Supramolecular Chemistry

DOI: 10.1002/ange.200502434

Nucleobases in Molecular Recognition: Molecular Adducts of Adenine and Cytosine with COOH Functional Groups**

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The current advancements in the areas of solid-state chemistry, supramolecular chemistry, and crystal engineering of molecular complexes, including metal–organic hybrids, illustrate the ability of a variety of organic compounds possessing specific functional groups to create exotic supramolecular assemblies with tailor-made properties after either self-

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[**] We thank Dr. S. Sivaram (Director, NCL) and Dr. K. N. Ganesh (Head, Division of Organic Chemistry, NCL) for their constant support and encouragement. We also thank DST and BRNS for funding ongoing research projects and the University Grants Commission (UGC) for the award of a Junior Research Fellowship (JRF) to S.R.P.

Supporting information for this article is available on the WWW under http://www.angewandte.org or from the author.

assembly processes or molecular recognition of complimentary functional moieties.[1–5] For example, numerous assemblies of trimesic acid,[6] 1,2,4,5-benzenetetracarboxylic acid,[7] cyanuric acid,[8] trithiocyanuric acid,[9] and related compounds demonstrate the spectrum of versatile assemblies available in the literature.

In fact, the molecular recognition of complimentary nucleobases (adenine (A) and thymine (T); guanine (G), and cytosine (C)) through the formation of A-T and G-C base pairs leads to the complex structure of DNA.[10] However, it is rather surprising that utilization of the native nucleobases in molecular recognition studies for the creation of adducts or assemblies is rare, except for a few studies reported by Sasada and co-workers conducted as part of a study on the interactions of nucleic acids and amino acids.[11] An analysis of the Cambridge Structural Database (CSD),[12] with conquest version 1.7, reveals that only a handful of structures of molecular adducts of nucleobases are known.

Considering the present developments in the areas of nucleic acid/protein interactions, and in particular, the interaction of nucleobases with bioactive molecules, we believe that evaluation of a large cluster of molecular adducts of nucleobases is essential as it would enable the formulation of ideal basis sets for accurate predictions in biomolecular modeling experiments.

In this context, the potential ability of the nucleobases having both acceptor and donor functionalities (Scheme 1) led us to initiate the synthesis of numerous molecular adducts of nucleobases with the complimentary carboxylic acid derivatives shown in Scheme 1. However, we noted that only A and C formed complexes readily while G, T, and uracil (U) did not yield any complexes: XRD analysis of the resulting precipitates revealed a mixture of reactants.[13] Thus, herein we report the molecular adducts of A with benzoic acid (BA); C with BA, phthalic acid (PA) and isophthalic acid (IA) as single crystals; we also report the adducts of A with the dicarboxylic acids in the crystalline powder form. These adducts can serve as representative examples in future studies of supramolecular assemblies involving nucleobases as well as for better evaluation of biological studies.

Cocrystallization of A and BA from a CH_3OH solution gave good quality single crystals and structure determination by XRD methods revealed that the adduct of A and BA formed in a 1:2 ratio.[14] In the crystal lattice, molecules of A and BA interact with each other through the formation of a cyclic arrangement of hydrogen bonds involving COOH, NH_2, and hetero N atoms (N^1 and N^7)[15] similar to Watson–Crick and Hoogsteen base pairs. The 2D recognition pattern and molecular arrangement is shown in Figure 1. Thus, BA interacts with A through both the pyrimidine and imidazole rings with the formation of O–H···N (H···N, 1.83 and 1.86 Å)

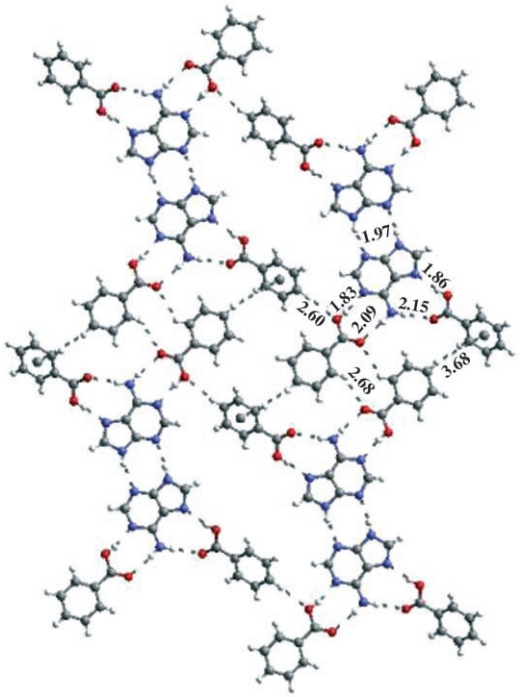
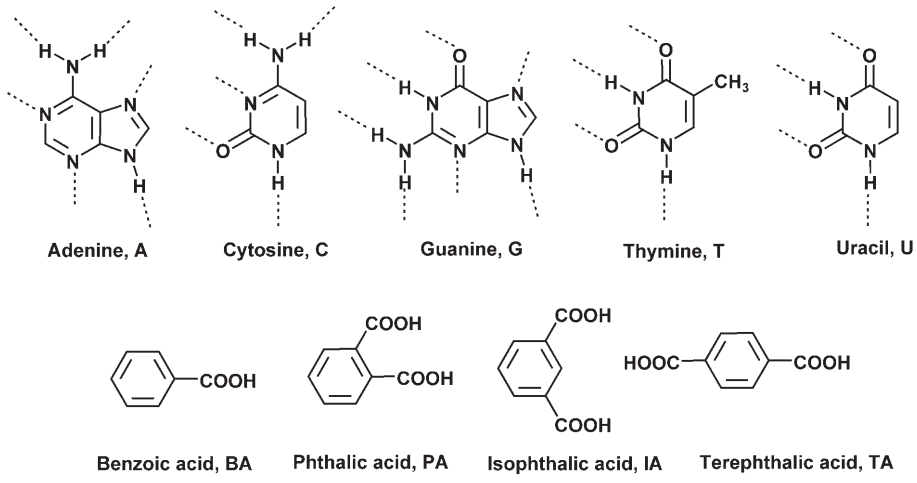


Figure 1. Arrangement of adenine (A) and benzoic acid (BA) in the molecular adduct. Hydrogen bonds are shown as dashed lines. Lines between hydrogen atoms and the center of the phenyl moiety of BA molecules represent C–H···π interactions.



Scheme 1.

and N–H···O (H···O, 2.09 and 2.15 Å) hydrogen bonds. Furthermore, the 1:2 units are held together by centrosymmetric N–H···N hydrogen bonds between the pyrimidine N^3 atom and imidazole NH at the 9-position. The H···N distance is 1.97 Å. Such aggregates form 1D networks through a cyclic arrangement of C–H···O hydrogen bonds (H···O, 2.68 Å) formed between BA molecules to yield infinite molecular tapes. The adjacent tapes are held together by further single C–H···O hydrogen bonds (H···O, 2.60 Å) as well as C–H···π interactions (3.68 Å; Figure 1).

We also anticipated similar interactions with dicarboxylic acids but unfortunately, to date, we have not been successful in obtaining single crystals for the evaluation of intermolecular interactions.[16] However, evidence for the formation of adducts has been obtained by XRD analysis of the residues isolated from cocrystallization experiments.[13] Nevertheless, we were able to isolate single crystals for the adducts of cytosine, except with terephthalic acid, and the analyses disclose intriguing features.

In the 1:1 molecular adduct of C and BA, however, two molecules of each C and BA, are present in the asymmetric unit.[14] While one pair of C and BA exists in a neutral form, in the other pair proton transfer from the COOH group to the pyrimidine N^3 atom occurs. Furthermore, the interaction between C and BA is established through N^1, such that each deprotonated acid interact with both the symmetry-independent molecules of C, while the adjacent molecules of C exist as dimers connected together by a triple hydrogen bond involving N^3H, carbonyl, and the NH_2 groups, thus resembling a pseudo Watson–Crick pattern. A pictorial representation of the interactions between the cytosine and BA molecules is shown in Figure 2. The hydrogen bond lengths (H···O and H···N) in the cytosine duplex are 1.65, 1.84, and 1.94 Å (Figure 2a). Furthermore, the adjacent cytosine dimers are held together by two N–H···O hydrogen bonds with H···O distances of 2.13 and 2.15 Å, formed by NH_2 and carbonyl groups (Figure 2b). An intriguing ladderlike structure is formed in the 3D arrangement of these species (Figure 2c).

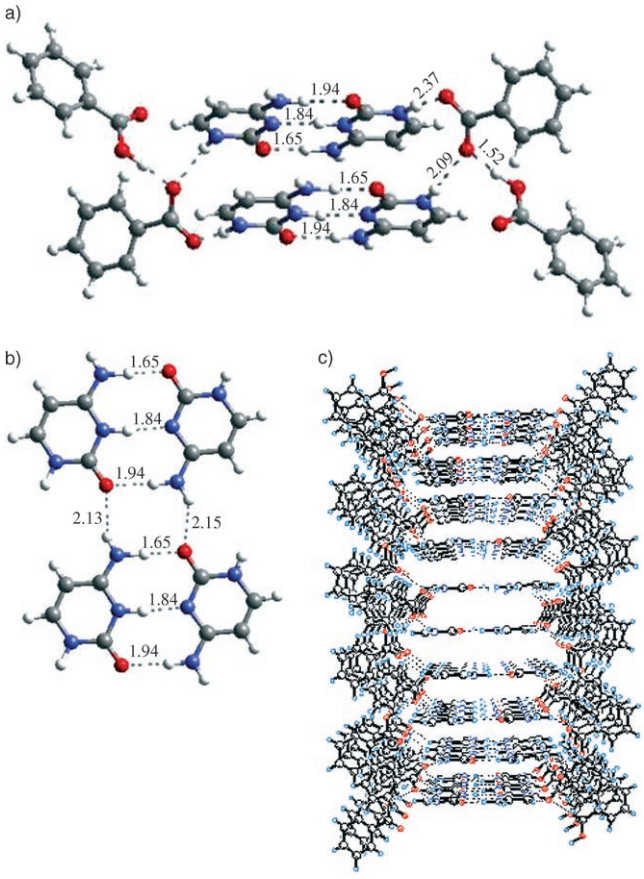


Figure 2. a) Recognition pattern between cytosine (C) and benzoic acid (BA) in the molecular adduct. b) Duplexes of cytosine residues connected together by N–H···O hydrogen bonds. c) 3D packing of C and BA in the molecular adduct forming a supramolecular ladder.

The interaction of C with PA and IA is much more interesting, with the formation of novel supramolecular structures. In both the adducts the cytosine dimers were observed as found in the complex with BA. The molecular packing in a typical 2D arrangement of the adduct between C and PA is shown in Figure 3. The adduct of C with PA is a 2:1

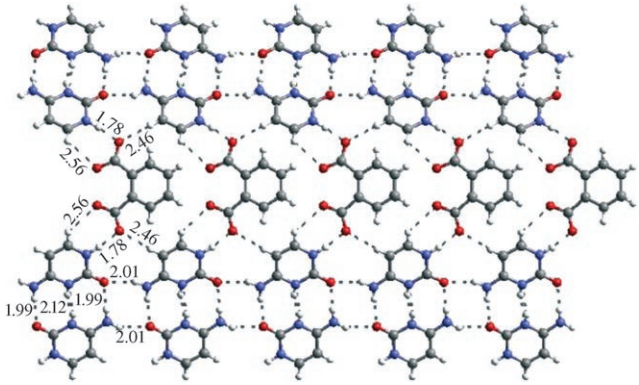


Figure 3. Arrangement of molecules of cytosine (C) and phthalic acid (PA) in the adduct forming a pillarlike structure.

complex,[14] with C and PA interacting through the deprotonated carboxyl groups of PA and C to form cyclic hydrogen-bonding patterns consisting of N–H···O (H···O, 1.78 Å) and C–H···O (H···O, 2.56 Å). Such adjacent units further interact with each other through molecules of C to yield dimers of C connected by triple hydrogen bonds, as observed in the complex of C and BA, but with different hydrogen bond lengths (H···O, 1.99 and H···N, 2.12 Å). As a result, crinkled chains are formed in the 2D arrangement (Figure 3) which are further held together by N–H···O hydrogen bonds (H···O, 2.01 Å) between molecules of C, and by C–H···O hydrogen bonds (H···O, 2.46 Å) between C and PA molecules. Thus, in each sheet the PA molecules appear as though they are inserted between tapes of C molecules.

Although 3D packing into a stacked sheets arrangement prevails in the adduct of C with IA,[14] as observed in the adduct with PA, the molecular packing is quite different within the 2D arrangement (Figure 4). Molecules of IA and C appear to exist as homomeric chains formed by strong hydrogen bonds such that while the adjacent IA molecules are held together by catemeric type O–H···O hydrogen bonds (H···O, 1.80 Å) through COOH and COO^-, molecules of C are held together by two different hydrogen bonding networks. Further, the adjacent chains are held together by a centrosymmetric cyclic arrangement of C–H···O hydrogen bonds (H···O, 2.69 Å) as shown in Figure 4b, which leads to the formation of a quartet of IA molecules (Figure 4c). In the two patterns of C, one of them is identical to that observed in

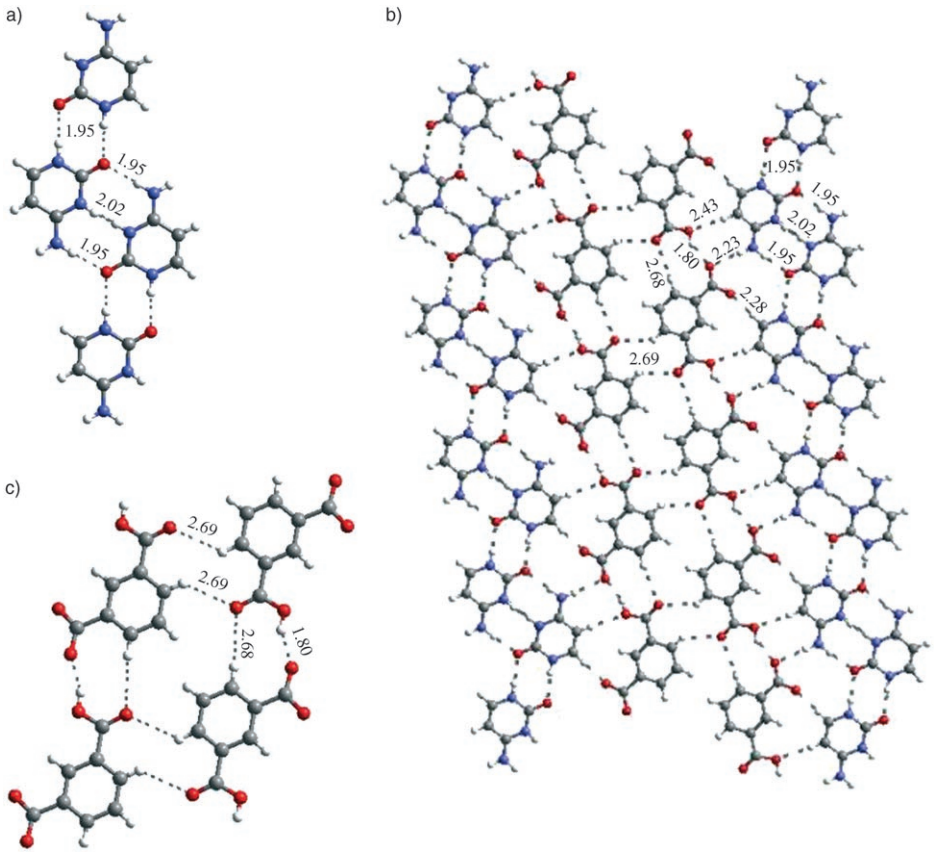


Figure 4. a) Interaction of the adjacent triple hydrogen-bonded duplexes of cytosine (C) through a dimeric hydrogen-bonding pattern. b) 2D arrangement of C and isophthalic acid (IA) in the crystal lattices of their adduct. c) Quartet arrangement of IA molecules.

the complex formed between C and PA with a triple hydrogen-bonding pattern. In contrast to the patterns observed in the complexes with BA and PA, the triplet dimers are further held together by dimeric hydrogen-bonding patterns in the adduct with **IA** through N–H···O hydrogen bonds (H···O, 1.95 Å) formed between pyridyl NH rather than NH_2 groups (Figure 4a).

Comparisons of the three adducts of C discussed above show that in all cases C exists as dimers connected together by triple hydrogen bonds and yields molecular tapes. These molecular tapes are arranged in the crystal lattice as rungs in a ladderlike structure with BA, but are sandwiched in the 2D arrangement in the adducts of PA and IA. A schematic representation of systematic variations in the arrangement of molecules in the different adducts is shown in Figure 5.

In conclusion, we have reported the formation of 3D assemblies of molecular adducts of cytosine with benzoic, phthalic, and isopthalic acids, as well as the adduct of adenine with benzoic acid. It was noted that cytosine and adenine both show the tendency to form duplexes, irrespective of the nature of the other species involved in the recognition process. Furthermore, by correlating the patterns obtained in this study with the patterns observed in other structures available in the literature, it appears that cytosine duplexes with triple hydrogen-bonding patterns are predominant in the vicinity of COOH functional groups. The cocrystallization studies with molecules containing COOH functional groups also shows that adenine binds with the other molecules through the N^1 and N^7 sites, in a similar manner to binding generally observed with thymine in the DNA structure. However, cytosine participated in molecular recognition preferentially through the N^1-position, which is generally connected to the sugar moiety in DNA, but mimics the hydrogen-bonding pattern that it forms with guanine in a G-C base pair by a homomeric process. Although these results are quite intriguing, a large number of synthetic studies of molecular adducts of nucleobases and their systematic analysis need to be made to address several problems in biological studies. We are engaged in the synthesis of cocrystals of nucleobases with different functional moieties, aimed in particular to identify groups that could interact with guanine and thymine.

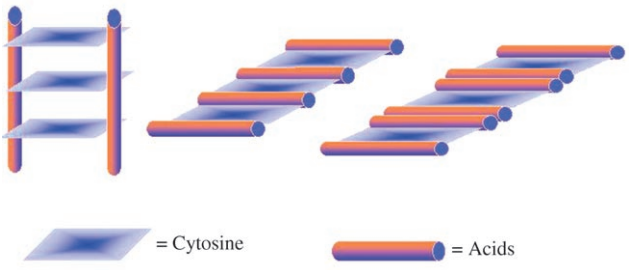


Figure 5. Schematic representation of the packing of molecules in the adducts of cytosine (C) with (left) benzoic acid (BA), (middle) phthalic acid (PA), and (right) isophthalic acid (IA).

Received: July 12, 2005
Published online: November 7, 2005

Keywords: carboxylic acids · hydrogen bonds · molecular recognition · nucleobases · supramolecular chemistry

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[13] Powder patterns are given in the Supporting Information.

[14] Crystal data for adenine and benzoic acid adduct: $C_5H_5N_5{\cdot}2\,C_7H_6O_2$, $M_r = 379.38$, colorless blocks, $0.32 \times 0.21 \times 0.13$ mm, space group $P\bar{1}$, $a = 6.949(2)$, $b = 10.324(3)$, $c = 14.286(5)$ Å, $\alpha = 80.46(1)$, $\beta = 76.40(1)$, $\gamma = 71.21(1)^\circ$, $V = 938.6(5)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.342$ g cm^3, $\mu = 0.097$ mm^{-1}, $2\theta = 56.66$, $(Mo_{K\alpha}) = 0.71073$ Å, $T = 298(2)$ K, 8200 total reflections, $R_1 = 0.070$ and $wR_2 = 0.148$ for 4268 reflections. Crystal data for cytosine and benzoic acid adduct: $C_7H_6O_2{\cdot}C_4H_6N_3O{\cdot}C_7H_5O_2{\cdot}C_4H_5N_3O$, $M_r = 466.46$, colorless needles, $0.35 \times 0.24 \times 0.14$ mm, space group $P2_1/c$, $a = 22.410(1)$, $b = 7.450(1)$, $c = 13.060(1)$ Å, $\beta = 91.918(1)^\circ$, $V = 2179.2(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.422$ g cm^3, $\mu = 0.106$ mm^{-1}, $2\theta = 56.58$, $(Mo_{K\alpha}) = 0.71073$ Å, $T = 298(2)$ K, 12642 total reflections, $R_1 = 0.079$ and $wR_2 = 0.160$ for 5066 reflections. Crystal data for cytosine and phthalic acid adduct: $2\,C_4H_6N_3O{\cdot}C_8H_4O_4$, $M_r = 388.35$, colorless needles, $0.35 \times 0.22 \times 0.13$ mm, space group $P2_1/m$, $a = 3.684(1)$, $b = 29.770(4)$, $c = 7.338(1)$ Å, $\beta = 92.76(1)^\circ$, $V = 803.8(3)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.604$ g cm^3 $\mu = 0.126$ mm^{-1}, $2\theta = 56.44$, $(Mo_{K\alpha}) = 0.71073$ Å, $T = 298(2)$ K, 4517 total reflections, $R_1 = 0.057$ and $wR_2 = 0.169$ for 1847 reflections. Crystal data for cytosine and isophthalic acid adduct: $C_4H_5N_3O{\cdot}C_8H_6O_4$, $M_r = 277.24$, colorless needles, $0.32 \times 0.25 \times 0.13$ mm, space group $P\bar{1}$, $a = 8.588(1)$, $b = 8.963(2)$, $c = 9.061(2)$ Å, $\alpha = 100.81(1)$, $\beta = 105.20(1)$, $\gamma = 113.08(1)^\circ$, $V = 585.1(2)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.574$ g cm^3 $\mu = 0.125$ mm, $2\theta = 56.56$, $(Mo_{K\alpha}) = 0.71073$ Å, $T = 298(2)$ K, 5071 total reflections, $R_1 = 0.040$ and $wR_2 = 0.111$ for 2651 reflections. CCDC-281299–281302 contain the supplementary crystallographic data for this paper. These data can be obtained free of

charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
[15] Labeling of N atoms have been adopted from IUPAC labeling of atoms in the nucleobases.
[16] In the literature, a 3:1 adduct of phthalic acid and adenine is known as an hexahydrate,[11b] in which the phthalic acid was produced in situ as an hydrolyzed product of *N*,*N*-phthaloyl-DL-glutamic acid. A comparison of the simulated powder patterns of it with the one we obtained show drastic differences,[13] thus suggesting the possibility of a new solid-state structure of phthalic acid and adenine in our adduct.

