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A Proton Magnetic Resonance Study of the Amide Configurations of 2-Acetoacetamido Derivatives of 4-Methylpyridine and Pyrimidine

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Synopsis. It has been found by ^{1}H NMR spectroscopy that 2-acetoacetamido-4-methylpyridine (**1**) and 2-acetoacetamidopyrimidine (**2**) exist predominantly in keto forms in $CDCl_3$ and DMSO. The amide group of **1** seems to be in a *s-trans* configuration in both solvents, whereas that of **2** is in a *s-cis* form in $CDCl_3$, but predominantly in a *s-trans* isomer in DMSO at room temperature. Configurations of the enol forms are discussed.

It is well known that β-diketones and a number of derivatives of acetoacetic acid undergo keto-enol tautomerism in solution and that ^{1}H NMR spectroscopy has been used as a powerful tool to study such kinds of equilibrium.[1] However, only a few papers have been concerned with acetoacetamide derivatives, which have been proved to exist predominantly as keto forms.[2,3]

It is also familiar that *N*-monosubstituted amides undergo *cis-trans* rotational isomerism and that the isomers are almost all *s-trans* in the cases of acetylamino and higher acylamino derivatives.[4] For a few acetanilides with bulky ortho substituents, it has been reported that the *s-cis* isomers are appreciable.[5] The terms *s-cis* and *s-trans* refer to the relative location of the NH and CO group about the amide bond.

This paper will be concerned with 2-acetoacetamido-4-methylpyridine and 2-acetoacetamidopyrimidine, which undergo keto-enol tautomerism and *cis-trans* isomerism concurrently.

Experimental

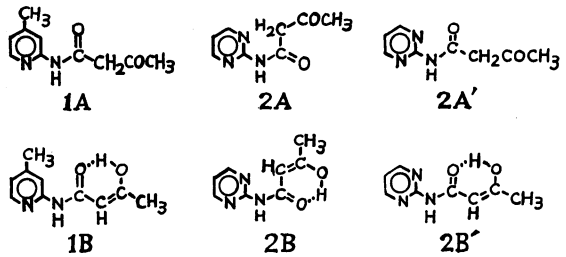
2-Acetoacetamido-4-methylpyridine (**1**) was prepared according to the literature method.[6] Commercial 2-acetoacetamidopyrimidine (**2**) was purified by recrystallization from water.

The ^{1}H NMR spectra were recorded on A Varian XL-100A-15 spectrometer, using TMS as the internal standard. In all spectra, the pulsed Fourier transform (FT) operation was utilized. The concentrations were 0.3—0.5% w/v.

Results and Discussion

Signal Assignment. The ^{1}H NMR spectra of **1** and **2** in $CDCl_3$ and DMSO seem to be explainable in terms of two molecular species, a keto and an enol tautomer, with preponderance of the keto tautomer (85—92%). The olefinic and the methylene proton signals almost completely disappeared when **1** and **2** were dissolved in CD_3OD, as did the amide and the enolic proton, on account of the replacement of H by D at the methylene and olefinic sites. The ^{1}H NMR spectra of the aromatic protons were of the first order. Therefore, signal assignment could be done straightforwardly. The chemical shifts thus determined are collected in Table 1. The large magnitude of "acylation shift" observed for the ring proton 3 of **1** suggests a *s-trans* configuration of the amide group of this compound in these solvents, on the basis of extensive studies[4b] concerning the acylation shifts of a number of anilides. Unfortunately, this kind of information was not obtained for **2**, because of the absence of a proton ortho to the acetoacetamide substituent.

Keto Tautomers. The methylene protons of **1** resonate at about the same field in both $CDCl_3$ and DMSO solution (δ 3.59 and 3.63), whereas those of **2** resonate at a very low field in $CDCl_3$ (δ 4.00) and at δ 3.81 in DMSO. These results suggest that the amide configuration of **1** is the same (*s-trans*) in both solvents, but that of **2** is solvent dependent. Lower field resonances of the methylene protons of **2** suggest that these protons are close to an electronegative atom, *e.g.*, the ring nitrogen atom; this can be realized in the *s-cis* configuration (**2A**).



Enol Tautomers. The methyl signals for the enol tautomers are located at fields higher by about 0.25—0.35 ppm than those for the keto tautomers. This value of about 0.3 ppm is very close to that for ethyl acetoacetate, but it is clearly larger than that for acetylacetone.[7] The enolic OH proton resonates at δ 13.5—14.2, intermediate between those for acetylacetone and ethyl acetoacetate (δ 15.6 and 12.2 in pure liquid, respectively[7]). From these results, it is reasonable to explain the enol-spectrum of **1** in terms of structure **1B** or the alternate enol form (**1C**: Ar–HNC(OH)=CHC(=O)CH_3), rather than in terms of a rapidly interconverting state between **1B**⇄**1C**. The olefinic proton signal of **1** in DMSO was observed as a broad quartet (J=0.7 Hz). This favors the structure **1B**. The structures **2B** and **2B'** are preferable to **2C** and **2C'** ((2-pyrimidyl)HNC(OH)=CHC(=O)CH_3) for the same reason (J=0.7 Hz for the DMSO solution).

Other enol forms, Ar–HNCOCHC=(OH)CH_3; Ar: pyridyl or pyrimidyl, which have no intramolecular hydrogen bond between the amide carbonyl oxygen and the enolic OH, could be neglected because of the

Table 1. Chemical shifts (δ) of various protons of **1** and **2**

Compd.	Solvent	Form	CH_3	CH_2	=CH	NH	OH	H-3	H-4(CH_3)	H-5	H-6	p(%)[a]
1	$CDCl_3$	keto	2.33	3.59	—	9.17	—	7.99	2.36	6.88	8.15	88
		enol	1.98	—	5.00	b	13.5	b	b	b	b	12
	DMSO	keto	2.19	3.63	—	10.5	—	7.91	2.31	6.94	8.15	92
		enol	1.90	—	5.37	b	b	b	b	b	b	8
	CD_3OD	keto	2.29		(4.83)[c]			7.94	2.34	6.97	8.12	90
		enol	1.94					b	b	b	b	10
2	$CDCl_3$	keto	2.33	4.00	—	9.60	—	—	8.58	7.00	8.58	85
		enol	2.07	—	6.20	b	14.1	—	8.60	6.99	8.60	15
	DMSO	keto	2.20	3.81	—	10.6	—	—	8.62	7.15	8.62	91
		enol	1.95	—	5.79	10.4	14.2	—	8.64	b	8.64	9
	CD_3OD	keto	2.29		(4.83)[c]				8.59	7.13	8.59	88
		enol	1.98						b	b	b	12

a) Population was estimated from the methyl peak heights of the two isomers. These values are in good agreement with the values obtained from the integration value measured under the CW mode for much concentrated solutions. b) Not identified. c) Averaged signal of the methylene, olefinic, amide, and enolic protons.

results of the ^1H NMR spectroscopic study of ethyl 3-(methylamino)crotonate, where the corresponding species have been found to be minor components.[8]

The olefinic proton of **1** in $CDCl_3$ resonates at δ 5.00, this value being almost the same as those for ethyl acetoacetate and 2′,5′-dichloroacetoacetanilide.[3] This signal shifts downfield a little with the solvent change from $CDCl_3$ to DMSO, as in the case of *N*-(2,5-dichlorophenyl)-3-aminocrotonamides.[9] In contrast to this, the olefinic proton of **2** in $CDCl_3$ resonates at δ 6.20, a field lower by as much as 1.20 ppm than that for **1**; furthermore, this signal even demonstrates an upfield shift of 0.41 ppm upon changing solvents from $CDCl_3$ to DMSO. These facts strongly suggest a solvent dependence of the amide configuration of **2**.

^1H NMR Spectra at Low Temperatures. Because of the low solubility of **2** in $CDCl_3$, recording the ^1H NMR spectra at low temperatures was not attempted. In a mixed solvent of $CDCl_3$ and DMSO (6: 1 v/v), the methylene protons of **2** were observed at δ 3.89 as a singlet at room temperature. Lowering the temperature of this solution below −10 °C caused an appreciable broadening in the methylene-signal and at −40 °C the methylene signal split into a clear doublet (δ 4.11 and 3.74) with about equal intensity. The olefinic proton showed an upfield shift as well as signal-broadening with temperature decrease and at −40 °C it was observed around δ 5.55 as a very broad signal. Further decrease of the temperature caused significant reduction of spectral resolution, probably due to solidification of DMSO. The amide proton shifted downfield a little with temperature decrease and gave an asymmetric signal, due to the occasional overlapping of two signals corresponding to the two rotational isomers. The ring proton signals also showed the expected complexity.

In the case of an acetone solution of **2**, lowering the temperature did not cause any sign of splitting in the methylene signal, which was located at δ 4.01 at room temperature. These results indicate that the chemical shift of the methylene protons well reflects the amide configuration of **2** in the solvents tested. A similar solvent dependence of the amide configuration has been reported for 2-acetamidopyrimidine (**3**).[10]

Conclusion. Compound **2** exists almost exclusively in the *s-cis*-keto and *s-cis*-enol forms in $CDCl_3$, but predominantly in the *s-trans*-keto and *s-trans*-enol in DMSO, though some appreciable contribution of the *s-cis* form cannot be discounted on the basis of a rather large difference of about 0.5 ppm between the olefinic proton resonances of **1** and **2**. A DMSO molecule intermolecularly hydrogen bonded with the amide proton may induce electrostatic repulsion with the amide carbonyl group in the *s-cis* form. This may be one reason why **2** in DMSO favors the *s-trans* form. On the other hand, **1** exists in the *s-trans*-keto and *s-trans*-enol in both solvents, $CDCl_3$ and DMSO.

The electrostatic repulsion between two lone pair electrons on the ring nitrogen and on the carbonyl oxygen, which is unavoidable in the *s-trans* form of **2** but avoidable in **1**, may be responsible for the considerable *s-cis* contribution in **2**.

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