Structure property relationships in halogenated aromatic amides and imides.

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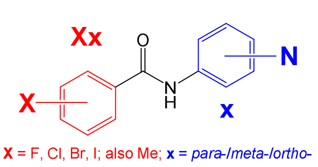
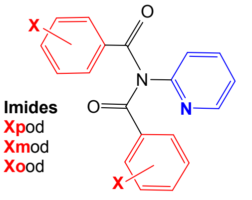
Introduction

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**) ($C_{12}H_9N_2OX$, **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]



1a



1b

X = F, Cl, Br, I; also Me; **x** = *ortho-*, only

Scheme 1*a* **Xxx** benzamide isomers (above left), carboxamides as amide bridge reversed.
Scheme 1*b* 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°).

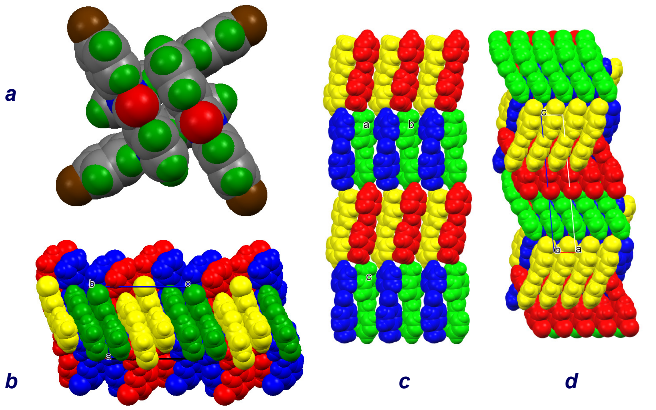
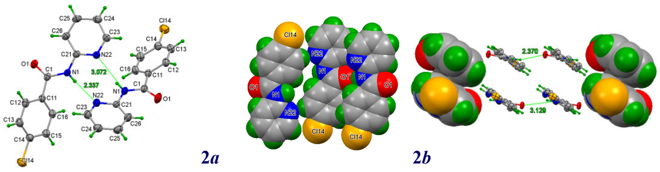
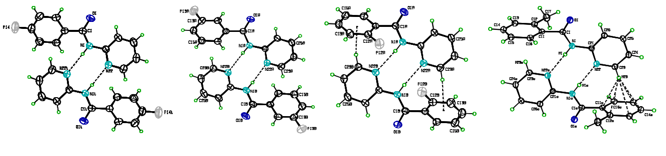


Fig. 1: (*a*) The **NmpF** tetramer,[2] (*b*) **Clmp**,[5] (*c*) **Mpm**[1] and (*d*) **Clpm**,[5] stacking; all with *Z*'=4



2a **2b**

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



3*a* **3*b*** **3*c*** **3*d***

Fig. 3: The **Fxo** **N-H…N** hydrogen bonded dimers (*a*: **Fpo**, *b*: **Fmo**, *c*: **Foo**)[4] and (*d*) **Moo**[1]

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

Name	SG	Z/Z'	Volume	R-factor	C_6/C_5N	N…N/O	Packing
Fpp	*P*2$_1$/*c*	4/1	1006.40(3)	0.034	52.14(4)	**3.0581(15)**	*C*(6) chains
Fmp	*P*2$_1$/*c*	4/1	995.76(3)	0.034	48.86(4)	**3.0788(14)**	*C*(6) chains
Fop	*P*2$_1$/*c*	4/1	1009.72(3)	0.037	46.14(4)	**3.0587(16)**	*C*(6) chains
Fpm_O	*P*2$_1$/*n*	4/1	992.74(3)	0.042	1.02(9)	**3.0575(13)**	*C*(4) chains
Fpm_N	*P*2$_1$/*n*	4/1	1009.69(9)	0.053	28.95(8)	**3.151(3)**	*C*(6) chains
Fmm	*Pca*2$_1$	4/1	1019.67(5)	0.033	43.97(6)	**3.077(3)**	*C*(5) chains
Fom_O	*P*2$_1$	12/6	2999.41(12)	0.068	4.5(4)- 9.1(4)	**3.066(8)- 3.111(9)**	*C*(4) chains
Fom_F	*P*2$_1$/*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) 65.30(6)	**3.0608(18) 3.0721(17)**	$R^2_2(8)$ rings
Fmo	*P*$\bar{1}$	4/2	1034.48(6)	0.046	47.92(6)	**3.0502(18)**	$R^2_2(8)$ rings
Foo	*P*$\bar{1}$	4/2	1048.88(7)	0.044	66.31(5) 52.02(5)	**3.0460(14) 3.0408(15)**	$R^2_2(8)$ rings

In silico methods

The **Xxx** isomer optimisations and conformational analyses were typically performed using *ab initio* calculations (B3LYP/6-311++G**; 6-311++G, 6-311G**) on isolated (*gas-phase*) and solvated molecules (PCM-SMD solvation model with CH_2Cl_2 or H_2O as solvents) using Gaussian03/09.[1-4]

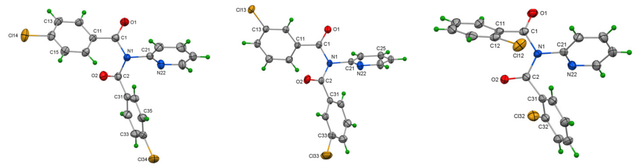


Fig. 4: Conformations of halogenated imides: the three **Clxod** molecular structures

Table 2: Average melting points[a] of the **Mxx**[1], **NxxF**[2], **NxxM**[3] and **Fxx**[4] 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
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

[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 $R^2_2(8)$ rings *via* N-H...N interactions, as exemplified by **Fxo** and **Mxx** (Fig. 3*d*)[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 **Mxx**[1], **NxxF**[2], **NxxM**[3], **Fxx**[4] (**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 **Ixx** 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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