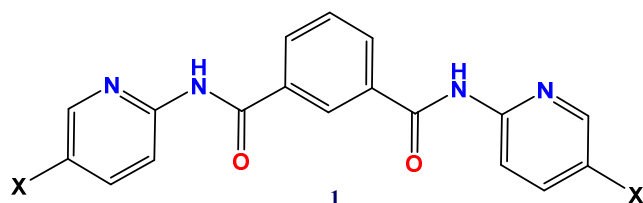


Introduction

The effect of halogens (**X**) and the pyridine **N** atom substitution patterns on molecular structure and conformation in a series of isophthalamides is analyzed. The work is based on previous and on-going research on isomer grids of halogenated benzamides.¹⁻³ The analysis integrates crystal structure analyses, computational chemistry and conformational analyses together with NMR data and melting point data.¹⁻³ The study highlights the structural systematics survey of several halogenated isophthalamides (**X-DIPs**) as represented by **1** (Scheme 1; Figures 1-4) with only the salient features of the conformations presented herein.⁴



Scheme 1: A representative X-DIP isophthalamide with X = H, F, Cl, Br and I.

Experimental methods

Nucleophilic acyl substitution (condensation) reactions of isophthaloyl dichloride with the 2-amino-5-X-pyridines produces five X-DIP compounds. Purification was by standard organic washing and chromatography.¹⁻³

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 at least to 25°).

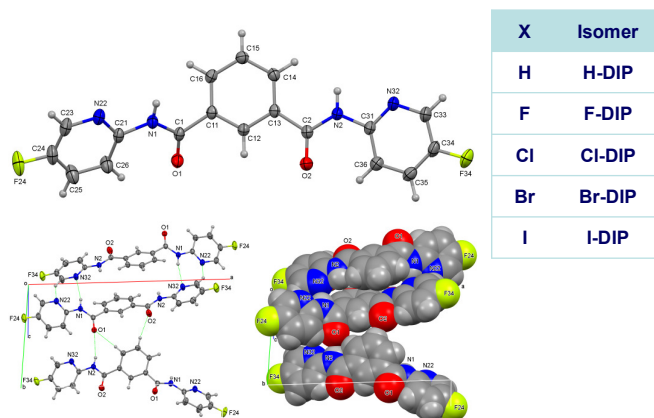


Figure 1: An ORTEP diagram of F-DIP (highlighting the *anti-lanti*-conformation)⁵ together with the primary hydrogen bonding (unit cell) and a CPK style view.

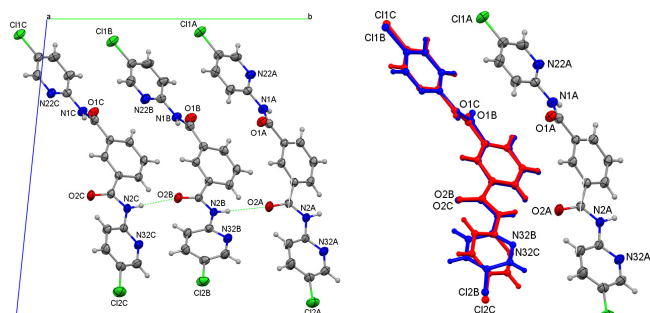


Figure 2: Cl-DIP ($Z=3$) together with the molecular overlap of molecules **B** and **C**.

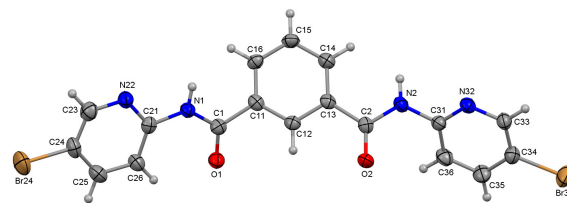


Figure 3: An ORTEP diagram of Br-DIP (*anti-lanti*)⁵ with 30% displacement ellipsoids.

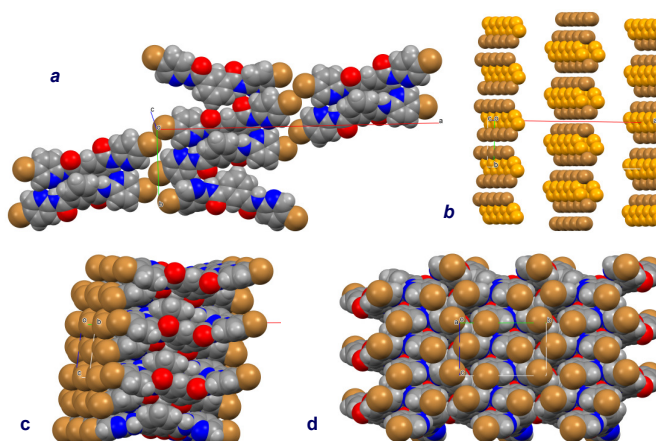


Figure 4: CPK views of the (a) primary hydrogen and halogen bonding interactions, (b) the wall of bromine atoms with Br24 (brown) and Br34 (orange) at the sheet interface and (c, d) the Br rich sheet that lines the sheet interface in Br-DIP.

In silico methods

The X-DIP molecular modelling optimisations and conformational analyses were usually performed using *ab initio* calculations (B3LYP/6-311++G**; 6-311++G, 6-311G**) on isolated (*gas-phase*) molecules with Gaussian03/09.¹⁴

Results and Conclusions

Structures in the X-DIP series preferentially adopt the *anti-lanti*- or *syn-lanti* molecular conformations with relatively small energy differences between the conformations.⁵ H-DIP adopts the *syn-lanti* conformation, F-DIP adopts the *anti-lanti* conformation (Figure 1), whereas Cl-DIP ($Z=3$) has two molecules **B** and **C** that are *syn-lanti* (Figure 2) and one molecule (**A**) adopting the *anti-lanti*-molecular conformations. I-DIP (as a monohydrate) can be considered as a molecule influenced by both hydrogen and halogen bonding.

Br-DIP is twinned in space group $C2/c$ and molecules in the crystal structure aggregate *via* reciprocal N-H...N and C-H...N interactions about inversion centres forming molecular pairs [graph sets $R_2^2(7)$, $R_2^2(20)$]. Br-DIP pairs connect by N-H...O and C-H...O interactions forming a one molecule wide sheet (~20 Å or $\frac{1}{2}$ unit cell *a*-axis) that is parallel with the *bc* plane. Strong intermolecular interactions within the sheet involve amides and pyridines (as N-H...O=C/N-H...N), together with C-H...O/N interactions. Two sheets form per unit cell intersecting at $x = 0, 0.5$. The sheet surface contains Br atoms interspersed regularly as a halide array with the five shortest Br...Br distances from 4.1 to 5.1 Å on each surface. Sheets are linked by Br...Br halogen bonding with shortest Br...Br = 3.6197(17) Å, ($N_c = 0.98$). Two other Br...Br contacts span the sheet interface at distances of 3.8534(14) Å and 3.8988(16) Å. The sheet surface does not contain any other type of intermolecular interaction and one can surmise that sheets can glide over one another easily and may explain the observed Br-DIP twinning. Twinning analysis in Br-DIP can be compared with extensive twinning in related series of isophthalamides.

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