

Conformational tuning of molecular network stabilized *via* C-H.... π & π - π interaction in 2-[2-(3-cyano-4, 6-dimethyl-2-oxo-2*H*-pyridin-1-yl-methyl)-benzyloxy]-4, 6-dimethylnicotinonitrile

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Abstract

2-[2-(3-Cyano-4,6-dimethyl-2-oxo-2*H*-pyridin-1-ylmethyl)benzyloxy]-4,6-dimethylnicotinonitrile (**1**) has been synthesized and characterized by ^1H and ^{13}C NMR. In solid state, the molecular conformation of sterically hindered compound (**1**) is stabilized in such a way that *gauche* conformation is attained by both heterocyclic rings with respect to phenyl ring *via* intramolecular CH-O and CH- π interactions. The weak CH-X (π , O, N) interactions manifest an interesting role in stabilizing the packing mode of compound. X-ray crystal structure of compound shows a cavity of 13 members formed *via* intramolecular CH- π interaction.

Keywords: 1,2-Dihydro-4,6-dimethyl-2-oxonicotinonitrile, Intra/intermolecular interactions, conformations, self assembly

Introduction

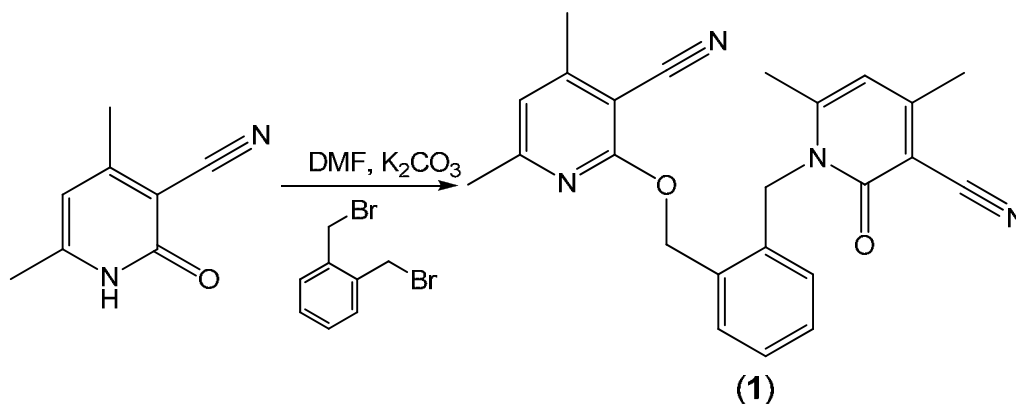
Synthesizing an organic molecule is synonymous to crystal growth in crystal engineering and requires a systematic design which accounts additional stabilization by intermolecular force of attraction.¹ Supramolecular chemistry enables us to synthesize new crystals with desired physical and chemical properties.² Various intermolecular interactions are responsible for crystal self assembly and represent a major endeavor in crystal engineering.³

Intermolecular π - π stacking interactions belong to one of the most directional forces responsible for self assembly of molecules within the crystals.⁴ These intermolecular arene interactions along with other important intermolecular weak interactions like CH...X (X = N, O, S, Cl, F, π) and C=O...C are important in chemistry as well as in biology.⁵ Out of these interactions, the CH... π interaction⁶ which is probably formed between soft acid (CH) and soft base (π system) is known to play an important role in determining the conformation of organic compounds.⁷ The presence of the strongest CH... π interactions is found in acidic alkynyl

hydrogens^{8,9} or other acidic hydrogens.¹⁰ For participation in a CH... π interaction, it is not necessary that the hydrogen atom is positioned directly above the π -plane; it may be slightly offset outside the ring.¹¹ Earlier reports confirm that heterocyclic compounds are engaged in favorable interactions with one another and with aromatic hydrocarbon units, however possible sources of heteroaromatic “stickiness” remained unclear.¹²

Substituted biaryl compounds containing a phenethyl side chain adopt such a conformation which is thermodynamically stabilized *via* intramolecular CH... π interaction.¹³ *N,N*-bis-(phthalimidopropyl)-*N*-propylamine stabilizes the crystal structure intramolecularly due to the presence of CH...O and intermolecularly by CH... π interactions.¹⁴ CH...O, π - π and CH...N interactions have been utilized in stabilizing supramolecular self assembled crystal structure of 1,1'-(1,3-propanediyl)bis(5-benzyl-6-methylsulfanyl-4,5-dihydro-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-one).¹⁵ Earlier synthesized family of di-pyrrolyl monomers, namely di(1-pyrrolylmethyl)-*o*-benzene, di(1-pyrrolylmethyl)-*m*-benzene and di(1-pyrrolylmethyl)-*p*-benzene stabilized their conformation through CH... π interaction with other weak non bonded interactions.¹⁶

In this paper, we report the synthesis and conformational property of *o*-xylene linked flexible model 2-[2-(3-cyano-4, 6-dimethyl-2-oxo-2*H*-pyridin-1-ylmethyl)-benzyloxy]-4, 6-dimethylnicotinonitrile (**1**) to see the effect of disubstituted benzene derivatives with bulky substituent (Scheme- 1).



Scheme 1

Results and Discussion

Organic chemists have thought that bulkier substituents at the ortho position of a benzene ring may create steric hinderance. However, the presence of weak non-bonded interactions within the molecule **1** stabilized the conformational property. Presence of lactam-lactim type of tautomerism has been observed in the molecule and due to that the heterocyclic moiety is joined through nitrogen at one side and through oxygen atom at the other side. The molecule is rich in C-H donors and O, N and π acceptors. Electronic environment of individual rings in the

molecule is overall neutral as two electron donating groups CH_3 and one cyano group along with amide function are present. Thus, two sp^2 nitrogen atoms of the molecule are present as amide and amino function, whereas two oxygen atoms are present, i.e., one as carbonyl and other as ether group. Here, the methyl protons due to adjacency of cyano group act as a proton donor, as well as the benzylic (PhCH_2) and methylene protons having an acidic nature act as good donors. ORTEP diagram of molecular conformation together with atom numbering scheme is shown in Figure 1.

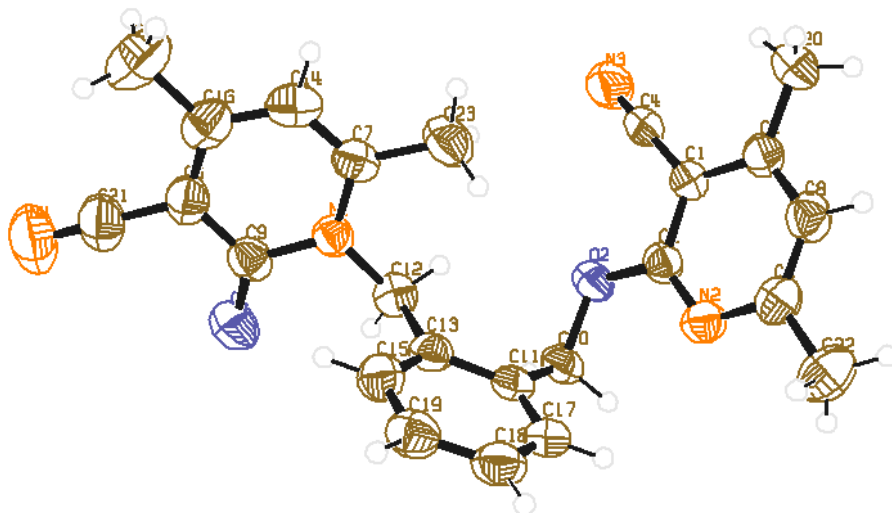


Figure 1. The ORTEP diagram of molecular conformation of molecule **1**.

Intramolecular $\text{CH}\dots\pi$ with other $\text{CH}\dots\text{X}$ (O, N) interactions stabilize the geometry of the molecule. Both heterocyclic rings are away from each other having an angle of 113.64° with the phenyl ring linked through the nitrogen atom and 112.28° with the ring linked through ethereal oxygen. Ethereal oxygen participated in bifurcated $\text{CH}\dots\text{O}_2$ [(2.54 Å, 131.43°), (3.05 Å, 114.91°)] interaction, whereas CN side group interacts with methyl proton of other heterocyclic ring through weak $\text{CH}\dots\text{N}_3$ (2.92 Å, 141.03°) interaction, (Figure 2). The presence of $\text{CH}\dots\pi$ interaction forms a cavity of 13 members. Details of these intramolecular interactions are given in Table 1.

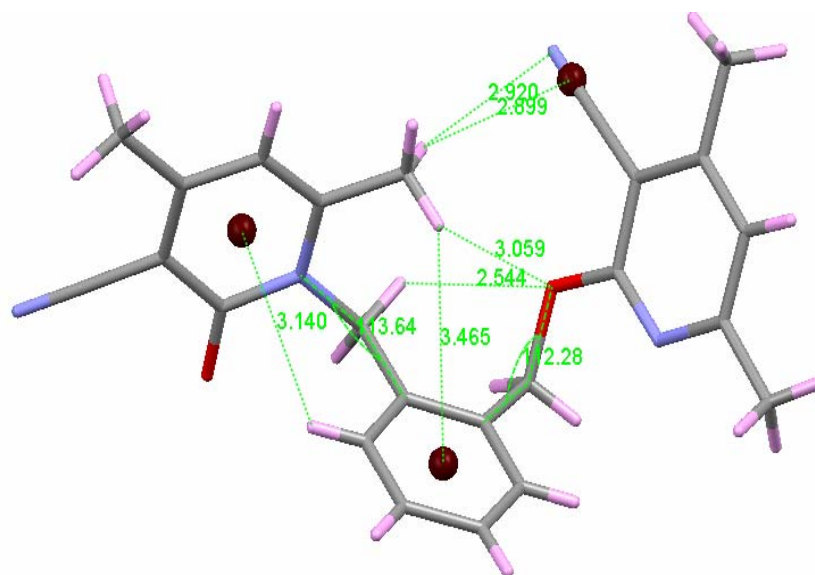


Figure 2. Intramolecular CH...X interactions in compound **1**.

Table 1. Hydrogen – bonding geometry (Å and deg) for **1**

D-H...A	d (H...A)	d (D...A)	<(DHA)
CH15.... π	3.14	3.71	121.98
CH23A... π	3.46	4.26	142.03
CH23C... π	2.89	3.62	133.04
CH15...N1	2.57	2.88	99.98
CH10A....N2	2.42	2.91	95.47

The supramolecular structure of **1** is unique. The molecules are organized into a three-dimensional network by weak intermolecular interactions. Thus, within the crystal, an intermolecular π - π interaction is observed between a pair of two molecules out of six in such a way that a heterocyclic ring linked through ethereal oxygen is oriented just above the heterocyclic ring of another molecule linked through the nitrogen atom of the ring. An intermolecular CH...O interaction links the pairs with each other. The CH.... π interaction with other CH...O and CH...N interactions also provide the stability of molecule (Figure 3). The intermolecular weak interactions are summarized in Table 2.

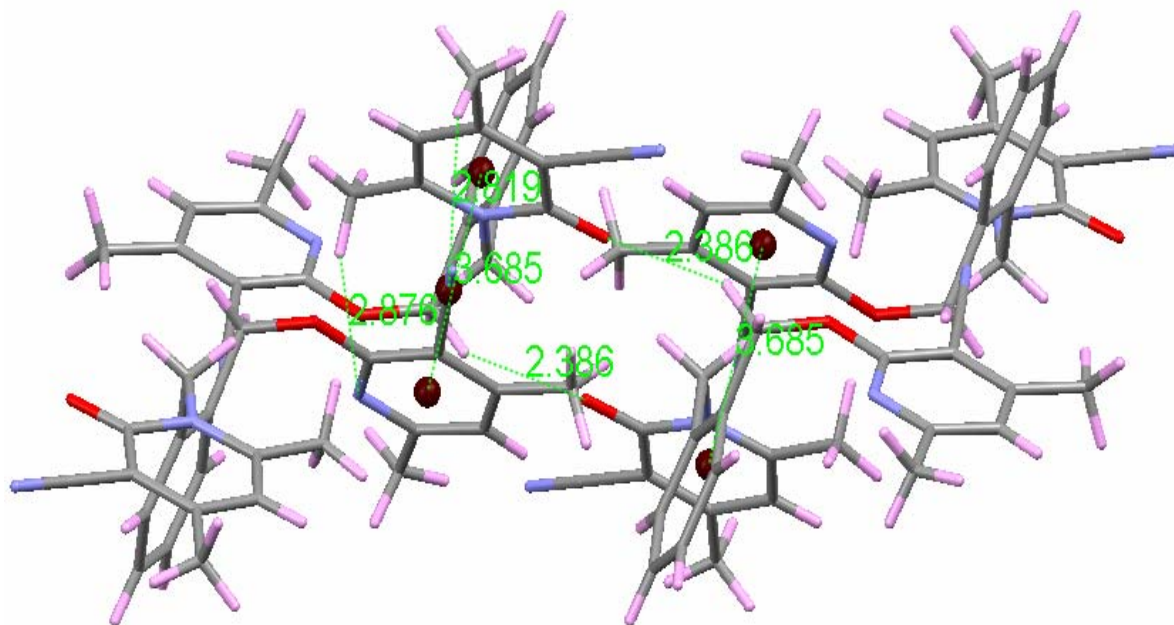


Figure 3. Packing diagram of compound **1** showing intermolecular π - π and CH...X interaction along b-plane.

Table 2. Intermolecular hydrogen – bonding geometry (Å and deg) for **2**

D-H...A	d (H...A)	d (D....A)	<(DHA)
CH- π	2.81	3.58	136.87
CH- π	3.02	3.91	152.97
CH...N	2.89	3.70	142.29
CH...N	2.66	3.50	146.65
CH...N	2.67	3.53	153.41
CH...O	2.38	3.16	136.90
π - π	3.68

A network of molecules has been formed which is stabilized by intermolecular π - π (3.685 Å) interaction joining the chain of molecules (Figure 4). The bifurcated CH...N interaction is formed between nitrogen atom of CN group with phenyl hydrogen (2.677 Å, 153.41°), and methyl hydrogen (2.66 Å, 146.65°), respectively. All these interactions arrange the network in centrosymmetrical manner.

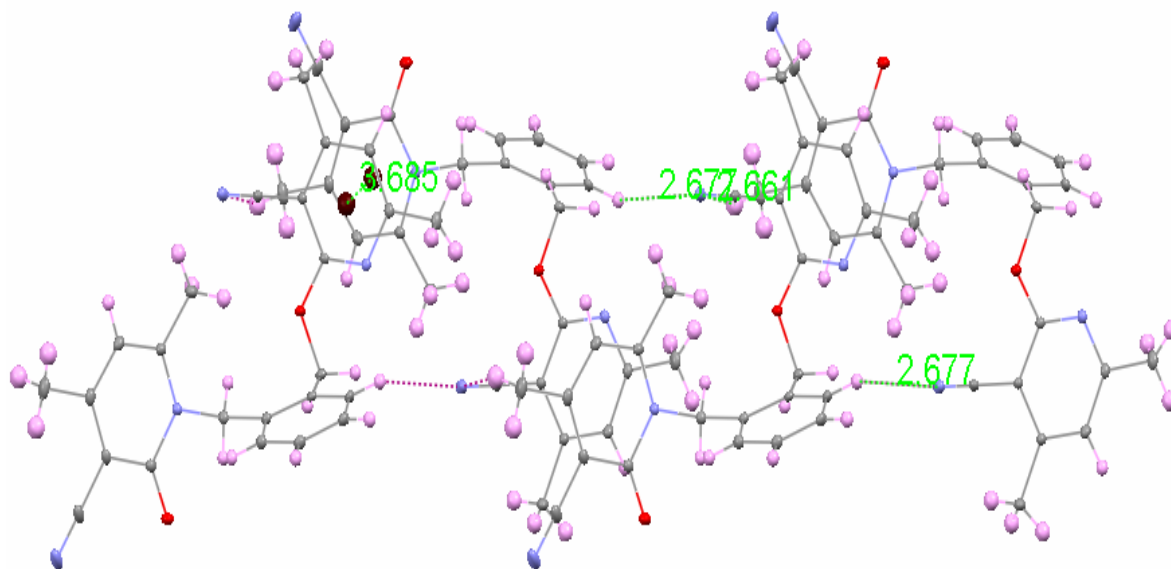


Figure 4. Network of molecules stabilized in centrosymmetrical manner.

Conclusions

In summary, the crystallography data analysis on the self-assembly of 2-[2-(3-cyano-4, 6-dimethyl-2-oxo-2*H*-pyridin-1-ylmethyl)-benzyloxy]-4,6-dimethylnicotinonitrile(**1**) shows the presence of intra/intermolecular π - π , CH...X (N, O, π) interactions, which stabilize the molecular conformation and, make possible the synthesis of this sterically hindered structure.

Experimental Section

General Procedures. Melting points were taken in an electrically heated instrument and were uncorrected. Compounds were routinely checked for their purity on silica gel G TLC plates and the spots were visualized by iodine vapors. Column chromatography was carried out by packing the column with 60 to 120 mesh silica gel G were used for purifying the compound. IR spectra were recorded on Varian 3100 FT-IR spectrometer. ^1H and ^{13}C – NMR spectra were recorded on a JEOL AL 300 MHz FTNMR instrument. NMR data is represented as follows: chemical shifts δ (in ppm relative to $\delta_{\text{TMS}} = 0$), multiplicity, coupling constant J (quoted in hertz, Hz) integration and assignment.

Synthesis of 2-[2-(3-Cyano-4,6-dimethyl-2-oxo-2H-pyridin-1-ylmethyl)-benzyloxy]-4,6-dimethylnicotinonitrile (1). 3-Cyano-4,6-dimethyl-2-oxo-nicotinonitrile (3g, 0.02mole) was dissolved in dry DMF and stirred for 15 min. Potassium carbonate (2.76 g, 0.02 mole) was added and stirring continued for 2 h. 1,2-Bis-bromomethyl-benzene (2.64 g, 0.01 mole) was added and reaction continued for 15 h. Completion of reaction was monitored through TLC. DMF was removed through rotary evaporator and residue was extracted by chloroform: water (1:1) (3 x 100 ml) Organic layer was dried with anhydrous sodium sulfate and TLC was monitored for purity showing the presence of three compounds. Compounds were purified by column chromatography (EtOAc:Hexane). M.p.180-182 °C; Yield: 1.49 g (37.43%); ¹H NMR (CDCl₃, 300 MHz): δ 2.40 (s, 3H, CH₃), δ 2.42 (s, 3H, CH₃), δ 2.44 (s, 3H, CH₃), δ 2.50 (s, 3H, CH₃), δ 5.55 (s, 2H, CH₂), δ 5.57 (s, 2H, CH₂), δ 6.11 (s, 1H, HetArCH), δ 6.73 (s, 1H, HetArCH), δ 7.26 (d, 2H, J = 6.0, ArCH), ¹³C NMR (CDCl₃, 300 MHz): δ 20.01 (CH₃), δ 20.98 (CH₃), δ 21.22 (CH₃), δ 24.55 (CH₃), δ 45.35 (NCH₂), δ 67.09 (OCH₂), δ 93.76 (CCN), δ 101.47 (CCN), δ 109.54 (CN), δ 115.00 (CN), δ 115.34 (HetArCH), δ 118.05 (HetArCH), δ 124.28 (ArCH), δ 127.50 (ArCH), δ 129.43 (ArCH), δ 131.06 (CCH₃), δ 132.91 (NCH₂-C), δ 134.84 (OCH₂-C), δ 151.85 (CCH₃), δ 154.54 (CCH₃), δ 158.49 (CCH₃), δ 160.97 (C-O-C), δ 163.20 (C=O), IR (KBr, Cm⁻¹): 698-869 (CH bending), 1156 (COC stretching), 1419-1598(C=C stretching), 1653 (C=O stretching), 2219 (CN stretching), 2926-3075 (CH stretching), 3448 (O...H hydrogen bonding); FAB MS: m/z 397 (M+1); Elemental analysis for C₂₄H₂₂N₄O₂: calcd.: C; 72.36 %, H; 5.52 %, N; 14.07 %, Found: C; 72.38 %, H; 5.00 %, N; 14.06 %.

X-Ray crystallography

Diffraction quality crystal of **1** was obtained from a mixture of distilled methanol and ethyl acetate (2:1) by slow evaporation in air in the form of white transparent hexagonal shaped crystals. Unit cell determination and intensity data collection for the compound was performed on a SHELXL-97 (Sheldrick, 1997) detector at 273(2) K equipped with molybdenum sealed tube (0.71073 Å) and highly oriented graphite monochromator. The lattice parameters were obtained by least-square-fit to reflections (1.88°<2θ<27.42°) for compound **1**. All the non-hydrogen atoms were refined anisotropically. The hydrogen atoms were generated in the ideal positions and the parameters were constrained during the refinements. All the relevant information regarding crystal data, data collection and refinements are given below. The visualization of structure and processing were performed using the program MERCURY.

Crystal data and structure refinement **1**

Compound	1
Formula	C ₂₄ H ₂₂ N ₄ O ₂
<i>M</i>	295.32
Crystal system	Monoclinic
T (K)	273(2)
Wavelength (Å)	0.71073
Unit cell dimensions	
a/Å	8.359
b/Å	13.222
c/Å	19.003
α°	90
β°	97.448
γ°	90
V/Å ³	2082.54
<i>Z</i>	5
D _c (Mg/m ³)	1.177
μ/mm	0.081
F (000)	775
Reflections measure	15909
<i>R</i> – Factor (%)	5.5
<i>hkl</i> range	-10 ≤ <i>h</i> ≤ 10 -16 ≤ <i>l</i> ≤ 15 -23 ≤ <i>k</i> ≤ 24

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