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Communication

Theoretical Studies on the Tautomerism of 1,5,6,7-Tetrahydro-4*H*-indazol-4-ones

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Abstract: Computational studies on three tautomeric forms of four 1,5,6,7-tetrahydro-4*H*-indazol-4-one derivatives: 1,5,6,7-tetrahydro-4*H*-indazol-4-one (**1**), 6,6-dimethyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (**2**), 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**), have been performed at different levels, ranging from semiempirical AM1, *ab initio* Hartree-Fock HF/6-31G* and HF/6-31G** to B3LYP/6-31G** density functional calculations. These calculations have been used to establish the most stable tautomer, which in all cases was in agreement with the experimental data.

Keywords: Tautomerism, tetrahydroindazoles, theoretical calculations

Introduction

Annular tautomerism of pyrazole and indazole derivatives has been investigated in depth both theoretically and experimentally [1,2]. A theoretical estimation of the annular tautomerism of 52 N*H*-indazoles concluded 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* one [3]. Recently we approached the study of the tautomerism of tetrahydroindazoles (also known as tetramethylenepyrazoles) bearing a trifluoromethyl group at the 3-position and we found that in all cases they exist as 1*H*-3-CF$_3$ tautomers [4]. We present here our studies on the tautomerism of a more complex case, that of the 1,5,6,7-tetrahydro-4*H*-indazol-4-ones **1-4**, in which three tautomeric forms have been considered (Scheme 1).

Scheme 1.

$$R_1 = H, R_2 = H, \ \mathbf{1}$$
$$R_1 = H, R_2 = CH_3, \ \mathbf{2}$$
$$R_1 = CH_3, R_2 = H, \ \mathbf{3}$$
$$R_1 = CH_3, R_2 = CH_3, \ \mathbf{4}$$
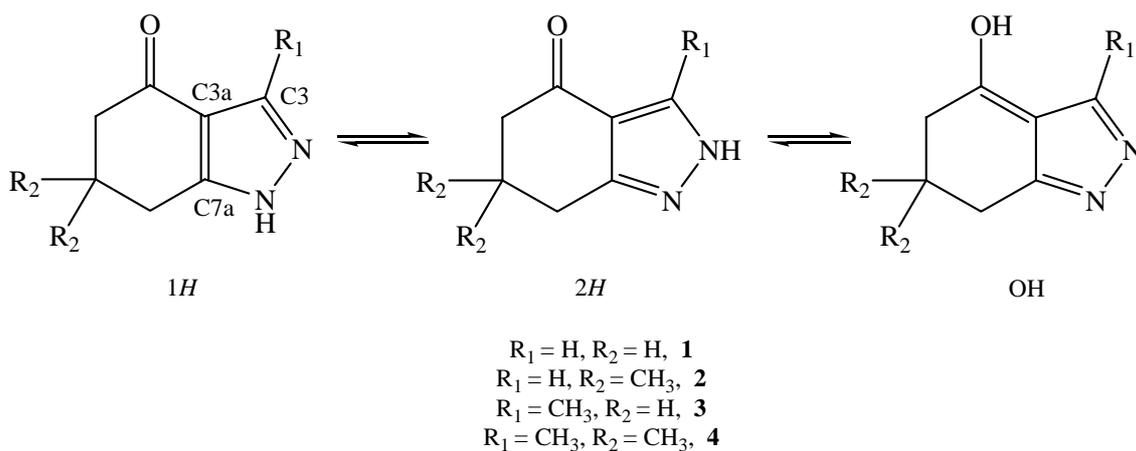
Results and Discussion

The results of the calculations at the semiempirical AM1 level are gathered in Table 1, showing that the OH form in which the heterocyclic ring loses its aromaticity is clearly unfavorable.

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

Comp.	E			μ		
	1H	*2H*	**OH**	*1H*	*2H*	**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. They are consistent and show the expected decrease in energy with the increasing level of the basis set used [5].

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

Comp.	E			μ		
	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).

Comp.	E			μ		
	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).

Comp.		E			μ		
		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 in Tables 1-4 shows that, for the gas phase, according to the semiempirical AM1 and DFT B3LYP/6-31G** methods, the 2*H* tautomer is the most stable one in all cases, followed by the 1*H* one and distantly by the OH forms.

The linear regression between the AM1 and B3LYP/6-31G** calculated energy values afforded r^2 coefficients of 0.997 and 0.995 (+ZPE), showing that in the present tautomerism study, similarly to what has been reported in reference [3], the inexpensive AM1 method can be used as exploratory tool with good results.

Ab initio Hartree-Fock calculations with the 6-31G* and 6-31G** basis sets, give rise to a different stability order: i) 1*H* > 2*H* > OH in 1,5,6,7-tetrahydro-4*H*-indazol-4-one (**1**) and 6,6-dimethyl-1,5,6,7-tetrahydro-4*H*-indazol-4-one (**2**) and ii) 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 the 1*H* and 2*H* tautomers are very small in all cases, with an average value of 1 kJ mol^{-1}.

All the theoretical methods predict the 4-hydroxy tautomer as the most unfavorable one, the explanation being the loss of the aromaticity of the pyrazole ring [6]. Finally, an analysis of the calculated dipole moments show that the 1*H*-tautomers have higher dipole moments than the 2*H*-tautomers (Tables 1-4). As the influence of the solvent on the tautomeric equilibrium is related to the dipole moment, the higher the dipole moment the more stable the corresponding tautomer in polar solvents. Therefore the conclusions reached for the gas phase can be modified in solution or in solid phases. We can advance that the foregoing theoretical results are in agreement with the experimental data obtained by multinuclear NMR in solution and in solid state for all compounds [7]. As an example, we reproduce here the ^{13}C-NMR spectra of compound **4**, proving that in solid state it exists only as the

2*H* tautomer, while in DMSO-*d₆* solution both the 2*H* and 1*H* forms are observed in a ratio of ca. 55:45.

Figure 1. ¹³C CPMAS NMR spectrum (aromatic region) of compound **4** at 298 K.
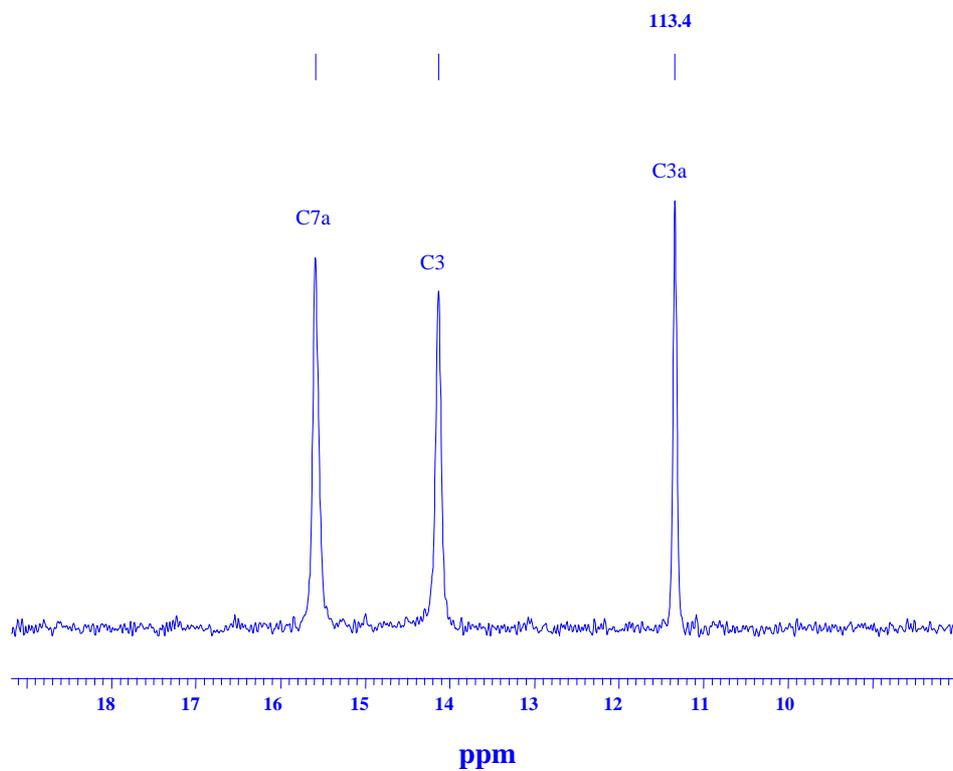
Figure 2. ¹³C-NMR spectrum (aromatic region) of compound **4** in DMSO-d₆ at 298 K.
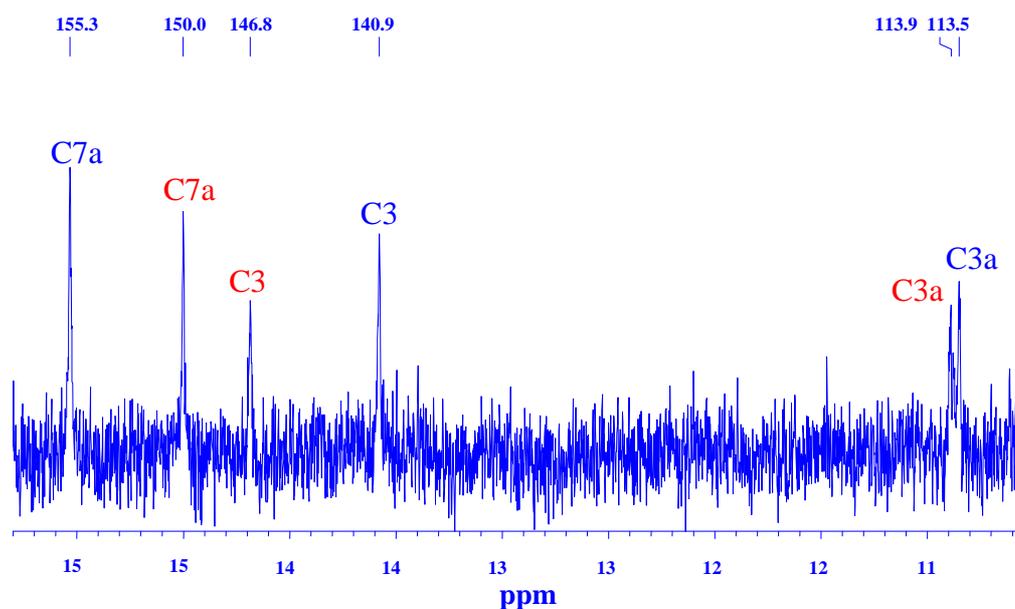
Conclusions

AM1 and B3LYP/6-31G** calculations on 1,5,6,7-tetrahydro-4*H*-indazol-4-ones **1-4** provide similar results concerning 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 Table 2 (1.7 kJ mol^{-1}) and Table 3 (1.9 kJ mol^{-1}). Besides, the dipole moment favours the 1*H*-tautomer in DMSO solution explaining why the difference is so small.

Acknowledgements

Experimental

The SPARTAN program [8] working on a Silicon Graphics Octane Workstation has been used to build and optimize the structures of the 1*H*, 2*H* and OH tautomers of the 1,5,6,7-tetrahydro-4*H*-indazol-4-ones **1**-**4** at the different computational levels (AM1, HF/6-31G*, HF/6-31G** and B3LYP/6-31G**). No symmetry restriction has been imposed in the optimization process.

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