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Analysis of intra- and intermolecular hydrogen bonding in androstane derivatives: A case study of steroids

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Abstract. Analysis of intra- and intermolecular hydrogen bonds for a series of sixty androstane derivatives has been made in the present paper. The CCDC survey sets out to collate existing diffraction data on androstane derivatives and its interpretation with special emphasis on intra- and intermolecular hydrogen bonds. X–H…A intra- and intermolecular hydrogen bonds in the identified molecules are described with the standard bond distance and angle cut-off criteria. D–θ and d–θ scatter plots for intra- and intermolecular interactions have been made for better understanding of packing interactions existing in this series of steroids. The frequency of occurrence of contacts like H(C) to O is compared with the frequency of occurrence of contacts like H(O) to O and it has been found that H(O) to O contacts are predominant over H(C) to O contacts. Solvent-solute/solute-solvent interactions have also been investigated to understand more complicated processes that occur for biomolecules in aqueous solutions.

Introduction

The hydrogen bond unfurls a unique phenomenon that occupies a special and unparallel domain in structural chemistry and biology. A general survey as carried out by Taylor and Kennard (1982) [1] on more than hundred organic crystal structures revealed the existence of a number of X–H…A interactions in which thrust was on whether C can be regarded as a H-bond or not. The interest in hydrogen bonding arose from the publications of Steiner and Saenger [2] who examined the geometry of both C–H…O and O–H…O hydrogen bonds by using the criterion i.e. H…O < 2.7 Å and angle C–H…O > 90°, thereby confirming that 65% of the bonds were considered to have been formed as C–H…O hydrogen bonds.

The present work has been undertaken in view of the fact that there appears to be no such study in the literature which could provide a comprehensive information about packing interactions in androstane derivatives and this study is a part of our on-going work on the role of hydrogen bonding in various series of steroids viz. cholestane, cholane, pregnane, andro-

stane, estrane [3]. In the present paper we identify sixty derivatives of androstane from the literature (CCDC) and considered the structural data of only those compounds whose crystal data has been collected by X-ray diffraction methods. A few of the structures of androstane derivatives have also been reported by our research group and a comparative study has been evolved *vis-a-vis* what exists in the literature.

Backed up by some recent studies which have been carried out by various workers on hydrogen bonding interactions [4-5], we got interested in the analysis of various kinds of hydrogen-bonded interactions (particularly C–H…O and O–H…O) present in the molecules of androstane series of steroids and the study has been carried to: (i) know whether intra- or intermolecular C–H…O/O–H…O bonding is predominant in this class of steroids and to reason out predominance of one type of interaction over another, (ii) examine the role of hydrogen bonding in molecules existing in aqueous solutions and crystal packing through solvent-solute/solute-solvent interactions and (iii) know the preference of linearity for C–H…O/O–H…O/N-H…O/O-H…N/C-H…F/C-H…N/O-H…S/N-H…N. The intra- and intermolecular bonds of the type C–H…O, O–H…O, N-H…O, O-H…N, C-H…F, C-H…N, O-H…S and N-H…N as observed in the identified molecules of androstane derivatives are deposited.

Frequency of occurrence of intra- and intermolecular hydrogen bonds

A better way to analyze the frequency of occurrence of various types of intra- and intermolecular hydrogen bonds is to draw the histogram charts (Figure 1). From these charts it is observed that (i) the frequency of occurrence of C–H…O and C–H…N intramolecular hydrogen bonds is equal (16.7%); whereas for O–H…O and O–H…S intramolecular hydrogen bonds, it is 33.3%, (ii) the frequency of occurrence of C–H…O and O–H…O hydrogen bonds is 41.9% and 41%, respectively; whereas for C–H…N and O–H…N hydrogen bonds it is 4.3% and 5.6%, respectively. Few hydrogen contacts have been observed between N–O, C–F and N–N.

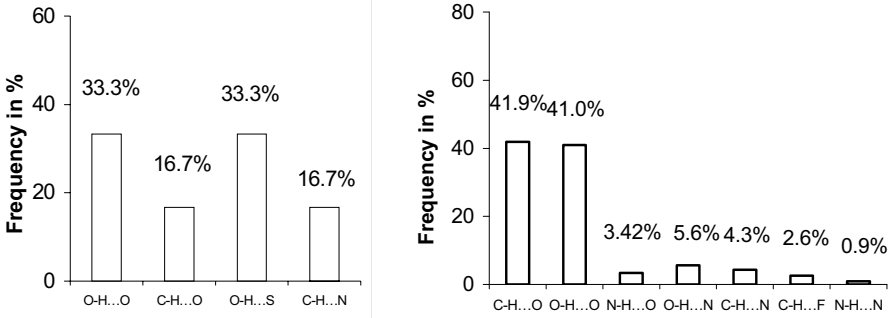

Figure 1. Frequency of occurrence of (a) C–H…O, O–H…O, O–H…S and C–H…N intramolecular hydrogen bonds and (b) C–H…O, O–H…O, N–H…O, O–H…N, C–H…N, C–H…F and N–H…N intermolecular hydrogen bonds.

d – θ and D – θ scatter plots

The main structural feature distinguishing the hydrogen bond from the other non-covalent interactions is the preference for linearity [6]. A better way to analyze linearity preference is to draw the *d–θ* and *D–θ* scatter plots. The plots include all contacts found in molecules (1-60) with d < 2.90 Å and D < 3.70 Å at any occurring angle. The graphical projection of d(H…A) against θ(X–H…A) and D(X…A) against θ(X–H…A) i.e. d–θ and D–θ scatter plots have been made for intramolecular hydrogen bonds and are shown in Figures 2a and 2b, respectively.

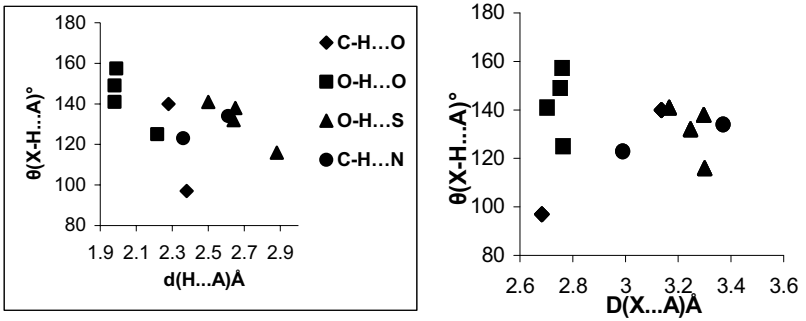

Figure 2(a, b). d–θ and D–θ scatter scatter plots for intramolecular C–H…O, O– H…O, O–H…S and C–H …N hydrogen bonds.

No clear observation can be drawn from the Figures 2a and 2b regarding the d(H…A) and D(X…A) distances whereas the more data points have been observed near the 140°(±10°) of θ(X–H…A). The scatter plots have also been made for intermolecular hydrogen bonds which are presented in Figures 3a and 3b, respectively.

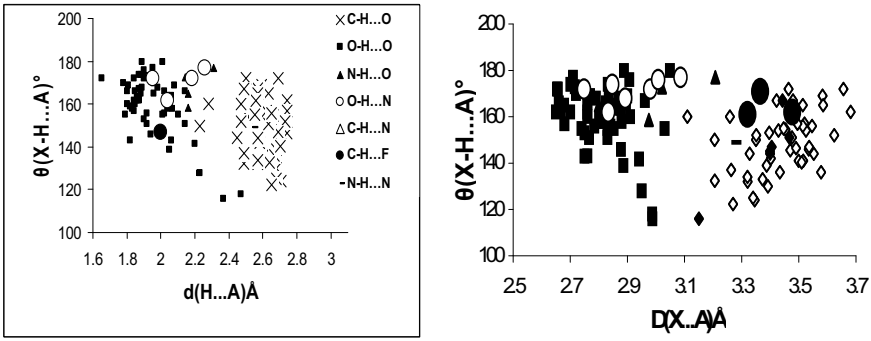

Figure 3(a, b). d–θ and D–θ scatter plots for intermolecular C–H…O, O–H…O, N–H…O, O–H…N, C–H…N, C–H…F and N–H…N hydrogen bonds.

In case of intermolecular hydrogen bonds, there are densely populated clusters of data points at short distances and fairly linear angles and each point in these clusters represents a hydro-

gen bond. It is observed that C–H…O points cluster around *d*(2.66 Å) and θ ~ 150°, whereas O–H…O points cluster around *d*(1.85 Å) and θ ~165° are highlights of these plots. From the analysis of nearest-neighbor contacts of each H-atom bonded to C/O atom in intra- as well as intermolecular hydrogen bonds following observations have been made:
(i) Upon comparison of frequency of occurrence of contacts from H(C) to O, N, F, *vis-a-vis* their crystal structures, it is observed that H(C) atoms have a statistical preference for contacts to 'O' rather than 'F' or 'N' atoms,
(ii) Similarly, the contacts from H(O) to O, N, S etc. are compared with the stoichiometry of crystal structures. It is revealed that H(O) atoms have a statistical preference for contacts to 'S' rather than 'O' or 'N' atoms, (iii) Upon comparison of the contacts from H(C) to O and H(O) to O, *vis-a-vis* their crystal structures, it is revealed that hydrogen contacts from H(O) to O predominate over H(O) to O contacts and
(iii) Most of the C–H…O contacts have distance d(H…O) less than 2.7 Å and based on the criterion that van der Waals distance should be < 2.7 Å, it was regarded as a certain indication of hydrogen bonding.

Solvent-solute interactions

The effect of solvent on the properties of organic and biological molecules have been successfully described by various workers using different and complementary theoretical models [7,8]. In this direction the investigation as carried out by Allen and Tildesley (1987) [9] on the solvation mechanism and the specific role of the solute-solvent interactions could be used as a tool for supramolecular structures [10, 11]. It has been suggested by Jedlovszky and Turi (1997) [12] that C-H…O hydrogen bonds are present in the liquid along with the stronger O-H…O bonds and both types of hydrogen bonds play an important role in stabilizing the extended structures. It is found that in solutions, the anions and cations interact with one another via weak hydrogen bonds in a highly ordered manner. This self-organization results in a definite supramolecular identity in aqueous solution [13].

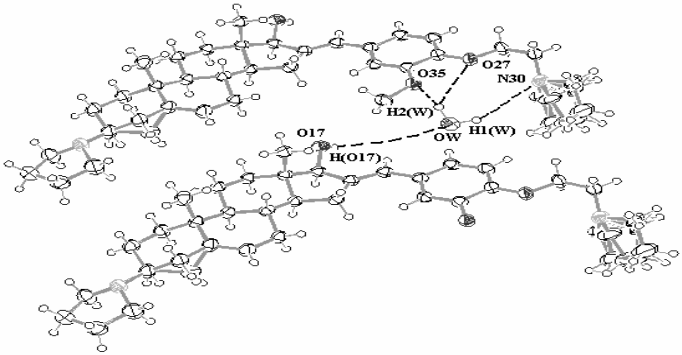

Figure 4. Solvent-solute interactions in molecule-50.

The presence of solvent in some androstane derivatives leads to the formation of solute-solvent and solvent-solute interactions. The solute-solvent interactions O(Solute)–

H…O(Water) viz. [O3–H…O(W2); O19–H…O(W1)], [O17–H…O(W)], [O17-H…O1W], [O17–H…O(W)] and [C16-H16A… O(W)] have been observed for molecules 3, 8, 42, 50 and 60, respectively. Similarly, solvent-solute interactions O(W)–H(W)…O(Solute) viz. [O(W1)–H1(W1)…O17; O(W1) –H(W1)…O3; O(W2)–H1(W2) …O17; O(W2)–H2(W2)…O19], [O(W)–H1(W) ….O17; O(W)–H2(W)….O3], [O(W)–H1(W)…O17; O(W)–H2(W)…O17′], [O(W)–H1(W)… O3; O(W)–H2(W)…O17], [OW–H1(W)…N24; OW–H2(W)…N31], [OW–H1(W)… N31; OW–H2(W)…N38] and [O(W)–H1(W)…N30; O(W)–H2(W)…O35; O(W)– H2(W)…O27] have been observed for molecules 3, 8, 16, 40, 42, 43 and 50, respectively. The solvent-solute interactions as observed in molecule-50 are depicted in figure 4. The asymmetric unit in molecule-45 contains two crystallographically independent molecules and two acetic acid molecules. The two acetic acid molecules are connected to one another through solvent-solvent [O6(Acetic acid)–H6C(O6)…. O5′(Acetic acid); O6′(Acetic acid)–H6′C(O6′)….O5(Acetic acid)] interactions. The solvent-solvent interactions as observed in molecule-45 are rarely found in steroids and such investigations could be important to understand more complicated processes that occur for biomolecules in aqueous solutions [14].

Concluding remarks

The research work reported in this article is another statement in the chemical-crystallographic relation that has existed between X-ray crystallography and organic chemistry throughout the last century. This relationship is quite friendly and may lead to unexpected and fruitful developments in both subjects. The crystallographic analysis of hydrogen bonding in androstane derivatives shows that the substituents in these molecules are either linked by intra- or intermolecular hydrogen bonds which help in understanding the stacking interactions in supramolecular structures.

The C–H…O hydrogen bonding is observed mostly in molecules having a keto group as substituent in which O atom of the keto group acts as a proton acceptor. The frequency of contacts from H(C) atoms have a statistical preference to ‘O’ rather than ‘F’ or ‘N’, whereas the frequency of contacts from H(O) atoms have a statistical preference to ‘S’ rather than ‘O’ or ‘N’ atoms. Upon comparison of the contacts from H(C) to O and H(O) to O, *vis-a-vis* their crystal structures, it is revealed that hydrogen contacts from H(O) to O predominate over H(C) to O contacts.

The presence of solvent leads to the formation of solvent-solute/solute-solvent intermolecular interactions. The solvent-solvent interactions as observed in molecule-45 are rarely found in steroids and such investigations could be important to understand more complicated processes that occur for biomolecules in aqueous solutions. The understanding of intermolecular interactions in crystal packing and utilization of such understandings in the design of new molecules/supramolecules with desired physical and chemical properties is the future intention for chemists/crystallographers.

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