Introduction

The synthesis and characterisation of a 3×3 isomer grid (NxxF) (x = para-meta-/ortho-) of nine N-(fluorophenyl)pyridinecarboxamides (Scheme 1A, Figs. 1-3) is reported with comprehensive crystal structure (Table 1) and conformational analyses on gas-phase and solvated forms. The conformational features and differences between the solid-state and model conformations (syn/anti, Scheme 1B), together with structural and property trends were explored using potential energy surface (PES) diagrams (Figs. 4, 5), bridging two different areas of structural science. The influence of the aromatic group substitution patterns was also evaluated in terms of the preferred primary hydrogen bonding (N-H...N or N-H...O=C) in the solid-state, in tandem with the influence and effect of weaker interactions on molecular aggregation.1-3

Experimental methods

The NxxF compounds were synthesised using Schotten-Baumann reaction between 4-/3-/2-pyridinyl chlorides and 4-/3-/2-fluoroureas. Purification was accomplished by standard organic wash up and column chromatography. Single crystals were grown from chloroform or ethyl acetate solutions. X-ray data for all nine NxxF isomers were collected on an Enraf-Nonius KappaCCD diffractometer at the University of Toronto at 150(1) K (except for NppF at 200(1) K), 0 range 2-27.5° with 100% data coverage to 25° (on 0). Data have also been collected at 294(1) K.

Conformational analysis

The NxxF isomer optimisation and conformational analysis giving PES diagrams was performed using ab initio calculations (B3LYP/6-31+1+G, corresponding B3LYP/6-311+G** studies are in progress) on isolated (gas-phase) and solvated molecules (PCM-SMD solvation model with CHCl3 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 (Fig. 4) relative to optimised structures dihedral angles.

Conclusion

The molecular and crystal structures of all nine NxxF isomers have been determined and compared with the global minima from calculations. Eight NxxF structures have the syn/-N-H…N syn/anti hydrogen bond as the primary interaction with the NppF isomer as the only structure with aggregation via N-H…O=C interactions. An unusual hydrogen bonded tetramer of NppF (Fig. 2) has the tetrameric assembly rationalised in terms of the directional and spatial arrangement of the N-H donor and N acceptor groups. In the last three NxxF molecules an intramolecular syn/-N-H…N syn/anti hydrogen bonding is observed, as well as the weaker F-H…N syn/anti interaction in NppF (Fig. 3). Conformational analysis of optimised structures in different media allowed in-depth rationalisation and explanation of the observed disorder and energetically meta- or unstable conformations in solid state packing. The NppF and NxxF modelled structures prefer the N syn/anti-conformation, while NxxF prefers N syn/-anti conformation.

References:

Table 1. Selected crystallographic data and relevant structural features for the nine NxxF Isomers

| NxxF | Space group | Z | Volume (Å³) | β (°) | Cα-N (Å) | Cα-C (Å) | Cα-N (Å) | Cα-N (Å) | β′ (°) | α′ (°) | γ′ (°) | Packing |
|------|-------------|---|-------------|------|------------|----------|----------|----------|----------|--------|--------|---------|---------|
| NppF | P2₁ | 2 | 2940.34(6) | 89.51(2) | 2.675(4) | 3.69(1) | 2.88(1) | 2.88(1) | 89.08(2) | 88.03(2) | 89.04(2) | Orthorhombic |
| NppF | C | 1 | 1802.23(3) | 84.82(1) | 6.09(1) | 18.01(2) | 27.98(1) | 2.98(1) | Orthorhombic |
| NppF | C | 1 | 1827.30(4) | 84.82(1) | 6.09(1) | 18.01(2) | 27.98(1) | 2.98(1) | Orthorhombic |

Fig. 1. A: The NppF molecular structure with group disorder for F12 in the F syn conformation [91.7(9%)] and F16 as F anti [8.3(9%)]; B: NppF and NmpF molecular structure overlay.

Fig. 2. ORTEP (A) and CPK (B) diagrams of the tetrameric assembly of NmpF (form of “St. Beigie’s Cross”).

Fig. 3. The Ni-H1...N22/F12 intramolecular interactions in NppF, with the minor Cl site at C25.

Fig. 4. The PES-conformational analysis diagrams for the NppF isomers optimised in the gas phase: the equivalent solid state angle is depicted as an α, with, if applicable, assigned identification letter and partial occurrence (%) in brackets.

Fig. 5. The PES-conformational analysis diagrams for the nine NxxF isomers optimised in gas phase (full line), CHCl3 (dashed line) and in H2O (dotted line) using the PCM-SMD solvation method.