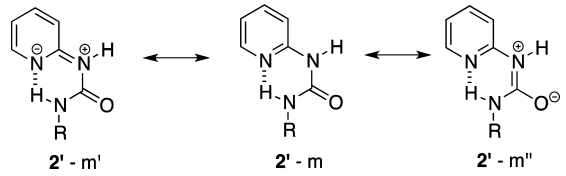
Chart 11. Possible Modes of Conformational Change in *N*-(Pyridin-2-yl),*N*′-substituted Ureas and Relative Energies (E_{rel}) of Structures Involved [kJ/mol]



oxygen is more electronegative than nitrogen, the **2′-m″** (Chart 12) form is most probably more populated than the **2′-m′**. This has consequences on the transition state energies.

Chart 12. Mesomerism in *N*-(Pyridin-2-yl),*N*′-methylurea (2′, R = Me)



The dimerization of **2′** was studied by optimizing the three possible self-associated molecules. These are two symmetric and one unsymmetric complex stabilized by two NH···O (*Z,E,Z* isomer) or two NH···N (*E,Z,Z* conformer) in symmetric structures and by NH···O and NH···N hydrogen bonds (*Z,E,Z* + *E,Z,Z* isomers, Supporting Information). The intramolecular hydrogen bond in the *Z,E,Z* isomer causes the symmetric dimer to be the most stable one (Chart 2). The intermolecular interaction data for **2′** are collected in Supporting Information.

Regarding the dimerization of naphthyridines, the rotamerism in the -NH-CO-Me moiety is crucial (Table 5). All values reported here are BSSE (basis set superposition error) and ZPE (zero-point energy) corrected. The energy of interaction (E_{int}) was calculated by the counterpoise procedure,[90] while the energy of each hydrogen bond (Table 6) was calculated with the QTAIM[91] based Espinosa approach.[92,93] Originally Espinosa used the properties of H-BCP (hydrogen bond critical point) for various hydrogen bond bridges except the NH···N one. Interactions such as XH···O (X = N, O, C),[92−97] FH···F,[96] CH···F and NH···F,[97] NH···O and OH···O,[92] and FH···N[97] have been used to test and develop this methodology. We have successfully used this approach to describe and explain the properties of intramolecular NH···N[98] and intermolecular[37,48] hydrogen bonding.

Table 5. Relative Energies (E_{rel}) and E_{int} [kJ/mol] for 6[a]

	E_{rel}	E_{int}
monomer (*E,Z*)	0.00	
monomer (*Z,E*)	9.69	
dimer 6_2-**1** (*E,Z*)	11.36	−14.71
dimer 6_2-**2** (*Z,E*)	6.50	−38.95
dimer 6_2-**3** (*E,Z* + *Z,E*)	0.00	−35.76

[a]See Chart 3 for structures.

Table 6. Laplacians (First Row), Electron Density at H-BCP (Second Row in *italic*), and E_{HB} (Third Row in bold, H···X Distance [Å]) for Dimers of 6

interaction	dimer 6_2-**1**	dimer 6_2-**2**	dimer 6_2-**3**
NH···N[a]	0.034		0.033
	0.012		*0.012*
	−8.6, 2.378		**−8.6**, 2.368
NH···O		0.078	0.091
		0.022	*0.028*
		−21.5, 1.980	**−28. 8**, 1.883
CH···N			0.045
			0.016
			−11.4, 2.278

[a]Due to steric reasons the NH···N interaction is formed by the NH of amide group and N8.

Table 6 collects the QTAIM-based data for the dimers of **6**.

In all self-associated structures the positive values of the Laplacian reveal that interaction is of the hydrogen bonding type (for the use of properties of H-BCPs in hydrogen bonding see the definition of *hydrogen bond* by IUPAC[99]). The higher electron density at H-BCP suggests that the interaction is stronger, that is also manifested by the E_{HB} (hydrogen bond energy) and the X···H distances. The QTAIM-derived data support the conclusion based on the E_{int} and experimental observations. It is clearly seen that the 6_2**−2** and 6_2**−3** dimers should be more stable than 6_2**−1**. Moreover, this is in agreement with the lack of a strong effect of the C═O anisotropy on the H3 chemical shift in 6_2. The *E,Z*-to-*Z,E* conformational change in **6** is compensated by the association. Thus the low association (K_{dim}) of **6** may be explained by the need of conformational change that is the *condicio sine qua non* for efficient self-interaction.

The computational methods used for dimers were also used for heterocomplexes. Table 7 contains the interaction energy (E_{int}) between **2′** and **5−16**. For all complexes with benzoate

Table 7. BSSE and ZPE Corrected E_{int} [kJ/mol] for the Studied Complexes

counterpart	urea **2′**	counterpart	urea **2′**
5	−48.94	**11**	−56.03
6	−45.82	**12**	−56.38
7	−48.27	**13**	−54.68
8	−45.72	**14**	−54.41
9	−59.39	**15**	−54.25
10	−56.86[a]	**16**	−51.70

[a]E_{int} for the complex with bifurcated hydrogen bonding (Chart 10) is −17.63 kJ/mol.

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Table 8. Laplacians (First Row), Electron Densities at H-BCP (Second Row in *italic*), and E_{HB} (Third Row in bold, H···X Distances) for Complexes of 2′ with 5−8

	hydrogen bond		
complex of **2′** with **5−8** (angle between rings [deg])	(**2′**)N1···H9−N9(**5−8**)	(**2′**)N7−H7···N1(**5−8**)	(**2′**)N10−H10···N8(**5−8**)
5 (13.7)	0.073	0.044	0.072
	0.028	*0.017*	*0.027*
	−23.8, 1.985	**−12.1**, 2.233	**−23.0**, 2.002
6 (32.9)	0.063	0.050	0.070
	0.024	*0.019*	*0.026*
	−19.8, 2.053	**−14.2**, 2.170	**−22.2**, 2.010
7 (23.8)	0.071	0.051	0.066
	0.027	*0.020*	*0.024*
	−22.6, 2.002	**−14.8**, 2.157	**−20.3**, 2.042
8 (34.5)	0.062	0.053	0.066
	0.024	*0.020*	*0.024*
	−19.6, 2.056	**−15.3**, 2.145	**−20.2**, 2.043

anions the interacting counterparts are coplanar except for the structure **2′/10** with bifurcated hydrogen bonds (see Chart 10).

For triply hydrogen-bonded complexes with the amides the E_{int} is slightly lower than that for amines. The calculations show that in the optimized structures of **2′/5** vs **2′/6** and **2′/7** vs. **2′/8** the acylation causes molecules to twist one against another. This may be noticed by inspection of the angle between the ring planes of the pyridine in **2′** and the closest ring in **5−8** (Table 8). In general the interaction energy for the **2′/9−16** complexes depends on the substituent with a high correlation coefficient (R = 0.96).

The QTAIM properties of H-BCP (Laplacian [$\nabla^2\rho$] and electron density [ρ]), energies of hydrogen bonds E_{HB} [kJ/mol]), and H···X distances [Å] are collected in Tables 8 and 9 (the types of hydrogen bonds are labeled as follows: (**y**)X−H···Z(**y′**) or (**y**)X···H−Z(**y′**), where **y** and **y′** are labels of the compounds .

The above data show that the association is driven by the acidity of the NH proton (free base vs acylated one), small methyl and acetyl groups (steric reasons) in triply hydrogen-bonded complexes, and the substituent that influences the basicity of carboxylate in doubly hydrogen-bonded ones. Table 10 collects the correlation coefficients for computational data (QTAIM) based on the properties of H7 and H10 H-BCPs. The first two lines contain all data available, while the third one has some points excluded (see the table footnotes).

We also calculated many correlations between the molecular distances and angles and the substituent constants. The correlations between σ_p and geometrical parameters are collected in Table 11.

The correlations of crucial distances and angles within the hydrogen-bonded benzoate anion are high. This means that the substituent effect is transmitted in a regular fashion within this species. Further, for the intermolecular distances related to the O8 oxygen of benzoate the correlations are high when the 4-NMe_2 group is excluded from the calculation, which can be due to the high acidity of H7 (a better hydrogen bond donor than H10) or to the strong N1/O8 electronic repulsion in **2′/9**. In ^{1}H NMR the hydrogen bond donor ability of H7 is manifested by its deshielding when compared with H10. This, in turn, is because H7 is attached to the nitrogen atom lying between two electron-withdrawing groups, the CO group and the pyridin-2-yl. This conclusion is supported by computational data for the NH groups, i.e., the N−H bond distance (the N7−H7 is longer than the N10−H10 in the complex with benzoate) and natural

Table 9. Laplacians (First Row), Electron Densities at H-BCP (Second Row in *italic*), and E_{HB} (Third Row in bold, H···X Distances [Å]) for Complexes of 2′ with 9−16

	hydrogen bond	
complex of **2′** with	(**2′**)N7−H7···O8(**9−16**)	(**2′**)N10−H10···O9(**9−16**)
9	0.089	0.099
	0.030	*0.033*
	−29.5, 1.877	**−33.3**, 1.847
10[a]	0.093	0.094
	0.031	*0.031*
	−31.1, 1.866	**−30.9**, 1.864
11	0.093	0.094
	0.031	*0.031*
	−31.0, 1.862	**−30.8**, 1.873
12	0.090	0.099
	0.030	*0.033*
	−30.0, 1.873	**−33.4**, 1.845
13	0.092	0.093
	0.030	*0.031*
	−30.6, 1.867	**−30.4**, 1.880
14	0.089	0.093
	0.029	*0.031*
	−29.3, 1.889	**−30.6**, 1.864
15	0.085	0.096
	0.028	*0.032*
	−27.4, 1.904	**−31.6**, 1.865
16	0.085	0.092
	0.028	*0.030*
	−27.6, 1.901	**−30.0**, 1.884

[a]QTAIM data ($\nabla^2\rho$, ρ, E_{HB}) for the complex with bifurcated hydrogen bonds (Chart 10) are as follows: 0.054, *0.016*, **−14.4**, 2.164 and 0.059, *0.017*, **−16.0**, 2.122 for H7···O and H10···O interactions, respectively.

Table 10. Correlation Coefficient for $\nabla^2\rho$, ρ at H-BCP and E_{HB} in 2′/9−16 as a Linear Function of σ_p

	$\nabla^2\rho$	ρ	E_{HB}
R	0.65 (H7)	0.69 (H7)	0.67 (H7)
	0.55 (H10)	0.59 (H10)	0.57 (H10)
$R^{a,b}$	0.94 (H7)	0.97 (H7)	0.96 (H7)

[a]4-NMe_2 excluded. [b]No correlation has been found for H10 even when some extreme points were excluded.

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Table 11. Correlation Coefficients for 2′/9−16 Complexes Derived from Optimized Geometry

parameter	*R*
N7−H7···O8[a]	0.71 (0.93)[b]
N10−H10···O9[a]	0.60
H7···O9[a]	0.12
H10···O8[a]	0.35 (0.91)[c]
C8−C7[a]	0.74 (0.99)[b]
N7−O9[a]	0.12
N10−O8[a]	0.38 (0.92)[c]
N1−O8[a]	0.10
H3−O9[d]	0.87
N7−O8[a]	0.66 (0.94)[b]
N9−O9[a]	0.60
C7[a]−O8[a]	0.98
C7[a]−O9[a]	0.97
O8[a]-O9[a]	0.97
O8[a]−C7[a]−O9[a]	0.97
N7−C8−N10	0.26[e]

[a]Atom in the benzoate anion. [b]4-NMe_2 (**e**) excluded. [c]4-NMe_2 (**9**) and H (**12**) excluded. [d]Weak intramolecular interaction. [e]The value for this angle is practically constant, i.e., 113.45 ± 0.05°.

charge (comment in Supporting Information). It is worth mentioning that the natural charges at H7, H10, N7, N10, O8 (benzoate), and O9 (benzoate) correlate with substituent constants. The more electron-donating group (R^4) makes the N−H bond in **2′/(9−16)** longer, the electron density at H7/H10 lower, and the charge at oxygen and nitrogen atoms higher (elongation of the N−H bond). Since the E_{int} (Table 7) and K_{assoc}/CIS depend on the substituent, it is not surprising that the atomic charges involved in hydrogen bonding follow that trend. Table 12 collects the crucial data about the correlation of natural charges.

Table 12. Correlation between Natural Charges at Crucial Atoms and Substituent Constants

atom	*R*
H7	0.92
H10	0.97
N7	0.89
N10	0.92
O8	0.96
O9	0.99

Since a complicated titration curve behavior has been observed for electron-donating groups, we studied it more carefully using calculations. These are, however, limited only to the 4-NMe_2 derivative due to the large computational cost of taking all structures into account. As shown by the data presented above, an electron-donating substituent causes a higher electron density at the oxygen atoms. This in turn influences secondary interactions[52] (repulsive SI_r or attractive SI_a[100]) that act diagonally between molecules with respect to the hydrogen bonding pattern (Chart 13).

The SI_r between N1 and O8 oxygen of benzoate is most probably responsible for the multiple equilibria yielding nonstandard titration curves. A strong electronic repulsion causes changes in the geometry of the complex and in the type of the interaction. This causes a weaker association in **2′/9**-2 or **2′/9**-3 (compare K_{assoc} values based on H10 in the decreasing and increasing part of curves, Table 3). Table 13 collects the crucial data for the complexes shown in Chart 13.

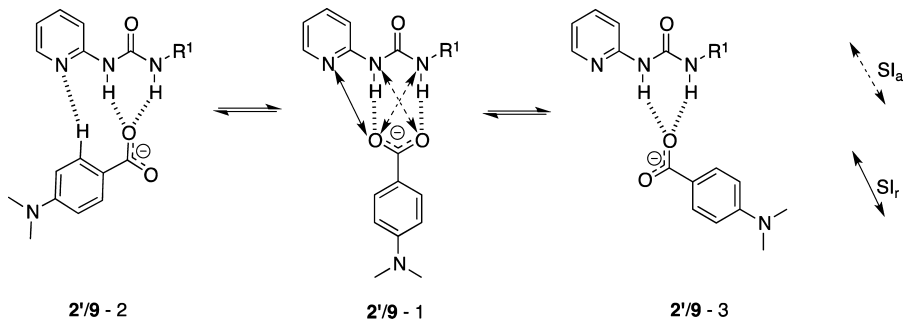
Table 13. Parameters of Hydrogen-Bonded Complexes of 2′ and 9 in Various Conformations

conformation property	**2′/9**-2	**2′/9**-1	**2′/9**-3
E_{int} [kJ/mol]	−52.07	−59.39	−45.87
(**2′**)H7···O8(**9**)			
$\nabla^2\rho$	0.093	0.089	0.082
P	*0.026*	*0.030*	*0.024*
E_{HB}	**-26.7**	**-29.5**	**-23.4**
H···O length [Å]	1.913	1.877	1.963
(**2′**)H10···O9(**9**)			
$\nabla^2\rho$	0.102	0.099	0.108
P	*0.031*	*0.033*	*0.031*
E_{HB}	**-32.1**	**-33.4**	**-33.7**
H···O length [Å]	1.858	1.847	1.837
(**e**)*ortho*-CH···N1(**2′**)			
$\nabla^2\rho$	0.015		
P	*0.006*		
E_{HB}	**-3.91**		
H···N length [Å]	2.837[a]		

[a]Weak interaction. It is 0.087 Å longer than the sum of the vdW radii.

The experimental and computationally derived data show that triple and double hydrogen bonding in *N*-(pyridin-2-yl),*N*′-substituted ureas is able to influence the conformation of these molecules. In the charge-assisted hydrogen bonding the basicity of benzoate affected by the substituent influences the electron distribution in the -CO_2^- fragment, and this in turn influences the association. For the H7 and H10 protons the experimental and computational data show that the correlation coefficients are much higher for H7 than those for H10. This may be caused by the fact that H10 is involved in

Chart 13. Secondary Interactions in 2′/9 (4-NMe_2-Benzoate)



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intramolecular hydrogen bonding, which is stronger than the intermolecular one, and the change in its chemical environment is more dramatic, while H7 is always involved in intermolecular interaction both in the dimer of urea and the heterocomplex. The change in the chemical shift of H10 after reaching its minimal value (Chart 9) may also be caused by the proximity of the aromatic ring (magnetic anisotropy) in the structure with bifurcated hydrogen bonds (**2′**/**9**-3, Chart 13). The similar E_{int} values for these structures may explain the probable coexistence of these forms (Table 13).

CONCLUSIONS

Breaking of the intramolecular hydrogen bond in *N*-(pyridin-2-yl)ureas and the conformational change in these molecules can be caused by the association with double and triple hydrogen-bonding counterparts. In the case of triply hydrogen-bonded complexes a methyl substituent does not significantly affect the association constants, although its effect is clearly visible in the CIS values. Linear correlations between the properties of complexes and substituent constants were found for benzoates. Multiple equilibria were detected in strong electron donors. These effects are caused by the strong electronic repulsion between the pyridinyl nitrogen and the negatively charged oxygen of benzoate. Computation results suggest that other urea/benzoate complexes are characterized by a bifurcated NH···O···HN interaction. The prerequisite for the association of *N*-(pyridin-2-yl)ureas is the rotation around single bonds. The energy barrier for the rotation around the C2−N7 bond in *N*-(pyridin-2-yl)ureas is lower by ca. 9 kJ than that around the N7−C8 bond. It was demonstrated that benzoic acid itself does not cause the conformational change in *N*-(pyridin-2-yl)urea, while benzoate does it readily. It means that pH-dependent conformational changes can take place in the studied compounds.

EXPERIMENTAL SECTION

The acetyl derivatives of 2-amino-1,8-naphthyridines[101,102] were obtained by reactions with an acylating agent as previously described.[55] Tetrabutylammonium benzoates were obtained in a reaction of the respective acid with tetrabutylammonium hydroxide. The products were dried in a desiccator over P_2O_5. Urea derivatives were synthesized as described earlier.[44] The dimerization and association constants were determined in $CDCl_3$. Dilution experiments were used to find the dimerization constants (K_{dim}). For the determination of association constants, aliquots of solid titrant were added to a $CDCl_3$ solution of the analyte at a known concentration.[37,48] The Benesi−Hildebrand equation[103] was used to calculate the association constants (K_{assoc}). These constants are based on two titration experiments (with errors less than 15%). For the **2**/**9** complex three titrations were performed. The chemical shift variability in these titrations was within ±0.1 ppm for the NH protons. As the heterocomplexation of **1**−**4** does not depend on R^1 (no steric effect was found because the O9−C8−N10−R^1 dihedral angle was close to 0°), **2** was chosen for further studies with **9**−**16** due to its higher solubility in $CDCl_3$ compared with that of the remaining three ureas. NMR titrations were finished when the additive caused a change <0.1 ppm in the chemical shift of the NH proton. The calculations were performed with Gaussian[104] software using the 6-311+G(2d,2p) basis set and the PCM[105−107] model of solvation (chloroform). The use of diffuse functions is crucial for calculations of long-distance interactions, especially in anions. The M05 functional suggested for noncovalent interactions[108,109] was used to sustain the methodology used in our previous publications.[37,48,53−56] The Synchronous Transit-Guided Quasi-Newton method[110] was used for finding the transition state for rotamerism in **2′** (the Me analogue of **2**). Frequency calculations were ran for all optimized structures to be sure that the geometry corresponds to an energy minimum (i.e., all frequencies are positive except the ones referring to transition states). The E_{int} energies are ZPE and BSSE corrected with the use of a counterpoise method[90] as a single-point run on the optimized geometry as explained above.[37,48] Single-crystal XRD studies were performed for **1**−**3**, and their high quality crystal structures were obtained. The data from **1**−**3** were collected at 123(2) K on a diffractometer with an ApexII detector using graphite monochromated Mo Kα radiation. COLLECT[111] data collection software was utilized for data collection, and the data were processed with DENZO-SMN.[112] The data were corrected for absorption effects using SADABS.[113] The structures were solved by direct methods (SIR2004[114]) and refined anisotropically by full-matrix least-squares on F^2 values utilizing SHELXL-97.[115] Hydrogen atoms bound to carbon atoms were positioned according to the expected geometry and were refined only isotropically riding on the parent atom. Hydrogen atoms bound to nitrogen atoms were located from the electron density map and restrained to the ideal distance of 0.88 Å from the parent atoms, with U_{iso}(H) factors of 1.2 times the parent atom factor. Figures were drawn with Ortep-3[116] and Mercury.[117] Compound **4** did not yield proper single crystals for an XRD study. The ^{1}H, ^{13}C, and ^{15}N NMR data for **1**−**4** were recorded as reported in our previous publications.[37,48,53] The CIS values referring to titrations were calculated as differences between the chemical shift of the proton used as a probe at the beginning of the experiment and after addition of 1 equiv of the guest. The CIS values were usually calculated as a difference between the chemical shift of the probe at the beginning of experiment and the same probe chemical shift extrapolated to an infinite concentration. Here the CIS values were calculated in a different way because the solubility of the compounds used as titrants was variable and the association was weak, causing difficulties in an exact extrapolation of the chemical shift to infinite concentration of the titrant. Also, for some complexes, a complicated sigmoidal titration curve was observed (see text). This caused extra problem in judging the CIS values based on the initial and extrapolated chemical shifts.

Compound Characterization. *N-(Pyridin-2-yl)-N′-ethylurea (**1**).* ^{1}H NMR ($CDCl_3$): δ 9.35 (bs, 1H), 9.30 (bs, 1H), 8.15 (m, 1H), 7.55 (m, 1H), 6.91 (d, $^3J_{H,H}$ = 8.31 Hz, 1H), 6.83 (m, 1H), 3.44 (m, 2H), 1.26 (t, 3H). ^{13}C NMR: δ 156.4, 153.8, 145.9, 138.0, 116.4, 112.1, 34.6, 15.4. Mp: 118.8−122.1 °C (EtOH) (lit. mp 119 °C[118]).

*N-(Pyridin-2-yl)-N′-n-butylurea (**2**).* ^{1}H NMR ($CDCl_3$): δ 9.33 (bs, 1H), 8.70 (bs, 1H), 8.15 (m, 1H), 7.57 (t, $^3J_{H,H}$ = 7.28 Hz, 1H), 6.86 (d, $^3J_{H,H}$ = 7.14 Hz, 1H), 6.84 (d, $^3J_{H,H}$ = 7.72 Hz, 1H), 3.38 (q, $^3J_{H,H}$ = 5.60 Hz, 2H), 1.61 (m, 2H), 1.45 (m, 2H), 0.96 (t, 3H). ^{13}C NMR: δ 156.9, 154.0, 145.8, 138.0, 116.4, 112.3, 39.5, 32.1, 20.2, 13.8. ^{15}N NMR: δ −114.3, −258.0, −279.7. Mp: 85.8−88.5 °C (EtOH) (lit. mp 87−88 °C[119]).

*N-(Pyridin-2-yl)-N′-phenylurea (**3**).* ^{1}H NMR ($CDCl_3$): δ 11.73 (bs, 1H), 9.32 (bs. 1H), 8.17 (d, $^3J_{H,H}$ = 4.20 Hz, 1H), 7.58 (m, 3H), 7.26 (t, $^3J_{H,H}$ = 7.92 Hz, 2H), 7.02 (t, $^3J_{H,H}$ = 7.36 Hz, 1H), 6.92 (d, $^3J_{H,H}$ = 8.16 Hz, 1H), 6.86 (t, $^3J_{H,H}$ = 5.72 Hz, 1H). ^{13}C NMR: δ 154.0, 153.2, 145.8, 138.6, 138.6, 128.9, 123.4, 120.3, 117.2, 112.4. Mp: 188.6−191.2 °C (EtOH) (lit. mp 201−204 °C[44]).

*N-(Pyridin-2-yl)-N′-tert-butylurea (**4**).* ^{1}H NMR ($CDCl_3$): δ 9.40 (bs, 1H), 9.24 (bs, 1H), 8.12 (d, $^3J_{H,H}$ = 5.2 Hz, 1H), 7.55 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 6.94 (d, $^3J_{H,H}$ = 7.2 Hz, 1H), 6.81 (t, $^3J_{H,H}$ = 6.0 Hz, 1H), 1.46 (s, 9H). ^{13}C NMR: δ 156.9, 154.0, 145.8, 137.4, 116.4, 112.3, 39.5, 32.1, 20.2, 13.8. Mp: 85.8−88.5 °C (EtOH) (lit. mp 87−88 °C[119]).

*2-Amino-1,8-naphthyridine (**5**).* ^{1}H NMR ($CDCl_3$): δ 8.84 (d, $^3J_{H,H}$ = 2.5 Hz, 1H), 7.93 (d, $^3J_{H,H}$ = 8.4 Hz, 1H), 7.84 (d, $^3J_{H,H}$ = 8.72 Hz, 1H), 7.18 (m, 1H), 6.79 (d, $^3J_{H,H}$ = 8.72 Hz, 1H), 5.50 (bs, 2H). ^{13}C NMR: δ 159.6, 156.6, 152.7, 138.3, 136.2, 118.3, 117.5, 112.8. Mp: 134.7−136.8 °C (lit. mp 135.5−137.1 °C[37]).

*2-Acetylamino-1,8-naphthyridine (**6**).* ^{1}H NMR ($CDCl_3$): δ 9.03 (m, 2H, NH), 8.55 (d, $^3J_{H,H}$ = 8.00 Hz, 1H), 8.20 (d, $^3J_{H,H}$ = 8.84 Hz, 1H), 8.14 (d, $^3J_{H,H}$ = 8.00 Hz, 1H), 7.43 (m, 1H), 2.30 (s, 3H). ^{13}C NMR: δ 169.6, 154.8, 153.8, 153.7, 139.6, 136.6, 120.9, 120.6, 115.3,

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24.9. Mp: 217.0–220.4 °C. Anal. Calcd for $C_{10}H_9N_3O$: C 64.16, H 4.85, N 22.45. Found: C 64.10, H 4.92, N 22.59.

2-Amino-7-methyl-1,8-naphthyridine (7). ^{1}H NMR ($CDCl_3$): δ 7.81 (two overlapping doublets, 2H), 7.07 (d, $^3J_{H,H}$ = 7.96 Hz, 1H), 6.71 (d, $^3J_{H,H}$ = 8.6 Hz, 1H), 5.17 (bs, 2H), 2.69 (s, 3H). ^{13}C NMR: δ 162.2, 159.4, 156.1, 138.1, 136.2, 118.9, 115.3, 111.4, 25.4. Mp: 215–217.5 °C (toluene) (lit. mp 217–218 °C[101]).

2-Acetylamino-7-methyl-1,8-naphthyridine (8). ^{1}H NMR ($CDCl_3$): δ 8.83 (bs, 1H), 8.46 (d, $^3J_{H,H}$ = 8.80 Hz, 1H), 8.15 (d, $^3J_{H,H}$ = 8.80 Hz, 1H), 8.01 (d, $^3J_{H,H}$ = 8.20 Hz, 1H), 7.27 (d, $^3J_{H,H}$ = 8.20 Hz, 1H), 2.76 (s, 3H), 2.29 (s, 3H). ^{13}C NMR: δ 169.5, 163.3, 154.5, 153.5, 139.1, 136.4, 121.6, 118.5, 114.2, 25.6, 25.0. Mp: 275.5–279.3 °C (lit. mp 278–281 °C[120]). We were unable to obtain accurate melting points for these hygroscopic salts; however, we recorded their NMR spectra (in dried $CDCl_3$) after storing the salts in a desiccator.

Tetrabutylammonium 4-Dimethylaminobenzoate (9). ^{1}H NMR ($CDCl_3$): δ 7.98 (d, $^3J_{H,H}$ = 8.70 Hz, 2H), 6.63 (d, $^3J_{H,H}$ = 8.70 Hz, 2H), 3.24 (m, 8H), 1.56 (m, 8H), 1.38 (m, 8H), 0.95 (t, $^3J_{H,H}$ = 7.30 Hz, 12H). ^{13}C NMR: δ 171.7, 151.3, 130.9, 128.5, 110.9, 58.4, 40.5, 23.9, 19.6, 13.7.

Tetrabutylammonium 4-Methoxybenzoate (10). ^{1}H NMR ($CDCl_3$): δ 8.03 (d, $^3J_{H,H}$ = 8.80 Hz, 2H), 6.80 (d, $^3J_{H,H}$ = 8.80 Hz, 2H), 3.80 (s, 3H), 3.25 (m, 8H), 1.55 (m, 8H), 1.37 (m, 8H), 0.95 (t, $^3J_{H,H}$ = 7.21 Hz, 12H). ^{13}C NMR: δ 171.0, 160.3, 133.4, 131.1, 112.3, 58.4, 55.2, 23.9, 19.6, 13.7.

Tetrabutylammonium 4-methylbenzoate (11). ^{1}H NMR ($CDCl_3$): δ 7.97 (d, $^3J_{H,H}$ = 8.00 Hz, 2H), 7.09 (d, $^3J_{H,H}$ = 8.00 Hz, 2H), 3.30 (m, 8H), 1.59 (m, 8H), 1.39 (m, 8H), 0.96 (t, $^3J_{H,H}$ = 7.30 Hz, 12H). ^{13}C NMR: δ 171.1, 138.2, 129.6, 127.8, 58.4, 23.9, 21.3, 19.6, 13.7.

Tetrabutylammonium Benzoate (12). ^{1}H NMR ($CDCl_3$): δ 8.07 (m, 2H), 7.30 (m, 3H), 3.27 (m, 8H), 1.58 (m, 8H), 1.38 (m, 8H), 0.95 (t, $^3J_{H,H}$ = 7.30 Hz, 12H). ^{13}C NMR: δ 171.3, 140.3, 129.4, 128.9, 127.2, 58.2, 23.8, 19.5,13.6.

Tetrabutylammonium 4-fluorobenzoate (13). ^{1}H NMR ($CDCl_3$): δ 8.07 (m, 2H), 6.95 (m, 2H), 3.29 (m, 8H), 1.61 (m, 8H), 1.39 (m, 8H), 0.96 (t, $^3J_{H,H}$ = 7.30 Hz, 12H). ^{13}C NMR: δ 170.4, 164.9, 162.4 139.3, 131.5, 113.7, 58.4, 23.8, 19.6, 13.6. Some signals are split due to the coupling with fluorine (see spectra).

Tetrabutylammonium 4-Chlorobenzoate (14). ^{1}H NMR ($CDCl_3$): δ 8.07 (d, $^3J_{H,H}$ = 8.40 Hz, 2H), 7.25 (d, $^3J_{H,H}$ = 8.40 Hz, 2H), 3.30 (m, 8H), 1.62 (m, 8H), 1.39 (m, 8H), 0.97 (t, $^3J_{H,H}$ = 7.40 Hz, 12H). ^{13}C NMR: δ 170.1, 139.1, 134.6, 131.0, 127.2, 58.5, 23.9, 19.6, 12.6.

Tetrabutylammonium 4-Trifluorometylbenzoate (15). ^{1}H NMR ($CDCl_3$): δ 8.17 (d, $^3J_{H,H}$ = 8.20 Hz, 2H), 7.54 (d, $^3J_{H,H}$ = 8.20 Hz, 2H), 3.31 (m, 8H), 1.62 (m, 8H), 1.39 (m, 8H), 0.96 (t, $^3J_{H,H}$ = 7.32 Hz, 12H). ^{13}C NMR: δ 169.8, 144.3, 130.3, 129.7, 124.7, 124.2, 58.6, 23.9, 19.7, 13.6.

Tetrabutylammonium 4-Nitrobenzoate (16). ^{1}H NMR ($CDCl_3$): δ 8.20 (d, $^3J_{H,H}$ = 8.90 Hz, 2H), 8.15 (d, $^3J_{H,H}$ = 8.90 Hz, 2H), 3.36 (m, 8H), 1.66 (m, 8H), 1.43 (m, 8H), 0.98 (m, $^3J_{H,H}$ = 7.22 Hz, 12H). ^{13}C NMR: δ 169.0, 148.0, 147.2, 130.2, 122.5, 58.7, 23.9, 19.7,13.6.

■ ASSOCIATED CONTENT

Supporting Information

NMR spectra, dilution curves, titration curves, collective titration charts, correlation charts, Cartesians of the optimized structures, XRD data and computational data for dimerization of urea derivatives. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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