JOC The Journal of Organic Chemistry

Article

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2-Acylamino- and 2,4-Bis(acylamino)pyrimidines as Supramolecular Synthons Analyzed by Multiple Noncovalent Interactions. DFT, X-ray Diffraction, and NMR Spectral Studies

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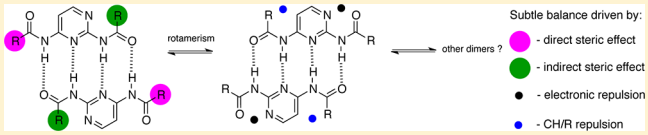
Supporting Information

ABSTRACT: Intermolecular interactions of ten 2-acylamino and 2,4-bis(acylamino)pyrimidines (7 of which are previously unknown) have been investigated by X-ray structural, quantum chemical (DFT), and NMR spectral methods. Especially the concentration dependencies of the ^{1}H NMR chemical shifts and titrations with other molecules capable of multiple hydrogen bonding provided useful information regarding their association via triple or quadruple hydrogen bonding, which is controlled by the conformational preferences of 2-acylamino- and 2,4-bis(acylamino)pyrimidines. On comparison of the properties of 2-acylamino- and 2,4-bis(acylamino)pyrimidines with the corresponding pyridines, an additional nitrogen in the heterocyclic ring is the crucial factor in explaining the stability of various conformers and dimers of pyrimidines. Computational modeling of their dimerization (self-association) and heteroassociation supports the experimental findings. The substituent effects in 2-acylamino- and 2,4-bis(acylamino)pyrimidines are discussed via inter- and intramolecular terms. The subtle balance between several structural factors and their influence on the aggregation of studied pyrimidines was confirmed also by variable-temperature NMR and NOE experiments. X-ray structures of 2-methyl- and 2-adamantyl-CONH-pyrimidines revealed very different intermolecular interactions, showing the importance of the substituent size on the self-assembly process. As a whole NMR spectral, X-ray structural, and computational data of 2-acylamino- and 2,4-bis(acylamino)pyrimidines can be interpreted in terms of multiple intra-/intermolecular interactions.



INTRODUCTION

Molecular self-assembly via noncovalent interactions between supramolecular synthons[1−4] with predictable associations[5,6] is of continuing interest in organic and bioorganic chemistry. Studies on 2-aminopyridine and its acyl derivatives,[7−10] 2,6-diaminopyridines and their derivatives,[11−17] various naphthyridines,[18−24] and other compounds capable of multiple hydrogen bonds have been reported. The strengths of the intermolecular interactions are determined by the number of hydrogen bonds, the array of hydrogen bond donors (D) and acceptors (A), secondary interactions[25,26] in multiply hydrogen bonded systems,[27−29] the character of influence of the substituents (electronic[30,31] or steric[32−34]), weak CH···N/O hydrogen bonds,[15,35,36] cooperative effects,[37] and proton transfer reactions,[38−43] as well as the types of atoms involved in hydrogen bonding (Etter's rules).[6]

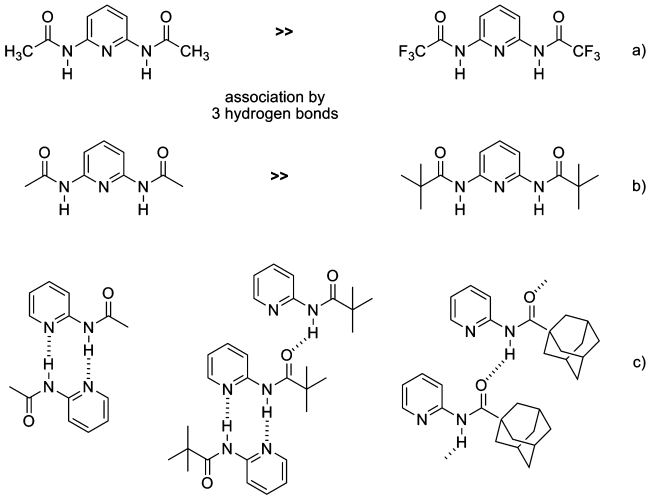
Our recent interest has focused especially on the steric effects in the formation of doubly,[32,44] triply,[34,45,46] and quadruply[47] hydrogen bonded assemblies. The electronic repulsion (Chart 1a)[45] and steric effects (Chart 1b)[34] influence the association in solution. Steric effects are also responsible for the very different arrangement of molecules in the unit cell in the crystalline state (Chart 1c).[32] Although some papers describe how intramolecular hydrogen bonding[47,48] controls the form of a molecule and thus its interactions with other molecules,[49−56] only a couple of papers have focused on the significance of conformational equilibrium.[57,58]

An inspiration for our present study on pyrimidines and their comparison with pyridines originates from the different behavior of pyridines vs diazines[59,60] and triazines,[11,49] where the association in solution[11,59] or specific interactions in the solid state[49,60] depends mainly on the presence of a nitrogen atom (instead of CH) in positions 3 and 5 in the heterocyclic ring (Chart 2). The effects of related structural changes were also studied by Limbach et al. in doubly hydrogen bonded *N,N′*-bisarylformamidines[42,43] vs *N,N′*-bisaryltriazenes.[41,43] In 2,6-bis(acylamino)pyridines the weak CH···O interaction favors the close mutual proximity of CH and C═O groups, which does not depend on the mesomerism of the amide moiety (in red and blue, Chart 2). Rotation about the NH−CO bond causes repulsion between aromatic and aliphatic protons. Thus, the 2,6-bis(acylamino)pyridines exist in a conformation that gives a DAD hydrogen bonding array but not the ADADA

Received: August 6, 2012
Published: September 30, 2012

dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609−9619

Chart 1. Association Influenced by the Electronic (a) and Steric (b) Effects in Solution and the Structure of 2-Acylaminopyridines in the Solid State (c)



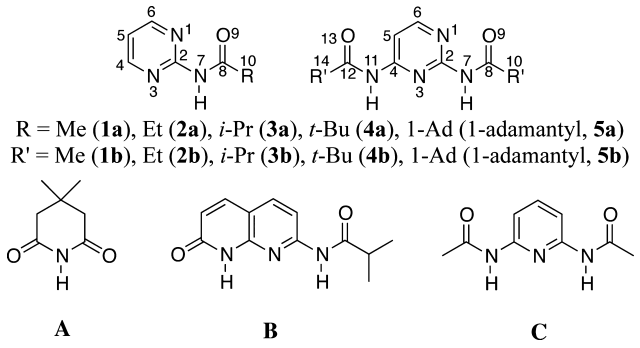
array. In 2,4-bis(acylamino)-*s*-triazine CH···O attractions are replaced by electronic repulsions between N and O atoms. This leads to increased rotational freedom about the NH−CO bond and formation of DADA and ADADA self-complementary hydrogen bonded arrays. The subtle balance between the two dimers of *s*-triazine shown in Chart 2 arise from the fact that in one intramolecular electronic repulsion takes place (dimer on the left-hand side), while in the other (right-hand side) two additional repulsions are present. The rotamerism of *s*-triazines is probably more or less similar in 2,4-bis(acylamino)-pyrimidines.

The intramolecular hydrogen bond can act as a conformational lock.[61] This interaction is frequently used in supramolecular chemistry,[30,62−72] although in the current study such an interaction is not important. Knowledge of the intermolecular interactions of pyrimidine derivatives is also important from a medicinal chemistry point of view.[73,74]

The aim of this study is to (a) determine the self-association constants of 2-acylamino- and 2,4-bis(acylamino)pyrimidines, (b) study their heterocomplexation with selected triply and quadruply hydrogen bonding counterparts, (c) find their conformational preferences, and (d) characterize the type of their dimers. The tautomerism/rotamerism of similar compounds (2-acylaminopyridines) was studied before by Katritzky et al.,[75] while publications by Wilson et al. have described the conformation-independent binding of hydrogen-bonded molecules.[48,76]

Chart 3 collects the structures of compounds used in this study and their atom numbering.

Chart 3. Compounds Studied and Their Atom Numbering

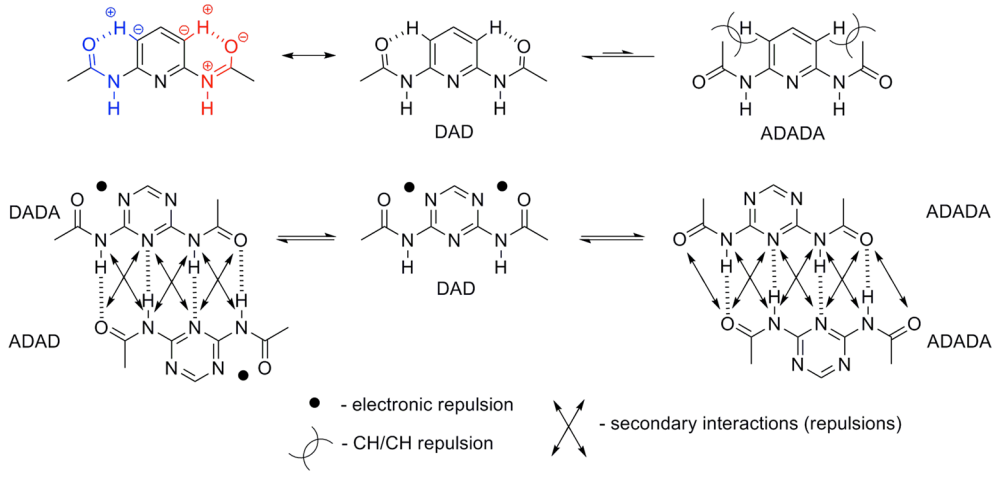


RESULTS AND DISCUSSION

Self-Association of 2-Acylaminopyrimidines. 2-Acylaminopyrimidine contains three basic centers (two nitrogen atoms and an oxygen) and an acidic proton (NH) capable of hydrogen bonding. **1a** was previously used by us in studies of the influence of cycloalkyl ring size on the heteroassociation of 2,6-bis(cycloalkylcarbonylamino)pyridines.[33] The ^{1}H NMR dilution experiments revealed that 2-acylaminopyrimidines form dimers in $CDCl_3$ solution (current study). The dimerization constant (K_{dim}) is low and comparable to those for 2-acylaminopyridines:[32] i.e., K_{dim} (M^{-1}) = 8.0[33] (**1a**), 4.0 (**2a**), and 1.4 (**3a**).

In the X-ray crystal structures of the two derivatives **1a** (R = methyl) and **5a** (R = adamantyl) (Figure 1) the major difference is in the conformation of the −NHCO− group. In **1a** the conformation is cis (H7N7C8O9 = 4°), whereas in **5a** it is trans (H7N7C8O9 = 165°). **1a** forms quadruply hydrogen bonded dimers, which further interact via nonconventional

Chart 2. Intramolecular Interactions That Control the Structures of 2,6-Bis(acylamino)pyridines and 2,4-Bis(acylamino)-*s*-triazines



dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609−9619

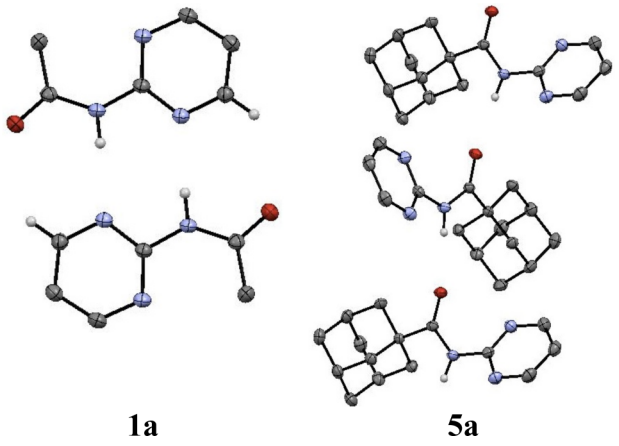


Figure 1. ORTEP[77] plots for **1a** and **5a** (most CH protons omitted for clarity).

CH···O contacts to form two-dimensional sheets (Figures S1–S3, Supporting Information). The dimer is stabilized by two NH···N and two CH···O hydrogen bonds (compare 2-acylaminopyridines[32]). In the NH···N bridge the H···N and N···N distances are 2.08(2) and 2.973(2) Å, respectively, while the CH···O distances (H···O and C–O) are 2.67 and 3.405(3) Å. Three other weak C–H···N/O type interactions were found to connect the dimers to neighboring ones.

The structure of **1a** was also modeled by DFT methods (three dimers, with two different amide group conformations). Table 1 collects the calculated energy of interaction (E_{int}),

Table 1. QTAIM and E_{int} Data for Dimers of 1a

form	E_{int}, ρ, $\nabla^2\rho$, E_{HB} for NH···N	ρ, $\nabla^2\rho$, E_{HB} for CH···O
form a	−86.9, 0.024, 0.066, −20.5	0.008, 0.026, −6.5
form a[a]	−, 0.022, 0.067, −19.0	0.006, 0.022, −5.1
form b	−40.3, 0.023, 0.061, −18.7	
form c	−35.5, 0.022, 0.022, −20.7[b]	[c]

[a]Calculations based on geometry from XRD. Two more CH···O contacts are present in the solid state (Figure S2 (Supporting Information), H5···O9″ and H6···O9″) with the H-BCP properties 0.006, 0.023, −5.2 and 0.005, 0.021, −4.3, respectively. [b]NH···O interaction. [c]Two weak CH···N and CH···O interactions (from CH_3 group) are present with ρ, $\nabla^2\rho$, and E_{HB} values of 0.005, −0.004, −3.5 and 0.007, −0.006, −5.4, respectively.

QTAIM-derived data (electron density (ρ) and the Laplacian of electron density ($\nabla^2\rho$)) at H-BCP (hydrogen-bond critical point), and the energy of the hydrogen bonds (E_{HB}) according to the Espinosa approach[78,79] for **1a** in different arrangements: i.e., the dimer stabilized by two NH···N and two CH···O interactions (Chart 4a), the NH···N doubly hydrogen bonded dimer (Chart 4b), and the associated N···H(N)···O arrangement (Chart 4c). **5a** does not form dimers but a ribbonlike structure like that of 2-(1-adamantoylamino)pyridine;[32] therefore, this compound was not taken into consideration for calculations.

The self-association of 2-acylaminopyrimidines is controlled by the size of R. The correlation of K_{dim} with Taft's constants (E_s)[80] is poor (R^2 = 0.76, n = 3) and can be explained by competitive association via hydrogen bond bifurcation or formation of various dimers instead of exclusive stabilization of the dimer by two NH···N hydrogen bonds (form *b* in Chart 4). The interaction shown by *c* in Chart 4 was observed in the crystal structures of other derivatives and will be published in due course (the NH···N and NH···O distances are 2.296 and 2.432 Å in one molecule and 2.355 and 2.172 Å in the other, respectively).[81]

The QTAIM data for the structures (Table 1) are in agreement with those obtained from computations based on X-ray structures. Also, the different dimers (Chart 4) and the calculated E_{int} values suggest the existence of NH···N dimers stabilized further by weak CH···O interactions (Table 1), as claimed by Zimmerman et al. for DNA bases.[82]

Pyrimidines with large alkyl substituents do not form dimers in chloroform solution. The intermolecular steric crowding of pyrimidines with bulky substituents prevents their efficient dimerization (DA pattern, *Z* conformer, Chart 4b), as previously found for other derivatives.[32,34,83] This is called a *direct* steric effect. On the other hand, a large substituent in pyrimidine hinders the rotation about the NH–CO bond, decreasing the stability of the ADA hydrogen bonding array (*E* conformer, Chart 4a). This effect is called an *indirect* steric effect.

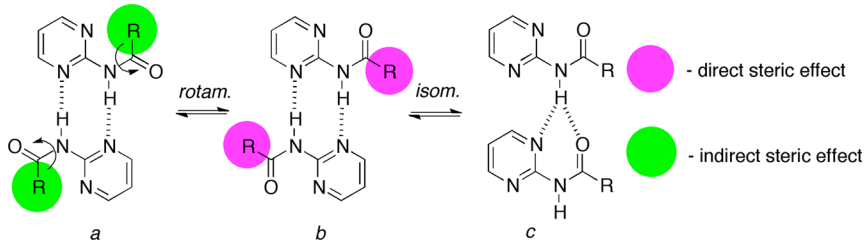
Heteroassociation of 2-Acylaminopyrimidines. The heteroassociation of **1a–4a** with **B** and **C** (Chart 3) was studied by ^{1}H NMR titration, as done before for 2-acylamino-6-[1*H*]pyridones.[46] The association constants (K_{assoc}) for the **1a** + **B** pair are 450 M^{-1} (probe NH proton) and 500 M^{-1} (probe aromatic CH **1a**) (titration curves are given in the Supporting Information). K_{assoc} values and complexation-induced shifts (CIS) of **1a–3a** with **C** are collected in Table 2, and Chart 5 depicts the structures of the complexes.

The chemical shift data did not allow the calculation of K_{assoc} values of **4a** and **5a** with **C**, suggesting that the association is completely restricted or is very weak.

Table 3 contains the calculated data for complexes **1a** + **B** and **1a** + **C**.

The greater association constant of **1a** + **B** (Chart 5b) compared to the **1a–3a** + **C** complexes (order of magnitude) can be explained by the higher rigidity of **B** with respect to **C**

Chart 4. Two Isomeric (*isom.*) Dimers (*b*, *c*) of the 2-Acylaminopyrimidines and One Rotameric (*rotam.*) Dimer Obtained by NH–CO Rotation (*a*)



dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609–9619

Table 2. Association Constant Values for Complexes of 2,4-Bis(acylamino)pyrimidines with C

compd	K_{assoc} (M^{-1}) with C	CIS (ppm)[a]
1a	36	1.54
2a	35	1.40
3a	20, 15[b]	0.94

[a]CIS ($\Delta\delta$(H7)) observed for the same [titrant]:[titrated compound] ratio equal to 8.5. [b]Value based on changes of the chemical shift of methine CH in the *i*Pr group.

Chart 5. Association of 2-Acylaminopyrimidines with B and C

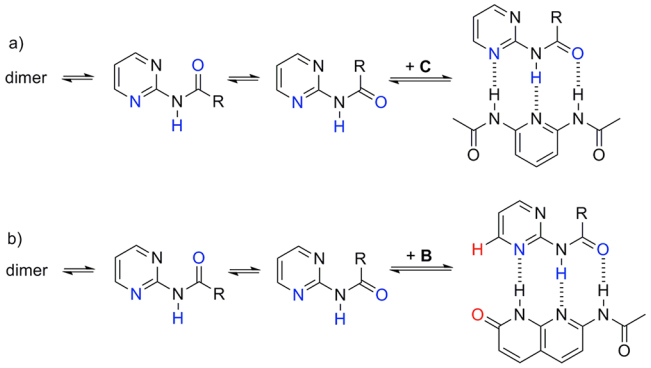


Table 3. Calculated Energy of Interaction (E_{int}) and Energy of NH···N and NH···O Hydrogen Bonds (E_{HB}) in Heterocomplexes of 2-Acetylaminopyrimidine with B and C

		E_{HB} (kJ/mol)			
complex	E_{int} (kJ/mol)	NH···N	NH···N	NH···O	$\sum E_{HB}$ (kJ/mol)
1a + **B**	−65.0	−30.4	−10.4	−24.1	−72.6[a]
1a + **C**	−43.5	−16.0	−12.7	−25.1	−53.8

[a]Weak CH···O interaction (Chart 5) with E_{HB} = −7.7 kJ/mol included.

and to some extent by the presence of the weak CH···O interaction (Chart 5b, atoms in red). The chemical shift changes of aromatic protons in **1a** (doublet signal, see the titration curve in the Supporting Information) are in line with the changes in NH and can be caused by weak hydrogen bonding and/or by magnetic anisotropy of the C═O group of **B**. In general, the *indirect* steric effect plays a dominant role in heteroassociation of **1a**−**5a** with **C**, which is seen not only in K_{assoc} but also in CIS values. The computational results reveal that the measured association constants are in agreement with the calculated intermolecular interaction energies and the sum of hydrogen bond energies calculated by the Espinosa approach.[78,79]

2,4-Bis(acylamino)pyrimidines. The 2,4-bis(acylamino)-pyrimidine can exist in several conformations (Chart 6). Their hydrogen bond arrays can be AD, DAD/ADA, DADA, and ADADA (*EEEE* rotamer). In some conformations electronic repulsions (solid black dot, Chart 6) or CH/CH interactions (solid blue dot) are also possible. The latter repulsion is especially important in pyrimidines with large substituents and was also found in *N*,*N*′-bisarylformamidines.[43] Among the arrays, *ZEEZ* is complementary with *ZEZE*, which is also complementary with *ZEEE*, but in this case a weak CH···O hydrogen bond can be formed. All rotamers shown in Chart 6 and their dimers were energetically optimized (Supporting Information, Tables S3 and S4). Because triply[34] and quadruply[83] hydrogen bonded systems are generally more stable than doubly hydrogen bonded systems,[32] these were not taken into account.

Table 4. Dimerization Constants (K_{dim}) for Compounds 1b−5b

compd	K_{dim} (M^{-1})
1b	550[a] (600)[b]
2b	140[c]
3b	30[d] (25)[e]
4b	*f*
5b	*f*

[a]Based on two NH's and one aromatic proton. [b]Based on CH_3 protons (two methyl groups). The different nuclei gave the same K_{dim} value. [c]Based on two NH's, one methylene group, and one aromatic proton. [d]Based on two NH's and one methine proton. [e]Based on one methine and one aromatic proton. [f]Compound does not dimerize in $CDCl_3$.

Self-Association of 2,4-Bis(acylamino)pyrimidines. In Table 4 are collected the dimerization constants (K_{dim}) obtained by observing the chemical shift changes of several protons (charts are given in the Supporting Information).

The data in Table 4 show that K_{dim} is related to the size of the substituent, which is in agreement with our previous results.[34] As mentioned before in 2,4-bis(acylamino)-pyrimidines two types of steric effects are present, i.e. indirect and direct, related to the steric interactions[34] of R groups (Chart 7).

Table 5 gives the energy of interaction (E_{int}) for all dimers of **1b**, which varies from −28.5 to −69.7 kJ/mol. For simplification only compound **1b** was studied.

The E_{int} energy cutoff at ca. 20 kJ/mol was used as a barrier above which other dimeric forms are less probable. From 11 dimers lying below that cutoff (E_{int} values in bold font), 8 structures contain weak CH···O interactions. Only these dimers are shown in Figure 2. The same figure collects the data of relative energy of the monomer that builds the respective dimer (E_{rel}, kJ/mol) and the sum of the energies of hydrogen bonds ($\sum E_{HB}$, kJ/mol) derived from QTAIM (Espinosa approach[78,79]).

In Table 6 are collected the energies of hydrogen bonds (from left to right as in Figure 2) in dimers of **1b** lying under the 20 kJ/mol E_{int} cutoff (the remaining energies are collected in the Supporting Information).

On the basis of dilution experiments alone, it is not possible to conclude which of the many possible rotameric forms interacts, but simultaneous probing of several protons can help to draw conclusions on the complex equilibrium. In 2,4-bis(acylamino)pyrimidines exist two NH and two non-equivalent CH protons. There is no significant correlation between K_{dim} and Taft's constant (R^2 = 0.578, n = 3). K_{dim} values suggest that the dimerization takes place by triple and/or quadruple hydrogen bonding. K_{dim}(**1b**) = 550−600 M^{-1} is slightly higher than K_{dim} for 2-acylamino-6-[1*H*]pyridones[46] and does not fit either a triply or quadruply hydrogen bonded dimer—compare K_{dim}= 1800−1900 M^{-1} for **B**[83] and K_{assoc} = 15 M^{-1} for 2-acetylaminopyrimidine (**1a**) with 2,6-bis-(cyclopropylcarbonylamino)pyridine.[33] Moreover, both NHs and one aromatic CH proton behave similarly during the dilution experiments, while the other aromatic CH proton behaves more or less randomly (see the Supporting

dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609−9619

Chart 6. Rotamers of 2,4-Bis(acetylamino)pyrimidine with the Intramolecular Repulsions Crucial to Destabilization of the Respective Forms

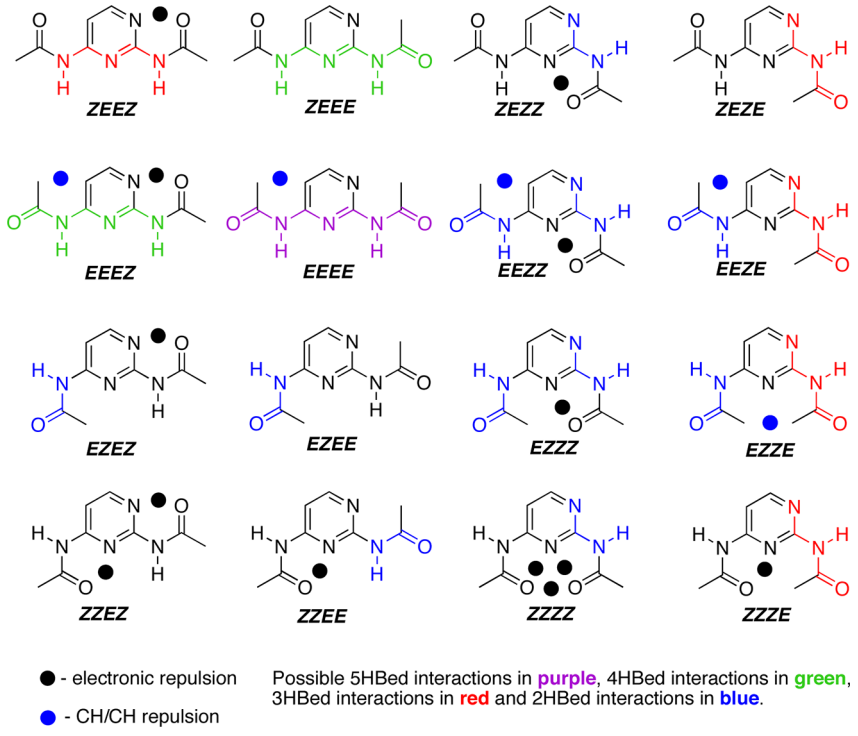
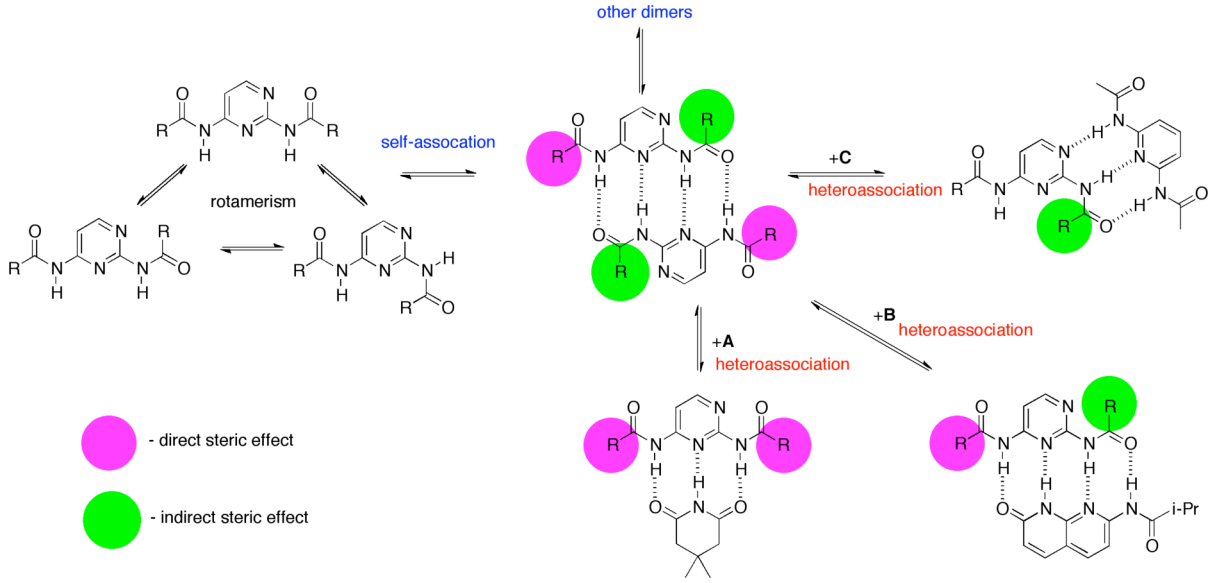


Chart 7. Dimerization and Heteroassociation in 2,4-Bis(acylamino)pyrimidines Highlighting Direct and Indirect Steric Effects



Information). This suggests that both NH protons are involved in hydrogen bonding and one aromatic CH is located in the vicinity of moieties responsible for magnetic anisotropy or it forms a weak CH···O═C hydrogen bond. Finally, the NOESY spectrum of **3b** recorded at −50 °C revealed weak NOE contacts (see the Supporting Information). Also, the variable-temperature (VT) spectra suggested that 2,4-bis(acylamino)-pyrimidines exist as a mixture of dimers. At −50 °C we have observed three NH signals, which split at −40 °C into four signals. These signals became more shielded as the temperature was raised, and the intensity of two of them decreased. For H5 at −50 °C two doublets were observed, which coalesce as the temperature increased. The methine of the *i*-Pr group is a good indicator for the coexistence of various dimeric forms of **3b**. Four CH multiplets with very different chemical shifts (range 2.5−4.1 ppm) have been observed. The methine proton was previously used by us as an additional probe in the determination of association constants.[33] The VT ^{1}H NMR spectra are collected in the Supporting Information. The K_{dim} values and their poor dependence on steric E_s constant suggest a coexistence of two different dimers as in 2-acylaminopyr-imidines. At this stage the results can be summarized shortly that the 2,4-bis(acylamino)pyrimidines dimerize by three or

dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609−9619

Table 5. Interaction Energy (E_{int}) for All Dimers of 1b Considered[a]

dimer (form)	E_{int} (kJ/mol)	dimer	E_{int} (kJ/mol)	dimer	E_{int} (kJ/mol)
ZEEE/ZEEE	**−69.7**	*ZEEZ/EEZE* (2)	−49.6	*EEEE/ZZZE* (1)	−42.8
ZEEE/ZZZE (2)	**−65.9**	*ZEEZ/ZEZE* (2)	−49.4	*EEEE/EEZE* (1)	−42.6
ZEEE/EZZE (2)	**−63.6**	*EEEE/ZZZE* (2)	−48.8	*EEEE/ZEZE* (1)	−41.5
ZEEE/EEZE (2)	**−61.5**	*EEEE/EZZE* (2)	−48.7	*EEEZ/ZZZE* (2)	−40.1
EEEZ/ZZZE (1)	**−60.7**	*ZEEZ/ZZZE* (1)	−48.5	*EEEZ/EZZE* (2)	−39.1
ZEEE/ZEZE (2)	**−60.6**	*ZEEZ/EZZE* (1)	−47.1	*EEEZ/ZEZE* (2)	−38.7
EEEZ/EEZE (1)	**−57.4**	*EEEE/EEZE* (2)	−46.5	*EEEZ/EEZE* (2)	−37.6
EEEZ/ZEZE (1)	**−55.8**	*ZEEZ/ZEZE* (1)	−45.4	*ZEEE/ZZZE* (1)	−36.2
EEEZ/EZZE (1)	**−54.2**	*EEEE/ZEZE* (2)	−44.9	*ZEEE/ZEZE* (1)	−35.1
ZEEZ/ZZZE (2)	**−51.8**	*ZEEZ/EEZE* (1)	−44.3	*ZEEE/EEZE* (1)	−33.2
ZEEZ/EZZE (2)	**−49.9**	*EEEE/EZZE* (1)	−43.7	*ZEEE/EZZE* (1)	−28.5

[a]For graphic representations of dimers and related Cartesian coordinates see the Supporting Information.

four hydrogen bonds (or both of that within two dimers), while the analogous pyridine derivatives do not.[33,34,59]

The possibility of formation of associates in various rotameric states of 2,4-bis(acylamino)pyrimidines can be studied by titrations (see later in text), while computational methods provide the relative energies of various dimers.

From Table 6 it is easy to notice that the CH···O interaction contributes to the overall stabilization of dimers at a level of ca. 13%. The difference between the sums of E_{HB} and E_{int} is the sum of the repulsive energy according to Jorgensen's secondary interactions[25] model. This difference is ca. 10 kJ/mol lower for dimers lying below the said cutoff than for those that have higher relative energy. This, most probably, is because the NH/CH bond dipoles do not repulse as strongly as, for example, NH/NH or NH/OH dipoles. The calculated interaction energies also suggest that in **1b** more than one dimer is present.

Heteroassociation of 2,4-Bis(acylamino)pyrimidines. The X-ray structure of **1a** reveals that the presence of N1 and N3 allows free rotation within the NHCOR moiety and therefore **1b**−**5b** can form various heteroassociates due to the same "N1+N3 effect". To screen the conformational preferences of 2,4-bis(acylamino)pyrimidines and their potential association with various counterparts, compounds **A**−**C** were used as ^{1}H NMR titrants. The *i*-Pr derivative **B** was chosen instead of one bearing a smaller substituent (Me or Et) due to the good solubility of **B** in comparison with other naphthyridine congeners.[83] It is also worth mentioning that the dimerization constants (K_{dim} (M^{-1})) for titrants are 2.3 for **A**[33] and 1800−1900 for **B**,[83] while 2,6-bis(acetylamino)pyridine (**C**) does not dimerize in $CDCl_3$.[34,59]

The possible heterocomplexes of 2,4-bis(acylamino)-pyrimidines with **A**−**C** are shown in Chart 8.

In Table 7 are collected K_{assoc} values for the complexes shown in Chart 8 (data for **5b** are missing due to the reasons given below).

The geometry optimization for heterocomplexes of **1b** with **A**−**C** were performed for these rotamers that fit the hydrogen-bonding pattern of **A**−**C** counterparts. Tables 8−10 collect the crucial data. Due to the very time-consuming calculations, these were only performed for the **1b** derivative.

There are four rotamers of 2,4-bis(acylamino)pyrimidines that are able to form three hydrogen bonds with **A**. These are *ZEEZ*, *ZEEE*, *EEEZ* and *EEEE* forms (Chart 6). Table 8 collects the energy of interaction in **1b**+**A** complex with various rotameric forms of **1b**.

Three rotameric forms of **1b** (*EEEZ*, *ZEEE* and *EEEE*) may form complexes with **B** (Table 9). One rotamer is able to form two forms with different spatial arrangements of the molecules.

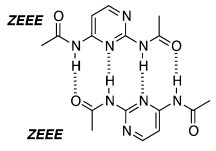
The respective data for **1b** + **C** are summarized in Table 10.

5b was excluded from titrations due to a higher rigidity of its R moiety in comparison with the other moieties. However, **5b** + **A** (a complex that should be stabilized by three hydrogen bonds) was studied. The NH chemical shifts in **5b** did not change more than 0.1 ppm, suggesting very weak association owing to the large size and rigidity of the 1-adamantyl group. The situation is comparable with that for 2-acylaminopyridines, where the methyl derivative forms a doubly NH···N hydrogen bonded complex, adamantyl forms ribbonlike polymers stabilized by NH···O interactions, and *tert*-butyl forms both species, as reported by us.[32] Thus, the change from *t*-Bu to 1-adamantyl is crucial for intermolecular interactions of the NHCOR group, its rotation about the N−C bond, and steric crowding. This is also confirmed by the magnitude of the E_s constant found by us for 1-adamantyl.[83] The reported E_s for 1-adamantyl is 33% higher with respect to the value for the *t*-Bu group.

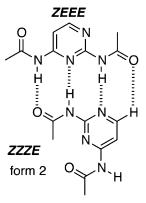
Direct comparisons between series of heterocomplexes can only be done for **A** and **B**, due to the missing data in the **C** series (Table 7). It is interesting that the association constants of 2,4-bis(acylamino)pyrimidines with **A** and **B** behave similarly. The association constant decreases on going from R = Me to R = Et and then strongly increases to R = *t*-Bu (Figure 3). The mutual correlation between K_{assoc} for **1b**−**4b** + **A** and K_{assoc} for **1b**−**4b** + **B** is high (R = 0.974). This means that both **A** and **B** titrants act in a similar fashion, decomposing the dimers of 2,4-bis(acylamino)pyrimidines. On the other hand, the magnitudes of K_{assoc} values suggest that heterocomplexation is easier when the substituent is larger because its size hinders efficient dimerization. There are three or four large substituents in the dimer (Figure 2) that hinder dimerization in a *direct* or *indirect* fashion, while in the heteroassociate one or two of them influences aggregation (Chart 8). In other words, the larger substituent preventing dimerization causes the high concentration of the monomer capable for heterocomplexation.

Some titration curves possess complex shapes, making them impractical for the calculation of the association constant. Those sigmoidal shapes can be caused by multiple monomer/oligomer equilibria, as argued before.[46,80] Interestingly, titration curves behave differently: decreasing (**1b** with **A**) or increasing (**3b** and **4b** with **A**) and first decreasing and after that increasing (**2b** + **A**, sigmoidal shape). In Figure 4 example curves are shown. Curve *c* shows evidently that more than two

dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609−9619



E_{rel}(top) =2.3
E_{rel}(bottom) =2.3
E_{int} =-69.7
ΣE_{HB}= -84.2



E_{rel}(top) =2.3
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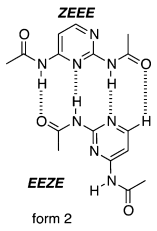
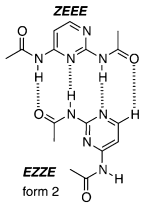
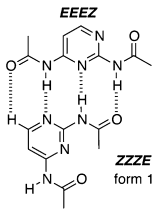
E_{int} =-65.9
ΣE_{HB}= -72.0



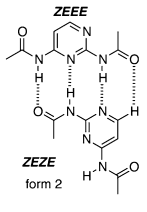
E_{rel}(top) =2.3
E_{rel}(bottom) =22.6
E_{int} = -63.6
ΣE_{HB}=-70.5



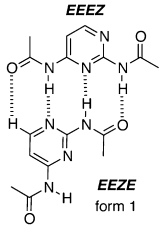
E_{rel}(top) =2.3
E_{rel}(bottom) =27.9
E_{int} =-61.5
ΣE_{HB}=-70.5



E_{rel}(top) =33.5
E_{rel}(bottom) =22.9
E_{int} =-60.7
ΣE_{HB}=-70.5



E_{rel}(top) =2.3
E_{rel}(bottom) =0.0
E_{int} =-60.6
ΣE_{HB}=-70.1



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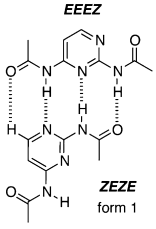
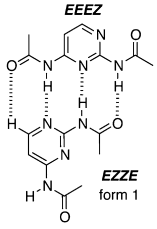
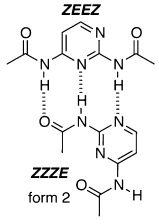
E_{rel}(bottom) =22.6
E_{int} =-57.4
ΣE_{HB}=-69.4



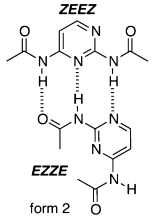
E_{rel}(top) =33.5
E_{rel}(bottom) =0.0
E_{int} =-55.8
ΣE_{HB}=-69.4



E_{rel}(top) =33.5
E_{rel}(bottom) =27.9
E_{int} =-54.2
ΣE_{HB}=-67.4



E_{rel}(top) =13.2
E_{rel}(bottom) =22.9
E_{int} =-51.8
ΣE_{HB}=-58.1



E_{rel}(top) =13.2
E_{rel}(bottom) =27.9
E_{int} =-49.9
ΣE_{HB}=-58.8

Figure 2. The chosen 11 dimers of **1b** with the highest energies of interaction.

individual species are present in solution. These are, most probably, two dimers and the heterocomplex **2b** + **A**.[80] For similar examples see our previous work.[46]

The sigmoidal shape is observed only with **A**. The probable explanation is that in the case of **B** and **C** at least one rotamer of the initial mixture of two dimers does not change. This means that **A** associates with the *ZEEZ* form of 2,4-bis(acylamino)pyrimidines, while **B** and **C** associate with rotamers that are also present in more stable dimers of 2,4-bis(acylamino)pyrimidine. Thus, the most dramatic changes in the ratio and the type of rotamers present in solution (dimers vs heteroassociates) are the easiest to observe during the titration with **A**. In other words, compounds **B** and **C** replace one of the rotamers in the dimer of 2,4-bis(acylamino)-

Table 6. Energy (E_{HB}) of Individual Hydrogen Bonds

dimer[a]	E_{HB} (kJ/mol) NH···O	NH···N	NH···N	CH···O	$\sum E_{HB}$
ZEEE/ZEEE	−32.8	−9.3			−84.2
ZEEE/ZZZE (2)	−27.8	−23.3	−10.2	−10.7	−72.0
ZEEE/EZZE (2)	−27.3	−22.2	−9.5	−11.5	−70.5
ZEEE/EEZE (2)	−26.8	−22.9	−9.7	−11.1	−70.5
EEEZ/ZZZE (1)	−24.6	−25.8	−10.7	−9.4	−70.5
ZEEE/ZEZE (2)	−27.2	−22.3	−9.8	−10.8	−70.1
EEEZ/EEZE (1)	−24.2	−25.1	−10.5	−9.5	−69.3
EEEZ/ZEZE (1)	−24.6	−25.0	−10.7	−9.1	−69.4
EEEZ/EZZE (1)	−24.9	−22.8	−8.9	−10.8	−67.4
ZEEZ/ZZZE (2)	−27.1	−17.4	−13.6		−58.1
ZEEZ/EZZE (2)	−26.5	−17.7	−14.6		−58.8

[a]The dimers are sorted as in Table 5 (by E_{int} energy).

Chart 8. Association of 2,4-Bis(acylamino)pyrimidines with Chosen Counterparts

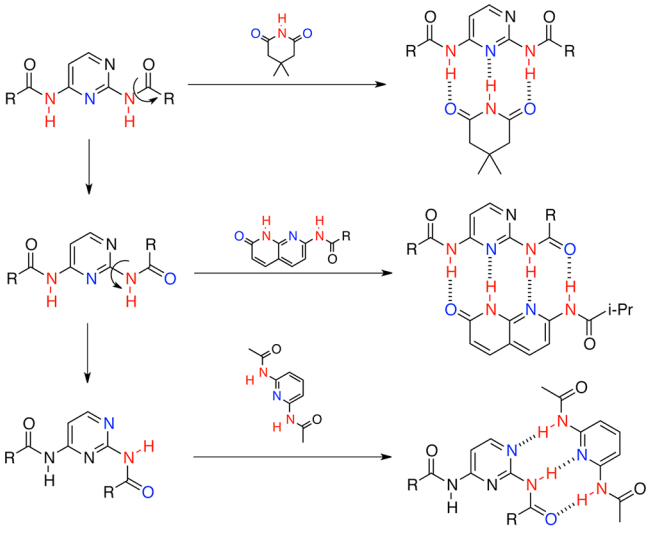


Table 7. K_{assoc} Values for the Complexes Studied[a]

compd	K_{assoc} (M^{-1}) A	B	C
1b	40,[b] 25,[c] 25,[d] **30**	700,[b] 600,[d] 800,[e] **700**	18,[b,e] 11[g]
2b	7,[e] 16,[d] 28,[f] **17**	200,[b] 190,[e] **195**	23,[b] 90,[g] 80[j]
3b	20,[b] 20,[e] 24,[d] 14,[g] 95,[h] 14,[i] **31**	550,[b] 300,[e] **425**	*k*
4b	180,[b] **180**	1800,[b] **1800**	*k*

Values based on:

[a]Average values are given in boldface. [b]Value based on NH (low-field signal). [c]Value based on CH_3 signal. [d]Value based on aromatic CH proton (low-field signal). [e]Value based on NH (high-field signal). [f]Value based on CH_2 (low-field signal). [g]Value based on aromatic CH signal (high-field signal). [h]Value based on methine CH proton (low-field signal). [i]Value based on methine CH proton (high-field signal). [j]Value based on CH_2 (high-field signal). [k]It was not possible to calculate the association constants due to the linear (**3b**) or random (**4b**) character of $\delta = f([\text{titrant}])$ function.

dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609−9619

Table 8. Calculated Energies of Interaction between 1b and A

form of **1b**	E_{int} (kJ/mol)	$\sum E_{HB}$ (kJ/mol)
ZEEZ + **A**	−54.4	−63.0
ZEEE + **A**	−43.8	−62.4
EEEZ + **A**	−58.7	−64.9
EEEE + **A**	−31.1	−64.3

Table 9. Calculated Energies of Interaction between 1b and B

form of **1b**	E_{int} (kJ/mol)	$\sum E_{HB}$ (kJ/mol)
EEEZ + **B**	−74.8	−86.6
ZEEE + **B**	−84.1	−88.3
EEEE + **B** (form 1)	−56.5	−86.0
EEEE + **B** (form 2)	−63.7	−90.2

Table 10. Calculated Energies of Interaction between 1b and C

form of **1b**	E_{int} (kJ/mol)	$\sum E_{HB}$ (kJ/mol)
ZEZE + **C**	−43.4	−54.7
EEZE + **C**	−42.1	−54.3
EZZE + **C**	−45.2	−56.2
ZZZE + **C**	−45.9	−54.8

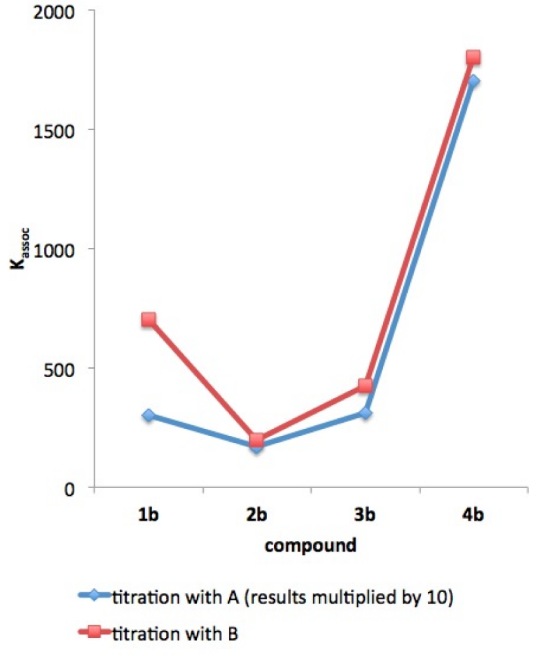


Figure 3. Relationship between K_{assoc} values of 2,4-bis(acylamino)-pyrimidines with **A** and **B**.

pyrimidine, leaving the remaining rotamer unchanged, while **A** changes the rotameric form of both constituents of the dimer.

The computational data support conclusions based on experiments. The energy of interaction of **1b** + **A** (see also Supporting Information) is comparable to the energy of triply hydrogen-bonded dimers of **1b** (Table 8). The energy of interaction for two forms of the **1b** + **B** associate (Table 9) is higher than any interaction for the dimer of **1b** (Table 5). This is in agreement with the K_{dim} (Table 4) and K_{assoc} (Table 7) data obtained by experimental methods. With regard to the associate **1b** + **C**, four rotamers are capable of efficient hydrogen bonding. Since the rotation of one acylamino group is free, due to not having any contribution to intermolecular hydrogen bonding, the E_{int} energies (Table 10) are very close to one another.

CONCLUSIONS

A change of carbon-3 to nitrogen in the pyridine ring leads to the formation of pyrimidine and an additional basic center in the heteroaromatic ring. This structural change results in an easy rotation in the RCONH moiety of 2-acylamino- and 2,4-bis(acylamino)pyrimidines and consequently several conformers are possible, which are further capable of multiple intermolecular interactions. The subtle balance among intra-/intermolecular steric effects, intramolecular electronic repulsions, intermolecular secondary interactions, and weak CH···O hydrogen bonding is characteristic of self-assembly and heteroassociation of 2-acylamino- and 2,4-bis(acylamino)-pyrimidines. This study reveals that in supramolecular assemblies of these pyrimidines the structure of the frontier (interacting) part of the molecule is crucial but also that the whole molecular backbone is important and should be taken into account. The conclusions are drawn via a multidisciplinary approach, combining NMR spectral, X-ray structural, and computational data, which are all needed for this very complex research topic.

EXPERIMENTAL SECTION

General Considerations. All substrates for synthesis were purchased from Aldrich and were used as received. The melting points were determined with the use of a Büchi apparatus with 5 °C/min gradient. Compounds **1a**−**5a** were synthesized as described earlier for 2-acylaminopyridines.[32] The yields of syntheses varied from 74 to 85%. Compounds were purified by recrystallization from a hexane/ethyl acetate mixture (10/1 v/v). Crystals suitable for X-ray determination were obtained during slow evaporation of solutions used in NMR experiments. Compounds **1b**−**5b** were obtained by heating 2,4-diaminopyrimidine with the respective acid chloride (2 equiv) in boiling, dry pyridine for 10 h. After this time the mixture was evaporated to dryness and a saturated aqueous Na_2CO_3 solution was added (20 mL). The mixture was extracted several times with chloroform, and the combined organic fractions were evaporated. The solid was heated to 70 °C under ca. 3 mmHg vacuum to remove the residual pyridine. The remaining solids were recrystallized twice from hexane/ethyl acetate.

The recording of NMR spectra[46] and solution of the solid-state structures by X-ray diffractometry[91] were performed as described in our previous papers.

Spectral and Characterization Data. It is quite hard to assign the signals to the respective protons in molecules **1b**−**5b** in $CDCl_3$. The problem arises when one realizes that (a) the low-field (deshielded) NH proton should belong to the acylamino group located at position 2 (two electronegative nitrogen atoms close to the NH group), (b) the same NH proton forms the hydrogen bond with the nitrogen atom of another molecule, and (c) the high-field NH (shielded) proton should belong to the acylamino in position 4 but (d) this proton forms a hydrogen bond with the oxygen in another molecule. Since the NH···O hydrogen bond is stronger than the NH···N bond, the aforementioned interactions cause opposite effects. Thus, the assignment of chemical shifts in **1b**−**5b** is based on the $^{1}H,^{15}N$ HMBC spectra in DMSO-d_6. The assumption was made that in this solvent compounds do not form dimers.

*2-Acetylaminopyrimidine (**1a**, R = Me).* ^{1}H NMR ($CDCl_3$): δ 9.52 (bs, 1H, H7), 8.62 (d, 2H, H4 and H6, $^{3}J_{H,H}$ = 4.9 Hz), 6.99 (t, 1H, H5, $^{3}J_{H,H}$ = 4.9 Hz), 2.51 (s, 3H, CH_3). ^{13}C NMR: δ 171.4 (C8), 158.3 (C4 and C6), 157.8 (C2), 116.0 (C5), 25.2 (CH_3). ^{15}N NMR: δ

dx.doi.org/10.1021/jo301643z | J. Org. Chem. 2012, 77, 9609−9619

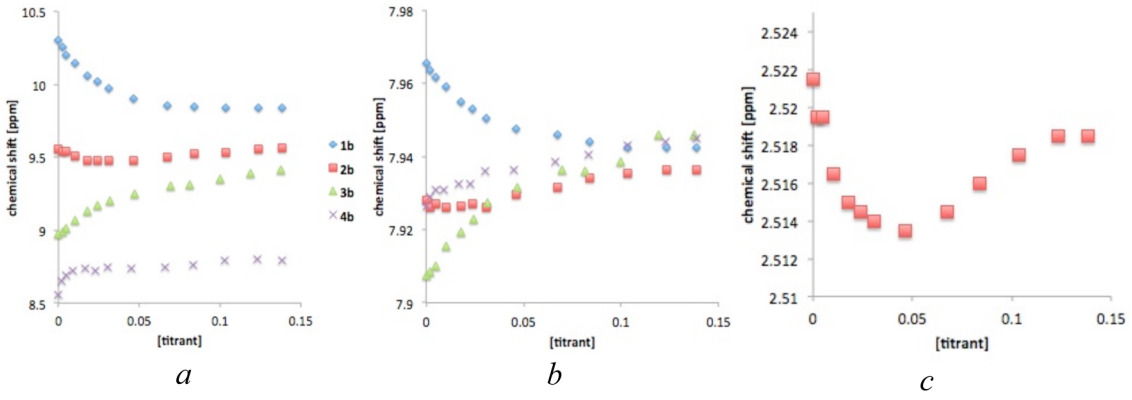


Figure 4. Comparison of the shapes of titration curves for the **1b**−**4b** series: (*a*) titrant **A**, low-field NH; (*b*) titrant **A**, high-field aromatic CH; (*c*) sigmoidal shape of the methylene (**2b**) based titration curve.

−120.0 (N1 and N3), −232.8 (N7). Mp: 146.3−148.0 °C (lit.[84] mp 146−147 °C).

*2-Propionylaminopyrimidine (**2a**, R = Et).* ^{1}H NMR ($CDCl_3$): δ 8.95 (bs, 1H, H7), 8.61 (d, 2H, H4 and H6, $^3J_{H,H}$ = 4.9 Hz), 6.98 (t, 1H, H5, $^3J_{H,H}$ = 4.9 Hz), 2.80 (q, 2H, CH_2), 1.24 (t, 3H, CH_3). ^{13}C NMR: δ 174.3 (C8), 158.3 (C4 and C6), 157.7 (C2), 116.0 (C5), 30.8 (CH_2), 9.0 (CH_3). ^{15}N NMR: δ −118.5 (N1 and N3). Mp: 127.2−128.3 °C (lit.[85] mp 125−126 °C).

*2-Isobutyryloaminopyrimidine (**3a**, R = i-Pr).* ^{1}H NMR ($CDCl_3$): δ 9.09 (bs, 1H, H7), 8.61 (d, 2H, H4 and H6, $^3J_{H,H}$ = 4.9 Hz), 6.97 (t, 1H, H5, $^3J_{H,H}$ = 4.9 Hz), 3.12 (m, 1H, methine CH, $^3J_{H,H}$ = 6.9 Hz), 1.23 (d, 6H, CH_3, $^3J_{H,H}$ = 6.9 Hz), ^{13}C NMR: δ 176.8 (C8), 158.3 (C4 and C6), 157.7 (C2), 116.1 (C5), 35.5 (methine CH), 19.1 (CH_3). ^{15}N NMR: δ −118.4 (N1 and N3), −238.4 (N7). Mp: 125.4−126.9 °C. Anal. Calcd: C, 58.17; H, 6.71; N, 25.44. Found: C, 58.15; H, 6.73; N, 25.40.

*2-Pivaloylaminopyrimidine (**4a**, R = t-Bu).* ^{1}H NMR ($CDCl_3$): δ 8.61 (d, 2H, H4 and H6, $^3J_{H,H}$ = 4.9 Hz), 8.09 (bs, 1H, H7), 7.00 (t, 1H, H5, $^3J_{H,H}$ = 4.9 Hz), 1.33 (s, 9H, CH_3). ^{13}C NMR: δ 175.7 (C8), 158.3 (C4 and C6), 157.7 (C2), 116.6 (C5), 40.2 (quaternary C), 27.4 (CH_3). ^{15}N NMR: δ −116.4 (N1 and N3), −247.1 (N7). Mp: 112.0−113.5 °C. Anal. Calcd: C, 60.32; H, 7.31; N, 23.45, Found: C, 60.18; H, 7.40; N, 23.19.

*2-Adamantoylaminopyrimidine (**5a**, R = 1-Adamantyl).* ^{1}H NMR ($CDCl_3$): δ 8.60 (d, 2H, H4 and H6, $^3J_{H,H}$ = 4.9 Hz), 8.08 (bs, 1H, H7), 7.00 (t, 1H, H5, $^3J_{H,H}$ = 4.9 Hz), 2.10−1.70 (15H, 1-adamantyl). ^{13}C NMR: 175.2 (C8), 158.3 (C4 and C6), 157.9 (C2), 116.6 (C5), adamantyl 42.2, 39.1, 36.4, 28.1. ^{15}N NMR: δ −115.9 (N1 and N3), −247.6 (N7). Mp: 188.8−190.1 °C. Anal. Calcd: C, 70.01; H, 7.44; N, 16.33. Found: C, 69.97; H, 7.47; N, 16.31.

*2,4-Bis(acetylamino)pyrimidine (**1b**, R = Me).* ^{1}H NMR (DMSO-d_6): δ 10.63 (bs, 1H, H11), 10.22 (bs, 1H, H7), 8.45 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H6), 7.70 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H5), 2.21 (s, 3H, H14 in R′, CH_3), 2.14 (s, 3H, H10 in R′, CH_3). ^{13}C NMR: δ 170.68 (C12), 169.31 (C8), 159.24 (C6), 158.44 (C4), 157.36 (C2), 104.62 (C5), 24.64 and 24.15 (CH_3). ^{15}N NMR: δ −125.2 (N1), −143.9 (N3), −235.1 (N11), −234.0 (N7). Mp: 235.0−238.4 °C (lit.[86] mp 240−243 °C).

*2,4-Bis(propionylamino)pyrimidine (**2b**, R = Et).* ^{1}H NMR (DMSO-d_6): δ 10.58 (bs, 1H, H11), 10.21 (bs, 1H, H7), 8.42 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H6), 7.73 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H5), 2.51 (q, 2H, CH_2), 2.45 (q, 2H, CH_2), 1.05 (t, 6H, CH_3). ^{13}C NMR: δ 174.16 (C12), 172.57 (C8), 159.02 (C6), 158.44 (C2), 157.28 (C4), 104.63 (C5), 29.63 (CH_2), 29,45 (CH_2), 9.18 (CH_3), 8.99 (CH_3). ^{15}N NMR: δ −125.1 (N1), −143.7 (N3), −237.1 (N11), −236.5 (N7). Mp: 215.0−217.9 °C (pale yellow crystals). Anal. Calcd: C, 54.04; H, 6.35; N, 25.21. Found: C, 53.89; H, 6.42; N, 25.10.

*2,4-Bis(isobutyrylamino)pyrimidine (**3b**, R = i-Pr).* ^{1}H NMR (DMSO-d_6): δ 10.65 (bs, 1H, H11), 10.29 (bs, 1H, H7), 8.47 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H6), 7.77 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H5), 2.83 (m, 2H, CH), 1.07 (s, 6H, CH_3), 1.06 (s, 6H, CH_3). ^{13}C NMR: δ 177.54 (C12), 175.18 (C8), 159.21 (C6), 158.68 (C2), 157.35 (C4), 105.12 (C5), 34.48 (CH, substituent), 34.31 (CH, substituent), 19.18 (CH_3, substituent) (CH_2), 29.45 (CH_2), 9.18 (CH_3), 8.99 (CH_3), ^{15}N NMR: δ −122.9 (N1), −140.9 (N3), −238.6 (N11). Mp: 195.6−199.4 °C (off-white crystals). Anal. Calcd: C, 57.58; H, 7.25; N, 22.38. Found: C, 57.41; H, 7.41; N, 22.22.

*2,4-Bis(tert-butylamino)pyrimidine (**4b**, R = t-Bu).* ^{1}H NMR (DMSO-d_6): δ 10.08 (bs, 1H, H11), 9.806 (bs, 1H, H7), 8.53 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H6), 7.80 (d, $^3J_{H,H}$ = 5.5 Hz, 1H, H5), 1.23 (s, 9H, CH_3), 1.21 (s, 9H, CH_3). ^{13}C NMR: δ 178.29 (C12), 175.94 (C8), 159.09 (C6/C2 overlapped), 157.53 (C4), 106.28 (C5), 26.87 (CH_3, substituent), 26.54 (CH_3, substituent), quaternary carbon belonging to *t*-Bu overlapped with DMSO-d_6. ^{15}N NMR: δ −117.6 (N1), −244.2 (N11), −245.3 (N7). Mp: 130.2−134.9 °C (off-white crystals). Anal. Calcd: C, 60.41; H, 7.97; N, 20.13. Found: C, 60.32; H, 8.04; N, 20.02.

*2,4-Bis(1-adamantoylamino)pyrimidine (**5b**, R = 1-Adamantane).* ^{1}H NMR (DMSO-d_6): δ 9.95 (bs, 1H, H11), 9.667 (bs, 1H, H7), 8.50 (d, $^3J_{H,H}$ = 5.6 Hz, 1H, H6), 7.79 (d, $^3J_{H,H}$ = 5.6 Hz, 1H, H5), 1.996−1.657 (30H, 1-adamantyl), ^{13}C NMR: δ 177.58, (C12), 175.35 (C8), 159.00 (C6), 158.97 (C2), 157.53(C4), 106.09 (C5), 41.52, 41.08, 37.93, 37.44, 35.88, 35.72, 27.62, 27.55 (two adamantyls). ^{15}N NMR: δ −118.0 (N1), −135.2 (N3), −244.4 (N11), −245.4 (N7). Mp: 228.4−230.7 °C (yellowish crystals). Anal. Calcd: C, 71.86; H, 7.89; N, 12.89. Found: C, 71.72; H, 7.99; N, 12.67.

Calculations. The calculations were run at the DFT level with the use of the M05 functional (M05/6-311G(d,p)). This functional was chosen to sustain the methodology related to our other papers.[32,34,45,46,83] All optimizations and frequency calculations (only positive frequencies were obtained) were performed in Gaussian 03[87] under vacuum. The QTAIM-based properties of hydrogen bond critical points were computed with the use of AIM2000 software.[88] The calculated energies of interaction (difference between the energy of the complex and the sum of energies of its constituents) were corrected to BSSE with the use of the counterpoise[89,90] method as implemented in Gaussian with default settings. The zero-point energy correction was applied.

■ ASSOCIATED CONTENT

Supporting Information

Figures, tables, and CIF files giving NMR spectra, XRD data, dilution and titration curves, sigmoidal curves, and computational data (Cartesian coordinates, energies, relative energies, hydrogen bond energies, energies of interaction). 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.

■ ACKNOWLEDGMENTS

Financial support from the National Science Centre in Kraków (Grant No. N N204 356840) is gratefully acknowledged. We are very much indebted to the ICM in Warsaw for providing computer time and programs.

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