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Analysis of weak interactions involving organic fluorine: Insights from packing features in substituted 4-keto-tetrahydroindoles

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Abstract

The role of "organic fluorine" in controlling the packing motifs in crystal structures which possess both strong and weak intra- and intermolecular interactions reveal that C—H…F hydrogen bonded networks provide additional stability. In this context, the crystal structures of seven new compounds have been investigated based on the molecular motif 1,5,6,7-tetrahydro-4*H*-indol-4-one with 4-fluorophenyl substitutions at the "*para*" position on the 1-phenyl ring in four compounds and different substituents on the five-membered ring in the remaining three compounds. The features of conformational changes and the flexibility in packing based on C—H…O, C—H…π and C—H…F have been analyzed.

Keywords: Weak interactions; Hydrogen bonds; Organic fluorine; Molecular conformation

1. Introduction

The discovery of new and active drugs based on "structure based drug design" (SBDD) has evoked considerable interest in recent times [1]. Crystal Structure data available in the Cambridge Crystallographic Database (CSD) for small molecules and the Protein Data Bank for macromolecules have been used to design and develop a rationale for drug design [1]. The three-dimensional structure of the active site (receptor) is considered along with that of a protein–drug complex of known activity for deriving these features. An alternative approach uses small-molecule crystal structure data, and consists of deriving the stereochemical requirements of the unknown binding sites of the macromolecule by complementarity to the pharmacophore, common to a family of active molecules [2,3]. The binding of a drug to its receptor is generally controlled by van der Waals, electrostatic, π–π stacking interactions and by hydrogen bond of varying strengths [2,4]. Intra-molecular hydrogen bonds generally provide directives for conformational rigidity in small molecules. On the other hand, intermolecular interactions provide precise topological control which direct the packing of molecules in a crystalline organic solid generated by conventional hydrogen bonds such as O—H…O, N—H…O, O—H…N and N—H…N and these have been well studied and illustrated in detail in the literature [5–10]. Interactions of the type C—H…O, C—H…π and π…π provide weak but highly directional packing motifs, which aid in the evaluation of molecular assemblies [11–13].

Compounds containing organic fluorine have found widespread application as drugs [14] and agrochemicals [15]. Because of the isosteric relationship of F and H group, binding characteristics at the receptor site will be similar to that of the non-fluorinated analogue. The interactions involving fluorine have been questioned time and again and it has been argued that fluorine does not readily accept hydrogen bonding in an organic environment [16–19]. However studies of recent origin, have clearly established that interactions of the type C—H…F and C—F…π provide both directional and energetically favorable path-

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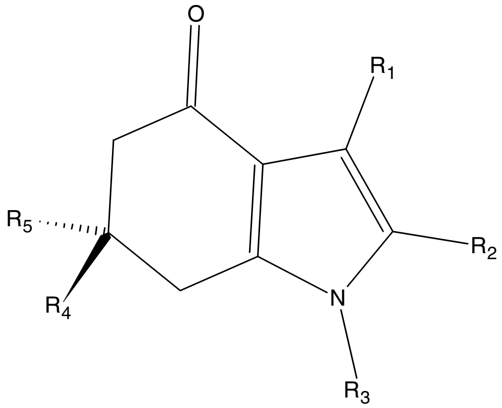
ways to hold the molecules together in the crystalline lattice [20–24]. In a systematic survey of intermolecular interactions involving organic fluorine, a series of fluorinated benzanilides have been synthesized and the importance of such weak yet directional interactions been unraveled [24c]. In an earlier article, [25a] the propensity for the formation of interactions involving fluorine, in the absence of any other intermolecular interactions has been analyzed to provide insights into the nature of such contacts. Structural studies in a series of monofluorinated cyclopropane carboxylates showed the presence of an extremely short intermolecular C—H...F contact [25b]. Further studies in a series of 2-fluoro-2-phenyl cyclopropane derivatives indicate that such short intermolecular C—H...F contacts of fluorine with hydrogen atoms are not solely due to crystal packing effects but present because of weak C—H...F bridges [25c]. A comparative study on the nature and strength of such weak hydrogen bonding interactions were performed using different basis sets and utilizing *ab-initio* and DFT methods of analysis [25d]. It was concluded that the nature of C—H...F contact depends on the subtle differences in the Lewis donor acidity and Lewis acceptor basicity. When the donor is C(sp)—H and the fluorine atom connected to sp^3 carbon the resulting interaction, although weak, exhibits the same characteristics as hydrogen bridges. More recently, the versatility of such weak interactions involving organic fluorine acting cooperatively in presence of strong hydrogen bonds like N—H...O, O—H...O and N—H...F has also been demonstrated [25c–28a]. Furthermore, there are also indicators to the formation of weak C—H...F interactions in preference to the classical N—H...N hydrogen bond observed by *in situ* cryocrystallization in fluorinated amines [28a]. This technique has also been successfully applied to unravel the importance of C—F...F—C contacts in a series of low melting substituted trifluoroacetophenones [28b]. Such interactions have also been explored in terms of careful charge density measurements and evaluation of the topological properties associated with these [28c]. Interactions of the type C—H...O [29] and C—H...π [30] have also been analyzed and their significant features have been established [31].

In this article, an attempt is made to evaluate and establish the formation of interactions involving fluorine, despite the presence of other strong and weak intra- and intermolecular interactions in a series of substituted tetrahydroindole derivatives. These compounds have been tested for their activity as anti-implantation agents in rats [32,33].

2. Experimental

Compounds 1–7 (Scheme 1) were synthesized according to the procedure reported in the literature [33]. Single crystals of suitable size and quality of all the compounds were grown by slow evaporation process at ~5 °C from different organic solvents [Aldrich Analytical Grade] (Table 1). The single crystal X-ray diffraction data were collected on a Bruker AXS SMART APEX CCD diffractometer using graphite monochromated MoK$_\alpha$ ($\lambda = 0.7107$ Å) radiation and the intensities were measured using ω scan with a scan width of 0.3°. A total of 606 frames per set were collected in different settings of ϕ($\phi = 0°$, 90° and 180° if the system is monoclinic; $\phi = 0°$, 90°, 180° and 270° if it is triclinic) keeping the sample to detector distance of 6.03 cm. The data were reduced by SAINTPLUS [34] and an empirical absorption correction was applied using the package SADABS [34] available in the Bruker software package. All the crystal structures were solved by direct methods using SIR92 [35] and refined by full matrix least squares method using SHELXL97 [36] present in the program suite WinGX (Version 1.63.04a) [37]. All the hydrogen atoms were located from a Difference Fourier Map and refined isotropically, except methyl hydrogens, which were fixed geometrically in calculated positions. ORTEP diagrams of all the compounds were generated using ORTEP32 [38] and packing diagrams were generated using CAMERON [39] available in the WinGX program suite. Geometrical calculations were done using PARST95 [40] and PLATON [41]. Theoretical calculations based on B3LYP/6-31G** using Gaussian98 [42] have also been performed and compared with the experimental values. The details of the data collection and refinement are shown in Table 2. Table 3 contains relevant torsion angles obtained experimentally and theoretically from B3LYP/6-31G** calculations. Table 4 contain information on the details of the analysis of least square



Scheme 1. Chemical Sketch of the studied functionalised 4-keto-tetrahydroindoles.

Table 1
Growth of crystals of compounds in different organic solvents

Compounds	Solvents
1	Acetone
2	MeOH/DCM
3	DCM/Hexane
4	$CHCl_3$/MeOH
5	DCM/Hexane
6	CH_3CN
7	MeOH/DCM