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Short communication

Aggregation of fluorine-substituted pyridines

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ABSTRACT

The influence of fluorine substituents on the crystallisation behaviour of pyridine was investigated by crystal structure determinations. The low melting compounds 2-fluoropyridine, 2,6-difluoropyridine and 2,4,6-trifluoropyridine were crystallised by *in situ* crystallisation directly on the single crystal X-ray diffractometer.

1. Introduction

The importance of fluorine substituted compounds is based on the fluorine atom which has an immense effect on the physical, chemical, and biological properties of such compounds. The negative inductive and the positive mesomeric effects of the fluorine substituents [1] greatly determine the intermolecular interactions and the aggregation behaviour of these molecules [2]. In the case of fluorinated aromatic compounds, the electron density distribution depends on the substitution pattern on the aromatic scaffold. A non-fluorinated aromatic molecule shows a typical pi-cloud, whereas a perflourinated aromatic one features an inverse electron density distribution [3,4].

These electronic effects of fluorine can be used for crystal engineering [5]. For example, in contrast to benzene and hexafluorobenzene, which crystallise in an edge-to-face structure (T-shape motif), the co-crystals of a 1:1 mixture of these compounds show a stacked structure with an alternate sequence of molecules [6,7]. According to Pauling [8], it is expected that hydrogen bonds are preferably formed with the electronegative fluorine. While the F^- anion is an excellent acceptor [9], the organic C–F group forms only weak interactions compared to typical H-bond acceptors such as oxygen and nitrogen [10]. Analysis of structural data and calculations pointed out the weakness of covalently bound fluorine as hydrogen-bond acceptor [10–12]. Additionally several studies showed that the C–F group does not favour the formation of F···F contacts as the C–Cl, C–Br, and C–I groups do [13,14]. Based on the low polarisability of the fluorine atom, the dispersion forces of attraction in F···F contacts should be small [14].

In previous studies, we have shown that the substitution pattern on the benzene backbone of iodo-substituted benzonitriles and nitrobenzenes has an influence on the formation of the packing motifs in corresponding crystal structures [15,16]. Recently, it was shown that the substitution of deuterium against hydrogen atoms on the pyridine backbone leads to a low-temperature polymorph for pentadeuteropyridine [17]. Basing on these observations, here in this article we have studied influence of fluorine substituents on the crystal packing and the aggregation behaviour of fluorinated pyridines. The study is a subject of particular interest as these aromatics offer the possibility for the study of packing modes, which specially involve weak F···F contacts as well as weak F···H hydrogen bonds.

The question is whether fluorine substituents influence the aggregation of substituted pyridines. Is there a relation between the substitution pattern of fluorine atoms and the crystal packing of the substituted pyridines? Continuing our investigations on aggregation of substituted arenes in the solid state [15,16], the low melting compounds 2-fluoropyridine, 2,6-difluoropyridine and 2,4,6-trifluoropyridine were crystallised by *in situ* crystallisation directly on the single crystal X-ray diffractometer and their crystal structures were studied in detail.

2. Experimental section

Single crystal X-ray diffraction measurements of 2-fluoropyridine, 2,6-difluoropyridine and 2,4,6-trifluoropyridine were carried out on a Bruker Smart 1000 CCD diffractometer using

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Table 1
Crystal data and details of structure refinement for 2-fluoropyridine, 2,6-difluoropyridine and 2,4,6-trifluoropyridine.

	2-Fluoropyridine	2,6-Difluoropyridine	2,4,6-Trifluoropyridine
Chemical formula	C_5H_4NF	$C_5H_3F_2N$	$C_5H_2F_3N$
Temperature (K)	157(2)	203(2)	208(2)
Formula weight	97.09	115.08	133.08
Radiation type	Mo Kα	Mo Kα	Mo Kα
Wavelength (Å)	0.71073	0.71073	0.71073
Crystal system	Orthorhombic	Monoclinic	Monoclinic
Space group	*Pbca*	*Pn*	*C2/c*
Unit cell dimensions (Å)	$a = 5.683(7)$ $b = 11.770(19)$ $c = 14.22(2)$	$a = 3.832(3)$ $b = 6.348(6)$ $c = 10.441(9)$ $\beta = 92.34(3)$	$a = 8.5928(17)$ $b = 14.792(3)$ $c = 8.2461(16)$ $\beta = 96.13$
Volume (Å^3)	951(2)	253.8(4)	1042.1(4)
Z	8	2	8
Calculated density (g/cm^3)	1.356	1.506	1.696
Absorption coefficient (mm^{-1})	0.110	0.143	0.179
$F(000)$	400	116	528
Θ-Range for data collection (°)	2.86–24.81	3.21–24.91	2.75–25.01
Reflect. collected/unique	2525/665	600/385	1347/766
Data/restrains/parameters	665/0/65	385/2/74	766/0/83
Goodness-of-fit on F^2	0.965	1.328	1.385
Final R_1/wR_2 ($I > 2\sigma$)	0.0597/0.1264	0.0908/0.2565	0.1118/0.3159
R_1/wR_2 (all data)	0.0933/0.1401	0.0936/0.2614	0.1295/0.3434
Largest diff. peak and hole (e Å^{-3})	0.216 and −0.230	0.258 and −0.298	0.603 and −0.475

graphite-monochromated Mo Kα radiation. The compounds were first purified by distillation in high vacuum, and then transferred into an attached capillary. The sealed capillary was transferred to the diffractometer with a detachable cooling device. The single crystals suitable for X-ray diffraction were grown *in situ* using a computer-controlled device that applied a focused CO_2 laser beam along the capillary. Based on the geometry of the crystallisation device one omega-scan was collected [18]. Structures were solved by the heavy-atom methods, and all non-hydrogen atoms were refined anisotropically on F^2 (program SHELXTL-97, G.M. Sheldrick, University of Göttingen, Göttingen, Germany). The H atoms were positioned geometrically and refined using a riding model. The crystallographic data and processing parameters are shown in Table 1.

3. Results and discussion

According to the observation of Mootz and Wussow [19] pyridine crystallises with four independent molecules in generally independent positions of the space group *Pna2₁* and contains layers perpendicular to the *c*-axis direction. In the case of 2-fluoropyridine, the substitution of one hydrogen by a fluorine atom at the pyridine backbone leads to a rearrangement of the molecules. 2-Fluoropyridine crystallises in the orthorhombic space group *Pbca* (Fig. 1). The observed crystal structure is shown in Fig. 4a. The molecules built a herringbone arrangement with a slightly distorted edge-to-face configuration. The angle between two neighbouring layers is about 58.8°. For comparison, the T-shape motifs in the crystal structure of benzene show a torsion angle of about 90°. In contrast to benzene (5.97 Å) the centroid-centroid distance in 2-fluoropyridine is reduced to 4.76 Å.

No significant C–H···F or F···F interactions were found. The shortest C–H···F distance is 2.71 Å, which is in the range of the sum of van der Waals radii of F···H (2.67 Å). Almost similar structural motifs of distorted edge-to-face configuration are found in the crystal structure of fluorobenzene [20]. In the case of fluorobenzene, however, the C–H···F interactions of 2.60 Å form intermolecular synthons. Such synthons show a close relationship to structure-determining motifs in pyridinium fluoride, pyridine-1-oxide, and benzonitrile [20].

2,6-Difluoropyridine crystallises in the monoclinic space group *Pn* (Fig. 2). The analysis of the X-ray measurement shows a distorted edge-to-face arrangement (Fig. 4b), similar to the crystal structure in 2-fluoropyridine and 1,3-difluorobenzene. In the case of 2,6-difluoropyridine, the angle between two neighbouring layers is slightly reduced to 46.8°. Comparable with 2-fluoropyridine, the possible intermolecular contacts are C–F···H hydrogen bonds and F···F dipole···dipole contacts. In reality, only weak C-H···F contacts of about 2.70 Å are found.

2,4,6-Trifluoropyridine crystallises in the monoclinic space group *C2/c* (Fig. 3). The substitution pattern of fluorine atoms on the pyridine backbone leads to a significant change of the aggregation. The molecules are coplanarly arranged and form stacking layers with an angle of 10.9° between two neighbouring layers. Interestingly, the analysis of the crystal structure reveals different types of weak intermolecular interactions (Fig. 4c).

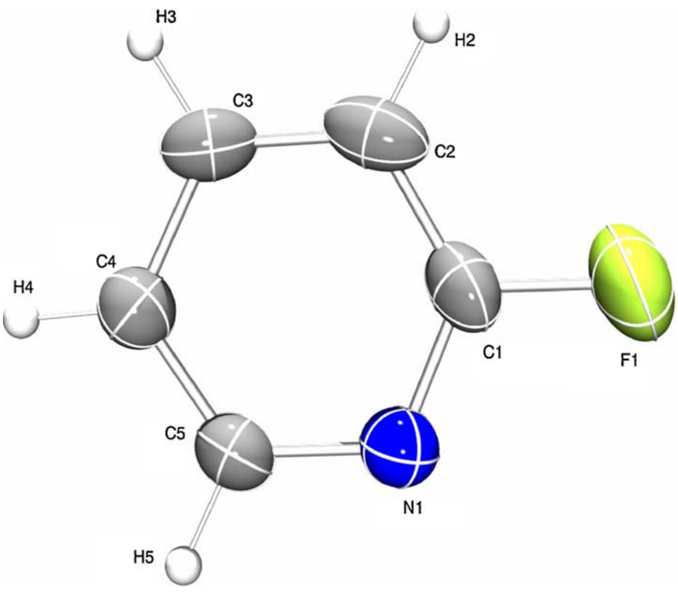

Fig. 1. Molecule structure of 2-fluoropyridine.

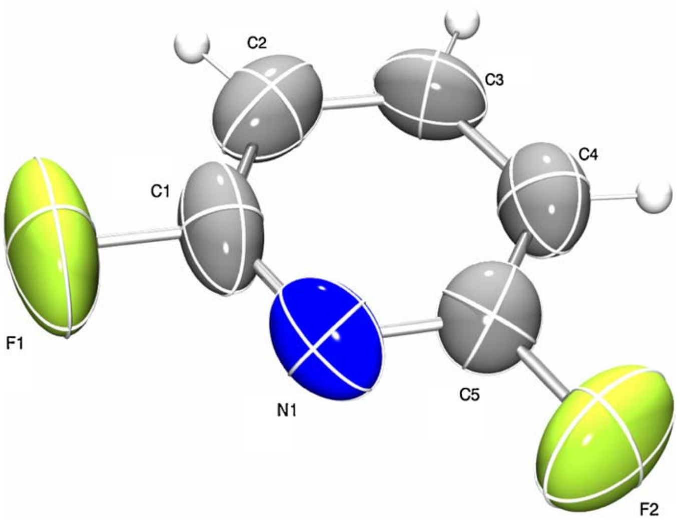

Fig. 2. Molecule structure of 2,6-difluoropyridine.

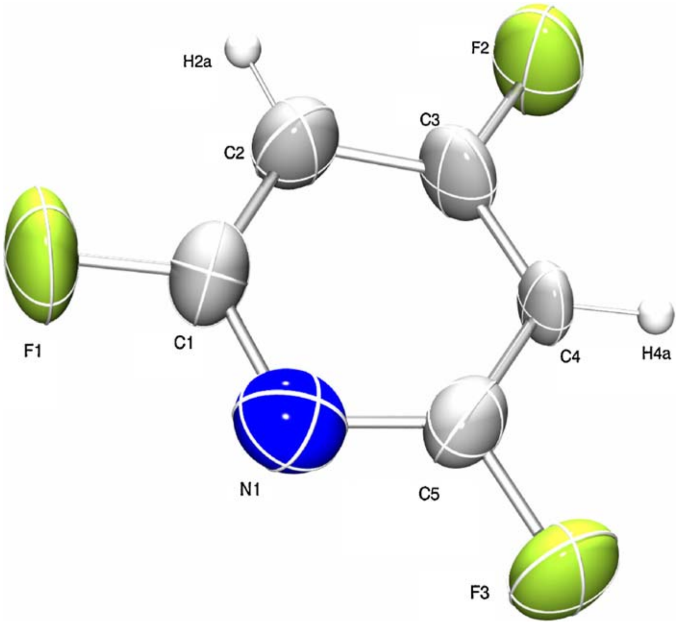

Fig. 3. Molecule structure of 2,4,6-trifluoropyridine.

The determined F···F contact of 2.82 Å is slightly shorter than the sum of van der Waals radii of two fluorine atoms (2.94 Å). Additionally, C–H···F (2.54 Å) and C–H···N (2.60 Å) bonds involving highly polarised H-atoms are also observed here. In accordance to our results, similar influence of fluorination on neighbouring C–H bonds was previously described by Smart [21].

Noteworthy is the structural similarity between 2,4,6-trifluoropyridine, 1,3,5-trifluorobenzene and 1,3,5-triazine (Fig. 5). These structures are constructed with topological similar motifs of C–H···F or C–H···N hydrogen bonds. A detailed study of the similarity between 1,3,5-trifluorobenzene and 1,3,5-triazine was reported by Thalladi et al. [20]. The comparison of 2,4,6-trifluoropyridine with 1,3,5-trifluorobenzene and 1,3,5-triazine indicates that even the nature and character of the weak C–H···F hydrogen bonds can be as important as C–H···N hydrogen bonds in stabilising specific crystal structures.

The detailed investigations on fluorine-substituted pyridines show that the self-organisation of molecules in crystals depends on a variety of parameters. Although simple causal relationships of

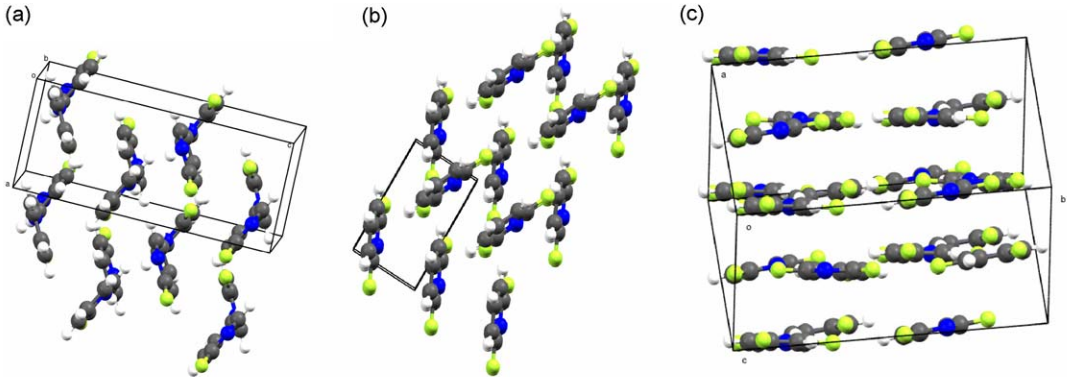

Fig. 4. Crystal structures of 2-fluoropyridine (a), 2,6-difluoropyridine (b) and 2,4,6-trifluoropyridine (c).

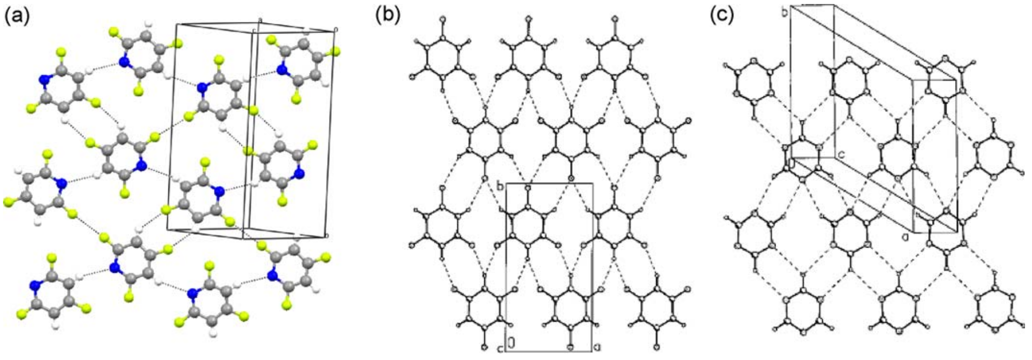

Fig. 5. Structural similarity between 2,4,6-trifluoropyridine (a), 1,3,5-trifluorobenzene (b) and 1,3,5-triazine (c).

molecular structures and crystal structures are generally not possible, some specific characteristics of the aggregation behaviour can be observed. Halogen···Halogen intermolecular contacts can be described by two preferred geometries based on the C–X1···X2 and X1···X2–C angles θ_1 and θ_2, respectively. In contrast to interactions with $\theta_1 = 90^\circ$ and $\theta_2 = 180^\circ$, geometries with θ_1–θ_2 are of the van der Waals type and does not form stabilising interactions [22–24]. The crystal structure database (CSD) contains 788 compounds with F···F distances below 3.0 Å, out of which only 13 compounds do not have the geometries with θ_1–θ_2 [2]. This result is in line with our investigation on the fluorine-substituted pyridines presented here. Intermolecular F···F distances below 3.0 Å are only found in 2,4,6-trifluoropyridine and the C-F···F and F···F-C motifs in this compound has a geometry with $\theta_1 \sim \theta_2$.

But interestingly, there is a dependence of the coplanar arrangement of pyridine molecules with increasing number of fluorine substituents. In contrast, a comparable planarisation effect depending on the number of fluorine substituents is not visible in fluorinated benzenes. However, the T-shape aggregation of crystalline perfluorobenzene and the crystal structure of pressure frozen perfluoropyridine [25] is remarkable and could be interpreted by the lack of C–H···F contacts. In contrast to the dominant electrostatic contributions in strong X···H bonds with X = Cl, Br and I, fluorine behaves distinctly differently. Hyla-Kryspin et al. [26] showed that the electrostatic term in weak F···H hydrogen bridges can be even smaller than the dispersion term. Our studies on fluorine-substituted pyridines give an indication that weak C–H···F contacts stabilise specific crystal structures.

4. Conclusions

The X-ray crystallographic studies of 2-fluoropyridine, 2,6-difluoropyridine and 2,4,6-trifluoropyridine indicate that fluorine determines the aggregation of the molecules in the solid-state. The replacement of hydrogen by fluorine leads to significant changes in the crystal structures. Based on the negative inductive effect and the positive mesomeric effect of the growing number of fluorine substituents on the pyridine backbone, there is an influencing factor on the packing motifs, visible in an increasing coplanar arrangement of the molecules.

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CIF-files giving X-ray data with details of refinement procedures for 2-fluoropyridine, 2,6-difluoropyridine and 2,4,6-trifluoropyridine (CCDC 742847–742849) are available free of charge via the Internet at http://pubs.acs.org.

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