Synthesis, structural and conformational analysis of a 3×3 isomer grid based on nine Methyl-*N*-(pyridyl)benzamides

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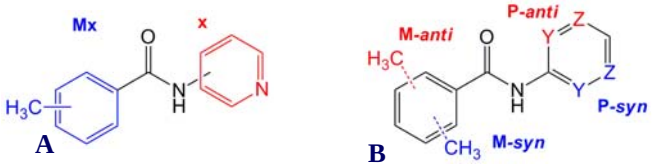
Introduction

The focus of our research is to bridge solid state structural studies with computational (*ab initio*) modelling methods by exploring the influence of different functional groups and their position in semi-rigid small *drug-like* molecules.[1-3] A 3×3 isomer grid of nine Methyl-*N*-(pyridyl)benzamides ($C_{13}H_{12}N_2O$) as **Mxx** (**x** = *para-*/*meta-*/*ortho-*) has been synthesised and characterised to evaluate and correlate structural relationships from both solid-state (Table 1, Figs. 1,2,4) and *ab initio* calculations (Fig. 3). The effect of methyl group (**Mx**) and pyridine N atom (**x**) substitution patterns on molecular structure and conformations (*syn*/*anti*, Scheme 1B) from calculations (*gas phase* and solvated forms), as well as on crystal packing and conformations in solid state is explored, allowing evaluation and rationalisation of disorder and unexpected conformations observed in solid state structures.



Scheme 1. **A**. General structure diagram of **Mxx** compounds; **B**. Possible **Mxx** conformations isomers

Experimental methods

Classical nucleophilic acyl substitution reactions (Schotten–Baumann) of the 4-, 3- or 2-toluoyl chlorides with 4-, 3- or 2-aminopyridines produced a series of nine **Mxx** compounds. The **Mxo** triad was synthesised under solventless conditions. Purification was accomplished by standard organic wash up and column chromatography. Single crystals were grown from chloroform or ethyl acetate. The single crystal X-ray data were collected on an Enraf-Nonius κ-CCD diffractometer at 150(1) K and for **Mpo** on a Bruker ApexII at the University of Toronto : θ range from 2-27.5° with 100% data coverage to 25°. Data have also been collected at 294(1) K.

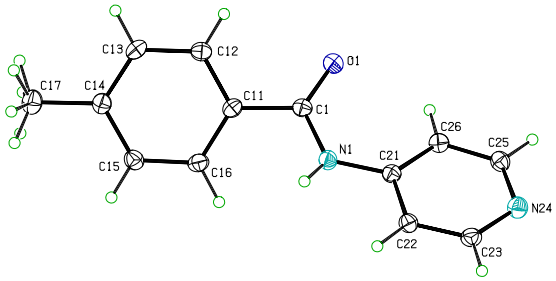


Fig. 1 Molecular structure of **Mpp** with displacement ellipsoids drawn at the 30% probability level.

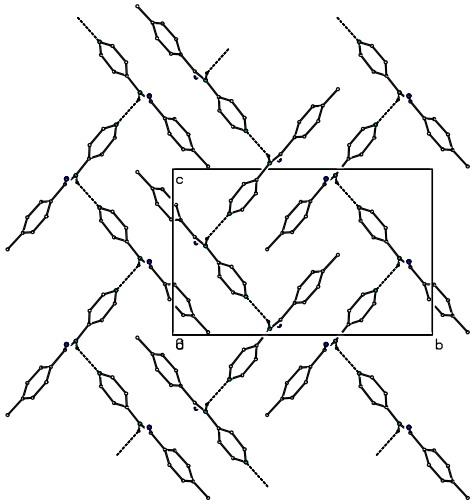


Fig. 2 The intermolecular N-H…$N_{pyridine}$ interactions in **Mpp**.

Table 1. Selected crystallographic data and relevant structural features for the nine **Mxx** isomers

Mxx	Space group	Z'	Volume (Å³)	R-factors	C_6/C_5N (°)	C_6/amide (°)	C_5N/amide (°)	N…N/O (Å)	Packing
Mpp	$P2_1/n$	1	1038.49(12)	0.066, 0.202	46.03(9)	28.99(11)	17.40(13)	3.105(3)	1D chains
Mmp	$P\bar{1}$	2	1056.41(16)	0.066, 0.183	4.84(15)	15.70(13)	10.94(13)	3.058(3)	2D chains
					5.47(12)	19.88(10)	17.73(9)	3.059(3)	
Mop	*Pc*	2	1123.65(12)	0.056, 0.161	81.79(15)	54.60(17)	28.34(17)	2.952(5)	1D chains
					81.58(14)	54.85(15)	27.96(16)	2.950(5)	
Mpm	*P1*	4	1071.37(8)	0.059, 0.154	65.13(11)	29.45(15)	35.83(14)	3.029(6)	1D chains
					64.04(10)	29.70(15)	34.57(13)	3.016(5)	
					1.5(2)	24.47(16)	24.16(16)	3.085(6)	
					1.9(2)	24.79(16)	24.79(16)	3.085(5)	
Mmm	$P\bar{1}$	2	1079.21(9)	0.076, 0.254	55.57(10)	25.55(8)	31.33(14)	2.998(4)	1D chains
					65.70(10)	36.43(10)	29.54(14)	3.006(4)	
Mom	$Pca2_1$	1	1109.94(5)	0.041, 0.096	71.20(5)	57.33(6)	13.91(10)	2.946(2)	1D chains
Mpo	$P\bar{1}$	1	525.04(5)	0.039, 0.109	45.34(4)	35.93(5)	17.51(8)	3.1081(15)	Dimer
Mmo	$P2_1/c$	1	1065.04(15)	0.065, 0.195	70.55(7)	35.99(8)	35.05(11)	3.106(3)	Dimer
Moo	$P\bar{1}$	1	546.42(6)	0.063,0.184	84.79(5)	77.28(6)	10.93(10)	3.076(3)	Dimer

In silico methods

The **Mxx** isomer optimisation and conformational analysis giving PES diagrams was performed using *ab initio* calculations (B3LYP/6-311++G , corresponding B3LYP/6-311++G** studies are in progress) on isolated (*gas-phase*) and solvated molecules (PCM-SMD solvation model with CH_2Cl_2 or H_2O 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 *gas phase* PES diagrams relative to optimised structures dihedral angles.

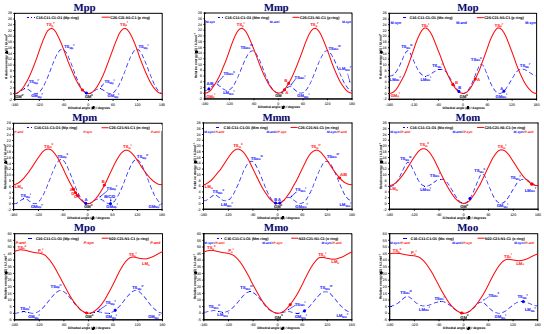


Fig. 3 The PES conformational analysis diagrams for the **Mxx** isomers optimised in the *gas phase*: the equivalent solid state angle is depicted as a (•), with, if applicable, assigned identification letter and partial occurrence (%).

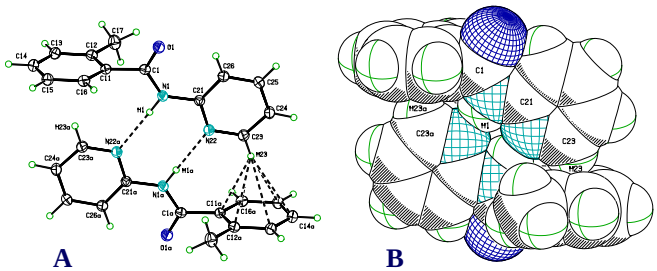


Fig. 4 A: The **Moo** hydrogen bonded dimer with symmetrical C-H…π(arene) interaction depicted for H23 only. **B**: The **Moo** 'dimer' with atoms as their van der Waals spheres.

Conclusion

The primary hydrogen bonding is $_{amide}$N-H…$N_{pyridine}$ in eight isomers but is $_{amide}$N-H…O=C_{amide} in **Mpm**. The N-H…N interactions form *C*(6) chains in the **Mxp** series, *C*(5) chains in **Mmm**, **Mom** and cyclic centrosymmetric $R^2_2(8)$ rings in the **Mxo** series. Of note is the short intradimer C-H…π(arene) interaction in **Moo** (Fig. 4), **one of the shortest reported in a neutral organic system** C…Cg = 3.3875 (18) Å, H…Cg = 2.46 Å [2.33 Å] and C-H…Cg = 167° [166°] [with normalised C-H distances]. For five of the nine isomers the torsion angle derived from *ab initio* calculations are reasonably consistent with the crystallographic data (Fig. 3). The ***M-anti*/*P-syn*** conformation is preferred in all modelled structures. However, for **Mmp**, **Mmm**, **Mom** and **Moo**, the crystallographic torsion angles are not located in an energetically favourable conformation based on our *ab initio* results, adopting meta-stable or unstable conformations.

References:

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3. P. Mocilac, M. Tallon, A. J. Lough and J. F. Gallagher, *CrystEngComm*, 2010, published.