Self-Assembly of 9-Allyladenine Hydrochloride in Crystalline State: Formation of Infinitely Stacked Supramolecular Sheets *via* Hydrogen Bonding Network

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(Received October 15, 2001; CL-011009)

This report describes solid state structure of a chemically-modified nucleobase 9-allyladenine hydrochloride. The crystal structure of the protonated nucleobase extends into an infinitely stacked, sheet like-supramolecular aggregates stabilized by multiple conventional and non-conventional hydrogen bonds.

Non-conventional hydrogen bonds are now widely recognized as important molecular interactions that contribute to the stabilization of a wide variety of crystalline frameworks of chemical and biochemical origin. Such hydrogen bonds (H-bonds), first identified by Sutor,[1] followed much later by Taylor and Kennard,[2] have redefined the area of targeted crystal engineering due to recent pioneering efforts by Desiraju, Steiner[3] and others. The hallmark of these interactions includes unusual donor-acceptor pairs and a low, bond stabilization energy profile (<4 kcal/mol), compared to conventional H-bonds. This apparent drawback is generally offset by multiplicity of these interactions, while other molecular forces also aid in the overall stability of crystal packing.

Several weak donor and acceptor pairs that effectively support molecular structures based on non-conventional H-bonding interactions have been identified. For example, C-H group is a weak H-bond donor but it interacts with acceptors like O, N, S, Se, Cl^- and pi-acceptor species,[4] to form supramolecular networks. Such H-bonding contacts also significantly contribute to the organization of secondary structures and recognition events in biomolecules.[5–8] We have been engaged in the synthesis and development of novel nucleic acid-like polymeric catalysts. In this connection, synthesis of 9-allyladenine (9-AA) based metallated, cross-linked polymeric resins has been achieved and their potential to accelerate phosphate ester hydrolysis[9,10] and phenol oxidation reactions,[11] have been explored by us. While continuing with catalytic studies, we also sought to determine the crystal structure of the modified nucleobase to unequivocally establish the site of alkylation. We have found that 9-allyladenine hydrochloride (9AA•HCl),[12] forms a sheet-like supramolecular assembly through synergistic participation of conventional and non-conventional H-bonds, in its crystalline state. As depicted in ORTEP diagram, the unit cell consists of the modified nucleobase protonated at N1, counter anion Cl^- and a water molecule (Figure 1). Interaction between two 9AA•HCl molecules results in a symmetrical dimer by invoking a pair of conventional H-bonds between the exocyclic amino group and N7 nitrogen [N6-H6----N7], through the Hoogsteen face (Figure 2). This pairing is in accordance with the previously reported structure of adenosine at acidic pH.[13]

A novel feature of this crystal structure is the participation of three non-conventional hydrogen bonds for each modified nucleobase, which promotes sheet-like assembly. A 9AA•HCl dimer is further connected to other dimeric units by through-space H-bonds involving weak donors, C2-H2 and C8-H8, two Cl^- acceptor anions and a water molecule (Figure 2, Table 1). The

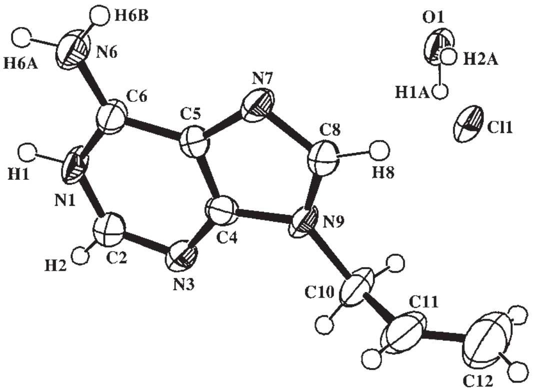

Figure 1. ORTEP diagram of 9-AA unit cell containing a Cl^- anion and a water molecule.

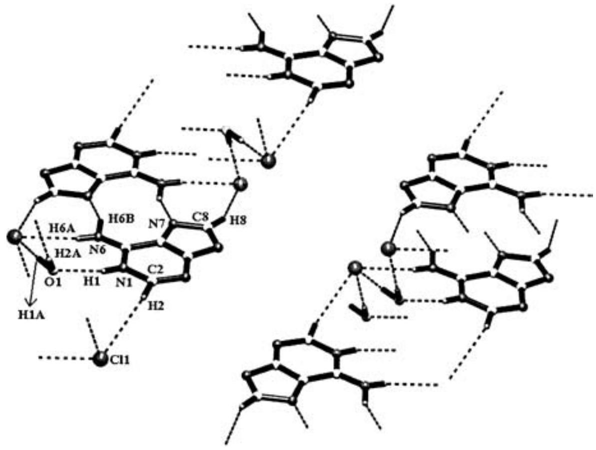

Figure 2. POVRAY diagram of 9-AA showing multiple H-bonding interactions.

Table 1. Geometrical data (Å,°) for the H-bonds in 9AA•HCl

System (X-H···A)	d(X-H)	d(H···A)	∠(X-H···A)	Symmetry equivalent
C2-H2···Cl1	1.10	2.76	122	1 − x, −y, 1 − z
C8-H8···Cl1	0.99	2.75	157	−x, 1 − y, 1 − z
N1-H1···O1	0.84	1.96	168	x, −1 + y, 1 + z
N6-H6A···Cl1	0.76	2.39	170	x, −1 + y, 1 + z
N6-H6B···N7	1.05	1.90	159	−x, −y, 2 − z
O1-H1A···Cl1	1.07	2.05	177	x, y, z
O1-H2A···Cl1	0.85	2.33	165	1 + x, y, z

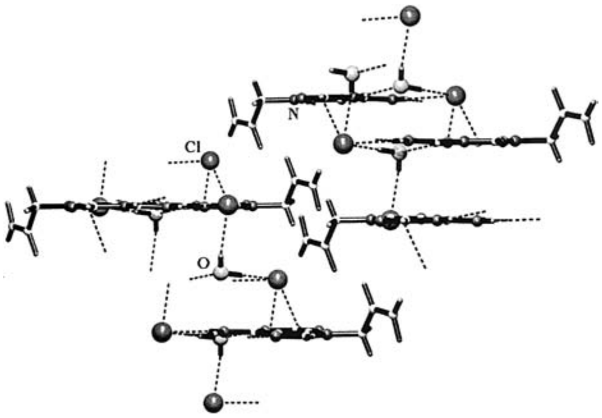

Figure 3. POVRAY diagram of 9-AA displaying a sheet-like array with a hydrophobic face and a hydrophilic cavity.

C2-H2- - - -Cl1 H-bond is angular (122 °), but highly crucial for the extended structure. N1-H1- - - -O1 and N6-H6A- - - -Cl1 H-bonding is also invoked for the strengthening of this architecture. Such an arrangement leads to the formation of an infinite sheet-like array, which eventually culminates in a stacked structure possessing a zigzag pattern (Figure 3). Although weak H-bonding interactions have been previously implicated in adenine nucleobase crystals,[14,15] a notable feature of the reported crystal packing is the presence of a hydrophobic face formed by the allyl groups and an internal hydrophilic cavity formed by Cl^- anions and water molecules (Figure 3).

Stacking interactions in 9AA•HCl assembly were further ascertained by observing change in UV absorbance over a varying pH range, at 260 nm. As the pH was lowered from 6.65, absorbance of modified nucleobase reached to a minimum value at pH 2.7. However, the absorbance increased when the pH was further lowered to 1.69 (Figure 4). Qualitatively, these observations indicate a gradual approach and existence of a stacked structure in solution for 9-AA at pH 2.7 and at a still lower pH, disruption of stacking is evident due to increased absorbance. This can be logically explained on the basis of sequential protonation of ring nitrogens. At pH 2.7, only N1 nitrogen is protonated thus facilitating formation of dimeric species and a sheet-like aggregate. At still lower pH 1.69, the formation of N1, N7-diprotonated species[16] prevents dimerization thereby disrupting an overall ordered structure.

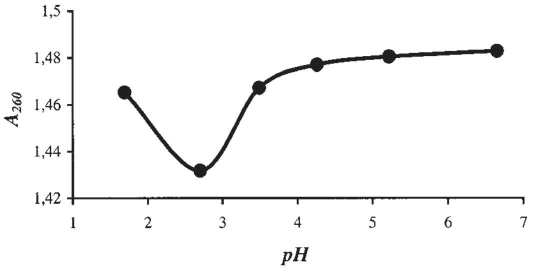

Figure 4. UV titration of 9-AA at varying pH, measured at 260 nm.

In summary, a remarkable example of a supramolecular sheet-like architecture in 9AA•HCl crystals has been demonstrated. The aggregate formation is strongly pH-dependent and is supported by multiple conventional and non-conventional H-bonding interactions and this synergism leads to an interesting structural motif in the solid state. It is proposed that appropriately modified nucleobases, dictated by subtle pH variations, could be harnessed for the design of unusual nucleic acid architectures for a variety of applications.[17]

Financial support from AICTE as a Career Award to one of us (SV) is gratefully acknowledged. We thank DST for funding the National Facility for X-ray Crystallography at IIT-Kanpur. Prof. P. K. Bharadwaj and his associates are thanked for their help in data collection and analysis.

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12 9-AA was synthesized by the reaction of adenine with allyl bromide in presence of sodium hydride. The compound was characterized using NMR and mass spectroscopy (Ref. 9). 9-AA was crystallized from 0.1 M HCl in 50% aqueous methanol. Crystal data for $C_8H_{12}ClN_5O$: $M = 229.68$, triclinic, $a = 4.9359(12)$, $b = 9.859(4)$, $c = 11.222(7)$ Å, $\alpha = 82.29(4)$, $\beta = 78.44(3)$, $\gamma = 88.30(3)^\circ$, $U = 530.2(4)$ Å^3, $d_c = 1.439$ g.cm^{-3}, $T = 293$ K, space group $P\text{-}1$, $Z = 2$, $\mu(Mo\text{-}K) = 0.343$ mm^{-1}, 1573 reflections measured, 1380 unique ($R_{int} = 0.0427$), final $R1 = 0.0598$, $wR2 = 0.1436$ $[I > 2\sigma(I)]$, $R1 = 0.1443$ and $wR2 = 0.1841$ (all data). The structure was solved using the WINGX crystallographic collective package (L. J. Farrugia, WINGX ver 1.63.02). The structure was solved with SIR92 and refined with the SHELXL-97 (Sheldrick, 1997) package incorporated in WINGX. The structure was refined against F^2 with a full-matrix least-squares algorithm. All hydrogen atoms were located and suitable riding model was used.
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