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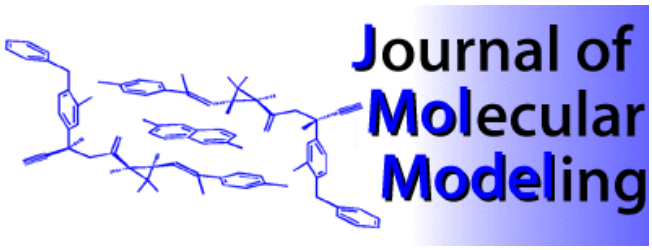

Study of the Tautomerism by Experimentally and Theoretically Estimated ^{13}C and ^{15}N Chemical Shifts[$]

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Abstract

2-Substituted 5-Me-7OH-1,2,4-Triazolo[1,5-a]pyrimidines can exist as different tautomeric forms. The tautomeric equilibrium of these compounds were determined by various NMR spectroscopic methods and quantum-chemical calculations. The tautomeric equilibria of 2-substituted 1,2,4-Triazolopyrimidines depend on the used solvent. In order to take solvent effects into account, *ab initio* calculations using the SCI-PCM method were carried out. The solvation energy depends on the polarity of the substituents in position 2. The comparison of chemical shifts determined by experimental methods and theoretical *ab initio* methods were used to definitely find out the the tautomeric equilibria of these compounds.

Keywords: NMR spectroscopy, Solvent effects, Chemical shifts, GIAO, SCIPCM

Introduction

1,2,4-Triazolo[1,5-a]pyrimidines are biologically active compounds, which are applied as herbizides, pestizides, growth regulators, vasodilators. They have also photostabilizing properties. These compounds can exist at least in four tautomeric forms and in seven tautomeric forms if the substituents at position 2 are included in the process of tautomerism (Figure 1 and 2).

The ^{13}C and ^{15}N NMR spectra of the following compounds [1] were recorded in DMSO-$_{d6}$ and assigned by employing the whole arsenal of 1D and 2D NMR spectroscopic methods (Scheme 1).

The process of proton exchange proved to be fast on the NMR time scale. Therefore the determination of different tautomeric forms **a-d** of these compounds is difficult. Only this fast equilibrium of the most stable tautomeric forms can be studied by NMR spectroscopy. The relative stabilities of the different tautomeric forms cannot be concluded from the corresponding experimental results.

In principle, the relative stabilities of the various tautomeric forms can be determined using theoretical *ab initio* methods. Outgoing from the results of *ab initio* calculations at a high level of theory the relative energies of the structures participating in tautomeric equilibria can be concluded. However, these quantum chemical calculations of tautomeric equilibria are very complicate. In the studied compounds **1-12** each tautomer has a different type of conjugation. Typical quantum chemical errors, as basis set error, electron correlation error, solvent effects, are not easily to be compensated as e.g. along the conformational search of a molecule. The

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Table 1. *Experimental (red) ^{13}C chemical shifts of the 2,5-Me-7- 1,2,4-triazolo[1,5-a]pyrimidine* ***13*** *and results from* ab initio *calculations (GIAO) using various basis sets and various methods*

Atom	Exp.	STO-3G	3-21G	6-31G*	6-31+G**	BLYP6-31G*	BLYP6-31+G**
C2	154.9	157	154	155	157	148	152
C5	164.3	159	159	168	172	152	157
C6	110.6	110	99	101	101	103	105
C7	146.8	138	143	150	153	136	141
C9	154.4	155	148	154	155	148	152
C10	16.3	32	25	25	25	25	26
C11	24.3	29	20	17	18	18	19

calculations of the tautomeric equilibria of **1-12** are even more difficult because these tautomeric equilibria are characteristically depend on present substituents and solvents employed.

However, a combination of both NMR spectroscopy and theoretical calculations seems to be very promising by concluding the position of present tautomeric equilibria. In addition the comparison of calculated and experimentally determined chemical shifts can be used to find out the most stable tautomeric form of the studied compounds.

Methodology

The GAUSSIAN 94 program [2] and 6-31G* split valence basis sets [3]were used at the Hartree-Fock-level and at the DFT-BLYP-level [4]. Relaxed conformational energies were calculated by minimizing the whole structures of the compounds. The solvent effects of DMSO were taken into account using a self-consistent reaction field model (SCRF). The SCI-PCM method [5] was employed. The dielectric constant of DMSO (46.7) which was used in the parallel NMR studies and the molare volume defined by a 0.0004 a.u. isodensity value of the electron density were applied [6].

The NMR chemical shifts were calculated using the "gauge-including" atomic orbital (GIAO) method [7]. The chemical shift is a difference of the chemical shielding, (^{13}C and ^{15}N), of the molecule and the chemical shielding of a reference compound. The GIAO method is implemented into the GAUSSIAN 94 program [2].

In order to be comparable the calculation of the nuclear shieldings of the reference compounds (TMS for ^{13}C and nitromethane for ^{15}N) and **1-13** has to be carried out at the same level of theory. It should be noted that the calculation of nuclear shieldings is strongly depend on the used basis sets. Therefore we checked the results of calculated chemical shifts of compound **13** using various basis sets and levels of theory (HF/STO-3G, HF/3-21G, HF/6-31G*, HF/6-31+G**, BLYP/6-31G*, BLYP/6-31+G**) (Table 1). Results at the HF/6-31G* level of reference compound **13** show sufficient agreement with the experimental values [8] and there-

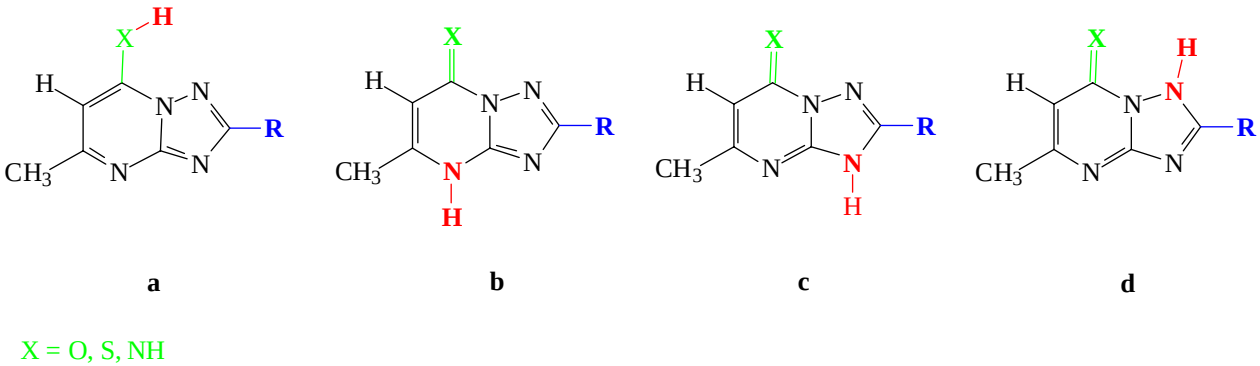
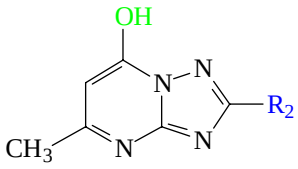
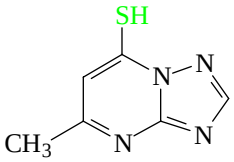
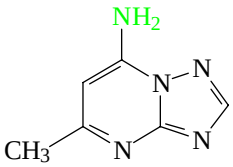
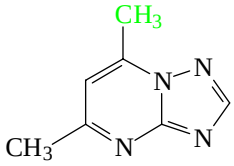


Figure 1. *Mostly relevant tautomeric forms of 2-substituted 5-Me-7-OH-1,2,4-triazolo[1,5-a]pyrimidines four tautomers.*









No.	R_2
1	C_7H_{15}
2	CH_2OCH_2COOH
3	COOH
4	$COSCH_2COOH$
5	CONHPh
6	OH
7	SCH_2COOH
8	COOH (5-C_7H_{15})
9	$NHNO_2$
10	H
11	
12	
13	

Scheme 1. *Compounds **6,9** correspond to Figure 2, no tautomeric forms exist for compound **13***

fore the chemical shieldings of **1-12** were calculated at this level.

The ^{13}C and ^{15}N NMR spectra of the compounds **1-13** were recorded in DMSO-d_6 as the solvent on a BRUKER ARX 300 NMR spectrometer and on a JOEL NMR spectrometer Alpha 500. 1D- and 2D-experiments were carried out. We already reported the details of experimental determination and the experimental results in references [1,8].

Results and Discussion

In our previous work [8,9] we already reported the application of the relative stabilities of the tautomeric forms in order to find out the position of present tautomeric equilibria . The tautomeric equilibria of **1-12** are influenced by solvents, especially when using polar solvents like DMSO. Solvation energy of the various tautomeric forms depends on the present substituents. Table 2 shows the solvation energy of all tautomeric forms of each molecule calculated using SCI-PCM method with a dielectric constant of DMSO (46.7) and the HF/6-31G* method.

Table 2. *Solvation energies of variuos tautomeric forms in kcal/mol calculated as differences of HF/6-31G* energies and the SCI-PCM//HF/6-31G* energies*

Compound	a	b	c	d
1	7.9	12.9	13.4	12.3
2	22.1	20.8	22.6	18.1
3	13.3	20.1	15.2	14.3
4	17.7	21.2	20.6	19.7
5	15.6	17.5	13.5	12.9
7	13.0	18.2	17.9	16.7
8	12.9	20.0	15.2	14.2
10	8.5	13.0	14.2	13.4
11	7.3	13.9	17.2	12.8
12	11.0	10.2	12.5	11.7

Comp.	a	b	c	d	e	f	g
6	10.9	17.0	16.2	14.8	23.0	18.4	12.8
9	12.6	19.8	22.2	18.5	24.4	22.1	15.6

The more polar the substituent in position 2 (**3, 4, 5, 7, 8**), the more tautomers **b** were stabilized. Non-polar substituents in position 2 (**1, 2, 10, 11, 12**) lead to stronger stabilization of tautomers **c** relative to the other tautomeric forms.

For all compounds **1-11** the tautomeric lactim forms **b** have been shown as the most stable tautomeric forms [8]. For compound **12** the tautomeric form **a** is more stable than the other forms. On the other hand, the calculated chemical shifts of these most stable forms are the best in accordance with the experimentally obtained values (cf. Table 3 for ^{13}C and Table 4 for the corresponding ^{15}N chemical shifts). These results are illustrated in Figure 3 and Figure 4 by compound **4** as an example of the whole set **1-12**. The determination of the experimental results are shown in reference [8]. For compound **6** we got no experimental data of ^{15}N chemical shifts and broad lines of ^{13}C chemical shifts. This is in agreement with the theoretical results. The differences of the relative energies of tautomers **6b**, **6f** and **6g** are very small (SCIPCM/ /HF/6-31G* energies differ less than 1 kcal/mol). But the best correlation of ^{13}C chemical shifts between experimental and theoretical results exist for tautomer **6b**.

Both the calculated ^{15}N and ^{13}C chemical shifts of the most stable tautomers of all compounds **1-12** studied show significant better correlations to experimental data than the other tautomeric forms of these compounds.

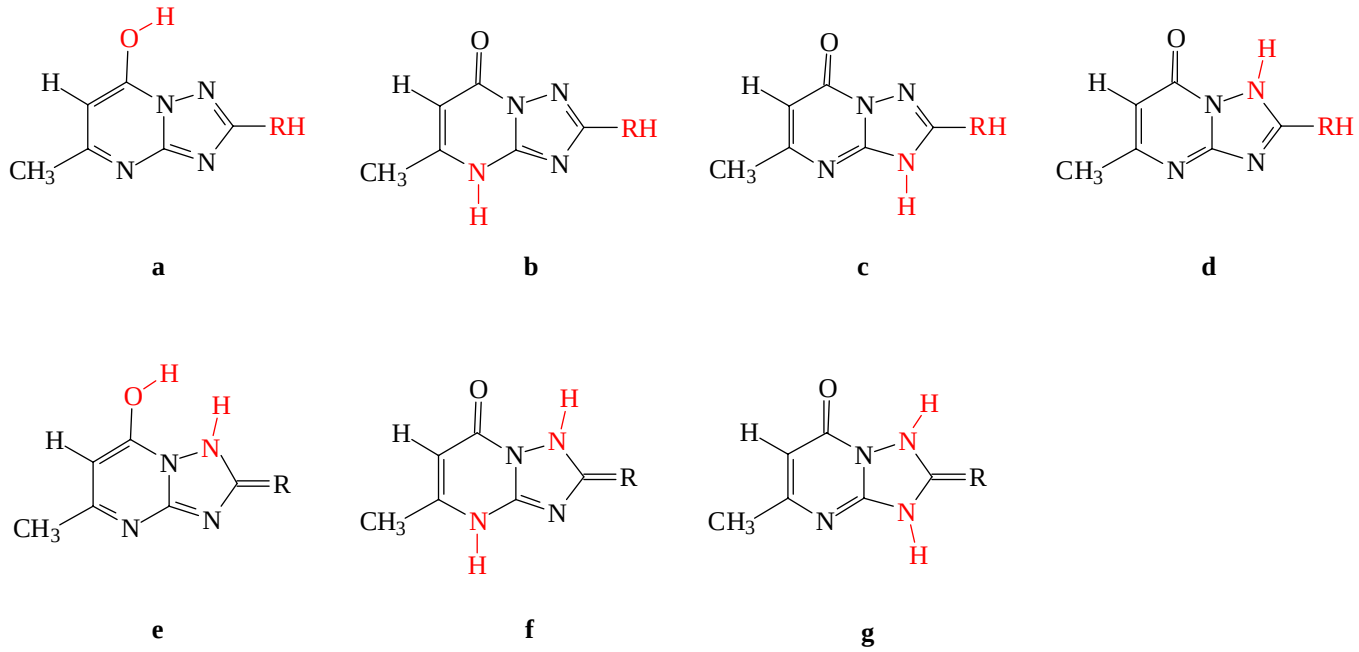


Figure 2. *Seven tautomers of compounds* ***6, 9***

Conclusions

The tautomeric equilibria of 2-substituted 5-Me-7-OH-1,2,4-triazolo[1,5-a]pyrimidines are depending strongly on the used solvent. The process of proton exchange is fast on the NMR time scale and therefore it is not possible to determine the tautomeric equilibria definitely. These solvent effects must be taken into account for the *ab initio* calculations of these equilibria. The combination of $^{13}C/^{15}N$ NMR studies and *ab initio* calculations of the relative stability of the tautomeric forms together with their $^{13}C/^{15}N$ chemical shifts can be employed to easily determine the position of these tautomeric equilibria. The calculated chemical shifts of the most stable tautomeric forms correspond to the experimentally determined chemical shifts. The results of the GIAO method at the HF/6-31G* level are in agreement with the experimentally determined chemical shifts checked for compound **13**. All compounds **1-11** exist as the lactim form **b**, if the polar solvent DMSO is used. Compound **12** occures as the tautomer **a**.

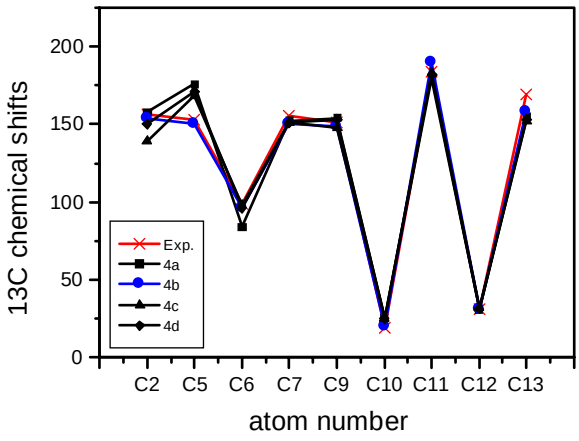


Figure 3. *^{13}C chemical shifts of compound* ***4*** *experimental data (red) and calculated values (HF/6-31G*)*

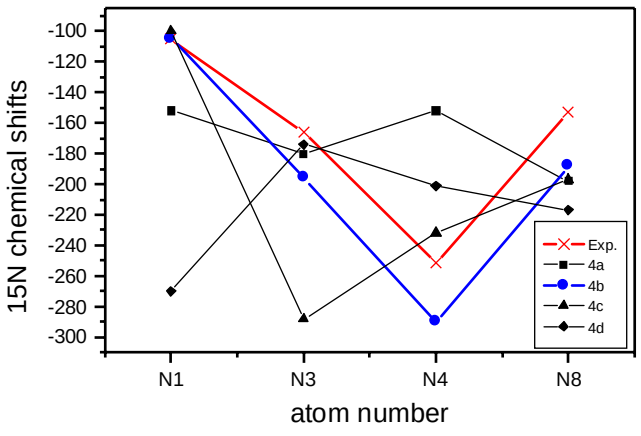


Figure 4. *^{15}N chemical shifts of compound* ***4*** *experimental data (red) and calculated values (HF/6-31G*)*

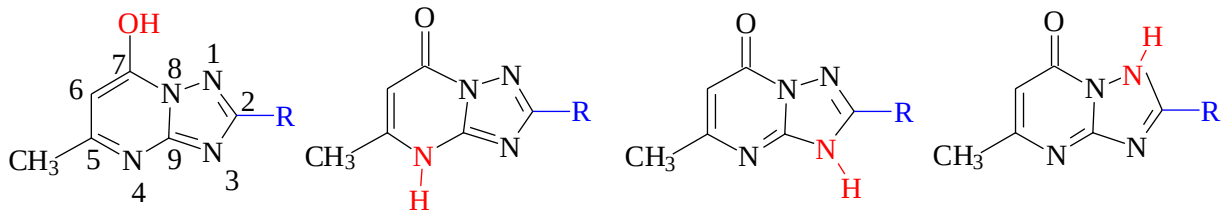
Table 3. *Experimental (italic)* ^{13}C *chemical shifts of the 2-substituted 1,2,4-triazolo[1,5-a]pyrimidines* ***1-12*** *and results from* ab initio *calculations (GIAO HF/6-31G*)*

Comp.	C2	C5	C6	C7	C9	C11
1	*164.1*	*151*	*98.1*	*155.6*	*150.7*	*18.5*
1a	170	174	81	152	156	25
1b	163	146	95	150	149	19
1c	146	165	97	151	149	24
1d	165	171	94	152	155	25
2	*160.4*	*151.5*	*98.2*	*155.7*	*151.5*	*18.6*
2a	165	174	82	152	156	25
2b	160	147	95	150	149	19
2c	147	166	96	151	149	24
2d	160	171	93	152	154	25
3	*154*	*152.4*	*98.5*	*155.6*	*150.9*	*18.6*
3a	157	176	84	152	154	25
3b	151	148	96	149	148	19
3c	139	167	97	150	148	24
3d	150	171	95	151	152	25
4	*156.5*	*152.8*	*98.9*	*155.6*	*151.2*	*18.7*
4a	158	176	84	152	154	25
4b	154	150	96	150	149	20
4c	139	168	98	151	148	25
4d	150	171	96	151	153	25
5	*156.2*	*152.4*	*98.7*	*155.7*	*151*	*18.7*
5a	160	176	84	153	154	25
5b	154	147	96	149	148	19
5c	142	167	96	151	148	24
5d	153	171	95	152	153	25
6	*163.9*	*149.3*	*99.2*	*154.7*	*151.6*	*19.2*
6a	163	174	82	153	155	25
6b	160	146	96	149	150	19
6c	146	164	98	151	148	24
6d	159	170	96	142	154	25
6e	150	176	75	149	155	25
6f	148	148	95	148	149	19
6g	139	168	96	150	144	23
7	*161.7*	*150.7*	*98.4*	*154.8*	*151.1*	*18.4*
7a	169	176	82	152	156	25
7b	168	148	96	149	150	19
7c	153	166	98	150	148	24
7d	171	170	96	151	152	25
8	*154*	*152.4*	*98.4*	*155.6*	*150.9*	*18.6*
8a	157	179	84	152	154	29
8b	151	152	93	149	148	23
8c	139	171	94	151	148	28
8d	150	175	93	152	152	29
9	*153.8*	*151.5*	*98.8*	*155.2*	*150.3*	*18.6*
9a	165	176	83	153	154	25
9b	151	146	97	149	149	18
9c	148	166	98	150	147	24
9d	149	171	95	152	152	25
9e	165	180	78	151	157	25
9f	158	150	95	147	148	19
9g	148	168	97	149	141	24
10	*151.9*	*151.7*	*98.2*	*155.9*	*150.6*	*18.7*
10a	156	174	82	152	155	25
10b	150	147	95	150	149	19
10c	133	166	97	151	148	24
10d	148	171	94	152	154	25
11	*151.8*	*148.7*	*114.5*	*177*	*147.6*	*19.2*
11a	155	168	100	153	154	24
11b	152	140	107	202	146	18
11c	134	161	113	199	146	23
11d	146	169	111	188	151	24
12	*154.2*	*163.1*	*89.9*	*155.5*	*148.4*	*24.4*
12a	156	172	80	150	156	25
12b	150	140	97	144	147	19
12c	133	157	98	146	146	24
12d	146	166	91	151	153	25

Table 4. *Experimental (italic)* ^{15}N *chemical shifts of the 2-substituted 1,2,4-triazolo[1,5-a]pyrimidines* ***1-5,7-12*** *and results from* ab initio *calculations (GIAO HF/6-31G*)*

Comp.	N1	N3	N4	N8
1	*-117.4*	*-187.6*	*-253.9*	*-156.2*
1a	-173	-183	-156	-206
1b	-139	-247	-306	-197
1c	-142	-283	-234	-204
1d	-270	-179	-204	-221
2	*-124.3*	*-165.4*	*-253*	*-156.1*
2a	-163	-178	-153	-204
2b	-129	-195	-305	-196
2c	-139	-280	-231	-201
2d	-266	-191	-206	-219
3	*-101.7*	*-162.4*	*-252.8*	*-153.6*
3a	-151	-187	-155	-198
3b	-107	-203	-306	-188
3c	-128	-287	-231	-201
3d	-267	-182	-203	-216
4	*-105.2*	*-166.3*	*-251.8*	*-153.2*
4a	-152	-180	-152	-198
4b	-105	-196	-305	-188
4c	-100	-288	-232	-197
4d	-270	-174	-201	-217
5	*-204.8*	*-108.6*	*-62.6*	*-109.7*
5a	-246	-210	-242	-202
5b	-291	-198	-94	-210
5c	-267	-115	-169	-199
5d	-135	-214	-196	-184
7	*-124.3*	*-168.5*	*-254.3*	*-155.1*
7a	-180	-185	-157	-204
7b	-162	-199	-305	-198
7c	-165	-283	-231	-206
7d	-272	-192	-206	-222

Comp.	N1	N3	N4	N8
8	*-101.7*	*-162.4*	*-254.4*	*-153.4*
8a	-150	-187	-160	-198
8b	-107	-203	-306	-188
8c	-128	-287	-230	-202
8d	-268	-182	-203	-217
9	*-128.8*	*-175.5*	*-254.2*	*-161*
9a	-192	-210	-161	-209
9b	-165	-219	-305	-201
9c	-170	-290	-184	-211
9d	-282	-211	-206	-225
9e	-277	-208	-158	-248
9f	-274	-220	-303	-236
9g	-285	-300	-225	-240
10	*-110.6*	*-165.4*	*-252.3*	*-155*
10a	-164	-181	-154	-203
10b	-127	-196	-305	-193
10c	-129	-286	-234	-202
10d	-269	-174	-203	-220
11	*-102.4*	*-173.1*	*-230.5*	*-142.6*
11a	-147	-178	-140	-193
11b	-122	-198	-299	-178
11c	-123	-285	-216	-187
11d	-254	-177	-179	-203
12	*-120.4*	*-156.6*	*-148.6*	*-173.4*
12a	-158	-185	-167	-207
12b	-140	-198	-314	-206
12c	-140	-287	-243	-216
12d	-266	-179	-215	-235



10 **11** **12** **13**

R = $COSCH_2COOH$

Figure 5. *Tautomeric forms of compound* ***4*** *(numbering of atoms)*

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