



# The potential of CH...N interactions in determining the crystal structures of novel 3,4-disubstituted-5-pyridinyl-isoxazoles

Monika Mazik,<sup>a,\*</sup> Dieter Bläser<sup>b</sup> and Roland Boese<sup>b</sup>

<sup>a</sup>*Institut für Organische Chemie der Universität Essen, D-45117 Essen, Germany*

<sup>b</sup>*Institut für Anorganische Chemie der Universität Essen, D-45117 Essen, Germany*

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## Abstract

The crystal structures of novel 3,4-disubstituted-5-pyridinyl-isoxazoles, such as 3-methyl-4-phenyl-5-pyridinyl-isoxazole (**1**), 4-methyl-3-phenyl-5-pyridinyl-isoxazole (**2**) and 3,4-diphenyl-5-pyridinyl-isoxazole (**3**), are governed by significant CH...N interactions. © 2000 Elsevier Science Ltd. All rights reserved.

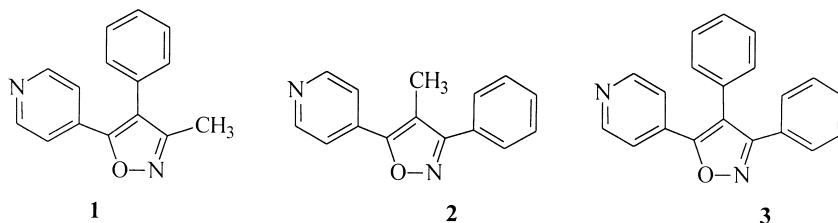
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Although it is now well-recognized that C–H groups can act as weak hydrogen bond donors and particularly the hydrogen–bond nature of the CH...O contacts found in molecular crystals has been well-established,<sup>1</sup> the nature of the CH...N interactions is still a subject of controversy.<sup>2</sup> Taylor and Kennard already suggested in 1982 that some short CH...N interactions should be similar to the CH...O type, that is, hydrogen bond-like.<sup>3</sup> Establishing the limits between ‘true’ hydrogen bonds and classical van der Waals contacts for weak CH...Y (Y = O, N, Cl) interactions is a subject of current interest and active research.

In this contribution the potential of CH...N interactions in determining the crystal structures of 3-methyl-4-phenyl-5-pyridin-4'-yl-isoxazole (**1**), 4-methyl-3-phenyl-5-pyridin-4'-yl-isoxazole (**2**) and 3,4-diphenyl-5-pyridin-4'-yl-isoxazole (**3**) is presented. Compounds **1–3** provide new examples for solid state structures, in which the CH...N interactions are not only important as secondary interactions, but in which they play a dominant role (besides aryl–aryl interactions) in determining the crystal packing. Additionally, the synthesis of new isoxazole derivatives is important owing to the potential biological activity and pharmaceutical or agricultural applications of these compounds.<sup>4a</sup>

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\* Corresponding author. E-mail: monika.mazik@ocl.orgchem.uni-essen.de



Isoxazoles **1–3**<sup>5</sup> were obtained in almost quantitative yields by cyclization of 3-phenyl-4-(pyridin-4'-yl)-3-buten-2-on-oxime, 2-methyl-1-phenyl-3-(pyridin-4'-yl)-2-propen-1-on-oxime, and 1,2-diphenyl-3-(pyridin-4'-yl)-2-propen-1-on-oxime in the presence of silica gel and chloroform as solvent at room temperature. The starting pyridinyl- $\alpha,\beta$ -unsaturated ketoximes were prepared as described in Ref. 2c,d and 6. Compounds **1–3** can also be prepared by the known method involving cyclization of  $\alpha,\beta$ -unsaturated ketoximes by heating in ethanol in the presence of sodium hydroxide as base;<sup>4b</sup> however, with lower yields. Crystals of **1–3** were obtained by slow evaporation of the solvent from ethanol solutions. X-ray crystallography<sup>7</sup> established that the crystal structures are governed by short C–H $\cdots$ N interactions. The molecules of **1** and **2** involve both C( $sp^2$ )–H and C( $sp^3$ )–H donors. Contrary, **3** involves only C( $sp^2$ )–H donor groups. The potential acceptors for hydrogen bonds in all these compounds are the pyridine nitrogen, isoxazole nitrogen and isoxazole oxygen atoms. In all cases, the pyridine nitrogen atom participates in C–H $\cdots$ N interactions with H $\cdots$ N distances between 2.41–2.62 Å and C–H $\cdots$ N angles in the range of 133–161°. Additionally, the molecules in the crystal structure of **1** and **3** are held together by C–H $\cdots$ N-isoxazole interactions with H $\cdots$ N separations of 2.53–2.67 Å and C–H $\cdots$ N angles varying between 145–164°. In all these C–H $\cdots$ N contacts the distance between the proton and the acceptor atom are shorter than the sum of their van der Waals radii (2.75 Å). Both the relatively large angles at the hydrogen atom and the short H $\cdots$ N separations indicate the hydrogen bond nature of these CH $\cdots$ N interactions.

The characteristic feature of the crystal structures of **1** and **2** is the participation of the substituent in 3 position (methyl and phenyl, respectively) in C–H $\cdots$ N hydrogen bonds with the pyridine nitrogen atom of the adjacent molecule (Fig. 1a and 2). The C( $sp^3$ )–H $\cdots$ N-pyr distances between the methyl hydrogen and the pyridine nitrogen of the neighbours in the crystal structure of **1** are 2.41 Å (C $\cdots$ N 3.45 Å, C–H $\cdots$ N angle 161°, Fig. 1a). These hydrogen-bonded chains are linked with the chains from the other layer by C( $sp^2$ )–H $\cdots$ N-isoxazole hydrogen bonds as shown in Fig. 1b (H $\cdots$ N 2.53 Å, C $\cdots$ N 3.58 Å, C–H $\cdots$ N angle 164°).

The molecules of **2** are arranged in infinite hydrogen-bonded chains with C( $sp^2$ )–H $\cdots$ N-pyr distances of 2.62 Å (C $\cdots$ N 3.44 Å, C–H $\cdots$ N angle 133°). The molecules of **2** adopt a head-to-tail orientation (Fig. 2). The isoxazole nitrogen atom of **2** participates only in longer CH $\cdots$ N interactions varying from 2.81 to 2.93 Å (C $\cdots$ N 3.65 Å, CH $\cdots$ N angles 125–135°).

The crystal structure of **3** is characterized by the hydrogen bonding motif involving both the C( $sp^2$ )–H $\cdots$ N-pyr and the C( $sp^2$ )–H $\cdots$ N-isoxazole bonds shown in Fig. 3. The C( $sp^2$ )–H $\cdots$ N-pyr distances are 2.62 Å (C $\cdots$ N 3.60 Å, C–H $\cdots$ N angle 150°) and the C( $sp^2$ )–H $\cdots$ N-isoxazole distances amount to 2.67 Å (C $\cdots$ N 3.61 Å, C–H $\cdots$ N angle 145°).

The crystal structures of **1–3** also show some other common features. The isoxazole oxygen atoms of **1–3** have the tendency to participate in C–H $\cdots$ O contacts with longer H $\cdots$ O separation of 2.80–2.90 Å and relatively low angles at the hydrogen atom (CH $\cdots$ O angle 124–129°). The pyridine and the phenyl rings adopt the edge-to-face and offset face-to-face orientations.

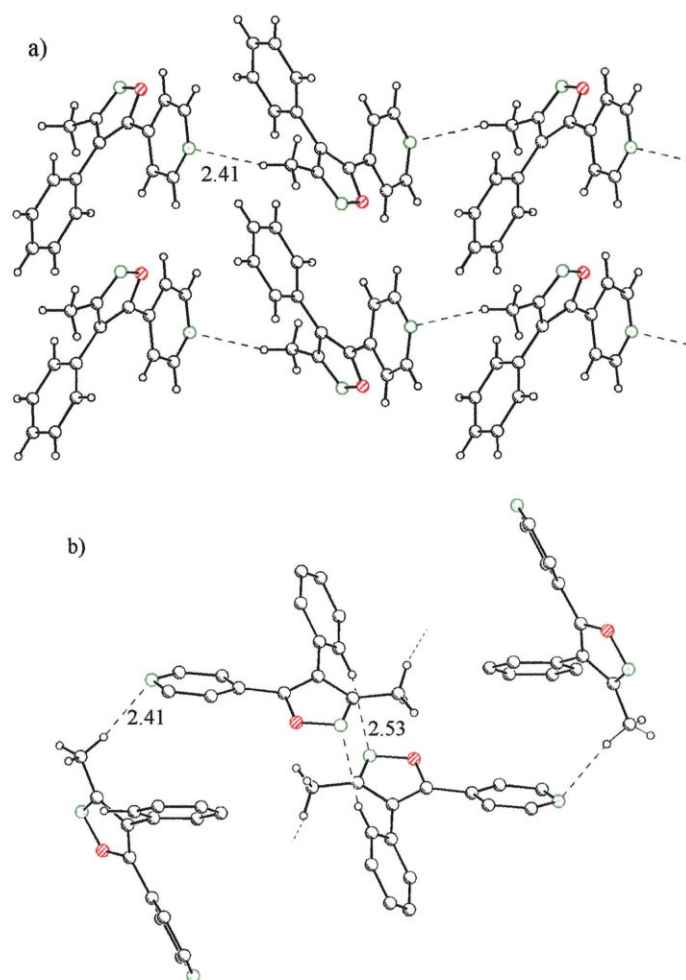


Figure 1. The C(*sp*<sup>3</sup>)-H...N-pyr (a), and C(*sp*<sup>2</sup>)-H...N-isoxazole (b) hydrogen bonds in the crystal structure of **1**

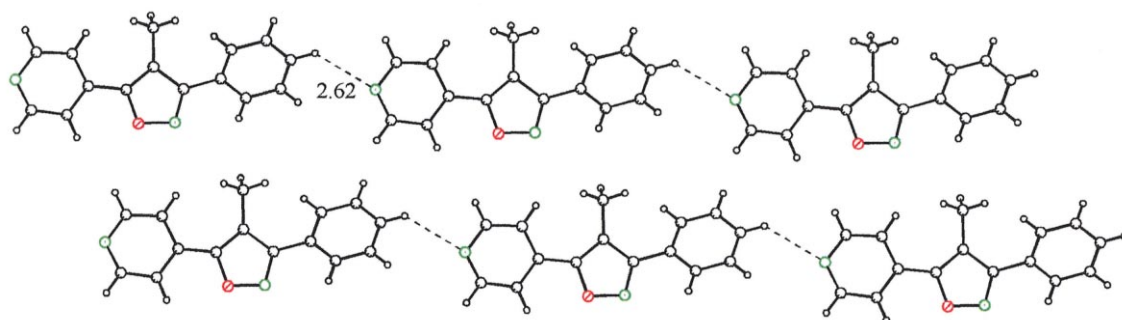


Figure 2. CH...N hydrogen-bonded chains in the crystal of **2**

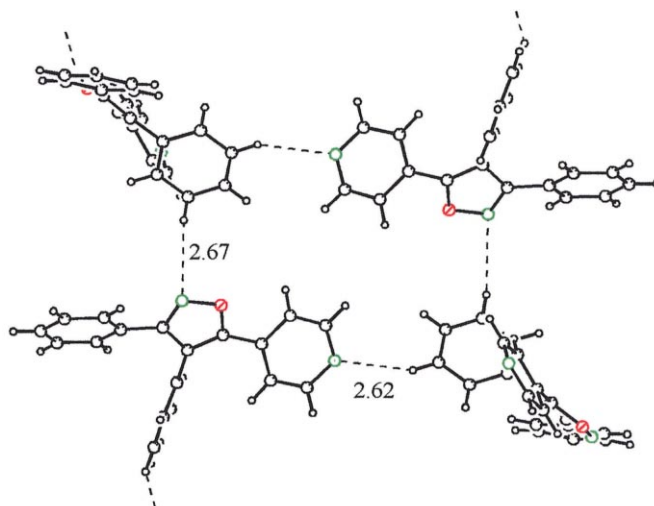


Figure 3. Hydrogen bonding motif in the crystal of **3**

The analysis of the crystal structures of pyridinyl–isoxazoles provides an interesting contribution to the discussion about weak hydrogen bonds and to a better understanding of molecular recognition phenomena.

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### References

- (a) Novoa, J. J.; Lafuente, P.; Mota, F. *Chem. Phys. Lett.* **1998**, *290*, 519–525, and references cited therein. (b) Steiner, T.; Desiraju, G. R. *Chem. Commun.* **1998**, 891–892; (c) Steiner, T. *Chem. Commun.* **1997**, 727–734. (d) Desiraju, G. R. *Acc. Chem. Res.* **1997**, *29*, 441–449. (e) Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*, Elsevier, Amsterdam, 1989, pp. 142–164, and references cited therein. (f) Jeffrey, G. A. *An Introduction to Hydrogen Bonding*, New York, 1997, pp. 79–97, and references cited therein.
- For examples of CH $\cdots$ N hydrogen bonds, see: (a) Cotton, F. A.; Daniels, L. M.; Jordan IV, G. T.; Murillo, C. A. *Chem. Commun.* **1997**, 1673–1674, and references cited therein. (b) Desiraju, G. R. *Crystal Engineering. The Design of Organic Solids*; Elsevier: Amsterdam, 1989; pp. 166–167, and references cited therein. (c) Mazik, M.; Bläser, D.; Boese, R. *Tetrahedron* **1999**, *55*, 7835–7840. (d) Mazik, M.; Bläser, D.; Boese, R. *Chem. Eur. J.* **2000**, in press, and references cited therein.
- Taylor, R.; Kennard, O. *J. Am. Chem. Soc.* **1982**, *104*, 5063–5070.
- (a) Lang Jr., S. A.; Lin, Y.-I. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. E., Ed.; Pergamon Press, 1984; Vol. 6, pp. 127–130. (b) *ibid.* pp. 61–88.
- Compound **1**:  $^1\text{H}$  NMR:  $\delta$  = 2.18 (s, 3H, CH $_3$ ), 7.21–7.23 (2H $_{\text{Ph}}$ ), 7.32–7.33 (2H $_{\text{Pyr}}$ ), 7.40–7.42 (3H $_{\text{Ph}}$ ), 8.50–8.52 (2H $_{\text{Pyr}}$ ).  $^{13}\text{C}$  NMR: 10.86, 119.45, 120.66, 129.15, 129.74, 129.93, 129.98, 135.17, 150.76, 160.94, 161.74. C $_{15}\text{H}_{12}\text{N}_2\text{O}_4$  calcd: 236.0950; found: 236.0938. M.p. 126–128°C.  $R_f$  = 0.58. Compound **2**:  $^1\text{H}$  NMR:  $\delta$  = 2.36 (s, 3H, CH $_3$ ), 7.49–7.50 (3H $_{\text{Ph}}$ ), 7.62–7.68 (2H $_{\text{Ph}}$ , 2H $_{\text{Pyr}}$ ), 8.75–8.77 (2H $_{\text{Pyr}}$ ).  $^{13}\text{C}$  NMR: 9.35, 111.75, 120.52, 128.46, 128.83, 128.87, 129.76, 135.50, 150.42, 162.66, 164.25. C $_{15}\text{H}_{12}\text{N}_2\text{O}_4$  calcd: 236.0950; found: 236.0933. M.p. 125°C.

$R_f=0.55$ . Compound **3**:  $^1\text{H}$  NMR:  $\delta=7.28\text{--}7.48$  (12H, 2H<sub>pyr</sub>, 10H<sub>Ph</sub>), 8.62–8.63 (2H<sub>pyr</sub>).  $^{13}\text{C}$  NMR: 118.07, 120.33, 128.31, 128.36, 128.55, 128.69, 129.40, 129.57, 129.71, 130.16, 134.75, 150.34, 162.46, 162.60.  $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$  calcd: 298.1106; found: 298.1100. M.p. 198°C.  $R_f=0.57$ .  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Bruker DRX 500 spectrometer (solvent  $\text{CDCl}_3$ ). Analytical TLC was carried out on Merck Kieselgel 60 F<sub>254</sub> plates employing methanol:chloroform 1:7 (v/v) as the mobile phase.

- Mazik, M.; Bläser, D.; Boese, R. *Tetrahedron Lett.* **1999**, *40*, 4783–4786.
- The data of the crystals of **1–3** were obtained with a Siemens SMART-CCD three circle diffractometer (MoK $\alpha$ -radiation, graphite-monochromator) at 293 K. The structures were solved using Direct Methods and refined on F<sup>2</sup> using SHELXTL (Version 5.03). All non-H atoms were anisotropically refined and aromatic and methyl H atoms were treated as riding groups with the 1.2 fold U-value (1.5 for methyl hydrogens) of the corresponding C-atoms. The mentioned distances to H-atoms are based on normalized C–H distances ( $d_{\text{C–H}}=1.08$  Å). Crystal data for **1**:  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}$ ,  $M=236.27$ , crystal dimensions  $0.28\times 0.26\times 0.8$  mm, crystal system orthorhombic, space group *Pbca*,  $a=13.554(2)$ ,  $b=12.1238(19)$ ,  $c=14.615(2)$  Å,  $\alpha=\beta=\gamma=90^\circ$ ,  $V=2401.6(7)$  Å<sup>3</sup>,  $Z=8$ ,  $\rho_{\text{calcd}}=1.307$  gcm<sup>-3</sup>, 31340 reflections collected (full sphere,  $\theta$ -range 2.23–28.28°), 2980 independent reflections ( $R_{\text{int}}=0.065$ ), 1943 observed [ $F_o\geq 4s(F_o)$ ], 163 parameters,  $R1=0.0592$ ,  $wR2=0.1293$ . Crystal data for **2**:  $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}$ ,  $M=236.27$ , crystal dimensions  $0.34\times 0.18\times 0.16$  Å<sup>3</sup>, crystal system orthorhombic, space group *Pnc2*,  $a=11.8661(15)$ ,  $b=14.3359(18)$ ,  $c=7.0752(9)$  Å,  $\alpha=\beta=\gamma=90^\circ$ ,  $V=1203.6(3)$  Å<sup>3</sup>,  $Z=4$ ,  $\rho_{\text{calcd}}=1.304$  gcm<sup>-3</sup>, 16020 reflections collected (full sphere,  $\theta$ -range 2.23–28.28°), 3000 independent reflections ( $R_{\text{int}}=0.0517$ ), 2392 observed [ $F_o\geq 4s(F_o)$ ], 163 parameters,  $R1=0.0489$ ,  $wR2=0.1052$ . Crystal data for **3**:  $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$ ,  $M=298.33$ , crystal dimensions  $0.38\times 0.22\times 0.16$  mm, crystal system monoclinic, space group *P2<sub>1</sub>/n*,  $a=5.853(2)$ ,  $b=16.345(5)$ ,  $c=16.054(4)$  Å,  $\alpha=90$ ,  $\beta=96.32(2)$ ,  $\gamma=90^\circ$ ,  $V=1526.5(8)$  Å<sup>3</sup>,  $Z=4$ ,  $\rho_{\text{calcd}}=1.298$  gcm<sup>-3</sup>, 2223 reflections collected (full sphere,  $\theta$ -range 1.78–22.49°), 1994 independent reflections ( $R_{\text{int}}=0.0633$ ), 1096 observed [ $F_o\geq 4s(F_o)$ ], 208 parameters,  $R1=0.0633$ ,  $wR2=0.13848$ . Crystallographic data for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, as supplementary publication no. CCDC-141768 (**1**), 141769 (**2**) and 141770 (**3**).