Acta Crystallographica Section C
Crystal Structure Communications
ISSN 0108-2701

Unconventional hydrogen bonding and π-stacking in two substituted pyridine carboxamides

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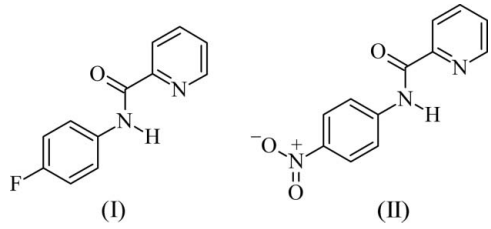
Received 24 August 2010
Accepted 8 September 2010
Online 17 September 2010

The crystal structures of two *para*-substituted aryl derivatives of pyridine-2-carboxamide, namely *N*-(4-fluorophenyl)pyridine-2-carboxamide, $C_{12}H_9FN_2O$, (I), and *N*-(4-nitrophenyl)-pyridine-2-carboxamide, $C_{12}H_9N_3O_3$, (II), have been studied. Compound (I) exhibits unconventional aryl–carbonyl C—H···O and pyridine–fluorine C—H···F hydrogen bonding in two dimensions and well defined π-stacking involving pyridine rings in the third dimension. The conformation of (II) is more nearly planar than that of (I) and the intermolecular interactions comprise one-dimensional aryl–carbonyl C—H···O hydrogen bonds leading to a stepped or staircase-like progression of loosely π-stacked molecules. The close-packed layers of planar π-stacked molecules are related by inversion symmetry. Two alternating interplanar separations of 3.439 (1) and 3.476 (1) Å are observed in the crystal lattice and are consistent with a repetitive packing sequence, $ABA'B'AB\ldots$, for the π-stacked inversion pairs of (II).

Comment

Amide functional groups are among the most common and prominent in nature. They are the principal C—N bond type linking amino acids together in proteins, with the latter arguably being the most specialized and versatile of all macromolecules in biology. There are numerous studies of simple carboxamides reporting their biological activity, from antimicrobial agents (Kumar *et al.*, 2007) to potent metabotropic glutamate subtype 5 (mGlu5) receptor antagonists (Bonnefous *et al.*, 2005) and cyclooxygenase-1 selective inhibitors (Kakuta *et al.*, 2008). Furthermore, carboxamide derivatives are ideal molecules for chelating metal ions since deprotonation of the amide N—H group affords a powerful σ-donor group. Coupled with additional functional groups based on N-, O- or S-donor atoms, polydentate carboxamides may be synthesized with variable arrays of metal-binding sites (Zhang *et al.*, 2002; Dasgupta *et al.*, 2008; Cornman *et al.*, 1999; Jiang *et al.*, 2004).

As part of ongoing work in our laboratory, we have isolated crystals of two previously prepared (Ray *et al.*, 1997; Dutta *et al.*, 1999), but hitherto crystallographically uncharacterized, pyridine-2-carboxamides, namely *N*-(4-fluorophenyl)pyridine-2-carboxamide, (I), and *N*-(4-nitrophenyl)pyridine-2-carboxamide, (II). In these derivatives, metal binding is possible through the pyridine N atom, the deprotonated amide N atom or the carbonyl O atom. The modes of binding can be controlled in some cases by the reaction conditions. Thus, in basic medium, the amide N—H group is deprotonated and metal ion coordination occurs through the amide anion (Qi, Ma *et al.*, 2003). However, if the reaction conditions are slightly acidic, binding occurs through the carbonyl O and pyridine N atoms (Morsali *et al.*, 2003). The molecular and crystal structures of metal-free carboxamides (I) and (II) are described below. In both cases, a single independent molecule occupies the asymmetric unit.



The pyridine ring and amide group of (I) are essentially coplanar (Fig. 1), while the 4-fluorophenyl ring is twisted out of the pyridine–amide plane with a C7—N1—C1—C6 torsion angle of 30.3 (2)° and a dihedral angle of 31.3 (5)° between the pyridine and benzene ring planes. The out-of-plane twist evident in (I) presumably reflects a balance between three factors: (i) a possible conformational adjustment to ameliorate nonbonded steric interactions between the benzene ring *ortho*-H atoms and neighbouring atoms of the amide functional group; (ii) the formation of an extended structure based on unconventional hydrogen bonds (see below); (iii) the intrinsic preference for a planar structure in a fully conjugated (resonance-delocalized) aromatic amide system. Noteworthy short intramolecular contacts that at least partly support the first notion are: H6···O1 = 2.39 (2) Å and H2···H100 = 2.38 (3) Å. The amide N1—C7 bond length is 1.346 (2) Å, while the C7—O1 bond length is 1.2178 (19) Å, *i.e.* slightly

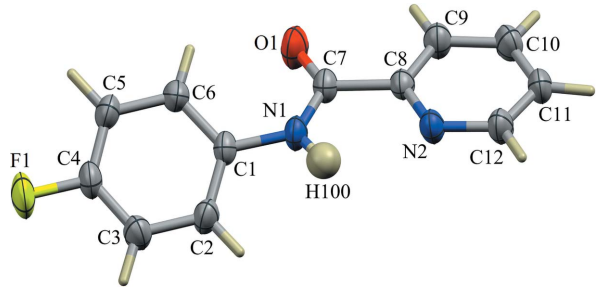


Figure 1
The molecular structure of (I), with displacement ellipsoids drawn at the 40% probability level, including for the amide H atom H100; all other H atoms are rendered as end-capped cylinders.

 doi:10.1107/S0108270110036218

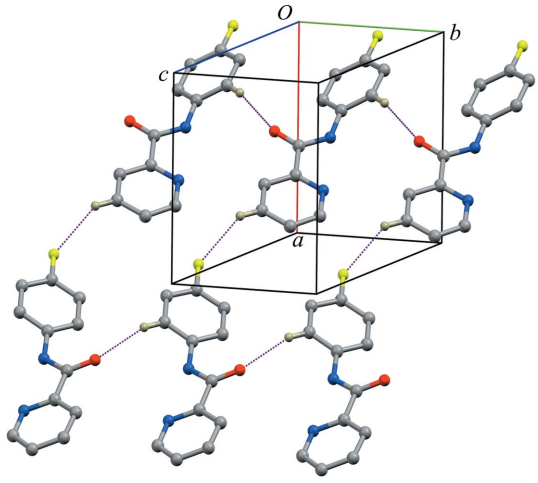


Figure 2
Representation of part of the lattice contents of (I), viewed approximately down the cell diagonal bisecting the *c O b* angle. Only the H atoms involved in significant hydrogen-bonding interactions are shown. All other atoms and bonds are represented as balls and cylinders, respectively.

shorter and longer, respectively, than the typical distances in non-amide systems (Orpen *et al.*, 1989); all other distances are normal.

Inspection of Fig. 2 suggests that unconventional hydrogen bonding is significant in the crystal lattice of (I). Specifically, individual molecules are linked by a two-dimensional network of C—H···O and C—H···F hydrogen bonds (Table 1). The C—H···O hydrogen bond occurs between the aryl H atom appended to C2 of one molecule and the carbonyl O atom of an adjacent molecule, while the C—H···F hydrogen bond occurs between the *para*-F atom of the benzene ring and pyridine atom H10 of an adjacent molecule (*i.e. para* to the pyridine N atom).

To better understand the nonplanar conformation of (I), we calculated the gas-phase geometry of the compound, starting from the X-ray coordinates, by energy optimization of the molecule using standard DFT (density functional theory) methods (Frisch *et al.*, 2004) at the B3LYP/6–31G** level of theory (Becke, 1993; Ditchfield *et al.*, 1971). The geometry-optimized conformation was completely planar, in distinct contrast to that of the X-ray crystal structure. No negative eigenvalues were obtained from a frequency calculation on the final planar conformation of the molecule, consistent with location of a true minimum on the potential energy surface. Although we have not conducted a full scan of conformational space for (I), it is highly likely that a planar geometry is preferred on energetic grounds (due to resonance delocalization) for an isolated molecule in the gas phase. The nonplanar conformation of (I) observed in the X-ray structure evidently reflects the principal conformational adjustment that enables formation of the extended one-dimensional hydrogen-bonded structure of (I) in the crystal lattice.

Experimentally significant π-stacking is present between the pyridine rings of adjacent molecules of (I). The interaction has the usual offset antiparallel geometry with inversion

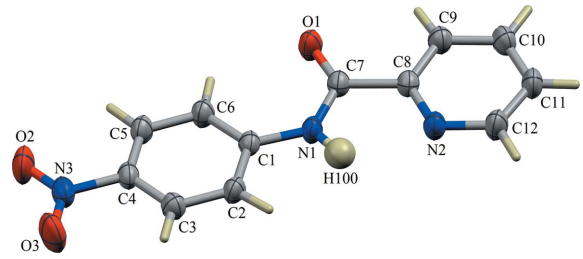


Figure 3
The molecular structure of (II), with displacement ellipsoids drawn at the 40% probability level, including for the amide H atom H100; all other H atoms are rendered as end-capped cylinders.

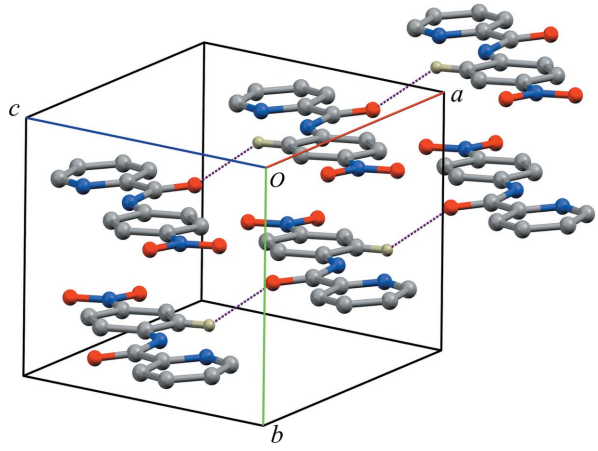


Figure 4
Representation of part of the lattice contents of (II), viewed approximately down the cell diagonal bisecting the *c O a* angle. Only the H atoms involved in significant hydrogen-bonding interactions are shown. All other atoms and bonds are represented as balls and cylinders, respectively.

symmetry (Janiak, 2000) in which the N atom of the first pyridine ring is positioned above the centre of the second ring. The metrics of the interaction, where *Cg* is the centre of gravity of the pyridine ring, β the angle between the $Cg \rightarrow Cg^{i}$ vector and the pyridine plane normal, IPS the interplanar separation [or perpendicular distance between *Cg* and the mean plane passing through Cg^{i}; symmetry code: (i) $-x+1, -y+1, -z+1$] and LS the lateral shift (or distance between *Cg* and the perpendicular projection of *Cg* on the partner ring), are: $Cg\cdots Cg^{i}$ = 3.858 (2) Å, β = 23.7 (2)°, IPS = 3.532 (2) Å and LS = 1.552 (2) Å. The interplanar separation is slightly longer than the graphite spacing of 3.35 Å (Bacon, 1951), but nevertheless still ideal for π-stacking interactions (Hunter & Sanders, 1990).

In (II), the pyridine ring and the amide moiety are again effectively coplanar, while the 4-nitrobenzene ring is slightly twisted out of the amide group plane (Fig. 3). The nonplanarity is markedly less than for (I); the C6—N2—C7—C8 torsion angle is 6.6 (2)° and the dihedral angle between the pyridine and nitrobenzene rings is 4.1 (2)°. The amide N2—C6 and carbonyl C6—O1 bond lengths are 1.3580 (15) and 1.2195 (14) Å, respectively, in agreement with those of (I).

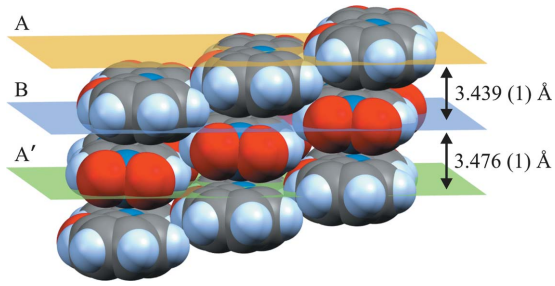


Figure 5
Space-filling view (van der Waals radii) of the staircase-like π-stacking for three layers (A, B and A') of molecules in the crystal lattice of (II). The two experimentally distinct interplanar separations are indicated, leading to the packing sequence $ABA'B'AB\ldots$, *etc*. Each molecule constitutes a 'step' and is hydrogen bonded to the preceding and next step in the 'staircase' (as in Fig. 4).

Intermolecular C—H···O hydrogen bonds between the *meta*-H atom of the nitrobenzene ring and the carbonyl O atom of a neighbouring molecule lead to the formation of stepped one-dimensional chains of molecules that extend in the [100] direction (Table 2). Furthermore, adjacent one-dimensional chains combine to form sheets that lie parallel to the (010) plane in the lattice (Fig. 4). One such sheet, for example, lies in the (040) plane.

Molecules of (II) stack one on top of another as inversion pairs. The π-stacking sequence is defined by the repeating pattern $ABA'B'AB\ldots$ in which the distances between the molecular mean planes for the structurally distinct inversion pairs AB (or $A'B'$) and BA' (or $B'A$) are 3.44 (1) and 3.48 (1) Å, respectively. The π-stacking axis is collinear with the crystallographic b axis, leading to an array of inversion-paired π-stacked hydrogen-bonded ribbons in the crystal lattice (Fig. 5). Inspection of the π-stacked molecules in a given one-dimensional hydrogen-bonded chain, *i.e.* along the 'staircase' axis if each member of the chain represents a 'step', indicates that molecules connected by hydrogen bonds exhibit short (ring edge)···(ring edge) nonbonded interactions. The tightest of these occurs between nitrobenzene rings: $Cg\cdots Cg^{ii}$ = 4.433 (2) Å, β = 39.9 (2)°, IPS = 3.400 (2) Å and LS = 2.845 (2) Å [symmetry code: (ii) $-x+2, -y+1, -z+1$], where the variables are as defined previously. The staircase-like packing, π-stacking and hydrogen bonding in the crystal lattice of (II) evidently lead to only a minor conformational twist for the experimental structure since the DFT-calculated gas-phase conformation of (II) was completely planar, in accord with the calculated conformation of (I) discussed earlier.

Finally, it is clear that changing the *para* substituent on the benzene ring from fluorine in (I) to a nitro group in (II) significantly changes the crystal packing and extended structure between the derivatives and thus the observed molecular conformation. In both carboxamides, unconventional hydrogen bonds between amide carbonyl O atoms and aryl C—H donors constitute the primary interaction for the extended solid-state structure. This is augmented by significant π-stacking interactions roughly orthogonal to the planes containing the extended structures in both compounds. Interestingly, the isomorphous *para*-chloro (Zhang *et al.*, 2006) and *para*-bromo (Qi, Yang *et al.*, 2003) analogues of (I), which crystallize in the space group $P\overline{1}$, have pyridine–halogen C—H···X (X = Cl, Br) and aryl–carbonyl C—H···O hydrogen-bond networks that lead to two-dimensional hydrogen-bonded sheets somewhat different to those present in monoclinic (I). Specifically, the orientations of the individually planar molecules in the *para*-chloro and *para*-bromo derivatives are such that all carbonyl groups point in the same direction, in distinct contrast to the orientational preference observed for nonplanar (I), namely rows of oppositely oriented carbonyl groups. Evidently, the presence of a small highly electronegative *para*-fluoro substituent in (I) appreciably alters the most efficient way in which to pack the carboxamide derivative such that it is not isomorphous with the heavier halogenated congeners in the series.

Deprotonated compounds (I) and (II) are currently being used as anionic ligands for a number of metal ions in our laboratory and their coordination chemistry will be reported elsewhere.

Experimental

Compounds (I) and (II) were synthesized according to the literature method of Barnes *et al.* (1978). X-ray-quality crystals of (I) were grown by slow evaporation of the reaction mixture, while X-ray-quality crystals of (II) were grown by slow evaporation from a saturated solution of (II) in dimethyl sulfoxide.

Compound (I)

Crystal data

$C_{12}H_9FN_2O$
M_r = 216.21
Monoclinic, $P2_1/c$
a = 8.2500 (3) Å
b = 6.0649 (2) Å
c = 20.5484 (8) Å
β = 96.479 (4)°
V = 1021.58 (6) Å^3
Z = 4
Mo $K\alpha$ radiation
μ = 0.10 mm^{-1}
T = 296 K
0.60 × 0.45 × 0.35 mm

Data collection

Oxford Diffraction Xcalibur2 CCD diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2008)
T_{min} = 0.960, T_{max} = 1.000
10495 measured reflections
2005 independent reflections
1593 reflections with $I > 2\sigma(I)$
R_{int} = 0.027

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.049
$wR(F^2)$ = 0.145
S = 1.03
2005 reflections
182 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.18 e Å^{-3}
$\Delta\rho_{min}$ = −0.21 e Å^{-3}

Table 1
Hydrogen-bond geometry (Å, °) for (I).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···O1^{iii}	0.95 (2)	2.38 (2)	3.260 (2)	155 (2)
C10—H10···F1^{iv}	1.00 (2)	2.53 (2)	3.397 (2)	145 (2)

Symmetry codes: (iii) $x, y+1, z$; (iv) $x+1, -y+\frac{1}{2}, z+\frac{1}{2}$.

Table 2
Hydrogen-bond geometry (Å, °) for (II).

D—H···A	D—H	H···A	D···A	D—H···A
C2—H2···O1^{v}	0.973 (18)	2.425 (18)	3.277 (2)	145.9 (12)

Symmetry code: (v) $x+1, y, z$.

Compound (II)

Crystal data

$C_{12}H_9N_3O_3$
M_r = 243.22
Triclinic, $P\overline{1}$
a = 6.1490 (3) Å
b = 7.3055 (3) Å
c = 13.6613 (5) Å
α = 100.162 (4)°
β = 97.147 (3)°
γ = 112.760 (4)°
V = 544.33 (4) Å^3
Z = 2
Mo $K\alpha$ radiation
μ = 0.11 mm^{-1}
T = 295 K
0.60 × 0.45 × 0.05 mm

Data collection

Oxford Diffraction Xcalibur2 CCD diffractometer
Absorption correction: multi-scan (*CrysAlis RED*; Oxford Diffraction, 2008)
T_{min} = 0.938, T_{max} = 1.000
4092 measured reflections
2148 independent reflections
1722 reflections with $I > 2\sigma(I)$
R_{int} = 0.016

Refinement

$R[F^2 > 2\sigma(F^2)]$ = 0.041
$wR(F^2)$ = 0.124
S = 1.07
2148 reflections
199 parameters
All H-atom parameters refined
$\Delta\rho_{max}$ = 0.13 e Å^{-3}
$\Delta\rho_{min}$ = −0.26 e Å^{-3}

H atoms were refined isotropically without restraints. For compounds (I) and (II), the refined N—H and C—H distances are in the ranges 0.86 (2)–0.899 (17) Å and 0.932 (17)–1.014 (19) Å, respectively.

For both compounds, data collection: *CrysAlis CCD* (Oxford Diffraction, 2008); cell refinement: *CrysAlis RED* (Oxford Diffraction, 2008); data reduction: *CrysAlis RED*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 2008); program(s) used to refine structure: *SHELXL97* (Sheldrick, 2008); molecular graphics: *Mercury* (Macrae *et al.*, 2008); software used to prepare material for publication: *WinGX* (Farrugia, 1999).

The authors thank the University of KwaZulu-Natal and AuTEK Biomed (Mintek and Harmony) for financial support.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: LN3145). Services for accessing these data are described at the back of the journal.

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