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Tetrahedron Letters 46 (2005) 7187–7191

Tetrahedron Letters

Dynamic molecular recognition in the generation of a new crystal-engineering motif: a unique case study of a dicarboxylic acid with a ditopic receptor favouring a polymeric over a dimeric hydrogen-bonded supramolecular complex

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Received 7 July 2005; revised 9 August 2005; accepted 17 August 2005

Abstract—A new crystal-engineering motif has been developed where a ditopic receptor **1** shows a novel *syn–syn* hydrogen-bonded polymeric supramolecular complex (Fig. 4b) (instead of a 1:1 dimeric *syn–syn* or polymeric *syn–anti complex*) giving rise to a hydrogen-bonded stair-like polymeric ribbon structure between the binding groups of the receptor pyridine amide and the carboxyl groups of the guest substrate.

The binding of carboxylic acids[1] by designed receptors is of enormous interest in the field of molecular recognition research because such binding mimics certain biological events. Of all the known hydrogen-bonding groups, the amide group is the most promising functionality used in designing extended self-assemblies with reasonably predictable hydrogen-bonding patterns with dicarboxylic acids.[2] There are many scientists involved in synthesizing different types of synthetic receptors for the recognition of mono and dicarboxylic acids.[3,4a–c] The artificial inhibition of hydrogen bonding in molecular recognition was first reported by us,[4d] where a ditopic receptor could be converted to a monotopic receptor by the formation of its first mono *N*-oxide. A study with straight chain diacids containing four, eight and twelve carbon spacers was reported[5] with a variety of aromatic spacers ranging from simple phenyl to more complex spacers to generate cavities of different sizes for the recognition of dicarboxylic acids of varied lengths. In this communication, we report, for the first time to our knowledge, a *syn–syn* polymeric hydrogen-bonded complex between a ditopic pyridine diamide receptor **1** containing a smaller dimethylene ether spacer (compared to terephthaloyl) and 1,4-phenylenediacetic acid as the guest substrate. The result shows stair-like ribbons in the polymeric complex for supramolecular assembly (Fig. 1a) instead of a *syn–syn* dimeric 1:1 structure (Fig. 1b) or the other hypothetical possibility of a cyclic tetrameric hydrogen-bonded square complex structure (Fig. 1c). Thus, the polymeric complex is shown to exist in the solid state by crystallographic results though the situation in solution could be different and the NMR data could not distinguish between the different possibilities.

Dicarboxylic acid receptors generally have been designed using a common strategy that involves linking two aminopyridine groups through a rigid aromatic spacer. Two terminal hydrogen-bonding pockets are forced to adopt a *syn–anti*-conformation, an arrangement most suitable for generating continuous self-assemblies in preference to discrete complexes with

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Keywords: Molecular recognition; Supramolecular chemistry; Polymeric *syn–syn* hydrogen bond in crystal design.

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0040-4039/$ - see front matter © 2005 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2005.08.078

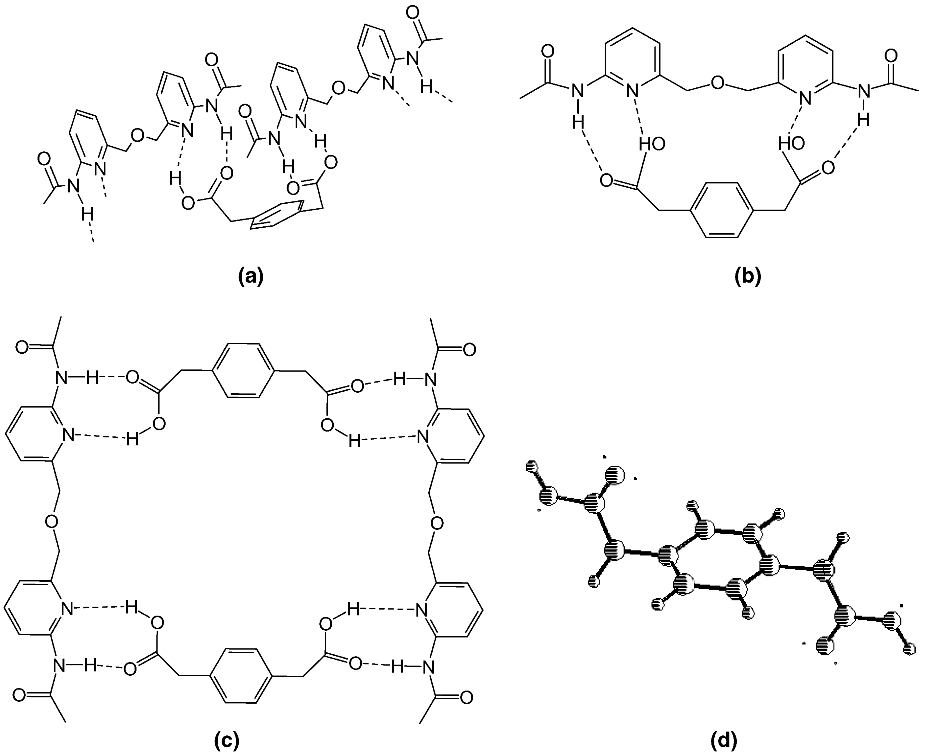
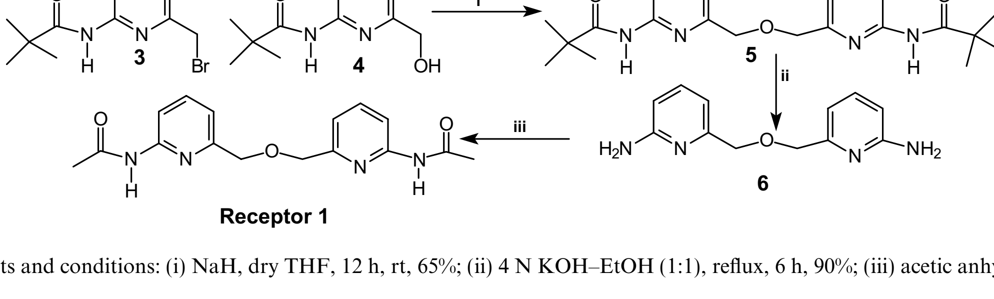


Figure 1. (a) Polymeric 1:1 co-crystal structure of receptor **1** with 1,4-phenylenediacetic acid; (b) a dimeric 1:1 structure; (c) a (2:2)-tetrameric hypothetical, cyclic, hydrogen-bonded square complex structure; (d) the carboxyl groups in the *anti* direction in the energy-minimized (MMX) structure of 1,4-phenylenediacetic acid.

complementary hydrogen-bonding partners. Hamilton and co-workers[5] have reported that if the length of the spacer and that of the guest carboxylic acid correspond well, a tight 1:1 complex will be formed, but when the carboxylic acid is longer than the receptor's cavity size, an alternative mode of binding will be observed in the form of infinite ribbons.[6] The dynamic supramolecular structure was also observed by increasing the length of the chain of the dicarboxylic acid beyond the optimum. By increasing the length of the dicarboxylic acid, the formation of a ribbon or supramolecular helical structure, was also obtained with an isophthaloyl spacer.[6b] The reversible association of a number of individual molecules formed a self-assembled structure, representing a thermodynamic minimum. The effect of unfavourable conformational constraints might be diminished by the symmetrical incorporation of an additional binding site into the receptor. It has been shown that the stability of a dynamic supramolecular structure can be enhanced by an entropy effect, if additional binding sites are present in the host molecules.[7] We have also previously reported a series of supramolecular assemblies of pyridine and pyrimidine diamides with different dicarboxylic acids.[8]

In receptor **1**, 2-aminopyridine is also present as a hydrogen-bonding motif and it has the two bis-2-acetamidopyridine groups linked through a benzylic ether linkage. 2-(*N*-Pivaloylamino)-6-bromomethylpyridine (**3**) and 2-(*N*-pivaloylamino)-6-hydroxymethylpyridine (**4**) were coupled using sodium hydride[9] in dry THF to afford compound **5**. Removal of the pivaloyl groups in **5** with 4 N KOH–ethanol (1:1) solution under reflux gave the intermediate **6** in a 90% yield and this was followed by acetylation to afford the desired receptor **1** (Scheme 1). Replacement of the pivaloyl group with an acetyl group was necessary to avoid the bulkiness



Scheme 1. Reagents and conditions: (i) NaH, dry THF, 12 h, rt, 65%; (ii) 4 N KOH–EtOH (1:1), reflux, 6 h, 90%; (iii) acetic anhydride, dry CH_2Cl_2, 4 h, rt, 85%.

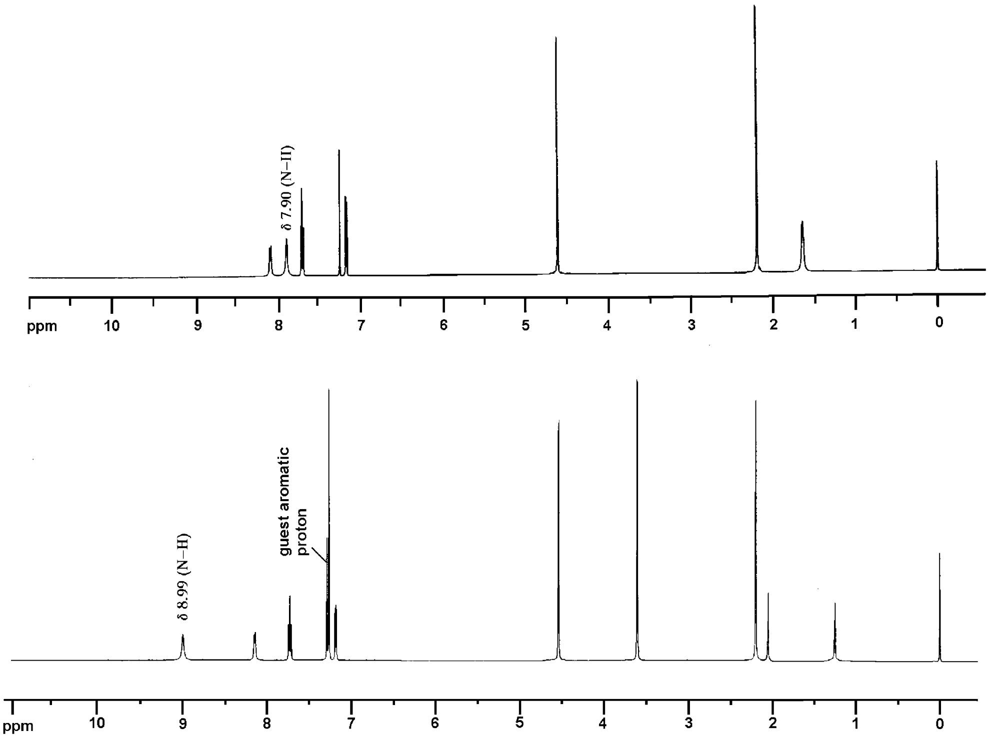


Figure 2. (a) ^1H NMR of receptor **1** in $CDCl_3$; (b) ^1H NMR of a 1:1 complex of receptor **1** with 1,4-phenylenediacetic acid in 1% DMSO-d_6 in $CDCl_3$.

of the pivaloyl group. The less hindered pyridine acetylamino moiety can bind carboxyl groups more freely.

The addition of a solid 1,4-phenylenediacetic acid to a $CDCl_3$ solution of receptor **1** led to dissolution of the normally insoluble acid substrate. To make a homogeneous solution, one drop of DMSO-d_6 was added to the NMR solution. From the integration of the ^1H NMR, a large downfield shift was observed for the amide proton (δ 7.90 to δ 8.99 ppm, $\Delta\delta = 1.09$ ppm) (Fig. 2a and b) and a [G]/[H] versus $\Delta\delta$ plot suggested 1:1 stoichiometry for the formation of a H-bonded complex ([G] and [H] are the molar concentrations of guest and host, respectively) (Fig. 3). The benzene ring protons and the CH_2 protons of the guest acid appeared at δ 7.30 and δ 3.59 ppm, respectively, but this NMR experiment alone could not prove the presence of a polymeric complex,[10] which was, however, confirmed in the solid-state by single crystal X-ray results.

The receptor **1** showed a strong absorbance at $\lambda_{max} = 281$ nm, which gradually decreased on addition of the guest solution as monitored by UV titration. To measure the association constant (K_a) between the receptor **1** and the carboxylic acid, a 10^{-5} mmol ml^{-1} solution of the receptor in $CHCl_3$ was taken. The value of K_a was found to be 2.57×10^3 M^{-1} for the receptor **1** with 1,4-phenylenediacetic acid by the UV-method.[11a] The association constant ($K_a = 2.09 \times 10^3$ M^{-1}) by the NMR method was also calculated from the plot of $\Delta\delta$ versus $\Delta\delta$/[G] (Fig. 3) linear regression analysis.[11b] The K_a value determined by NMR was somewhat less due to the presence of DMSO-d_6, a competitive binding solvent.[11c]

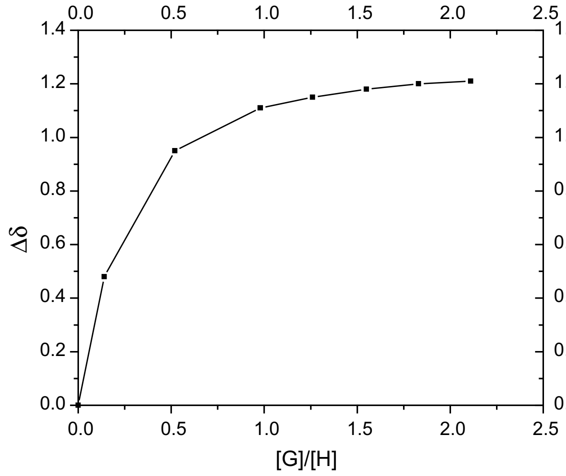


Figure 3. ^1H NMR titration curve (molar ratio of guest–host vs chemical shift) of receptor **1** with 1,4-phenylenediacetic acid.

To confirm whether the structure of the complex in the solid-state is a simple dimeric 1:1 complex (Fig. 1b) or a polymeric hydrogen-bonded complex (Fig. 1a), we carried out an X-ray analysis of a single crystal of this complex (crystallization from $CHCl_3$–MeOH; 90:10). A [2+2]-cyclic *syn–syn* aggregate was reported when a ditopic receptor containing an adamantane diamide spacer was crystallized with succinic acid.[7] However, a supramolecular ribbon structure resulted when 1:1 co-crystallization was performed with the receptor **1** and 1,4-phenylenediacetic acid and this showed a unique case of a polymeric 1:1 *syn–syn* aggregate.

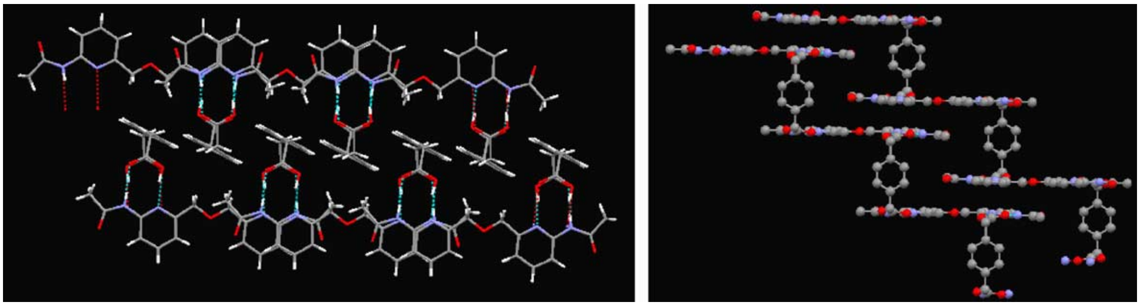


Figure 4. X-ray structure of the complex of receptor **1** and 1,4-phenylenediacetic acid: (a) hydrogen-bonded infinite ribbon; (b) stair-like structure of the polymeric complex (edge on view).

The X-ray analysis of the complex (Fig. 4) suggests a supramolecular ribbon structure in which one carboxylic acid binds with a pyridine-amide of one molecule and the other acid binds with the pyridine amide of another molecule. It is also shown that the two acid groups of the guest acid are *syn* to each other and are at ca. 90° angles to the benzene ring. Normally 1,4-phenylenediacetic acid exists in its more stable *anti* conformer with a 7.56 Å bond distance between $HO_2C–CO_2H$. This distance was reduced to 5.88 Å when it was complexed with the receptor **1**. The distance between the two amidopyridine groups (PyNH–PyNH) in the receptor (11.70 Å) was not complementary with 1,4-phenylenediacetic acid. Thus the new motif of a *syn–syn*-bound, polymeric, co-crystal of a host–guest has been found instead of the *top–bottom*-bound, co-crystal as in a previously reported[5] case. The two benzene rings of the two guest dicarboxylic acids in adjacent supramolecular chains are parallel to each other with the opposite orientation of the carboxylic acid groups and are separated by a distance of 3.29 Å. The distance between –CONH–O=C–(CO_2H) and PyN–HO–C–(CO_2H) are 2.066 and 1.784 Å, respectively. Four hydrogen bonds are seen in one unit of the polymeric chain and their bond distances fall in the normal range. The new motif has to be stronger than the single hydrogen bond between each end of a simple diamide. The result is a stair shaped molecular ribbon made up of alternating subunits with the hydrogen-bonding network imposing the dimensions of the ribbon (Fig. 4b). A wider separation of the two hydrogen-bonding regions would both minimize repulsive interactions between the carboxyl groups and change the binding specificity transforming longer dicarboxylic acid substrates into a shorter length. The model studies of the bond lengths, bond energies and the energy-minimized calculations of the different modes of this complex suggest the presence of the polymeric ribbon structure.[12]

Thus, this motif is unique in forming such *syn–syn* hydrogen-bonded polymeric stair-like ribbons where the benzene rings are oriented away from each other and are possibly not involved in π-stacking interactions. This finding is important in designing new supramolecular assemblies involving polymeric 1:1 host–guest complexes instead of dimeric 1:1 complexes.

Supporting information: The crystallographic data for the complex has been deposited with the Cambridge Crystallographic Data Centre, CCDC 277485. Copies of this information may be obtained free of charge from the Director, CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK (Fax: +44-1223-336033; e-mail: deposit@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk).

Acknowledgements

We wish to express our appreciation to CSIR [Project No. 01(1913)/04/EMR-II] for financial support and DST-FIST (Government of India) for providing IR and UV facilities to our department.

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10. The ^{1}H NMR spectrum of compounds **3**, **4**, **5** and **6** were found to be identical to those reported earlier. ^{1}H NMR of

compound **1** (CDCl$_3$, 500 Hz): δ 8.10 (d, $J = 8.0$ Hz, 2H), 7.90 (br s, 2H), 7.71 (t, $J = 7.8$ Hz, 2H), 7.18 (d, $J = 7.4$ Hz, 2H), 4.61 (s, 4H), 2.19 (s, 6H). ^{1}H NMR of compound **1** with 1,4-phenylenediacetic acids (CDCl$_3$, 500 Hz): 8.99 (br s, 2H), 8.14 (d, $J = 8.0$ Hz, 2H), 7.72 (t, $J = 7.8$ Hz, 2H), 7.29 (s, 4H), 7.18 (d, 2H, $J = 7.4$ Hz), 4.54 (s, 4H), 3.60 (s, 4H), 2.20 (s, 6H).

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12. For model studies we used PCMODEL Serena Software 93.