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Studies of Inter/intramolecular Weak Interactions with CH···S and S···arene Interaction in Symmetrical and Dissymmetrical Models

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Evidences have proved the versatile role of sulfur atom in supramolecular chemistry.[1] Presence of S atom in the molecule usually results in the specific structural properties of molecules. In the present study, S···arene, N···arene, CH···π, CH···S and CH···N type of weak interactions stabilize the conformation and self assembly of symmetrical as well as dissymmetrical molecules.

Key Words: Intermolecular interaction, Intramolecular interaction, Weak interactions, Self assembly, Substituent effect

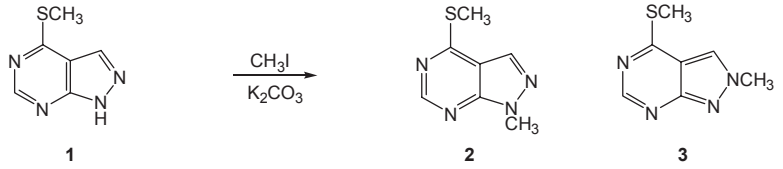
Introduction

Interaction between aromatic rings can influence the stereochemistry of organic reactions[2], protein stability,[3] and chemistry of nucleic acids.[4] These interactions play a vital role in chemistry[5] and biology.[3] As about 20% amino acids[6] are aromatic in nature, the role of aromatic interactions becomes prominent in drug receptor interactions.[7] Although studies of π-π interaction started over last decades, they are still being actively investigated. However, at present, these processes are poorly understood.[8] Off set geometry is the most common geometry for arene interactions, but the least studied.[9] According to electrostatic model of interaction, it has been suggested that electron withdrawing substituents on the aromatic ring can favor edge-tilted T conformation in benzene rings.[10] Polymethylene linked nucleic acid bases were first synthesized by Leonard and co workers for detecting the intramolecular stacking interactions.[11] The importance of trimethylene bridge as synthetic spacer for the detection of intramolecular interactions has been well documented.[12] The synthesis and X-ray studies of a variety of novel purinophanes have been described,[13] where two adenine rings are joined together by two or more polymethylene chains. Various purine and pyrimidine based models evidently forms "stacks" due to presence of weak interactions.[14-16]

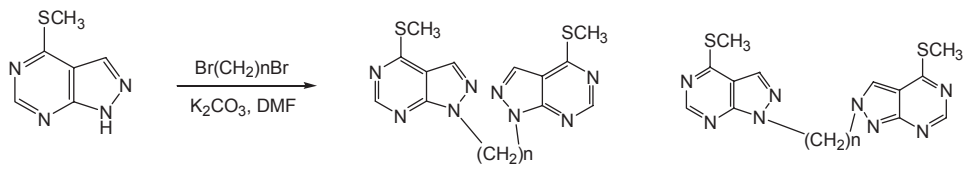
Various other derivatives with stacked geometry have been synthesized by replacing the substituents at position 4.[17-22] Aforementioned studies prompted us to synthesized 4-SCH_3 substituted pyrazolo[3,4-*d*]pyrimidine based polymethylene linked flexible models. In solution state, studies have been carried out by NMR and circular dichroism spectra and in solid state by X-ray crystallography.

Result and Discussion

As degree of freedom of molecules in solution state remains free, there is an immediate possibility that molecule may adopt



Scheme 1



Scheme 2

Table 1. ^{1}H NMR data of monomers and dimers

Protons	**2**	**3**	**4**	**5**	**6**	**7**
δ SCH_3	2.72	3.37	2.69	2.72	2.66, 2.70	2.73
δ H6	8.04	7.74	7.92	8.02	7.76, 8.03	8.07, 8.12
δ H3	8.72	8.86	8.55	8.59	8.60, 8.76	8.72, 8.79

Table 2. Concentration variable ^{1}H NMR data of molecule **4**, **5**, **6** and **7**

concentration (mg/ml)	4			5			6			7		
	δ SCH_3	δH3	δH6	δ SCH_3	δH3	δH6	δ SCH_3	δH3	δH6	δ SCH_3	δH3	δH6
5	2.62, 2.72	7.92	8.55	2.65, 2.67	7.98	8.52	2.66, 2.70	7.77, 8.04	8.60, 8.77	2.74, 2.75	8.06, 8.18	8.75, 8.78
10	2.61, 2.65	7.85	8.48	2.64, 2.67	7.95	8.52	2.67	7.77, 8.04	8.66, 8.77	2.72, 2.75	8.05, 8.13	8.74, 8.78
20	2.61, 2.64	7.84	8.48	2.64, 2.67	7.94	8.52	2.66, 2.70	7.77, 8.03	8.59, 8.76	2.79	8.03, 8.15	8.71, 8.71
40	2.59, 2.62	7.83	8.46	2.63, 2.65	7.94	8.51	2.66, 2.70	7.77, 8.03	8.59, 8.76	2.64	7.90, 8.03	8.66, 8.78

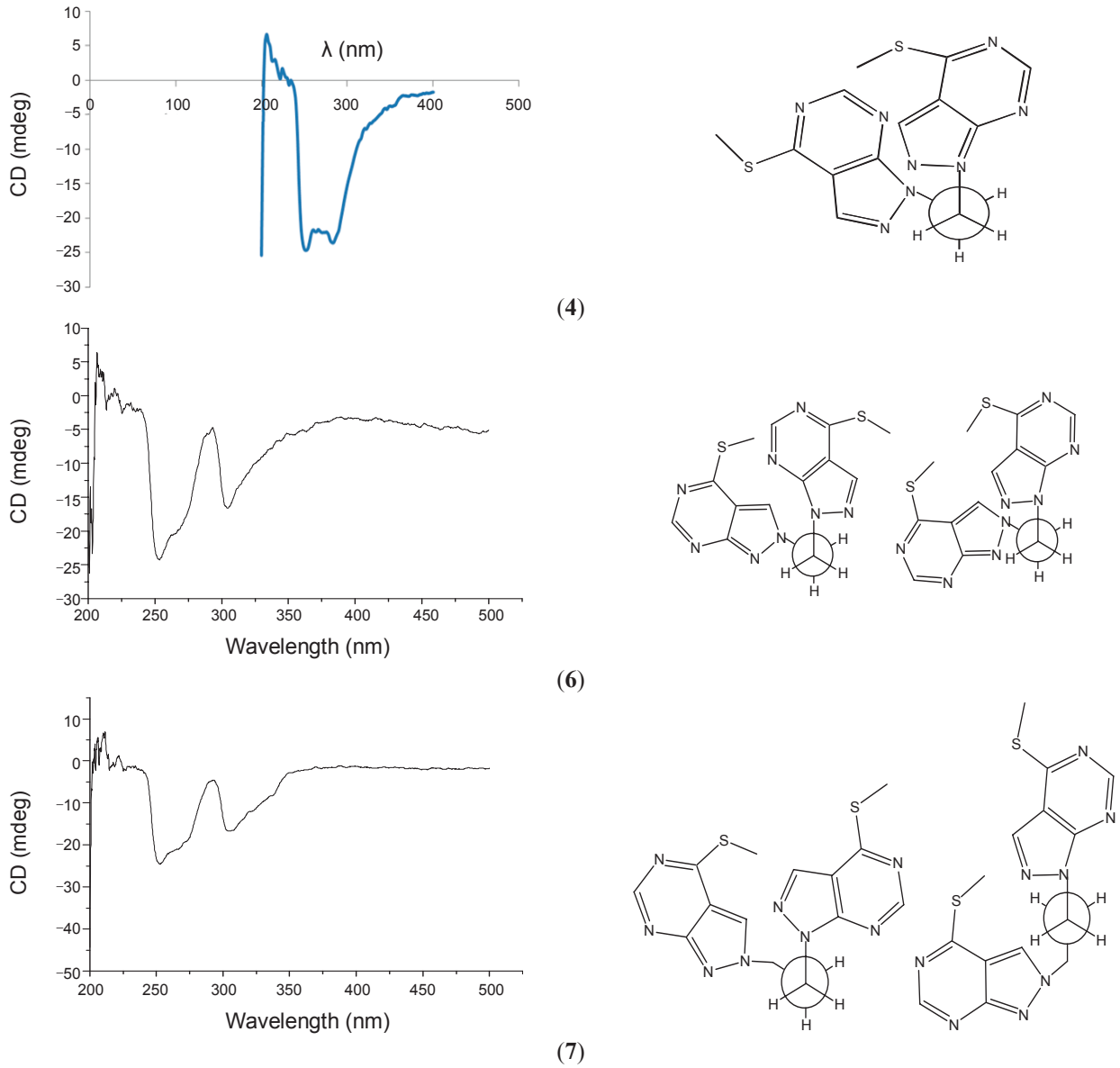


Figure 1. CD spectrum and proposed conformation of molecule **4**, **6** and **7**, respectively.

Table 3. Crystal data, data collection and structure refinement for **5**

Molecule	**5**
Empirical Formula	$C_{15}H_{16}N_8S_2$
Formula Weight	372.48
Crystal System	Monoclinic
Space Group	*C*2/*c*
Unit cell dimensions	
a (Å)	30.830(3)
b (Å)	7.1546(6)
c (Å)	7.7907(7)
α (°)	90.00
β (°)	99.9890(10)
γ (°)	90.00
Cell Volume, V (A^{03})	1692.4(3)
Z, Z'	Z: 4 Z': 0
R Factor (%)	3.46
μ (mm^{-1})	0.332
T (K)	273(2)
D (Mg/m^3)	1.462
F(000)	776
hkl Range	$-35 \le h \le 36$
	$-8 \le k \le 8$
	$-9 \le l \le 9$

folded conformation. However, in solid state, molecule exists in one stable conformation. In present strategy, solution state ^{1}H NMR spectra of dimers show the presence of intramolecular folding pattern, when compared with that of their monomeric molecules (Table 1). Upfield shifts of 0.12 and 0.17 ppm were observed in heteroaromatic protons (H3 and H6, respectively) of molecule **4** as compared to that of molecule **2**. Upfield shifts were observed in SMe (0.67 ppm), H3 (0.28 ppm) and H6 (0.12 and 0.10 ppm) protons of molecule **6**, when compared with molecules **2** and **3**. Presence of upfield shift of 0.54 ppm (SMe) and 0.07 ppm (H6 proton) in ^{1}H NMR spectra also supports the folding pattern in molecule **7**. However, down field shifts of 0.03 and 0.38 ppm in H3 protons indicate presence of intra molecular interaction. Presence of intermolecular interactions in molecules has been studied by concentration variable ^{1}H NMR[23] spectra.

Earlier studies on adenine bases confirmed that tendency to form supramolecular aggregates increases with an increase in concentration due to intermolecular interaction. However, effect of change in concentration on CH_2 protons in poly methylene linkers is not much considerable.[24] The effect of concentration on SCH_3, H6, H3 protons is evident in the present study. SCH_3 proton participated to form CH···S type of weak intermolecular hydrogen bond. In case of molecule 4 and 5, the methysulfanyl protons shifted upfield with an increase in concentration. However, slight changes were observed in molecule 6 and 7. In case of molecule 4 and 7, heteroaromatic H3 and H6 protons shifted maximum upfield than that of molecule 5 and 6 showing that possibility of intermolecular interaction in these cases are prominent. All data of concentration variable NMR are summarized in Table 2.

The molecular nature was helical due to presence of weak

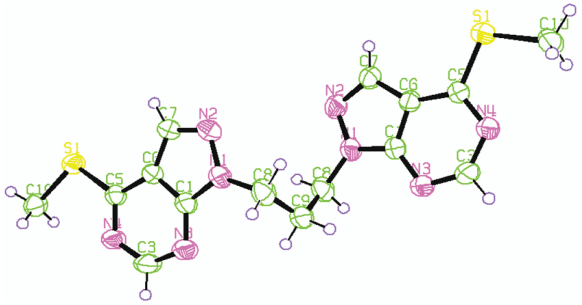


Figure 2. An ORTEP diagram of the molecular conformation of **5** together with the atom numbering scheme.

Table 4. Hydrogen-bonding geometry (Å and deg) for **5**

D-H···A	d (D-H)	d (H···A)	d (D····A)	< (DHA)
CH9A····N3	0.97	2.73	3.33	45.09
CH8A····N3	0.97	2.98	3.03	77.60
CH8B····N1	0.97	2.50	1.45	108.98
CH7····S1	1.79	3.30	3.42	74.72

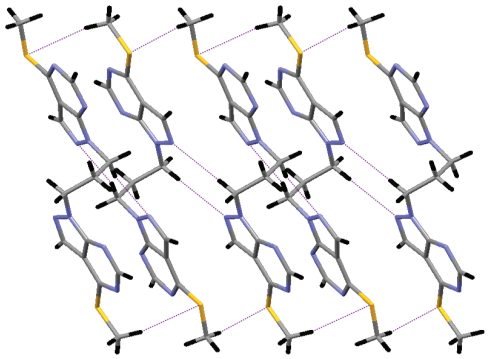


Figure 3. The molecule **5** linked in a layer manner *via* CH···S and CH···N interaction.

interactions which stabilized their conformational properties. Negative cotton effect (CE) in CD spectrum of molecule 4, 6 and 7 confirms the presence of negative torsion angle with ***M*** - helical conformation in solution state. Negative CE also reveals the presence of anti conformation. However, heterocyclic moieties cancel the transition moments of each other making it inactive towards CD. On the basis of results obtained in CD spectrum, we have proposed given conformation for molecule **4**, **6** and **7** in solution state.

We were unable to obtain X-ray quality crystal for all the molecules. However, the X-ray quality crystal of molecule 5 was obtained by slow evaporation in the mixture of ethyl acetate, chloroform and dichloromethane solution (1:1:1). All details of the measurements, crystal data and structure refinement are given in Table 3.

Methyl thio protons possess greater acidity and should form strong hydrogen bonds. The molecule **5** adopts a gauche conformation with an angle of 96.55° between its pyrazolo[3, 4-*d*]pyrimidine residues. In addition, owing to disorder in the 'propylene linker', the angle at the central carbon is usually larger at 115.59° and stabilized by the weak intramolecular CH-N and CH-S interaction (Table 4).

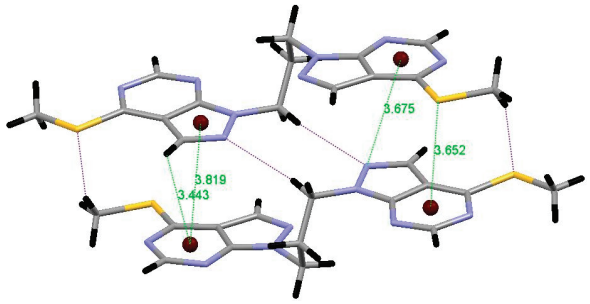


Figure 4. Showing intermolecular CH-π, π-π, N-π and S-arene interaction in molecule **5** in forming building of molecule and in packing mode respectively.

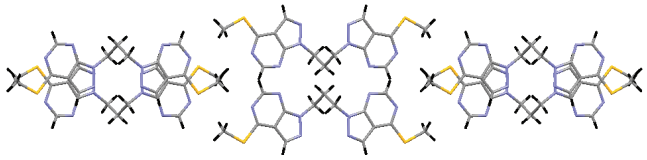


Figure 5. Showing packing mode of molecule **5** showing along c plane.

Centro symmetrical arrangement of molecule is stabilized *via* CH····S and CH····N intermolecular interaction having a distance of 2.88 and 2.69 Å, respectively.

Network of weak hydrogen bonding shows intermolecular arene-arene interactions between five and six membered heterocyclic ring systems with a distance of 3.819A,° whereas S··· arene and N···arene interactions were having a distance of 3.65 and 3.67A,° respectively. CH···π interaction also stabilized the intermolecular self assembly with a distance of 3.44 A°.

In the packing of molecule, six molecules were observed in one cell. Out of these, outer four in the pair of two stabilized the structure *via* CH···S and CH···N type of weak hydrogen bond along with S···arene and N···arene interaction. These have not been shown by earlier synthesized molecules.

Experimental

Melting points were taken in an electrically heated instrument and were uncorrected. Molecules 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 to120 mesh silica gel G were used for purifying the molecule. IR spectra were recorded on Varian 3100 FT-IR spectrometer. ^{1}H and ^{13}C-NMR spectra were recorded on a JEOL AL 300 MHz FTNMR instrument. NMR data are as follows: chemical shifts δ (in ppm relative to δ_{TMS} = 0), multiplicity, coupling constant J (quoted in hertz, Hz) integration and assignment. Elemental analysis of molecules has been recorded on a CE- 440 CHN Analyzer. Circular dichroism spectra were recorded on JASCO J-815 in chloroform having 1 mg/mL concentration. Polarimeter spectral data was measured on Autopool III(Serial number 30166), manufactured by Rudolph Research Analytical. Hackettstown. NJ. USA.

Synthesis of 4-methylthio-*N*-methyl-pyrazolo[3,4-*d*]pyrimidine (2). In a 100 mL R. B. flask, 4-methylthio-1*H*-pyrazolo [3,4-*d*]pyrimidine (1 g, 0.006 moles) was dissolved in dry DMF and stirred for 15 min. anhy. Potassium carbonate (0.83 g, 0.006 moles) was added to the stirring reaction mixture for 2 h. Methyl iodide (0.4 mL, 0.006 moles) was added in it and stirring continued over night in an ice bath. Completion of reaction was monitored by TLC (EtOAc: hexane). DMF was removed under rotary evaporator and residue was extracted with chloroform: water (1:1) (2 × 50 mL). The organic layer was dried with anhydrous sodium sulfate and was evaporated. Column chromatography was done for obtaining the molecule. At 5% EtOAc: hexane the titled molecule was obtained. Recrystallized the molecule with EtOAc. mp 99 °C; Yield: 0.12 g (11.8%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.72 (s, 3H, SCH_3), δ 4.09 (s, 3H, NCH_3), δ 8.04 (s, 1H, HetArCH3), δ 8.72 (s, 1H, HetArCH6), ^{13}C NMR ($CDCl_3$, 300 MHz); δ 11.83 (SCH_3), δ 33.96 (NCH_3), δ 112.19 (CCH), δ 131.16 (ArCH3), δ 150.83 (CN), δ 154.04 (ArCH6), δ 165.68 ($CSCH_3$); FAB MS 182 (M+2); Elemental analysis for $C_7H_8N_4S$: calcd: C; 46.66%, H; 4.44 %, N; 31.11%, Found: C; 46.65%, H; 4.42%, N; 31.15%.

Synthesis of 4-methylthio-*N*-methyl-2*H*-pyrazolo[3,4-*d*]pyrimidine (3). The isomer obtained under above reaction by column chromatography at 20% EtOAc: hexane was characterized as title molecule. mp 95 °C; yield: 0.05 g (5%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.37 (s, 3H, SCH_3), δ 3.89 (s, 3H, NCH_3), δ 7.74 (s, 1H, HetArCH3), δ 8.86 (s, 1H, HetArCH6), ^{13}C NMR ($CDCl_3$, 300 MHz); δ 11.95 (SCH_3), δ 41.07 (NCH_3), δ 112.00 (CCH), δ 124.19 (ArCH3), δ 154.62 (ArCH6), δ 156.96 (NCN), δ 167.94 ($CSCH_3$); FAB MS 182 (M+2); Elemental analysis for $C_7H_8N_4S$: calcd: C; 46.66%, H; 4.44%, N; 31.11%, Found: C; 46.67%, H; 4.45%, N; 31.10%.

General synthesis of dibromoalkane linked regioisomers of 4-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine. In a 100 mL R.B. flask, 4-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidine (2.0 g, 0.012 moles) was dissolved in dry DMF and stirred for 15 min. In it anhydrous potassium carbonate (1.66 g, 0.012 moles) was added and stirred for 2 hr. Dibromo alkane (0.006 moles) was added in it and left for over night stirring. Completion of reaction was monitored through TLC. DMF was removed through rotary evaporator and residue was extracted by chloroform: water (1:1) (3 × 100 mL). Organic layer was dried with anhydrous sodium sulfate and TLC was monitored for purity showing the presence of two molecules. Molecules were purified by column chromatography (EtOAc:hexane). In case of dimethylene linker two different isomers were isolated, where as in trimethylene linker three regioisomers were obtained. Molecule obtained at 20% EtOAc: hexane was symmetrically linked (4, 5) while at 50% EtOAc: hexane unsymmetrical isomers (6, 7) were obtained. Each isomer was characterized by spectral data given below:

1,2-Bis (4-methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl) ethane (4): mp 150 °C; yield: 0.41 g (23%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.69 (s, 6H, SCH_3), δ 4.95 (t, 4H, CH_2, J = 6), δ 7.92 (s, 2H, HetArCH3), δ 8.55 (s, 2H, HetArCH6), ^{13}C NMR ($CDCl_3$, 300 MHz); δ11.83 (SCH_3), δ 46.48 (CH_2), δ 112.27 (CCH), δ 131.88 (ArCH3), δ 153.97 (ArCH6), δ 151.19 (NCN), δ 165.59 ($CSCH_3$); IR (KBr, cm^{-1}); 666-860 (CH bending), 1350 (CN stretching), 156-1652 (C=C, aromatic stretching), 2855-3081 (CH stretching); FAB MS 360 (M+2); Elemental analysis for $C_{14}H_{14}N_8S_2$: calcd: C; 46.92%, H; 3.91%, N; 31.28%, Found:

C; 46.90%, H; 3.92%, N; 31.27%.

1,3-Bis (4-methylthio-1*H*- pyrazolo[3,4-*d*]pyrimidin-1-yl) propane (5): mp 222 °C; yield: 0.45 (24.3%); ^{1}H NMR ($CDCl_3$, 300 MHz); δ 2.65 (q, 2H, CH_2, J = 6), δ 2.72 (s, 6H, SCH_3), δ 4.49 (t, 4H, CH_2, J = 6), δ 8.02 (s, 2H, HetArCH3), δ 8.59 (s, 2H, HetArCH6), ^{T3}C NMR ($CDCl_3$, 300 MHz); δ 11.88 (SCH_3), δ 28.95 (CH_2), δ 44.47 (NCH_2), δ 112.27 (CCH), δ 131.59 (ArCH3), δ 150.81 (NCN), δ 153.91 (ArCH6), δ 165.68 ($CSCH_3$); IR (KBr, cm^{-1}); 668-872 (CH bending), 1345 (CN stretching), 1568-1649 (C=C, aromatic stretching), 2856-3078 (CH stretching); FAB MS 374 (M+2); Elemental analysis for $C_{15}H_{16}N_8S_2$: calcd: C; 48.38%, H; 4.30%, N; 31.10%, Found: C; 48.39%, H; 4.28%, N; 31.00%.

1(4-Methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-2-(4-methylthio-1*H*-pyrazolo[3,4-*d*] pyrimidin-1-yl) ethane (6): mp 110 °C; yield: 0.46 g (26%); ^{1}H NMR ($CDCl_3$, 300 MHz); δ 2.66 (s, 3H, SCH_3), δ 2.70 (s, 3H, SCH_3), δ 4.99 (t, 2H, CH_2, J = 6), δ 5.05 (t, 2H, CH_2, J = 6), δ 7.76 (s, 1H, HetArCH3), δ 8.03 (s, 1H, HetArCH3), δ 8.60 (s, 1H, HetArCH6), δ 8.76 (s, 1H, HetArCH6); ^{13}C NMR ($CDCl_3$, 300 MHz); δ 11.89 (SCH_3), δ 46.72 (N^1CH_2), δ 52.82 (N^2CH_2), δ 123.82 (CCH), δ 132.37 (HetArCH3), δ 154.30 (NCN), δ 154.80 (HetArCH6), δ 166.03 ($CSCH_3$); IR (KBr, cm^{-1}); 671-949 (CH bending), 1348 (CN stretching), 1457-1559 (C=C, aromatic stretching), 2853-3088 (CH stretching); FAB MS 360 (M+2); Elemental analysis for $C_{14}H_{14}N_8S_2$: calcd: C; 46.92%, H; 3.91%, N; 31.28%, Found: C; 46.93%, H; 3.90%, N; 31.29%.

1(4-Methylthio-1*H*-pyrazolo[3,4-*d*]pyrimidin-1-yl)-3-(4-methylthio-1*H*-pyrazolo[3, 4-*d*] pyrimidin-1-yl) propane (7): mp 224 °C; Yield: 0.29 g (15.6%); ^{1}H NMR ($CDCl_3$, 300 MHz); δ 2.72 (q, 2H, CH_2, J = 6), δ 2.73 (s, 6H, SCH_3), δ 4.41 (t, 2H, CH_2, J = 6), δ 4.46 (t, 2H, CH_2, J = 6), δ 8.07 (s, 1H, HetArCH3), δ 8.12 (s, 1H, HetArCH3), δ 8.72 (s, 1H, HetArCH6), δ 8.79 (s, 1H, HetArCH6); ^{13}C NMR ($CDCl_3$, 300 MHz); δ 11.56 (SCH_3), δ 29.08 (CH_2), δ 43.98 (N^1CH_2), δ 50.95 (N^2CH_2), δ 125.40 (CCH), δ 131.58 (HetArCH3), δ 151.34 (NCN), δ 153.82 (HetArCH6), δ 167.01 ($CSCH_3$); IR (KBr, cm^{-1}); 549-950 (CH bending), 1350 (CN stretching), 1402-1558 (C=C, aromatic stretching), 2854-3085 (CH stretching); FAB MS 374 (M+2); Elemental analysis for $C_{15}H_{16}N_8S_2$: calcd: C; 48.38%, H; 4.30%, N; 31.10%, Found: C; 48.36%, H; 4.29%, N; 31.15%.

Conclusion

In solution state, NMR spectra indicate the presence of folded structure and CD spectra indicate that presence of weak interactions which stabilized the helical nature of molecules. Moreover, sulfur atom plays an important role in packing of molecular network in solid state. Both intra as well as intermolecular weak interactions were present in the molecule, which stabilized the conformation in solution as well as solid state.

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Supporting Information Available. All NMR data and CIF information of molecules are available on request from the correspondence author (rashmibhu8@yahoo.com).

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