

DENSITY FUNCTIONAL CALCULATIONS ON HETEROCYCLIC
COMPOUNDS. PART 2.¹ ON THE PROTONATION OF 4,5-DICHLORO-
2-METHYL-3(2*H*)-PYRIDAZINONE

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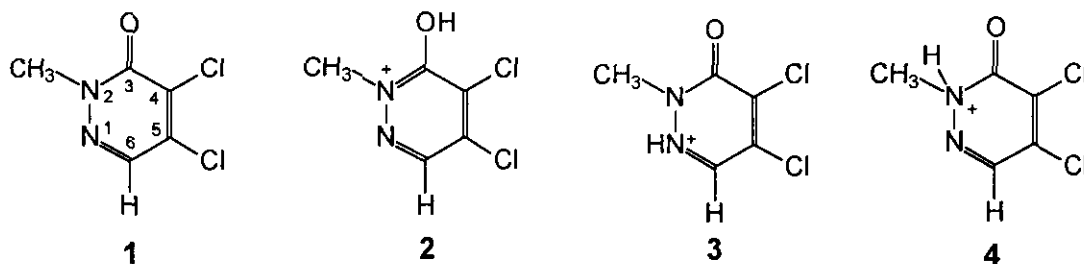
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Abstract - Studies on protonation of the title compound by DF and *ab initio* quantum chemical methods as well as ¹³C-nmr relaxation measurements revealed that *O*-protonation took place.

The regiochemistry of nucleophilic displacement reaction of 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone (**1**) was found to be dramatically influenced by strongly acidic medium, and the protonation of (**1**) with hydrobromic acid was supposed to proceed at *N*-1 on the basis of unexpected formation of the 4-bromo derivative.³ In this paper we describe our studies on the site of protonation of **1**.

We recently performed density functional (DF) calculations for a variety of heterocycles, and proton affinities gained by this way were in excellent agreement with the experimental values.¹



Total energy values for **1** and its protonated ions (**2-4**), were calculated by using DZVP/2⁴ basis set at LSD⁴ and NLSD⁴ (BP) levels of DF theory,⁴ and are listed in Table 1. For comparison, data obtained at 4-21G(*) and 6-31G** *ab initio* HF levels are also included,⁵ which are also expected to reproduce the basicity order correctly.⁶ According to the NLSD level of DF theory, which could even approximate the experimental proton affinities numerically, the total energy differences between **2** and **3** or **4** are as large as -48.9 and -141.0 kJ/mol, respectively, *i.e.* the *O*-protonated form (**2**) should predominate. The same conclusion could be drawn on the basis of *ab initio* data.

Table 1. Energetic values for compounds (**1-4**)

Compound	Energies by DF theory			Energies by <i>ab initio</i>		
	Total ^{a,b}	Relative ^{c,d}	PA ^{c,e}	Total ^{a,f}	Relative ^{c,d}	PA ^{c,e}
1	-1292.0738			-1289.4478		
	-1298.2594			-1294.3585		
2	-1292.4108	-171.7	884.8	-1289.8019	-131.9	929.7
	-1298.6041	-141.0	905.0	-1294.7124	-146.7	929.2
3	-1292.3942	-128.1	841.2	-1281.7655	-36.3	834.1
	-1298.5856	-92.1	856.4	-1294.6821	-67.2	849.7
4	-1292.3454	0	713.1	-1289.7516	0	797.8
	-1298.5504	0	764.0	-1294.6565	0	782.5

a) In au, 1 au (hartree)=2625.5 kJ mol⁻¹; b) the first values were obtained by LSD⁴, the second ones by LDF+BP⁴; c) in kJ mol⁻¹; d) the energy of the given form relatively to the less stable protonated ion (**4**); e) defined as the negative of the protonation enthalpy, *ie* the energy difference of the protonated ion and **1**; f) the first values were calculated at 4-21G(*) and the second ones at 6-31G** levels

To support the above theoretical results, the protonation of **1** was studied experimentally. ¹H Nmr shifts at pyridazinones as function of *pH* gave no information on the site of protonation⁷ Neither the ¹³C-nmr chemical

shifts were found to be of value in this respect, since all carbon lines for **1** were shifted downfield at about equal extent upon protonation, as shown in Table 2. We measured then ^{13}C -nmr T_1 relaxation times for pyridazinone (**1**) in $\text{CDCl}_3 + \text{TFA}$ and $\text{CDCl}_3 + \text{TFA-}d$ solutions by inversion recovery method. Nmr relaxation parameters have already been successfully used to investigate prototropic tautomerism,¹⁰ and protonation of nitrogen bases.¹¹ This method proved to be useful also in our case. The differences between the relaxation times measured in $\text{CDCl}_3 + \text{TFA}$ and $\text{CDCl}_3 + \text{TFA-}d$ are much larger for C-3 and C-4 than for the other carbons establishing that O-protonation took place.

Table 2. ^{13}C -nmr chemical shifts ($\delta_{\text{TMS}}=0$ ppm) and $T_1(^{13}\text{C})$ relaxation times for compound (**1**) at 20 MHz

Carbon	δ C (ppm)		T_1 (^{13}C) spin lattice relaxation time (sec)				
	CDCl_3	TFA/TFA- <i>d</i>	CDCl_3	TFA	TFA- <i>d</i>	Difference ^a	Difference ^b
CH ₃	40.6	41.6	9.2	6.9	6.8	0.1	1.5
C-3	156.4	158.5	158	48	140	-92	66
C-4	133.6	133.9	129	115	228	-113	50
C-5	136.1	138.3	99	73	80	-7	9
C-6	135.0	137.5	4.6	2.5	2.3	0.2	9

a) Difference in T_1 (^{13}C) measured in TFA and in TFA-*d*, b) the same in %.

In conclusion, the protonation of **1** was predicted by DF theory and *ab initio* methods to afford O-protonated form (**2**), in agreement with the experimental result based on ^{13}C -nmr relaxation time measurements.

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8. Samples were prepared from 0.6 mmol of 1 with 0.5 ml of CDCl₃ containing 1% TMS; for protonation or deuteration, 1.2 mmol of anhydrous TFA or TFA-*d*, respectively, were also added. The samples were measured at room temperature on a BRUKER AC-80 spectrometer operating at 80 MHz. Values for quaternary and protonated carbons were obtained from inversion recovery spectra Assignments agree with ref. 9.
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