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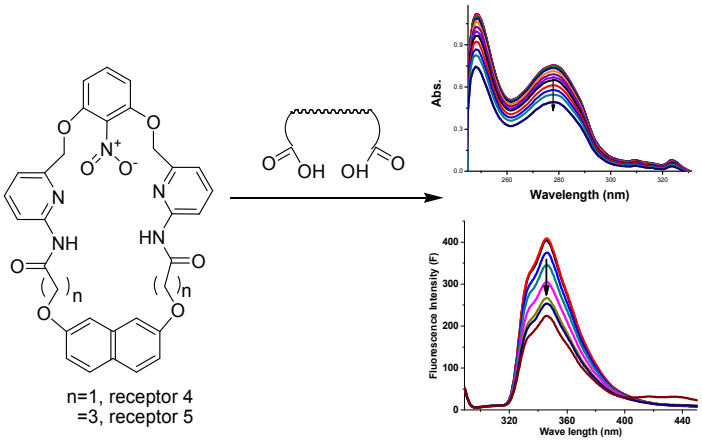
Table of contents entry



Steric inhibition of Hydrogen bonding in molecular recognition of dicarboxylic acids: Di-topic receptors containing nitro group designed to behave like monotopic receptors

Shyamaprosad Goswami,[a*] Rinku Chakrabarty,[a] Swapan Dey[a] and Hun.-Kun Fun[b]

Five receptors (**1**-**5**) including two macrocyclic receptors have been designed and synthesized for the recognition of dicarboxylic acids. The receptors having NO_2 group shows inhibition in hydrogen bonding molecular recognition towards the dicarboxylic acid and this effect becomes more prominent in the case of macrocyclic receptors **4** and **5** in $CHCl_3$. The binding behavior of these receptors has been studied by UV-vis, fluorescence and 1:1 ^1H NMR binding studies.

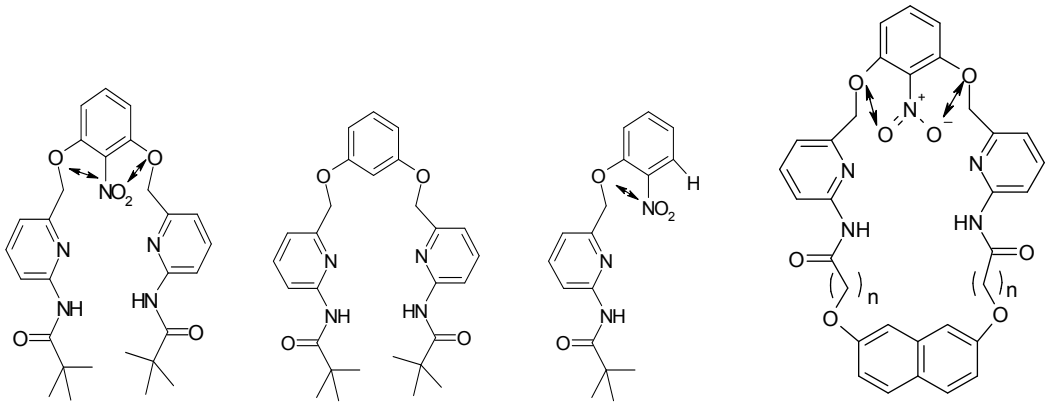
Introduction

The recognition of dicarboxylic as well as monocarboxylic acids with designed receptors has got considerable attention due to its application in pharmaceutical science[1] and different supramolecular architectures[2] and also due to their presence in many biologically active molecules, for example, in drugs such as ibuprofen,[3] aspirin, bilirubin, bile acids, folic acid and biotin etc. For designing synthetic receptors H-bonding interaction is one of the major important forces. Among all the binding forces used in the development of artificial receptors, hydrogen bonding is potentially the most directed and powerful.[4] Different types of receptors[5] for di-carboxylic acids have been designed and synthesized by many research groups and the different aspects of recognition process have also been elegantly studied. Hydrogen bonding interactions influence a lot for the whole recognition process.

For the recognition of mono and dicarboxylic acids we have synthesized receptors having three point hydrogen bonds[6] with different spacers.[5a,5b,5g,5h] We have also reported the case of hydrogen bond inhibition by N-oxide formation[7] in the recognition of dicarboxylic acids, intramolecular hydrogen bond inhibition with dipicolyl urea.[5e] Macrocyclic receptors[5f] have also been synthesized for the recognition of dicarboxylic acids. A major portion of the earlier synthesized receptors contain pyridine amide moiety in a suitable position to bind the carboxylic acid group. In this paper, we wish to report the synthesis of a series of ditopic receptor **1** and macrocyclic receptors **4** and **5** containing nitro group which behave like monotopic receptors though they have two binding pyridine amide groups for dicarboxylic acids. However, it is interesting to see that though nitro group inhibits binding of one of the

carboxyl groups of saturated dicarboxylic acids i.e. it forces the dicarboxylic acids to behave like a monocarboxylic one (*Ka* is in the order of 10^2 similar to that of mono carboxylic acid and not 10^4 as normally expected for dicarboxylic acid), it also probably binds the hydroxy group in malic acid increasing the binding constant from 10^2 to 10^3 for the extra hydrogen bond formation. We have also synthesized receptors **2** (without nitro group) and **3** (mono-pyridine amide with adjacent nitro group) for comparison studies.

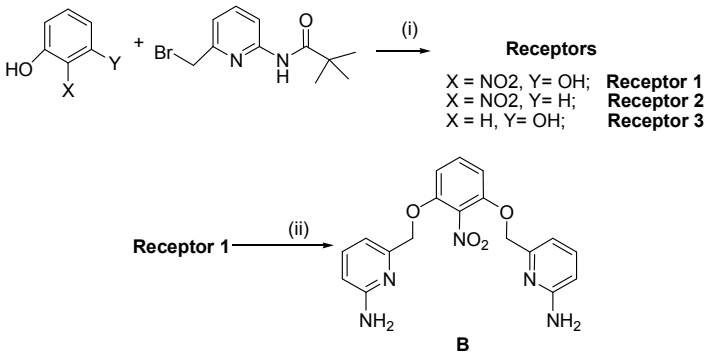
Results and discussions:

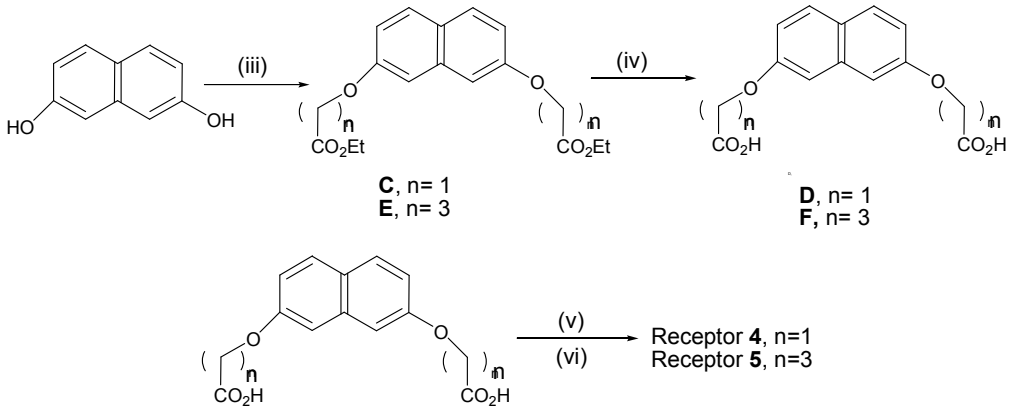


Receptor **1** Receptor **2** Receptor **3** n=1, receptor **4**

n=3, reeptor **5**

Figure 1: Structures of the receptors **1**-**5**.





Scheme 2. Synthesis of receptors **1**, **2**, **3, 4** and **5.**

reagents and conditions: (i) dry K_2CO_3, dry acetone, TBAB, r.t, 15 h; (ii) 4(N) KOH in 1:1 ethanol-water, reflux, 10h; (iii) ethyl chloroacetate (n= 1), ethyl-4-bromobutyrate (n= 3), dry K_2CO_3, dry acetone, r.t., 10 h; (iv) 4(N) KOH in 1:1 etanol-water, reflux, 12h; (v) oxalyl chloride, dry CH_2Cl_2, dry DMF (cat.), 3h; (vi) **B,** high dilution, dry THF, dry NEt_3, 14h.

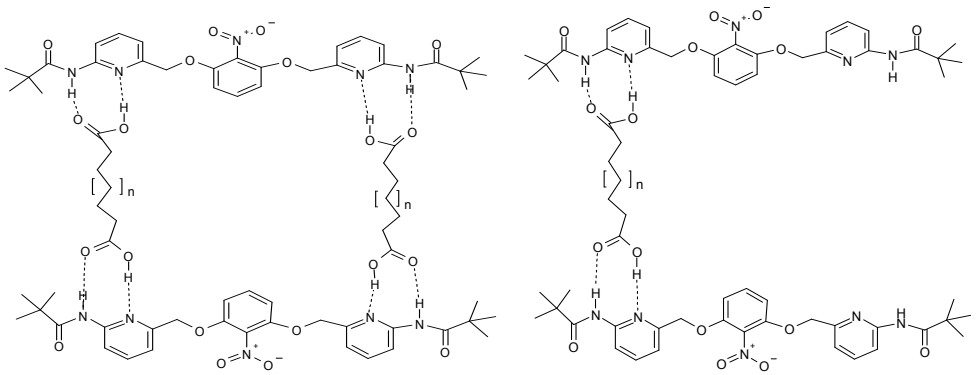
Binding studies:

^{1}H NMR studies

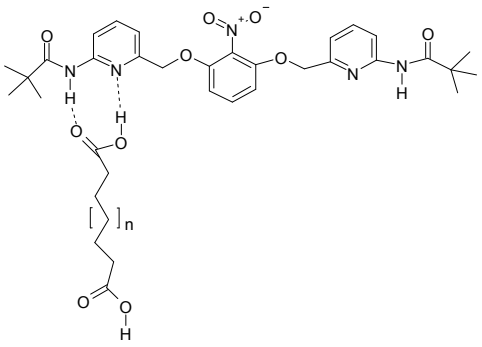
Three pyridine amide based receptors have been synthesized and characterized by ^{1}H nmr studies. The binding behavior of the receptors has been studied by UV method and these results have also been compared with the binding result of monocarboxylic acid (propionic acid).

In NMR spectra of receptor **1** the NH proton appears as singlet at δ 7.96 ppm. But after complexation with adipic acid and DL-malic acid the amide proton has shifted its position and the shifts are Δδ= 2.8 ppm and Δδ= 2.7 ppm respectively, i.e. receptor **1** behaves like monocarboxylic acid receptor. For receptor **5** NH protons appear at δ 8.10 ppm but after complexation with DL-malic acid the δ value becomes 9.06 and the OH proton of malic acid appears at around 3.03 ppm as a broad peak. For receptor **4** NH value appears at δ 8.90 ppm but after addition of DL-malic acid at δ 9.06 but the OH proton appears at δ~ 2.83 ppm from δ 3.92 (OH of DL-malic acid). But for receptor **1** in the 1:1 complex with DL-malic acid the OH proton of DL-malic acid gets shifted from δ 3.92 ppm to δ 6.37 ppm (Δδ= 2.45 ppm). Therefore the shift of OH proton of malic acid reveals the strong binding of the nitro group with the OH proton.

The different modes of binding of receptor **1** with dicarboxylic acids have been represented in figure 2.



1a **1b**



1c

Figure 2: Proposed mode of binding of dicarboxylic and monocarboxylic acids by receptors **1**.

UV-vis studies

We have studied the binding behavior of the receptors **1**, **2**, **3**, **4** and **5** towards the dicarboxylic and monocarboxylic acids by UV-vis method. Receptor **1** shows λ_{max} at 332 nm, which gradually decreased on addition of the guest solution. Similar trend was observed during the titrations with benzoic acid and propionic acid. Receptor **2** shows better binding and behaves like dicarboxylic acid receptor by its UV-vis spectra after addition of dicarboxylic acids. Receptor **3** behaves like as usual receptor for monocarboxylic acids. Receptor **4** possesses λmax at 278 nm in its UV-vis spectra. The UV-vis spectra of **4** almost remain unaffected upon addition of mono as well as dicarboxylic acids except DL-malic acid (Figure 3). Similar observation is found in case of receptor **5** having λmax at 277 nm.

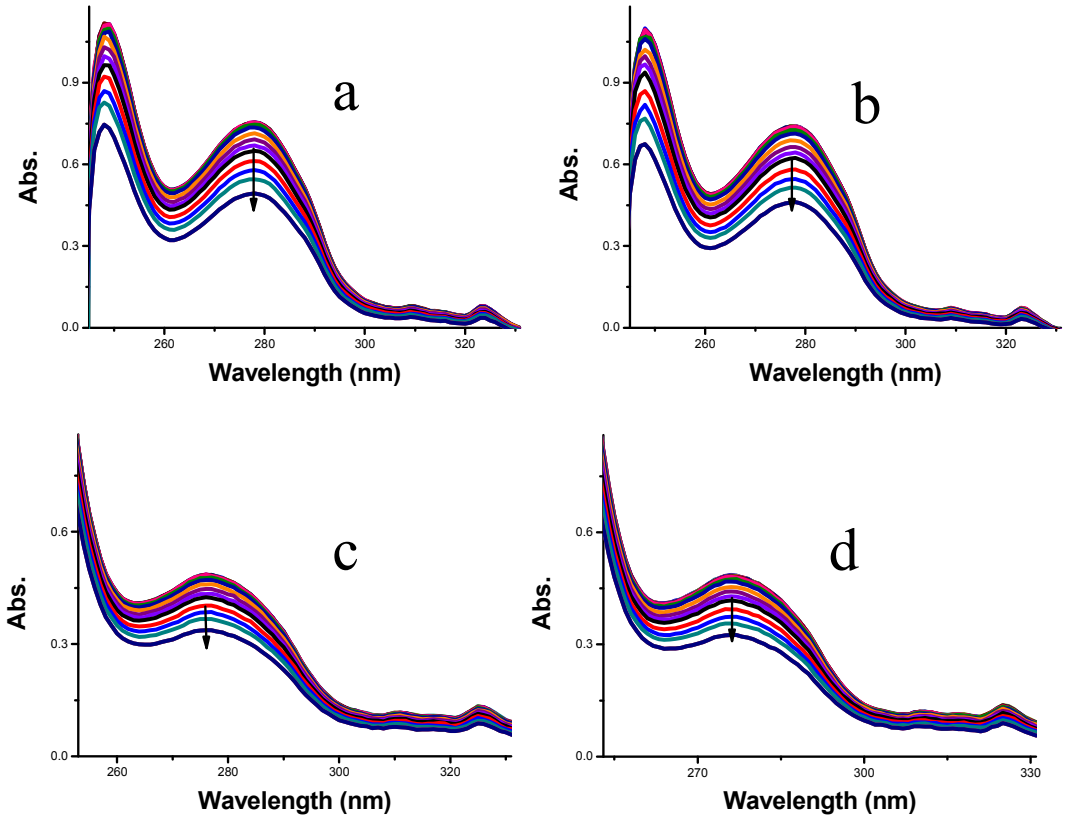


Figure 3: UV-vis spectra of receptor **4** with adipic acid (a); receptor **4** with DL-malic acid (b); receptor **5** with adipic acid (c); receptor **5** with DL-malic acid (d).

Fluorescence studies:

We have studied the binding behavior of the receptors **4** and **5** by fluorescence method (Figure 4). The λmax for receptor **4** appears at 348 nm when excited at 278 nm. Upon addition of dicarboxylic acids like adipic acid, glutaric acid etc. fluorescence intensity decreases but the amount of decrease is more prominent with DL-malic acid. Here also receptor **5** behaves in a similar fashion but the λmax appears at 346 nm.

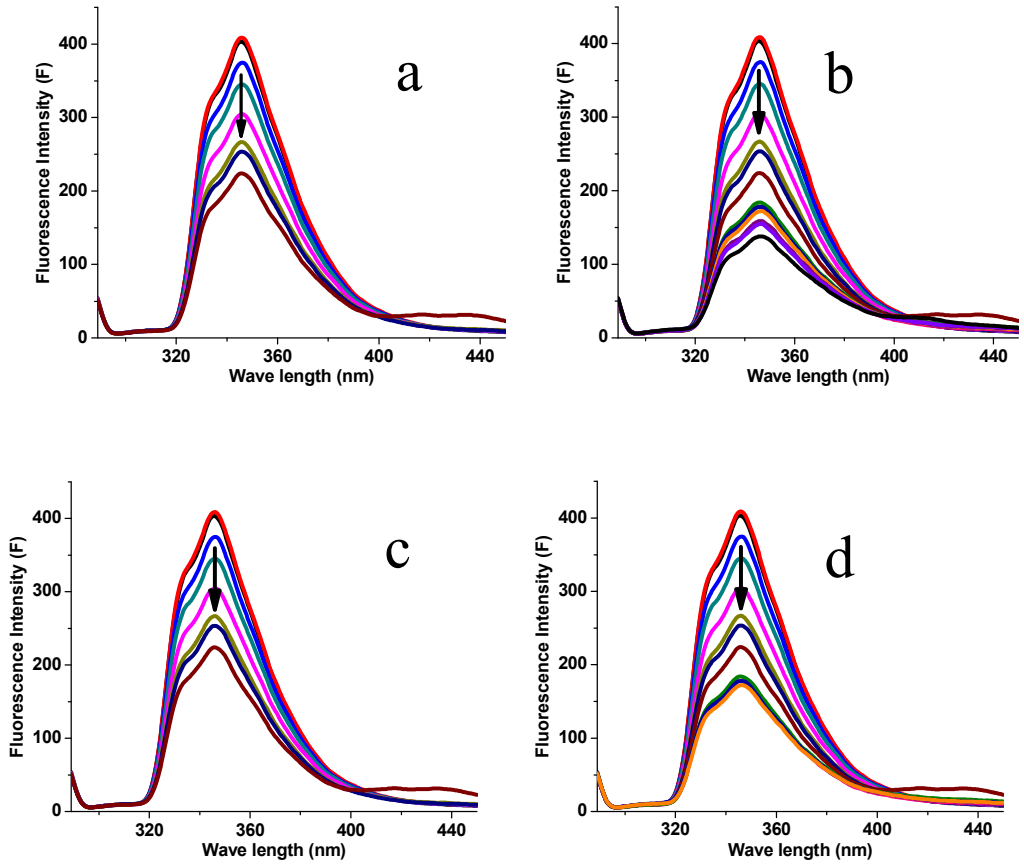
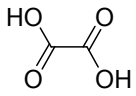
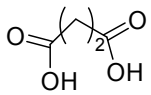
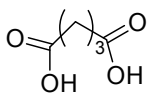
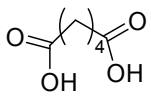
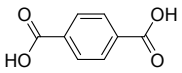
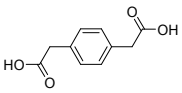
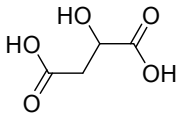
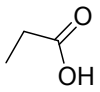
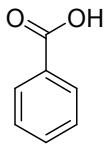


Figure 4: Fluorescence spectra of receptor **4** with adipic acid (a); receptor **4** with DL-malic acid (b); receptor **5** with adipic acid (c); receptor **5** with DL-malic acid (d).

Table 1: Binding constant values[8a] of the five receptors in UV-vis and fluorescence methods (errors in the brackets (±a) refer to errors for the slope "a").

Ka values (M^{-1}) / Acids	Receptor **1** (UV)	Receptor **2** (UV)	Receptor **3** (UV)	Receptor **4**		Receptor **5**	
				UV	Fluorescence	UV	Fluorescence
Oxalic acid 	$1.90 \times 10^2(\pm 0.02)$	$1.08 \times 10^2(\pm 0.002)$	$1.62 \times 10^2(\pm 0.001)$	$1.22 \times 10^2(\pm 0.001)$	$1.24 \times 10^2(\pm 0.01)$	$1.29 \times 10^2(\pm 0.001)$	$1.24 \times 10^2(\pm 0.001)$
Succinic acid 	$1.58 \times 10^2(\pm 0.02)$	$2.64 \times 10^2(\pm 0.001)$	$1.13 \times 10^2(\pm 0.002)$	$1.34 \times 10^2(\pm 0.001)$	$1.32 \times 10^2(\pm 0.01)$	$1.24 \times 10^2(\pm 0.001)$	$1.22 \times 10^2(\pm 0.001)$

Glutaric acid 	2.71 × 10^2(±0.004)	7.76 × 10^2(±0.001)	1.98 × 10^2(±0.001)	1.10 × 10^2(±0.002)	1.11 × 10^2(±0.01)	1.24 × 10^2(±0.001)	1.23 × 10^2(±0.001)
Adipic acid 	2.87 × 10^2(±0.01)	1.37 × 10^2(±0.001)	1.92 × 10^2(±0.001)	3.52 × 10^2(±0.001)	3.53 × 10^2(±0.01)	3.86 × 10^2(±0.002)	3.86 × 10^2(±0.002)
Terephthalic acid 	2.17 × 10^2(±0.01)	1.46 × 10^2(±0.001)	2.08 × 10^2(±0.001)	1.34 × 10^2(±0.001)	1.32 × 10^2(±0.01)	1.36 × 10^2(±0.001)	1.33 × 10^2(±0.001)
1,4-Phenylenediacetic Acid 	1.08 × 10^2(±0.01)	4.18 × 10^2(±0.001)	1.35 × 10^2(±0.001)	1.22 × 10^2(±0.001)	1.21 × 10^2(±0.01)	1.24 × 10^2(±0.001)	1.32 × 10^2(±0.001)
DL-Malic acid 	2.61 × 10^2(±0.01)	4.01 × 10^2(±0.003)	7.21 × 10^2(±0.001)	3.34 × 10^3(±0.0001)	4.00 × 10^3(±0.01)	4.06 × 10^3(±0.003)	4.10 × 10^3(±0.001)
Propionic acid 	1.25 × 10^2(±0.01)	6.07 × 10^2(±0.001)	1.35 × 10^2(±0.001)	1.30 × 10^2(±0.001)	1.31 × 10^2(±0.01)	1.24 × 10^2(±0.001)	1.22 × 10^2(±0.001)
Benzoic acid 	1.01 × 10^2(±0.01)	1.22 × 10^2(±0.001)	1.11 × 10^2(±0.001)	1.23 × 10^2(±0.001)	1.20 × 10^2(±0.01)	1.11 × 10^2(±0.001)	1.13 × 10^2(±0.001)

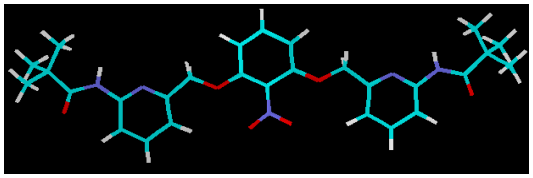
Association constant (*Ka*) was measured by the UV method[8b] between the receptor **1** with different dicarboxylic acids, propionic acid and malic acid. We have taken malic acid to understand the role of the nitro group which may have extra binding capability with the hydroxy group of malic acid. If we see the binding behavior of the three receptors with oxalic acid we can see that the binding constant value is higher for receptors **1** and **3** when they are

compared to that with the receptor **2** which may be due to the presence of the nitro group. The carboxyl group of oxalic acid is strongly acidic and so it may bind in a stronger way with the nitro group and so the binding constant values for receptors **1** and **3** are higher than that when it is compared with receptor **2**. In case of succinic acid the binding constant value for receptor **2** is higher and the *Ka* values for the receptors **1** and **3** are almost the same. This may be due to the fact that succinic acid fits better to the cavity of the receptor **2**. This trend remains the same in case of adipic acid, i.e. *Ka* value is higher in case of receptor **2.** So we can say that receptor **1** behaves as a receptor of monocarboxylic acid as the binding constant values in case of oxalic acid, succinic acid, adipic acid and terephthalic acid are almost similar and this happens only due to the presence of the nitro group because to which in receptor **1** the two pyridine amide moieties remain almost in a linear fashion (the X-ray structure of **1**) instead of making a cavity because of nitro group or being forced to make a macrocyclic cavity as in receptors **4** and **5**.

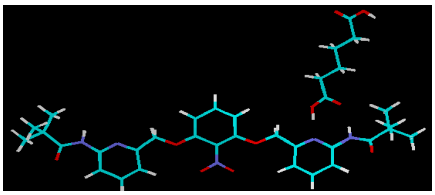
In the cases of receptors **4** and **5** the inhibition property however increases resulting in the binding of acid moiety and the OH of malic acid which gets tightly bound with the NO_2 group (almost outside these macrocycles). Here the two pyridine binding moieties remain almost in parallel fashion. Therefore when one pyridine moiety engages in binding with the carboxyl moiety the other one can't take part in binding of the carboxyl moiety of the same dicarboxylic acid. These facts also correlate with our proposed binding modes (Figure **2**). Macrocyclisation in **4** and **5** tried to force them to behave like dicarboxylic acid receptors by arranging the two pyridyl amide moieties in proper orientation, which apparently doesn't go so well with **4** an **5** and they are more likely to behave like monocarboxylic acid receptors.

Model studies

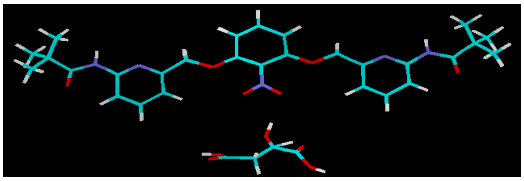
To correlate the binding behavior of receptor **1** in both solutions as well as in solid phases, we have performed a modeling study[9] (Figure 5). The energy minimization predicts the stable geometry of the molecule. It depends on the receptors and the guest. The presence of nitro group is always diverting the positioning of pyridine amide group to remain opposite to the nitro group (as found in energy minimized structures in the receptors as well as in the complexes with carboxylic acids in cases of both the receptors **1** and **3** having bulky nitro group adjacent to the binding pyridine amide site staying though a little away by $–O-CH_2-$ spacer in between. This opposite geometry of the pyridine amide groups flanked by the nitro group is thus responsible of such opposite orientation due to steric repulsion.



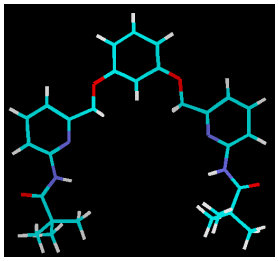
1



1a



1m



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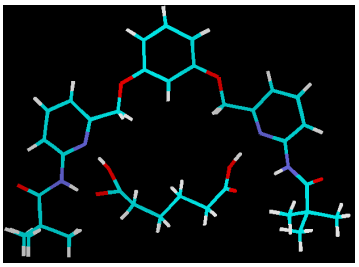
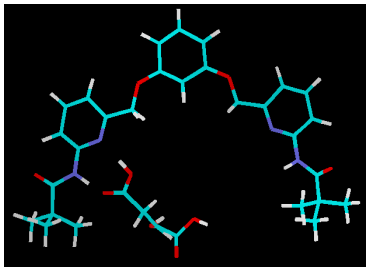
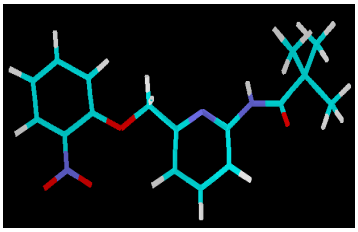


2a



2m



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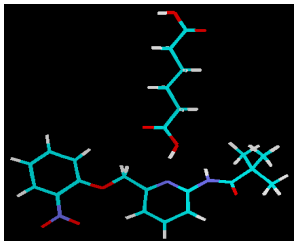
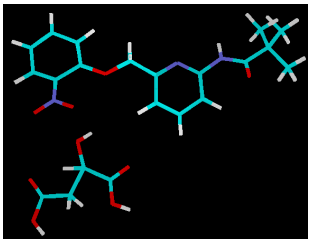
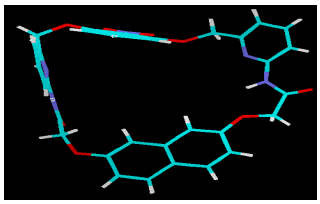


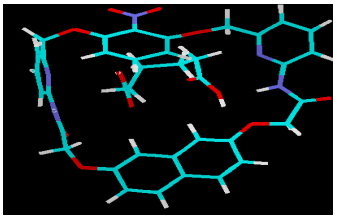
3a



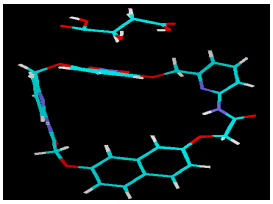
3m



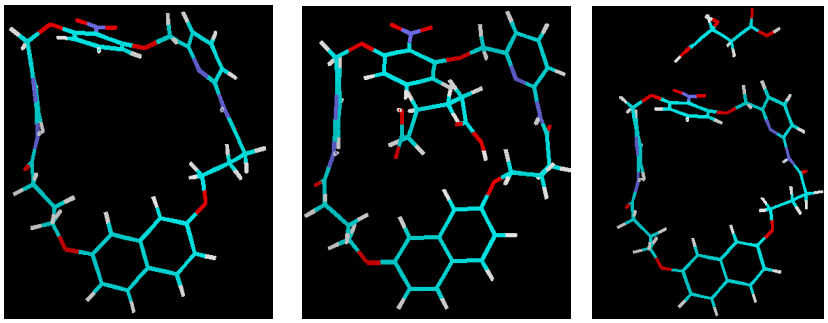
4



4a



4m



5 **5a** **5m**

Figure 5: Energy minimized forms of receptors: (1) receptor **1**; (1a) receptor **1** with adipic acid; (1m) receptor **1** with malic acid; (2) receptor **2**; (2a) receptor **2** with adipic acid; (2m) receptor **2** with malic acid; (3) receptor **3**; (3a) receptor **3** with adipic acid; (3m) receptor **3** with malic acid; (4) receptor **4**; (4a) receptor **4** with adipic acid; (4m) receptor **4** with malic acid; (5) receptor **5**; (5a) receptor **5** with adipic acid; (5m) receptor **5** with malic acid.

Table 2: Minimum energy (kJ mol^{-1}) of the receptors

1	**28.96**	**1a**	**26.99**	**1m**	**16.11**
2	**26.66**	**2a**	**1.33**	**2m**	**10.23**
3	**45.22**	**3a**	**34.12**	**3m**	**40.12**
4	**12.12**	**4a**	**5.12**	**4m**	**-30.33**
5	**10.33**	**5a**	**4.43**	**5m**	**-45.12**

From the *Emin.* values (Table 2) it can be concluded that receptor **1** behaves as a receptor of monocarboxylic acid, receptor **2** as a receptor of dicarboxylic acid, receptor **3** as a receptor of monocarboxylic acid, but in **4** and **5** the inhibition property of NO_2 group is very much prominent giving rise to more complex stability of receptor-malic acid complex compared to receptor-adipic acid or receptor-benzoic acid or receptor-propionic acid complex. Again in case of receptor **4** energy of the complex of receptor **4** and malic acid is much more lowered compared to its complex with adipic acid. Similar phenomena is observed in the case of receptor **5** which is sound enough from the spectroscopic results and the energy values in theoretical calculation method.

X-ray studies

For solid phase recognition study of dicarboxylic acid with receptor **1** and also to confirm the structure of receptor **1,** we have been able to grow single crystals of receptor **1** and X-ray studies[10] confirmed the structure of receptor **1**. Single crystals were obtained by dissolving the material in chloroform followed by slow evaporation at ambient condition.

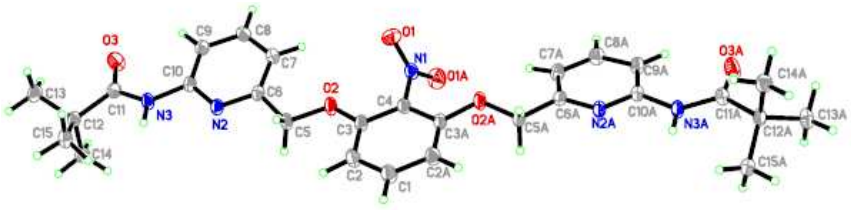


Figure 6: ORTEP diagram of receptor **1**.

From the crystal structure of receptor **1** it is clear that the NO_2 group stays in the opposite direction to that of the pyridine amide moieties which make it behave more like a receptor for monocarboxylic acids even when dicarboxylic acids stay in action. This fact clearly describes macrocycle formation with eventually low yield. So after macrocyclisation due to strain within the cavity receptor **4** and **5** denies to be behaved like a dicarboxylic acid receptor, i.e. in other words it is forced to behave like a monocarboxylic one. Even when we are considering malic acid, which is a hydroxy dicarboxylic acid, the macrocycles are behaving more like a hydroxyl monocarboxylic acid receptors.

Receptor **1** crystallizes in monoclinic *C2/c* space group. Two weak intermolecular C-H…O hydrogen bonds[11] (H-bond) have been found in the crystal lattice where one layer attached with other through by unusual C-H…O hydrogen bonds one is C2-H2…O3 and another one is C5-H5A...O1 (Table 3). In the hydrogen bonding network two oxygens of the nitro group makes H-bonding with two benzylic hydrogens of the two parallel layers. These two layers are arranged in opposite directions. Here we report, another C-H…O hydrogen bonding between the C-H of one pyridine ring with the nitro group of another molecule, which makes a beautiful stairlike structure[12] (Figure 7).

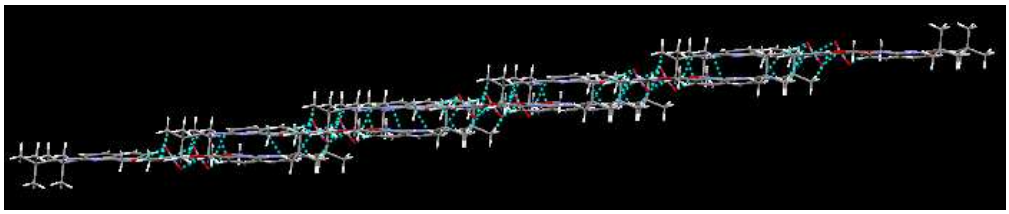


Figure 7: Stairlike structure of receptor **1** showing infinite hydrogen bonding arrays.

Table 3: Selected Hydrogen Bond Parameters of Crystal of Receptor **1**

D-H···A	*d*(D-H)/Å	*d*(H···A)/Å	*d*(D···A)/Å	*θ*(D-H···A)/deg
C2-H2…O3[i]	0.982(15)	2.553(16)	3.3522(14)	138.6(12)
C5-H5A...O1[ii]	0.964(15)	2.408(15)	3.2015(14)	139.4(11)
C7-H7...O2 (Intra)	0.959(15)	2.385(14)	2.7407(12)	101.4(10)
C9-H9...O3 (Intra)	0.977(15)	2.313(15)	2.8910(13)	117.1(10)

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

Conclusion: In summary, we have synthesized five receptors for the study of inhibition property of nitro group in hydrogen bonding in molecular recognition. The observations from behavior of macrocyclic receptors **4** and **5** are sound enough to fulfill this aim to demonstrate the effect of nitro group in inhibition of hydrogen bonding in molecular recognition.

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