

Investigación

Crystal and Molecular Structure of *N*-2-Pyridylethyl-*N*'-3-Tolylthiourea

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In memoriam Raymundo Cruz Almanza

Abstract. The crystal and molecular structure of *N*-2-pyridylethyl-*N*'-3-tolylthiourea, **1**, was determined. **1** crystallizes as triclinic, P-1, $a = 9.024(2)$ Å, $b = 9.718(3)$ Å, $c = 9.765(4)$ Å, $\alpha = 102.26(3)^\circ$, $\beta = 114.18(3)^\circ$, $\gamma = 103.12(2)^\circ$, $V = 714.4(4)$ Å³, $Z = 2$. Both thiourea N-H groups form intermolecular hydrogen bonds, N'H with the thione sulfur atom and the NH with the pyridine nitrogen. When compared with other *N*-2-pyridylethyl-*N*'-arylthioureas it is observed that the centro-symmetric N'H...S hydrogen bond is always present and the NH...N always H-bonds to the pyridine N atom but in some cases as an intra-molecular H-bond and in the other as an intermolecular H-bond. This difference may be due to variables introduced by the flexibility of the molecules, whose effects on the crystal packing can not be predicted.

Key words: Hydrogen bonds, thioureas, X Ray

Resumen. La estructura molecular y cristalina de la *N*-2-piridiletill-*N*'-3-toliltiourea, **1**, fue determinada. **1** cristaliza como triclinico, P-1, $a = 9.024(2)$ Å, $b = 9.718(3)$ Å, $c = 9.765(4)$ Å, $\alpha = 102.26(3)^\circ$, $\beta = 114.18(3)^\circ$, $\gamma = 103.12(2)^\circ$, $V = 714.4(4)$ Å³, $Z = 2$. Los dos hidrógenos de N-H en **1** forman enlaces de hidrógeno, uno intramolecular con el átomo de nitrógeno de la piridina, y el otro intermolecular con el átomo de azufre. Un análisis comparativo con otras *N*-2-piridiletill-*N*'-ariltioureas muestra que el enlace de hidrógeno N'H...S siempre esta presente y el N-H siempre forma enlaces de hidrógeno con un átomo nitrógeno de la piridina, este último es en algunas ocasiones intramolecular y otras intermolecular. Esta diferencia puede deberse a que la flexibilidad de las moléculas introduce variables cuyos efectos sobre la red cristalina son difíciles de predecir.

Palabras clave: Enlaces de hidrógeno, tioureas, Rayos X

Introduction

There are several fundamental reasons to study the S...H interaction. From a biological point of view, living systems have important sulfur-containing molecules, such as the amino acids cysteine and methionine, the study of S...H interactions may help to understand and predict protein folding and biomolecular interactions [1,2]. From a material point of view, crystal engineering, the rational design, synthesis and assembly of functional material, is built upon a detailed understanding of the way in which non-covalent forces interact. The study of hydrogen bonding interactions has centered mainly in the interaction between good hydrogen donors and electron-rich acceptors, usually oxygen or nitrogen atoms. As long as sulfur atoms are, in a first approach, bad hydrogen acceptors, few systematic studies have been done with them. However, a recent study showed that the S atom in R₁R₂C=S systems is an effective acceptor when R₁ and R₂ can form an extended delocalized system with C=S [3]. We propose that thioureas are ideal molecules to study S...H interactions: the N₁N₂C=S thiourea moiety forms an extended delocalized system, and they are pharmacologically interesting molecules, for example, a recent rational drug design study has identified phenylethylthioureas as potent nucleotide inhibitors of human immunodeficiency virus-1 reverse transcriptase [4].

The crystal structure of several *N*-2-pyridyl-*N*'-arylthioureas have been reported [5]. These compounds present an intra-molecular N'-H ... N hydrogen bond, as well as NH hydrogen bonding with a sulfur atom of a neighboring molecule to form centro-symmetric dimers. In a recent report of the crystal structure of *N*-2-pyridylethyl-*N*'-aryl thioureas [6], an intermolecular six-membered ring, between N'H and the pyridyl nitrogen atom was observed in three of the five structures studied in addition to the expected N-H intermolecular hydrogen bond to a sulfur atom present in all of them, see Figure 1. An approach to analyze these structures is the so called Etter rules.

Etter proposed a series of rules which are very useful for the understanding of hydrogen bonding patterns [7], and supramolecular synthesis, as was, for example, elegantly shown by Aakeröy in a recent paper on the hydrogen-bond-directed assembly of ternary supramolecules [8].

Two of this rules are relevant for the present study. The first one indicates that if six-membered ring intra-molecular hydrogen bonds can be formed, they will usually do so in preference to intermolecular H-bonds. The second one states that the best proton donors and acceptors remaining after intra-molecular hydrogen-bond formation will form intermolecular hydrogen bonds to one another.

This rules are followed by the *N*-2-pyridyl- and partially by the *N*-2-pyridylethyl-*N*'-arylthioureas we have studied. To

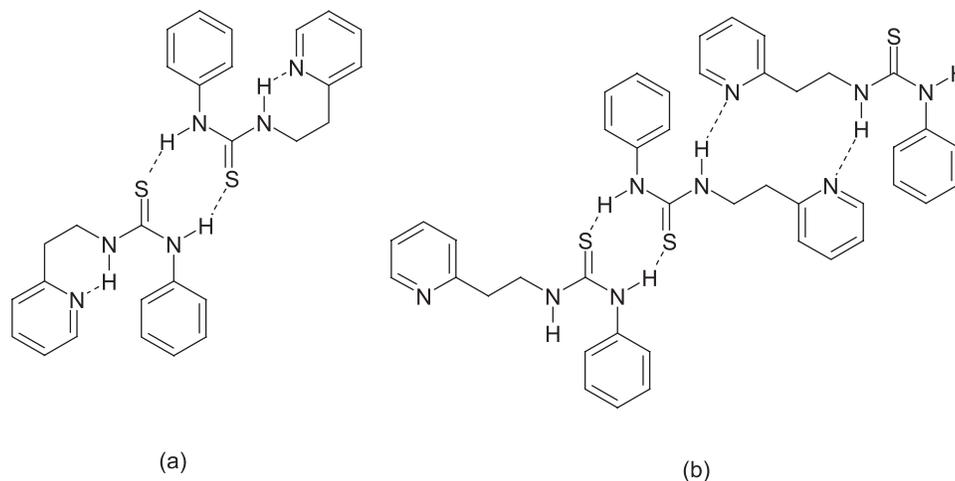


Fig. 1. *N*(2)-pyridylethyl-*N'*-arylthioureas showing: (a) one inter- and one intramolecular hydrogen bonded, (b) two intermolecular H-bonds.

contribute to the understanding of the S...H interactions in thioureas in this paper the crystal and molecular structure of *N*-2-pyridylethyl-*N'*-3-tolylthiourea, **1**, is presented and analyzed using Etter's approach.

Experimental

Synthesis

The *p*-tolylisothiocyanate, and 2-aminoethylpyridine were purchased from Aldrich and used as received. The *p*-tolylisothiocyanate was mixed in a 1:1 molar ratio with 2-aminoethylpyridine in anhydrous EtOH, and the resulting mixture gently refluxed for a minimum of 1 h. The thiourea precipitate from solution on cooling and slowly evaporating the reactant mixture. The solid was filtered, washed with cold isopropanol followed by anhydrous ether and dried. Crystals were grown by slow evaporation of 1:1 acetone-anhydrous ethanol solution at room temperature.

X-ray

A crystal of **1** was mounted in random orientation on a glass fiber on a Nonius Kappa CCD Diffractometer. The structure was solved by direct methods and missing atoms were found by difference-Fourier synthesis. All non-hydrogen atoms were refined with anisotropic displacement parameters and all hydrogen atoms were found on the difference Fourier map. The H atoms of CH₂ and CH₃ were allowed to ride on the C atoms and assigned a fixed isotropic displacement parameter, $U = 0.05 \text{ \AA}^2$. The coordinates of the H atoms attached to nitrogen atoms and aromatic carbons were refined. Scattering factors from Wassmaire and Kirfel [9], calculations were done by maXus, version 2.0 [10], refinement by SHELX97 [11], the material for publication done with PLATON [12].

Table 1. Crystallographic data and methods of data collection, solution and refinement for **1**.

Crystal data	1
Empirical formula	C ₁₅ H ₁₇ N ₃ S
Color, habit	colorless, prism
Crystal size mm	0.26 × 0.21 × 0.16
Crystal system	triclinic
Space group	P-1
a, Å	9.024(2)
b, Å	9.718(3)
c, Å	9.765(4)
α,	102.26(3)
β,	114.18(3)
γ,	103.12(2)
Volume, Å ³	714.4(4)
Z	2
Formula weight	271.39
D _{calc} , gcm ⁻³	1.262
Abs. coeff., mm ⁻¹	0.217
F(000)	288
Index ranges	0 < h < 11 -12 < k < 12 -12 < l < 11
θ, °	2.29 to 27.41
Refls collected	3262
Ind. refls., Rint	2608, 0.0100
Abs. correct.	ψ-scan
Max. & min. trans.	1.000 & 0.964
Data/parameters	2608/229
Goodness-of-Fit	1.100
Lgst. diff. peak eÅ ⁻³	0.192
Lgst. diff. hole eÅ ⁻³	-0.204
R, wR	0.0359, 0.0869
R, wR (all refls.)	0.0523, 0.1033

The crystallographic data and methods of data collection, solution and refinement are given in Table 1. CCDC 206931 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road,

Cambridge CB2 1EZ, UK; fax: +4401223-336033; email: deposit@ccdc.cam.ac.uk]

Results

The thermal ellipsoid plots of **1** are shown in Figure 2. Selected bond distances and angles are in Table 2. The conformation of **1** is such that the C10 atom of the phenyl ring and the S atom are *anti*-with respect to the N3-C9 bond, and C8 atom and the S atom are *syn* with respect to C9-N2 bond. The angles between the mean planes of the thiourea moiety with the phenyl and pyridine rings are 39.2(1) and 86.9(1)°, respectively; the angle between the mean plane of the pyridine and phenyl rings is 52.9(1)°.

Both N-H's form intermolecular centro-symmetric H-bonds, see Table 3. N3-H3a hydrogen bonds to a S1 atom giving $R^2_2(8)$ rings and N2-H2 hydrogen bonds to the N1 atom producing $R^2_2(12)$ rings. These two motifs combine to produce 1D hydrogen bonded chains, Figure 3, that pack as shown in Figure 4.

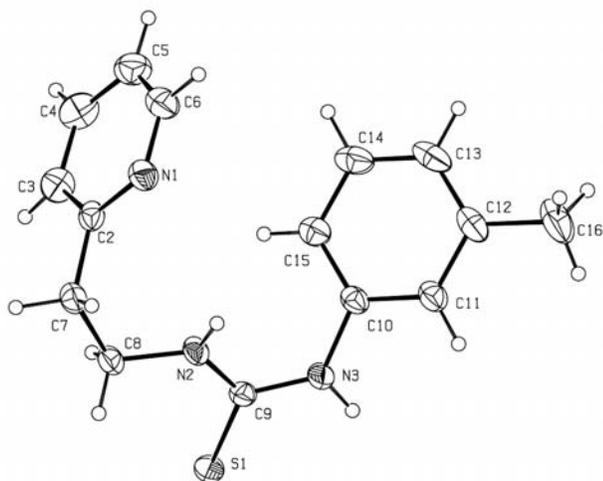


Fig. 2. Thermal ellipsoid plot (30% probability) of **1**, with atom numbering scheme.

Table 2. Selected Bond Distances, Å, and Angles, (°), for **1**.

Bond	
S1-C9	1.692(2)
N1-C2	1.335(2)
N1-C6	1.340(2)
N2-C8	1.456(2)
N2-C9	1.327(2)
N3-C9	1.360(2)
N3-C10	1.426(2)
Angle	
N1-C2-C7	116.8(2)
C7-C8-N2	110.4(1)
C8-N2-C9	123.1(1)
C9-N3-C10	127.0(1)
S1-C9-N2	122.8(1)
S1-C9-N3	120.3(1)
N2-C9-N3	117.0(1)

Discussion

Two hydrogen bond patterns observed in the reported structures *N*-2-pyridylethyl-*N'*-arylthioureas [6], both are shown in Figure 1. In one case there is a N-H...N six membered intra-molecular ring and one intermolecular N-H...S hydrogen-bond. In the second there are two intermolecular hydrogen bonds. If Etter rules are applied the N-H...N intra-molecular six-membered ring is favored with respect to the intermolecular N-H...S. The best donor-best acceptor rule is followed in the structures so far reported, the N'H is always, intra or intermolecular, hydrogen bonded to the pyridine N atom, and the S to the N-H. As long as the pyridine N atom is the best acceptor it follows that N'H is the best donor. This results are in agreement with computational calculation on *N*-2-pyridylmethyl-*N'*-arylthioureas [5].

Crystal structures are the result of the subtle balance between a multitude of non-covalent forces we hardly understand [13]. The difference in intra- intermolecular H-bonding patterns in *N*-2-pyridylethyl-*N'*-arylthioureas may be due to variables introduced by the flexibility of the molecule not considered in Etter rules, variables whose effects we do not understand. These results indicate that to do a rational study of the non-covalent interactions, in this and other systems, it is convenient to use as building blocks less flexible molecules.

Table 3. Intermolecular hydrogen bond distances (Å) and angles (°) for **1**.

D-H...A	D-H	H...A (Å)	D...A (Å)	∠(D-H...A) (°)	S ^(a)
N2-H2...N1	0.86(2)	2.25(2)	2.983(2)	144(2)	1-x, -y, 1-z
N3-H3a...S1	0.85(2)	2.56(2)	3.403(2)	170(2)	-x, -1-y, 1-z

^(a) Symmetry transformations used to generate equivalent atoms

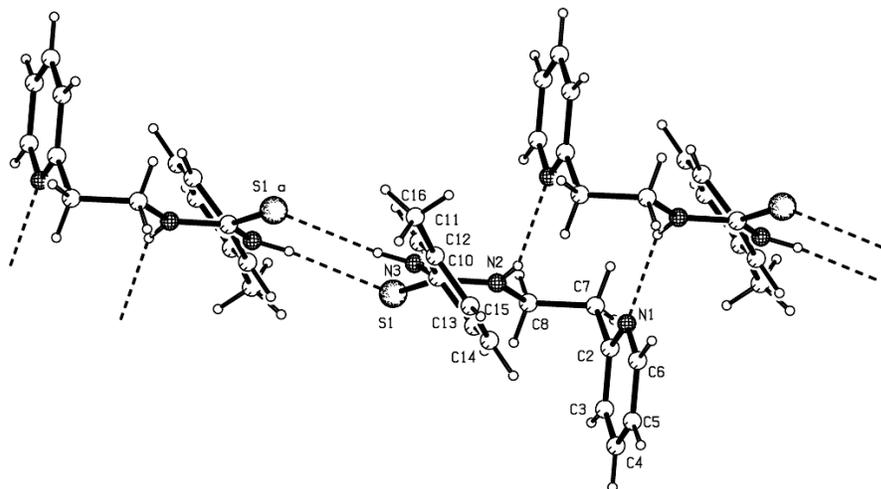


Fig. 3. Hydrogen bonding in **1**.

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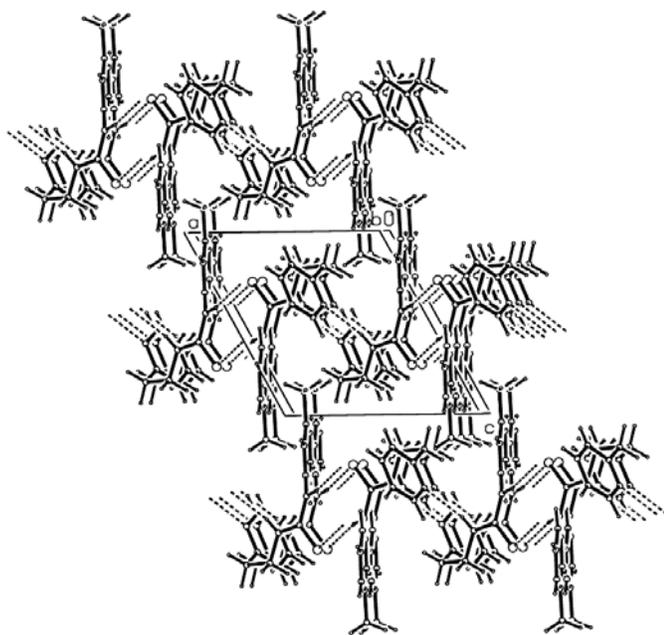


Fig. 4. Packing diagram of **1**.