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Proton and Carbon-13 Nuclear Magnetic Resonance Studies of Substituted Pyrimidines. 2. Monoprotonation of Methyl- and Aminopyrimidines

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Abstract: The monoprotonation of methyl- and aminopyrimidines has been studied by carbon-13 NMR spectroscopy. The chemical shift parameters associated with the protonation of methylpyrimidines have been determined for the aromatic and methyl group carbons from the salts of certain symmetric compounds. The results indicate that a significant difference exists for certain parameters for a given carbon, depending on whether a hydrogen atom or a methyl group is attached to it. The study of the influence of the medium on the protonated forms shows that an especially large solvent effect exists for carbons bearing a methyl group in the position para to the site of protonation. The percentages of the forms monoprotonated at sites N-1 or N-3 of pyrimidines have been evaluated from their chemical shifts in trifluoroacetic acid and dimethyl sulfoxide solutions. The results for methylpyrimidines indicate a higher percentage (ca. 71%) of the form where the protonated nitrogen is in the para position to the methyl group. In the case of the 4-amino-6-methylpyrimidines the influence of the amino group is greater than that of the methyl group and the percentage reaches about 94% for the form where the protonated nitrogen is in the para position to the amino group.

I. Introduction

In connection with our research on pyrimidines,[1,2] we have undertaken the study of protonation, a phenomenon which is of considerable interest as has been demonstrated by numerous publications on nitrogen heterocycles.[3-20]

Carbon-13 nuclear magnetic resonance spectroscopy (^{13}C NMR) has been used since carbon-13 chemical shifts are very sensitive to the effects of protonation.[14]

We have determined first the protonation parameters and then the relative populations of the monoprotonated species, N(1)H or N(3)H, for the methyl and amino derivatives of pyrimidine.

In the case of the protonation parameters there have been relatively few detailed studies.[14,21] It was of interest therefore to evaluate the influence of substitution and solvent on the protonation parameters and to compare their values with those of some similar heterocycles (2-methyl- and 4-methylpyridines).

In the case of the site of protonation of nitrogen heterocycles however, a number of different spectroscopic techniques have been employed, namely UV,[4,18,19] NMR,[7-12,16,17] calorimetry,[20] and potentiometry.[18] There have been some investigations of the protonation of pyrimidines using ^1H NMR[3,5,6,9-11] and ^{13}C NMR,[13-15] but no quantitative evaluation has yet been made of the relative percentages of the tautomeric forms.

The problem of carrying out such a determination on the pyrimidine hydrochlorides is that they may undergo partial deprotonation in the convenient media used for neutral materials, i.e., dimethyl sulfoxide (Me_2SO) and water. This led us to use trifluoroacetic acid (CF_3CO_2H) as solvent for pyrimidines in the study of their monoprotonation.

II. Experimental Section

A. Products. The sources of the compounds **1-21** have been previously reported.[1] The hydrochlorides of pyrimidines **1, 3, 7, 8,** and methylpyridines, and the hydrobromide of pyrimidine **7,** were prepared by passing a current of dry hydrochloric or hydrobromic acid gas through a stirred ether solution of the appropriate product. The perchlorate of pyrimidine **7** was prepared by the action of aqueous perchloric acid on the 4,6-dimethylpyrimidine, and the 1,5-dimethylpyrimidine hydroiodide by treating 5-methylpyrimidine with methyl iodide. CF_3CO_2H was distilled together with $(CF_3CO)_2O$ prior to use.

B. Instrumentation. Carbon-13 spectra were recorded at 25.2 MHz on a Varian XL-100-12 (ENSCP, laboratoire de spectrographie RMN, Université de Paris VI) and at 20 MHz on a Varian CFT-20. Solutions were made up in Me_2SO, H_2O, and CF_3CO_2H in the concentration range 0.3-1.8 M; in this range, the variation of chemical shifts was verified to be negligible. Chemical shifts were measured with respect to internal dioxane. The chemical shift of dioxane with respect to Me_4Si is 68.3 ppm in CF_3CO_2H solution. The accuracies of the chemical shifts and of the coupling constants are 0.05 ppm and 0.5 Hz, respectively. Typical conditions for noise decoupled spectra were: acquisition time: 1.0 s, flip angle: 30°.

III. Results and Discussion

The carbon-13 chemical shifts of pyrimidines **1-21** in Me_2SO solutions have been published previously.[2] The chemical shifts of these pyrimidines in CF_3CO_2H solutions are summarized in Table I.

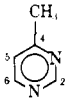
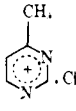
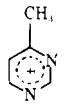
The assignments of the spectra of the symmetric pyrimidines were made with the help of off-resonance decoupling and comparison of the signal intensities. For the nonsymmetric pyrimidines and the methylpyridines, it was necessary to use selective decoupling and long-range coupling constant data. Some assignments were based on the following results (Table II): in neutral and acidic media, one has, for pyrimidines, $^1J(C_2H_2) > {}^1J(C_6H_6)$ and, for aromatic carbons C_i of both pyrimidines and pyridines,[22] $^3J(C_iH) > {}^2J(C_iH)$; protonation increases the values of the $^1J(CH)$ coupling constants, with the largest effect on the carbon adjacent to the protonation site.

Table I. Carbon-13 Chemical Shifts[a] of Pyrimidines in CF_3CO_2H Solution

R_2	R_4	R_5	R_6	No.	C_2	$(CH_3)_2$	C_4	$(CH_3)_4$	C_5	$(CH_3)_5$	C_6	$(CH_3)_6$
H	H	H	H	1	153.5		159.8_5		126.1		159.8_5	
CH_3	H	H	H	2	166.3	22.6_5	160.0		123.1_5		160.0	
H	CH_3	H	H	3	152.9		177.3_5	24.3	126.2_5		155.4	
H	H	CH_3	H	4	150.7		159.4		138.9_5	16.3	159.4	
CH_3	CH_3	H	H	5	165.2_5	22.6	176.0_5	23.8_5	122.9		155.9	
H	CH_3	CH_3	H	6	150.2_5		174.8	21.9	137.6_5	16.2	155.3	
H	CH_3	H	CH_3	7	152.4		172.6_5	22.8_5	126.1_5		172.6_5	22.8_5
CH_3	CH_3	H	CH_3	8	164.8_5	22.2_5	172.3_5	22.7	122.9		172.3_5	22.7
H	CH_3	CH_3	CH_3	9	149.2		170.1_5	21.6_5	135.8_5	14.4_5	170.1_5	21.6_5
NH_2	H	H	H	10	157.4_5		159.4		112.8_5		159.4	
NH_2	CH_3	H	H	11	157.0		177.4	23.4	113.4		154.0_5	
NH_2	H	CH_3	H	12	156.0		158.9_5		124.1_5	14.4	158.9_5	
NH_2	CH_3	CH_3	H	13	155.8		175.5_5	21.4	123.1	14.6	153.4_5	
NH_2	CH_3	H	CH_3	14	156.8		172.0_5	22.1	133.5_5		172.0_5	22.1
NH_2	CH_3	CH_3	CH_3	15	154.4_5		170.1	20.8_5	121.8	12.7_5	170.1	20.8_5
H	NH_2	H	H	16	153.6_5		166.7		108.9_5		144.6	
CH_3	NH_2	H	H	17	166.3_5	21.4_5	165.9		107.1_5		144.8_5	
H	NH_2	CH_3	H	18	151.7_5		166.5_5		119.5	14.0	142.2	
H	NH_2	H	CH_3	19	153.5_5		166.4		107.5		158.0	19.5
CH_3	NH_2	H	CH_3	20	165.8	21.1	165.7		105.7		158.3_5	19.4
H	NH_2	CH_3	CH_3	21	150.8_5		165.6_5		116.2_5	11.5_5	154.2_5	17.9_5

[a] Chemical shifts are in parts per million with respect to Me_4Si.

Table II. Coupling Constants J(CH) in 4-Methylpyrimidine and 2-Methylpyridine Neutral and Protonated[a] (Hz)

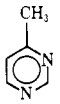
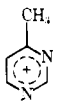
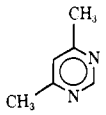
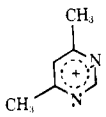
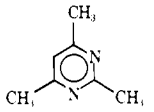
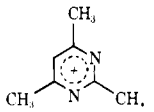
Compound	Solvent	C_2	C_5	C_6	$(CH_3)_4$
	Me_2SO	$^1J(C_2H_2)$ = 201.4 $^3J(C_2H_6)$ = 10.7	$^1J(C_5H_5)$ = 166.7 $^2J(C_5H_6)$ = 7.6 $^3J(C_5(CH_3)_4)$ = 3.8 $^4J(C_5H_2)$ = 1.4	$^1J(C_6H_6)$ = 180.6 $^3J(C_6H_2)$ = 9.2 $^2J(C_6H_5)$ = 3.2	$^1J((CH_3)_4)$ = 127.6 $^3J((CH_3)_4-H_5) \sim 1.7$
	H_2O	$^1J(C_2H_2)$ = 204.2 $^3J(C_2H_6)$ = 10.3	$^1J(C_5H_5)$ = 169.1 $^2J(C_5H_6)$ = 7.4 $^3J(C_5(CH_3)_4)$ = 3.7 $^4J(C_5H_2)$ = 1.4	$^1J(C_6H_6)$ = 182.1 $^3J(C_6H_2)$ = 9.1 $^2J(C_6H_5)$ = 4.5	$^1J((CH_3)_4)$ = 128.5 $^3J((CH_3)_4-H_5)$ = 2.2
	Me_2SO	$^1J(C_2H_2)$ = 211.4 $^3J(C_2H_6)$ = 9.3	$^1J(C_5H_5)$ = 176.4	$^1J(C_6H_6)$ = 187.8 $^3J(C_6H_2)$ = 7.8 $^2J(C_6H_5)$ = 3.5	$^1J((CH_3)_4)$ = 130.0 $^3J((CH_3)_4-H_5)$ = 2.0
	H_2O	$^1J(C_2H_2)$ = 216.6 $^3J(C_2H_6)$ = 8.8	$^1J(C_5H_5)$ = 179.7	$^1J(C_6H_6)$ = 192.8 $^3J(C_6H_2)$ = 7.3 $^2J(C_6H_5)$ = 2.4	$^1J((CH_3)_4)$ = 130.6 $^3J((CH_3)_4-H_5)$ = 2.4
	CF_3CO_2H	$^1J(C_2H_2)$ = 219.4 $^3J(C_2H_6)$ = 7.8	$^1J(C_5H_5)$ = 181.0	$^1J(C_6H_6)$ = 195.2 $^3J(C_6H_2)$ = 6.8 $^2J(C_6H_5)$ = 2.2	$^1J((CH_3)_4)$ = 131.1 $^3J((CH_3)_4-H_5)$ = 1.8

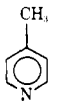
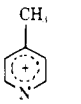
Compound	Solvent	C_3	C_4	C_5	C_6	$(CH_3)_2$
	Me_2SO[b]	$^1J(C_3H_3)$ = 161	$^1J(C_4H_4)$ = 163	$^1J(C_5H_5)$ = 163	$^1J(C_6H_6)$ = 177	$^1J((CH_3)_2)$ = 127
	H_2O	$^1J(C_3H_3)$ = 163.7	$^1J(C_4H_4)$ = 163.8	$^1J(C_5H_5)$ = 165.8	$^1J(C_6H_6)$ = 177.4	$^1J((CH_3)_2)$ = 127.2
	CF_3CO_2H	$^1J(C_3H_3)$ = 173.6	$^1J(C_4H_4)$ = 171.2	$^1J(C_5H_5)$ = 176.9	$^1J(C_6H_6)$ = 189.7	$^1J((CH_3)_2)$ = 131.4
	$\Delta^2J^{CF_3CO_2H}_{H_2O}$	9.9	7.4	11.1	12.3	4.2

[a] The coupling constants of the hydrochloride have not been corrected for the effect of deprotonation. The long-range coupling constants for 2-methylpyridine and for the C_4 carbon (and in certain solvents for C_5) of 4-methylpyrimidine have not been determined with precision. [b] Reference 22.

In the series of pyrimidines studied, the only sites for monoprotonation that have to be considered are the nitrogen atoms N-1 and N-3, because the ^1H NMR chemical shifts of the amino group in the protonated form are similar to those determined by Wagner and Von Philipsborn, who concluded that there was no protonation of the amino group.[10] This result

Table III. Carbon-13 Chemical Shifts[a] of Some Pyrimidines, Methylpyridines, and Their Salts[b]

Compound	Anion	Solvent	C_2	$(CH_3)_2$	C_4	$(CH_3)_4$	C_5	C_6	$(CH_3)_6$
		Me_2SO	92.0$_5$		90.5$_5$		55.5	90.5$_5$	
		H_2O	90.8		90.6		55.8$_5$	90.6	
	Cl^-	Me_2SO	89.8$_5$		90.7$_5$		56.2	90.7$_5$	
	Cl^-	H_2O	85.7		91.1		57.2	91.1	
	Cl^-	CF_3CO_2H	85.0		91.4$_5$		57.7$_5$	91.4$_5$	
		Me_2SO	91.6		100.1$_5$	−42.7$_5$	54.7$_5$	90.0$_5$	
		H_2O	90.2$_5$		101.5	−43.7	55.3	89.8	
	Cl^-	Me_2SO	87.2		103.1	−43.3$_5$	56.3	88.6$_5$	
	Cl^-	H_2O	84.8$_5$		105.6	−43.8$_5$	57.2	88.2	
	Cl^-	CF_3CO_2H	84.4		108.8	−44.1$_5$	57.7	86.9$_5$	
		Me_2SO	91.2		99.5$_5$	−42.9$_5$	53.7	99.5$_5$	−42.9$_5$
		H_2O	89.8$_5$		100.7$_5$	−44.0$_5$	54.5	100.7$_5$	−44.0$_5$
	Cl^-	Me_2SO	85.8		101.1	−44.2$_5$	56.0	101.1	−44.2$_5$
	Br^-	Me_2SO	86.2$_5$		101.1$_5$	−44.0	55.9$_5$	101.1	−44.0
	ClO_4^-	Me_2SO	85.1$_5$		101.6	−44.2$_5$	56.3	101.6	−44.2$_5$
	Cl^-	H_2O	83.9		102.6$_5$	−44.7$_5$	57.0$_5$	102.6$_5$	−44.7$_5$
	Br^-	H_2O	84.1		102.6$_5$	−44.7$_5$	57.0$_5$	102.6$_5$	−44.7$_5$
	ClO_4^-	H_2O	83.7$_5$		102.7	−44.9	57.1$_5$	102.7	−44.9
	Cl^-	CF_3CO_2H	84.0		104.0	−45.5	57.6$_5$	104.0	−45.5
	Br^-	CF_3CO_2H	84.0		104.1$_5$	−45.4	57.8$_5$	104.1$_5$	−45.4
	ClO_4^-	CF_3CO_2H	84.2		104.4$_5$	−45.4	58.6$_5$	104.4$_5$	−45.4
		Me_2SO	99.9	−40.9$_5$	99.5$_5$	−43.0$_5$	50.4	99.5$_5$	−43.0$_5$
		H_2O	99.4	−42.7	100.7	−44.1$_5$	51.2	100.7	−44.1$_5$
	Cl^-	Me_2SO	95.5$_5$	−44.6$_5$	101.2	−44.6$_5$	53.5$_5$	101.2	−44.6$_5$
	Cl^-	H_2O	95.6	−45.3$_5$	102.5$_5$	−45.0$_5$	54.0	102.5$_5$	−45.0$_5$
	Cl^-	CF_3CO_2H	96.6$_5$	−46.2$_5$	104.0$_5$	−45.7	54.8	104.0$_5$	−45.7
		Me_2SO	97.1		91.5		43.7	91.5	
		H_2O	95.5		91.9$_5$		44.9	91.9$_5$	
	Cl^-	Me_2SO	89.8$_5$		90.6		43.5$_5$	90.6	
	Cl^-	H_2O	89.1		90.7		44.0$_5$	90.7	
	Cl^-	CF_3CO_2H	88.8$_5$		91.1		44.5$_5$	91.1	

Compound	Anion	Solvent	C_2	$(CH_3)_2$	C_3	C_4	$(CH_3)_4$	C_5	C_6
		Me_2SO	91.4	−42.4$_5$	56.5$_5$	69.6$_5$		54.3	82.4
		H_2O	91.0$_5$	−43.7	57.2	70.8$_5$		54.6$_5$	81.2$_5$
	Cl^-	Me_2SO	86.9$_5$	−47.5	61.5$_5$	79.4$_5$[c]		58.1$_5$	74.1[c]
	Cl^-	H_2O	87.3	−47.4$_5$	61.4	79.9$_5$[c]		57.8	73.8$_5$[c]
	Cl^-	CF_3CO_2H	88.0$_5$	−47.9	61.7$_5$	80.7[c]		58.2	73.9$_5$[c]
	$CF_3CO_2^-$	CF_3CO_2H	87.9$_5$	−47.9$_5$	61.6$_5$	80.3$_5$[c]		58.0$_5$	74.1[c]
		Me_2SO	82.9		58.1$_5$	80.2	−46.1	58.1$_5$	82.9
		H_2O	81.6		58.4$_5$	82.2$_5$	−46.4	58.4$_5$	81.6
	Cl^-	Me_2SO	73.9		61.4	93.2$_5$	−44.6	61.4	73.9
	Cl^-	H_2O	73.6		61.3$_5$	95.0	−44.6$_5$	61.3$_5$	73.6
	Cl^-	CF_3CO_2H	73.7		61.6	96.4$_5$	−45.3$_5$	61.6	73.7
	$CF_3CO_2^-$	CF_3CO_2H	73.8		61.5	95.9	−45.4	61.5	73.8

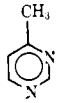
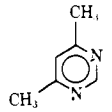
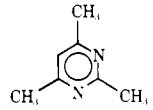
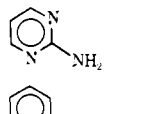
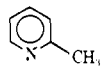
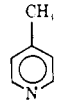
[a] Chemical shifts are in parts per million with respect to dioxane. [b] The chemical shifts of the salts have to be corrected for the effect of deprotonation in Me_2SO and H_2O prior to use in the calculations. [c] These assignments, based on the increase of the $^1J(CH)$ coupling constants due to protonation, are reversed with respect to published data.[25]

is in agreement with previous works on aminopyrimidines.[3,18,23]

The carbon-13 chemical shifts in the protonated pyrimidines are dependent on the position of carbons relative to the site of protonation. This allows the determination of sets of protonation parameters (for the aromatic as well as the methyl carbons) and hence the evaluation of the respective populations of the different monoprotonated species.

A. Protonation Parameters. The protonation parameters are determined from the differences between the carbon-13

Table IV. Extent of Monoprotonation of the Hydrochlorides

Compound	Solvent	pK_a	Concn, M	Extent, %
	H_2O	1.31[a]	1.44	83.2
	Me_2SO	1.1[b]	1.0	75.0
	H_2O	1.98[a]	1.0	90.3
	Me_2SO	1.8[c]	0.72	86.2
	H_2O	2.7[d]	0.96	95.5
	Me_2SO	2.7[c]	0.48	93.8
	H_2O	3.95[c]	0.35	98.2
	Me_2SO	3.0[c]	0.78	96.5
	H_2O	3.71[e]	0.69	98.3
	Me_2SO	4.0[c]	0.49	98.6
	H_2O	5.95[c]	0.48	99.85
	Me_2SO	4.1[c]	1.2	99.2
	H_2O	6.1[c]	1.85	99.9

[a] A. Albert, R. Goldacre, and J. Phillips, *J. Chem. Soc.*, 2240 (1948). [b] The value of pK_a in Me_2SO has been evaluated from that determined in H_2O by analogy with results obtained for 4,6-dimethylpyrimidine in these two solvents. [c] J. C. Halle, private communication. [d] M. P. V. Boarland and J. F. W. McOmie, *J. Chem. Soc.*, 3722 (1952). [e] D. J. Brown, B. T. England, and J. M. Lyall, *J. Chem. Soc. C*, 226 (1966).

chemical shifts of the neutral and protonated molecules in solution in the same solvent (Me_2SO or H_2O). They depend both on the position of the carbon C_i under consideration, relative to the site of protonation, and on the nature of the substituent R_i on that carbon. They are symbolized by α_R, β_R, γ_R for the aromatic carbons, and by a, b, c for the methyl group carbons respectively in ortho, meta, para positions to the site of protonation.

The additivity relationships[14] which allow calculation of the protonation parameters imply that the effect of protonation is the same on the two carbons adjacent to the protonation site if they carry the same substituent. This is consistent with the theoretical work of Grant et al.,[14,24] and has been verified using the hydroiodide of 1,5-dimethylpyrimidine as a model compound. The effects of N-methylation on the carbons C-2 and C-6 are respectively -4.3_5 ppm and -4.5_5 in Me_2SO.

We have further verified that the chemical shifts do not depend on the nature of the anion in pyrimidine salts. This was done by studying three salts of 4,6-dimethylpyrimidine with different anions, hydrochloride, hydrobromide, and perchlorate in Me_2SO, water, and CF_3CO_2H solutions. The results demonstrate that the nature of the anion has an influence which may be considered as negligible (see Table III).

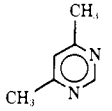
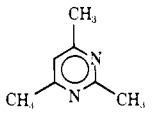
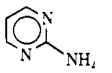
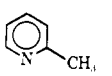
The partial deprotonation of the pyrimidine and pyridine hydrochlorides in Me_2SO and H_2O has been calculated as a function of the pK_a of the compounds in these solvents, and of the concentration of the solutions studied (see Table IV). The pK_a of pyrimidine **1** in Me_2SO is, however, too weak to be determined with accuracy.

The chemical shifts of the symmetric pyrimidines and pyridines, corrected for the effect of deprotonation, were used to determine the protonation parameters given in Table V.

There is a significant difference between the values of the protonation parameters α_R in a given solvent for a hydrogen bearing carbon α_H compared to a methyl bearing carbon α_{CH_3}. In contrast, the values of the parameters γ_H and γ_{CH_3} are similar for aqueous solutions, which allows one to use the value of γ_{CH_3} instead of γ_H for Me_2SO solution. This is convenient since γ_H cannot be determined accurately due to the uncertainty associated with the estimation of the percentage of deprotonation of the hydrochloride of pyrimidine in Me_2SO.

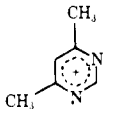
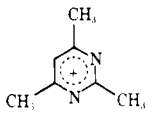
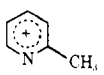
It is important to note that the sum of the parameters α_R and γ_R is sensitive to the nature of the substituent in position 2.

Table V. Protonation Parameters[a] of the Pyrimidines and the Methylpyridines

Compound	Solvent	α_H	β_H	γ_H	$\alpha_H + \gamma_H$	α_{CH_3}	γ_{CH_3}	$\alpha_{CH_3} + \gamma_{CH_3}$	*a*	*c*	*a* + *c*
	H_2O	−6.1	1.6	7.3	1.2	...	...	...	...	...	...
	Me_2SO	−6.3	2.7	...	...			3.6			−3.0
	H_2O	−6.2	2.6_5	...	...			4.0			−1.5
	Me_2SO	...	3.3_5	...	...	-4.6_5	8.1_5	3.5	-3.9_5	0.5	-3.4_5
	H_2O	...	2.8_5	...	...	−3.9	7.6_5	3.7_5	−2.7	0.9_5	-1.7_5
	Me_2SO		-0.1_5		-1.8_5	...	...	...	...	...	...
	H_2O		−0.9		−2.5	...	...	...	...	...	...
	Me_2SO	-8.4_5	5.0_5[b] 4.0[c]	9.9	1.4_5	-4.5_5	...	...	−5.1	...	...
	H_2O	-7.4_5	4.2_5[b] 3.1_5[c]	9.1	1.6_5	-3.7_5	...	...	−3.8	...	...
	Me_2SO	−9.1	3.3	...	...	...	13.1_5	...	...	1.5_5	...
	H_2O	−8.0	2.9	...	...	...	12.7_5	...	...	1.7	...

[a] In parts per million with respect to dioxane. [b,c] The values *b* and *c* refer respectively to carbons C_3 and C_5.

Table VI. Values of the Solvent Effects[a] Determined from the Hydrochlorides of the Symmetric Pyrimidines and Methylpyridines

Compound	Solvents	$\Delta S_{\alpha,H}$	$\Delta S_{\beta,H}$	$\Delta S_{\gamma,H}$	$\Delta S_{\alpha,H}$ + $\Delta S_{\gamma,H}$	$\Delta S_{\alpha,CH_3}$	$\Delta S_{\gamma,CH_3}$	$\Delta S_{\alpha,CH_3}$ + $\Delta S_{\gamma,CH_3}$	$\Delta S_{o\text{-}CH_3}$	$\Delta S_{p\text{-}CH_3}$	$\Delta S_{o\text{-}CH_3}$ + $\Delta S_{p\text{-}CH_3}$
	CF_3CO_2H–H_2O	0.3_5	0.3	0.1_5	0.5	...	...	...	...	...	...
	CF_3CO_2H–Me_2SO	−0.9	1.3	...	...			5.7			-2.0_5
	CF_3CO_2H–H_2O	0.4	0.5	...	...			2.8_5			−1.4
	CF_3CO_2H–Me_2SO	...	1.0_5	...	...	1.4	4.1_5	5.5_5	-1.3_5	−0.5	-1.8_5
	CF_3CO_2H–H_2O	...	0.7_5	...	...	1.1	1.9	3.0	-0.8_5	-0.4_5	-1.2_5
	CF_3CO_2H–Me_2SO		1.0		1.0	...	...	...	...	...	...
	CF_3CO_2H–H_2O		0.5		0.8	...	...	...	...	...	...
	CF_3CO_2H–Me_2SO	-0.0_5	0.1_5[b] 0.0[c]	1.1_5	1.1	1.2	...	...	−0.3	...	...
	CF_3CO_2H–H_2O	0.1	0.3_5[b] 0.4_5[c]	0.7_5	0.8_5	0.7_5	...	...	−0.4	...	...
	CF_3CO_2H–Me_2SO	-0.1_5	0.1_5	...	...	...	3.1	...	...	-0.7_5	...
	CF_3CO_2H–H_2O	0.1	0.2_5	...	...	...	1.4_5	...	...	−0.7	...

[a] In parts per million with respect to dioxane. [b,c] The values *b* and *c* refer respectively to carbons C_3 and C_5.

Substitution of a hydrogen by an amino group (compare 2-aminopyrimidine **10** with pyrimidine **1**) modifies this sum significantly in contrast to what is observed when a hydrogen is replaced by a methyl group (compare 4,6-dimethylpyrimidine **7** with 2,4,6-trimethylpyrimidine **8**). The difference between the effects of the methyl and the amino groups is due to the conjugation of the latter with the ring as has been indicated by the study of pyrimidines in neutral medium.[1] It is thus impossible to use the parameters derived from the methylpyrimidines in the case of the aminopyrimidines. Nor is it possible to determine for these compounds the protonation parameters of the aromatic carbons.

The only protonation parameter of importance for the methyl group in the methylpyrimidines is obtained when the methyl group is ortho to the site of protonation.

Furthermore, a comparison of the protonation parameters for methylpyridines and methylpyrimidines shows that they are of the same order of magnitude but nevertheless significantly different. This implies that one cannot justify using the parameters obtained for one series of compounds to make accurate calculations for another series. Finally, one notes that the protonation parameters obtained for methylpyrimidines in Me_2SO solutions are similar to those in aqueous solutions.

B. Percentages of N-1 and N-3 Monoprotonated Species. The problems due to the low solubility of certain aminopyrimidines in water led to the choice of Me_2SO as solvent to facilitate the study of all neutral molecules in the same medium.[1] The use of this same solvent for the protonated species, however, would require a determination of the pK_a of the pyrimidines to be able to evaluate the extent of deprotonation for the salts. In order to avoid such a systematic study, which is often difficult, the monoprotonation of the pyrimidines was carried out in CF_3CO_2H. The accurate study of Wagner and Philipsborn[10] makes clear that exact monoprotonation of the pyrimidines occurs in this solvent.

The evaluation of the populations of the monoprotonated forms is based on the study of the neutral and protonated molecules in two different media, so it was important to evaluate the respective influence of protonation and change of solvent on the differences between the chemical shifts of these two species.

1. Solvent Effects on the Hydrochlorides. The use of the same internal reference in the three media considered (Me_2SO, H_2O, CF_3CO_2H) minimizes the contribution due to the reference in the evaluation of the solvent effects. Dioxane was chosen as the internal reference throughout this study for reasons of solubility. Furthermore, its chemical shift is not very sensitive to the change of medium: 40.1_5 ppm in Me_2SO, 39.9 ppm in H_2O, 39.2_5 ppm in CF_3CO_2H, with respect to cyclohexane as external standard, corrected for bulk susceptibility effects.

The comparison of the chemical shifts of the pyrimidine hydrochlorides in CF_3CO_2H solution to those corrected for the effects of deprotonation in Me_2SO and H_2O (cf. Table III) indicates that large solvent effect are present, which cannot be ascribed to the anion effect.

The solvent effects were evaluated from the symmetric pyrimidine hydrochlorides with the aid of additivity relationships analogous to those used for the determination of the protonation parameters. The chemical shifts involved are those induced by the change of solvent. These solvent effects are symbolized for the aromatic and methyl carbons by: $\Delta S_{\alpha,R}$, $\Delta S_{\beta,R}$, $\Delta S_{\gamma,R}$, and $\Delta S_{o\text{-}CH_3}$, $\Delta S_{p\text{-}CH_3}$ respectively, where the position of the carbon with respect to the site of protonation is indicated by the subscript.

In order to evaluate these effects it was assumed that the solvent effect $\Delta S_{\alpha,R}$ is the same for the two carbons adjacent to the protonated site, provided that they bear the same substituent.

The solvent effects are relatively large (see Table VI). An especially high value of $\Delta S_{\gamma,CH_3}$ (4.1_5 ppm) is obtained for the hydrochloride of 2,4,6-trimethylpyrimidine between the two solvents CF_3CO_2H and Me_2SO and confirmed by the data for the hydrochlorides of 4,6-dimethylpyrimidine and 4-methylpyridine. Furthermore, substitution of a hydrogen by a methyl group increases the solvent effects ΔS_α and ΔS_γ, which can be explained by the difference between the polarizabilities of

Table VII. Differences $\Delta\delta'$ for Carbon-13 Chemical Shifts[a] of Pyrimidines in CF_3CO_2H and Me_2SO

Compound	C_2	$(CH_3)_2$	C_4	$(CH_3)_4$	C_5	$(CH_3)_5$	C_6	$(CH_3)_6$
1	-6.9		0.9		2.2		0.9	
2	-2.8	-5.0	1.1_5		2.6		1.1_5	
3	-7.1		8.8_5	-1.3_5	3.1_5		-3.0	
4	-7.1		0.6_5		5.9	-0.8_5	0.6_5	
5	-3.4	-5.0	7.7	-1.7_5	3.1_5		-2.6	
6	-7.4_5		7.7	-1.7_5	6.4	-1.0	-2.5_5	
7	-7.2		4.7_5	-2.5_5	4.1		4.7_5	-2.5_5
8	-3.4	-5.2	4.4_5	-2.6	4.1_5		4.4_5	-2.6
9	-7.3		4.4	-2.4_5	6.6_5	-1.1_5	4.4	-2.4_5
10	-8.0		-0.5		0.7_5		-0.5	
11	-8.3		8.4_5	-2.1_5	2.0		-5.4_5	
12	-7.9_5		-0.7		4.2_5	-1.8	-0.7	
13	-8.1_5		8.1	-2.2	4.8	-1.7_5	-5.5	
14	-8.4		3.4	-3.2_5	2.9		3.4	-3.2_5
15	-8.3		3.8	-3.1	5.5	-1.9_5	3.8	-3.1
16	-6.6_5		1.5		1.8_5		-12.0_5	
17	-2.0_5	-6.1_5	0.7		3.1_5		-11.9_5	
18	-6.3_5		2.4		4.6_5	-1.9	-13.3	
19	-6.2_5		0.8_5		2.5_5		-7.5_5	-5.9
20	-2.1_5	-6.3	0.0_5		3.7		-7.3	-6.0
21	-5.7_5		1.7_5		4.7_5	-2.1	-8.4_5	-5.6

[a] In parts per million with respect to dioxane.

Table VIII. Parameters Used for Calculations of the Percentage of the Form Monoprotonated on the Nitrogen N-1 of the Pyrimidines[a]

Compound	Solvents	α'_H	α'_{CH_3}	γ'_H	γ'_{CH_3}	a'	c'
Methylpyrimidines	CF_3CO_2H–Me_2SO	-7.2 ± 0.2 (1,3,4,6,7,9)	-3.2 ± 0.3 (2,5,8)	$8.5_5 \pm 0.1_5$ (1,4)	12.3_5 (8)	$-5.0_5 \pm 0.1$ (2,5,8)	-0.0_5 (8)
	CF_3CO_2H–H_2O	$-5.7_5 \pm 0.0_5$ (1,3,7)	-2.9_5 (8)	7.3_5 (1)	9.5_5 (8)	-3.4 (8)	0.4_5 (8)
Aminopyrimidines	CF_3CO_2H–Me_2SO					$-6.2_5 \pm 0.08$ (17,20)	$-0.1_5 \pm 0.2$ (14,15)

[a] The pyrimidines which have been used for the calculations of these parameters are shown in parentheses. The errors indicated are the mean deviations.

the C-H and C-CH_3 bonds. The solvent effects on the methyl groups are weaker than those of the aromatic carbons but nevertheless significant, especially in the case of $\Delta S_{o\text{-}CH_3}$.

2. Calculation of the Percentages of N(1)H and N(3)H Monoprotonated Species. The chemical shift differences $\Delta\delta'$ between the monoprotonated species in CF_3CO_2H and the neutral species in Me_2SO are given in Table VII. The values represent both the influence of the monoprotonation and the effect of changing solvent. They may be considered as the sum of an effect of protonation in Me_2SO and the effect, on the monoprotonated molecule, of changing solvent from Me_2SO to CF_3CO_2H. This is carried out by relationships which may be written more simply by introducing new sets of parameters α', β', γ', for the aromatic carbons and a', b', c' for the methyl carbons

$$\Delta\delta'_{C_2} = \alpha_{R_2} + \Delta S_{\alpha,R_2} = \alpha'_{R_2}$$

$$\Delta\delta'_{C_4} = (\alpha_{R_4} + \Delta S_{\alpha,R_4})(1 - x) + (\gamma_{R_4} + \Delta S_{\gamma,R_4})x = \alpha'_{R_4}(1 - x) + \gamma'_{R_4}x$$

$$\Delta\delta'_{C_5} = \beta_{R_5} + \Delta S_{\beta,R_5} = \beta'_{R_5}$$

$$\Delta\delta'_{C_6} = (\alpha_{R_6} + \Delta S_{\alpha,R_6})x + (\gamma_{R_6} + \Delta S_{\gamma,R_6})(1 - x) = \alpha'_{R_6}x + \gamma'_{R_6}(1 - x)$$

$$\Delta\delta'_{(CH_3)_2} = a + \Delta S_{o\text{-}CH_3} = a'$$

$$\Delta\delta'_{(CH_3)_4} = (a + \Delta S_{o\text{-}CH_3})(1 - x) + (c + \Delta S_{p\text{-}CH_3})x = a'(1 - x) + c'x$$

$$\Delta\delta'_{(CH_3)_5} = b + \Delta S_{m\text{-}CH_3} = b'$$

$$\Delta\delta'_{(CH_3)_6} = (a + \Delta S_{o\text{-}CH_3})x + (c + \Delta S_{p\text{-}CH_3})(1 - x) = a'x + c'(1 - x)$$

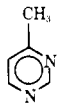
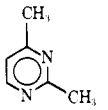
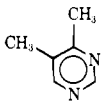
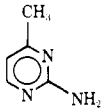
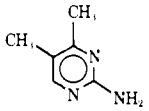
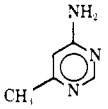
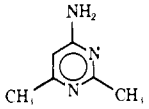
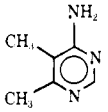
It can be shown that x represents the population of the N(1)H species in the solvent used for the protonated pyrimidines, but the protonation parameters must be determined in the solvent used for the neutral species.

The values of α'_H, α'_{CH_3}, and a' calculated for the asymmetric methylpyrimidines (**3, 5**) are in good agreement (different by less than 0.3 ppm) with the corresponding values for the symmetric methylpyrimidines (**1, 2, 4, 7, 8, 9**). In order to calculate the populations of the monoprotonated forms in the asymmetric pyrimidines, one therefore uses the average values of the parameters α' and a' determined from the whole series of methylpyrimidines (see Table VIII). For the parameters γ'_H or γ'_{CH_3} we have assumed that, to a first approximation, they are identical in the symmetric and asymmetric molecules.

The large difference between the values α'_H and α'_{CH_3} comes as much from the substitution effect as from a change of solvent, in contrast to the case of relative values of γ'_H and γ'_{CH_3} where the effect of solvent change predominates (see Tables V and VI).

It is important to note that the values of the parameters depend on the choice of reference. For example, the use of Me_4Si instead of dioxane as reference increases the value of each parameter by 2.0 ppm in the solvent system CF_3CO_2H-Me_2SO. This corresponds exactly with the difference in scale between the chemical shifts of Me_4Si and dioxane in these two solvents. Similarly, the use of sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) instead of dioxane leads to an increase of 1.2_5 ppm for each parameter in the system CF_3CO_2H-H_2O. Therefore, the choice of both the reference and the solvent system has a significant influence on the values of the parameters. This explains the observed differences between our results (see Table VIII) and those of Pugmire and Grant[14] for pyrimidine ($\alpha_H = -7.3$ ppm, $\gamma_H = 9.95$ ppm)

Table IX. Populations of the Form Monoprotonated on Nitrogen N-1 for the Asymmetric Pyrimidines

Compound	Solvents: Protonated species	Solvents: Neutral species	Percentage N(1)H: C_4	$(CH_3)_4$	C_6	$(CH_3)_6$	Av
	Me_2SO	Me_2SO	67	71	69		69 ± 2
	H_2O	H_2O	73	70	68		70 ± 3
	H_2O	Me_2SO	70	68	67		68 ± 2
	CF_3CO_2H	Me_2SO	78	74	73		75 ± 3
	CF_3CO_2H	H_2O	84	78	77		80 ± 4
	CF_3CO_2H	Me_2SO	70	66	71		69 ± 3
	CF_3CO_2H	Me_2SO	70	66	71		69 ± 3
	CF_3CO_2H	Me_2SO		67			67
	CF_3CO_2H	Me_2SO		66			66
	CF_3CO_2H	Me_2SO				95	95
	CF_3CO_2H	Me_2SO				96	96
	CF_3CO_2H	Me_2SO				90	90

where neutral pyrimidine was observed as neat liquid (internal standard:TMS) and pyrimidine sulfate in aqueous solution (internal standard: DSS).

In the case of aminopyrimidines the calculation of the parameters is more complex. We have in fact noted that the values of the sum ($\alpha' + \gamma'$) determined for the symmetric 2-aminopyrimidines (**10, 12** or **14, 15**) were different from the values of the corresponding methylpyrimidines (**1, 4** or **7, 9**). If the effects of conjugation of the amino group with the ring make it impossible to use the chemical shifts of the ring carbons to determine these parameters (cf. Discussion IIIA), one can, however, consider that the methyl group carbons are significantly less sensitive to these conjugation effects. This is consistent with the results obtained for neutral aminopyrimidines in Me_2SO.[1] They show that the introduction of an amino group in position 2 has the same influence on the chemical shift of a methyl carbon in position 4 (−0.1 ppm) as that due to the introduction of an amino group in position 4 on the chemical shift of a methyl carbon in position 2 (0.0_5 ppm). In contrast, large differences are observed for the chemical shifts of the aromatic carbons. One may suppose that the modification of the conjugation of the amino group with the ring following protonation will have a similar influence on the methyl carbons, whether the amino group is in position 2 or 4. Under these conditions, the determination of the parameters a' and c' is made in an analogous way to that of the parameters for the methylpyrimidines. The value a' is obtained from the asymmetric compounds **17** and **20**, which allows the determination of the value c' from data related to compounds **14** and **15** (see Table VIII).

The percentages of the monoprotonated form N(1)H of methyl- and aminopyrimidines are given in Table IX.

In the case of methylpyrimidines the average of the results obtained in the solvents CF_3CO_2H and Me_2SO leads to a population of ca. 71% of the species monoprotonated at N-1. This population is not significantly modified by the introduction of an amino group in position 2; this is not surprising given the equivalence of this position in relation to the two nitrogen atoms N-1 and N-3. In contrast, in the 4-aminopyrimidines the monoprotonation occurs almost completely on the nitrogen atom N-1 para to the amino group, in spite of the presence of a methyl group in position 6 which normally favors protonation of the other nitrogen atom N-3. One may conclude that protonation of the nitrogen atom para to a substituent is considerably favored in the case of an amino group compared to a methyl group. These quantitative results confirm proposals in the literature as to the preferential site of protonation in the 4-aminopyrimidines.[11,18]

In order to evaluate the validity of the method used, the hydrochloride of the 4-methylpyrimidine has been studied in

water and the parent neutral compound in water and Me_2SO. The results of the calculations (see Table IX) are in very good agreement. Such an agreement is also observed for the populations of the monoprotonated forms of 4-methylpyrimidine in CF_3CO_2H when the neutral solvent is water or Me_2SO.

Finally, no appreciable solvent effect was found on the values of the percentages of the monoprotonated form N(1)H for Me_2SO or water solutions (ca. 69%). However, this percentage increases slightly (ca. 77%) in CF_3CO_2H.

V. Conclusion

The results of this study show that for methylpyrimidines the values of the protonation parameters α are different for a carbon attached to a hydrogen than for one attached to a methyl group; this is in contrast to the case of the γ parameter. Furthermore, one observes a large protonation parameter for the carbon of a methyl group when the methyl group is in the ortho position relative to the site of protonation. An analogous result is also found in 2-methylpyridine. Finally, the nature of the anion and solvent has negligible influence on the value of the protonation parameters.

The study of the influence of the medium on the protonated form has demonstrated an especially large solvent effect on the carbon carrying a methyl substituent which is in the para position to the site of protonation. A similar effect was noted for 4-methylpyridine.

The percentages of the tautomeric forms which are monoprotonated on nitrogen N-1 or N-3 have been evaluated. The results for the methylpyrimidines in CF_3CO_2H solutions indicate a high percentage (ca. 71%) of the form protonated on the nitrogen atom para to the methyl group. In the case of the 4-amino-6-methylpyrimidines, the influence of the amino group predominates over that of the methyl group and the percentage of the form protonated on the nitrogen atom para to the amino group reaches 94%.

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