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A Proton Magnetic Resonance Study of the Amide Configurations of 2-Acylaminopyrimidines

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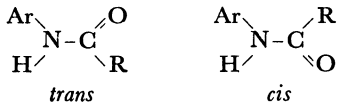
Synopsis. It has been found, from the ^1H NMR spectra at various temperatures, that 2-formylaminopyrimidine (**2**) exists in a *cis* configuration in chloroform and dimethyl sulfoxide, whereas 2-acetylaminopyrimidine (**3**) exists in a rapid rotational equilibrium between *cis* and *trans* configurations in $CDCl_3$, but almost exclusively in a *trans* configuration in DMSO at room temperature.

It is well known that *N*-monosubstituted amides undergo *cis-trans* rotational isomerism and that the equilibrium is a function of many factors. In the cases of acetylamino and higher acylamino derivatives, the isomers are almost all *trans*.[1] In polypeptides and proteins, it is also found that the peptide bonds are predominantly *trans*, except for a few peptide bonds in some cyclic oligopeptides.[2] For a few acetanilides with bulky *ortho* substituents, however, it has been reported that the *cis* isomers were appreciable.[3] On the other hand, formylamino derivatives usually exist as both *cis* and *trans* forms.[1b,4]

It seemed that it would be interesting, therefore, to find formylamino derivatives in a *cis* configuration exclusively or to find acetylamino derivatives without substituents in a *cis* configuration appreciably. This paper will be concerned with 2-acylaminopyrimidines as such compounds.



trans

cis

Ar: 2-pyrimidyl
R: H or CH_3

Experimental

2-Formylaminopyrimidine (2). Acetic anhydride (10 ml) was added to a solution of 2-aminopyrimidine (**1**) (5 g) in formic acid (20 ml). The reaction mixture became warm and foamed gently, and it was then allowed to stand overnight. Repeated recrystallizations of the precipitates from water gave pure **2**.

2-Acetylaminopyrimidine (**3**) was prepared from **1** and acetic anhydride.

The ^1H NMR spectra were recorded on a Varian A-60D spectrometer at various temperatures, using TMS as the internal standard. The concentration was 1% (w/v) unless otherwise noted. All the spectra were of the first order. The concentration dependence of the chemical shifts was examined for **3** in $CDCl_3$ and was found to be negligible for all protons but the amide proton.

Results and Discussion

The fact that H-4 and H-6 have the same chemical shift suggests a free flip-rotation around the C_{ring}–N_{amide} bond in **2** and **3** on the NMR time scale.

The chemical shift of the formyl proton is in good agreement with that reported for 2-formylamino-4-methylpyridine (**5**) in a *cis* form,[5] but it is fields lower than that of formanilide.[3a] This downfield shift can be attributed to a deshielding effect of an electric field due to the lone-pair electrons on the ring nitrogen atoms nearby.

The J_{CHONH} value was found to be about 10 Hz. A comparison of this value with two coupling constants for **5** (11 Hz for the *cis* and 2 Hz for the *trans* isomer)[5] leads to the conclusion that **2** in $CDCl_3$ and DMSO has a *cis* configuration almost exclusively. The two component peaks of the formyl proton signal in a DMSO solution coalesce at about 155 °C at almost the center of the doublet. This also seems to suggest a negligible contribution of **2** to the *trans* configuration, if any at all, because it has previously been reported that the formyl proton of **5** in the *trans* form resonated at a field higher by 0.92 ppm than did that in the *cis*.[5] Electrostatic repulsion between the lone-pair electrons on the ring nitrogen atoms and those on the carbonyl oxygen atom must play a key role, for **2** has a *cis* form, whereas 5 is subject to a *cis-trans* isomerism with a moderate equilibrium constant at room temperature.

The chemical shift of the acetyl protons of **3** in $CDCl_3$ is δ 2.53, lower by as much as about 0.4 ppm than that of acetanilide.[6] This fact strongly suggests that **3** has a configuration different from that of the latter compound, which has been proved to have a *trans* configuration. When the solvents were changed from $CDCl_3$ to DMSO, the acetyl signal was shifted upfield (−0.3 ppm); this shift was much larger than that observed for **4** upon the same solvent change. This large upfield shift could be explained in terms of a significant shift of the *cis-trans* equilibrium in **3** toward a *trans* preference, because the acetyl signal for the *trans* form can be expected to be at higher fields. It has been reported that the addition of DMSO to a $CDCl_3$ solution of formanilide shifted the equilibrium of the rotational isomers toward the intensification of the *trans* signal.[7]

Lowering the temperature of a $CDCl_3$ solution of **3** below 0 °C caused an appreciable broadening in the acetyl signal, and at −52 °C the acetyl signal split into a broad but clearly separated doublet (δ 2.33 and 2.73) with almost equal intensities. Of course, the amide proton gave two distinct signals, at δ 11.35 and 10.25. The ring proton signal also showed due complexity. The addition of a drop of DMSO to this solution caused an intensification of the upper-field signals for both the acetyl and amide protons at the expense of the lower-field ones. The acetyl proton signal of a solution of **3** in the $CDCl_3$–DMSO (3: 2) mixed solvent was observed at δ 2.23, almost equal to the value in DMSO. Lowering the temperature of the solution caused no splitting, but only a broadening, of the acetyl proton signal,

Table 1. Proton magnetic resonance spectral parameters of 2-amino- (**1**), 2-formylamino- (**2**), 2-acetylaminopyrimidine (**3**), and 2-acetylamino-4-methylpyridine (**4**)

Compd	Solvent	Chemical shift (δ)							Coupling constant (Hz)	
		H-3	H-4	H-5	H-6	NH	CHO	CH_3CO	$J_{4,5}$	J_{NHCHO}
1	$CDCl_3$	—	8.31	6.62	8.31	5.20	—	—	4.8	—
	DMSO-d_6	—	8.23	6.56	8.23	6.52	—	—	4.8	—
	C_6D_6	—	7.98	5.98	7.98	4.90	—	—	4.7	—
2	$CDCl_3$[a]	—	8.56	7.07	8.56	9.1	9.52	—	4.8	10
	DMSO-d_6	—	8.55	7.13	8.55	10.7	9.34	—	4.7	9.8
	C_6D_6[b]	—	—	—	—	—	—	—	—	—
3	$CDCl_3$	—	8.59	7.02	8.59	9.1	—	2.53	5.0	—
	DMSO-d_6	—	8.64	7.15	8.64	10.5	—	2.19	4.8	—
	C_6D_6	—	8.22	6.08	8.22	10.2	—	2.47	4.8	—
4	$CDCl_3$	8.07	2.37[c]	6.89	8.16	8.47	—	2.19		—
	DMSO-d_6	7.96	2.30[c]	6.93	8.18	10.3	—	2.08		—
	C_6D_6	8.45	1.89[c]	6.44	8.05	8.33	—	1.54		—

a) A saturated solution. b) Almost insoluble. c) CH_3.

probably as a result of a reduced mobility of solute molecules at an increased viscosity of the solvent. These observations are indicative of an almost complete preponderance of the *trans* form for **3** in DMSO.

The replacement of a formyl proton by a methyl group would cause significant change in the van der Waals interactions with the pyrimidine ring, but not in the electronic structure, as may be seen by the very close similarity in their UV spectra. In the case of **2**, the *trans* form is unfavorable from the viewpoints of both the van der Waals interaction and the electrostatic repulsion between the lone-pair electrons on the ring nitrogen and the carbonyl oxygen atoms, as compared with the *cis* form. As for **3**, however, the *cis* form is preferable to the *trans* form from the point of view of the electrostatic repulsion; on the contrary, though, the *trans* form is preferable from the point of view of the van der Waals' interaction. Therefore, the *trans* form is not so unfavorable in **3** as in **2**, resulting in an appreciable contribution of the *trans* form for **3** even in $CDCl_3$.

Consistent with the description given above, two absorption bands in the IR spectrum of **3** in a dilute $CDCl_3$ solution assignable to NH stretching vibrations were observed at 3425 and 3395 cm^{-1}. As for **2**, on the other hand, a single NH band was observed at 3390 cm^{-1}. Needless to say, there were other broad bands due to the amide protons involved in intermolecular associations.

The benzene-induced upfield shift is large for the acetyl protons of **4** (+0.65 ppm), whereas it is small for **3** (+0.06 ppm). As for the amide protons, on the contrary, the benzene-induced shift is very small for **4** (+0.14 ppm), but very large for **3** (−1.1 ppm). These observations are also indicative of different situations in the acetylamino groups of these two compounds, taking the specific interactions[8] between benzene molecules and these amide groups into account.

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