DENSITY FUNCTIONAL CALCULATIONS ON HETEROCYCLIC COMPOUNDS. PART 2.[1] ON THE PROTONATION OF 4,5-DICHLORO-2-METHYL-3(2*H*)-PYRIDAZINONE

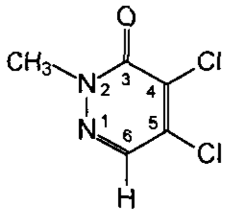
Péter Mátyus,[2]* Kaoru Fuji, and Kiyoshi Tanaka,*
Institute for Chemical Research, Kyoto University, Uji, Kyoto-Fu 611, Japan

János Rohonczy, Richárd Hargitai, and Pál Sohár*
Department of General and Inorganic Chemistry, Lóránd Eötvös University,
H-1518 Budapest-112, P O. Box 38, Hungary

Abstract - Studies on protonation of the title compound by DF and *ab initio* quantum chemical methods as well as ^{13}C-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]



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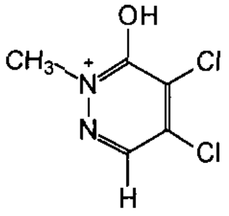

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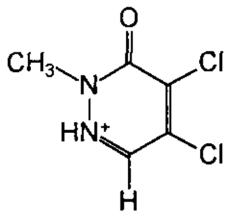

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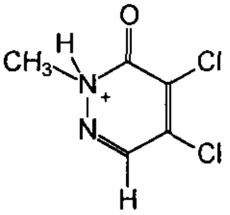

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Total energy values for **1** and its protonated ions (**2-4**), were calculated by using DZVP/2[4] basis set at LSD[4] and NLSD[4] (BP) levels of DF theory,[4] and are listed in Table 1. For comparison, data obtained at 4-21G(*) and 6-31G** *ab initio* 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 *ab initio*		
	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 LSD[4], the second ones by LDF+BP[4]; 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 protonation.[7] Neither the ^{13}C-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 $CDCl_3$ + TFA and $CDCl_3$ + 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 $CDCl_3$ + TFA and $CDCl_3$ + 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 (δ_{TMS}=0 ppm) and T_1(^{13}C) relaxation times for compound (**1**) at 20 MHz

Carbon	δC (ppm)		T_1 (^{13}C) spin lattice relaxation time (sec)				
	$CDCl_3$	TFA/TFA-*d*	$CDCl_3$	TFA	TFA-*d*	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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4. All calculations were done on Cray-YMP supercomputer with DGAUSS 1.1.1./ UC-1 1.1 program Full geometric optimizations were carried out. The Becke-Perdew (BP) treatments were done after the final SCF. For details of calculations see ref. 1, and J. Andzelm and E. Wimmer, *J. Chem. Phys.*, 1992, **96**, 1280.
5. All calculations were done on IBM RS6000 workstation with TX90 program Full geometric optimizations were carried out by the GDIIS algorithm (P. Pulay, *Theor. Chim. Acta*, 1979, **50**, 299) The split-valence 4-21G(*) basis set contains polarization function on atoms differ from carbon and hydrogen (G. Fogarasi, X. Zhou, P W Taylor, and P Pulay, *J. Am. Chem. Soc.*, 1992, **114**, 8191).
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8. Samples were prepared from 0.6 mmol of **1** with 0 5 ml of $CDCl_3$ 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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