Tetrahedron 64 (2008) 6426–6433

Contents lists available at ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Recognition of a dicarboxylic acid with dipicolyl urea in solution and in solid phases: intramolecular hydrogen bond inhibiting both pyridine nitrogens from binding carboxyl groups

Shyamaprosad Goswami [a,*], Subrata Jana [a], Swapan Dey [a,†], Debabrata Sen [a], Hoong-Kun Fun [b], Suchada Chantrapromma [c]

[a] Department of Chemistry, Bengal Engineering and Science University, Shibpur, Howrah 711 103, India
[b] X-ray Crystallography Unit, School of Physics, Universiti Sains Malaysia, 11800 USM, Penang, Malaysia
[c] Department of Chemistry, Faculty of Science, Prince of Songkla University, Hat-Yai, Songkhla 90112, Thailand

ARTICLE INFO

Article history:
Received 4 April 2008
Accepted 17 April 2008
Available online 22 April 2008

Keywords:
Molecular recognition
Hydrogen bonding
Host–guest
Supramolecular assembly

ABSTRACT

Recognition of a dicarboxylic acid in solution as well as in the solid phase by the pyridyl urea based pseudoditopic receptor **1** has been studied. The X-ray structures of both the receptor and its complex with 1,4-phenylenediacetic acid are also presented. Intramolecular hydrogen bonding inhibits both the pyridine ring nitrogens from forming hydrogen bonds with the carboxyl group and force the receptor to behave in a monotopic manner, using the *syn* urea amide moiety to bind carboxyl group of a dicarboxylic acid to form a 2:1 complex. Binding of receptor **1** with a monocarboxylic acid is also compared.

1. Introduction

The study of recognition of dicarboxylic acids with different receptors in both solution and in solid state is important due to its application in pharmaceutical science[1] and in the synthesis of noncovalent molecular complexes[2a] to build different supramolecular architectures.[2] We and other research groups have elegantly designed and synthesized many synthetic receptors[3,4] for dicarboxylic acids and studied different aspects of the recognition process. Among these receptors, a major portion contains a pyridine amide unit in a suitable position to bind the carboxylic acid group. The intra as well as intermolecular hydrogen bonding plays a key role in the rearrangement of hydrogen bonding functional groups within the receptor. The arrangement of donor–acceptor arrays may change during the time of recognition. Both intra and intermolecular hydrogen bonding play a major role in molecular recognition, crystal engineering, as well as in gel formation.[5] Substituted ureas and thioureas are important type of receptors for recognition of anion[6] as well as generating different supramolecular architectures by self-assembly or coordination with guests.[7]

In the present work, receptor **1** has two sets of hydrogen bonding for the recognition of a carboxylic acid moiety. The hydrogen bonding sites of receptor **1** is arranged in ADDA array for the binding of two carboxylic acid moieties in open form [Fig. 1a]. But the receptor can rearrange to an AD array for the recognition of only one carboxylic acid moiety due to strong intramolecular hydrogen bond [Fig. 1b]. This form of the receptor **1** may bind mono and dicarboxylic acid in a 1:1 and 2:1, respectively [Fig. 1c and d]. Our prime goal was to study whether and how both sets of donor–acceptor array are involved in the recognition of a carboxylic acid moiety in both solution and solid phases.

2. Binding studies

2.1. ^{1}H NMR studies

To study the recognition aspect of a dicarboxylic acid by a receptor, which can rearrange its donor–acceptor array, we have synthesized pyridyl urea[8] based receptor **1** from 2-aminopicoline and triphosgene, which is characterized by different spectroscopic data. The binding behavior of the receptor **1** with 1,4-phenylenediacetic acid has been studied by UV titration methods. This result has also been compared with the binding results of monocarboxylic acids.

* Corresponding author. Tel.: +91 33 2668 4561–3; fax: +91 33 26682916.
E-mail address: spgoswamical@yahoo.com (S. Goswami).
† Present address: Department of Applied Chemistry, Indian School of Mines University, Dhanbad 826 004, India.

0040-4020/$ – see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2008.04.066

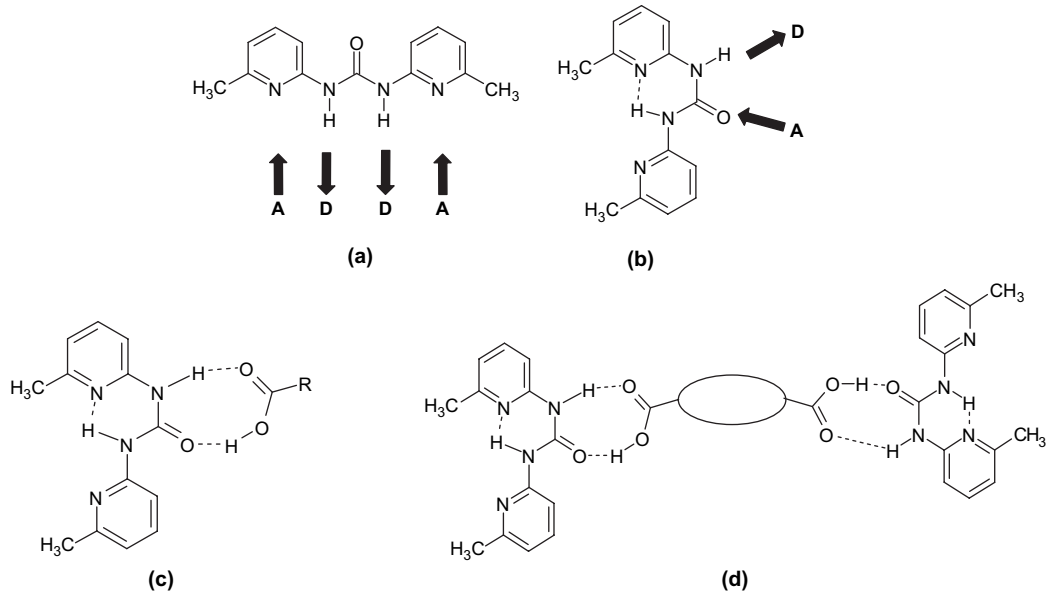

Figure 1. Donor–acceptor array of receptor **1**: (a) no intramolecular hydrogen bond; (b) change of donor–acceptor array by intramolecular hydrogen bond; (c) mode of complexation with carboxylic acid moiety; (d) mode of actual complexation as observed in the single crystal X-ray structure.

The ^{1}H NMR of the receptor **1** is important due to the different nature of hydrogens. From the spectra, it is found that ArH protons appeared as one doublet at 6.85 ppm (J=7.5 Hz), one triplet at 7.57 ppm (J=7.8 Hz) and one broad singlet at 7.27 ppm, respectively. Six methyl protons appeared at 2.56 ppm. Surprisingly ureido protons are not observed at 300 K [Fig. 2] in the spectrum measured by 500 MHz instrument as these are merged with the base line, which was reported by Bolte et al.[9]

Another interesting aspect of the ^{1}H NMR spectra is that no ureido protons also appeared upon 1:1 complexation with guest 1,4-phenylenediacetic acid at 300 K. To locate actual position of the ureido protons we performed low temperature experiment at 276 K. In this case one broad singlet appeared at 11–14 ppm with maxima at 12.55 ppm. From the integral value, it is clear that two ureido protons were present in this region. Here broad singlet of the aromatic protons is shifted toward downfield (δ 7.25–7.80 ppm, $\Delta\delta$=0.55 ppm) at 276 K. So each ureido proton is equivalent even at 276 K, which confirms the dynamic equilibrium of the receptor **1** [Fig. 3]. But further lowering of the temperature may distinguish two ureido protons, which is beyond our experimental set up. Besides this, binding constant of the receptor **1** with 1,4-phenylenediacetic acid was not determined due to peculiar behavior of the ureido protons.

2.2. UV–vis studies

We have studied the binding behavior of receptor **1** toward the dicarboxylic acid (1,4-phenylenediacetic acid) by UV–vis method and receptor **1** showed a strong absorbance at λ_{max}=281 nm, which gradually decreased on addition of the guest solution. Similar trend of absorbance spectra of receptor **1** was observed during the titration with monocarboxylic acids [Fig. 4].

Association constant (K_a=1.9×10^4 M^{-1}) was measured by the UV method[10] between the receptor **1** and 1,4-phenylenediacetic acid using a 10^{-5} M solution of the receptor in $CHCl_3$ (1% DMSO). To compare the binding constant of a dicarboxylic acid (1,4-phenylenediacetic acid) with receptor **1**, with that of a monocarboxylic acid, we performed the UV titration with phenylacetic acid and the association constant (K_a=8.8×10^3 M^{-1}) has been found to be almost half of the 1,4-phenylenediacetic acid. So receptor **1** behaves like a monotopic[3e] one toward a dicarboxylic acid recognition. But when the binding studies were performed with propanoic acid, the binding constant (K_a=5.4×10^3 M^{-1}) was further lowered compared with other two cases. This is probably due to the π–π interaction between receptor **1** and carboxylic acids containing benzene ring in solution phase. The binding constants [Fig. 5a] and free energy

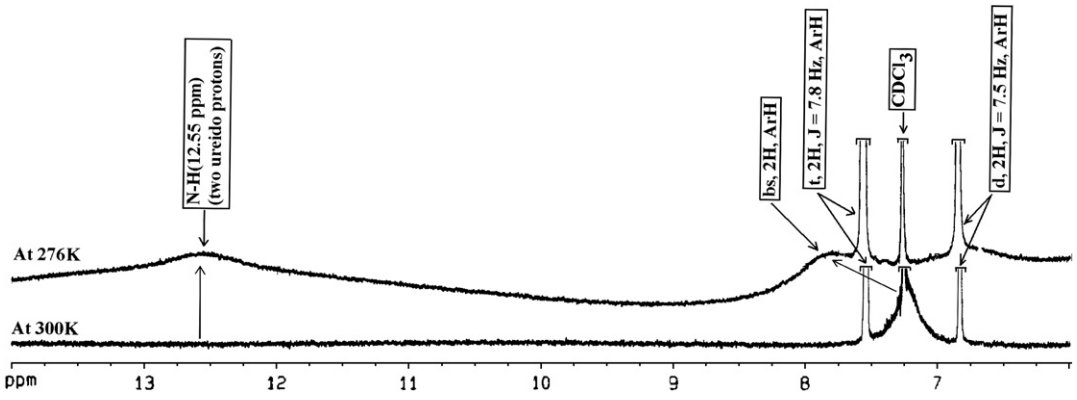

Figure 2. Partial ^{1}H NMR (500 MHz) of receptor **1** in $CDCl_3$ at 300 K and 276 K.

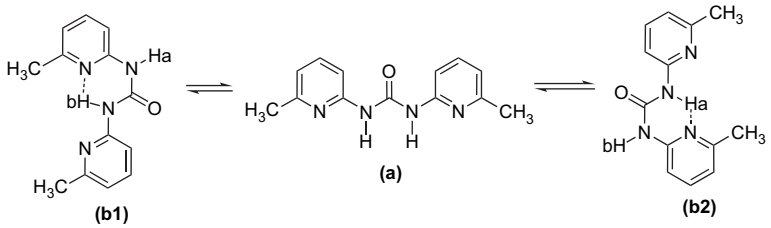

Figure 3. Dynamic equilibrium of the receptor **1** in solution phase.

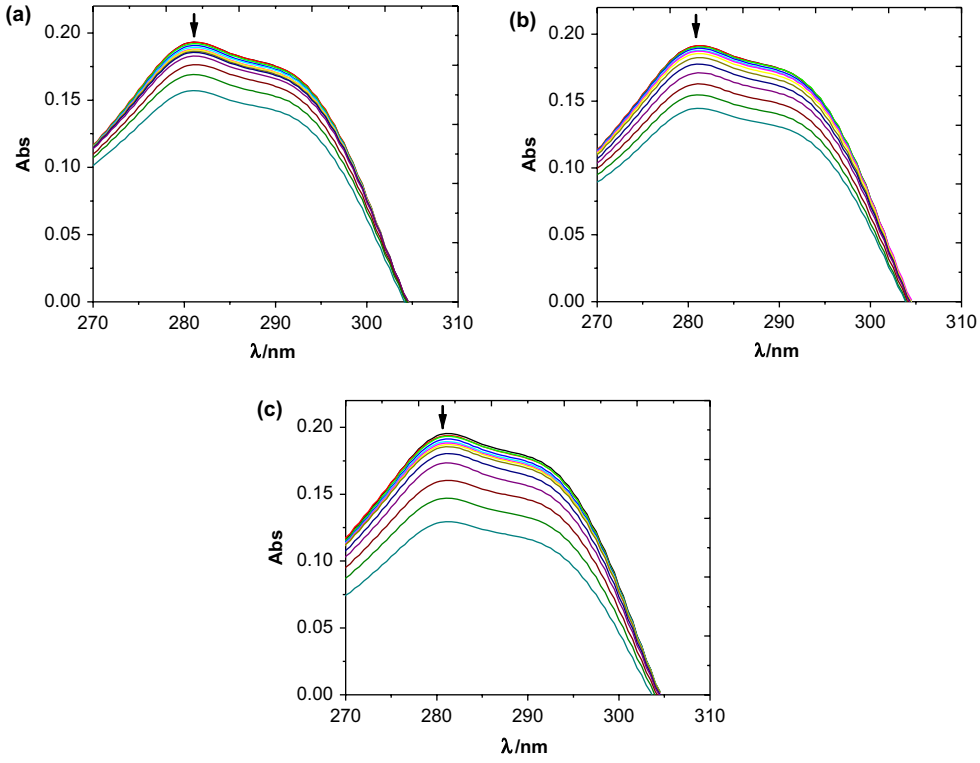

Figure 4. UV–vis titration spectra of the receptors **1** with (a) 1,4-phenylenediacetic acid, (b) phenylacetic acid, and (c) propionic acid.

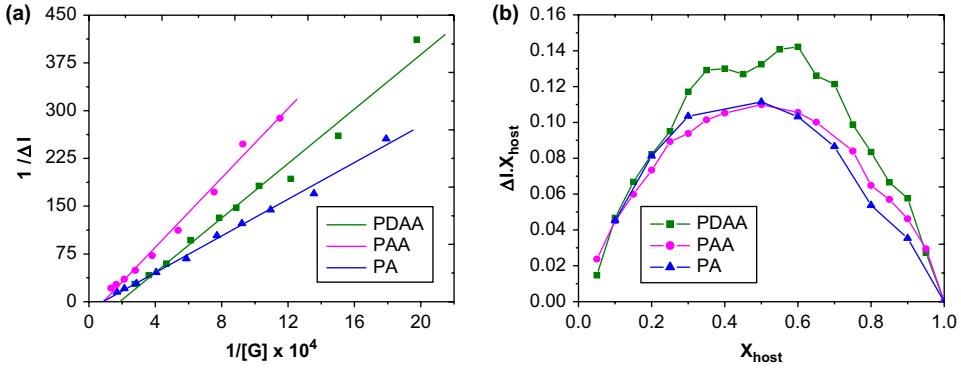

Figure 5. (a) Binding constant calculation curve and (b) Job plots determined by UV–vis method of receptor **1** with 1,4-phenylenediacetic acid (PDAA), phenylacetic acid (PAA), and propanoic acid (PA), respectively.

changes at 25 °C upon complexation with guests are summarized in Table 1.

The mode of interaction of receptor **1** with both mono and dicarboxylic acids is interesting in solution phase. To establish the stoichiometry of the host–guest in solution we have used UV–vis titration method. From the Job plots it is found that dicarboxylic acid passes through almost 2:1 mode of host–guest interaction whereas monocarboxylic acid passes through 1:1 mode of interaction [Fig. 5b]. Therefore intramolecular hydrogen bonding between one ureido proton and one ring 'N' is strong enough in solution phase to force the receptor to behave as a monotopic receptor.

3. Model studies

To correlate the binding behavior in both solution and solid phases we have performed a modeling study.[11] Receptor **1**,

Table 1
Binding constants [K_a (M^{-1})][a] and free energy changes [ΔG (kcal mol^{-1})] at 25 °C of receptor **1** with mono and dicarboxylic acids by UV–vis method

Mono/dicarboxylic acid	K_a (M^{-1})	ΔG
1,4-Phenylenediacetic acid	1.9×10^4	−5.8
Phenylacetic acid	8.8×10^3	−5.4
Propionic acid	5.4×10^3	−5.1

[a] All the errors are ±10%.

Table 2
Minimum energy (kJ mol^{-1}) of the receptor **1** and its different modes of complexation with 1,4-phenylenediacetic acid

Receptor **1**	Self	**H**/**G** (**1**:**1**)	**H**/**G** (**2**:**1**)	**H**/**G** (**2**:**2**)
$\mathbf{H_a}$	9.04 (a)	9.55 (a1)	12.60 (a2)	16.16 (a3)
$\mathbf{H_b}$	4.86 (b)	2.53 (b1)	-3.32 (b2)	—

Host (**H**)=Receptor **1**; Guest (**G**)=1,4-phenylenediacetic acid; $\mathbf{H_a}$=Host in form a; $\mathbf{H_b}$=Host in form b.

exists in both form a ($\mathbf{H_a}$) and form b ($\mathbf{H_b}$) depending upon the environment.

The minimum energies (E_{min}) of the receptor $\mathbf{H_a}$ and $\mathbf{H_b}$ are 9.04 kJ mol^{-1} and 4.86 kJ mol^{-1}, respectively [Table 2]. Upon complexation with guest acid, the minimum energy of the receptor **1** ($\mathbf{H_a}$) [Fig. 6] has been increased slightly, which is observed in the case of a1, a2, and a3 [Fig. 7], respectively. The stepwise interactions between receptor **1** ($\mathbf{H_b}$) and guest acid passing through the energetically most stable form b1 [E_{min}=2.53 kJ mol^{-1}, Table 2] ultimately forms the 2:1 complex b2 [E_{min}=−3.32 kJ mol^{-1}, Table 2] [Fig. 7]. So from these model studies, it is found that receptor **1** recognizes acid using form b ($\mathbf{H_b}$), which is also observed in solid phase.

4. X-ray studies

To study the solid phase recognition of a dicarboxylic acid with receptor **1**, we have been able to grow single crystals of both receptor **1** and its complex with 1,4-phenylenediacetic acid, which shows intramolecular hydrogen bonding and also the intermolecular hydrogen bonding with only one carboxyl moiety of a dicarboxylic acid. The presence of strong intramolecular hydrogen bonding is confirmed in the solid state by the X-ray structure of the receptor **1** as well as in the complex with the dicarboxylic acid [Fig. 8]. In the solid state, receptor **1** has strong intramolecular hydrogen bonding and it further dimerizes through intermolecular hydrogen bonding by the outward donor–acceptor array.

In the case of its complexation with dicarboxylic acid, however, it is found that the external set of donor–acceptor array of the receptor is involved in the recognition of carboxylic acid moiety of the dicarboxylic acid and the internal set did not get involved for the recognition of acid moiety, which supports the weaker association constant in solution phase. The single crystal X-ray structure of the complex of receptor **1** with 1,4-phenylenedicarboxylic acid shows the strength of the six-membered intramolecular hydrogen bond of the ureido proton with the pyridine ring nitrogen in receptor **1**, which of course is not broken to welcome the carboxyl moiety for hydrogen bonding and also interestingly inhibits the other pyridine ring nitrogen toward hydrogen bonding with the carboxylic acid moiety,[12] and the created *syn* amide moiety (like a lactam group) forms a hydrogen bond with carboxyl group of dicarboxylic acid. The crystallographic data are summarized in Table 3.

4.1. Receptor 1

The analysis[13] of the X-ray crystal structure of the receptor **1** reveals that one ureido N–H was intramolecularly [N3–H1···N1, 1.91(2) Å, Table 4] hydrogen bonded with one ring nitrogen atom.[9] The other ureido N–H and carbonyl moiety were directed outwards and made a donor–acceptor array, which is further intermolecularly hydrogen bonded with another molecule to make a planar dimeric supramolecular synthon [Fig. 9a]. So, both inter as well as intramolecular hydrogen bonds play a major role for both dimerization and supramolecular architecture. Each molecule forms a dimer through an eight-membered cyclic intermolecular hydrogen bond network [N2–H1···O1, 1.86(2) Å, Table 4]. These dimers elongate in a polymeric network by weak interaction between [C9–H9A···N4, 2.69 Å] ring C–H of one dimer and ring nitrogen of another dimmer.

4.2. Complex 1

When receptor **1** recognizes the dicarboxylic acid in the solid phase it disrupts the dimer of the self-assembly. Both carboxylic acid moieties of the dicarboxylic acid interact with the outward donor–acceptor array of receptor through an eight-membered [Fig. 10a] hydrogen bonded ring, which consists of N–H···O [N2–H1···O2, 1.980(19) Å, Table 5] and O–H···O [O3–H1···O1, 1.673(19) Å, Table 5] hydrogen bonds. So each molecule of dicarboxylic acid recognizes two molecules of receptor (in a 1:2 ratio) to make a supramolecular synthon, which finally made different supramolecular architectures in comparison with the network formed by receptor itself. Each unit makes supramolecular arrangement through C–H···N [C17–H17A···N4, 2.582 Å, Table 5], C–H···O[C17–H17B···O2, 2.589 Å, Table 5] [Fig. 10b] interactions and slip mode π-stacking.[14]

Interestingly, both pyridine rings are directed toward the same side of the intramolecular hydrogen bonded six-membered ring. The other pyridine nitrogen is not oriented in the same side of the *syn* amide, which is participating in hydrogen bonding with carboxyl group. This is also true in receptor **1** as well as in the complex structure as proved by X-ray, which may be due to the need to avoid dipolar repulsion of the carbonyl oxygen lone pair with the pyridine ring nitrogen. The receptor **1** arranges in polymeric fashion through C–H···N interactions [Fig. 11a], whereas its complex with 1,4-phenylenediacetic acid (complex **1**) forms polymeric chain through π-stacking interactions [Fig. 11b].

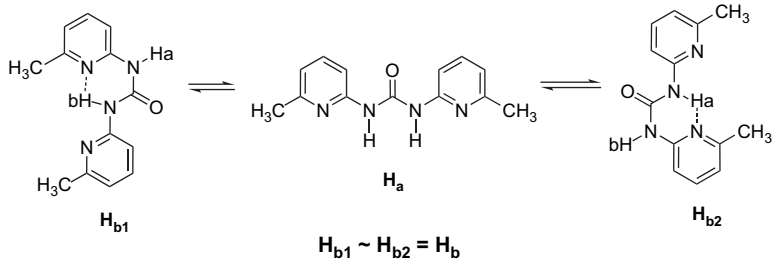

Figure 6. Dynamic equilibrium of the receptor **1** in solution phase.

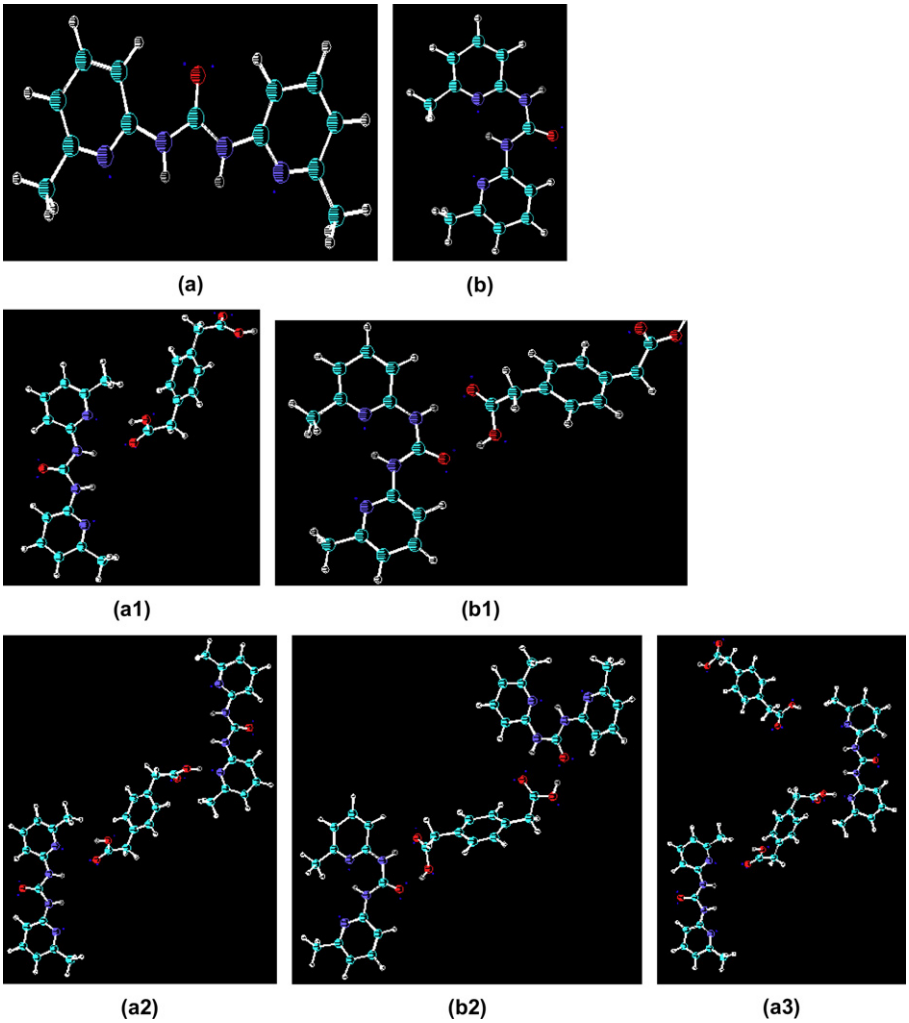

Figure 7. Energy minimized forms of receptors and their different modes of complexation with dicarboxylic acid: (a) receptor **1** in form a; (b) receptor **1** in form b; (a1) 1:1 complex with form a; (b1) 1:1 complex with form b; (a2) 2:1 complex with form a; (b2) 2:1 complex with form b; (a3) 2:2 complex with form a.

5. Discussion

The recognition pattern of a dicarboxylic acid by the same receptor in solution as well as in solid phases is studied by UV–vis titrations and X-ray, respectively. In solution, the receptor may be present in partially open form due to its dynamic nature and the intramolecular hydrogen bonding is playing the major role, which is observed by the comparatively lower binding constants in UV–vis method as expected for the receptor's behavior as a monotopic receptor. To compare the binding constant of dicarboxylic acid (1,4-phenylenediacetic acid), we performed the UV titration with a monocarboxylic acid (phenylacetic acid) and the association

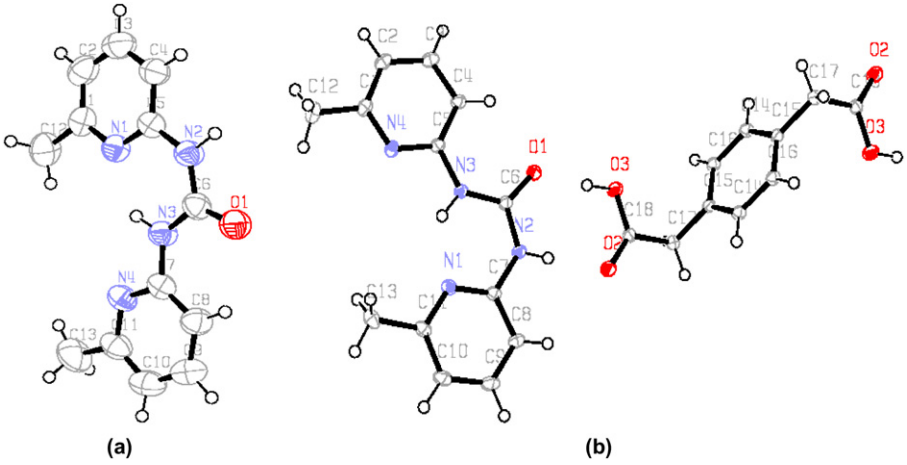

Figure 8. ORTEP diagrams (50% probability) of (a) receptor **1** and (b) its complex with 1,4-phenylenediacetic acid.

Table 3
Crystallographic data and structure refinement parameters of receptor **1** and complex **1**

Compound	Receptor **1**	Complex **1**
CCDC no.	635339	635338
Empirical formula	$C_{13}H_{14}N_4O$	$C_{18}H_{19}N_4O_3$
Formula weight	242.28	339.37
Crystal system	Monoclinic	Triclinic
Space group	$P_2(1)/c$	P-1
T [K]	297 (2)	100.0 (1)
a [Å]	7.1457 (2)	9.2720 (4)
b [Å]	10.9820 (3)	9.7283 (4)
c [Å]	16.7168 (5)	10.1266 (4)
α [°]	90	100.827 (2)
β [°]	91.307 (2)	109.470 (2)
γ [°]	90	94.649 (2)
Z	4	2
V [Å^3]	1311.49 (6)	835.62 (6)
$\ddot{I}$ [Å]	0.71073	0.71073
D_{calcd} [g cm^{-3}]	1.227	1.349
F [000]	512	358
μ [mm^{-1}]	0.082	0.094
2θ [°]	2.22–28.95	2.36–35.00
Index ranges	$-9\leq h\leq 9$	$-14\leq h\leq 14$
	$-9\leq k\leq 14$	$-15\leq k\leq 15$
	$-22\leq l\leq 22$	$-16\leq l\leq 16$
Reflections collected	13,959	16,550
Unique reflections	3454	7222
Observed reflections	1764	5859
R_1 [$I>2\sigma(I)$]	0.0605	0.0574
wR_2	0.1584	0.1569
GOF	1.045	1.064

Table 4
Hydrogen-bond parameters (Å, °) of receptor **1**

D–H···A	D–H	H···A	D···A	D–H···A
N2–H1···O1^{i}	1.00 (2)	1.86 (2)	2.853 (2)	176 (2)
N3–H1···N1	0.93 (2)	1.91 (2)	2.666 (2)	137.6 (18)
C8–H8A···O1	0.93	2.322	2.900 (3)	119.88

Symmetry codes: (i) $2-x, -y, 1-z$.

constant (K_a=8.8×10^3 M^{-1}) was found to be close. Receptor **1** therefore behaves as a monotopic[3e] one toward a dicarboxylic acid. In the solid state, both the receptor **1** and its complex are present in the most stable form where intramolecular hydrogen bonding forces the apparently ditopic receptor **1** to behave like a monotopic receptor. The supramolecular arrangement of both receptor **1** and its complex is quite significant and the dicarboxylic acid in the complex only interacts with the donor–acceptor array containing one amido proton and the carbonyl group of urea linkage (*syn* amide). Here the interesting point is that intramolecular hydrogen bonds remain intact in the solid phase of both receptor and complex. So *host–guest* interaction in solid phase may be insufficient to break the intramolecular stable six-membered hydrogen bonded ring, rather it easily breaks intermolecular hydrogen bonds between the lactam dimer of **1** to form the 2:1 complex. This shows that recognition pattern not only depends on *host–guest* but also on the strength of the intramolecular hydrogen bonds within the receptor. This type of rigid intramolecular hydrogen bonding is thus important to design 2:1 supramolecular synthon of the complexes over discrete 1:1 complex assembly.

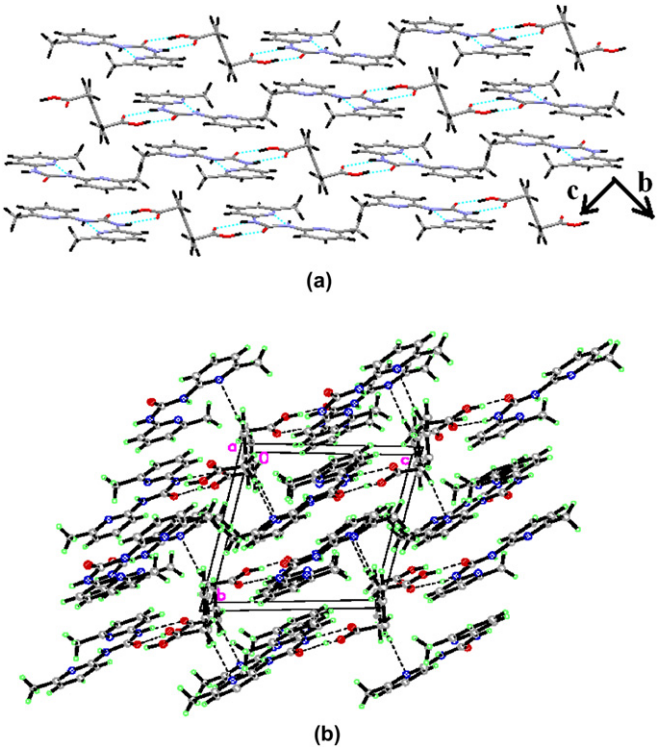

Figure 10. Illustrations for the crystal structure of the 1:1 complex of receptor **1** and 1,4-phenylenediacetic acid: (a) layered arrangement of complex viewed down crystallographic a axis; (b) the crystal packing of complex viewed down the a axis. Hydrogen bonds are shown as dashed lines.

6. Conclusion

In the present work, a case of hydrogen bonding inhibition of the pyridine ring nitrogens in dipicolyl urea receptor **1** has been discussed. It has also been found that recognition of dicarboxylic

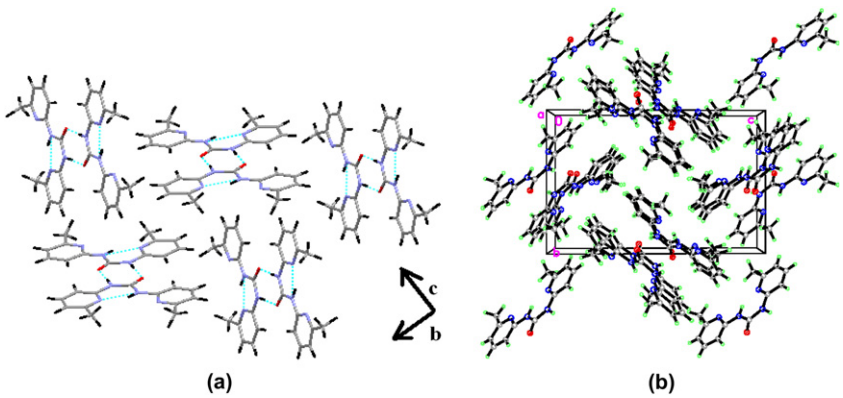

Figure 9. Illustrations for the crystal structure of the receptor **1**: (a) arrangement of dimers viewed down crystallographic a axis; (b) the crystal packing of receptor **1**, viewed down the a axis. Hydrogen bonds are shown as dashed lines.

Table 5
Hydrogen-bond parameters (Å, °) of complex **1**

D–H···A	D–H	H···A	D···A	D–H···A
N2–H1···O2	0.877 (19)	1.980 (19)	2.8506 (12)	171.4 (18)
N3–H1···N1	0.90 (2)	1.93 (2)	2.6512 (13)	135.8 (17)
O3–H1···O1	0.935 (19)	1.673 (19)	2.6031 (12)	172.4 (19)
C4–H4A···O1	0.93	2.326	2.9025 (12)	119.79
C17–H17A···N4^{i}	0.97	2.582	3.5111 (13)	160.41
C17–H17B···O2^{ii}	0.97	2.589	3.5533 (14)	172.83

Symmetry codes: (i) *x*, *y*, 1+*z*; (ii) 2−*x*, −*y*, 2−*z*.

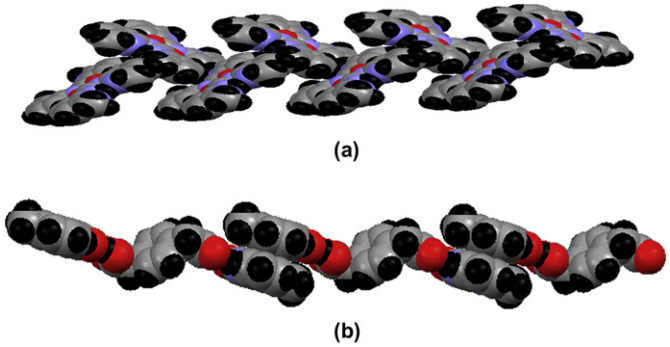

Figure 11. Polymeric arrangement (in spacefill model) of the receptor **1** and its complex with 1,4-phenylenediacetic acid (complex **1**): (a) C–H···N interaction in receptor **1**; (b) π-stacking interaction in complex **1**.

acid with this receptor is comparatively weak due to its intramolecular hydrogen bonding, which forces a ditopic receptor to behave like a monotopic one. Binding constant values with both dicarboxylic acid as well as monocarboxylic acid have been compared. The binding nature of this type of pyridyl urea toward the carboxylic acid moiety in solid phase was also studied by the analysis of single crystals of the receptor as well as its complex with 1,4-phenylenedicarboxylic acid. So in this study, a simple receptor has been designed in which intramolecular stable six-membered hydrogen bonding is utilized not only to inhibit the binding of carboxyl group but the other pyridine nitrogen present in the receptor has also refused to bind a carboxyl group in dicarboxylic acid recognition and the binding happens only from the outwardly created *syn* amide (carbonyl oxygen and N–H) group to the carboxyl to form a 2:1 complex with a dicarboxylic acid.

7. Experimental

7.1. General

Chromatographic separations were performed on silica gel (100–200 mesh). For preparative thin layer chromatographic (PTLC) purification, the layer was formed on a glass plate using water gel-GF 254 silica gel. The petroleum ether used has a boiling range of 40–60 °C. All the melting points were determined on a hot-coil stage melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 500 MHz spectrometers. For NMR spectra, $CDCl_3$ and DMSO-d_6 were used as solvents using TMS as an internal standard. Chemical shifts are expressed in δ units and ^{1}H–^{1}H, ^{1}H–C coupling constants in hertz. IR spectra were recorded using KBr discs.

7.2. General procedure for UV–vis titration

Stock solutions of the receptor **1** was taken in the order of ca. 1×10^{-5} mol dm^{-3} in $CHCl_3$. 1,4-Phenylenedicarboxylic acid was dissolved in 1% DMSO in $CHCl_3$ in order of ca. 1×10^{-4} mol dm^{-3} concentration. DMSO (1%) was added to form a homogeneous solution. But the solutions of other monocarboxylic acids were prepared in $CHCl_3$ in order of ca. 1×10^{-4} mol dm^{-3} concentration. Then the guest solution is added to the receptor solution (taking 2 mL in the UV-cell) and continuous decrease of absorbance in UV–vis spectra was recorded for each time. Association constants were calculated by plotting $1/[G]$ versus $1/\Delta I$ (ΔI=change of intensity of the absorbance spectrum during titration).

7.3. General procedure for drawing Job plot by UV–vis method

Stock solution of same concentration of receptor **1** and the guests were prepared in the order of ca. 1×10^{-5} mol dm^{-3} in $CHCl_3$ (in case of 1,4-phenylenedicarboxylic acid 1% DMSO was added). The absorbance in each case with different host–guest ratio but equal in volume was recorded. Job plots were drawn by plotting $\Delta I\cdot X_{host}$ versus X_{host} (ΔI=change of intensity of the absorbance spectrum during titration and X_{host} is the mole fraction of the host in each case, respectively).

*7.3.1. 1,3-Bis-(6-methyl-pyridin-2-yl)-urea (receptor **1**)*

To a solution of 2-amino-6-methylpyridine (110 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL), triphosgene (296 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise at room temperature under N_2 atmosphere. After 0.5 h, dry Et_3N (0.1 mL) was added dropwise. After another 0.5 h the solvent was evaporated under reduced pressure and dried well. Dry CH_2Cl_2 (10 mL) was added to it and another portion of 2-amino-6-methylpyridine (110 mg, 1.0 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise and refluxed for another 0.5 h. CH_2Cl_2 was evaporated and the residue was extracted with $CHCl_3$ (25 mL×4) after washing with $NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The crude residue was purified by column chromatography (silica gel 100–200 mesh) using 15% EtOAc in petroleum ether to afford the off-white crystalline solid receptor **1** (170 mg, 70%). Besides this (6-methyl-pyridine-2-yl)-carbamic acid ethyl ester as byproduct was obtained in very poor yield (7%).

Mp 184–186 °C [lit.[15] 189–90 °C].

^{1}H NMR ($CDCl_3$, 500 MHz): δ (ppm): 11.0–14.0 (br s, 2H), 7.57 (t, 2H, J=7.8 Hz), 7.25 (br s, 2H), 6.85 (d, 2H, J=7.5 Hz), 2.56 (s, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): 156.9, 153.8, 152.3, 138.9, 117.8, 110.2, 24.6.

FTIR (KBr): 3141, 3064, 2999, 2921, 1694, 1575, 1454, 1278, 1243, 886, 873 cm^{-1}.

Mass (LCMS): *m*/*z* (%): 265.2 [(M+Na)$^{+}$, 18], 243.2 [(M+H)$^{+}$, 38], 135.1 (34), 109.1 (100).

HRMS (FAB): *m*/*z* calculated for $C_{13}H_{14}N_4ONa$ (M+Na)$^{+}$: 265.1065; found: 265.1075.

7.3.1.1. (6-Methyl-pyridine-2-yl)-carbamic acid ethyl ester. Mp 50–53 °C [lit.[15] 55–56 °C].

^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm): 7.73 (d, 2H, J=8.2 Hz), 7.55 (t, 2H, J=7.9 Hz), 7.30 (br s, 2H), 6.82 (d, 2H, J=7.4 Hz), 4.21 (q, 2H, J=14.2 Hz), 2.42 (s, 6H), 1.29 (t, 3H, J=7.1 Hz).

Mass (LCMS): *m*/*z* (%): 181.1 [(M+H)$^{+}$, 100], 153.1 (68), 135.1 (45), 108.9 (17).

*7.3.2. Crystallization of receptor **1** and its 1:1 complexes with 1,4-phenylenediacetic acid*

*Receptor **1***. Single crystals were grown by slow evaporation of the solution of chloroform and methanol (2:3 v/v) of the synthesized pyridyl urea compound. Colorless block shaped crystals were obtained.

*Complex **1***. A 1:1 mixture of 1,3-bis-(6-methyl-pyridin-2-yl)-urea (12.1 mg, 0.05 mmol) and 1,4-phenylenediacetic acid (9.7 mg, 0.05 mmol) was dissolved in methanol and chloroform (1:1 v/v). Colorless block shaped crystals were obtained.

FTIR (KBr): 3120, 3057, 2990, 2923,1697, 1563, 1455, 1289, 1159, 957, 842 cm^{-1}.

7.3.3. X-ray crystallography

Intensity data of all the compounds were collected with a Bruker SMART *APEX2* CCD area-detector diffractometer (Mo Kα radiation, λ=0.71073 Å) using the APEX2 software.[16] The low temperature data for complex **1** was collected using the Oxford Cyrosystem Cobra low-temperature attachment. Data reductions were performed using *SAINT*.[16] Absorption corrections are performed using *SADABS*.[16] The structures were solved by direct methods. The C and N atoms were refined anisotropically whereas all the hydrogen atoms were located from the difference maps and were isotropically refined by full-matrix least squares on F^2 using the *SHELXTL* package and for receptor **1** and complex **1**, H atoms attached to O and N were located in a difference map and isotropically refined. The remaining H atoms were positioned geometrically and allowed to ride on their parent atoms, with the C–H distances in the range 0.93–0.97 Å. The U_{iso} values were constrained to be 1.2 U_{eq}.[17] The figures were plotted with the aid of *SHELXTL* and *ORTEP*.[18]

Acknowledgements

We wish to express our appreciation to DST [Project No. SR/S1/OC-13/2005] and CSIR [Project No. 01(1913)/04/EMR-II], Govt. of India for financial support. S.J. thanks CSIR, Govt. of India for a research fellowship. We also would like to thank the Malaysian Government and Universiti Sains Malaysia for the Scientific Advancement Grant Allocation (SAGA) Grant No. 304/PFIZIK/653003/A118.

Supplementary data

Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2008.04.066.

References and notes

1. (a) Almarsson, O.; Zaworotko, M. J. *Chem. Commun.* **2004**, 1889–1896; (b) Mcmahon, J. A.; Moulton, B.; Walsh, R. D. B.; Rodriguez-Hornedo, N.; Zaworotko, M. J. *Cryst. Growth Des.* **2003**, *3*, 909–919; (c) Walsh, R. D. B.; Bradner, M. W.; Fleischman, S.; Morales, L. A.; Moulton, B.; Rodriguez-Hornedo, N.; Zaworotko, M. J. *Chem. Commun.* **2003**, 186–187; (d) Remenar, J. F.; Morissette, S. L.; Peterson, M. L.; Moulton, B.; Macphee, J. M.; Guzman, H. R.; Almarsson, O. *J. Am. Chem. Soc.* **2003**, *125*, 8456–8457; (e) Childs, S. L.; Chyall, L. J.; Dunlap, J. T.; Smolenskaya, V. N.; Stahly, B. C.; Stahly, G. P. *J. Am. Chem. Soc.* **2004**, *126*, 13335–13342.
2. (a) Prins, L. J.; Reinhoudt, D. N.; Timmerman, P. *Angew. Chem., Int. Ed.* **2001**, *40*, 2382–2426; (b) Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: Amsterdam, 1989; (c) Lehn, J.-M. *Supramolecular Chemistry: Concepts and Perspectives*; VCH: Weinheim, Germany, 1995; (d) *Crystal Design: Structure and Function, Perspective in Supramolecular Chemistry*; Desiraju, G. R., Ed.; John Wiley and Sons: 2003; Vol. 7; (e) *Comprehensive Supramolecular Chemistry*; Atwood, J. L., Davies, J. E. D., MacNicol, D. D., Vogtle, F., Eds.; Pergamon: Oxford, UK, 1996; Vols. 6, 7, 9, 10; (f) Desiraju, G. R. *Science* **1997**, *278*, 404–405; (g) Goswami, S.; Jana, S.; Hazra, A.; Fun, H.-K.; Anjum, S.; Rahman, A.-U. *CrystEngComm* **2006**, *8*, 712–718.
3. (a) Goswami, S.; Ghosh, K.; Dasgupta, S. *J. Org. Chem.* **2000**, *65*, 1907–1914; (b) Goswami, S.; Ghosh, K.; Mukherjee, R. *Tetrahedron* **2001**, *57*, 4987–4993; (c) Goswami, S.; Ghosh, K.; Halder, M. *Tetrahedron Lett.* **1999**, *40*, 1735–1738; (d) Goswami, S.; Mahapatra, A. K. *Supramol. Chem.* **1999**, *11*, 25–33; (e) Goswami, S.; Dey, S.; Fun, H.-K.; Anjum, S.; Rahman, A.-U. *Tetrahedron Lett.* **2005**, *46*, 7187–7191; (f) Goswami, S.; Jana, S.; Dey, S.; Razak, I. A.; Fun, H.-K. *Supramol. Chem.* **2006**, *18*, 571–574; (g) Goswami, S.; Jana, S.; Fun, H.-K. *CrystEngComm* **2008**, *10*, 507–517.
4. (a) Etter, M. C. *Acc. Chem. Res.* **1990**, *23*, 120–126; (b) Nowick, J. S.; Ballester, P.; Ebmeyer, F.; Rebek, J., Jr. *J. Am. Chem. Soc.* **1990**, *112*, 8902–8906; (c) Yang, J.; Marendaz, J. L.; Geib, S. J.; Hamilton, A. D. *Tetrahedron Lett.* **1994**, *35*, 3665–3668; (d) MacDonald, J. C.; Whitesides, G. M. *Chem. Rev.* **1994**, *94*, 2383–2420; (e) Liu, S. Y.; He, Y. B.; Wu, J. L.; Wei, L. H.; Qin, H. J.; Meng, L. Z.; Hu, L. *Org. Biomol. Chem.* **2004**, *2*, 1582–1586; (f) Garcia-Tellado, F.; Goswami, S.; Chang, S. K.; Geib, S. J.; Hamilton, A. D. *J. Am. Chem. Soc.* **1990**, *112*, 7393–7394; (g) Geib, S. J.; Vicent, C.; Fan, E.; Hamilton, A. D. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 119–121; (h) Karle, I. L.; Ranganathan, D.; Haridas, V. *J. Am. Chem. Soc.* **1997**, *119*, 2777–2783; (i) Konig, B.; Moller, O.; Bubenitschek, P.; Jones, P. G. *J. Org. Chem.* **1995**, *60*, 4291–4293.
5. (a) Desiraju, G. R.; Steiner, T. *The Weak Hydrogen Bonds in Structural Chemistry and Biology*; Oxford University Press: Oxford, UK, 1999; (b) Desiraju, G. R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2311–2327; (c) Dunitz, J. D.; Gavezzotti, A. *Angew. Chem., Int. Ed.* **2005**, *44*, 1766–1787; (d) Kumar, D. K.; Jose, D. A.; Das, A.; Dastidar, P. *Chem. Commun.* **2005**, 4059–4061.
6. (a) Caltagirone, C.; Bates, G. W.; Gale, P. A.; Light, M. E. *Chem. Commun.* **2008**, 61–63; (b) Rashdan, S.; Light, M. E.; Kilburn, J. D. *Chem. Commun.* **2006**, 4578–4580; (c) Steed, J. W. *Chem. Commun.* **2006**, 2637–2649; (d) Wu, J.; He, Y.; Zeng, Z.; Wei, L.; Meng, L.; Yang, T. *Tetrahedron* **2004**, *60*, 4309–4314.
7. (a) Reddy, L. S.; Basavoju, S.; Vangala, V. R.; Nangia, A. *Cryst. Growth Des.* **2006**, *6*, 161–173; (b) Blondeau, P.; van der Lee, A.; Barboiu, M. *Inorg. Chem.* **2005**, *44*, 5649–5653; (c) Custelcean, R.; Moyer, B. A.; Hay, B. P. *Chem. Commun.* **2005**, 5971–5973.
8. (a) Lewis, D. F.; Santos, G. B. D.; Liu, W. *J. Org. Chem.* **2005**, *70*, 2974–2979; (b) Papadopoulon, M. V.; Goswami, S.; Hamilton, A. D. *J. Heterocycl. Chem.* **1995**, *32*, 2675.
9. Bolte, M.; Kühl, C.; Lüning, U. *Acta Crystallogr.* **2001**, *E57*, o502–o504.
10. (a) Benesi, H.; Hildebrand, J. H. *J. Am. Chem. Soc.* **1949**, *71*, 2703–2707.
11. (a) Energy minimization was carried out using MMX (PCMODEL Serena Software 1993). Molecular modeling was performed using standard constants and the dielectric constant was maintained at 1.5. (b) Goswami, S.; Jana, S.; Das, N. K.; Fun, H.-K.; Chantrapromma, S. *J. Mol. Struct.* **2008**, *876*, 313–321.
12. Goswami, S.; Dey, S.; Maity, A. C.; Jana, S. *Tetrahedron Lett.* **2005**, *46*, 1315–1318.
13. (a) Spek, A. L. *PLATON, A Multipurpose Crystallographic Tool*; Utrecht University: Utrecht, The Netherlands, 2002; (b) Different stereoveiws of the crystals were generated using Mercury 1.4.1 software.
14. (a) Hunter, C. A.; Sanders, J. K. M. *J. Am. Chem. Soc.* **1990**, *112*, 5525–5534; (b) Adams, H.; Hunter, C. A.; Lawson, K. R.; Julie Perkins, J.; Spey, S. E.; Urch, C. J.; Sanderson, J. M. *Chem.—Eur. J.* **2001**, *7*, 4863–4877.
15. (a) Clemo, G. R.; Fox, B. W.; Raper, R. *J. Chem. Soc.* **1954**, 2693–2701; (b) Katritzky, A. R. *J. Chem. Soc.* **1956**, 2063–2064.
16. Bruker. *APEX2 (Version 1.27), SAINT (Version 7.12a) and SADABS (Version 2004/1)*; Bruker AXS: Madison, WI, USA, 2005.
17. Sheldrick, G. M. *SHELXTL. Version 5.10*; Bruker AXS: Madison, WI, USA, 1998.
18. Johnson, C.K. *'ORTEPII'*. Report ORNL-5138. Oak Ridge National Laboratory: TN, USA, 1976.