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A Layered Artificial Dinucleotide Complex

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Abstract: An X-ray diffraction analysis of the 1 : 1 complex of *N,N'*-dimethyl-*N,N'*-bis[2-(3-methylureido)pyrid-5-yl]urea (**1**) and a 1,3-bis(cytosyl)propane derivative (**2a**) revealed layered triply-hydrogen-bonded pairings. The conformation of **1** in the complex is similar to that in the crystal structure of **1** alone, with *anti* conformation of the two aromatic rings.

keywords: Molecular recognition, Ureas, X-ray crystal structure, Nucleic acid analogs

Hydrogen-bonded pairing between complementary nucleobases is a fundamental feature of DNA structure and function,[1] and has been applied to molecular recognition in medicinal chemistry and materials science.[2] Synthetic receptors for mononucleotides or oligonucleotides are expected to have chemical and biological utility,[3,4] but so far, only a few compounds, other than peptide nucleic acids and other modified oligonucleotides,[5,6] are known to have stacked base pairings of the type seen in natural DNAs.

Previously, we reported that *N,N'*-dimethyl-*N,N'*-bis[2-(3-methylureido)pyrid-5-yl]urea (**1**), which was designed as a guanylyl-guanosine equivalent molecule, readily forms 1 : 1 complexes with bis(cytosyl) derivatives (**2a** – **c**) in dilute chloroform solution, the association constant (*Ka*) values being ca. 5×10^6 M^{-1} (Fig. 1).[7] When an *N*-desmethylated analog of **1** with the (*trans, trans*) conformation, or monomeric 1-methyl-3-(2-pyridyl)urea was used instead of **1**, only weak interactions ($Ka < 10^4$ M^{-1}) were observed. This result suggested that the complexes of **1** and **2** in $CDCl_3$ solution might have a dimeric folded structure, based on the (*cis, cis*) conformational preference of **1**.[8] However, the precise structures of the complexes in solution were unknown, including the possibility of the oligomeric interactions, because of the conformational flexibility of **1**. Further, there are two possible (*cis, cis*) conformations of **1**, that is, *anti*- and *syn*-forms (Fig. 1). In this paper, we describe the unique aromatic layered structure of the heterodimeric complex of **1** with **2a** in the crystal.

Cocrystallization of **1** and **2** from various solvents, such as CH_2Cl_2, $CHCl_3$, EtOH and AcOEt, afforded colorless powders with a 1 : 1 ratio of the two compounds, as deduced from NMR spectroscopy and/or elemental analysis.[9] Heterodimeric complex formation was confirmed by FAB mass spectroscopy (M^+, 917, 931, and 945 for the complexes of **1** and **2a** – **c**, respectively). An X-ray structure analysis of the cocrystal **1·2a**, obtained by careful recrystallization from ethanol, was carried out at –100 °C by using a laser-stimulated fluorescence image plate as a two-dimensional area detector. The crystal structure of the complex **1·2a** is shown in Fig. 2, in comparison with that of **1** alone.[10]

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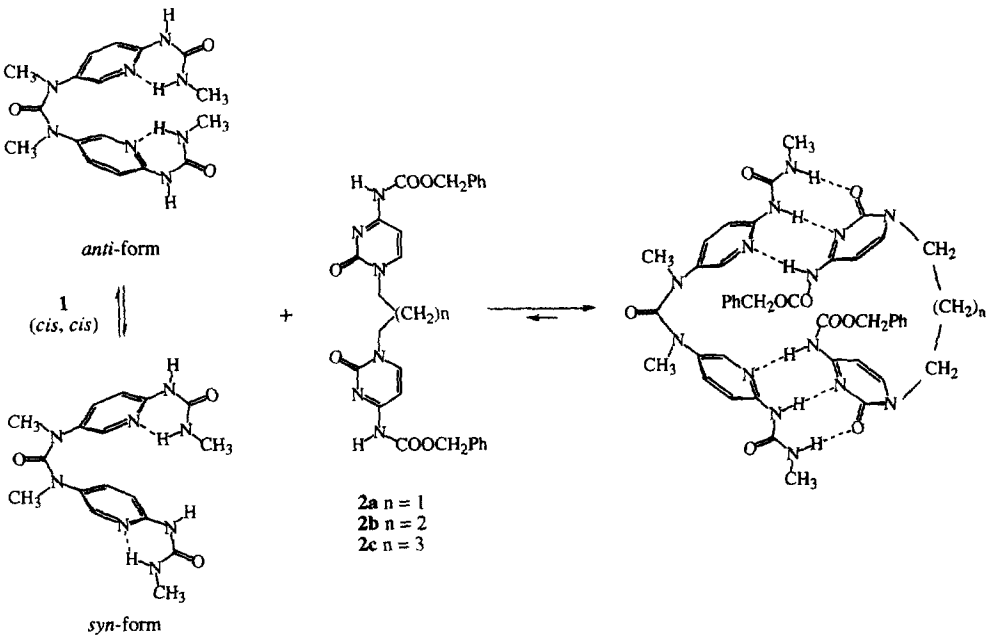


Fig. 1

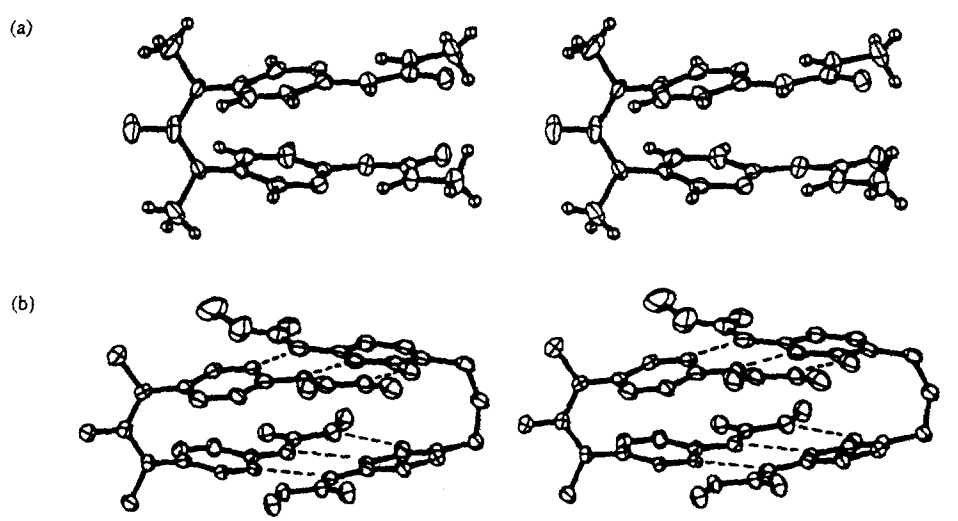
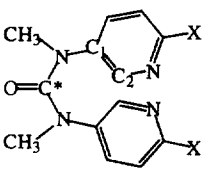


Fig. 2 ORTEP Stereoviews of crystal structures of (a) 1 and (b) the cocrystal 1·2a. The hydrogen atoms and the phenyl groups of the complex are omitted.

Compound **1** itself exists in the folded (*cis, cis*) structure, as expected (Fig. 2a). The methylureido groups on the pyridine rings form intramolecular hydrogen bonds with the pyridyl nitrogen atoms, which are also observed in $CDCl_3$, deduced from the chemical shifts of the protons on the nitrogen atoms or aromatic protons, and from NOE experiments (for example, 8 % NOE enhancements from Py–NH to the ortho Py–H). On the other hands, the side chains of **1** in the cocrystal are elongated owing to triply-hydrogen-bonded

Table 1 Selected Torsion and Dihedral Angles of Diarylurea Skeletons

	1 (alone)	**1** in the **1·2a** complex	*N,N'*-Dimethyl-*N,N'*-diphenylurea
Torsion Angles (deg)			
N–C*–N–C_1	26(2), 37(2)	23(1), 41(1)	31.4(5), 35.2(5)
C*–N–C_1–C_2	−122(2), −125(1)	−120.3(8), −127.9(8)	45.0(5), 47.8(4)
Dihedral Angles (deg)			
Ar vs Urea	71.8, 75.7	74.3, 74.4	65.3, 68.6
Ar vs Ar	16.5	17.0	35.4



X = $NHCONHCH_3$

interactions with the pyrimidine rings of **2a** (Fig. 2b), and the complex contains heterodimeric aromatic layers. The distances between the hydrogen-bonded heteroatoms are 2.78 – 2.79 Å (Me-N–H---O), 3.12 – 3.13 Å (O=C-N–H---N=C), and 2.94 – 3.06 Å ($N_{pyridine}$---H–N-C=O). The triple hydrogen bonds in each layer are nearly parallel to each other (less than 6° difference). The conformation of the complex **1·2a** is closely related to that of **1**, i. e., structural parameters such as the torsion angles and the dihedral angles in the pyridylurea skeleton of **1** are similar to those in the complex **1·2a**. Accordingly, the trimethylene linking group of **2a** exists in the gauche conformation with the dihedral angles of the N–C–C–C bonds being –84° and 44°.

Compound **1** exists in *anti* conformation in both crystals. The triple hydrogen bonded pairings of the side chains did not affect the conformation of **1**. Consequently, the corresponding hydrogen bonds in the two layers of the complex **1·2a** are nearly perpendicular (90 ± 2°). Significantly, the dihedral angle between the two pyridyl rings of **1** (16.5°) is less than that between the two phenyl groups in the folded crystal structure of *N,N'*-dimethyl-*N,N'*-diphenylurea (35.4°, Table 1). This is also observed in the structure of **1** in the complex (17.0°). The distances between the two pyridyl nitrogen atoms (3.50 Å for **1** itself, and 3.52 Å for **1** in the complex) or between the carbons at the *para* positions (4.30 Å for **1** itself, and 4.43 Å for **1** in the complex) are shorter than those of the corresponding carbon atoms of *N,N'*-dimethyl-*N,N'*-diphenylurea (4.33 Å of C_{meta}--C_{meta} distance is the shortest). The dihedral angles between the aromatic rings and the linking *N,N'*-dimethylurea group of **1** are larger than those of *N,N'*-dimethyl-*N,N'*-diphenylurea, which also means much preferential face-to-face conformation of **1** compared to *N,N'*-dimethyl-*N,N'*-diphenylurea.[11] Recently, the structures of several face-to-face bispyridine derivatives with fixed conformation, such as 1,8-di(3-pyridyl)naphthalene, have been elucidated.[12] In the latter compound, the two pyridyl rings are also *anti* in the crystal. However, two pyridyl rings of 1,8-di(3-pyridyl)naphthalene seem to be more repulsive with large dihedral angles (26°) than two phenyl groups (20°) of 1,8-diphenylnaphthalene.[12b] In the case of **1**, the linking *N,N'*-dimethylurea group between two pyridyl rings is more flexible than 1,8-naphthalene moiety, which causes the aromatic displaced parallel structure with less repulsive force.[13] The *anti* conformation of the complex **1·2a** may be more stable than the *syn* conformation with well-overlapping aromatic moieties.

In conclusion, we have shown that a unique heterodimer with aromatic layered structure is formed between artificial nucleotide analogs. The structure of the complex depends strongly on the conformation of **1**. Although the complex exists in the *anti* conformation, unlike the stacked base-pairings in DNA, the *cis* conformational preference of *N*-methylated ureas should be applicable to molecular recognition of nucleic acids.

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9 Physicochemical properties of the complexes: **1·2a**: colorless plates (EtOH); mp 197-198 °C; ^{1}H-NMR (DMSO-d_6, 30 °C) δ 10.69 (s, 2 H), 9.07 (s, 2 H), 8.08 (d, 2 H, J = 7.3 Hz), 7.67 (br s, 2 H), 7.67 (d, 2 H, J = 2.6 Hz), 7.41 - 7.32 (m, 10 H), 7.20 (dd, 2 H, J = 2.7, 8.8 Hz), 7.13 (d, 2 H, J = 8.8 Hz), 6.97 (d, 2 H, J = 7.0 Hz), 5.18 (s, 4 H), 3.82 (t, 4 H, J = 7.3 Hz), 3.04 (s, 6 H), 2.69 (d, 6 H, J = 4.6 Hz), 2.09 (m, 2 H). **1·2b**: colorless powder (EtOH); mp 227-228 °C; ^{1}H-NMR (DMSO-d_6, 30 °C) δ 10.67 (s, 2 H), 9.07 (s, 2 H), 8.06 (d, 2 H, J = 7.1 Hz), 7.67 (br s, 2 H), 7.67 (d, 2 H, J = 2.2 Hz), 7.42 - 7.33 (m, 10 H), 7.20 (dd, 2 H, J = 2.7, 8.8 Hz), 7.13 (d, 2 H, J = 8.8 Hz), 6.96 (d, 2 H, J = 7.0 Hz), 5.18 (s, 4 H), 3.79 (br t, 4 H), 3.04 (s, 6 H), 2.69 (d, 6 H, J = 4.6 Hz), 1.61 (br t, 4 H). **1·2c**: colorless powder (EtOH); mp 222-223°C; Anal Calcd for $C_{46}H_{52}N_{14}O_9$ C, 58.46; H, 5.55; N, 20.75. Found C, 58.19; H, 5.51; N, 20.47; ^{1}H-NMR (DMSO-d_6, 30 °C) δ 10.67 (s, 2 H), 9.08 (s, 2 H), 8.04 (d, 2 H, J = 7.2 Hz), 7.67 (br s, 2 H), 7.67 (d, 2 H, J = 2.8 Hz), 7.45 - 7.30 (m, 10 H), 7.20 (dd, 2 H, J = 2.2, 8.8 Hz), 7.13 (d, 2 H, J = 8.8 Hz), 6.96 (d, 2 H, J = 7.2 Hz), 5.18 (s, 4 H), 3.76 (t, 4 H, J = 7.2 Hz), 3.04 (s, 6 H), 2.69 (d, 6 H, J = 4.4 Hz), 1.65 (quint, 4 H, J = 7.5 Hz), 1.23 (br quint, 4 H).

10 Crystal data of the complex **1·2a**: monoclinic; space group, $P2_1/n$; Z, 4; a, 13.182(3) Å; b, 24.79(2) Å; c, 15.316(10) Å; β, 101.48(4)°; V 4905.8(9) Å^3; D_{calc}, 1.339 g/cm^3; R, 0132. There are unrefined solvent molecules in the unit cell. The crystal parameters for compound **1** were reported previously (ref. 7).

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13 The intermolecular packing interactions are also significant in both crystal structures. The aromatic rings of the adjacent molecules form the intermolecular displaced parallel structures. This may be caused by less repulsive interactions between the pyridyl moieties.