Quantitative Investigation of C-F···π Interaction in 4-(2-(((6-(trifluoromethyl)pyridin-2-yl)oxy)methyl)phenyl)-1,2-dihydro-3H-pyrazol-3-one

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Abstract

In this study, we have investigated the nature and characteristics of C-F···π interactions present in the crystal structure of 4-(2-(((6-(trifluoromethyl)pyridin-2-yl)oxy)methyl)phenyl)-1,2-dihydro-3H-pyrazol-3-one (**1**). This is a case of an lp···π interaction where the lp of the fluorine interacts with the pyridinyl π-ring. The molecular pairs consisting of C-F···π interactions were stabilized with dispersion being the dominant force. The existence of these F···π interactions were further confirmed by the presence of (3,-1) bond critical points between fluorine and the carbon atoms of the π-rings.

Keywords: Molecular; Crystal structure; Carbon atoms

Introduction

Non-covalent interactions plays a very important role in molecular self-assembly and are very important aspect of supra-molecular chemistry [1,2]. In recent years, weak interactions involving organic fluorine have garnered significant attention due to its unique properties such as high electronegativity and small size [3,4]. It was previously believed that organic fluorine cannot participate in formation of hydrogen bond [5] but it has been now firmly established that fluorine can form highly directional and stabilized hydrogen bonds [6-8]. Apart from hydrogen bonds, fluorine can also participate in the formation of F···π interaction also where the lp of the fluorine interact with π-rings [9]. F···π interactions has been observed to play an important role in molecular crystals and hence it is of interest to quantitatively investigate the nature and characteristics of F···π interactions [7, 10-12]. In this study, we have quantitatively investigate the role of C-F···π interactions in the crystal structure of 4-(2-(((6-(trifluoromethyl)pyridin-2-yl)oxy)methyl)phenyl)-1,2-dihydro-3H-pyrazol-3-one (**1**). The aim of this study was to evaluate the strength of the F···π interaction and their contribution towards molecular packing. Topological analysis was also performed in order to evaluate the magnitude of the electron density (ρ) and Laplacian (∇^2ρ) at the bond critical point of the interacting atoms.

Experimental Details

The present compound [4-2-({6-(trifluoromethyl)pyridin-2-yl]oxy}methyl)phenyl]-1,2-dihydro-3H-pyrazol-3-one] was synthesized by the process of reductive cyclization, using 0.367 gm,

0.001 mol of (2E)-3-methoxy-2-[2-({[6-(trifluoromethyl)pyridin-2-yl]oxy}methyl)phenyl]prop-2-enehydrazide, which is dissolved in 10 ml of methanol along with 2 drops of conc.H_2SO_4 **(Scheme 1)**. The reaction mixture was refluxed for 6 h at 80^{0}C temperature and cooled to separate out the final product. The final product is again re-crystallized by dissolving in ethanol and by the process of slow evaporation needle shaped white transparent crystals of the product were obtained. The cyclization of hydrazide is a well-known process and has been utilized extensively for synthesizing a variety of pyrazol derivatives [13,14].

X-ray data collection

Single crystal X-ray measurements were carried out on a Bruker AXS Kappa Apex 2 CCD diffractometer using monochromated Mo-Kα radiation (λ=0.71073 Å) in phi (φ) and omega (ω) scans
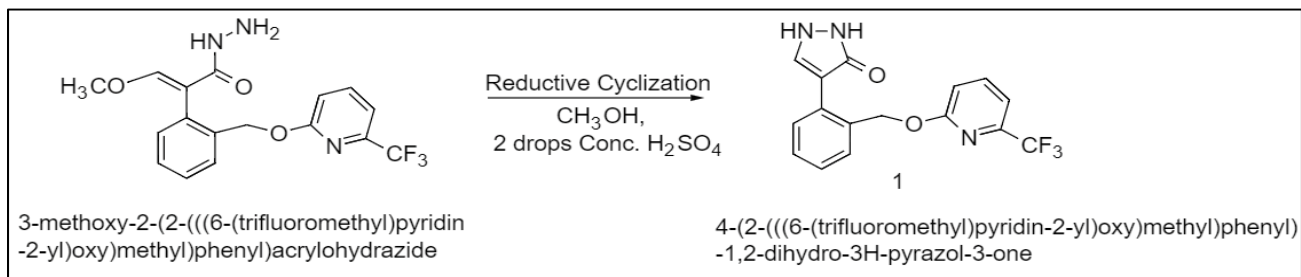
Scheme 1 Schematic representation of synthesis of 4-[2-({[6-(trifluoromethyl)pyridin-2-yl]oxy}methyl)phenyl]-1,2-dihydro-3H-pyrazol-3-one (**1**) with its chemical name.

at 100(2) K. Unit cell measurement, data collection, integration, scaling and absorption corrections were performed using Bruker Apex II software [15]. The intensity data were processed by using the Bruker SAINT [16] suite of programs. The crystal structure was refined by the full matrix least squares method using SHELXL14 [17] present in the program suite WinGX [18]. Empirical absorption correction was applied using SADABS [19]. The CF_3 group is disordered over two independent orientations and refines in the ratio of 2:1. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms bonded to C and N atoms were positioned geometrically and refined using a riding model with $U_{iso}(H)=1.2U_{eq}$ (C, N). The molecular connectivity and the crystal packing diagrams were generated using the Mercury 3.9 (CCDC) program [20]. Geometrical calculations were done using PARST [21] and PLATON [22]. The details of data collection and crystal structure refinement are shown in **Table 1**.

Theoretical calculations

Lattice energy and intermolecular interaction energies partitioned into coulombic (E_{coul}), polarization (E_{pol}), dispersion (E_{disp}), and repulsion energy (E_{rep}) terms were evaluated using the PIXEL method present in the CLP module [23] which has been utilized in several similar studies. Crystal Explorer (version 17.5) software was also utilized for mapping 2D fingerprint plots [24] which helped in evaluating the contribution of different intermolecular interactions present in a molecule in the crystalline environment. Topological analysis was performed at B3LYP/6-311G** level of theory by using AIMALL software [25] which is based on Bader's Quantum Theory of Atoms in Molecules [26]. For the purpose of quantitative analysis, fluorine atoms with major occupancy were considered for our calculations.

Results and Discussion

Figure 1 shows the *ORTEP* of the title molecule which crystallizes in monoclinic *P*2₁/c space group with Z=8. One of the molecules present in the asymmetric unit consisted of a disordered CF_3 group, with the occupancy of the major: minor orientation being in the ratio of 0.57:0.43. The lattice energy of **1** was calculated to be -190.3 kJ/mol with dispersion being the largest contributor towards the stabilization (~42%) followed by stabilization from coulombic (~40%) and polarization (~18%) contribution **(Table 2)**. Analysis of the crystal structure reveals that there are five different molecular motifs which are involved the formation of C-F···π interactions **(Figure 2; Table 3)**. The interaction energies

Table 1 Single crystal data collection and refinement details of 1.

Empirical formula	$C_{16}H_{12}F_3N_3O_2$
Formula weight	335.29
Crystal system	Monoclinic
Space group	P2₁/c
a (Å)	16.4436(17)
b (Å)	18.236(2)
c (Å)	10.4744(11)
α (°)	90
β (°)	108.57(3)
γ (°)	90
V (A3)	2977.3(5)
Z, Z^c	8, 2
Dcalc (gcm⁻³)	1.496
μ (mm⁻¹)	0.126
F (000)	1376
θmin, θmax	2.588, 27.626
Treatment of Hydrogens	Fixed
hmin, max, kmin, max, lmin, max	-21, 19, -23, 23, -13, 13
No. of ref.	24734
No. of unique reflections/Observed reflections	6067/3278
Goodness-of-fit	1
Final R indices [I>2σ(I)]	R1 = 0.0965, wR2 = 0.2434
R indices (all data)	R1 = 0.1750, wR2 =0.2793
Largest difference peak and hole (e Å-3)	0.55 and -0.52
CCDC reference number	1559231

Table 2 Lattice Energy of **1** partitioned into different energy components (in kJ/mol).

Code	E_{coul}	E_{pol}	E_{disp}	E_{rep}	E_{tot}
1	-154.9	-72.2	-163.5	200.3	-190.3

in these motifs ranged from -25.1 kJ/mol to -3.7 kJ/mol with dispersion being the largest contributor towards the stabilization **(Table 3)**. The C-F···π(C) distance in these motifs were in the range of 2.93-3.77 Å while the C-F···π(C) directionality is in the range of 108-142°. It is important to note that in case of motif I, II and III that the total stabilization energy was significantly
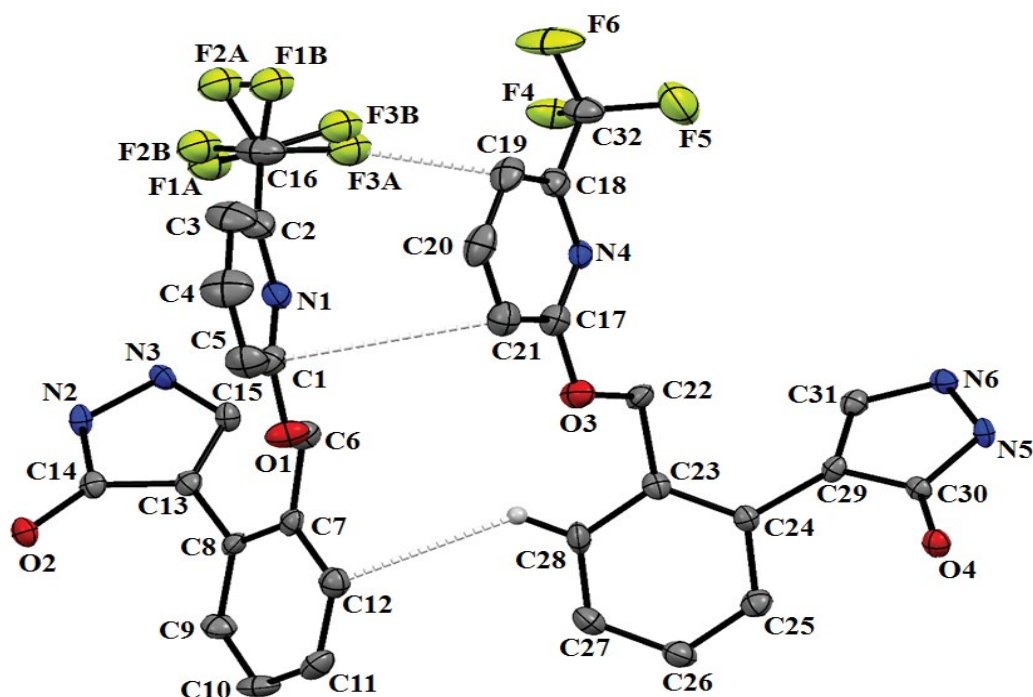
Figure 1 *ORTEP* of **1** drawn at 50% ellipsoidal probability. Dotted lines indicate C…C, C-H… π and C-F…π contacts between two molecules in the asymmetric unit.

a) I, -25.1 kJ/mol

b) II, -24.5 kJ/mol

c) III, -19.0 kJ/mol

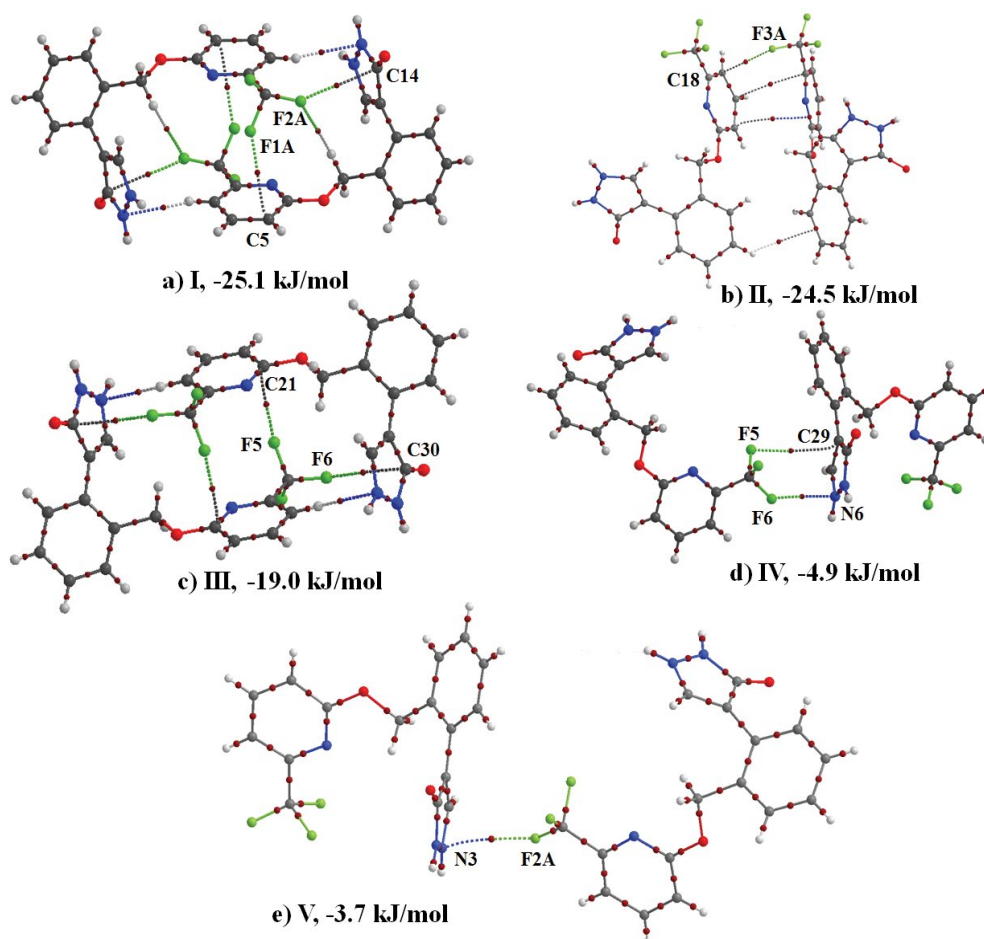d) IV, -4.9 kJ/mol

e) V, -3.7 kJ/mol

Figure 2 (a)-(e): Molecular graphs in 1 showing the existence of F…C(π) bond critical points.

larger as compared to the other two motifs due to the presence of hydrogen bonds in addition to the F⋯π interaction which provided additional stability to the respective motifs **(Table 3).**

The presence of the F⋯π(C) interactions in the above discussed motifs was further confirmed by a topological analysis due to the presence of a bond critical point between the interacting fluorine and the carbon atom of the π-ring **(Figure 2).** The F…C bond path length in these ranged from 2.937Å to 3.916 Å. It is important to note that while the magnitude of the bond path length was similar to that of bond length; their origin and physical significance were different. The magnitude of ρ ranged from 0.013-0.055 e/Å³ while the magnitude of $\nabla^2\rho$ ranged from 0.199-0.797 e/Å⁵ **(Table 4).** In general, the magnitude of both ρ and $\nabla^2\rho$ decreases with increasing value of BPL. The low value of ρ accompanied by positive value of Laplacian confirms F⋯C(π) interactions to be a case of closed-shell interactions. The Hirshfeld fingerprint plot also shows that F⋯C(π) interactions had 9.3% contribution towards the molecular packing and establish that F⋯π interaction

indeed plays a very important role in the crystal packing of the title compound **(Figure 3).**

Summary

In this study, we have quantitatively investigated the role of C-F…π(C) interactions in the crystal structure of 4-(2-(((6-(trifluoromethyl)pyridin-2-yl)oxy)methyl)phenyl)-1,2-dihydro-3H-pyrazol-3-one. It was evident that both dispersion and coulombic energy components had significant contribution towards the crystal lattice. Calculations on the interaction energy reveal that the motifs consisting of C-F…π interactions were attractive in nature with dispersion being the dominant contributor towards stabilization. Topological calculations further confirmed the existence of these weak interactions. Future study will be focussed on analysing the interplay between C-F…π and other non-covalent interactions, such as hydrogen bonds, present in the crystal structure of related molecules and their subsequent role in formation of the 3D molecular packing.

Table 3 List of molecular motifs consisting of C-F⋯π interactions along with interaction energies and geometrical parameters.

| Motif	Centroid-Centroid Distance	Ecoul	Epol	Edisp	Erep	Etot	Symmetry	Interaction	Geometrical Parameters
		(kJ/mol)	(kJ/mol)	(kJ/mol)	(kJ/mol)	(kJ/mol)			(Å/°)
I	5.869	-1.1	-11.8	-52.3	40	-25.1	2-x,1-y,-z	C16-F1A…C5	3.237/141
								C16-F2A…C14	3.438/141
								C3-H3…N2	2.55/159
II	6.362	-5.4	-3.6	-40.6	25.1	-24.5	x,y,z	C16-F3A…C18	3.165/132
								C28-H28…C12	2.91/132
								π(C1)…π(C21)	3.464
III	5.732	6.7	-8.5	-48.6	31.4	-19	1-x,1-y,-z	C32-F6…C30	3.400/150
								C32-F5…C21	3.223/162
								C19-H19…N6	2.63/163
IV	10.444	-0.2	-1.2	-9.4	5.9	-4.9	1-x,-0.5+y,0.5-z	C32-F6…N6	2.932/137
								C32-F5…C29	3.777/107
V	10.313	2.4	-1.2	-10.5	5.6	-3.7	2-x,-0.5+y,0.5-z	C16-F2A…N3	3.031/142
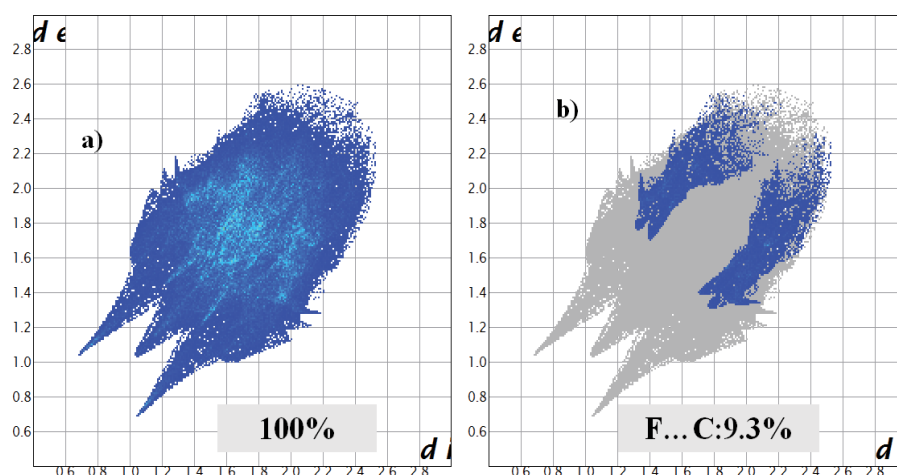
Figure 3 2D Fingerprint plot for 1 a) Overall b) F…C interaction.

Table 4 Topological parameters obtained for different C-F...π(C) interactions present in 1.

Interaction	BPL (Å)	ρ (e/Å³)	$\nabla^2\rho$ (e/Å⁵)
C32-F6...N6	2.937	0.055	0.797
C16-F2A...N3	3.056	0.046	0.697
C32-F5...C21	3.198	0.038	0.557
C16-F1A...C5	3.266	0.036	0.518
C32-F6...C30	3.409	0.018	0.301
C16-F2A...C14	3.445	0.017	0.290
C16-F3A...C18	3.784	0.043	0.555
C32-F5...C29	3.916	0.013	0.199

Acknowledgements

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