

Structure property relationships in halogenated aromatic amides and imides

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Understanding and controlling intermolecular interactions lies at the heart of molecular aggregation and plays a central role in molecular recognition, crystal engineering and biological sciences. The role of intramolecular interactions in predisposing molecules towards most favoured conformations that are for the most part retained in the crystal structure often needs careful consideration, with unusual geometries stabilised and contributing favourably to the solid state geometries. Halogen bonding has seen an enormous increase in fundamental and applied research and especially in the past decade. While fluorine is often treated as a distinct atomic/group entity, it is always convenient to both compare and contrast all halogens from fluorine to iodine so as to determine their steric and electronic influences on molecular structure, but especially their impact on molecular aggregation.

Herein, series of 3x3 isomer grids of halogenated benzamides (Hxx) and the amide-reversed pyridinecarboxamides (NxxH) are described, where Hx is the halobenzoyl (or Nx = pyridinoyl) and x is the pyridine (or xH = N-halobenzene ring), both substituted rings having either para-/meta-/ortho-substituents (as N or F, Cl, Br, I) [1]. In addition (Hxod) imides have been synthesised and isolated with the expected (1:1) Hxo benzamides for reactions involving ortho-aminopyridine. Their Hxx (NxxH) physicochemical properties (1H, 13C, 19F, IR, MS, melting point ranges) are analysed together with comprehensive structural studies of their crystal structures and interaction environments [1]. In addition, structural comparisons are made with results from conformational analyses (potential energy scans) and the modelled minima correlated with crystal structure data. For example, in terms of thermal behaviour, the chloro derivatives as Clxx have a higher average melting point range that is ~20C higher than the Fxx fluorine equivalent structures [1]. Furthermore, studies have shown that location is more important than the nature of the substituent as depicted in the melting point diagram below [1].

Extensive correlations between series are noted in the solid-state behaviour e.g. the isomorphous behaviour of (Hpp) derivatives, polymorphism in the (Fom) pairs where one polymorph aggregates via N-H...N interactions and the second by an alternative type as typical amide...amide hydrogen bonds. The (Hxo) triads typically exhibit the expected centrosymmetric cyclic N-H...N dimer formation (as 8-membered hydrogen bonded rings) expected for ortho-pyridine substituted benzamides. In summary, structural systematic studies of n x m isomer grids facilitates extensive physicochemical analysis and identification of trends and correlations between large sets of similar molecules (congeners) that differ primarily in the position of their substituents [2].

[1] Mocijac, P. et al. (2012). Acta Cryst. B68, 189-203.

[2] Mocijac, P. et al. (2016). CrystEngComm, 18, 5764-5776.

		benzamides			pyridinecarboxamides				
		Mxx	Mp	Mm	Mo	No	Nm	Np	NxxM
M	p	181♦	106	129	105	148	162♦		pM
	m	128	91	108	50*	115	142		mM
	o	105	79*	116	65	107	125		oM
F	o	120	77*	85	107	117	140♦		oF
	m	150, 148	151	89	78*	122	132		mF
	p	187♦	186	135	94	133	135		pF
		Fxx ^b	Fp	Fm	Fo	No	Nm	Np	NxxF

Average melting point range for all 37 compounds with highest denoted by ♦ and lowest by *

- Green labels highlight the N-H...N interaction
- Orange labels the N-H...O=C hydrogen bonds
- Melting points for compounds in non-centrosymmetric space groups are underlined.

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