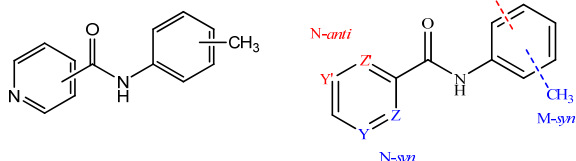


Introduction

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 *N*-(tolyl)pyridinecarboxamides (C₁₃H₁₂N₂O) as **NxxM** (x = *para*-/*meta*-/*ortho*-) (Scheme 1A) 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 pyridinoyl group (Nx) and methyl group (xM) 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 in the solid state structures.



Scheme 1A Schematic diagram of the **NxxM** isomers (above left).

Scheme 1B. **NxxM** conformational preferences as **N-anti/N-syn** and **M-anti/M-syn** (above right).

Experimental methods

Classical nucleophilic acyl substitution reactions (Schotten–Baumann) of the 4-, 3- or 2-pyridinoyl chloride hydrochlorides with 4-, 3- or 2-toluidines produces nine **NxxM** isomers as well as three 5-chloro-**NoxM** derivatives isolated as impurities with their respective **NoxM**. Purification was accomplished by standard organic washing and column chromatography. Single crystals were grown from CHCl₃ or EtOAc. Crystals of **NomM** were grown from cyclohexane, **NooM** from methanol after many trials. 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°).

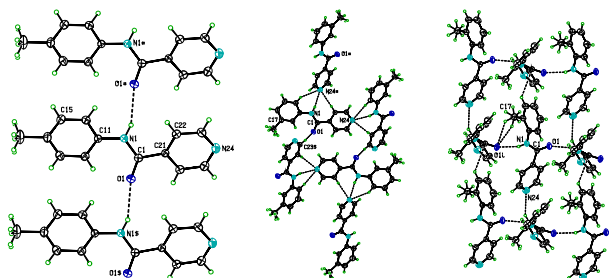


Fig. 1 Interactions in **NpxM** series as N-H...O=C in **NppM**, **NpoM** and N-H...N (**NpmM**, middle).

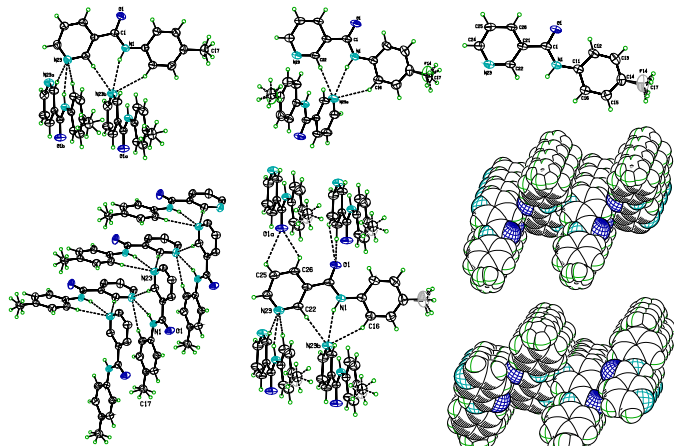


Fig. 2 The **NmpM** structure (left) crystallises as catemers with molecules parallel in *P*₂₁/*c* BUT when mixed with the **NmpF** (tetramers unit in *P*₂₁) produces **NmpFM** a 1:1 mixed structure (middle) in *Pca*₂₁ as catemers with molecules *anti*-parallel. The packing differences between **NmpFM** and **NmpM** are highlighted with atoms drawn as their van der Waals spheres (above right).

Table 1. Selected crystallographic data and relevant structural features for **NxxM**, 5-Cl-**NoxM**

| Name | SG | Z' | Volume | R-factor | C _v /C ₂ N | N...O | Packing |
|----------------|-----------------------------------|-----|--------|----------|----------------------------------|------------|-----------|
| NppM | <i>P</i> ₂₁ / <i>c</i> | 1 | 1090 | 0.051 | 66.45(3) | 3.0529(14) | 1D chains |
| NpmM | <i>P</i> ₂₁ / <i>n</i> | 1 | 1134 | 0.034 | 4.50(10) | 3.1265(18) | 2D sheets |
| NpoM | <i>Cc</i> | 1 | 1124 | 0.030 | 83.90(6) | 2.825(2) | 1D chains |
| NmpM | <i>P</i> ₂₁ / <i>c</i> | 1 | 1075 | 0.036 | 4.11(9) | 3.223(2) | Catemers |
| NmmM | <i>P</i> ₁ | 2 | 1085 | 0.057 | 57.23(6) | 3.090(2) | 1D chains |
| NmoM | <i>P</i> <i>bca</i> | 1 | 2240 | 0.040 | 89.99(5) | 2.8978(15) | 1D chains |
| NopM | <i>P</i> ₂₁ / <i>c</i> | 1 | 1100 | 0.035 | 33.63(4) | 2.6548(18) | 1D chains |
| NomM | <i>P</i> ₂₁ | 2 | 1179 | 0.029 | 14.64(14) | 3.241(3) | 2D sheets |
| NooM | <i>P</i> ₂₁ / <i>c</i> | 1 | 1099 | 0.037 | 1.91(5) | 2.6209(15) | Dimers |
| Cl-NopM | <i>Pca</i> ₂₁ | 1 | 1189 | 0.026 | 26.42(2) | 2.6514(9) | 2D sheets |
| Cl-NomM | <i>P</i> ₂₁ / <i>c</i> | 1 | 1204 | 0.066 | 4.35(13) | 2.683(4) | 1D chains |
| Cl-NooM | <i>P</i> ₂₁ / <i>n</i> | 1 | 1172 | 0.038 | 2.30(5) | 2.6690(15) | 1D tapes |
| NmpFM | <i>Pna</i> ₂₁ | 1:1 | 1063 | 0.035 | 5.00(14) | 3.207(2) | Catemers |

In silico methods

The **NxxM** isomer optimisation and conformational analysis providing PES diagrams was performed using *ab initio* calculations (B3LYP/6-311++G, corresponding B3LYP/6-311++G** studies are in progress) on 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 *gas phase* PES diagrams relative to optimised structures dihedral angles.

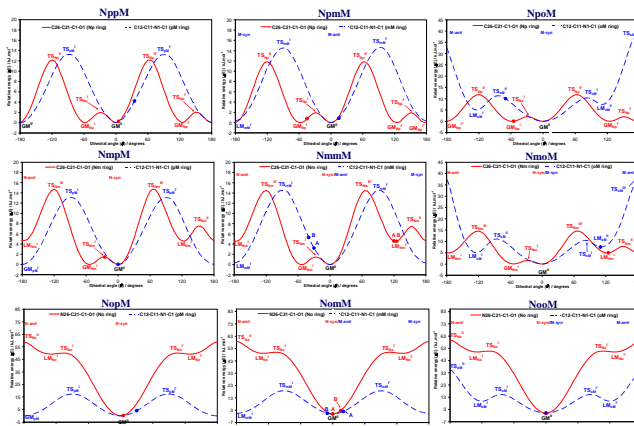


Fig. 3 The nine PES conformational analysis diagrams for the **NxxM** (*gas-phase*)

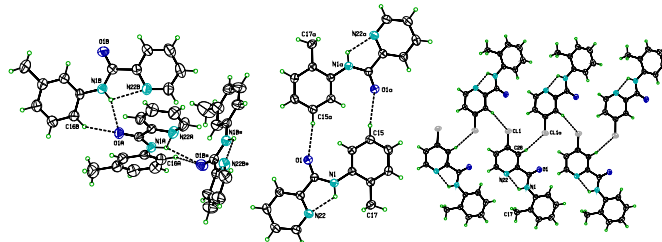


Fig. 4 The principal interactions in **NomM** (left), **NooM** (middle) and 5-Cl-**NooM** (right).

Results and Conclusion

Three **NppM**, **NpoM** and **NmoM** isomers aggregate via *amide* N-H...O=C hydrogen bonds whereas **NpmM**, **NmpM** and **NmmM** interact via *amide* N-H...N_{pyridine} interactions. All three **NoxM** exhibit intramolecular *amide* N-H...N_{pyridine} interactions with aggregation by C-H...O=C interactions (**NomM** also has intermolecular N-H...O=C interactions). For the 5-Cl-**NoxM** triad, only 5-Cl-**NomM** aggregates via *amide* N-H...O=C (with a shorter N...O than **NomM**); this effect is seen with lower melting points and crystallisation difficulties. The **NmpM** structure uses a similar primary hydrogen bonding pattern as **NmpF** but via catemeric chains not tetramers.² A mixture of **NmpM** and **NmpF** yields the mixed **NmpFM**, a crystalline solid solution in a different space group *Pna*₂₁ with 50:50% F/CH₃ occupancy and with N-H...N/C-H...N interactions forming catemeric chains. Of particular note is **NmmM** which is isomorphous and isostructural with **MmmM**¹ and is a rare case of *isotropy* between *bridge-flipped* isomers.⁴ Conformational analyses on *gas phase* and solvation models has enabled comparisons of optimised geometries with solid state molecular structures, highlighting unusual solid state conformations and relations with the aggregation processes. Future research will finalise the four F/CH₃ benzamide/pyridinecarboxamide series of 3×3 isomer grids, as well as explore related *oxm* isomer grids by introducing other functional groups/atoms and/or linker backbone using approaches similar to those reported previously.¹⁻³

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