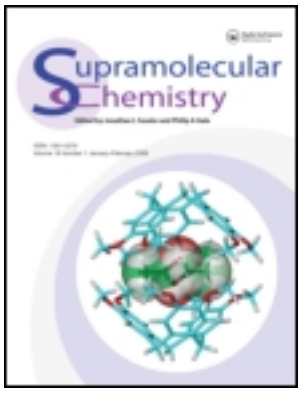

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Tuning the hydrogen-bonding strength in 2,6-bis(cycloalkylcarbonylamino)pyridine assemblies by variable flexibility. Association constants measured by hydrogen-bonded vs. non-hydrogen-bonded protons

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Tuning the hydrogen-bonding strength in 2,6-bis(cycloalkylcarbonylamino)pyridine assemblies by variable flexibility. Association constants measured by hydrogen-bonded vs. non-hydrogen-bonded protons

Borys Ośmiałowski[a]*, Erkki Kolehmainen[b], Reijo Kauppinen[b] and Magdalena Kowalska[a]

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The association of 2,6-bis(cycloalkylcarbonylamino)pyridines with rigid and non-rigid counterparts in chloroform solution was studied using ^{1}H NMR and computational methods. The angles within the cycloalkyl ring and the rotation of these substituents determine the strength of the association via triple hydrogen bonding. The dimerisation and methyl–methyl repulsion have been addressed as mechanisms restricting heterocomplexation of diacetamide. The association constants obtained by the shift changes of hydrogen-bonded protons are in agreement with those of methine protons. This 'dual shift' method was proposed as an additional verification of association constants obtained generally by amino protons.

Keywords: hydrogen bonding; association; steric effect; multi-probing

1. Introduction

The non-covalent assemblies of small molecules stabilised by weak and directional interactions such as hydrogen bonds (*1–3*) are under regular studies, so the number of publications on supramolecular chemistry is increasing rapidly (*4*). Various methods have been developed for understanding the stability of associates based on molecular properties (*5*). One of the most frequently used methods is the ^{1}H NMR titration. This is due to the very high sensitivity of chemical shifts of hydrogen-bonded nuclei (usually protons of OH and/or NH groups) to concentration, water content (*6*) and quite often to many coexisting hydrogen-bonding processes (*7–9*). Thus, monitoring several nuclei is the method of choice to improve the reliability of the obtained results. Moreover, this is especially useful if others overlap NH or OH signals or if the fast proton transfer in NMR time scale restricts direct observation of NH/OH signal. The experimentally obtained association constants and geometry of associates are compared to the results obtained from theoretical calculations (*10–13*).

Triple hydrogen-bonded associates are seen in many structures such as in DNA (*14*, *15*), amides (*16*, *17*), artificial sensors (*18–22*), materials (*23*), non-covalent polymers (*4*, *24–28*) and in recently observed associates of orotic acid (*29*, *30*). Triple hydrogen-bonded assemblies carrying 2,6-diaminopyridine DAD-hydrogen-bonding moiety were studied by some groups with the use of various methods (*4*, *6*, *31–47*) and also by us (*48*, *49*). We noticed that the use of NH and CH proton shifts as probes in NMR titration gave the similar results of K_{assoc} in case of compounds containing *i*-Pr group (*48*). This finding prompted us to enlarge the number of compounds carrying the CH methine proton. We synthesised symmetrical 2,6-bis(cycloalkylcarbonylamino)pyridines (cycloalkyl = -propyl, -butyl, -pentyl and -hexyl) and studied their association with some ADA-hydrogen-bonding motifs. The goal of this paper is (a) to test whether the monitoring of several nuclei in the single titration experiment is useful for the determination of association constants, (b) to tune the association of cycloalkylcarbonyl derivatives of 2,6-diaminopyridines with dipyridin-2-ylamine (**5**), 2-acetylaminopyrimidine (**6**), diacetamide (**7**), 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (**8**) and 4,4-dimethylpiperidine-2,6-dione (**9**) (Figure 1) and (c) to find out whether the size of the rotational cone determined by the $\beta-\alpha-\beta'$ angle in cycloalkyl group (Figure 2) might be a parameter crucial for the steric hindrance in non-covalent assemblies.

The cycloalkyl rotation about C8/C11-α bonds forms cones of different radii depending on the $\beta-\alpha-\beta'$ angle. Both the overall size of the cycloalkyl and the mentioned cone should influence the steric hindrance (Scheme 1).

Previously (*48*), we confirmed the results from other group (*50*) reporting that the 2,6-bis(acylamino)pyridine does not dimerise. As the cycloalkyl moieties are larger than methyl, it is reasonable to assume that compounds

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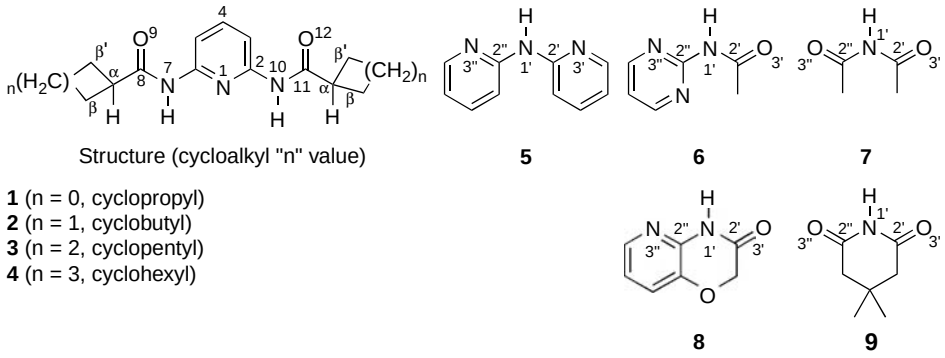


Figure 1. Formulas of the components of the complexes studied and atom labelling.

studied here behave similarly (Scheme 2) and do not form quadruple hydrogen-bonded dimers.

However, the related pyrimidines can behave differently from that of pyridines. The *conditio sine qua non* allowing the formation of dimeric structure is N3 in heterocyclic ring (Scheme 3) (*51*). This allows free rotation of alkylcarbonyl moiety about N—C bond (*51*, *52*).

2. Experimental

2.1 Instrumentation

The compounds **1**–**4** and **6** were synthesised as previously described for similar derivatives (*48*, *53*). Liquid state NMR acquisition and processing parameters are the same as those in our other publications (*54*). The IR spectra were recorded for solid samples on a Bruker Alpha-P equipment. The melting points were determined with the use of Buchi melting point apparatus (K-565) with the 2°C/min gradient. Remaining substances (**5**, **7**–**9**) were commercially available from Aldrich, and were used after drying for 20 days in a desiccator.

2.2 Materials

The data below describe the physicochemical properties of compounds obtained for this study.

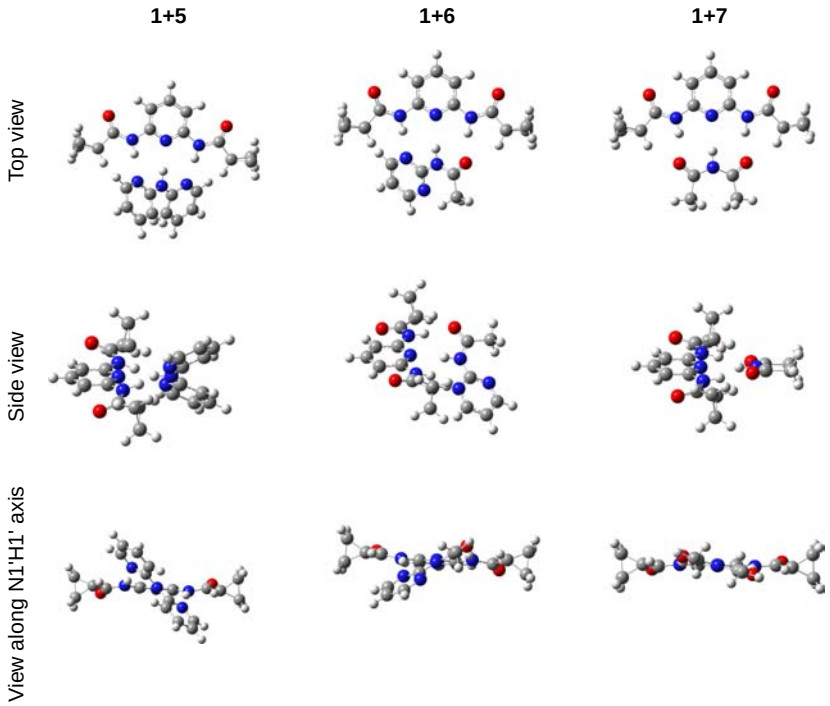
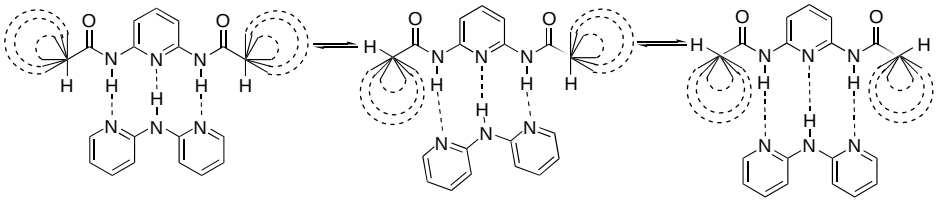
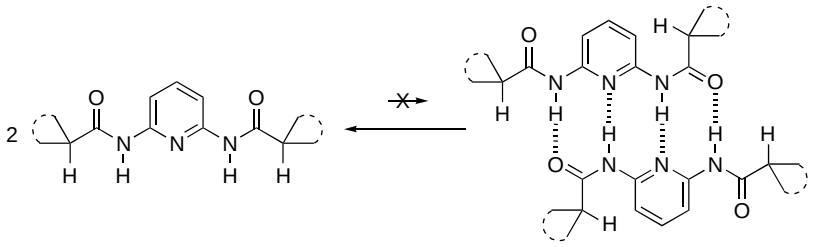


Figure 2. Optimised structures for complexes of **1** + **5** − **7**.



Scheme 1. Rotamerism in 2,6-bis(cycloalkylcarbonylamino)pyridine associates and the steric effect on intermolecular distances.



Scheme 2. Dimerisation of 2,6-bis(cycloalkylcarbonylamino)pyridines.

*2.2.1 2,6-bis(cyclopropylcarbonylamino)pyridine (**1**)*

(R = —$(CH_2)_2$—, $n = 0$) δ [ppm]:^{1}H NMR ($CDCl_3$) δ: 7.99 (bs, 2H, H7/H10), 7.84 (d, $^3J_{H,H} = 7.8$ Hz, 2H, H3/H5), 7.66 (t, $^3J_{H,H} = 7.8$ Hz, 1H, H4), 1.53 (tt, $^3J_{H,H} = 7.9$ Hz, $^3J_{H,H} = 4.2$ Hz, 2H, α-H), 1.11 (m, 4H, cycloalkyl), 0.92 (m, 4H, cycloalkyl), ^{13}C NMR 172.2, 149.5, 140.8, 109.3, 15.8, 8.4, ^{15}N NMR −240.1, mp 171–173°C (lit. 171–173°C (*55*)), IR (cm^{-1}) 1658.2 (amide I band), 1499.9 (amide II band).

*2.2.2 2,6-bis(cyclobutylcarbonylamino)pyridine (**2**)*

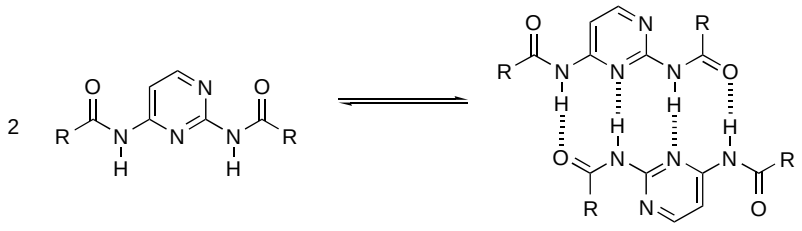
(R = —$(CH_2)_3$—, $n = 1$) ^{1}H NMR ($CDCl_3$) δ [ppm]: 7.91 (d, $^3J_{H,H} = 8$ Hz, 2H, H3/H5), 7.68 (t, $^3J_{H,H} = 8$ Hz, 1H, H4), 7.43 (bs, 2H, H7/H10), 3.15 (quintet, $^3J_{H,H} = 8.3$ Hz, 2H, α-H,), 2.48–1.88 (four multiplets, 12H, cycloalkyl), ^{13}C NMR 173.3, 149.5, 140.8, 109.3, 40.9, 25.2, 18.0, mp 147.6–148.7°C, IR (cm^{-1}) 1679.0 (amide I band), 1503.3 (amide II band), elemental analysis: calcd: C, 65.91; H, 7.01; N, 15.37; found: C, 65.87; H, 7.03; N, 15.34.

*2.2.3 2,6-bis(cyclopentanecarbonylamino)pyridine (**3**)*

(R = —$(CH_2)_4$—, $n = 2$) ^{1}H NMR ($CDCl_3$) δ [ppm]: 7.89 (d, $^3J_{H,H} = 8$ Hz, 2H, H3/H5), 7.69 (t, $^3J_{H,H} = 8$ Hz, 1H, H4), 2.69 (tt, $^3J_{H,H} = 8$ Hz, 2H, α-H), 7.60 (bs, 2H, H7/H10), 1.98–1.59 (3 multiplets, 16H, cycloalkyl), ^{13}C NMR 174.6, 149.6, 140.7, 109.2, 46.9, 30.3, 25.9, mp 143.2–145.0°C, IR (cm^{-1}) 1663.0 (amide I band), 1506.9 (amide II band), elemental analysis: calcd: C, 67.76; H, 7.69; N, 13.94; found: C, 67.72; H, 7.72; N, 13.90.

*2.2.4 2,6-bis(cyclohexylcarbonylamino)pyridine (**4**)*

(R = —$(CH_2)_5$—, $n = 3$) ^{1}H NMR ($CDCl_3$) δ [ppm]: 7.90 (d, $^3J_{H,H} = 8$ Hz, 2H, H3/H5), 7.67 (t, $^3J_{H,H} = 8$ Hz, 1H, H4), 7.57 (bs, 2H, H7/H10), 2.23 (tt, $^3J_{H,H} = 3.5$ Hz, 2H, α-H), 1.97–1.23 (multiplets, 20H, cycloalkyl), ^{13}C NMR 174.3, 149.6, 140.8, 109.3, 46.5, 29.5, 25.7, 25.6, mp 77.2–78.5°C, IR (cm^{-1}) 1672.1 (amide I band), 1523.1 (amide II band), elemental analysis: calcd: C, 69.27; H, 8.26; N, 12.76; found: C, 69.31; H, 8.23; N, 12.71.



Scheme 3. Dimerisation of 2,4-bis(alkylcarbonylamino)pyrimidine.

Table 1. K_{assoc}[a] determined for complexes of **1**–**4** with **5**, **6**, **8** and **9**[b].

Complex	K_{assoc}	Complex	K_{assoc}	Complex	K_{assoc}	Complex	K_{assoc}
1 + **5**	14, **24**	**1** + **6**	15, **10**	**1** + **8**	30, **27**	**1** + **9**	70, **60**
2 + **5**	5, **10**	**2** + **6**	6, **5**	**2** + **8**	24, **20**	**2** + **9**	30, **27**
3 + **5**	6, **8**	**3** + **6**	6, **4**	**3** + **8**	29, **23**	**3** + **9**	27, **25**
4 + **5**	6, **7**	**4** + **6**	5, **3**[c]	**4** + **8**	24, **22**	**4** + **9**	13[d]

[a] Values in bold refer to the K_{assoc} found by Hα (CH) proton chemical shift change.
[b] Since **1** does not form a complex with **7**, other complexes with **7** were not studied.
[c] Due to the low quality of fit the value is uncertain.
[d] Not determined due to signal overlap.

2.2.5 2-acetylaminopyrimidine (**6**)

^{1}H NMR ($CDCl_3$) δ [ppm]: 9.52 (bs, 1H, H1′), 8.63 (d, $^3J_{H,H} = 5$ Hz, 2H, H4″/H6″), 6.99 (t, $^3J_{H,H} = 5$ Hz, 1H, H5″), 2.51 (s, 3H, CH_3), ^{13}C NMR 171.4, 158.3, 157.8, 116.0, 25.2, ^{15}N NMR −231.5, −119.7, mp 146.3–148.0°C (lit. 144–145°C (*56*)) IR (cm^{-1}) 1669.5 (amide I band), 1516.8 (amide II band).

2.3 ^{1}H NMR titrations

The ^{1}H NMR titrations were performed by adding solid aliquots of **5**–**9** to the solution containing **1**–**4** at constant (0.0445 mol/dm^3) concentration. The 1:[titrant] ratios were as follows: 1:1, 1:2, 1:3, 1:5, 1:10, 1:20, 1:30 and in some cases 1:40 (see Supplementary Information, available online.). Due to the limited solubility of **7** and **8**, titration with these compounds was performed starting from 1:0.1 up to 1:3 or 1:4 ratio with the same relative steps. In all cases, the titration was finished when the next portion of the titrant did not made larger change to the H7/H10 chemical shift than ca. 0.1 ppm.

2.4 Calculations

The calculations were carried out with Gaussian 03 (*57*). For all monomers and complexes, the optimisations were performed at M05/6-311 + G(d,p) level using polarizable continuum model (PCM) model of solvation (chloroform) with M05 functionals developed by Truhlar et al. These are efficient in describing non-covalent interactions (*58*). The minimum energy was confirmed by the frequency calculation (only positive frequencies were obtained). To compare the experimental chemical shifts with those obtained by theoretical methods, the guage-independent atomic orbital (GIAO)-based (*59*, *60*) calculations were carried out at the same level of theory. The calculated chemical shifts (with respect to tetramethylsilane (TMS) (*61*)) were obtained by subtraction of the magnetic shielding tensor values of TMS protons and protons in the complex.

3. Results and discussion

3.1 Heterocomplexation

Table 1 gives the K_{assoc} values obtained based on H7/H10 (NH) and Hα (CH) chemical shift changes during titrations. The H7/H10 chemical shift did not change more than 0.1 ppm during titration of **1** with **7**. Moreover, the chemical shift of H1′ during titration vs. the H1′ chemical shift in dilution experiment of **7** did not differ much. The difference of $\Delta H1' =$ ca. 0.16 ppm is observed for 10:1 **1:7** ratio (see chart in SI file). This suggests that **7** prefers to dimerise rather than to form a triple hydrogen-bonded heterocomplex.

In all complexes, the association constants are low. However, the larger the cycloalkyl ring, the lower the association constant is. Also, the compounds **5**–**7** with a larger degree of freedom (rotation about N1′–C2′ or/and N1′–C2″ bonds) associate poorly with **1**–**4**. It is worth mentioning that the association of **5** with **1** is comparable to that with 2,6-bis(pivaloylamino)pyridine or 2-pivaloylamino-6-*iso*-butyroamino-pyridine (*48*). The use of both NH and CH protons as probes in NMR titration also affords, except K_{assoc}, other information. Table 1 shows that in the case of **1**–**4** + **5**, the K_{assoc} obtained by Hα proton are higher than those by obtained H7/H10 proton suggesting that the aromatic ring current of pyridine influences the Hα chemical shift significantly yielding deshielding and thus higher K_{assoc} values. In the case of other complexes, the Hα-based K_{assoc} values are always lower than H7/H10-based K_{assoc} values. The extrapolated values of H7/H10 chemical shift in the complex (**1**–**4** molecules are fully bound) are the highest for the complexes of **1**–**4** with **5** (Table 2), while the K_{assoc} for **1** − **4** + **5** are lower than, for example, that with **8** or **9**. On the other hand, the K_{assoc} of **1** − **4** + **5** are comparable to **1** − **4** + **6**. This suggests the stronger influence of ring current on H7/H10 chemical shift in complexes with **5** than with **6**.

The GIAO calculations allowed us to compare the theoretical results with the experimental data (Table 2). The experimental values were obtained from the titration data when the shifts did not change any more upon additions (see Experimental) assuming that all **1**–**4** are associated. Moreover, it is worth remembering that in the solution the complex–monomer equilibrium is fast in NMR time scale giving the averaged signal. Thus, the extrapolated values in Table 2 are only estimates.

Table 2. Calculated and extrapolated (in bold) chemical shifts of H7/H10 (first row) and Hα (second row) protons in the complexes studied.

Complex	Shift	Complex	Shift	Complex	Shift	Complex	Shift
1 + 5	11.5, **11.3**	**1 + 6**	10.8, **10.30**	**1 + 8**	10.6, **10.0**	**1 + 9**	10.2, **10.1**
	2.1, **1.8**		2.0, **1.8**		2.1, **1.8**		2.5, **2.0**
2 + 5	11.2, **10.2**	**2 + 6**	10.2, **9.3**	**2 + 8**	9.9, **9.3**	**2 + 9**	9.6, **9.5**
	3.3, **3.2**		3.0, **3.3**		3.2, **3.3**		3.5, **3.4**
3 + 5	11.2, **10.3**	**3 + 6**	10.5, **9.7**	**3 + 8**	10.8, **9.3**	**3 + 9**	9.7, **9.7**
	2.9, **2.8**		2.6, **2.9**		3.2, **2.8**		3.1, **3.0**
4 + 5	11.1, **10.3**	**4 + 6**	10.1, **9.5**	**4 + 8**	9.9, **9.2**	**4 + 9**	9.5, **9.5**
	2.7, **2.3**		2.8[a]		2.9, **2.4**		2.5[a]

[a] value missing due to signal overlap.

The comparison of the calculated and extrapolated chemical shifts is, in general, in agreement within ±1.4ppm for H7/H10 (sensitive NH protons) and 0.5ppm for Hα (CH protons).

3.2 Dimerisation

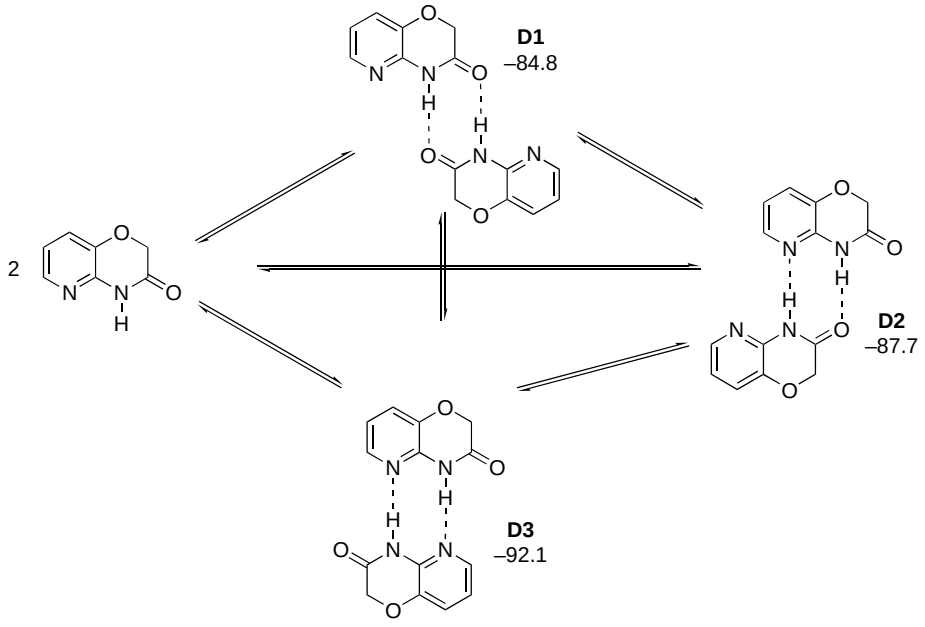
In studied mixtures, the self-association may be a competitive process. Thus, the dimerisation constants were determined for **6**, **7** and **8**. Table 3 shows the dimerisation constants for **5**–**9**.

The data presented in Table 3 show that due to the methyl–methyl interactions in **7** this compound favours dimerisation rather than triple hydrogen bonding with **1**–**4**. Although compound **8** has relatively high dimerisation constant (forming doubly hydrogen-bonded dimer), it still forms triple hydrogen-bonded heterocomplexes with **1**–**4**. However, the dilution experiment is not able to answer the question as to which dimer of **8** is more stable (Scheme 4). The calculations performed now suggest that **D3** dimer is the most stable. It is necessary to keep in mind that the relative difference between the energies of individual dimers is < 8 kJ/mol. Thus, all presented dimers of **8** can coexist in solution. All dimers of **8** are stabilised by two hydrogen bonds. Also, four repulsive secondary

Table 3. The dimerisation constants (K_{dim}) for compounds **5**–**9**.

Compound	K_{dim}	Compound	K_{dim}
5[a]	1.8	**8**	45.0
6	8.0	**9**[a]	2.3
7	18.0		

[a] From ref. (*48*).



Scheme 4. Calculated dimerisation energies [kJ/mol] of 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (**8**).

Table 4. The geometry (distance [Å], angles [°] and dihedrals [°]) of optimised complexes of **1** with **5**–**9**.

	Complex				
Distance, angle, dihedral angle	**1** + **5**[a]	**1** + **6**	**1** + **7**[b]	**1** + **8**	**1** + **9**
N1···H1′	2.112	2.198	2.298	2.038	2.129
H7···N3′/O3′	2.076	2.118	1.973	2.160	2.013
H10···N3″/O3″	2.076	1.945[c]	1.973	2.016[c]	2.013
Hα–N3′/O3′	2.731	2.791	2.360	2.687	2.348
Hα–N3″/O3″	2.731	2.425[d]	2.360	2.393[d]	2.348
N7H7N3″/O3″	170.0	163.8	169.5	167.5	169.1
N10H10N3′/O3′	170.0	172.5[e]	169.5	170.4[e]	169.1
C2N10N3′ (or O3′)C2′	49.6	43.9	25.4	35.3	17.3
C6N7N3″ (or O3″) C2″	49.6	48.3	25.4	37.7	17.3

[a] Two heterocyclic rings in **5** are twisted by 41.1° (C7′C2′C2″C7″ dihedral).
[b] The methyl–methyl repulsion is observed, i.e. the C2′–C2″ distance is equal to 2.579Å, while distance between methyl carbon atoms is equal to 3.068Å. The C2′N1′C2″ angle is equal to 136.1°.
[c] The NH···O hydrogen bond.
[d] Hα–O3″ distance.
[e] N10H10O3′ angle.

interactions (*39*) are present in each of them. The reason why **D3** is the most stable might be the weak interaction of *ortho*-CH proton with C═O group of the counterpart. This type of interaction is present in the associates of pyridine and carboxylic acids (*62*). The energies given in Scheme 4 are corrected for the zero-point energy and basis set superposition error.

2-Acetylaminopyrimidine (**6**) should be able to form similar dimers as 2*H*-pyrido[3,2-*b*]-1,4-oxazin-3(4*H*)-one (**8**) but the rotation around single bonds in **6** restricts its dimerisation. Moreover, the rigid structure of **8** explains why it dimerises more readily than **6**. Also, the electron-donating properties of sp^3 oxygen atom add the basicity of heterocyclic nitrogen atom yielding stronger hydrogen bonding than in **6**. Diacetamide is also able to form double hydrogen-bonded dimers in the solid state (*63*), similar to that of 2-[1*H*] pyridone, which, in turn, is considered as the most stable double hydrogen-bonded dimer known (*64*).

The optimised geometry allowed us to study the structural effects on the properties of complexes. Table 4 presents the chosen geometrical data for optimised complexes of **1** with **5**–**9**. The Cartesian coordinates of all complexes and monomers can be found in SI file.

Figure 2 shows the structures of optimised complexes. It is seen that the heterocyclic ring in **5** and **6** needs more space to bind effectively with **1**. The molecules in **1** + **7** are almost coplanar.

Figure 3 shows the association constants determined experimentally as a function of β–α–β′ angle optimised with computational methods. It is worth pointing out here that the mentioned angle influences the cone volume obtained by the rotation of the cycloalkyl group. Also the conformational flexibility of the cycloalkyl (especially cyclohexyl) group contributes to steric hindrance.

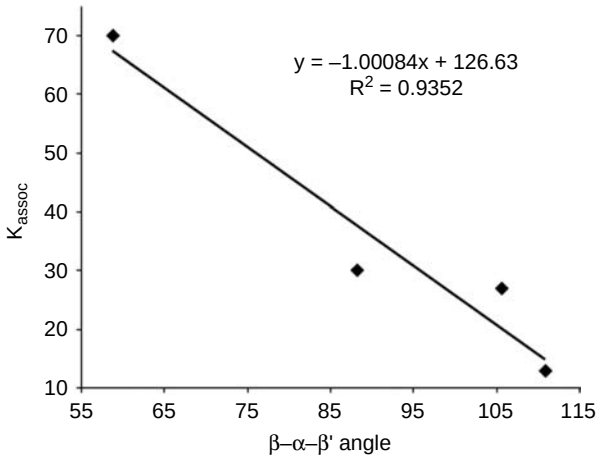


Figure 3. The $K_{assoc} = f(\beta-\alpha-\beta'$ angle) for **1**–**4** complexes with **9**.

4. Conclusions

The use of changes of chemical shifts of several protons obtained by NMR titrations is helpful in the estimation of association constants for hydrogen-bonded assemblies even when the proton probe is not involved in hydrogen bonding. The restricted rotation around a single bond in the assembly joined with an anisotropic effect of aromatic ring or polar groups may influence the association constants. In spite of the existence of methine group in the closest neighbourhood of hydrogen-bonded atoms in 2,6-bis(cycloalkylcarbonylamino)pyridines, the overall size of cycloalkyl and the β–α–β′ angle is the main driving force that hinders association. The major reason for steric effect in this series comes, most probably, from the variable volume of the cone obtained by the rotation of cycloalkyl around CO–cycloalkyl bond. Another may be

the conformational flexibility of cycloalkyls. The chemical shifts obtained by the extrapolation of titration data are in agreement with the calculated values. For the purpose of this research only the pyridine derivatives were included, although studies with pyrimidines are under progress.

Supplementary information available

The supporting information file contains ^{1}H, ^{13}C and ^{15}N NMR spectra, titration curves based on H7/H10 (NH) and Hα (CH) protons, dilution experiments results and Cartesian coordinates of optimised structures.

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