



Structural systematic studies and conformational analyses of a 3 × 3 isomer grid of fluoro-*N*-(pyridyl)benzamides; physicochemical correlations, polymorphism and isomorphism relationships.

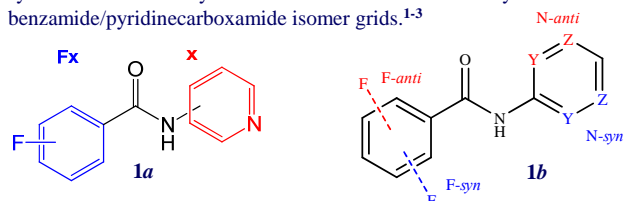
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Introduction

The effect of fluorine and pyridine N atom substitution patterns on molecular structure and conformation is probed in a 3 × 3 isomer grid (Scheme 1) of fluoro-*N*-(pyridyl)benzamides (**Fxx**) (C₁₂H₉N₂OF, *x* = *para*-/*meta*-/*ortho*-) to evaluate and correlate structural relationships between the solid-state and *ab initio* calculations. Physicochemical comparisons are analysed with an extended series of three related 3 × 3 isomer grids. Our analysis integrates crystal structure analyses, computational chemistry and conformational analyses together with NMR data and physicochemical trends such as melting point analysis. This study concludes structural systematics survey of four fluoro/methyl substituted benzamide/pyridinecarboxamide isomer grids.¹⁻³



Scheme 1a Schematic diagram of the **Fxx** isomers (above left). **Scheme 1b**. **Fxx** conformational preferences as **F-anti**/**F-syn** and **P-anti**/**P-syn** (above right).

Experimental methods

Nucleophilic acyl substitution reactions of the 4-, 3- or 2-fluorobenzoyl chlorides with 4-, 3- or 2-aminopyridines produces nine **Fxx** isomers. Purification was accomplished by standard organic washing and column chromatography. Single crystals were grown from EtOAc. Crystals of **Fpm_O** (Fig 1b) were grown from dichloromethane, **Fom_F** (Fig 2b) by very slow evaporation from methanol/diethylether. The single crystal X-ray data (Mo) were collected on an Oxford Diffraction Gemini S-Ultra diffractometer at 294(1) K: θ range from 2–26° (100% data coverage to 25°).

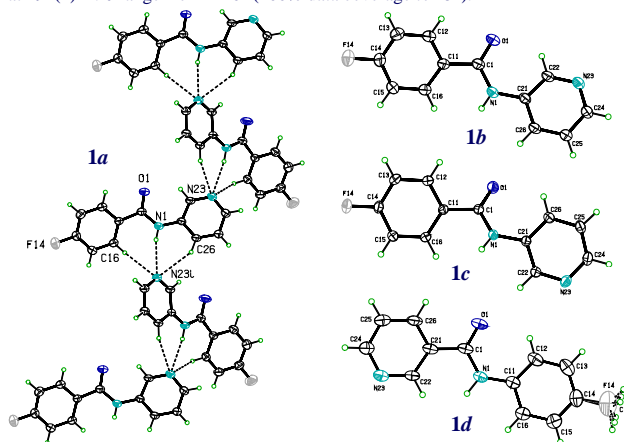


Fig. 1 A view of the (a) **Fpm_N** structure, (b) polymorph **Fpm_O**, (c) **Fpm_N** and (d) **NmpFM**³

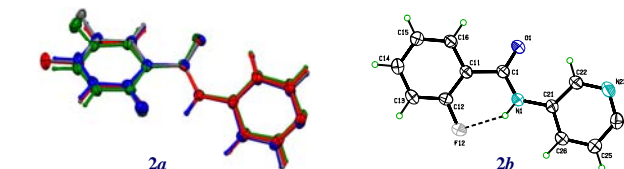


Fig. 2a: An overlay of the **Fxp** isomorphous series with **25_F₂**. **2b**: A view of the **Fom_F** molecule

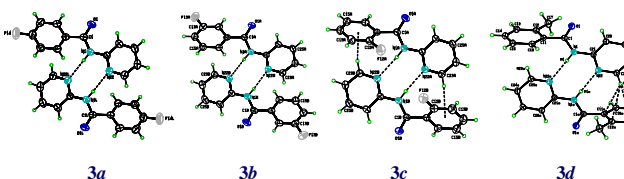


Fig. 3 A view of the **Fxo** hydrogen bonded dimers (a) **Fpo**, (b) **Fmo**, (c) **Foo** and (d) **Moo**¹

Table 1. Selected crystallographic data and relevant structural features for **Fxx**

Name	SG	Z'	Volume	R-factor	C ₆ /C ₅ N	N...O	Packing
Fpp	<i>P2₁/c</i>	4/1	1006.40(3)	0.034	52.14(4)	3.0581(15)	C(6) chains
Fmp	<i>P2₁/c</i>	4/1	995.76(3)	0.034	48.86(4)	3.0788(14)	C(6) chains
Fop	<i>P2₁/c</i>	4/1	1009.72(3)	0.037	46.14(4)	3.0587(16)	C(6) chains
Fpm_O	<i>P2₁/n</i>	4/1	992.74(3)	0.042	1.02(9)	3.0575(13)	C(4) chains
Fpm_N	<i>P2₁/n</i>	4/1	1009.69(9)	0.053	28.95(8)	3.151(3)	C(6) chains
Fmm	<i>Pca2₁</i>	4/1	1019.67(5)	0.033	43.97(6)	3.077(3)	C(5) chains
Fom_O	<i>P2₁</i>	6/12	2999.41(12)	0.068	4.5(4)-9.1(4)	3.066(8)-3.111(9)	C(4) chains
Fom_F	<i>P2₁/n</i>	4/1	987.35(7)	0.043	2.35(10)	3.322(17)	C(4) chains
Fpo	<i>Pbcn</i>	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	<i>Pī</i>	4/2	1034.48(6)	0.046	47.92(6)	3.0502(18)	R ² ₂ (8) rings
Foo	<i>Pī</i>	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 **Fxx** isomer optimisation and conformational analysis providing PES diagrams was 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 CH₂Cl₂ or H₂O as solvents) using Gaussian03/09 together with high accuracy energy calculations (CBS-QB3) and the ΔG of solvation. Corresponding solid state structure dihedral angles were plotted in the *gas phase* PES diagrams relative to the dihedral angles of the optimised structures.

Fig. 4 The nine PES conformational analysis diagrams for the **Fxx** (*gas-phase*)

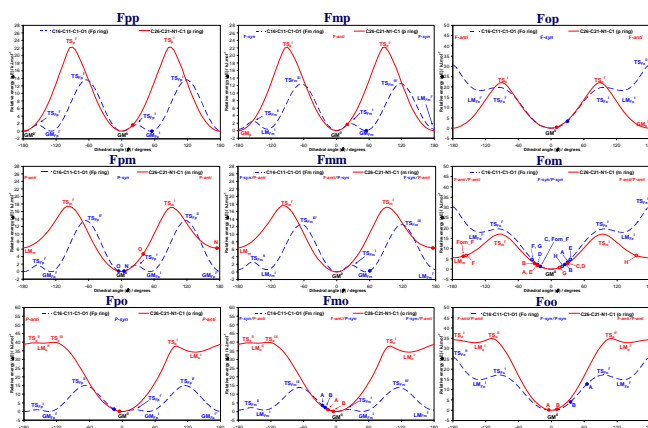


Table 2 Melting points^a of the **Mxx**¹, **NxxF**², **NxxM**³ and **Fxx** isomer grids

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
m	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

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

^bThe present study (Mocijac, Donnelly & Gallagher, 2012).

^cGreen labels highlight the N-H...N interaction and orange labels the N-H...O=C hydrogen bonds; melting points for compounds in non-centrosymmetric space groups are underlined.

Results and Conclusion

Eight **Fxx** isomers form N-H...N hydrogen bonds, and only one isomer (**Fom**, Fig. 2b) aggregates *via* intermolecular N-H...O=C interactions exclusively. Moreover, **Fpm** crystallises as two polymorphs, both in space group *P2₁/n* with **Fpm_O** (N-H...O=C chains, **P-syn**, Fig. 1c) and **Fpm_N** (N-H...N chains, **P-anti**, Fig. 1b). The **Fom** isomer forms two polymorphs as the disordered **Fom_O** (mostly **P-syn**) (*Z*=6), and the regular **Fom_F** (**P-anti**, Fig. 2b) with *Z*=1. The **Fxo** triad (Fig. 3a-b) form twisted dimers as cyclic R²₂(8) rings *via* N-H...N interactions, similar to **Mxx** (Fig. 3d)¹ Conformational analyses (Fig. 4) of the nine **Fxx** isomers demonstrate that the solid state conformations generally conform with the most stable modelled conformations except for **Fxm** triad. Calculations of the **Fxo** triad provide evidence for intramolecular N-H...F hydrogen interactions confirming spectroscopic and crystallographic data. Comparisons of **Fxx** with the related **Mxx**¹, **NxxF**² and **NxxM**³ series (**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.

References:

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- P. Mocijac, A.J. Lough and J.F. Gallagher, *CrystEngComm*, 2011, **13**, 1899-1909.
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