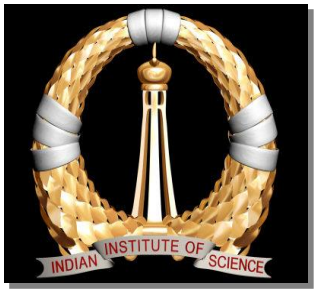


Why polymorphism? An Evaluation using Experimental Charge Densities Analysis

T. N. Guru Row
Solid State and Structural Chemistry Unit
Indian Institute of Science
Bangalore 560012 INDIA
Email: ***ssctng@sscu.iisc.ernet.in***
web: **http://guru.sscu.iisc.ernet.in**

This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

Sponsored by The International Centre for Diffraction Data

PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

Polymorphism issues are resolved primarily using the following:

1. PXRD to see the differences …Profile fit and Rietveld analysis
2. Bulk evaluation… DSC/TGA , FTIR
3. Supporting evidence…Solid state NMR, Raman , microscopy
4. PDF analysis, Charge density (theory and experimental) and CSP
5. Satisfy FDA!!!

Explained in terms of

1. Intra-and inter molecular contacts … Propensity of hydrogen bond
2. Crystal engineering principles…Energy Landscape
3. Interaction energies

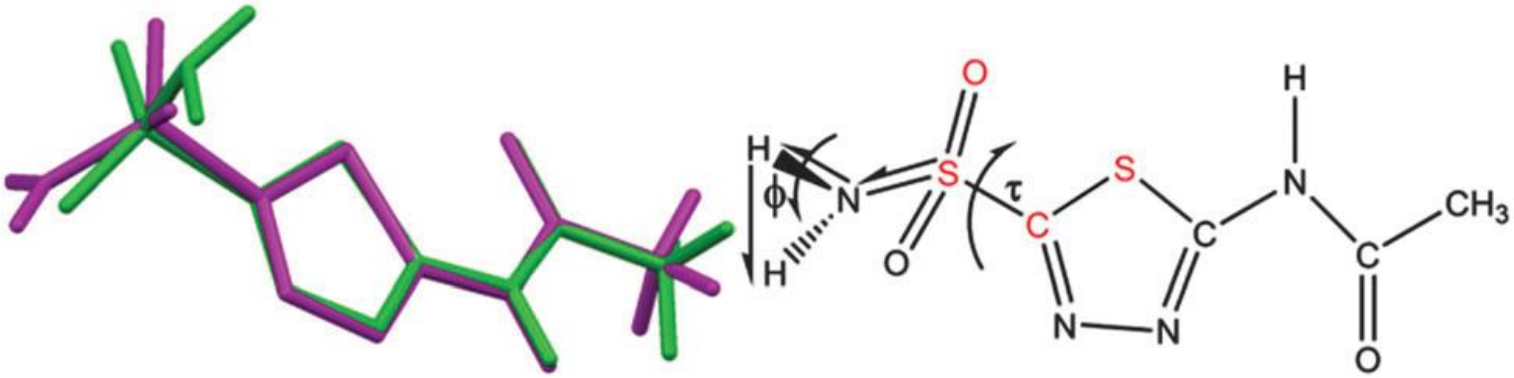
Part 1: A case study resolved by charge density analysis

Part 2: Cocrystallization …Solid Solutions – Charge density route

Case 1: Acetazolamide: a case of hybridization induced polymorphism?

Chem. Commun., 2016, 52, 5820--5823

Slow cooling of boiling aqueous solution of diuretic drug acetazolamide:
The kinetic form instead of the thermodynamic form is formed
Rapid cooling gives the thermodynamically stable form !!??



Overlay diagram of polymorphs I (green; P-1, thermodynamically stable) II (purple; P21/n ; kinetically stable)

The geometry of the NH2 group of the sulphonamide moiety is **pyramidal in I** and **planar in II** reflect different hybridization states for the N atom.

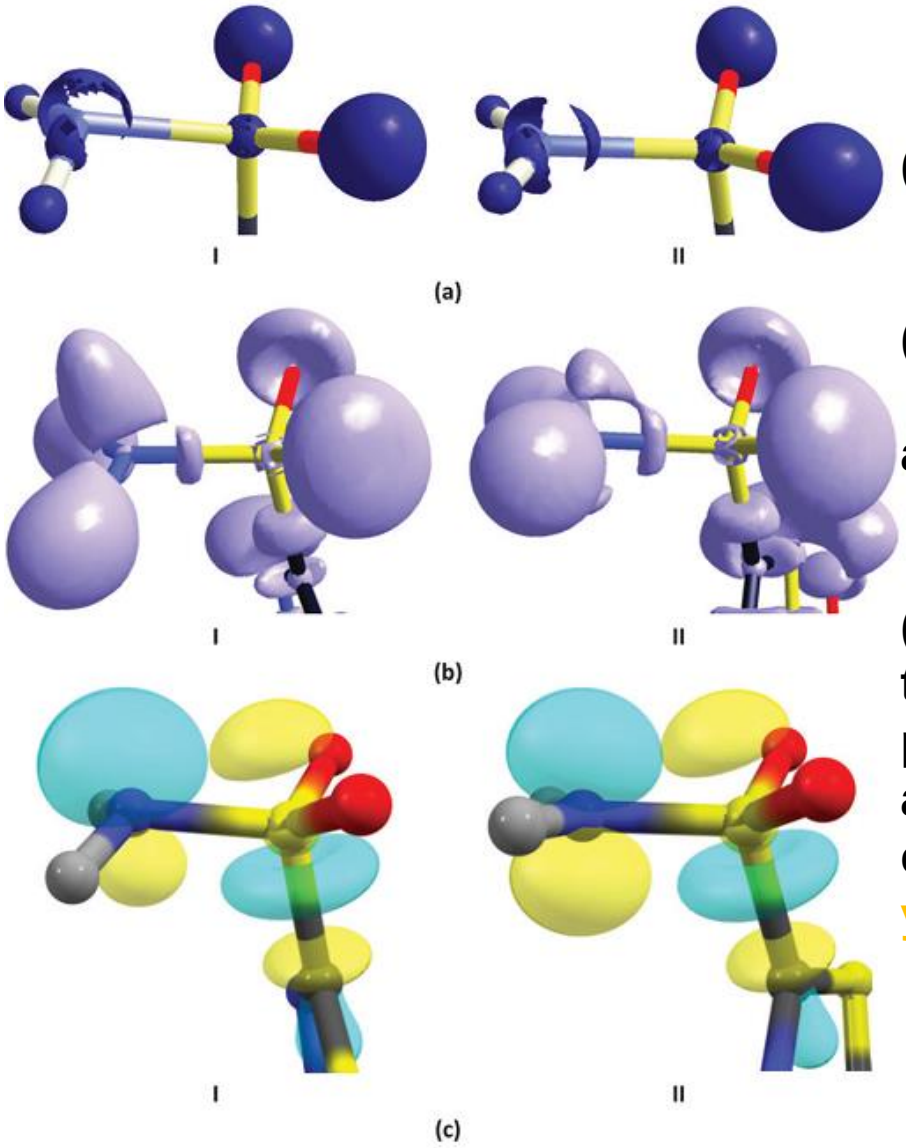
U. J. Griesser, A. Burger and K. Mereiter, J. Pharm. Sci., 1997, 86,352–358.

Questions:

1. **How to ratify the occurrence of the kinetic form on slow cooling as against the thermodynamic form on rapid cooling?**
2. **Why the difference in hybridization ?**
3. **Does the alteration in hybridization and simultaneous change in the S–N bond length and NH2 geometry has any bearing on the manifestation of polymorphism**?

Topological properties of the S–N bond at (3,-1) bcp (Bader's theory of Atoms and Molecules)

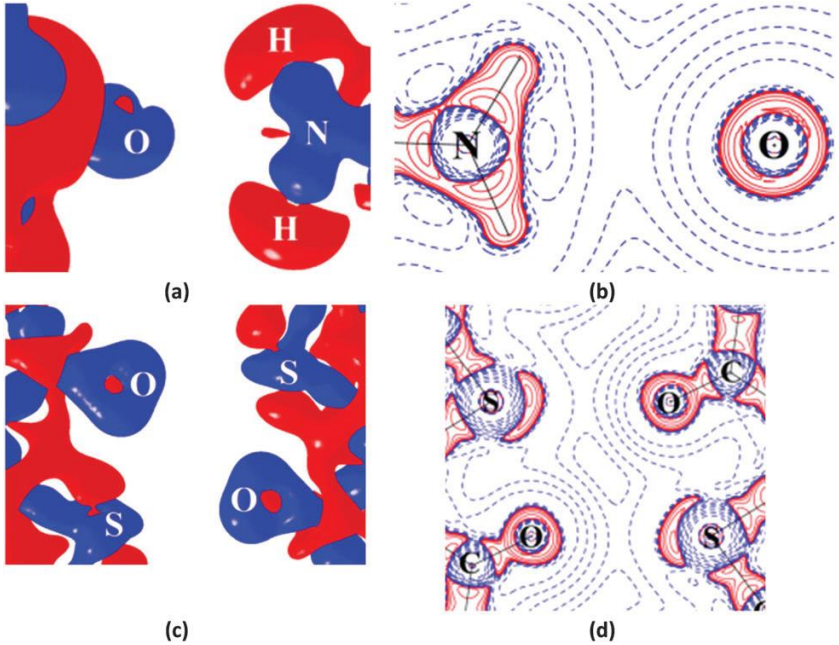
Polymorph	Rij	ρ(e Å-3)	δ2(e Å-5)	ε	Cohesive Energy
I	1.6036	1.866	-16.785	0.17	-254.5 kJ /mol
II	1.5791	2.097	-19.760	0.16	-258kJ/mol



(a) Experimental 3D Laplacian isosurfaces of I and II around the nitrogen atom plotted at-40 e Å $^{-5}$ (Distinct lone pair for I)

(b) 3D ELF surfaces of I and II plotted at an isovalue of 0.85 e Å $^{-3}$ (mono to dysynaptic lone pair)

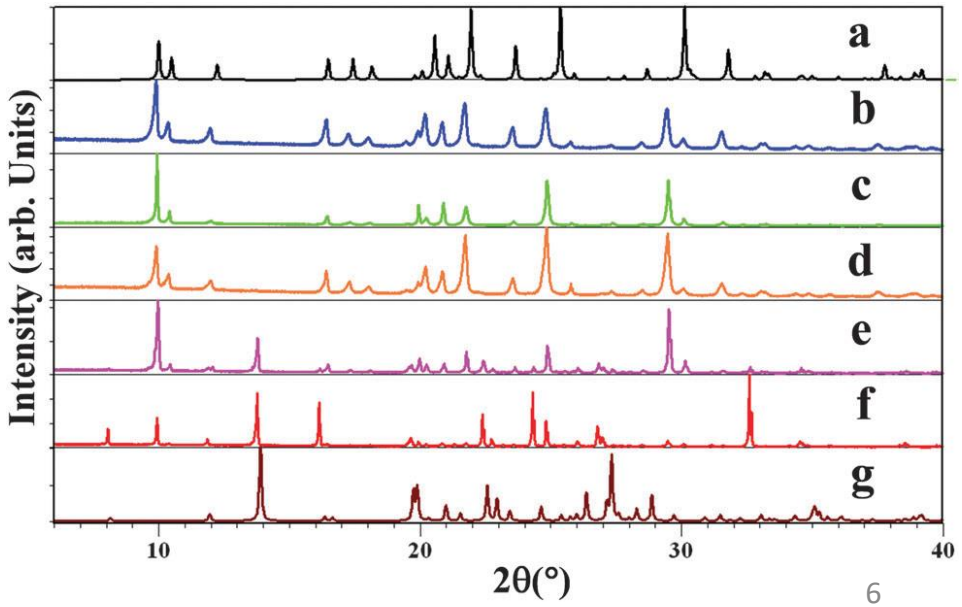
(c) NBO analysis portraying charge-transfer interaction between the lone-pair (LP) orbital of N with the σ* S–C antibonding orbital in I and II. The blue color depicts the positive lobes while yellow color indicates negative lobes.

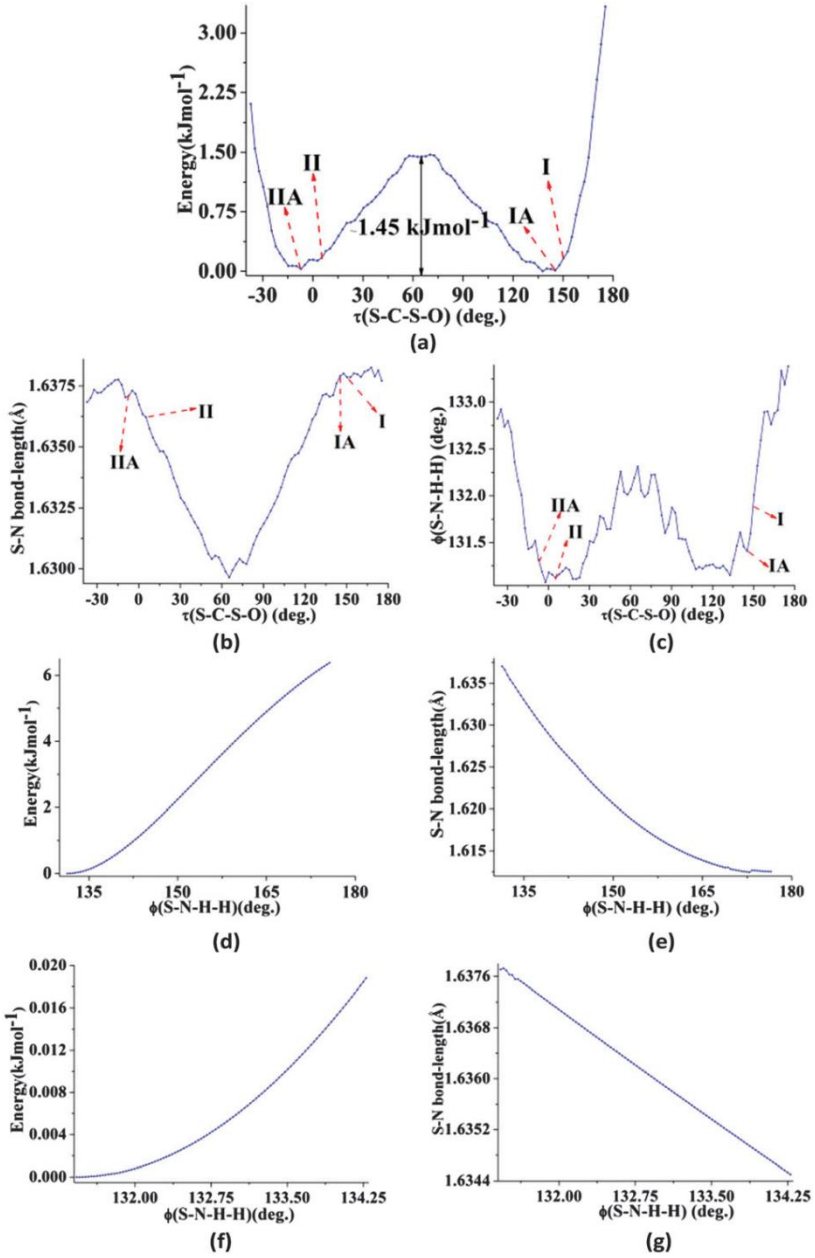


(a) 3D deformation density
(b) 2D Laplacian plot of the N … O pnicogen bond
(c) 3D deformation density and
(d) 2D Laplacian plot of the S O chalcogen interaction region.

Blue represents charge concentration (CC)
Red represents charge depletion (CD) in Deformation (intervals of 0.08 e Å3.
Laplacian is plotted on logarithmic contours where blue and red represent negative and positive contours.

PXRD patterns of AZM crystals obtained from boiling aqueous solution at different rates of cooling:
(a) simulated pattern of I
(b) rapid cooling in liquid nitrogen
(c) ambient cooling
(d) 10 °C/hr ; (e) 7 °C/hr ; (f) 5 °C /hr and (g) simulated pattern of II .



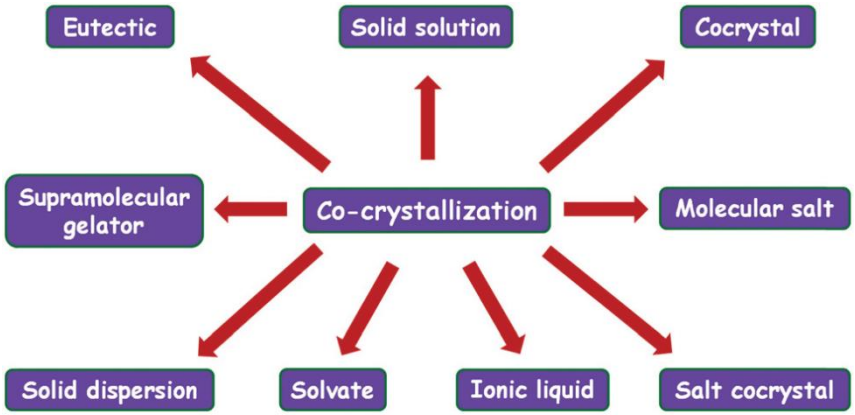


In the case of conformational polymorphism, an energy barrier should separate the gas phase optimized conformers belonging to different potential energy wells. It is thus evident that the occurrence of polymorphism cannot be attributed solely to conformational changes.

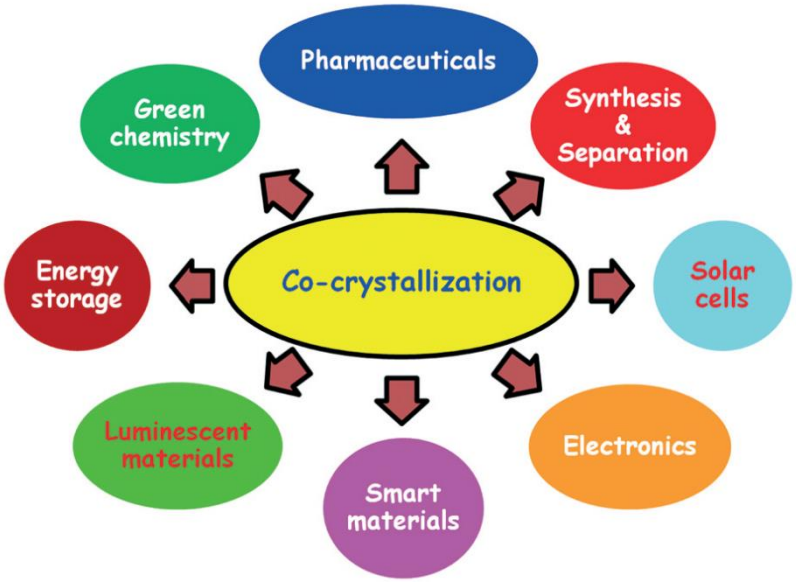
We have unambiguously established the influence of hybridization change on the N atom of the sulphonamide group to result in the polymorphic modifications of AZM.

This is the first-of-its kind study that emphasizes the importance of understanding the subtle molecular level phenomena that dictates polymorphism

Case study 2

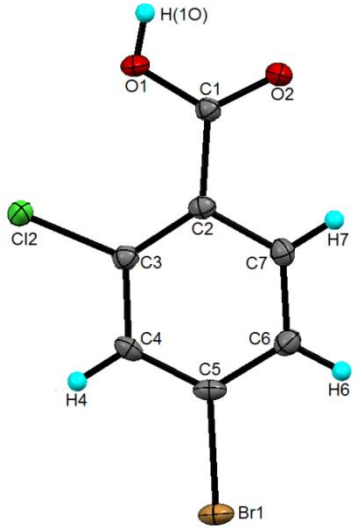


(a)

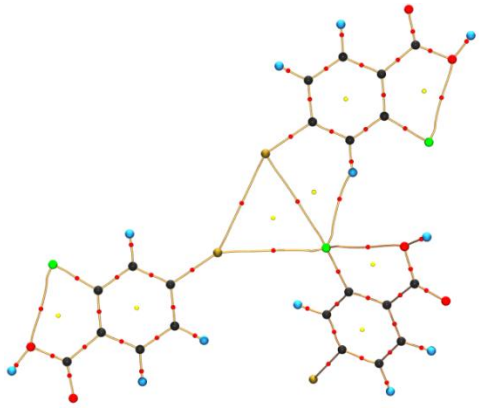


(b)

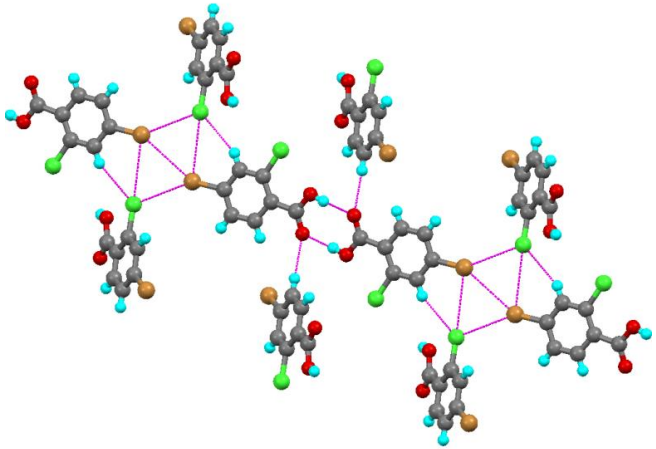
4-bromo-2-chlorobenzoic acid (**4Br**)



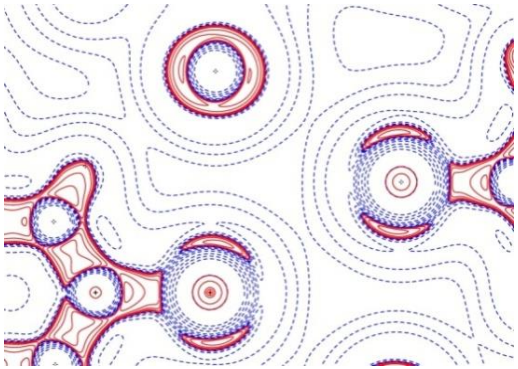
ORTEP diagram



Molecular Graph



Packing motifs

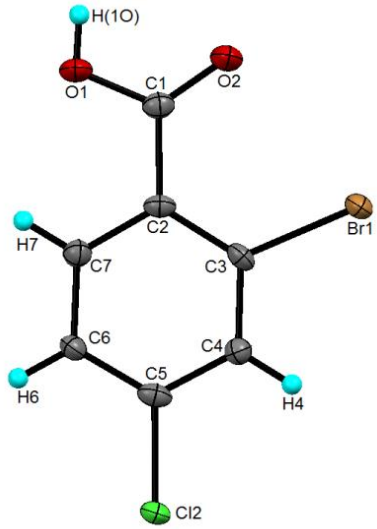


Laplacian plot from TOPOND
plotted on logarithmic contours

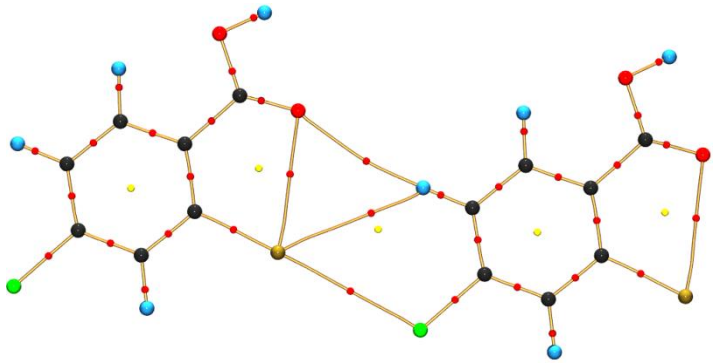
Crystallographic Table	
Space Group	*P*21/n
a (Å)	7.2738(3)
b (Å)	9.0627(3)
C (Å)	11.7233(5)
α (deg.)	90
β (deg.)	102.916(4)
γ (deg.)	90
Vol. (Å-3)	753.25
R_1 [I>2σ(I)]	2.76
Z / Z'	4/1
Δρmin,max (e Å-3)	-0.59, 0.63
CCDC no.	1534999

M. S. Pavan and T. N. G. *Row, J. Chem. Sci.,* 2016, **128**, *1579*

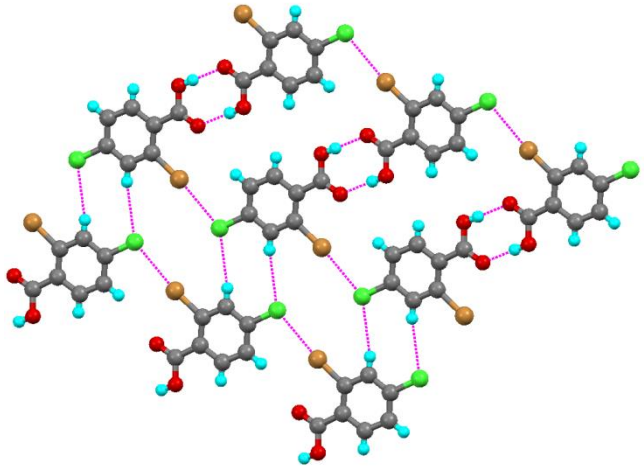
2-bromo-4-chlorobenzoic acid (**2Br**)



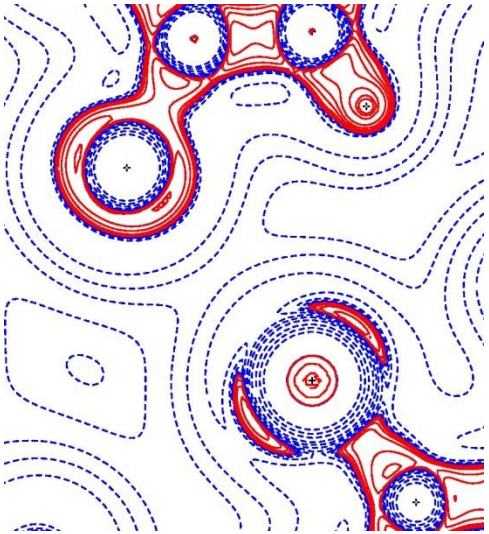
ORTEP diagram



Molecular Graph



Packing motifs

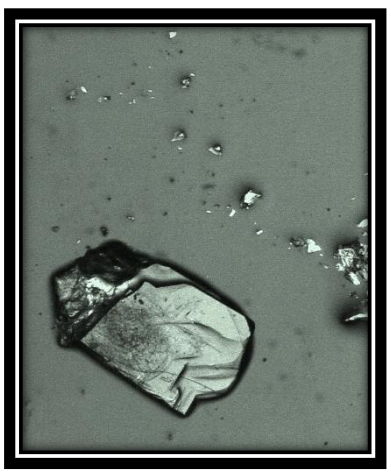


Laplacian plot from TOPOND
plotted on logarithmic contours

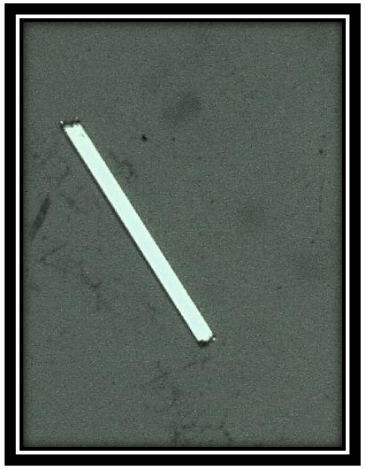
Crystallographic Table	
Space Group	*P*-1
a (Å)	3.8949(3)
b (Å)	8.2939(3)
C (Å)	11.8408(5)
α (deg.)	89.014(3)
β (deg.)	89.991(5)
γ (deg.)	78.651(5)
Vol. (Å-3)	374.967
R_1 [I>2σ(I)]	3.4
Z / Z'	2/1
Δρmin,max (e Å-3)	-0.44, 0.35
CCDC no.	1534998

Topological parameters for intermolecular interactions obtained from TOPOND for 4-bromo-2-chlorobenzoic acid (**4Br**) and 2-bromo-4-chlorobenzoic acid (**2Br**)

		R_{ij} (Å)	ρ (eÅ^{-3})	$\nabla^2\rho$ (eÅ^{-5})	ε	G (kJ mol^{-1}bohr^{-3})	V (kJ mol^{-1}bohr^{-3})	|V|/G	E_{int}(kJ mol^{-1})
4Br	**Br1···Br1**	**3.6673**	**0.05**	**0.46**	**0.03**	**11.0**	**-8.7**	**0.80**	**-4.2**
	Br1···Cl2	**3.7327**	**0.04**	**0.43**	**0.13**	**8.7**	**-6.4**	**0.74**	**-3.5**
	Cl2...Br1	**3.6133**	**0.05**	**0.48**	**0.01**	**11.3**	**-8.7**	**0.79**	**-4.3**
	O2···H1	**1.6455**	**0.32**	**3.38**	**0.01**	**108.1**	**-124.0**	**1.15**	**-62.0**
	Cl2···H4	2.6942	0.06	0.63	0.03	14.3	-11.5	0.80	-5.7
	Br1···C2	3.6099	0.05	0.48	0.70	10.8	-8.6	0.79	-4.3
2Br	**Br1...Cl2**	**3.313**	**0.08**	**0.82**	**0.04**	**19.6**	**-16.9**	**0.86**	**-8.4**
	O2...H1	**1.818**	**0.21**	**3.61**	**0.02**	**88.6**	**-78.7**	**0.89**	**-39.4**
	Cl2...H4	2.967	0.04	0.11	0.03	3.60	-4.08	1.13	-2.04



4Br

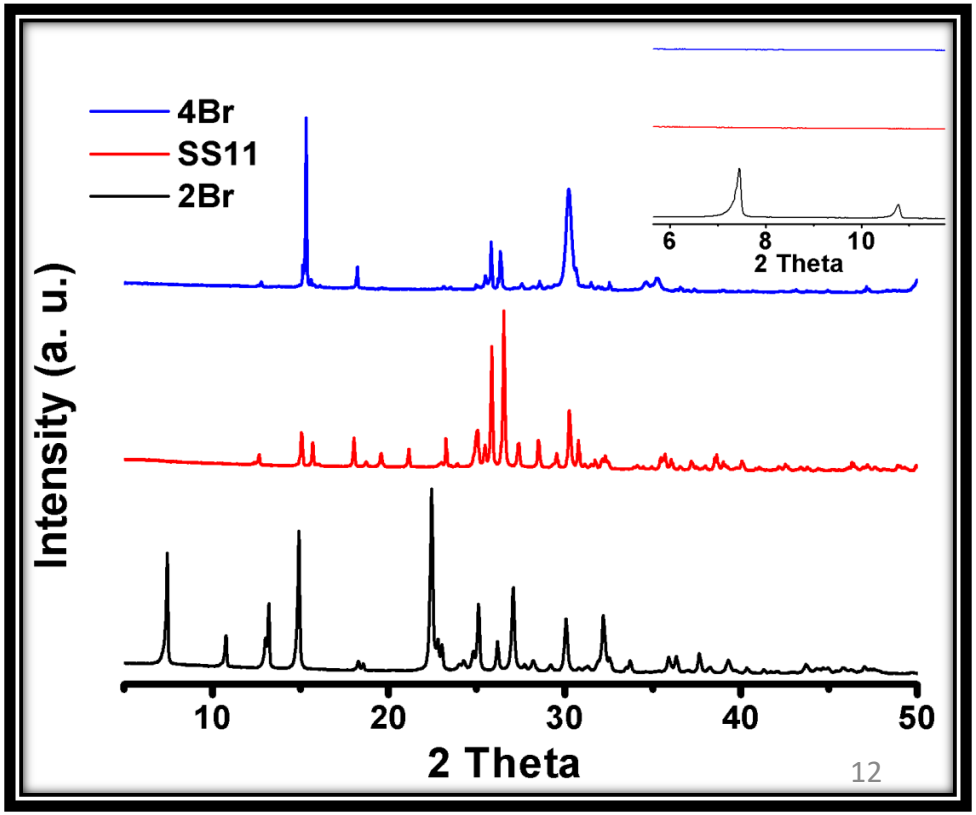


2Br

SS11

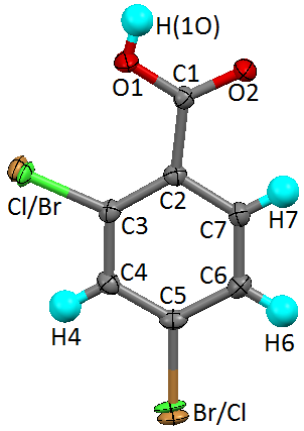
Morphology of single crystals

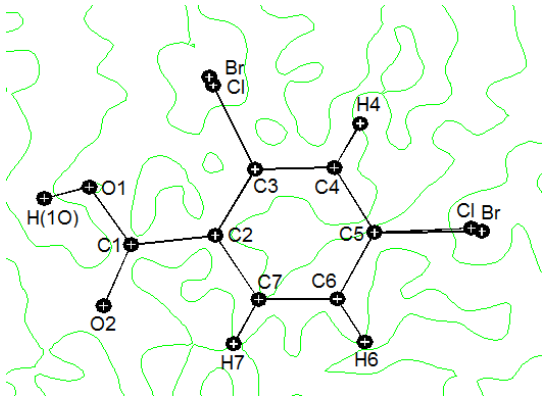
PXRD of 4Br, SS11 and 2Br. The inset shows that the first two peaks of 2Br are not present in case of SS11 and 4Br



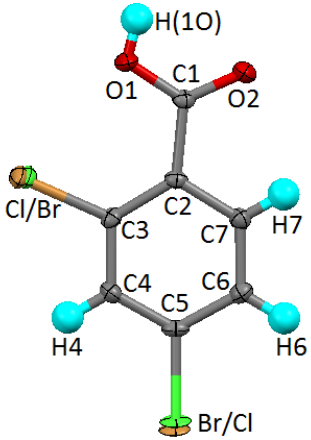
Crystallographic Table of Solid Solutions						
Composition	**4Br**:**2Br** (1:1), SS11	**4Br**:**2Br** (1:2), SS12	**4Br**:**2Br** (1:3), SS13	**4Br**:**2Br** (1:4), SS14	**4Br**:**2Br** (1:5), SS15	**4Br**:**2Br** (2:1), SS21
Space Group	*P*21/n	*P*21/n	*P*21/n	*P*21/n	*P*-1	*P*21/n
a (Å)	7.2560(2)	7.2399(3)	7.2385(4)	7.2271(7)	3.9007(4)	7.2577(3)
b (Å)	9.0227(2)	9.0087(2)	8.9976(5)	8.9480(7)	8.3070(4)	9.0397(3)
C (Å)	11.9855(3)	12.0539(4)	12.1313(6)	12.1887 (11)	11.9258 (12)	11.8561(4)
α (deg.)	90	90	90	90	88.909(6)	90
β (deg.)	104.676(3)	105.036(4)	105.406(5)	105.819(9)	89.987(8)	103.904(4)
γ (deg.)	90	90	90	90	78.731(6)	90
Vol. (Å-3)	759.074	759.264	761.711	758.368	378.912	755.057
Refined Occupancy Ratio	**52:48**	**38:62**	**29:71**	**25:75**	**19:81**	**74:26**
R_1 [I>2σ(I)]	1.98	2.77	3.33	4.58	6.01	2.43
Z / Z'	4/1	4/1	4/1	4/1	2/1	4/1
Δρmin,max (e Å-3)	-0.32, 0.39	-0.58, 0.38	-0.41, 0.41	-0.49, 0.58	-1.8, 1.1	-0.50, 0.47
CCDC no.	1534997	1535000	1535001	1535002	1535003	1535004

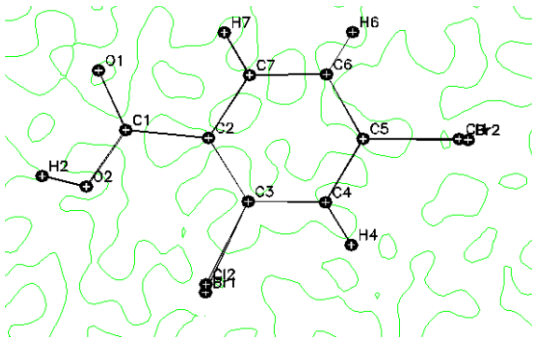
ORTEP diagrams and difference Fourier maps



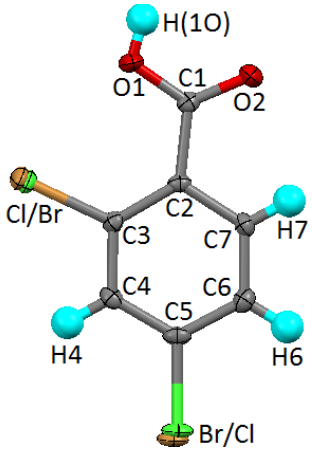


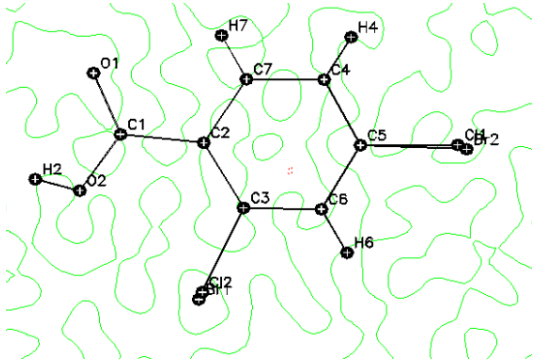
SS11





SS12

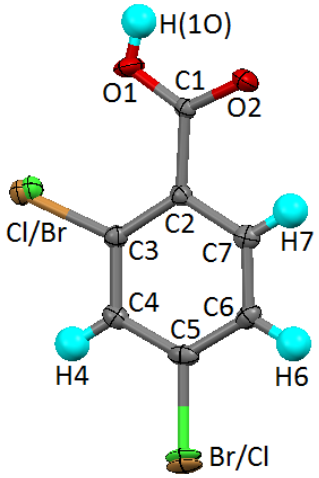


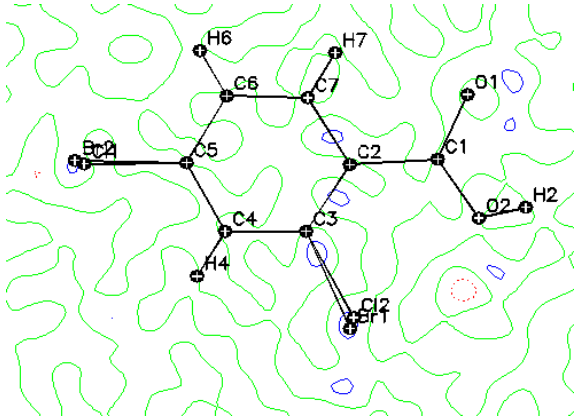


SS13

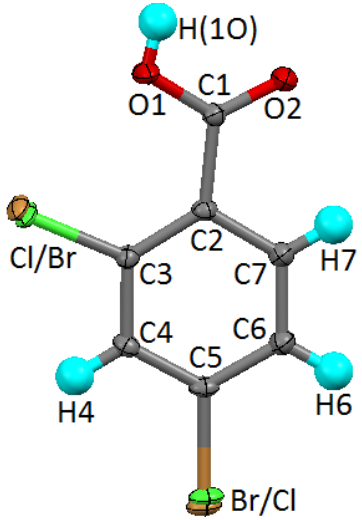
contours are drawn at the intervals of ±0.5 e Å^{-3}

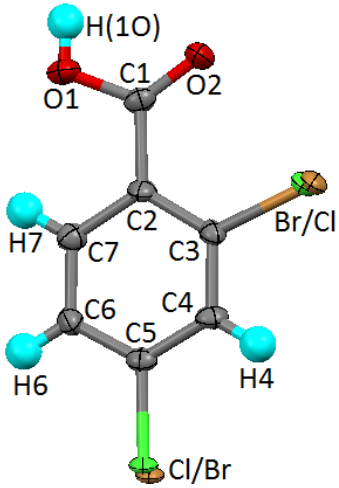
ORTEP diagrams and difference Fourier maps

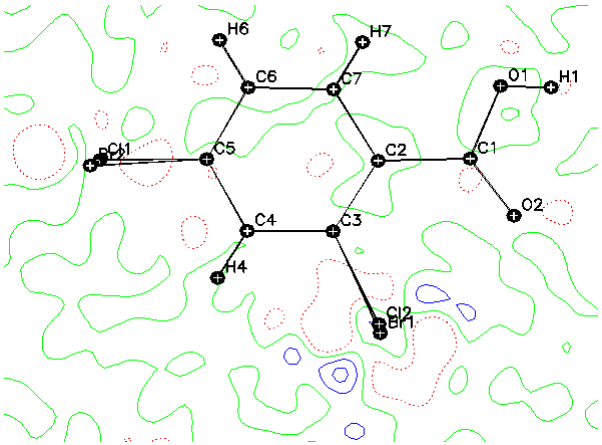




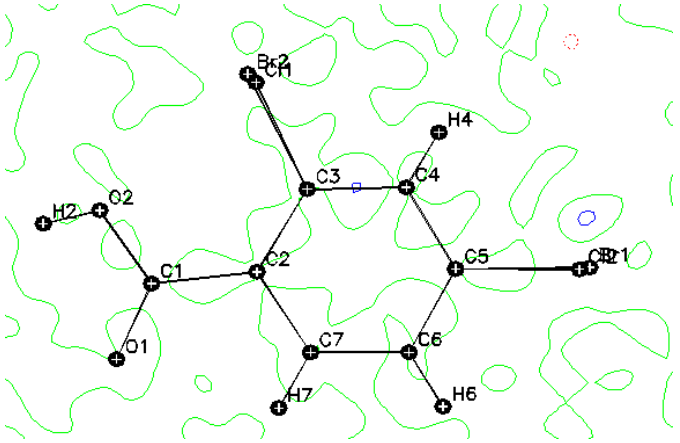
SS14





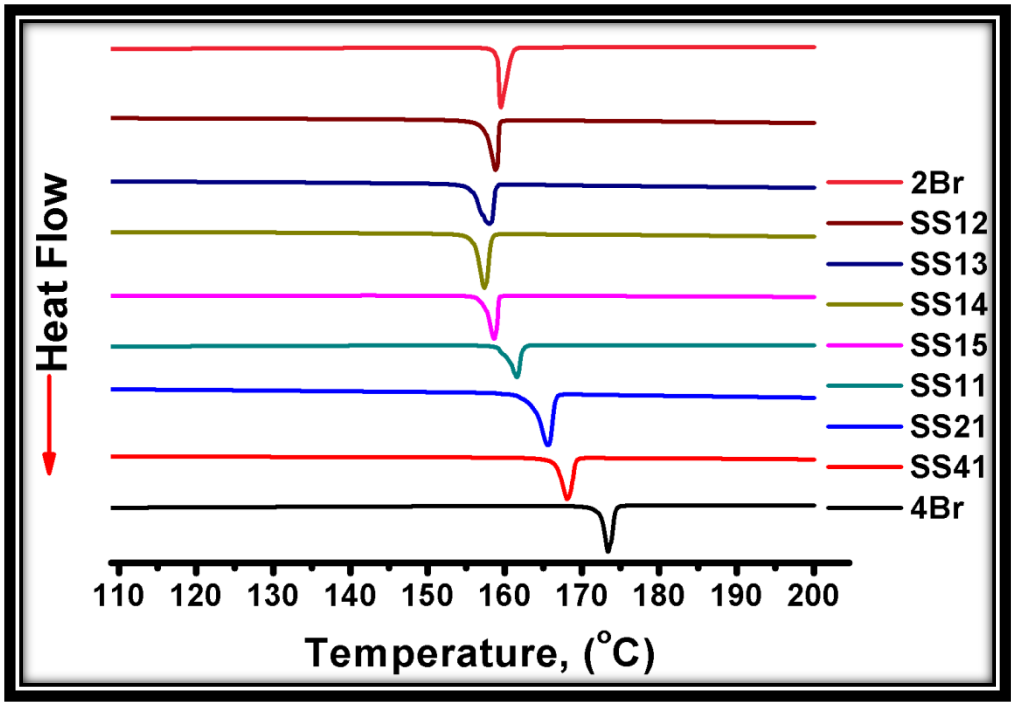


SS15



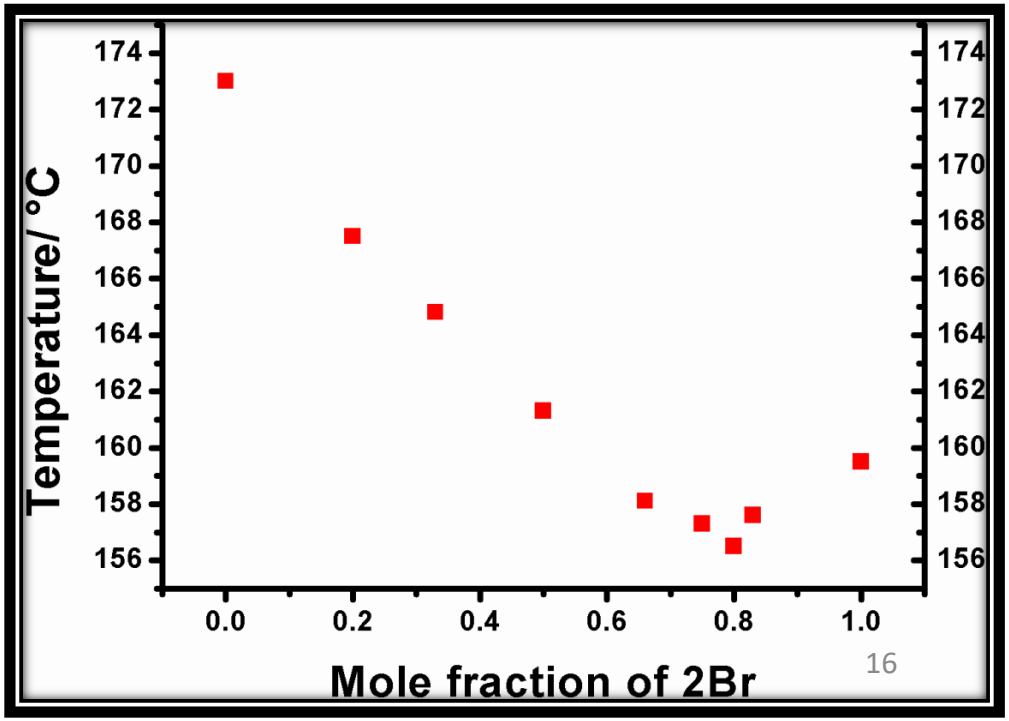
SS21

contours are drawn at the intervals of ±0.5 e Å^{-3}



DSC endotherms of pure compounds and all solid solutions depicting the monophasic nature of the samples.

Evolution of the solid solution compositions with respect to melting temperature and mole fraction of 2Br.



Acknowledgements

Sounak Sarkar and Titas Pramanik

J.C. Bose National fellowship from DST and IISc X-ray facility

Thank You