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Observation of a reversible Isomorphous Phase Transtion and an interplay of "σ-hole" and "π-hole" in Fmoc-Leu-ψ[CH$_2$-NCS]

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Fmoc–Leu–ψ[CH$_2$NCS], undergoes a reversible isomorphous phase transition upon cooling. The crystal structure at 100K displays a short N=C=S···N=C=S intermolecular interaction,
10 **which has been characterized based on experimental charge density analysis as a stabilizing interaction with both σ-hole and π-hole acting cooperatively.**

In recent years, it has been demonstrated that bioactive peptides when replaced with unnatural bonds in place of peptide bonds
15 show enhanced pharmacokinetic properties.[1, 2] In this context, organic isothiocyanates, which are versatile synthetic intermediates, have been subjected to extensive structure property correlation studies.[3] Though isothiocyanates are known to readily participate in nucleophilic addition and cycloadddition reactions
20 owing to their high electrophilicity, quantitative analysis of interactions involving isothiocyanate moiety in crystal structures have received very little attention. Interestingly, crystal structures of several thiocyanates (–SCN), isomers of isothiocyanates (–NCS), have been explored during the early days of experimental
25 and theoretical charge density analysis [4-6] to understand the features of non-covalent interactions involving the –SCN moiety. Some of the well studied non-covalent interactions in biological molecules are hydrogen bonding, π–π stacking, cation–π interactions, while anion–π and more generally the lone pair–π
30 interactions and halogen bonding are the new entrants. Halogen bonding is a subset of σ hole bonding which explains the anomaly of an electronegative halogen interacting attractively with a negative site on the same or another molecular system. The concept of σ-hole was invoked to describe the extension of a
35 covalent bond of an atom (group iv-vii of the periodic table) and its counterpart, π-hole, describes the region of positive electrostatic potential perpendicular to a portion of the molecular framework.[7, 8] Both σ-hole and π-hole are highly directional and the structural studies of N$_\beta$ Fmoc protected β amino alkyl
40 isothiocyanates {Fmoc–X–ψ[CH$_2$NCS] (X=Leu, Ile, Val and Ala)} provide a unique opportunity to investigate the features of the electrostatic potentials associated with the isothiocyanate moiety. Though computational studies on π-hole containing molecules are reported in literature elucidating the nature of π-
45 hole bonding,[9, 10] experimental results have not been studied in detail to the best of our knowledge. However, it may be mentioned that in the experimental charge density maps studied in case of thiocyanates, the deformation density maps did contain

a positive region corresponding to the presence of the π-hole.[4-6]
50 We have studied single crystal structures of four compounds, Fmoc–X–ψ[CH$_2$NCS] (X=Leu, Ile, Val and Ala; Scheme 1; Figure S2).
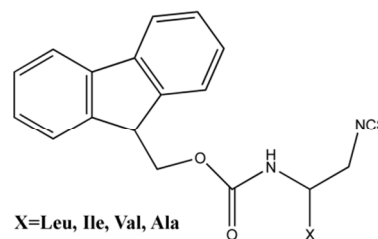
Scheme 1. Structural formula of Fmoc–X–ψ[CH$_2$NCS]

55 Among them, X=Leu, crystallizes in a tetragonal space group, P4$_1$ and displays an isomorphous reversible phase transition[11] upon cooling. The phase transition has been characterized by DSC isotherm, IR spectroscopic measurements and variable temperature cell determinations by single crystal X-ray
60 diffraction. Experimental and theoretical charge density analysis has been carried out to elucidate the nature of interactions involving isothiocyanate group using the data collected at 100K. The other three molecules, (X=Ile, Val, Ala) crystallize in a monoclinic space group, P2$_1$, and show no phase transitions with
65 temperature. It is interesting to note that the fluorene moiety forms edge to face C–H···π contacts in case of X=Leu whereas in the other three structures, face to face π···π contacts are observed. This ensures that in case X=Leu where the N=C=S moieties are perpendicular to each other whereas the N=C=S moieties are
70 parallel to each other in the other three structures (Figure S3). The reversible isomorphous single crystal to single crystal phase transition in Fmoc–Leu–CH$_2$NCS (room temperature P4$_1$, Z'=1 to low temperature P4$_1$, Z'=2) appears sharply at 230K. A variable temperature unit cell determination over the temperature
75 range of 290-100K at intervals of 10K depicts the evolution of cell parameters as shown in Figure 1. The transition at 230K is very clearly indicated. It is to be noted that during the cooling cycle, at the transition temperature, *a* axis increases by 41.4% (Δ*a*/*a*), which is equivalent to an increase of √2*a* (diagonal to the
80 original lattice) whereas *c* axis remains almost unchanged. During the heating cycle the cell dimension 'a' reverts to the original value, thus justifying the isomorphous nature of the

phase transition. In addition, the doubling of the unit cell volume causes a minor rearrangement in the conformation of the molecules (one rotated by nearly 6° with respect to the other) and reverts to the original Z'=1 structure on heating beyond 230K.

5 Figure 2 represents both these features. The sharp jump in '*a*' axis and volume of the unit cell at the transition temperature is suggestive of a first order phase transition.
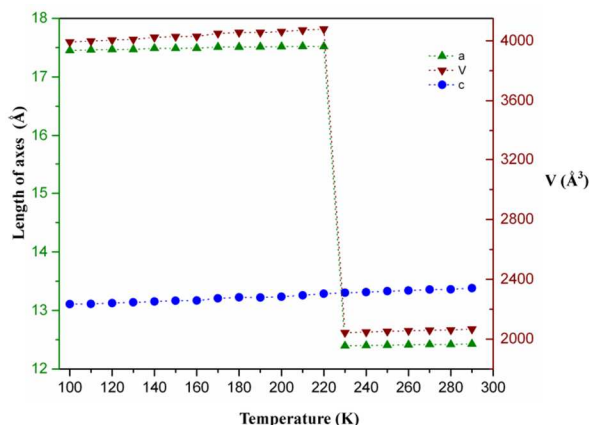

Fig. 1 Temperature dependence of the unit cell parameters, a and c axes
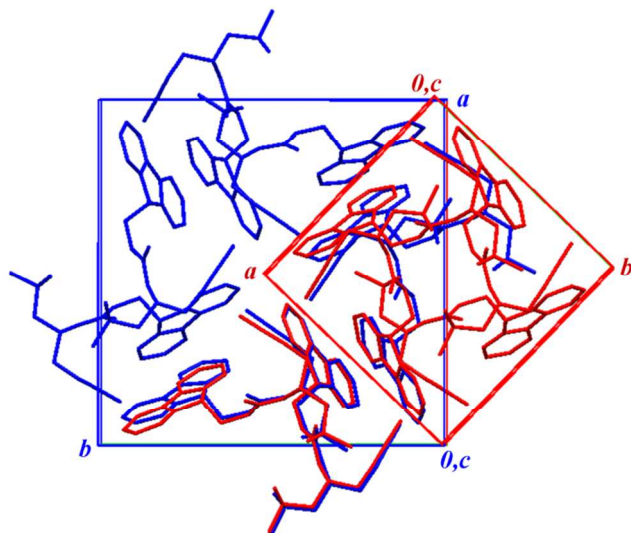10 and Volume (V); sharp jump in a and V is observed at the transition temperature.

Fig. 2 Overlay diagram of the two forms in tetragonal P4₁ space group, room temp. , Z'=1 (red) and low temp. Z'=2 (blue) along the *c* axis.

15 The phase transition has also been monitored using FT-IR spectroscopy in the solid state. Room temperature spectrum of Fmoc–Leu–CH₂NCS shows strong and very broad absorption with 3 distinct maxima in the range 2050-2200 cm⁻¹ characteristics of NCS asymmetric stretch, ν_{as}(NCS)[12]. The
20 compound was initially cooled to 133K and the spectrum showed almost doubling of the peaks in the ν_{as}(NCS) region, thus supporting the phase transition (Z'=1 to Z'=2) . Further spectra were recorded in the heating cycle in the temperature interval 133-253K (shown in Figure 3 in steps of 10K/min heating rate,
25 eventually reaching the room temperature supporting the isomorphous phase transition (Figure 3).

The approach of the two –NCS groups perpendicular to each other in the crystal structure and thus resulting in formation of a
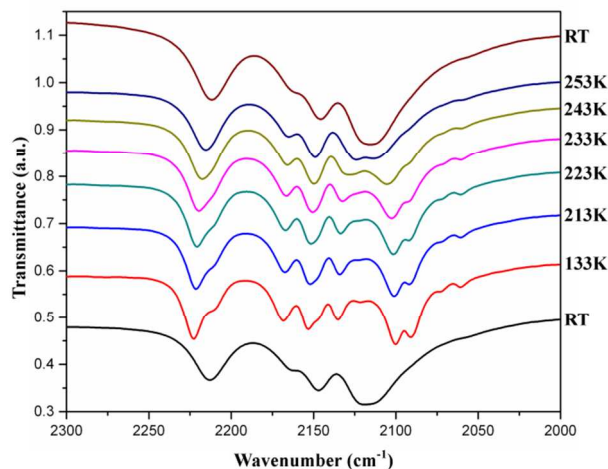

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Fig. 3 Changes in variable temperature IR spectra in the region of ν_{as} (NCS) vibration with temperature.

N=C=S···N=C=S chain along the 4₁ screw axis, prompted us to explore the intermolecular interaction before and after the phase
35 transition. A CSD (v5.35 February 2014) analysis (see ESI) reveals that this particular interaction mode of NCS groups is sparse in case of organic molecules. Early data base studies[13, 14] suggested that electrophiles approach divalent S at approximately 20° from the perpendicular to the plane containing sulfur. It
40 would indicate that the lone pair of electron density associated with the sulfur atom might interact with electropositive region of the approaching NCS group. In the low temperature Z'=2 structure, the two molecules in the asymmetric unit (MOL1 and MOL2) form similar chains of N=C=S···N=C=S contacts with
45 their symmetry equivalent counterparts (Figure 4).
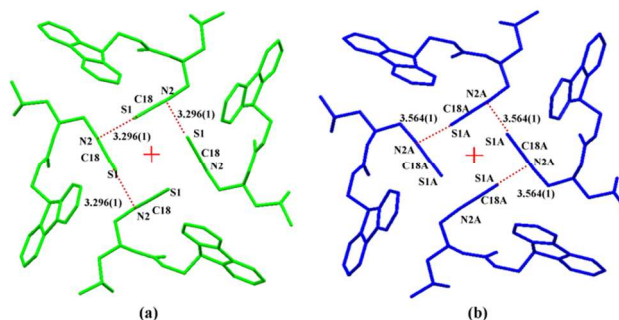
Fig. 4 N=C=S··· N=C=S interactions in (a) MOL1 (green), (b) MOL2 (blue), projection along c axis. '+' (in red) represents the 4₁ screw axis.

The N=C=S···N=C=S interaction length formed by MOL1 and its
50 symmetry equivalent gets shorter (S…N= 3.296(1) Å; Figure 4a) compared to the sum of the van der Waals radii of N and S (3.35Å) and we have analyzed the experimental charge density data (100K, see ESI) to gain insights into this unique interaction.

3D-deformation density($\Delta\rho=\rho_{multipole}-\rho_{spherical}$) maps obtained
55 from experimental and theoretical multipole model depict the presence of both electron rich (blue) and electron deficient regions (red) on S as well as along C=N bond (Figure 5). Topological analysis given in Table 1 reveals the relative strength of this closed-shell interaction based on the ratio of local potential
60 energy density to the kinetic energy density ($|V_{bcp}|/G_{bcp}$) derived

from the ρ(r) and ∇²ρ(r) values. Theoretical electron density properties calculated directly from wave function (TOPOND program as implemented in CRYSTAL14) are also given in Table 1 for comparison.

5 Moreover, the short N=C=S··· N=C=S interaction in MOL1 needs to be analyzed in terms of its property. Electrostatic potential map brings out the features vividly as shown in Figure 6. Electrostatic potential mapped on iso-density surface (0.5 eÅ⁻³) indicates a σ-hole formation on the S atom along the extension of covalent
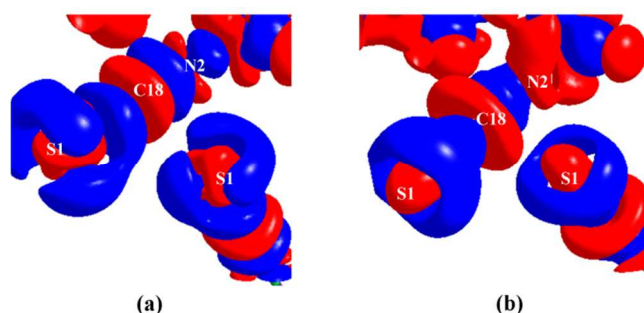10 bond of N=C=S group.

Fig. 5 3D deformation density plots obtained from (a) Experiment and (b) theoretical charge density analysis depicting the NCS region in MOL1.
15 Blue and red represent +ve and −ve values, respectively. The Δρ contours are drawn at ±0.05 eÅ⁻³.

Table 1 Topological parameters of the NCS···NCS interaction[a]

S···N	Rij (Å)	ρ(r) (eÅ⁻³)	∇²ρ(r) (eÅ⁻⁵)	|V|/G	E (kJ/Mol⁻¹)
MOL1	**3.297**	**0.06**	**0.7**	**0.81**	**-3.4**
S1···N2	3.296	0.06	0.7	0.78	-3.3
	3.294	*0.05*	*0.7*	*0.71*	*-3.0*
MOL2	**3.567**	**0.04**	**0.4**	**0.74**	**-3.1**
S1A···N2A	3.573	0.04	0.4	0.72	-3.0
	3.575	*0.03*	*0.4*	*0.67*	*-2.8*

[a] For each interaction first/second/third row represents **experimental**/theoretical multipole/*TOPOND calculated* values.

20

The characteristic of the σ-hole on S1 of MOL1 is clearly more prominent (indicated as blue region on the top surface of S in Figure 6, first row) compared to the corresponding one on S1A of MOL2 (Figure 6, second row). In addition, the electrostatic
25 potential values also suggest a π-hole formation on the C=N bond of the neighboring NCS moiety, as described by Politzer's group.[8, 15] Figure 6 displays an appearance of a "blue" band perpendicular to the C=N bond of the neighboring NCS moiety and thus indicative of a π-hole bonding. The positive σ-hole and
30 π-hole interact cooperatively with the negative sites of the NCS moieties thereby stabilizing the N=C=S··· N=C=S interaction.[15, 16]

Conclusions

The occurrence of both "σ-hole" and "π-hole" in the crystal
35 structure of Fmoc–Leu–ψ[CH₂NCS] brings out the relevance of weak but highly directional interactions to the fore and provides an unique first time experimental verification.
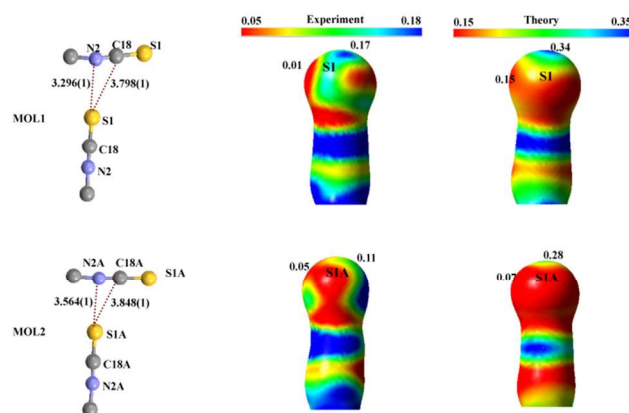

Fig. 6 Electrostatic potential mapped on isodensity surface (0.5 eÅ⁻³),
40 along with the geometrical representation of the C=N=S moiety depicting the characteristics of a σ-hole on S (blue) along the extension of NCS covalent bond and a π-hole (blue) perpendicular to CN bond. First/ second row displays C=N=S moiety for MOL1/ MOL2. Blue and red colours represent +ve and −ve regions, respectively.

Notes and references

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