



# A $^1\text{H}$ , $^{13}\text{C}$ and $^{15}\text{N}$ NMR spectroscopic and GIAO DFT study of ethyl 5-oxo-2-phenyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrrole-3-carboxylate

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## ABSTRACT

$^{15}\text{N}$ -Labelled ethyl 5-oxo-2-phenyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrrole-3-carboxylate was synthesized by azo-coupling of diazotized aniline (using  $\text{Na}^{15}\text{NO}_2$ , 99%  $^{15}\text{N}$ ) with ethyl 4,5-dihydro-5-oxo-2-phenyl-(1H)-pyrrole-3-carboxylate. The product was formed as a tautomeric hydrazone mixture as confirmed by  $^{13}\text{C}$  and  $^{15}\text{N}$  chemical shifts, and was obtained as a mixture of *E* and *Z* isomers according to  $^nJ(^{15}\text{N}, ^{13}\text{C})$ . A comparison of the  $^1\text{H}$  NMR data with GIAO DFT calculations enabled determination of the configuration of the carboxy ester group in both isomers.

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Ethyl 4,5-dihydro-5-oxo-2-phenyl-1H-pyrrole-3-carboxylate (**1**, pyrrolinone ester) is a virtually undetectable intermediate in the synthesis of diketo-pyrrolo-pyrrole (DPP) pigment (C.I. Pigment Red 255) from benzonitrile and diethyl succinate.<sup>1</sup> If synthesized independently,<sup>2</sup> the pyrrolinone ester can undergo, due to the presence of a strongly activated methylene group at position 4, reaction with the aromatic nitrile forming unsymmetrical DPPs,<sup>3</sup> or condensation with aromatic aldehydes,<sup>4</sup> carboxy esters and chlorides<sup>5</sup> or oxidative dimerization,<sup>2</sup> giving rise to various types of new dyes or pigments.

Both the condensation of pyrrolinone ester **1** with phenylhydrazine and azo-coupling with diazotized aniline result in the same product, as previously reported.<sup>6</sup> Since the structural details of the products were not described,<sup>6</sup> and because of our interest in dyes based on a pyrrolinone ester,<sup>3,4c</sup> we decided to study the reaction product of the azo-coupling with a pyrrolinone ester **1** in detail (Scheme 1).

The diazotization of aniline was carried out by the usual procedure,<sup>7</sup> and diazotization using  $\text{Na}^{15}\text{NO}_2$  (99%  $^{15}\text{N}$ )<sup>8</sup> was accomplished in the same way. The azo-coupling reaction gave product **2** in moderate yield and good purity.<sup>9</sup>

Ethyl 5-oxo-2-phenyl-4-(2-phenylhydrazono)-4,5-dihydro-1H-pyrrole-3-carboxylate (**2**) exists as a mixture of two components in  $\text{DMSO}-d_6$ , the content of which can change slightly over time. Two-dimensional NMR experiments<sup>10</sup> allowed assignment of all

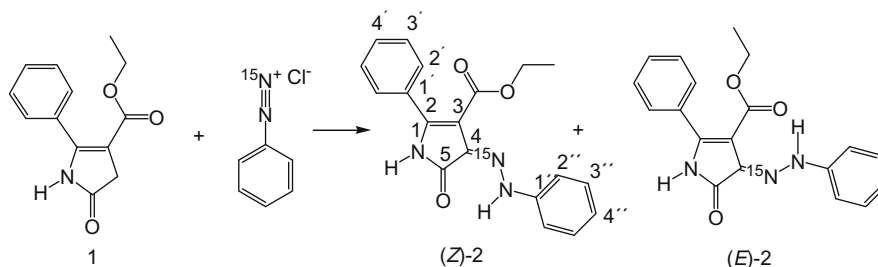
the proton and carbon resonances. It was found, based on  $^{13}\text{C}$  and  $^{15}\text{N}$  chemical shifts,<sup>11</sup> that both components existed completely as the hydrazones.

The existence of two components in the reaction mixture was due to the presence of two geometric isomers. The  $^2J(^{15}\text{N}, ^{13}\text{C})$  coupling constant values were used to assign the *Z* and *E* isomers. The values of the  $^2J(^{15}\text{N}, ^{13}\text{C})$  coupling constants for the (nearly) planar arrangement differed considerably (Fig. 1) and were not affected to any great extent by the character of the substituents.<sup>12</sup> It was necessary to use the  $^{15}\text{N}$ -labelled compound and good digital resolution during the  $^{13}\text{C}$  NMR spectral measurements in order to determine the  $^nJ(^{15}\text{N}, ^{13}\text{C})$  coupling constants precisely. The most important values are those of  $^2J(^{15}\text{N}, ^{13}\text{C})$  for carbons 3 and 5. The results are collected in Table 1.

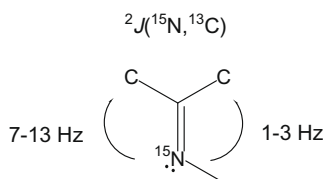
Rather surprisingly, the largest difference between the  $^1\text{H}$  chemical shifts of the *E* and *Z* isomers was found for the methylene group, and especially the methyl protons of the ethoxy group, which are relatively distant from the  $\text{C}=\text{N}$  bond. In order to explain these differences we modelled the structure of both isomers using density functional theory (DFT: B3LYP/6-311G(d,p)) and computed theoretical  $^1\text{H}$  chemical shifts by the gauge-including atomic orbital (GIAO) method.<sup>13</sup> Both methods were adopted from the GAUSSIAN03W program suite.<sup>14</sup> Two conformations were found for each isomer, differing in the orientation of the carboxy ester group with respect to the pyrrolinone ring (Fig. 2). The difference between the total energies of the most stable conformations of each isomer [(*Z*), *s-cis* and (*E*), *s-trans*] was low, which explains the simultaneous appearance of both isomers in the reaction mixture. The 4-(2-phenylhydrazono)-

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**Scheme 1.** Azo-coupling reaction with compound **1** and atom numbering in the reaction products.



**Figure 1.** Typical absolute values of the  ${}^2J({}^{15}\text{N}, {}^{13}\text{C})$  coupling constants in nearly planar systems depending on the orientation of the carbon atoms with respect to the nitrogen atom electron lone pair.

pyrrolinone is quasiplanar in all cases, and the pendant 2-phenyl group is significantly rotated out of plane ( $44\text{--}53^\circ$ ). Rotation of the carboxy ester group with respect to the pyrrolinone ring is moderate, the highest rotation being ( $26^\circ$ ) for the least stable (*E*), *s-cis* conformer, which is the only one not stabilized by an intramolecular NH–CO hydrogen bond.

Only one value of the  ${}^1\text{H}$  chemical shift was found experimentally for the two (three) protons of the methylene (methyl) group which indicates that free rotation of the ethyl group on the NMR time-scale must occur. On the other hand, the different average values for both isomers prove the stabilized position of the carboxy ester group. The GIAO-computed values were very similar for the *s-trans* and *s-cis* conformers of both isomers, showing that the  ${}^1\text{H}$  chemical shifts of the ethyl protons depend only on the conformation of the carboethoxy group with respect to the pyrrolidinone ring. Finally, the differ-

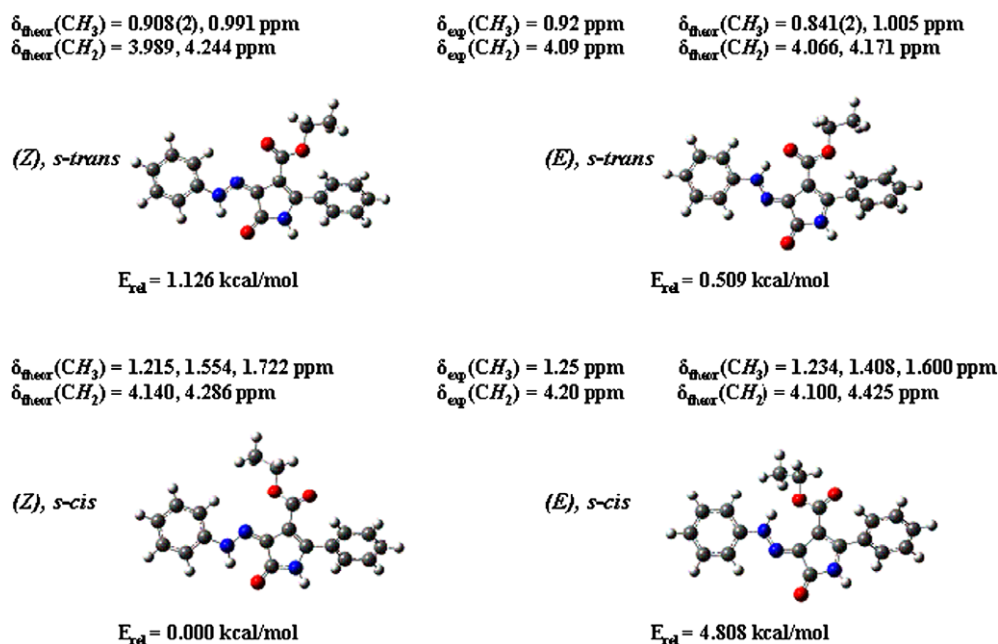
**Table 1**

${}^1\text{H}$ ,  ${}^{13}\text{C}$  and  ${}^{15}\text{N}$  chemical shifts and  ${}^nJ({}^{15}\text{N}, {}^{13}\text{C})$  coupling constants (Hz,  $\pm 0.3$  Hz) of the (*E*) and (*Z*) isomers of compound **2** measured in  $\text{DMSO-}d_6$

H/C/N	<i>(E)</i> -2			<i>(Z)</i> -2		
	$\delta$ ( ${}^1\text{H}$ )	$\delta$ ( ${}^{13}\text{C}$ )	${}^nJ({}^{15}\text{N}, {}^{13}\text{C})$	$\delta$ ( ${}^1\text{H}$ )	$\delta$ ( ${}^{13}\text{C}$ )	${}^nJ({}^{15}\text{N}, {}^{13}\text{C})$
1	11.31	–224.6 <sup>a</sup>	–	11.41	–232.6 <sup>a</sup>	–
2	–	156.0	2.6	–	146.5	3.7
3	–	99.0	3.2	–	102.4	7.5
4	–	128.9	7.4	–	129.8	6.0
5	–	164.3	12.1	–	161.3	<1
1'	–	131.0	–	–	129.8	–
2'	7.57	129.9	–	7.64	129.6	–
3'	7.51	127.9	–	7.51	128.1	–
4'	7.51	130.3	–	7.51	130.2	–
3-COO	–	166.0	–	–	162.3	–
OCH <sub>2</sub>	4.09	61.0	–	4.20	59.7	–
CH <sub>3</sub>	0.92	13.3	–	1.25	14.1	–
4-(=N)–NH–	–	–40.1 <sup>a</sup>	–	–	–34.7 <sup>a</sup>	–
=N–NH–	13.00	–215.4 <sup>a</sup>	–	13.10	–217.3 <sup>a</sup>	–
1''	–	142.8	6.5	–	142.8	6.5
2''	7.30	114.2	2.3	7.47	114.2	2.4
3''	7.43	129.1	–	7.43	129.1	–
4''	7.08	122.8	–	7.12	122.8	–

<sup>a</sup>  $\delta$  ( ${}^{15}\text{N}$ ).

ence between the values for both isomers infers that the conformation of the carboxy ester is different in both. The theoretical values match the experimental values significantly better for the



**Figure 2.** DFT-computed structures of both conformations of the carboethoxy group of the *E* and *Z* isomers of **2**, together with the relative total energies and GIAO NMR and experimental  ${}^1\text{H}$  chemical shifts of the methylene and methyl groups.

(*Z*), *s-cis* and (*E*), *s-trans* arrangements (Fig. 2), in accordance with thermodynamic stability. Thus we consider the chemical outcome displayed in Scheme 1 as definitely proved. The preference for the (*Z*), *s-cis* conformer was also the situation for the structurally similar isopropyl 1-phenyl-4-phenylhydrazono-5-oxo-3-pyrazolecarboxylate according to X-ray diffractometry.<sup>15</sup>

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### References and notes

- Iqbal, A.; Kirchmayr, R.; Pfenninger, J.; Rochat, A. C.; Wallquist, O. *Bull. Soc. Chim. Belg.* **1988**, *97*, 615.
- (a) Pfenninger, J.; Iqbal, A.; Rochat, A. C.; Wallquist, O., US Patent 4,659,775, 1987; *Chem. Abstr.* **1986**, *105*, 192864; (b) Morton, C. J. H.; Gilmour, R.; Smith, D. M.; Lightfoot, P.; Slawin, A. M. Z.; MacLean, E. J. *Tetrahedron* **2002**, *58*, 5547.
- (a) Luňák, S., Jr.; Vyňuchal, J.; Vala, M.; Havel, L.; Hrdina, R. *Dyes Pigment* **2009**, *82*, 102; (b) Luňák, S., Jr.; Havel, L.; Vyňuchal, J.; Horáková, P.; Kučerík, J.; Weiter, M.; Hrdina, R. *Dyes Pigment* **2010**, *85*, 27.
- (a) Adam, J. M.; Dalvi, P.; Ekkundi, V. S.; Bacher, J. P.; Tiwari, S. WO Patent 04/083170, 2004; *Chem. Abstr.* **2004**, *141*, 315838.; (b) Adam, J. M.; Dalvi, P.; Ekkundi, V. S.; Bacher, J. P.; Sreenivasan, R.; Rane, D. M. WO Patent 04/089941, 2004; *Chem. Abstr.* **2004**, *141*, 366917.; (c) Vyňuchal, J.; Luňák, S., Jr.; Hatlapatková, A.; Hrdina, R.; Lyčka, A.; Havel, L.; Vyňuchalová, K.; Jirásko, R. *Dyes Pigment* **2008**, *77*, 266.
- Morton, C. J. H.; Riggs, R. L.; Smith, D. M.; Westwood, N. J.; Lightfoot, P.; Slawin, A. M. Z. *Tetrahedron* **2005**, *61*, 727.
- Chamberlain, T. WO Patent 200174950, 2001; *Chem. Abstr.* **2001**, *135*, 290145.
- A mixture of aniline (0.134 g, 1.43 mmol), concentrated HCl (36%, 0.35 ml) and H<sub>2</sub>O (20 ml) was cooled to 0 °C, then a solution of Na<sup>15</sup>NO<sub>2</sub> (99% <sup>15</sup>N, 0.1 g, 1.43 mmol) in water (10 ml) was added dropwise over 20 min. The mixture was stirred for 40 min and then used for the coupling reaction (see Ref. 9).
- Aldrich (99% <sup>15</sup>N).
- Ethyl 4,5-dihydro-5-oxo-2-phenyl(1*H*)pyrrole-3-carboxylate (1, 0.33 g, 1.43 mmol) was dissolved in MeOH (25 ml), the mixture was cooled to 0 °C and the solution of the diazonium salt was added dropwise. The reaction mixture was stirred at 0–5 °C for 4 h and then at the rt for 12 h. The precipitated dye was filtered, washed with MeOH and H<sub>2</sub>O and recrystallized from EtOH. Yield 63%, mp 193–195 °C. Anal. Calcd (C<sub>19</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>): C, 68.05; H, 5.11; N, 12.53. Found: C, 68.10; H, 5.28; N, 12.63. Positive-ion MS: *m/z* 336 [M+H]<sup>+</sup>, 100%; 290 [M+H–C<sub>2</sub>H<sub>5</sub>OH]<sup>+</sup>. Negative-ion MS: *m/z* 334 [M–H]<sup>–</sup>, 100%; 288 [M–H–C<sub>2</sub>H<sub>5</sub>OH]<sup>–</sup>.
- The <sup>1</sup>H and <sup>13</sup>C NMR spectra were recorded on a Bruker Avance II 400 spectrometer (operating at 400.13 MHz for <sup>1</sup>H, and 100.62 MHz for <sup>13</sup>C) in DMSO-*d*<sub>6</sub>. The <sup>1</sup>H and <sup>13</sup>C chemical shifts were referenced to internal TMS ( $\delta = 0.00$ ). All 2D experiments (gradient-selected gs-COSY, gs-HMQC, gs-HMBC) were performed using Topspin 2.1. The <sup>15</sup>N NMR spectra were recorded on a Bruker Avance II 400 spectrometer at 40.54 MHz and the <sup>15</sup>N chemical shifts were referenced to external nitromethane ( $\delta = 0.0$ ).
- (a) Lyčka, A. *Annu. Rep. NMR Spectrosc.* **1993**, *26*, 247; (b) Lyčka, A. *Annu. Rep. NMR Spectrosc.* **2000**, *42*, 1.
- (a) Marek, R.; Lyčka, A. *Curr. Org. Chem.* **2002**, *7*, 35; (b) Marek, R.; Lyčka, A.; Kolehmainen, E.; Sieveren, E.; Toušek, J. *Curr. Org. Chem.* **2007**, *11*, 1154.
- The solvent effect was not taken into account. Absolute shielding for reference TMS computed at the same level was 32.00.
- Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Zazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *GAUSSIAN 03 W*, Gaussian, Inc., Wallingford CT, 2004.
- Skoweranda, J.; Bukowska-Strzyzewska, M.; Strzyzowski, W. *J. Chem. Crystallogr.* **1994**, *24*, 51.