

Struct Chem (2010) 21:1061–1067
DOI 10.1007/s11224-010-9646-2

ORIGINAL RESEARCH

NMR and quantum chemical studies on association of 2,6-bis(acylamino)pyridines with selected imides and 2,2'-dipyridylamine

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Received: 8 June 2010 / Accepted: 8 July 2010 / Published online: 20 July 2010
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Abstract Association constants of 2,6-bis(alkylcarbonylamino)pyridines (alkyl = methyl or ethyl) and their perfluoroalkyl analogues with succin- and maleimide as well as with 2,2'-dipyridylamine (complementary DAD and ADA hydrogen bonding motifs are responsible for formation of the associates) have been determined by NMR titrations and quantum chemical calculations. Interactions of 2,6-bis(alkylcarbonylamino)pyridines with imides differ by character from these of perfluoroalkyl analogues. Such large difference was not observed for the 2,2'-dipyridylamine associates. Since fluorine atoms cause carbonylamino groups to be stronger hydrogen bond donors, perfluorinated species of this type were found to be more stable. Single crystal X-ray structures of 2,6-bis(trifluoromethylcarbonylamino)pyridine and 2,6-bis(pentafluoroethylcarbonylamino)pyridine have been also determined.

Keywords Association · Hydrogen bond · Selective binding · NMR · DFT calculations

Electronic supplementary material The online version of this article (doi:[10.1007/s11224-010-9646-2](https://doi.org/10.1007/s11224-010-9646-2)) contains supplementary material, which is available to authorized users.

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Introduction

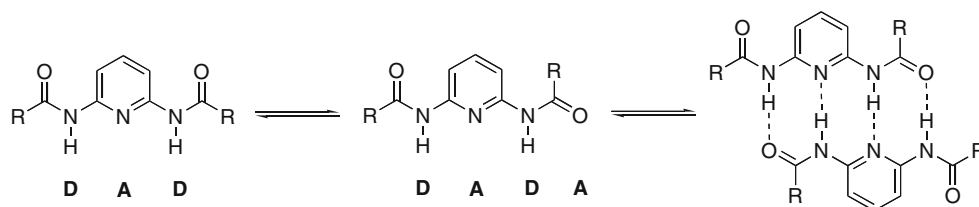
Intermolecular multiple hydrogen bonding (HB'ing) is of major importance in biochemistry and supramolecular chemistry. It plays a crucial role in formation of the double helix of DNA [1] and in action of artificial receptors used in biochemistry [2, 3]. Hydrogen bonding is the most common non-covalent interaction [2, 4] observed in bio-sensing, self-complementary aggregation, and non-covalent polymer formation [5–7]. Significance of hydrogen bonding is based on its directionality and reversibility [6]. There are few factors that influence the HB'ed complex stability. These are number of hydrogen bonds, hydrogen bonding pattern [8, 9], secondary interactions [10, 11]. Also the tautomeric equilibrium may be responsible for forming variously stabilized associates. This is due to group and HB'ing pattern changes upon proton transfer.

It is known that secondary interactions result in strengthening of the AAAA/DDDD-type [12] association in comparison with that of ADAD/DADA [13]. The same is true for AAA/DDD [14–17] versus DDA/AAD [18, 19] versus ADA/DAD pairs [7, 8, 20–22]. Although the ADA and the DAD motifs are not self-complementary, their self-association is still possible due to rotamerism (Scheme 1) or tautomerism [23–26]. On the other hand, 2,6-bis(acrylamido)pyridine does not form dimers [27].

Steric hindrance [28–31] weakens basicity of 2,6-di-*tert*-butylpyridine [32]. Thus, the parallel effect should be observed for non-covalent interactions. Also the electronic repulsion is believed to be responsible for weakening of the association of bis(acetylamino)triazine derivatives with imides [33].

The organized structures of 2,6-diacetylamino pyridines with imides were obtained by their aggregation on the Ag surface [34]. Hydrogen bonding in these compounds was

Scheme 1 Self-assembly of the DAD motif due to the group rotation resulting in the DADA pattern



studied mainly from the point of view of binding in nucleic bases [35–37], bisurea derivatives [38], structures stabilized by π - π interactions [39], receptors for barbituric acid [40], and fluorine anion [41], enhancement of the fluorescence of conjugated polymeric chain upon complexation [42], cooperative catalyst [43], and potentially drug delivery nanomaterials [44]. Hydrogen bonding and possibility of the complex formation in solution and in solid state between the 2,6-diacetylaminopyridine and enolate derivative of barbituric acid has been shown recently by the X-ray diffraction [45]. Interestingly, conformation of the amide group in *N*-(pyrimidin-2-yl)pentafluorobenzamide derivatives was found to be of the *cis* type, especially when the 2,6-diacetylaminopyridine derivative stabilized this form by hydrogen bonding [46].

Feibush have suggests that 2,6-bis(pivaloylamino)pyridine does not form complexes with imides due to steric crowding [47]. On the other hand, stronger hydrogen bonding capability of proton in the NHCOCF_3 group (as compared to that in NHCOCCH_3) is expected to strengthen the complex stability. 2,6-Bis(trifluoromethylcarbonylamino)pyridine has been investigated as a hydrogen bonding counterpart stabilizing the flavin radical anion [48] and as a hydrogen bonding receptor for barbiturate [49]. The acylation of amino moiety, however, not always led to the greater stability of non-covalent associates [33]. It was suggested that this is due to electronic repulsion/secondary repulsive interactions.

Imides are complementary by hydrogen bonding to with 2,6-bis(alkylcarbonylamino)pyridines. The triple hydrogen bonds are expected to strengthen the association especially with the perfluoroalkyl derivatives. Clarification of these interactions between succin- and maleimide, 2,2'-dipyridylamine and 2,6-bis(alkylcarbonylamino)pyridines is the main goal of this article.

Results and discussion

Formulas of 2,6-bis(acylamino)pyridines **1–4** with 2,2'-dipyridylamine (**5**) and imides (**6**) and (**7**) as well as numbering of positions in their molecules are depicted in Fig. 1.

NMR

Since NMR chemical shifts of the NH/OH protons are sensitive to the concentration and solvent properties, the ^1H NMR

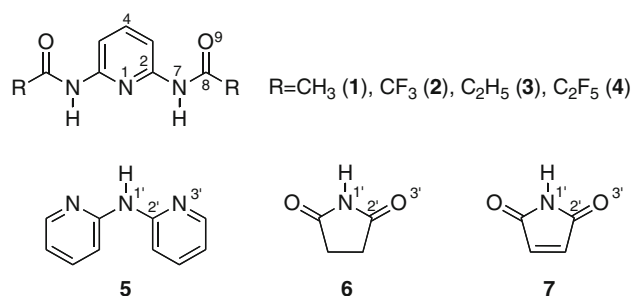


Fig. 1 Formulas of the compounds studied and atom numbering

spectra of all neat compounds and their 1:1 mixtures were recorded at the same concentration (see “Experimental”). On the other hand, their ^{13}C and ^{15}N spectra were run for the saturated solutions. The chemical shifts are available in the Supporting Information Section (SI, Table S1). H7 protons in **2** and **4** were found to be more acidic than these in **1** and **3**. Perfluorination of the alkyl groups results in deshielding of the $^1\text{H}7$ signal by 0.7–0.8 ppm.

The complexation induced shift (CIS) values of the amide protons ($\delta(\text{H}7)$) for **1–4** and their 1:1 mixtures with 2,2'-dipyridylamine (**5**), succinimide (**6**), and maleimide (**7**) are collected in Table 1 (see also Table S1).

Table 1 Complexation induced shifts (CIS) [$\Delta\delta(\text{H}7)/\Delta\delta(\text{H}1')$] for the 1:1 mixtures of 2,6-diacetylaminopyridines (**1–4**) with 2,2'-dipyridylamine (**5**), succinimide (**6**), and maleimide (**7**) and association constants (K_{assoc})

Entry	Mixture	CIS	K_{assoc}
1	1 + 5	1.74/1.35	420
2	2 + 5	1.86/1.90	540
3	3 + 5	1.20/1.01	240
4	4 + 5	1.09/1.08	270
5	1 + 6	0.97/3.03	700
6	2 + 6	0.06/0.20	40
7	3 + 6	0.90/2.41	620
8	4 + 6	0.03 ^a	<20
9	1 + 7	0.36/1.73	280
10	2 + 7	0.05 ^a	30
11	3 + 7	0.31/1.08	230
12	4 + 7	0.02 ^a	<20

^a Signal not observed

The association constants (Table 1) show that the most stable complexes are **1** + **6** and **3** + **6**. It is noteworthy that K_{assoc} obtained now are comparable to these for other triple hydrogen-bonded systems [44, 50–52].

Based on the CIS and K_{assoc} values for mixtures of **1–4** with **5** (Table 1) and $\delta(\text{H7})$ for the neat **1–4** (Table S1) one can see that perfluoroalkyl groups increase the hydrogen bond donor properties of H7. This results in increasing stabilities of complexes carrying the electron acceptor groups. Contrary to **1** and **3**, negligible effect of complexation of succin- and maleimide was found for perfluoro analogues **2** and **4** implying that their association with those imides is very weak. Such weak complexation was earlier observed in mixture of **2** with flavin [48]. An explanation for the weak association of **2** and **4** with **6** and **7** can be that CF_3 and C_2F_5 groups create electronic repulsions towards the hydrogen bond acceptors, i.e., carbonyl oxygens of the imide. Differing from that in 2,2'-dipyridilamine partial rotation of the pyridine ring around the N1–C2 bond [53] (Fig. 2) causes that this molecule can adopt a geometry that allows complex formation even when substituents show some repulsion with the pyridine rings of **5**.

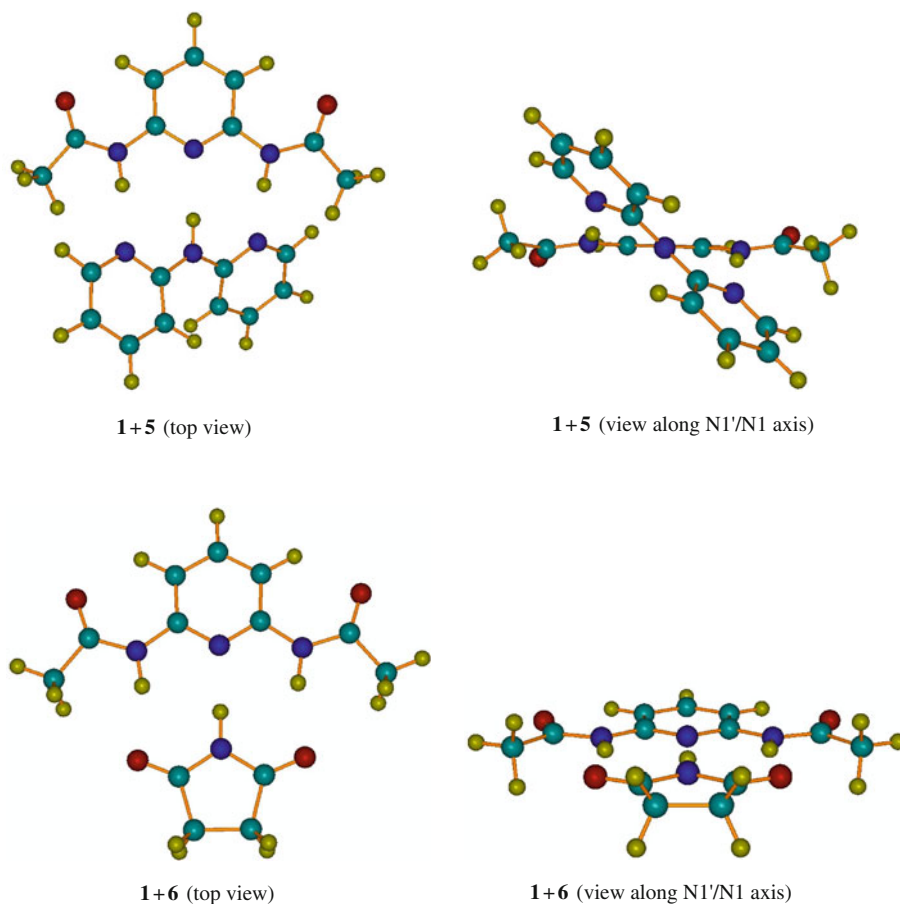
Owing to low rotation barrier of the perfluoroalkyl groups around the C–N bond in the amide [46], both the *trans* and *cis* forms (Scheme 2) may be expected to be present in the complexes of **2** and **4** with imides **6** and **7**. One should keep in mind, however, that electronic repulsion between the carbonyl oxygen of **6** and **7** and fluorine or oxygen atoms of **2** and **4** may destabilize the said complexes (Scheme 3).

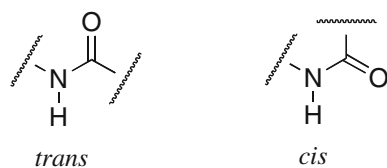
Additional ^1H NMR experiments were also run with three component mixtures to clarify what happens in case of competitive binding. The detailed results and discussion can be found in SI.

X-ray structural data

Single crystal structures of **2** and **4** (Fig. 3) show that all the substituent C atoms (except these of CF_3 groups in **4**) lie almost in the plane of pyridine ring. Although two-dimensional schematic drawings of **2** and **4** indicate these compounds to be symmetrical, there is no crystallographic mirror plane or other symmetry element found along the N1...C4–H4 axis. Despite the amide side chains in 2,6-bis(acylamino)pyridines are slightly twisted with respect to

Fig. 2 The optimized (M05/6-31G(2d,p) level) structure of **1** + **5** and **1** + **6** complexes





Scheme 2 The *trans* and *cis* forms of the carbonylamino group

the pyridine ring (Table S12) their geometries are comparable. Figure 2 shows molecular structures of **2** and **4** as the ORTEP-diagrams [54]. Compounds **2** and **4** are held in the crystal phase by a net of the intermolecular hydrogen bonds (Fig. S1, for distances $N7 \cdots O9$ and $N(R_2) \cdots O(R_2)$ see Table S12).

Calculations

Molecular geometries were calculated using the DFT method (M05). It is less time-invasive than, for example, calculations at the MP2 level. The M05 functional is optimized for calculation of many types of non-covalent interactions. This methodology has been previously compared [55] by us with B3LYP and MP2 ones for non-covalent intermolecular interactions in 1,8-naphthyridine derivatives. Detailed geometry data for complexes are collected in SI (Tables S3–S9).

Geometries of the optimized complexes support the results obtained by ^1H NMR spectrometry. Substitution of H by F atoms in the acylamino moieties makes H7 protons more acidic. The $H7 \cdots X3'$ distance ($X3'$ is the nitrogen and oxygen atom in **5** and **6** (and **7**), respectively) shows that hydrogen bond is always shorter in the fluorinated derivatives. However, there are some exceptions: $H7 \cdots X3'$ distances in **4** + **6** and in **3** + **6** are practically identical. Moreover, H7 in **4** + **7** is more faraway from $X3'$ than in **3** + **7**. As a result of shortening of the $H7 \cdots X3'$ distance, the $H1' \cdots N1$ hydrogen bonds in **2** + **5** and **4** + **5** complexes are noticeably shorter than these in **1** + **5** and **3** + **5**. The $X3' \cdots C8$ and $X3' \cdots C(R_3)$ distances are noticeably larger in the complexes carrying the CF_3 and C_2F_5 groups. Lower values of $C2-N7-C8$ angle (Table S7) in fluoroalkyl as compared to these in alkyl derivatives suggest that repulsion between the pyridine ring of **5** or oxygen atoms of imides and fluorine atoms of **2** and **4** takes place. It is noteworthy that energy of the complex formation for

Scheme 3 Electronic interactions in the **2** + **6** complex: arrows were used to show repulsions

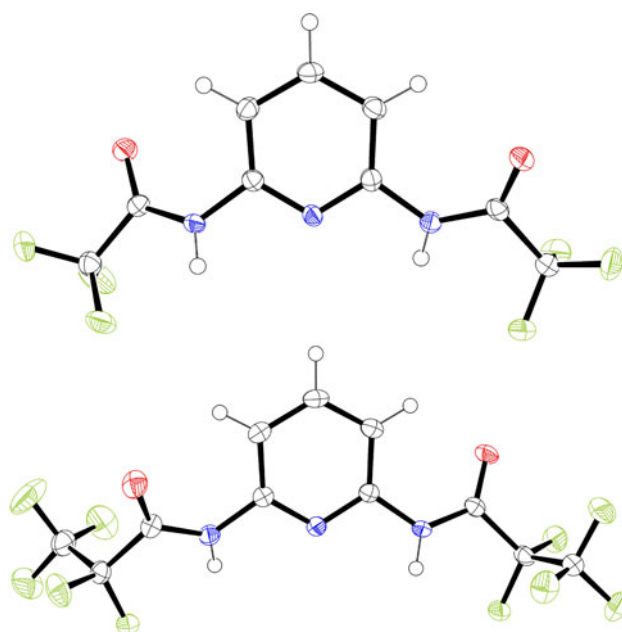
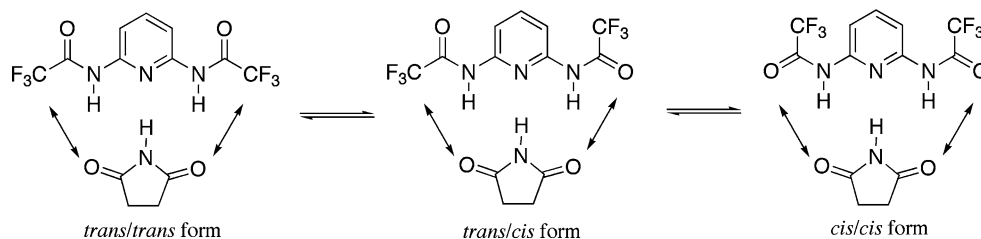


Fig. 3 The ORTEP-diagrams [54] of the compounds **2** (upper) and **4** with thermal ellipsoids drawn at 50% probability level (heteroatoms displayed as octant shaded model)

fluorinated derivatives **2** and **4** with imides **6** and **7** is ca. 18.4 ± 1 kJ/mol lower than that of **1** and **3** with the same imides (Table S10).

The intermolecular interactions influence electron distribution in each complex. The orbital contours of **1** + **6** and **2** + **6** show the interaction of the hydrogen bond character (exemplified on Fig. 4). Other orbitals (HOMO-20 and HOMO-14, HOMO-27 (no H-bond is visible at this contour level), and HOMO-24, HOMO-29 and HOMO-30, HOMO-35 and HOMO-41, HOMO-36 and HOMO-42) involved in hydrogen bonding in **1** + **6** and **2** + **6** were also considered. There are two orbitals in **2** + **6** (HOMO-38 and HOMO-40) that show the electron repulsion is present. No such orbitals were found for the **1** + **6** complex. Orbital contours are collected in the SI.

Conclusions

Complexes of 2,6-bis(alkylcarbonylamino)pyridines with succin- and maleimide as well as with 2,2'-dipyridylamine are stabilized by the triple hydrogen bonds. Substitution of

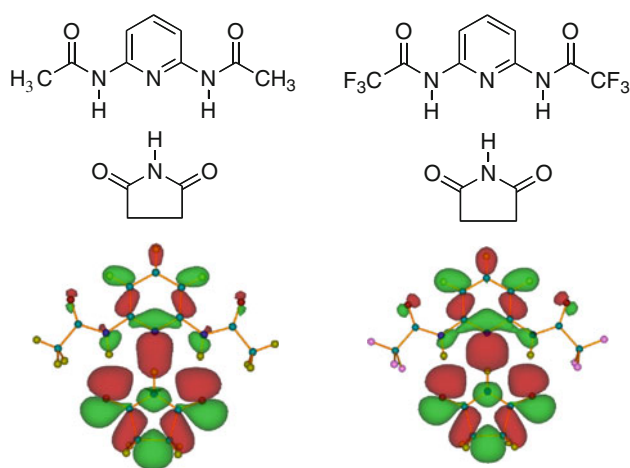


Fig. 4 Molecular orbitals (HOMO-9) of **1** + **6** and **2** + **6** showing the intermolecular hydrogen bond (continuous electron density along hydrogen bond axis)

H by F in the alkyl parts of 2,6-bis(alkylcarbonylamino)pyridines makes the amide protons better hydrogen bond donor. On the other hand, strong intermolecular CO/F electronic repulsion diminishes efficiency of these compounds to associate with imides whereas the conformational flexibility of 2,2'-dipyridilamine enables its association with 2,6-diacylaminopyridines. The association constants of imides and 2,2'-dipyridilamine with 2,6-diacylaminopyridines follow the concept of steric repulsion. The spectra of the double (**1** + **4** and **1** + **6**) versus triple mixtures (**1** + **4** + **6**) studied by ^1H NMR confirm complexes of imides with 2,6-bis(alkylcarbonylamino)pyridines to be much more stable than these with 2,6-bis(perfluoroalkylcarbonylamino)pyridines, showing the selective binding of imides by non-fluorinated derivatives. The linear dependence between the association constants and the complexation induced shifts enables the latter to be used as a preliminary probe for relative complex stability. The agreement of the computational data (geometry, energy and visualization of molecular orbitals) with experimental one, including the electronic repulsion between oxygen and fluorine, suggests that DFT method is able to describe hydrogen bonding and electronic repulsion reliably.

Experimental

Synthesis

Compounds **1–4** were obtained by refluxing (2 h) of the mixture of 2,6-diaminopyridine (0.2 g, 1.8 mmol) and 2 mL of the appropriate acid anhydride. Excess of the latter compound was decomposed by addition of water (10 mL) and saturated aqueous sodium carbonate solution (5 mL). The obtained mixture was then extracted with chloroform

(2 × 15 mL), organic layer dried (Na_2SO_4), and evaporated to dryness under reduced pressure. The crude products were further purified by recrystallization. Melting points: **1**, 199–202 °C ($\text{C}_6\text{H}_{14}/\text{AcOEt}$, white powder) (lit. 202–203 °C [56], 205–206 °C [57]), **2**, 154–158 °C ($\text{C}_6\text{H}_{14}/\text{AcOEt}$, pale-yellow needles), **3**, 127–128 °C ($\text{C}_6\text{H}_{14}/\text{AcOEt}$, white powder) and **4**, 105–107 °C ($\text{C}_6\text{H}_{14}/\text{AcOEt}$, pale-brown crystals). Satisfactory elemental analytical data were obtained for synthesized compounds, i.e., **1** calcd $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2$ C 55.95, H 5.74, N 21.75, found: C 55.68, H 5.70, N 21.52, **2** calcd $\text{C}_{11}\text{H}_{15}\text{N}_3\text{O}_2$ C 59.71, H 6.83, N 18.99 found: C 59.54, H 6.76, N 18.69, **3** calcd $\text{C}_9\text{H}_5\text{F}_6\text{N}_3\text{O}_2$ C 35.90, H 1.67, N 13.95 found: C 35.73, H 1.64, N 13.78, **4** calcd $\text{C}_{11}\text{H}_5\text{F}_{10}\text{N}_3\text{O}_2$ C 32.93, H 1.26, N 10.47 found: C 32.65, H 1.22, N 10.27. Compounds **5–7** were commercially available and were used as obtained after drying in desiccator.

NMR

^1H NMR experiments were run with a Bruker Avance DRX 500 spectrometer equipped with an inverse detection 5-mm diameter probehead with a z-gradient for equimolar CDCl_3 solutions at 303 K. ^1H and ^{13}C NMR chemical shifts are referenced to an internal TMS ($\delta = 0.00$ ppm). Owing to the limited solubility, ^{13}C and ^{15}N spectra of all compounds are run for their saturated solutions. Acquisition and processing parameters are the same as reported earlier [58]. The 2D pulsed field z-gradient (PFG) selected ^1H , ^{13}C HMQC, and ^1H , ^{13}C HMBC experiments were run to assign reliably the ^{13}C NMR spectra [58]. ^{15}N NMR chemical shifts (referenced to an external neat ^{15}N -natural abundance nitromethane, $\delta = 0.0$ ppm) are those obtained with the PFG ^1H , ^{15}N HMBC experiments [58].

Association experiments

Equimolar quantities (0.089 mmol) of **1** (17.2 mg), **2** (26.9 mg), **3** (19.7 mg), **4** (35.7 mg), **5** (15.3 mg), **6** (8.8 mg), and **7** (8.6 mg) were dissolved in acetone (10 mL). Solutions of **1–4** (3 mL) were then combined with solutions of **5–7** (3 mL) to obtain the **1** + **5**, **1** + **6**, **1** + **7**, **2** + **5**, **2** + **6**, **2** + **7**, **3** + **5**, **3** + **6**, and **3** + **7** complexes. Additional 3 mL solutions of compounds **1–7** were kept to prepare the references. Evaporation of the solvent from all solutions prepared and drying of the residue in vacuum desiccator was followed by its dissolving in CDCl_3 (0.6 mL). ^1H NMR spectra of chloroform solutions of the complexes were recorded within 1 h. The CIS values were obtained by subtraction of the $\delta\text{H}7$ and/or $\delta\text{H}1'$ values for the complexes from the chemical shift values of the neat compounds (reference). The NMR titrations were done for the constant concentration of **1–4**. Equivalents of

the solid titrants added equal to: 0.5–50 for **5**, 1–10 for **6**, and 1–20 for **7**. The titration was continued to obtain the $\Delta\delta(\text{H7})$ smaller than 0.1 ppm upon addition of the next portion. The δH7 (probe) obtained are collected in SI (titration charts). The Benesi–Hildebrandt [59] equation was used to calculate the K_{assoc} .

X-ray

Single crystals of **2** and **4** used in the X-ray crystallographic experiment were obtained by slow evaporation of the solvent (chloroform) from NMR tube. The structural data for these compounds were collected at 123 ± 2 K with a Bruker–Nonius KappaCCD diffractometer equipped with APEXII detector using the graphite monochromatized MoK_α radiation ($\lambda = 0.71073$ Å). Data were processed with DENZO-SMN [60]. The structures were solved by direct methods, using SIR-2004 [61], and refined on F^2 , using SHELXL-97 [61]. The reflections were corrected for Lorentz polarization effects and absorption correction was not used. The H atoms bonded to C atoms were calculated to their idealized positions with isotropic temperature factors (1.2 times the C atom temperature factor) and refined as riding atoms. The H atoms bonded to N atoms were found from electron density map and fixed to distances of 0.88 Å from N atom with isotropic temperature factor (1.2 times the N atom temperature factor). The figures were drawn with ORTEP-3 [54] and MERCURY [62]. Other experimental X-ray data are shown in Table 2. CCDC-763984 (**2**) and CCDC-763985 (**4**) contain the supplementary crystallographic data for this article. These data can be obtained free of charge at <http://www.ccdc.cam.ac.uk/conts/retrieving.html> [or from the Cambridge Crystallographic Data Centre (CCDC), 12, Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033].

Calculations

Calculations at the M05/6-31G(2d,p) level for geometry optimizations of all structures studied have been performed in Gaussian [63]. The energy minimum was confirmed by the frequency calculations (all positive frequencies were obtained). Energy of the complex formation was calculated as the difference between energy of the complex and a sum of the energies of its constituents. The basis set superposition error (BSSE) correction was used with default settings. The single-point calculations (MP2/6-31G(2d,p) level) in GAMESS [64] at the geometry taken from M05/6-31G(2d,p) optimizations provided the orbital contours that were drawn with the use of QMView [65].

Acknowledgements Financial support from the Polish Ministry of Science and Higher Education (Grant no. NN204 174138) is

Table 2 Selected crystallographic parameters of **2** and **4**

	2	4
Empirical formula	$\text{C}_9\text{H}_5\text{F}_6\text{N}_3\text{O}_2$	$\text{C}_{11}\text{H}_5\text{F}_{10}\text{N}_3\text{O}_2$
Formula weight	301.16	401.18
Crystal system	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$
Unit cell dimensions		
<i>a</i> (Å)	4.9550(3)	4.98060(10)
<i>b</i> (Å)	23.3587(12)	27.9899(9)
<i>c</i> (Å)	9.6277(4)	10.0263(3)
β (°)	98.809(3)	92.0470(10)
Volume (Å ³)	1101.19(10)	1396.84(7)
<i>Z</i>	4	4
Density (calculated) (Mg/m ³)	1.817	1.908
Absorption coefficient (mm ⁻¹)	0.196	0.220
<i>F</i> (000)	600	792
Crystal size (mm ³)	0.35 × 0.13 × 0.08	0.35 × 0.17 × 0.15
Theta range for data collection (°)	2.76–25.00	1.46–25.01
Index ranges	–5 ≤ <i>h</i> ≤ 5 –27 ≤ <i>k</i> ≤ 27 –11 ≤ <i>l</i> ≤ 11	–5 ≤ <i>h</i> ≤ 5 –33 ≤ <i>k</i> ≤ 33 –11 ≤ <i>l</i> ≤ 11
Reflections collected	3543	4840
Independent reflections	1908 [$R_{\text{int}} = 0.0352$]	2448 [$R_{\text{int}} = 0.0191$]
Completeness to theta (%)	98.9	100.0%
Data/restraints/parameters	1908/2/187	2448/8/241
Goodness-of-fit on F^2	1.047	1.030
Final <i>R</i> indices [$I > 2\sigma(I)$]	0.0405/0.0770 (wR_2)	0.0354/0.0826 (wR_2)
<i>R</i> indices (all data)	0.0564/0.0837 (wR_2)	0.0421/0.0868 (wR_2)
Largest diff. peak and hole (e Å ⁻³)	0.229 and –0.239	0.335 and –0.357

gratefully acknowledged. The authors are very much indebted to the Academic Computer Centre in Gdansk–TASK and CYFRONET in Cracow for providing computer time and programs.

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