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AN OVERVIEW OF INTERMOLECULAR HYDROGEN BONDING IN THE STRUCTURE OF METALLATED 4-AMINOPYRIDINE COMPLEXES

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ABSTRACT

A statistical analysis of strong and weak hydrogen bonds in synthesized complexes shows that the crystal packing of (C5H7N2)2 [CoCl4] has one N-H…Cl strong hydrogen bonding and no weak hydrogen bonding, the crystal packing of [Ni2 (Co3) (C5H6N2)8 (H2O)] Cl2.5H2O has five strong hydrogen bonding and three weak hydrogen bonding, and the crystal packing of [Cu Cl2 (C5 H6 N2)4] H2O has five strong hydrogen bonding and two weak hydrogen bonding. The chlorides of cobalt interact with 4-aminopyridine through donor N atom of both amine group and pyridine ring group. The chlorides of nickel interact with 4-aminopyridine through donor N atom of amine group. The chlorides of copper interact with 4-aminopyridine through donor N atom of amine group and donor C atom of pyridine ring. Hence the presence of weak hydrogen bonding C-H…O of copper metalized 4-aminopyridine [CuCl2 (C5 H6 N2)4] H2O and the presence of weak hydrogen bonding C-H…π of nickel metalized 4-aminopyridine [Ni2 (Co3) (C5H6N2)8 (H2O)] Cl2.5H2O shows that it can significantly contribute to the interaction with the protein in drug design approach for auto immune disorder like multiple sclerosis.

KEYWORDS Transition metals, 4-aminopyridine, drug design, multiple sclerosis.

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) (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 (Aparna et al 2005). Hydrogen bonds formed by good donors (O–H, N–H) and good acceptors (N,O, halide) are labelled '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. (Nishio et 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). Analysis of crystallographically characterized hydrogen bonds containing M-Cl, C-Cl and HO or NH groups show that M-Cl moieties are good , anisotropic hydrogen bond acceptors forming hydrogen bond similar in the length to those of the chloride anion while C-Cl moieties are very poor hydrogen bond acceptor. So metal bound chlorine often accepts hydrogen bonds [8]. Hydro phillic regions tend to surround hydrophobic areas which gather into the central hydrophobic core. It has tendency to biological molecule. Biological molecule interact 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 non trivial mechanism of protecting stable complex formation between drugs and non specific targets[10]. The H-bond of C-H…O plays expected role in bio molecules [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].

Materials and methods:

All the reagents used for the preparation of sample are analytical grade. Slow evaporation method was used for all the compounds. A solution of 4-aminopyridine (0.0946g, 1 mmol) in ethanol (10 ml) was added to a solution of $CoCl_4$ (0.169g,) in ethanol (10 ml) and blue crystals of $(C_5H_7N_2)_2$ $[CoCl_4]$ were obtained [16]. A solution of 4- aminopyridine (0.376 g) in pure methanol (20ml) was added to a solution of $NiCl_2.6H_2O$ (0.237g) in pure methanol (20ml) and Blue crystals of the compound $[Ni_2 (Co_3) (C_5H_6N_2)_8 (H_2O)]$ $Cl_2.5H_2O$ were obtained [17]. A solution of 4-aminopyridine (0.376g) 99.9% in pure distilled water (20ml) was added to a solution of $CuC1_2. 2H_2O$ (0.170g) 99.9% in pure distilled water (20ml) and Blue crystals of $[Cu\ Cl_2\ (C_5\ H_6\ N_2)_4]\ H_2O$ were obtained [18].

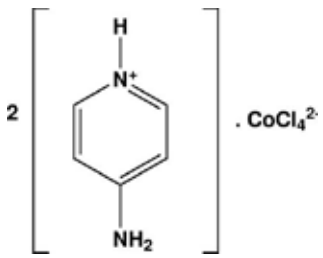
Result and discussions

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]

The crystal packing of $(C_5H_7N_2)_2$ $[CoCl_4]$ with resolution 2.7 Å is stabilized by intermolecular N-H…Cl hydrogen bonding forming a three dimensional network. There is one strong hydrogen bonding N-H…Cl and no weak hydrogen bonding were observed. Mean Hydrogen bonding distances N-H…Cl have ranges from 3.272(3) Å to 3.563(3) Å. The chlorides of cobalt interact with 4-aminopyridine through donor N atom

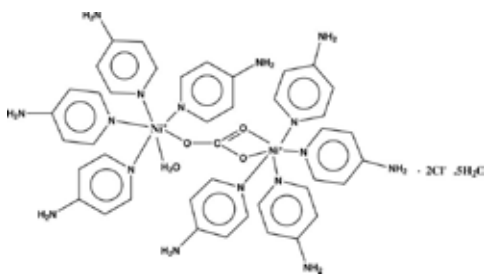
of both amine group and pyridine ring group. Fig 1shows the crystal structure of $(C_5H_7N_2)_2$ $[CoCl_4]$

Fig 1: The crystal structure of $(C_5H_7N_2)_2$ $[CoCl_4]$:



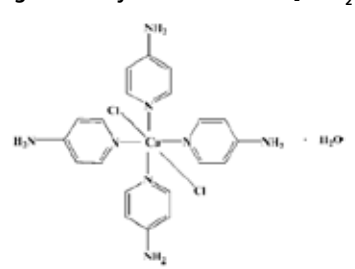
The crystal structure of $[Ni_2(Co_3)(C_5H_6N_2)_8(H_2O)]Cl_2.5H_2O$ with resolution of 1.7 Å is stabilized by the hydrogen bonding (O-H…O), (NH…Cl), (N-H…O), (O-H…N), (C-H…O), (C-H…N), (C-H…π) and (N-H…π) with mean hydrogen bonding distances of 2.8Å, 3.3Å, 3.0467Å, 3.058Å,3.075Å, 3.276Å, 3.6Å, 3.6586(5)Å and 3.7255(5)Å respectively. It has five strong hydrogen bonding and three weak hydrogen bonding. The chlorides of nickel interact with 4-aminopyridine through donor N atom of amine group. Fig 2 shows the crystal structure of $[Ni_2 (Co_3) (C_5H_6N_2)_8 (H_2O)] Cl_2.5H_2O$.

Fig 2: The crystal structure of $[Ni_2 (Co_3) (C_5H_6N_2)_8 (H_2O)] Cl_2.5H_2O$



The crystal $[CuCl_2(C_5H_6N_2)_4]$ H_2O packing with 2.5 Å resolution is stabilized by the (O-H…Cl), (N-H…O), (N-H…N), (N-H…Cl), (CH…Cl), (C-H…π) and (N-H…π) with the mean hydrogen bond distances of 3.06(16)Å, 3.03Å, 3.2036(17)Å, 3.3Å, 3.2Å, 3.636Å, and 3.3359(13)Å respectively. It has five strong hydrogen bonding and two weak hydrogen bonding. The chlorides of copper interact with 4-aminopyridine through donor N atom of amine group and donor C atom of pyridine ring. Fig 3 shows the crystal structure of $[CuCl_2 (C_5 H_6 N_2)_4]$ H_2O

Fig 3: The crystal structure of $[CuCl_2 (C_5 H_6 N_2)_4]$ H_2O



The donor of N-H…Cl hydrogen bonding in cobalt complex has high electro negativity, the donor of O-H…O and O-H…N hydrogen bonding in nickel complex has high electro negativity and the donor of O-H…Cl hydrogen bonding in copper complex has high electro negativity. The hydrophobic ligand atoms of Nickel complex has C-H…N and C-H…π with non polar covalent bonding, of copper complex has C-H…π, C-H…Cl and C-H…N with non polar covalent bond, but the formed hydrogen bonds of cobalt complex has polar covalent bond. The N-H…N of copper complex and O-H…O of nickel complex are considered to be that of a hydrogen atom forming two covalent bonds. The X-H…Y angle of all the complexes formed are shown in the following table 1.

Table 1: The observed X-H…Y angles:

Name of the Complex	X-H…Y hydrogen bond	Angle
Copper complex	N4-H4B…Cl1	175° strongest
	N10-H10B-Cl3	171°
Nickel complex	N12-H12B…Cg3	177 ° strongest
	O1W-H1W1…O3	171 °
	N6-H6A…Cl1	170 °
	O6WA-H2W6…O4W	170 °
	N16-H16A…Cl1	170 °
Cobalt complex	N7-H7A…Cl2	175 ° strongest

In the crystal of $(C_5H_7N_2)_2$ $[CoCl_4]$, all the hydrogen atoms were fixed on the calculated positions and allowed to ride on their parent atoms with the C—H= 0.95 Å (aromatic); N—H = 0.84–0.89 Å with Uiso(C) in the range of 1.2Ueq(C)-1.5Ueq(N) [16]

In The crystal of $[Ni_2(Co_3)(C_5H_6N_2)_8(H_2O)]Cl_2.5H_2O$ all the hydrogen atoms were positioned geometrically [C—H=0.93 Å; N—H=0.86 Å and O—H=0.85 Å] and refined using a riding model, with Uiso(H)=1.2–1.5Uequ(C,N and O). The two disordered water molecules are refined with the fixed site occupancy of 0.5:0.5 [17]

In crystal of $[CuCl_2(C_5H_6N_2)_4]$ H_2O, the H atoms of the water molecules were located in a difference map and refined with O—H and H···H distance restraints of 0.84 (1) and 1.37 (2) Å, respectively. The remaining H atoms were positioned geometrically [C—H = 0.93 Å and N—H = 0.86 Å] and refined using a riding model, with Uiso(H) = 1.2Ueq(C,N)]. [18]

The observed inter molecular X-H…π bonds shows that the N-H…π bond of copper complex has no deficiency of hydrogen bond acceptor, N-H…π and C-H…π bonds of nickel complex has no deficiency of hydrogen bond acceptor and the cobalt complex has deficiency of hydrogen bond acceptor.

Conclusion:

Hence the presence of weak hydrogen bonding C-H…O of copper metalized 4-aminopyridine $[CuCl_2(C_5H_6N_2)_4]$ H_2O and the presence of weak hydrogen bonding C-H…π of nickel metalized 4-aminopyridine $[Ni_2(Co_3)(C_5H_6N_2)_8(H_2O)]Cl_2.5H_2O$ shows that it can significantly contribute to the stability of molecular clusters. They are expected to interact with the protein in drug design approach for auto immune disorder like multiple sclerosis.

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