

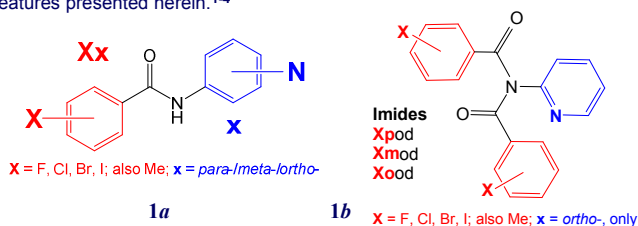


Structure property relationships in halogenated aromatic amides and imides.

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Introduction

The effect of halogens (X) and pyridine N atom substitution patterns on molecular structure and conformation is analyzed and discussed herein. Several series of 3 × 3 isomer grids (Scheme 1; Figs 1-3) of halo-*N*-(pyridyl)benzamides (Xxx) (C₁₂H₉N₂OX, x = *para*-*meta*-*ortho*-) and their corresponding imides (Fig. 4) have been evaluated and correlated in terms of their structural relationships. The analysis integrates crystal structure analyses, computational chemistry and conformational analyses together with NMR data and melting points (Tables 1, 2). The study highlights the structural systematics survey of several halo/methyl-substituted benzamide/pyridine-carboxamide isomer grids (Figs 1-3) and related imides with only the salient features presented herein.¹⁻⁴



Scheme 1a Xxx benzamide isomers (above left), carboxamides as amide bridge reversed. **Scheme 1b** The Xxod imides as synthesized from *ortho*-aminopyridine (above right).

Experimental methods

Nucleophilic acyl substitution reactions of the 4-, 3- or 2-halobenzoyl chlorides with 4-, 3- or 2-aminopyridines produces nine Xxx isomers. Purification was by standard organic washing and chromatography. Using *ortho*-aminopyridine as starting material, yields two products, the expected benzamide Xxx and an imide Xxod product with (%) yields depending on the reaction conditions. The single crystal X-ray data (Mo/Cu) were collected on an Oxford Diffraction Gemini S-Ultra (Rigaku) diffractometer at 294(1) K: with θ range typically from 2-26° (with 100% data coverage to 25°).

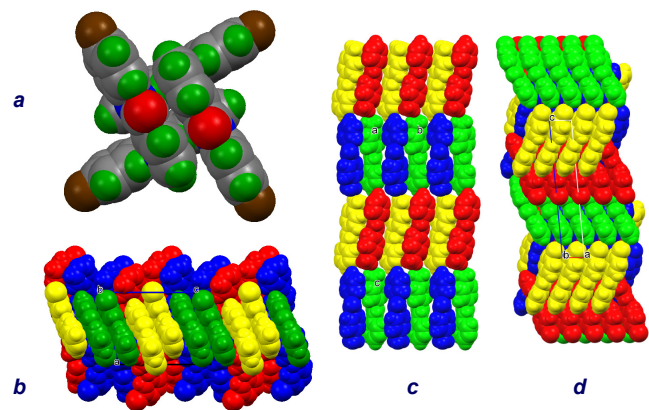


Fig. 1: (a) The NmpF tetramer,² (b) Clmp,⁵ (c) Mpm¹ and (d) Clpm,⁵ stacking; all with Z=4

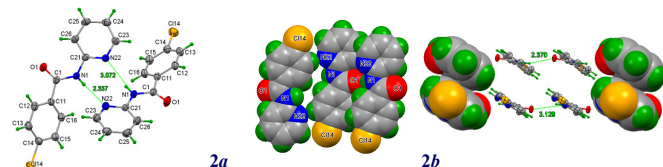


Fig. 2a: Clpo_N dimer (N-H...N) **2b:** N-H...O=C interactions and π ... π stacking in Clpo_O

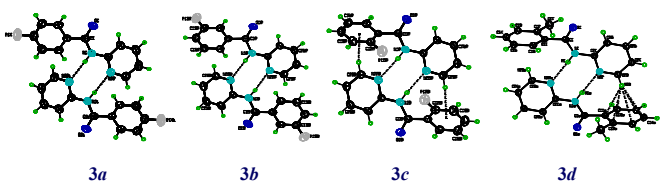


Fig. 3: The Fxo N-H...N hydrogen bonded dimers (a: Fpo, b: Fmo, c: Foo)⁴ and (d) Moo¹

Table 1: A typical 3 × 3 isomer grid (with Fxx represented below)

Name	SG	Z/Z'	Volume	R-factor	C _g C _s N	N...N/O	Packing
Fpp	P2 ₁ /c	4/1	1006.40(3)	0.034	52.14(4)	3.0581(15)	C(6) chains
Fmp	P2 ₁ /c	4/1	995.76(3)	0.034	48.86(4)	3.0788(14)	C(6) chains
Fop	P2 ₁ /c	4/1	1009.72(3)	0.037	46.14(4)	3.0587(16)	C(6) chains
Fpm _O	P2 ₁ /n	4/1	992.74(3)	0.042	1.02(9)	3.0575(13)	C(4) chains
Fpm _N	P2 ₁ /n	4/1	1009.69(9)	0.053	28.95(8)	3.151(3)	C(6) chains
Fmm	Pca2 ₁	4/1	1019.67(5)	0.033	43.97(6)	3.077(3)	C(5) chains
Fom _O	P2 ₁	12/6	2999.41(12)	0.068	4.5(4)-9.1(4)	3.066(8)-3.111(9)	C(4) chains
Fom _F	P2 ₁ /n	4/1	987.35(7)	0.043	2.35(10)	3.3322(17)	C(4) chains
Fpo	Pbcn	8/1	2100.58(6)	0.042	44.41(5)	3.0608(18)	R ² ₂ (8) rings
					65.30(6)	3.0721(17)	
Fmo	Pt	4/2	1034.48(6)	0.046	47.92(6)	3.0502(18)	R ² ₂ (8) rings
Foo	Pt	4/2	1048.88(7)	0.044	66.31(5)	3.0460(14)	R ² ₂ (8) rings
					52.02(5)	3.0408(15)	

In silico methods

The Xxx isomer optimisations and conformational analyses were typically performed using *ab initio* calculations (B3LYP/6-311++G**₁; 6-311++G, 6-311G**₂) on isolated (*gas-phase*) and solvated molecules (PCM-SMD solvation model with CH₂Cl₂ or H₂O as solvents) using Gaussian03/09.¹⁻⁴

Fig. 4: Conformations of halogenated imides: the three Clxod molecular structures

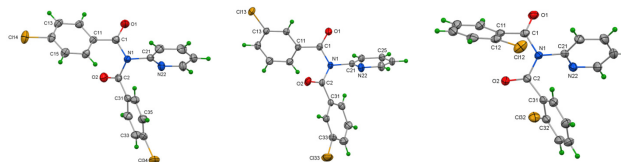


Table 2: Average melting points^a of the Mxx¹, NxxF², NxxM³ and Fxx⁴ isomer grids

Mxx	Mp	Mm	Mo	No	Nm	Np	NxxM
p	181*	106	129	105	148	162*	pM
m	128*	91	108	50*	115	142	mM
o	105	79*	116	65	107	125	oM
	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

^a Average melting point range for all 38 compounds with highest denoted by * and lowest by †.

^b Reference 4 (as Mocilac, Donnelly & Gallagher, 2012).

^c Green labels represent N-H...N interactions; orange labels for N-H...O=C hydrogen bonds: melting points for compounds in non-centrosymmetric space groups are underlined.

Results and Conclusions

The majority of Xxx crystal structures crystallise with Z=1, but cases with Z=4 are known, with NmpF, Clmp, Mpm and Clpm depicted in Fig. 1. The Xxo series is often isolated as Z=2 (Fig. 3).^{1,4} Hence for Z=4 a predisposition of 'mp' type benzamides/carboxamides is indicated.^{1,4,5}

Most Xxx derivatives form N-H...N hydrogen bonds (Fig. 3) and less common via intermolecular N-H...O=C interactions. For example, the Xxo triad (Figs 2,3) form twisted cyclic dimers as R²₂(8) rings via N-H...N interactions, as exemplified by Fxo and Mxx (Fig. 3d)¹, however, Clpo forms polymorphs with N-H...N (in Clpo_N) and N-H...O=C (in Clpo_O) interactions (Fig. 2).

Comparisons of Mxx¹, NxxF², NxxM³, Fxx⁴ (M = methyl) reveal a high degree of similarity in solid state aggregation and physicochemical properties, while correlation of the melting point data values indicates the significance of the (M/F) substituent position on melting point behaviour, rather than the nature of the (M/F) substituent (Table 2). The Clxx isomer series exhibits a higher average melting point (148°C) compared to Fxx (131°C) and Mxx (116°C), and comparable with the Brxx series (147°C). Five Clxx isomers are isomorphous with their Brxx analogues and exhibiting a high degree of similarity between the two sets of isomer grids.

Halogen bonding interactions increase on progressing to the Brxx and lxx series and compete effectively with the N-H...N and N-H...O=C interactions.

On-going work is focussed on expanding the size and scope of the n × m benzamide isomer grids.⁶

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