J Incl Phenom Macrocycl Chem (2010) 68:461–466
DOI 10.1007/s10847-010-9810-8

ORIGINAL ARTICLE

Recognition of dicarboxylic acids by a *bis* pyrimidine amine linked xylene spacer: a unique *gauche* dimeric complex of host and adipic acid detected by X-ray

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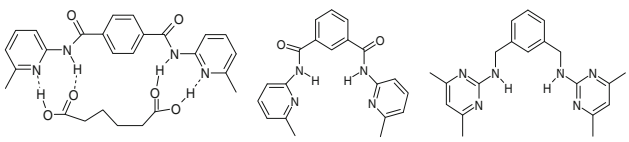
Received: 9 March 2010 / Accepted: 25 May 2010 / Published online: 9 June 2010

Abstract A pyrimidine based receptor (pyrimidine amine linked xylene spacer) has been synthesized for recognition of dicarboxylic acids. Binding studies have been performed by UV–vis method by varying the chain length of dicarboxylic acids. The downfield chemical shift of amine protons of receptor in presence of adipic acid or glutaric acid and the 1:1 dimeric crystal structure of the receptor and adipic acid reveal the strong binding interaction.

Keywords Molecular recognition · Supramolecular network · Host–guest interaction · Hydrogen bonding

Introduction

In molecular recognition [1, 2] synthesis of an artificial receptor for binding dicarboxylic acid is a massive interesting area of research due to the biological importance and the wide application of pharmaceutical science such as receptor-based drug design [3, 4]. Recognition of carboxylic acids is mainly based on hydrogen bonding interactions [5–7]. Among the all hydrogen-bonding groups, the amide group is frequently used functionality for designing extended self-assemblies with conventional hydrogen bonding patterns with the dicarboxylic acids [8–13]. To date, various receptors have been designed for selective binding of carboxylic acids [14–22]. Recognition of dicarboxylic acids having appropriate chain length selectively bind pyridylamide-based ditopic receptor to form a 1:1 *syn–syn* dimeric complex (**1**) [23, 24] whereas increasing the chain length of dicarboxylic acids, 1:1 polymeric complexes having ribbon structure are observed instead of dimeric complex [25, 26]. Previously Hamilton et al. [27] has shown that a *syn–syn* helical supramolecular structure is formed by the complexation of dicarboxylic acids with a receptor (**2**) having pyridylamide separated by an isophthaloyl spacer. Etter et al. [28] has demonstrated first the complexation of carboxylic acid using 2-amino pyrimidine. Here in this paper, for the first time we discuss the recognition of dicarboxylic acids by pyrimidine amine linked-xylene spacer (**3**) and report solid state 1:1 dimeric supramolecular structure of receptor **3** and adipic acid by showing the conformation of receptor in *gauche* form.



1 **2** **3**

Experimental

Receptor **3** has been synthesized in our laboratory [29] and it was crystallized with adipic acid. Melting points were recorded by hot coil stage melting point apparatus and were

Electronic supplementary material The online version of this article (doi:10.1007/s10847-010-9810-8) contains supplementary material, which is available to authorized users.

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uncorrected. ^{1}H NMR spectra were recorded on 500 MHz spectrometer. FT-IR spectra were recorded on a JASCO FT/IR-460 plus spectrometer using KBr discs.

Intensity data of the crystal structure was collected on Bruker SMART APEXII CCD area-detector diffractometer [30]. Data reductions were performed using SAINT. The structures were solved by direct methods and refined by full-matrix least squares on F^2 using the SHELXTL package [31]. The softwares used to prepare material for publication were SHELXTL and PLATON [32]. All hydrogen atoms were located from the difference Fourier maps and refined freely. The figures were plotted with the aid of ORTEP [33] and Mercury 1.4.1 software. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Center No. CCDC 757534.

General procedure for UV–vis titration

Stock solution of the receptor **3** was prepared in the order of 1.11×10^{-4} M in acetonitrile. The solutions of guest acids were also prepared in ca 1×10^{-3} M order in acetonitrile. Then the guest solution was added to the receptor solution (taking 2 mL in the UV-cell) and continuous decreases of absorbance in UV spectra were recorded each time. Association constants were calculated by plotting $1/\Delta I$ versus $1/[G]$.

Crystallization procedure of the co-crystal of receptor **3** and adipic acid

A 1:1 mixture of receptor **3** (20.1 mg, 0.06 mmol) and adipic acid (8.8 mg, 0.06 mmol) was dissolved in a mixture of chloroform methanol and hexane solution. The single crystals were grown by slow evaporation of solvent.

Mp 120–122 °C; IR: 3434, 3295, 2914, 2851, 1679, 1578, 1450, 1367, 1295, 1152, 1028, 787 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$): 7.35 (s, 1H), 7.29–7.26 (m, 3H), 7.08 (bs, 2H), 6.29 (s, 2H), 4.62 (d, 4H, $J = 5.60$ Hz), 2.30 (t, 4H, $J = 8.32$ Hz), 2.28 (s, 12H), 1.63 (t, 4H, $J = 2.85$ Hz).

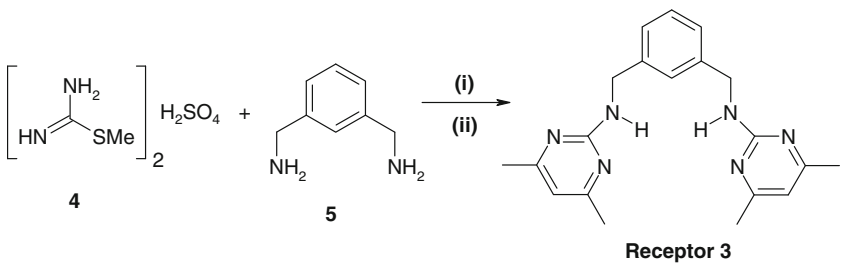
Crystallographic data and structure refinement parameters of the co-crystal: Empirical formula $C_{20}H_{24}N_6$. $C_6H_{10}O_4$; Formula weight 494.59 g mol^{-1}; Crystal system triclinic; Space group P-1; $T = 100$ K; $a = 7.3487(2)$ Å; $b = 8.8661(2)$ Å; $c = 19.4497(5)$ Å; $\alpha = 91.745(2)°$; $\beta = 90.02(2)°$; $\gamma = 97.147(2)°$; $Z = 2$; $V = 1256.79(6)$ Å^3; $I = 0.71073$ Å; $D_{calc} = 1.307$ g/cm^3; F [000] = 528; Crystal size = 0.05 × 0.12 × 0.37; θ min–max = 1.0–26.5°; $\mu = 0.090$ mm^{-1}; Index ranges $-9 \le h \le 9$; $-11 \le k \le 11$; $-24 \le l \le 24$; Reflections collected 23571; Unique reflections 5149; Observed reflections [$I > 2.0\sigma(I)$] 3567; R_1 [$I > 2\sigma(I)$] 0.0415; wR_2 0.1109; GOF 1.02.

Result and discussions

Receptor **3** has been easily synthesized in solid phase by microwave irradiation according to our recently reported procedure (Scheme 1) [29]. The compound is characterized by spectral analysis. The single crystal X-ray structure of receptor **3** and adipic acid is reported here.

Receptor **3** having two pyrimidine amines linked by a xylene spacer has two donor acceptor arrays for binding dicarboxylic acids. In receptor **3,** the benzylic carbons are sp^3 instead of sp^2 which makes the receptor **3** more flexible and as a result receptor **3** is free to rotate to adjust its conformation to a stable *gauche* dimeric complex with adipic acid (Fig. 1d as proved by X-ray structure determination) to match mutual size selectivity rather than the formation of polymeric (Fig. 1a: hypothetical) or tetrameric complex (Fig. 1b: hypothetical). Due to the small cavity of the *syn* form of receptor **3**, *syn–syn* dimeric complex is not observed (Fig. 1c: hypothetical).

The 1:1 dimeric complex crystallized out in space group P-1. The binding pattern of receptor **3** and adipic acid shows that both the receptor and the guest adipic acid accommodate each other by taking the advantage of the flexibility of the spacer methylenes attached in between the benzene ring and the pyrimidine amine moieties of the receptor and also the four methylenes between the carboxyl groups of the guest adipic acid (Fig. 2a). The receptor **3** interacts with the guest adipic acid in solid state by two eight-membered cyclic hydrogen bonding network. Each cyclic hydrogen bonding network contains (i) hydrogen bonding between



Scheme 1 Reagents and conditions: (i) K_2CO_3, 450 Watt, 25 min, MW; (ii) acetyl acetone, 300 W, 8 min, MW

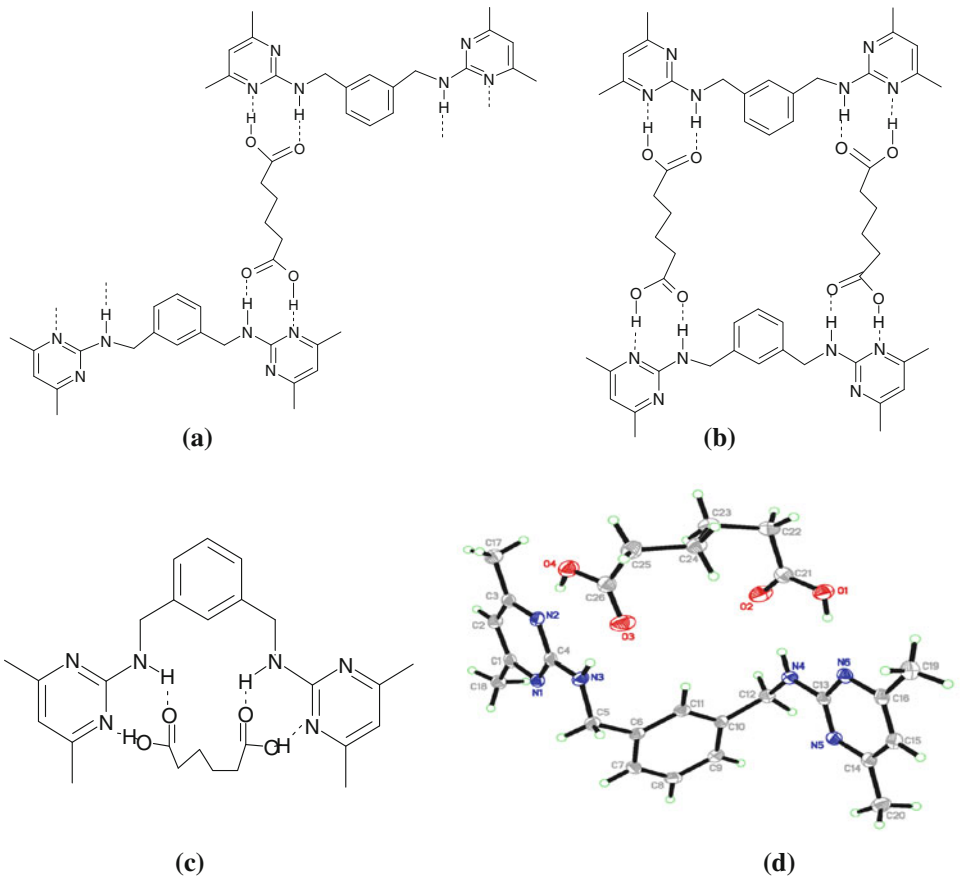


Fig. 1 **a** Hypothetical *anti–anti* 1:1 polymeric structure; **b** hypothetical *syn–syn* 2:2 tetrameric structure; **c** hypothetical *syn–syn* 1:1 dimeric structure; **d** *gauche* 1:1 dimeric structure (ORTEP diagram with 50% probability) (co-crystal structure of receptor **3** with adipic acid)

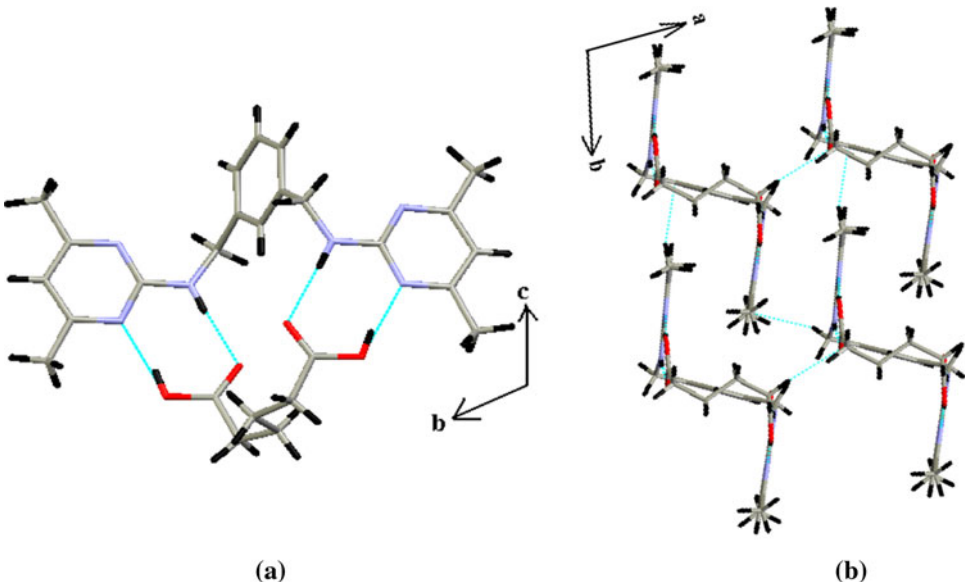


Fig. 2 **a** 1:1 *Gauche* top–bottom bound complex of receptor **3** with adipic acid along the crystallographic *a* axis; **b** chair-like motif viewed down crystallographic *c* axis. Hydrogen bonds are shown in *dashed line*

the pyrimidine amine of receptor **3** and the 'O' of carboxylic acid moiety [N3–H1N3···O3, 2.857(2) Å; N4–H1N4···O2, 2.879(2) Å; Table 1] and (ii) hydrogen bonding between the pyrimidine nitrogen and the hydroxy group of carboxylic acid [O1–H1···N6, 2.650(2) Å; O4–H4···N2, 2.638(2) Å; Table 1].

Previously Hamilton et al. [23] reported a *syn–syn* 1:1 dimeric co-crystal of adipic acid with pyridine amine linked with a terephthaloyl spacer. Here in our case the *gauche* 1:1 top–bottom bound dimeric co-crystal is observed (Fig. 2). One asymmetric unit interacts with other asymmetric units by secondary CH–π and C–H···O

Table 1 Hydrogen-bond parameters (Å, °) of co-crystal of receptor **3** and adipic acid

D–H···A	*d*(H···A)	*d*(D···A)	*θ*(D–H···A)
O1–H1···N6	1.84	2.650(2)	168
N3–H1N3···O3	2.00(2)	2.857(2)	173(2)
N4–H1N4···O2	2.01(2)	2.879(2)	177.7(16)
O4–H4···N2	1.83	2.638(2)	168
C22–H22A···O3^{i}	2.53	3.468(3)	163
C18–H18C···*Cg*3^{ii}	2.81	3.523(2)	131
C20–H20B···*Cg*3^{iii}	2.83	3.615(2)	140

Symmetry codes: (i) $-1 + x, y, z$; (ii) $x, 1 + y, z$; (iii) $x, -1 + y, z$; *Cg*3 is the centroids of the ring C6/C7/C8/C9/C10/C11

interactions to make chair like supramolecular architecture (Fig. 2b) [34, 35]. Thus, this case of complexation shows unique conformational adjustments of host and guest to compliment each other and this would have not been possible with rigid small spacer.

In ^{1}H NMR spectrum, the amine protons of receptor **3** appear at 5.26 ppm in $CDCl_3$. The 1:1 ^{1}H NMR spectra of receptor **3** with different carboxylic acids were performed in $CDCl_3$ solution. Generally dicarboxylic acids are insoluble in chloroform but upon addition of equivalent amount of solid adipic acid to the $CDCl_3$ solution of receptor **3**, the adipic acid is soluble in the solution of receptor **3** and the amine protons get shifted downfield with δ value at 7.08 ppm (Fig. 3). The amine proton of receptor **3** shifts downfield at 7.64 ppm upon addition of equivalent amount of glutaric acid and is readily soluble in the $CDCl_3$ solution of receptor **3**. The solubility of these acids in the receptor solution points toward strong binding interaction between host–guest. But in the case of 1,4-phenylenediacetic acid only small amount of chemical shift (0.34 ppm) occurs (see supporting information) and it is also only sparingly soluble in the $CDCl_3$ solution of receptor **3**. The large chemical shift of 2.38, 1.82 ppm for glutaric acid and adipic acid respectively indicate the strong hydrogen bonding complexation

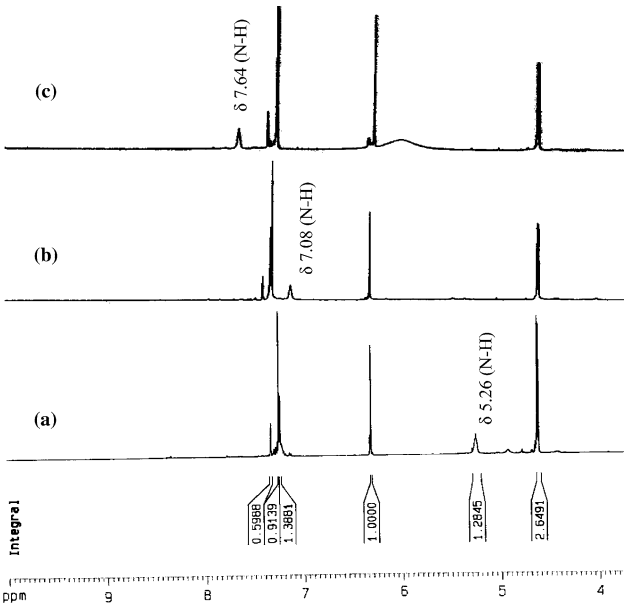


Fig. 3 Partial ^{1}H NMR (500 MHz) spectra of receptor **3** (**a**); addition of equivalent amount of adipic acid (**b**); and addition of equivalent amount of glutaric acid (**c**) in $CDCl_3$

of receptor **3** with those acids and the above crystal structure is the evidence of this observation.

The binding behavior of receptor **3** with different dicarboxylic acids has been studied by UV–vis method. A strong absorbance at $\lambda_{max} = 295$ nm is observed for receptor **3** (1.11×10^{-4} M) which is gradually decreased upon addition of guest acid solution (ca 1×10^{-3} M) (Fig. 4). To observe the binding affinity of receptor **3** towards dicarboxylic acids we have taken different acid solutions having different chain lengths. The association constant of receptor **3** with dicarboxylic acids are determined in acetonitrile (Fig. 5a) [36]. The binding constant of receptor **3** with adipic acid and glutaric acid are higher than those of other dicarboxylic acids (Table 2). From Job plots, a prominent 1:1 complexation between receptor **3** and adipic acid or glutaric acid are observed since the

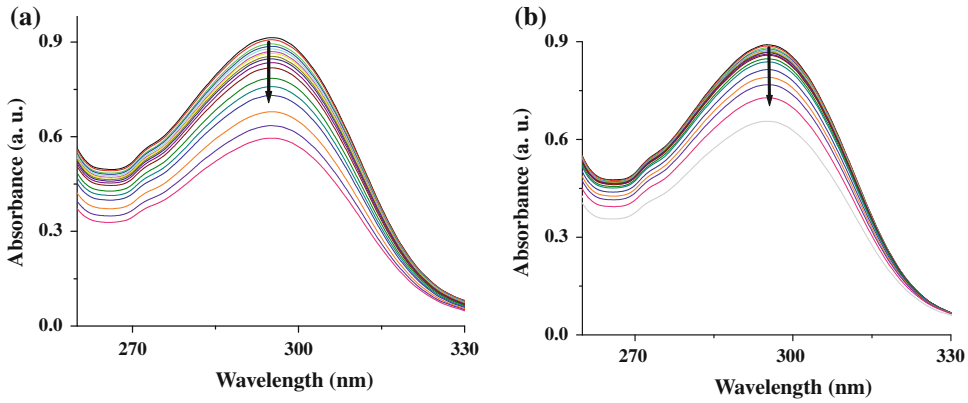


Fig. 4 UV–vis titration spectra of receptor **3** with **a** glutaric acid and **b** adipic acid

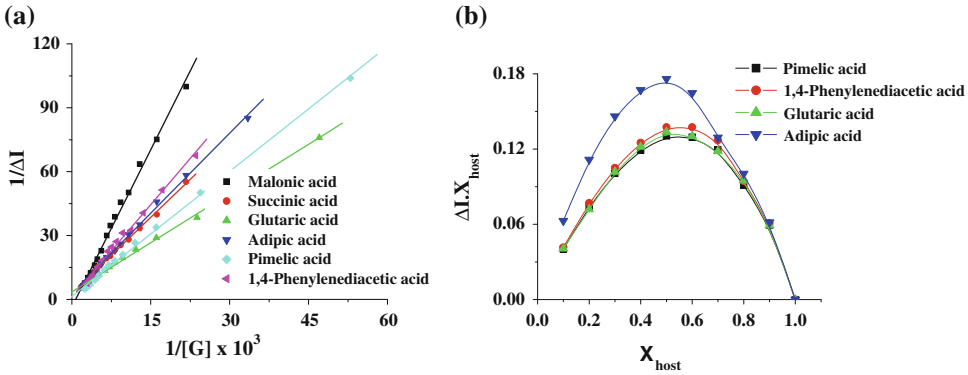


Fig. 5 **a** Binding constant calculation curves of receptor **3** with different dicarboxylic acids by UV–vis method; **b** Jobs plots of receptor **3** with different dicarboxylic acids at $\lambda_{max} = 295$ nm

Table 2 Binding constants [K_a (M^{-1})] of receptor **3** with dicarboxylic acids by UV–vis method

Guests	Receptor **1**
Malonic acid	7.40×10^2
Succinic acid	1.22×10^3
Glutaric acid	2.95×10^3
Adipic acid	2.31×10^3
Pimelic acid	6.74×10^2
1,4-Phenylenediacetic acid	8.17×10^2

All errors are ±10%

complex concentration goes maximum when molar fraction of receptor is about 0.5 (Fig. 5b).

Thus in conclusion, a flexible xylene spacer is introduced instead of conventional isophthaloyl spacer in a *bis* pyrimidine amine system (instead of usual pyridine amine binding motif) to give rise to a unique 1:1 *gauche* dimeric motif of receptor **3** and guest adipic acid in solid state. The binding behavior of receptor **3** has been studied by varying the chain length of dicarboxylic acids in solution phase. Glutaric acid shows strong binding affinity among all the dicarboxylic acids. The large shifting of amine protons of receptor **3** in proton NMR spectra and the association constants determined by UV–vis method also indicate the strong complexation between receptor **3** and adipic acid. The selective 1:1 dimeric complex of receptor **3** with adipic acid is observed by single crystal X-ray structure analysis rather than polymeric complex.

Acknowledgments We thank CSIR [No. 01(2292)/09/EMR-II], Government of India for financial support. A. H. thanks the CSIR, Government of India for a research fellowship. We would also like to thank the Malaysian Government and Universiti Sains Malaysia for a Research University Golden Goose grant No. 1001/PFIZIK/811012.

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