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Cyanurate Mimics of Hydrogen-Bonding Patterns of Nucleic Bases: Crystal Structure of a 1:1 Molecular Complex of 9-Ethyladenine and *N*-Methylcyanuric Acid

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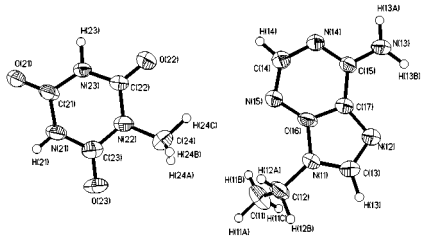
ABSTRACT



9-Ethyladenine forms a unique molecular complex with *N*-methylcyanuric acid consisting of homomeric and heteromeric hydrogen-bonding patterns. Also, the homomeric hydrogen bond pattern is different than that observed in its pure crystal structures.

The specific base pair recognition of A by T and T by A as well as G by C and C by G through hydrogen bond formation is the key factor in the formation of DNA duplex structure.[1] The unnatural/nonstandard nucleobases have gained importance in mimicking DNA structures as well as in the synthesis of novel molecular architectures.[2−5] For instance, cyanuric acid, (**CA**) and *N*-methylcyanuric acid (**MCA**) have a close structural resemblance to uracil and form a variety of hydrogen-bonded base pairs in their pure[5b] as well as mixed crystals[5d] to yield supramolecular networks such as rosette.[6] Recently, we have shown the ability of cyanurate-derivatized PNA monomer ethyl *N*-(2-Boc-aminoethyl)-*N*-(cyanuric-1-yl acetyl)glycinate to form a hydrogen-bonded supramolecular helical structure.[7] With our continued interest in the study of hydrogen-bonding capabilities of such nonstandard nucleobases, we chose to study the complexation of **CA** and

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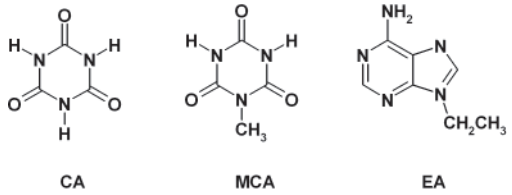
MCA with 9-ethyladenine (**EA**). In this context, **EA** has recently been shown to form interesting hydrogen-bonding networks[8] in its molecular complex with 5,5-diethylbarbituric acid and in combination with porphyrin forms a receptor for molecular imprinting.[9] While **CA** and **EA** cocrystals could not be obtained, **EA** forms crystals readily with **MCA**. We report here the structure of **MCA**:**EA** cocrystal that shows novel features that are unique among the hydrogen-bonding patterns so far realized in the related structures formed by **EA** with various barbiturates.[8]



The 1:1 adduct of **EA** with **MCA** was obtained upon cocrystallization from a CH_3OH solution. Crystal structure determination[10] gave an asymmetric unit of the cocrystals in a triclinic, $P\bar{1}$, space group, as shown in Figure 1.

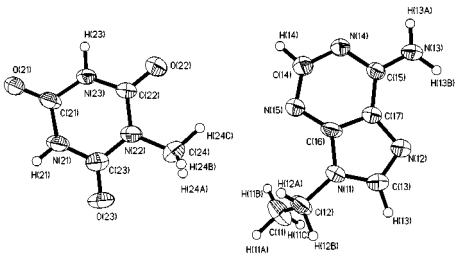


Figure 1. ORTEP drawing of the asymmetric unit of the molecular complex of *N*-methylcyanuric acid (**MCA**) and 9-ethyladenine (**EA**).

In this structure, both **EA** and **MCA** molecules are quite planar and the crystal structure involves two-dimensional sheets that are in turn stacked in three-dimensions. In each sheet (see Figure 2), the molecules are held together to form molecular strips as in the crystal structure of **EA** with 5,5-diethylbarbituric acid or other uracil derivatives.[11]

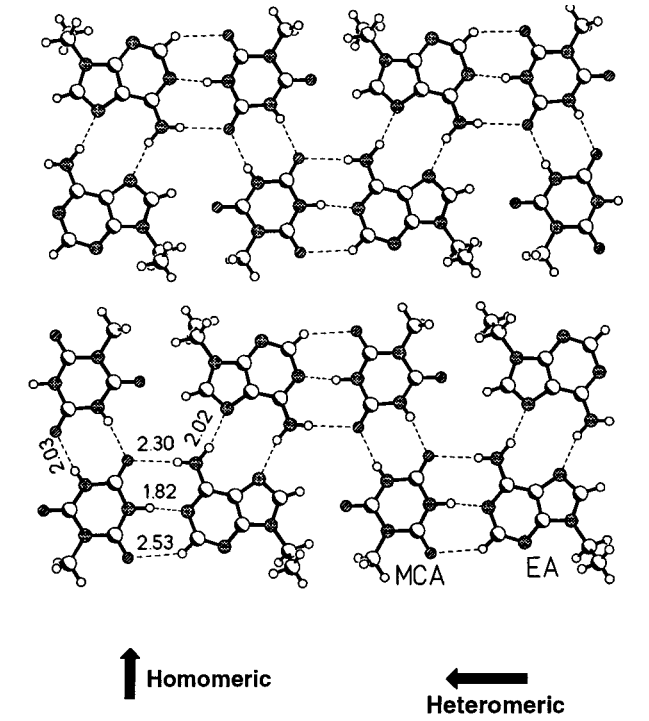


Figure 2. Molecular strips showing homomeric and heteromeric arrangement of the molecules of **MCA** and **EA** in the complex **MCA**:**EA**.

The arrangement of the molecular strips in two-dimensional sheets is however unique with each strip containing molecules of both **EA** and **MCA** existing as pairs.[12] There are two distinct types of hydrogen-bonded interactions in the complex of **EA** and **MCA**—homomeric (**MCA**···**MCA** and **EA**···**EA**) and heteromeric (**MCA**···**EA**). Each strip consists of a polymeric chain made up of continuous hydrogen-bonded networks of alternating homo- and heterodimers, **MCA**···**MCA**···**EA**···**EA**···**MCA**···**MCA**···. In both cases, the N−H···O and N−H···N hydrogen bonds form distinct cyclic rings. While in both **MCA**···**MCA** and **EA**···**EA** homomeric units the H···O and H···N distances are 2.03 and 2.02 Å, respectively, the corresponding distances in the heteromeric unit are 2.30 and 1.82 Å. Thus, heterodimer formation involves lengthening of the H···O distance by 0.28 Å but shortening of the H···N distance by 0.2 Å compared to the homodimers (see Table 1). The observed distances are in agreement with such distances noted in the related complexes. The strips are aligned in a two-dimensional arrangement in an *anti*-parallel manner, stabilized by hydrophobic interaction between the ethyl groups located in the adjacent strips, leading to a molecular zip as shown in Figure 2.

The observed complementary hydrogen-bonding interaction between **MCA** and **EA** is similar to that between

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(10) Crystal data, complex of **EA** and **MCA**: $C_7H_9N_5$: $C_4H_5N_3O_3$, M_r = 306.30, triclinic, space group $P\bar{1}$, a = 7.334(3), b = 8.164(2), c = 12.640-(5) Å, α = 75.12(3), β = 82.59(3), γ = 70.78(3)°, U = 689.8(4) Å^3, Z = 2, T = 293 K, $F(000)$ = 320, μ = 0.11 mm^{-1}, 2904 reflections measured of which 1944 were independent, full matrix least-squares refinement on F^2, R_1 = 0.078, wR_2 = 0.138. H atoms were obtained from Fourier differential maps. Data collection, SMART; refinement, SHELX-TL (Bruker-axis, Madison, WI, 1995).

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(12) **CA** and **EA** did not yield a complex perhaps due to the fact that **CA** forms an infinite chain of molecular network rather than simple dimers to yield a molecular strip.

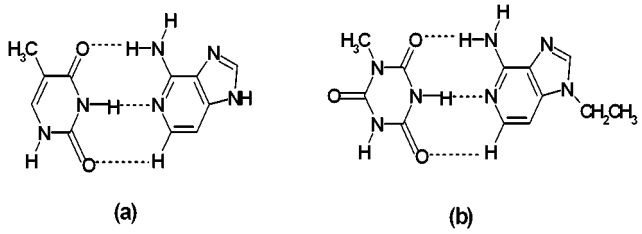
Table 1. Hydrogen Bond Distances (Å) in **EA** and **MCA**−**EA** Complex

hydrogen bond	**MCA**[a]	**EA**	**MCA**:**EA**	**MCA** in PNA[b]
(N−H···O)				
H···O	1.87	- - - -	2.03,[c] 2.30[d]	2.07
N···O	2.81		2.88, 3.22	2.86
(N−H···N)				
H···N		2.08, 2.12	2.02,[c] 1.82[d]	
N···N		3.07, 2.98	2.97, 2.79	

[a] From ref 5d. [b] From ref 7. [c] Hydrogen bond in homomeric unit. [d] Hydrogen bond in heteromeric unit.

thymine and adenine with respect to Watson−Crick base pairing of hydrogen bonds as shown in Scheme 1. However,

Scheme 1. A Comparison of Hydrogen Bonding Network between (a) Thymine···Adenine and (b) MCA···Adenine



the helical arrangement of units in a chain or a sheet is absent and only a σ-planar arrangement is seen.

Nevertheless, it is interesting to note the unusual features of hydrogen-bonding patterns in the homo- and heteromeric pairs, particularly the nature of N−H···O hydrogen bonds. The N−H···O hydrogen bond in heteromeric pattern is unusually longer and appears to be resultant of the presence of strong C−H···O hydrogen bond with an H···O distance of 2.53 Å. Such a correlation is in agreement with the statistical analysis of Leonard et al. from a series of crystal structures found in the literature.[13] Further, in the homomeric pattern, the N−H···O hydrogen bond between the **MCA** molecules is longer than the corresponding distance in the parent crystal structure of **MCA**.[5d] However, it is in agreement with the distance found in the crystal structure of cyanurate **PNA**[7] that has a similar structural topology. The N−H···N hydrogen bond pattern between dimeric **EA** molecules adopts a 10-membered homodimeric structure in a centrosymmetric pattern out of the possible six patterns annotated by Jeffrey and Saenger.[2a] Since, the three-dimensional crystal structure of pure **EA** is unknown[14] it is not possible to compare the hydrogen bond distances observed in the complex of **EA** and **MCA** with the parent **EA** structure. Hence, the crystal structure of **EA** was determined to know the salient features of **EA** that may also be helpful in its further applications in the synthesis of novel assemblies or as a receptor.

EA crystallizes in a monoclinic space group, $P2_1/c$ from an ethyl acetate solution.[15] The molecules are packed in a two-dimensional arrangement to yield the layer structure shown in Figure 3. In each layer, adjacent molecules are

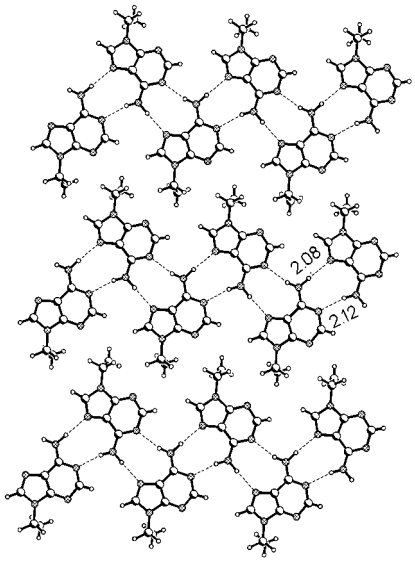


Figure 3. Two-dimensional arrangement of the adjacent molecules connected together by hydrogen bonds in the crystal structure of 9-ethyladenine (**EA**).

held together, yielding one-dimensional molecular tapes through the formation of unsymmetrical N−H···N hydrogen bonds, with H···N distances of 2.08 and 2.12 Å. These distances are similar to that noted in its complex with **MCA** (2.02 Å, Table 1). It is interesting to observe that the N−H···N hydrogen bond pattern in a typical two-dimensional sheet is not the kind of centrosymmetric pattern seen in the homomeric interaction in its complex with **MCA**. For a given pair of molecules, both the acceptor and donor moieties of a pyrimidine moiety interact with both the imadazole and pyrimidine moieties of the adjacent molecules to give a nine-membered dimer ring. The adjacent molecular tapes are then aligned to form layers in a two-dimensional arrangement in which the hydrocarbon groups are always oriented on one side and interlocked (Figure 3) as in the DNA-recognizing leucine zipper protein.[16]

Such a three-dimensional arrangement is unusual and unique. The layers arranged in a three-dimensional stack [Figure 4a] exhibit two types of interactions between them,

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(14) Allen, F. H.; Kennard, O. *Chem. Des. Automat. News* **1993**, *8*, 31.

(15) Crystal data of **EA**: $C_7H_9N_5$, $M_r = 163.19$, monoclinic, space group $P2_1/c$, $a = 8.712(1)$, $b = 12.524(2)$, $c = 8.438(4)$ Å, $\beta = 117.2(1)°$, $U = 818.9(2)$ Å^3, $Z = 4$, $T = 293$ K, $F(000) = 344$, $\mu = 0.09$ mm^{-1}, 3310 reflections measured of which 1175 were independent, full matrix least-squares refinement on F^2, $R_1 = 0.067$, $wR_2 = 0.142$. H atoms were obtained from Fourier differential maps. Data collection, SMART; refinement, SHELX-TL (Bruker-axis, Madison, WI, 1995).

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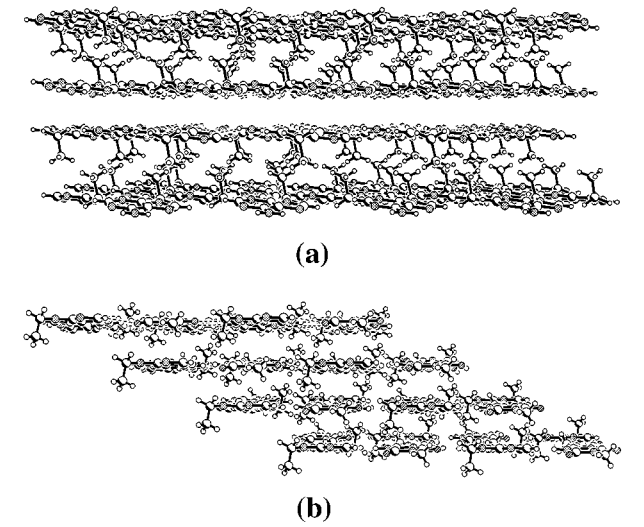

Figure 4. (a) Three-dimensional packing of the sheets noticed in the crystal structure of 9-ethyladenine (**EA**). (b) Three-dimensional arrangement of stacking of the sheets observed in the crystal structure of *N*-methylcyanuric acid, **MCA** and **EA**.

one due to $\pi-\pi$ stacking and the other resulting from the packing of the nonpolar ethyl side chain. In contrast, in the crystal structure of both **EA** [Figure 4b] and **MCA** or any other related structures, although the sheets stack to yield a three-dimensional structure, generally $\pi-\pi$ interactions are only involved in the stabilization of sheets.

In conclusion, the role of the nucleobases T or U in complementary base pairing with A can be mimicked by *N*-methylcyanuric acid **MCA** in its complexation with **EA**. It is observed that the complex forms a molecular tape of alternating homo- (**MCA**···**MCA**; **EA**···**EA**) and heterodimeric (**MCA**···**EA**) structures and the hydrogen-bonding distances H···N and N···N are always shorter in the heterodimers compared to that in homodimers. This suggests that molecular recognition in complementary base pairs leads to complexes stronger than the homomeric dimers in solid state also, similar to their behavior in solution.[1b] The **EA**:**MCA** molecular complex could be regarded as a substitution reaction through noncovalent synthesis with the lattice substitution of **MCA** in between the pair of **EA** molecules in each of the two-dimensional sheets. The complexation induces interesting changes in the three-dimensional packing stabilized by a combination of both base stacking and hydrophobic group interlocking. This is unlike barbiturate−**EA** complexes where the bulky diethyl and isopropyl groups on the barbiturates lead to the formation only heteromeric dimers. This present study along with previous reports[5−7] highlights the intriguing feature of cyanurate−adenine molecular recognition, with implications for development of different biorelevant experimental and computational structural models.

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Supporting Information Available: Cif data for compounds prepared. This material is available free of charge via the Internet at http://pubs.acs.org.

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