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Nature of Hydrogen Bonding in the Interaction of 4-Aminobenzoic, Nicotinic and Sulfonilic Acids With 4-Aminopyridine

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ABSTRACT

Even though N-H…O bond is considered as strong hydrogen bonding, based on the D-H<<H-A distance and the angle between them,the crystal packing of $C_7H_6NO_2^-.C_5H_7N_2^+.2H_2O$, has three weak N-H…O bonds with mean distance value as 0.88Å<<2.08Å, the angle between them lie in the ranges 143°-150° and has seventeen strong hydrogen bonding with good donor and good acceptor.The crystal packing of $C_5H_7N_2^+.C_6H_4NO_2^-$ has one weak hydrogen bonding with distance 0.92Å<<2.49Å, angles 127° for N-H…O bonding and three strong hydrogen bonding. The crystal packing of $C_5H_7N_2^+$ $C_6H_6NO_3S^-.C_6H_7NO_3S.H_2O$ has three weak N-H…O hydrogen bonding with distances ranges between 0.90Å<<2.96Å, angles ranging from 131°-144°, one C-H…π weak hydrogen bonding with 129° angles and four strong hydrogen bonding . Hence the presence of weak hydrogen bonding C-H…π of $C_5H_7N_2^+$ $C_6H_6NO_3S^-.C_6H_7NO_3S.H_2O$ shows that it can most significantly contribute to the interaction with the protein in drug design approach and other two complexes have fewer possibilities by having weak N-H…O bonding for interaction of protein for auto immune disorder like multiple sclerosis than the other heterocyclic complexes.

KEYWORDS : 4-aminobenzoic acid, nicotinic acid, Sulfonilic acid 4-aminopyridine, drug design, MS.

1. Introduction

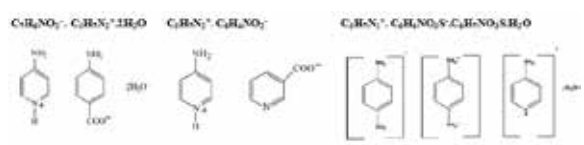
The 4-Aminopyridine (fampridine) is used in the treatment of neurological ailments, such as multiple sclerosis (MS), with tests showing that fampridine improves motor function in MS patients [Schwid et al., 1997]. The importance of weak C–H···O hydrogen bonds in macromolecules is a well-established phenomenon (Desiraju and Steiner 1999). The earlier works described their significance, as supporting interactions of stronger N–H···O and O–H···O bonds in protein–ligand complexation (Sarkhel and Desiraju 2004; Panigrahi and Desiraju 2007). Based on the assumption that strong hydrogen bonding in drug–receptor interactions are thus inherently assisted by weak hydrogen bonds (Aparnaet al 2005), the aim of the present study is to analyze the importance of strong and weak hydrogen bonds in drug–DNA complexes.Hydrogen bonds formed by good donors (O–H, N–H) and good acceptors (N,O, halide) are labeled 'strong'. Accordingly O–H···O, N–H···O, O–H···N and N–H···N hydrogen bonds will be termed 'strong' whatever be their energy stabilization, geometrical parameters or furcation status. (Nishioet al 1998). The reason we refer to Jeffrey's middle category as 'strong' originates from supramolecular chemistry considerations. By 'strong' we mean hydrogen bonds that are able to control crystal and supramolecular structure effectively (Panigrahi and Desiraju 2007). Hydrogen bonds between polarized atoms play a crucial role in protein interactions and are often used in drug design, which usually neglects the potential of C-H...O hydrogen bonds. A striking example is the hydroxyl group of the ligand that acts as an H bond donor and acceptor, leading to a synergy between classical and C-H...O hydrogen bonds. This interaction introduces both specificity and affinity within the hydrophobic ligand pocket. The similarity of intraprotein and protein-ligand C-H...O interactions suggests that such bonds should be considered in rational drug design approaches (Klaholz B et al 2002).

There are two factors contributing to the strength of hydrogen bonds: the charges on the donor and acceptor groups which deshield the proton or increase the electron density of the acceptor, and the configurationally constraint that forces a close contact between the donor and acceptor [8]. Hydrophilic regions tend to surround hydrophobic areas which gather into the central hydrophobic core. It has tendency to biological molecule. Biological molecule interacts mainly via electrostatic forces including hydrogen bonds or hydrogen bonding networks often formed through water molecules [9]. Depending on the structure of the substance and acceptor, the binding mechanism may proceed in nontrivial mechanism of protecting stable complex formation between drugs and non-specific targets[10]. The H-bond of C-H…O plays expected role in biomolecules [11,12,13]. Recently also the X-H…π,H-bonds (for X=O and C) were detected and it was shown that contrary to expectation they can significantly contribute to the stability of biomacromolecules and molecular clusters[14,15].

2. Materials and methods:

The crystal structures of 4-aminopyridinium 4-aminobenzoate dehydrate ($C_7H_6NO_2^-$. $C_5H_7N_2^+.2H_2O$),4-aminopyridinium nicotinate($C_5H_7N_2^+$. $C_6H_4NO_2^-$)and 4-Aminopyridinium 4-aminobenzenesulfonate 4-ammoniobenzenesulfonatemonohydrate($C_5H_7N_2^+$. $C_6H_6NO_3S^-.C_6H_7NO_3S.H_2O$), were taken for the hydrogen bonding analysis from the research articles published in the International union of crystallography journals [16,17].Figure I show the molecular structure for the analyzed complexes.

Figure 1: Molecular structures of selected three heterocyclic complexes



3. Result and discussions

H-bonds play a key role in determining the shapes, properties and functions of bio molecules [14,15]. In general, the strongest hydrogen bond donors pair off with strongest hydrogen bond acceptors. Similarly pairing process is repeated until all the hydrogen bond donors and acceptors have been utilized. However when a system contains excess donors or acceptors, at least two hydrogen –bonding strategies are available to accommodate the mismatch [Hanton, Hunter & Purvis,1992] (i) change in hybridization or (ii) the formation of hydrogen bonds involving the π system of an aromatic group as the acceptor. Several examples of the formation of intermolecular X-H… bonds for X= O or N have been observed where there is a deficiency of sterically accessible acceptors site of the conventional type[Hanton, Hunter & Purvis,1992, Rzepa,slawin &Williams 1991]

Table 1 show the structural detail of the selected three heterocyclic complexes and table 2 show the total number of hydrogen bonding present in the crystal packing.

Table 1: Structural detail of the selected three heterocyclic complexes

S.No	Details	$C_7H_6NO_2^-$. $C_5H_7N_2^+.2H_2O$	$C_5H_7N_2^+$. $C_6H_4NO_2^-$	$C_5H_7N_2^+.C_6H_6NO_3S^-$. $C_6H_7NO_3S.H_2O$
1	Interaction by	Pyridine ring group	Pyridine ring group	Amine group and pyridine ring group
2	Anion	Two 4-aminobenzoate	One nicotinate	One 4-aminobenzene sulfonate
3	Cation	Two 4-aminopyridine	One 4-aminopyridine	One 4-aminopyridinium
4	Other molecules	Four water molecules	One carboxyl group	One half of two water molecules

5	Zwitterion	-	-	One 4-ammoniobenzenesulfonate

Table 2: Total number of hydrogen bonds present in the complexes

S.No	Complexes	N-H…O	O-H…O	N-H…N	N-H…S	C-H…π
1	$C_7H_6NO_2^-$. $C_5H_7N_2^+$.$2H_2O$	12	8	--	--	--
2	$C_5H_7N_2^+$. $C_6H_4NO_2^-$	3	--	1	--	--
3	$C_5H_7N_2^+$. $C_7H_7NO_3S^-$. $C_6H_6NO_3S$. H_2O	8	1	--	1	1

Compound I has 20 hydrogen bonds, compound II has 4 hydrogen bonds and compound III has 11 hydrogen bonds.In compound$C_7H_6NO_2^-$. $C_5H_7N_2^+$.$2H_2O$, the hydrogen bonding N4B-H4B…O9B has D-H<< H-A as bond distances 0.88Å<<1.99Å with 143°bond angles, the hydrogen bonding N4D-H4D…O9C has D-H<< H-A as bond distances 0.88Å<<2.08Åwith 146° bond angles and the hydrogen bonding N4D-H4D…O8C has D-H<< H-A as bond distances 0.88Å<<2.09Å with 150° bond angles. The crystal packing of $C_5H_7N_2^+$. $C_6H_4NO_2^-$has one weakN1-H1…O15 hydrogen bondingD-H<< H-A with distance 0.92Å<<2.49Å, angles 127° and three strong hydrogen bonding. The crystal packing of ($C_5H_7N_2^+$. $C_6H_6NO_3S^-$.$C_6H_7NO_3S$.H_2O) has hydrogen bonding C12-H12A…π, N3-H1N3-O2W, N3-H1N3…O1 and N2-H1N2…S1 have D-H<< H-A bond distances as 0.93Å<<2.96Å, 0.90Å<<2.26Å, 0.90Å<<2.13Å and 0.90Å<<2.84Å with bond angles 129°,131°,140°, and 144° respectively.

4. Conclusion:

From the XRD patter of selected three heterocyclic complexes we propose that the presence of weak hydrogen bonding C-H…π of $C_5H_7N_2^+$ $C_6H_6NO_3S^-$.$C_6H_7NO_3S$.H_2O shows that it can most significantly contribute to the interaction with the protein in drug design approach and other two complexes have fewer possibilities by having weak N-H…O bonding for interaction of protein for auto immune disorder like multiple sclerosis than the other heterocyclic complexes.

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