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[G001]

Theoretical studies on the tautomerism of 1,5,6,7-tetrahydro-4*H*-indazol-4-ones

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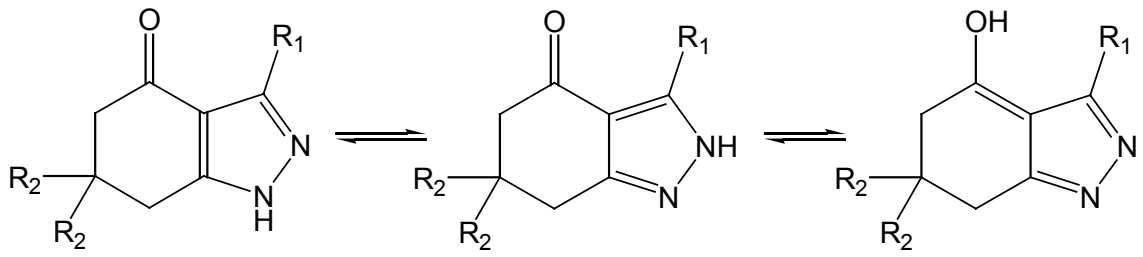
Abstract. Four derivatives of 1,5,6,7-tetrahydro-4*H*-indazol-4-one have been synthesized and computational studies on the tautomeric forms at different levels, from semiempirical AM1, *ab initio* Hartree-Fock HF/6-31G* and HF/6-31G** to density functional calculations B3LYP/6-31G** were carried out. They allowed to establish the most stable form in all cases. The results are in agreement with the experimental data.

Introduction

Annular tautomerism of pyrazole and indazole derivatives has been deeply investigated both theoretically and experimentally.[1,2] A theoretical estimation of the annular tautomerism of 52 N*H*-indazoles concluded[3] that although in most cases the 1*H*-tautomer is the most stable, in some indazoles, the 2*H*-tautomer was more stable than the 1*H*. Recently we approached the study of the tautomerism of tetrahydroindazoles, also known as tetramethylenepyrazoles, bearing a trifluromethyl group at position 3 and found that in all cases they are 1*H*-3-CF_3 tautomers.[4]

We present here our studies on the tautomerism of a more complex case, the 1,5,6,7-tetrahydro-4*H*-indazol-4-ones, in which three tautomeric forms have been considered (Scheme 1).



1*H* **2*H*** **OH**

R_1 = H, R_2 = H, **1**
R_1 = H, R_2 = CH_3, **2**
R_1 = CH_3, R_2 = H, **3**
R_1 = CH_3, R_2 = CH_3, **4**

Scheme 1

Results and Discussion

All calculations have been carried out using the Spartan '02 Linux/Unix software working on a Silicon Graphics Octane Workstation.[5]

The results of the calculations at semi-empirical AM1 level are gathered in Table 1.

Table 1. AM1 Differences in energy (kJ mol^{-1}), energies in brackets (kJ mol^{-1}) and dipole moments (Debye)

	E			μ		
Comp.	**1*H***	**2*H***	**OH**	**1*H***	**2*H***	**OH**
1	3.01	0.0 [74.42625]	60.78	5.08	2.05	5.64
2	2.43	0.0 [46.31270]	60.15	5.11	2.03	5.67
3	8.63	0.0 [36.13512]	63.18	4.67	1.85	5.54
4	8.02	0.0 [8.03202]	75.67	4.70	1.82	7.52

The corresponding *ab initio* energies based on geometries optimized at the HF/6-31G* and HF/6-31G** levels are shown in Tables 2 and 3.

Table 2. HF/ 6-31G* Differences in energy (kJ mol^{-1}), energies in brackets (hartree) and dipole moments (Debye)

	E			μ		
Comp.	**1*H***	**2*H***	**OH**	**1*H***	**2*H***	**OH**
1	0.0 [-453.48686]	0.59	135.24	5.64	2.14	8.61
2	0.0 [-531.55518]	0.81	134.34	5.63	2.14	8.56
3	1.86	0.0 [-492.53055]	134.65	5.25	1.96	8.40
4	1.73	0.0 [-570.59882]	125.38	5.23	1.97	5.80

Table 3. HF/ 6-31G** Differences in energy (kJ mol^{-1}), energies in brackets (hartree) and dipole moments (Debye)

	E			μ		
Comp.	**1*H***	**2*H***	**OH**	**1*H***	**2*H***	**OH**
1	0.0 [-453.50210]	0.45	127.80	5.66	2.12	8.63
2	0.0 [-531.57666]	0.68	128.14	5.65	2.12	8.58
3	2.03	0.0 [-492.54888]	129.67	5.25	1.94	8.42
4	1.89	0.0 [-570.62340]	120.56	5.24	1.94	5.84

Finally, the values obtained at the density functional B3LYP/6-31G** level are reported in Table 4.

Table 4. B3LYP/ 6-31G** Differences in energy (kJ mol^{-1}), energies in brackets (hartree) and dipole moments (Debye)

		E			μ		
Comp.		**1*H***	**2*H***	**OH**	**1*H***	**2*H***	**OH**
1		0.93	0.0 [-456.29158]	121.97	5.27	2.18	8.32
	+ZPE	1.18	0.0 [-456.14543]	118.91			
2		0.65	0.0 [-534.92481]	121.22	5.26	2.17	8.28
	+ZPE	0.91	0.0 [-534.72310]	118.07			
3		3.81	0.0 [-495.61836]	125.25	4.80	2.00	8.11
	+ZPE	3.64	0.0 [-495.44438]	121.39			
4		3.30	0.0 [-574.25151]	115.92	4.79	2.00	5.67
	+ZPE	3.14	0.0 [-574.02222]	113.22			

An analysis of the data reported in Tables 1-4 shows that, according to the semiempirical AM1 and the DFT B3LYP/6-31G** methods, the tautomer 2*H* is the most stable one in all cases, followed by the 1*H* and the OH forms. The linear regression between the AM1 and the B3LYP/6-31G** calculated energy values afforded r^2 coefficients of 0.997 and 0.995 (+ZPE), showing that in the present tautomerism studies, similarly to what has been reported in reference 3, the inexpensive AM1 method can be used as exploratory tool with excellent results.

Ab initio Hartree-Fock gives rise to different stabilities order, 1*H*>2*H*>OH in 1,5,6,7-tetrahydro-4H-indazol-4-one (**1**) and 6,6-dimethyl-1,5,6,7-tetrahydro-4H-indazol-4-one (**2**) and 2*H*>1*H*>OH in 3-methyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (**3**) and 3,6,6-trimethyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (**4**). However the energy differences between 1*H* and 2*H* tautomers are very small in all cases with an average value of 1 kJ mol^{-1}.

All theoretical methods predict tautomer 4-hydroxy as the most unfavorable one, the explanation being the loss of the aromaticity of the pyrazole ring.[6]

These results are in agreement with the experimental data obtained by multinuclear magnetic resonance in solution and in solid state for all compounds.[7] We reproduce here the ^{13}C NMR spectra of compound **4** confirming that in solid state it exists only as tautomer 2*H* and in DMSO-d_6 solution the two forms 2*H* and 1*H* are observed in a ratio of 55:45.

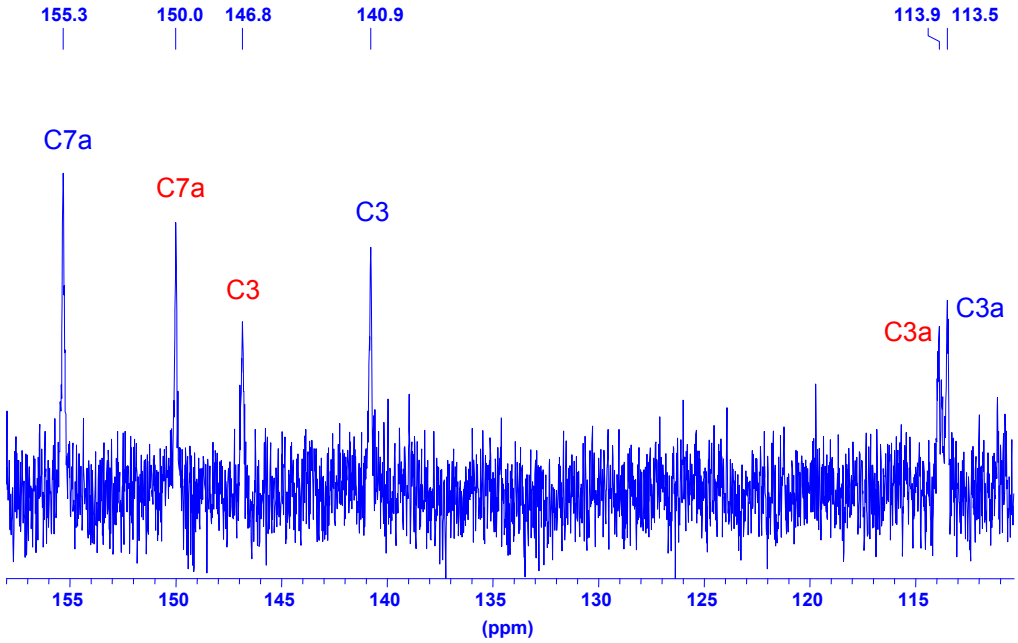


Figure 1. ^{13}C NMR spectrum (aromatic region) of compound **4** in DMSO-d_6 at 298 K

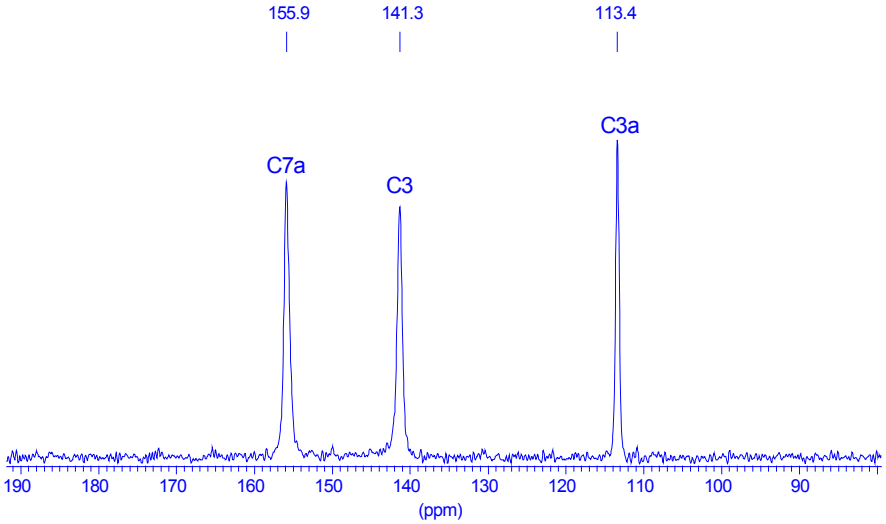


Figure 2. ^{13}C CPMAS NMR spectrum (aromatic region) of compound **4** at 298 K

Conclusions

In 1,5,6,7-tetrahydro-4*H*-indazol-4-ones the AM1 and B3LYP/6-31G** calculations provide similar results on the stability of the tautomeric forms and reproduce the experimental results. In the case of compound **4**, the 2*H*-tautomer is experimentally more stable than the 1*H*-one by 0.5 kJ mol^{-1} at 298 K (in DMSO-d_6). The closest calculated values are found in Tables 2 (1.7 kJ mol^{-1}) and 3 (1.9 kJ mol^{-1}). Besides, the dipole moment should favour the 1*H*-tautomer in DMSO solution explaining why the difference is so small.

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