^{1}H NMR STUDY OF 3,5-DISUBSTITUTED 6-OXO-1,6-DIHYDRO-1,2,4-TRIAZINES

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Received October 5, 1994
Accepted December 23, 1994

^{1}H NMR spectra have been measured of seven 3,5-disubstituted 6-oxo-1,6-dihydro-1,2,4-triazines, and tautomerism of these compounds has been evaluated in connection with the nature of substituents, medium, and temperature. The title compounds exist in their benzyl or benzylidene forms or as a mixture of both forms. Thermodynamic characteristics of the transition between the two forms have been determined from the temperature dependence of NMR spectra of three derivatives.

In the context of long-term studies of nitrogen-containing heterocycles we have also dealt with the synthesis and reactions of new 3,5-disubstituted 6-oxo-1,6-dihydro-1,2,4-triazines[1–6]. Reactions of these compounds indicate that they can exist in various tautomeric forms.

^{1}H NMR spectra represent a highly reliable method for investigating tautomeric equilibria inclusive of the effects of state variables and structure on these equilibria. Beside the classic studies of keto–enol and azo–hydrazone equilibria, the NMR method has also been used for quantitative evaluation of tautomeric equilibria of a number of heterocyclic nitrogen compounds. The problem of tautomerism of heterocyclic nitrogen-containing compounds is treated in a comprehensive way e.g. in monographs[7–10]. The most detailed studies include e.g. those of lactam–lactim tautomerism of 2- and 4-hydroxypyridines and 2- and 4-mercaptopyridines[11,12] and tautomerism of bis(2-quinolyl)-methane[10,13] whose authors also extensively investigated the effects of medium and temperature upon the respective tautomeric equilibria.

The aim of the present work is to study some of the compounds prepared by means of ^{1}H NMR spectroscopy and evaluate their tautomerism as a function of temperature, structure, and medium.

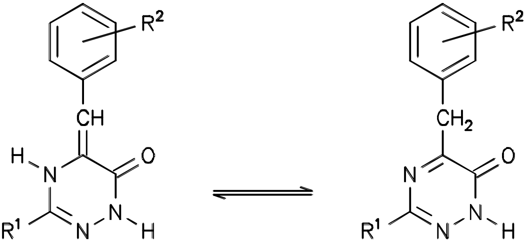
The reactions carried out so far indicate that the compounds investigated can exist in two tautomeric forms (Scheme 1).

EXPERIMENTAL

The NMR spectra were measured with an AMX-360 Bruker apparatus at the working frequency of 360.14 MHz for ^{1}H. The solutions measured were either of 0.1 mol l^{-1} concentration or, if less soluble, saturated. The equilibrium constants were calculated from the intensities of NMR signals of methoxyl groups. The thermodynamic characteristics were calculated from these equilibrium constants obtained for the individual temperatures using the least squares treatment according to the standard thermodynamic relationships.

RESULTS AND DISCUSSION

For the purpose of the present treatment we selected seven compounds whose reactions and IR spectra allowed the presumption of existence of tautomeric forms: 5-benzyl-3-phenyl-6-oxo-1,6-dihydro-1,2,4-triazine[14] (*I*), 5-benzyl-3-methyl-6-oxo-1,6-dihydro-1,2,4-triazine[1] (*II*), 3-phenyl-5-(4-methoxybenzyl)-6-oxo-1,6-dihydro-1,2,4-triazine[1] (*III*), 3-phenyl-5-(2-methoxybenzyl)-6-oxo-1,6-dihydro-1,2,4-triazine[1] (*IV*), 3-phenyl-5-(3,4-dimethoxybenzyl)-6-oxo-1,6-dihydro-1,2,4-triazine[1] (*V*), 3-phenyl-5-(3,4-methylenedioxybenzyl)-6-oxo-1,6-dihydro-1,2,4-triazine[2] (*VI*) and 3-phenyl-5-(2-hydroxybenzyl)-6-oxo-1,6-dihydro-1,2,4-triazine[6] (*VII*).



	R^1	R^2
I	C_6H_5	H
II	CH_3	H
III	C_6H_5	4-OCH_3
IV	C_6H_5	2-OCH_3
V	C_6H_5	3,4-$(OCH_3)_2$
VI	C_6H_5	3,4-(OCH_2O)
VII	C_6H_5	2-OH

SCHEME 1

Table I presents the ^{1}H NMR spectra (without the signals of aromatic protons) of these compounds measured at 20 °C in deuteriochloroform and hexadeuteriodimethyl sulfoxide solutions. The highest chemical shift can be observed with the protons of NH group of the benzyl form of these compounds. The corresponding range is about 11 ppm in the chloroform solutions and increases on going to the hexadeuteriodimethyl sulfoxide solutions. Both these facts indicate a high acidity of this proton due to the distinct electron-acceptor nature of the triazine cycle. This nature is also reflected in the increased chemical shift of CH_3 signal of benzyl form of compound *I* as compared with the respective signal of benzylidene form, and – in fact – it initiates here the phenomenon of tautomerism as a consequence of an attempt at saturation of this electron deficit from the benzene nucleus at 5 position through the benzylidene sp^2 carbon atom. The signals of NH groups of the benzylidene forms, if they are visible in the spectrum, exhibit lower chemical shifts, which indicates (in the case of the dimethyl sulfoxide solutions) a weaker hydrogen bond to the solvent molecules due to the lower electron-acceptor ability of the triazine system in this tautomeric form. The absence of signals of some NH groups is connected with a rapid exchange of these hydrogens which is well perceptible in the measurements at enhanced temperatures when these signals become gradually wider and coalesce with the signal of the water present.

The chemical shifts of signals of methoxyl groups are affected by the medium but slightly. In accordance with the previous conclusions about the distinct electron-acceptor nature of triazine cycle we can observe an increased chemical shift of methoxyl groups in the benzylidene form as compared with the benzyl form as well as with the chemical shift of this group in anisole[15]. In analogy with the fact that here the intensity of these signals of methoxy group clearly reveals the proportions of both tautomeric forms in their mixtures in compounds *III*, *IV*, and *V*, we can make conclusions about and state the correlation with the intensities of $-CH_2-$ and $=CH-$ signals in the case of the signal of $-O-CH_2-O-$ group in compound *VI* which is found in the region about 6 ppm in both the media.

Similarly, structure and medium also very little affect the chemical shift of CH_2 group of benzyl form which is found in the region of 4.09 – 4.24 ppm both in chloroform and in dimethyl sulfoxide solutions.

Whereas the chemical shift of benzylidene group $=CH-$ of most of the compounds studied (compounds *II* – *VI*) lies in a narrow region of 6.25 – 6.45 ppm irrespective of the medium, that of compound *I* lies at 7.19 ppm ($CDCl_3$) and 7.40 ppm (CD_3SOCD_3) and that of compound *VII* lies as high as 8.85 ppm ($CDCl_3$) and 8.67 ppm (CD_3SOCD_3). These distinctly higher chemical shifts could be a consequence of different structure of the benzylidene tautomers (NH at the positions 1,2 or 1,4) and/or of different configuration at the benzylidene double bond.

The signals of aromatic hydrogen atoms are found in a broad region of 6.8 – 8.2 ppm. When comparing the spectra of individual compounds we can see that the signals at the

TABLE I
^{1}H NMR chemical shifts (δ, ppm) and proton signal intensities of 3,5-disubstituted 6-oxo-1,6-dihydro-1,2,4-triazines studied

Compound	$-CH_2-$		$=CH-$		CH_3		NH	
	$CDCl_3$	$(CD_3)_2SO$	$CDCl_3$	$(CD_3)_2SO$	$CDCl_3$	$(CD_3)_2SO$	$CDCl_3$	$(CD_3)_2SO$
I	–	–	7.19 (1.00)	7.40 (1.00)	–	–	–	–
II	4.13 (0.01)	4.09 (0.14)	6.49 (0.99)	6.25 (0.93)	2.03 (0.99) 2.42 (0.01)	2.03 (2.80) 2.34 (0.20)	8.82 (0.99)	9.49 (0.93) 10.85 (0.93) 13.20 (0.07)
III	4.20 (2.00)	4.13 (1.36)	–	6.39 (0.32)	3.77 (3.00)	3.77 (2.04) 3.83 (0.96)	11.69 (1.00)	9.71 (0.32) 11.14 (0.32) 13.55 (0.68)
IV	4.24 (2.00)	4.19 (1.41)	–	6.47 (0.30)	3.76 (3.00)	3.76 (2.10) 3.91 (0.90)	11.80 (1.00)	11.22 (0.30)
V	4.20 (2.00)	4.14 (1.52)	–	6.39 (0.38)	3.84 (3.00) 3.87 (3.00)	3.77 (3.72) 3.78 (3.72) 3.83 (2.28) 3.91 (2.28)	11.43 (1.00)	11.13 (0.38) 13.55 (0.62)
VI	4.16 (2.00)	4.11 (1.4)	–	6.37 (0.30)	5.92[a] (2.00)	6.02[a] (1.4) 6.08[a] (0.6)	10.66 (1.00)	11.17 (0.30)
VII	–	–	8.85 (1.00)	8.67 (1.00)	–	–	8.83 (1.00)	9.71 (1.00)

[a] The signal of $-O-CH_2-O-$ group.

highest chemical shifts are due to the *ortho* and *para* hydrogen atoms of 3-phenyl group. The existence of two tautomeric forms is clearly reflected also in this region: a roughly double number of signals is seen with intensities corresponding to the proportion of the respective forms in the mixture. In accordance with the above-mentioned conclusion about the electron-acceptor nature of triazine cycle which is – to a certain extent – saturated by the formation of benzylidene form, the chemical shifts of aromatic hydrogens in 3-phenyl group of benzylidene form are markedly lower (by as much as 0.6 ppm) as compared with those of the benzyl form.

From Table I it is obvious that the proportion of tautomeric forms depends on the medium. Beside $CDCl_3$ and CD_3SOCD_3 solutions we also measured the ^1H NMR spectra of compound *IV* in hexadeuterioacetone and pentadeuteriopyridine (the respective proportions of benzylidene form are 24.8% and 14.9% at 20 °C). The proportions of tautomeric forms depend strongly upon the acids present. A low content of trifluoroacetic acid in chloroform (in which compound *IV* is present exclusively in its benzyl form) causes a marked shift of tautomeric equilibrium in favour of the benzylidene form. Thus the ratios of benzyl to benzylidene forms were 3.6 : 1, 1 : 1, and 0.24 : 1 in the presence of 2, 4, and 8% (v/v) trifluoroacetic acid in chloroform, respectively. The ratios of both forms in these solutions did not change with time. Increasing amounts of the acid present did not markedly affect the chemical shifts of any signals in the spectrum either.

TABLE II
Evaluation of temperature effect upon tautomeric equilibria of compounds *III*, *IV*, and *V* in dimethyl sulfoxide solutions

Temperature °C	*III*		*IV*		*V*	
	%benzyl form	*K*	%benzyl form	*K*	%benzyl form	*K*
20	67.9	2.115	70.3	2.488	60.1	1.506
40	73.0	2.707	73.9	2.831	65.8	1.924
60	77.1	3.367	76.6	3.273	71.3	2.484
80	80.2	4.051	78.2	3.587	75.2	3.032
100	81.9	4.525	79.5	3.878	77.7	3.484
120	83.7	5.135	80.6	4.155	80.0	4.000
ΔH_{298}, kJ mol^{-1}	8.51		4.97		9.47	
ΔS_{298}, J mol^{-1} K^{-1}	35.4		24.6		35.8	
ΔG_{298}, kJ mol^{-1}	–2.05		–2.36		–1.20	

[a] The equilibrium constant *K* is the quotient of intensities of NMR signals of methoxyl groups in the benzyl and benzylidene derivatives.

Table II presents the results of investigation of temperature effect (20 – 120 °C) upon the tautomeric equilibria of compounds *III*, *IV*, and *V* in dimethyl sulfoxide solutions: the content of benzyl form and equilibrium constants at the individual temperatures are given for each compound. As expected the entropy change is positive upon going from the more rigid benzylidene form to benzyl form, and its significantly lower value found for 2-methoxybenzyl derivative *V* could be due to the violation of rigidity of benzylidene arrangement by the adjacent bulky OCH_3 substituent. The entropy changes found for these tautomeric processes are significantly higher than those of intramolecular processes mediated by intramolecular hydrogen bonds. Thus e.g. in the case of hydrazo form to azo form conversion of 1-phenylazo-2-naphthol[16] the entropy change is only 13.6 J mol^{-1} K^{-1}.

The authors are indebted to the Grant Agency of The Czech Republic for financial support of this work (Grant No. 203940122).

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