



LETTER TO EDITOR

**Comments on DFT calculation, biological activity, anion sensing studies and crystal structure of (*E*)-4-chloro-2-((pyridin-2-ylimino)-methyl)phenol by Nuray Yıldırım, Neslihan Demir, Gökhan Alpaslan, Bahadır Boyacıoğlu, Mustafa Yıldız and Huseyin Ünver, published in the *Journal of the Serbian Chemical Society*, Volume 83, Issue 6, 2018, pp. 707–721**

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**Abstract:** The crystal structure of (*E*)-4-chloro-2-((pyridin-2-ylimino)-methyl)phenol, recently published by Yıldırım *et al.* in *J. Serb. Chem. Soc.* **83** (2018) 707–721, is revised. Refinement of the new structural model against original X-ray diffraction data, deposited with the Cambridge Crystallographic Data Centre, proved that the compound studied by single crystal X-ray diffraction was actually (*E*)-4-chloro-2-((pyridin-3-ylimino)methyl)phenol.

**Keywords:** *N*-(5-chlorosalicylidene)-3-aminopyridine; *N*-(5-chlorosalicylidene)-2-aminopyridine; X-ray crystallography; revision.

In the recent paper<sup>1</sup> by Yıldırım *et al.*, published in the *Journal of the Serbian Chemical Society*, the crystal structure of the (*E*)-4-chloro-2-((pyridin-2-ylimino)-methyl)phenol is reported (Fig. 1a). The visual inspection of ORTEP representation of the molecular structure (hereafter referred to as model A), as depicted in Fig. 1 of the original paper, already points to the suspicious looking displacement ellipsoids of atoms C10 and N2. To investigate the matter further, the original data were retrieved in CIF format from the Cambridge Crystallographic Data Centre (CCDC), deposited by the authors as CCDC 1564849.

The crystal structure validation of model A by PLATON,<sup>2,3</sup> reveals several serious problems with the proposed crystal structure. Several significant violations of Hirshfeld rigid-bond test are most severe.<sup>4</sup> As summarized in Table I, the difference between components of the atomic anisotropic displacement

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parameters, along chemical bonds involving atoms N2 and C10, deviate over five standard uncertainties from zero, which may be caused by the atomic sites assigned the wrong scattering type.<sup>3</sup>

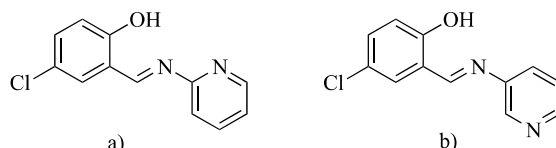


Fig. 1. Structural formulas of (*E*)-4-chloro-2-((pyridin-2-ylimino)-methyl)phenol (a) and (*E*)-4-chloro-2-((pyridin-3-ylimino)methyl)phenol (b).

TABLE I. Significant Hirshfeld rigid bond test violations ( $\Delta z^2 / \sigma(\Delta z^2) > 5$ ) present in model **A**, calculated by PLATON;  $\Delta z^2 = |z^2(I \rightarrow J) - z^2(J \rightarrow I)|$ , where  $z^2(I \rightarrow J)$  denotes the mean square displacement amplitude of atom *I* in the direction of atom *J* (parallel to the bond)

Bond <i>I</i> – <i>J</i>	$z^2(I \rightarrow J) / \text{Å}^2$	$z^2(J \rightarrow I) / \text{Å}^2$	$\Delta z^2 / \text{Å}^2$	$\Delta z^2 / \sigma(\Delta z^2)$
N2–C8	0.0535(17)	0.0387(12)	0.015(2)	7.5
N2–C12	0.0551(17)	0.0409(17)	0.014(2)	7.0
C9–C10	0.0375(16)	0.0254(14)	0.012(2)	6.0
C10–C11	0.0395(14)	0.0509(16)	0.011(2)	5.5

Additionally, the analysis of crystal packing of model **A** reveals exorbitantly short intermolecular H10⋯H3<sup>i</sup> contact of 2.13 Å [symmetry operation: (i)  $^{-3/2+x, 3/2-y, -1/2+z}$ ], which indicates that the incorrectly determined H10 atom position as this distance is significantly less than the sum of their van der Waals radii (2.4 Å).

Next, an alternative way of structure validation by the use of a vast amount of structural data available in the Cambridge Structural Database (CSD)<sup>5</sup> was performed. The Mogul program compares the geometrical parameters of the structure at hand to similar structures in the CSD and returns the assessment of how unusual a parameter is *via* an appropriate figure of merit.<sup>6</sup> A *Mogul* geometry check was performed for model **A** against the similar structures with  $R_1 \leq 0.05$ , excluding organometallics and powder structures, by using *Mercury CSD*<sup>7</sup> as interface and CSD version 5.39 (updated Aug, 2018). Table II lists all parameters detected as unusual by Mogul, together with the corresponding statistics. It is evident that bond lengths involving N2 and C10 are inconsistent with database entries, together with most valence angles belonging to pyridine ring. Interestingly, the mean values of database entries match very well those of structural parameters devised by the theoretical calculations reported by the authors.<sup>1</sup> The conformation around C8–N1 bond is in serious disagreement with the data in the CSD, as displayed by *ca.* 156° absolute difference between C9–C8–N1–C7 or N2–C8–N1–C7 torsion angles and the nearest torsion angle in the corresponding

CSD sample. This means that it is highly expected that conformation along C8–N1 bond is syn-periplanar, contrary to the situation found in model **A**.

TABLE II. *Mogul* geometry check results showing fragments with unusual geometry;  $x$ : query value;  $N$ : number of CSD hits (sample size);  $\mu$ : mean of sample distribution;  $\sigma$ : standard deviation of sample distribution;  $d_{\min}$ : the difference between  $x$  and the nearest torsion angle in the corresponding sample; Local density: the percentage of experimental measurements in the corresponding sample that are within  $10^\circ$  of the value  $x$ . Parameter  $x$  is classified as unusual if  $|x - \mu| / \sigma > 2$  for bond lengths and valence angles, or local density  $< 5\%$  for torsion angles

Bond	$x / \text{\AA}$	$N$	$\mu / \text{\AA}$	$\sigma / \text{\AA}$	$ x - \mu  / \text{\AA}$	$ x - \mu  / \sigma$
C8–N2	1.381	61	1.339	0.012	0.042	3.47
C12–N2	1.384	3242	1.340	0.010	0.044	4.43
C9–C10	1.343	8786	1.385	0.010	0.042	4.15
C10–C11	1.333	8781	1.380	0.014	0.047	3.44
Angle	$x / ^\circ$	$N$	$\mu / ^\circ$	$\sigma / ^\circ$	$ x - \mu  / ^\circ$	$ x - \mu  / \sigma$
C9–C8–N1	124.34	27	117.59	1.27	6.76	5.34
C9–C8–N2	117.54	48	122.31	1.16	4.77	4.13
C10–C9–C8	123.71	58	118.83	0.81	4.88	6.03
C11–C10–C9	117.49	9258	120.34	0.70	2.85	4.07
C10–C11–C12	122.76	2421	118.38	0.79	4.38	5.57
C11–C12–N2	119.46	3006	123.71	0.89	4.26	4.78
Torsion angle	$x / ^\circ$	$N$	$ d_{\min}  / ^\circ$	Local density / %		
C9–C8–N1–C7	-2.45	26	155.83	0.0		
N2–C8–N1–C7	178.01	26	156.09	0.0		

Finally, the crystallographic model **A** and diffraction data in SHELXL<sup>8</sup> readable formats were extracted from the deposited CIF file by the SHREDCIF<sup>8</sup> program. Inspection of the residual electron density map (Fig. 2a), generated after the refinement of the model **A** against original diffraction data, undoubtedly indicates a case of a wrong atom type assignment. It is clearly seen in Fig. 2a that model **A** has

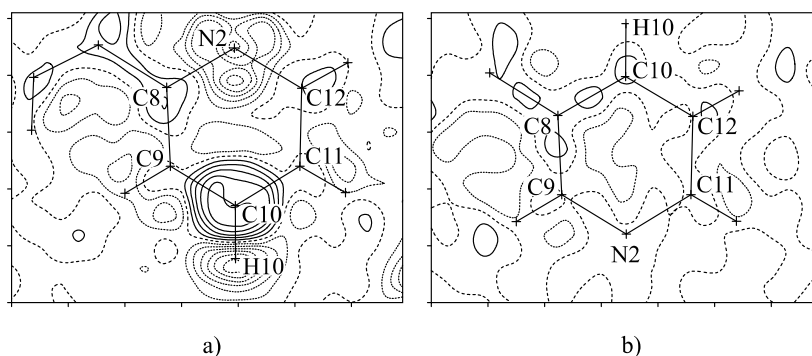


Fig. 2. Contours of residual electron density in the plane of pyridine ring for models **A** (a) and **B** (b). The contour lines are drawn with  $0.10 \text{ e\AA}^{-3}$  increments.  
(—)  $\Delta\rho > 0$ ; (---)  $\Delta\rho = 0$ ; (-.-)  $\Delta\rho < 0$ .

the excessive electron density (negative residual density) in the positions N2 and H10, as well as the insufficient electron density (positive residual density) in position C10.

Bearing in mind all previously discussed matter, a revision of the structural model is proposed and validated. In short, the compound is reformulated as (*E*)-4-chloro-2-((pyridin-3-ylimino)methyl)phenol, (Fig. 1b), hereafter referred to as model **B**. Structure was refined against original reflection data by SHELXL<sup>8</sup> and ShelXle.<sup>9</sup> Crystallographic and refinement details for models **A** and **B** are compared in Table III. The revised structure has been deposited with the CCDC (deposition number 1869718) and can be obtained free of charge *via* <https://www.ccdc.cam.ac.uk/structures/>. The ORTEP representation of the molecular structure of model **B** is represented in Fig. 3.

TABLE III. Crystallographic data and comparative refinement details for models **A** and **B**; weighting scheme:  $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ , where  $P = (F_o^2 + 2F_c^2)/3$ ; extinction correction by SHELXL:  $F_c^* = kF_c[1 + 0.001xF_c^2\lambda^3/\sin(2\theta)]^{-1/4}$

Chemical formula	C <sub>12</sub> H <sub>9</sub> ClN <sub>2</sub> O	
<i>M</i> / g mol <sup>-1</sup>	232.66	
Crystal system	Monoclinic	
Space group	<i>P</i> 2 <sub>1</sub> / <i>n</i>	
<i>a</i> / Å	4.5628(4)	
<i>b</i> / Å	19.3486(17)	
<i>c</i> / Å	12.0485(11)	
$\beta$ / °	95.270(3)	
<i>V</i> / Å <sup>3</sup>	1059.19(16)	
<i>Z</i>	4	
$\mu$ (Mo <i>K</i> $\alpha$ ) / mm <sup>-1</sup>	0.34	
No. of measured reflections	22333	
No. of independent reflections	2177	
No. of observed [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )] reflections	1715	
<i>R</i> <sub>int</sub>	0.052	
Refinement details	Model <b>A</b>	Model <b>B</b>
No. of parameters refined	150	150
Weighting scheme parameter <i>a</i>	0.117	0.0515
Weighting scheme parameter <i>b</i>	0.8219	0.4352
Extinction coefficient <i>x</i>	0.016(6)	0.025(3)
<i>R</i> <sub>1</sub> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.060	0.039
<i>R</i> <sub>1</sub> [all data]	0.075	0.053
<i>wR</i> <sub>2</sub> [ <i>I</i> > 2 $\sigma$ ( <i>I</i> )]	0.181	0.099
<i>wR</i> <sub>2</sub> [all data]	0.202	0.111
<i>S</i>	1.085	1.051
$\Delta\rho_{\max}$ , $\Delta\rho_{\min}$ / eÅ <sup>-3</sup>	0.65, -0.60	0.19, -0.26
C–C bond precision, Å	0.0037	0.0026

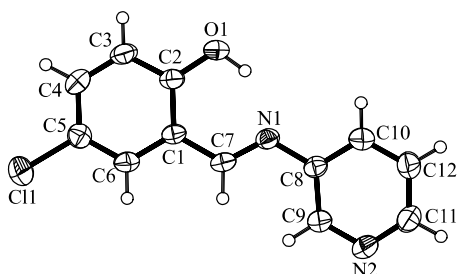


Fig. 3. The molecular structure of model **B** (*E*)-4-chloro-2-((pyridin-3-ylimino)methyl)phenol with atom numbering scheme. Displacement ellipsoids are drawn at 50% probability level. Hydrogen atoms are drawn as spheres of arbitrary radii.

The refinement of model **B** resulted in significant improvement of the crystallographic *R* factors. The residual density map corresponding to model **B** shows the extrema of  $-0.26$  and  $0.19 \text{ e}\text{\AA}^{-3}$ , compared to  $-0.60$  and  $0.65 \text{ e}\text{\AA}^{-3}$  in model **A**. It is more important that the residual density map for model **B** shows no significant features at atom positions (Fig. 2b), indicating the correct placement of the atom types. Additionally, six positive residual electron density peaks are located within atom–atom bonds, which is an indicator of a good quality of both diffraction data and structural model. Also, model **B** is free from violations of Hirshfeld rigid bond test. No unreasonably short intermolecular atom–atom contacts are observed in model **B**. Mogul geometry check reveals no unusual structural parameters when model **B** is validated using the same criteria as for model **A**. In addition to obvious superiority in matching experimental diffraction data, the model **B** has no contradiction with other data obtained by the experimental characterization (FTIR,  $^1\text{H-NMR}$ ,  $^{13}\text{C-NMR}$  and UV spectroscopy). Last but not least, the literature survey reveals that the synthesis of (*E*)-4-chloro-2-((pyridin-3-ylimino)methyl)phenol was already reported,<sup>10–13</sup> together with its NMR characterization,<sup>11</sup> and structural characterization by single crystal X-ray crystallography.<sup>12</sup>

To conclude, the detailed validation of the crystal structure of (*E*)-4-chloro-2-((pyridin-2-ylimino)methyl)phenol already published in the paper<sup>1</sup> proved incorrect as it suffers from the wrong atom type assignment errors. The corrected model of (*E*)-4-chloro-2-((pyridin-3-ylimino)methyl)phenol, proposed in this Letter is free from such flaws. The correction made should help to correctly guide the research that is built on the previous paper. Otherwise, such research may be ill-fated, misguided by faulty crystal structure and mistaken chemical identity of the compound under study. Finally, the conclusions drawn in the paper<sup>1</sup> should be reexamined in the light of corrections presented here. We hope that this Letter will help to avoid similar errors in future crystal structure determinations.

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## ИЗВОД

КОМЕНТАРИ НА РАД ПОД НАСЛОВОМ DFT ИЗРАЧУНАВАЊЕ, БИОЛОШКА АКТИВНОСТ, ПРОУЧАВАЊЕ ДЕТЕКЦИЈЕ АНЈОНА И КРИСТАЛНА СТРУКТУРА (E)-4-ХЛОРО-2-[(ПИРИДИН-2-ИЛИМИНО)-МЕТИЛ]ФЕНОЛА, АУТОРИ: NURAY YILDIRIM, NESLİHAN DEMİR, GÖKHAN ALPASLAN, VAHADIR BOYACIOĞLU, MUSTAFA YILDIZ И HUSEYİN ÜNVER, ОБЈАВЉЕН У *JOURNAL OF THE SERBIAN CHEMICAL SOCIETY*, VOLUME 83, ISSUE 6, 2018, PP. 707–721

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Ревидирана је кристална структура (E)-4-хлоро-2-((пиридин-2-илимино)-метил)-фенола, недавно објављена у *J. Serb. Chem. Soc.* **83** (2018) 707–721, аутора Yıldırım *et al.* Утачњавањем коригованог модела помоћу оригиналних дифракционих података, депонованих у Cambridge Crystallographic Data Centre, доказано је да је једињење испитивано рендгенском структурном анализом заправо (E)-4-хлоро-2-((пиридин-3-илимино)-метил)фенол.

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## REFERENCES

1. N. Yıldırım, N. Demir, G. Alpaslan, B. Boyacıoğlu, M. Yıldız, H. Ünver, *J. Serb. Chem. Soc.* **83** (2018) 707 (<https://dx.doi.org/10.2298/JSC171001009Y>)
2. A. L. Spek, *J. Appl. Crystallogr.* **36** (2003) 7 (<https://dx.doi.org/10.1107/S0021889802022112>).
3. A. L. Spek, *Acta Crystallogr., D* **65** (2009) 148 (<https://dx.doi.org/10.1107/S090744490804362X>)
4. F. L. Hirshfeld, *Acta Crystallogr., A* **32** (1976) 239 (<https://dx.doi.org/10.1107/S0567739476000533>)
5. C. R. Groom, I. J. Bruno, M. P. Lightfoot, S. C. Ward, *Acta Crystallogr., B* **72** (2016) 171 (<https://dx.doi.org/10.1107/S2052520616003954>)
6. I. J. Bruno, J. C. Cole, M. Kessler, J. Luo, W. D. Sam Motherwell, L. H. Purkis, B. R. Smith, R. Taylor, R. I. Cooper, S. E. Harris, A. Guy Orpen, *J. Chem. Inf. Comput. Sci.* **44** (2004) 2133 (<https://dx.doi.org/10.1021/CI049780B>)
7. C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek, P. A. Wood, *J. Appl. Crystallogr.* **41** (2008) 466 (<https://dx.doi.org/10.1107/S0021889807067908>)
8. G. M. Sheldrick, *Acta Crystallogr., C* **71** (2015) 3 (<https://dx.doi.org/10.1107/S2053229614024218>)
9. C. B. Hübschle, G. M. Sheldrick, B. Dittrich, *J. Appl. Crystallogr.* **44** (2011) 1281 (<https://dx.doi.org/10.1107/S0021889811043202>)
10. E. Hadjoudis, M. Vittorakis, I. Moustakali-Mavridis, *Tetrahedron* **43** (1987) 1345 ([https://dx.doi.org/10.1016/S0040-4020\(01\)90255-8](https://dx.doi.org/10.1016/S0040-4020(01)90255-8))
11. M. E. L. Saraiva, C. F. G. Geraldes, V. M. S. Gil, *Tetrahedron* **44** (1988) 163 ([https://dx.doi.org/10.1016/S0040-4020\(01\)85103-6](https://dx.doi.org/10.1016/S0040-4020(01)85103-6))
12. F. Robert, A. D. Naik, B. Tinant, R. Robiette, Y. Garcia, *Chem. Eur. J.* **15** (2009) 4327 (<https://dx.doi.org/10.1002/chem.200801932>)
13. A. Sekine, S. Ina, K. Johmoto, H. Uekusa, *CrystEngComm* **18** (2016) 7330 (<https://dx.doi.org/10.1039/C6CE01005A>).