# Proton and Carbon-13 Nuclear Magnetic Resonance Studies of Substituted Pyrimidines. Part 6.[1] Carbon-13-Proton Coupling Constants for Some Monoprotonated Methyl- and Amino-pyrimidines

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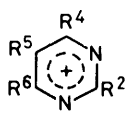
$J(^{13}C,^{1}H)$ coupling constants for some monoprotonated methyl- and amino-pyrimidines have been determined by $^{13}C$ n.m.r. spectroscopy. Both the one-bond and long-range coupling constants follow general trends which may be summarized in a few simple rules. Some of these rules differ from those observed for the neutral compounds, due to the effect of monoprotonation. (i) All the one-bond coupling constants increase; taking into account solvent effects, it appears that the increase observed is larger, the closer the carbon atom considered is to the site of protonation. (ii) The three-bond coupling constants $^{3}J(C,H)$ decrease across the protonated nitrogen.

FEW papers [2-7] have reported the effect of the protonation of heterocycles on their carbon–proton coupling constants. However, more knowledge of this effect is important not only as a test of the theory of coupling constants [8] but also as a tool for the assignment of carbon signals and the determination of the site of protonation.[4]

In connection with our previous study on the effect of monoprotonation on the carbon chemical shifts of substituted pyrimidines,[9] we have determined the one-bond and long-range $J(C,H)$ coupling constants of some methyl- and amino-pyrimidines in trifluoroacetic acid. In order to compare these data with those obtained for the neutral compounds [1] it is necessary, as for the chemical shifts,[9] to distinguish the protonation effect (referring to monoprotonated and neutral compounds in the same medium) from the solvent effect. For pyrimidine and some methyl derivatives, the former effect was studied in $H_2O$, and the latter in $H_2O$ and trifluoroacetic acid. Similar studies were carried out on 2- and 4-methylpyridine for the sake of comparison.

## RESULTS AND DISCUSSION

*Coupling Constants in Trifluoroacetic Acid.*—This study concerns protonated pyrimidine (1) and 16 methyl and amino-derivatives (2)—(17). For these compounds,



(1) $R^2=R^4=R^5=R^6=H$
(2) $R^2=R^5=R^6=H, R^4=CH_3$
(3) $R^2=R^4=R^6=H, R^5=CH_3$
(4) $R^2=R^4=CH_3, R^5=R^6=H$
(5) $R^2=R^6=H, R^4=R^5=CH_3$
(6) $R^2=R^5=H, R^4=R^6=CH_3$
(7) $R^2=R^4=R^6=CH_3, R^5=H$
(8) $R^2=NH_2, R^4=R^5=R^6=H$
(9) $R^2=CH_3, R^4=NH_2, R^5=R^6=H$
(10) $R^2=R^5=H, R^4=NH_2, R^6=CH_3$
(11) $R^2=R^6=CH_3, R^4=NH_2, R^5=H$
(12) $R^2=H, R^4=NH_2, R^5=R^6=CH_3$
(13) $R^2=R^4=CH_3, R^5=NH_2, R^6=H$
(14) $R^2=R^4=NH_2, R^5=R^6=H$
(15) $R^2=R^6=H, R^4=R^5=NH_2$
(16) $R^2=H, R^4=R^5=NH_2, R^6=CH_3$
(17) $R^2=R^5=H, R^4=R^6=NH_2$

it has been shown that only monoprotonation can occur in trifluoroacetic acid; furthermore, the only sites for monoprotonation are N-1 and -3.[10] The respective populations of the 1- and 3-H species depend on the nature and position of the substituent.[9] At room temperature, these species are rapidly exchanging systems and only average values can be observed for their n.m.r. parameters.

The proton-coupled $^{13}C$ spectra were analysed on a first-order basis: this was based on the following arguments. Such an analysis is possible if the corresponding proton part of the spectrum is first order. For the pyrimidines where the proton-coupled $^{1}H$ spectra were first order it is only necessary that the introduction of a $^{13}C$ atom does not involve an overlap between resonance lines.[11] This overlap would appear when the value of the ratio $\Delta\delta$ (proton chemical shift difference between 5- and 6-H) and $^{1}J$(C-6, 6-H)/2 or $^{1}J$(C-5, 5-H)/2 is 1. This ratio is always different from 1 for the monoprotonated substituted pyrimidines. The only exception is for pyrimidinium chloride in $H_2O$ for which the ratio 1 is approached (0.99). Consequently, the non-symmetrical nature of the paired splitting patterns for C-4, -6 and C-5 observed in the proton-coupled $^{13}C$ spectrum requires a detailed spectral analysis to obtain accurate coupling constants. For this compound the calculated $^{1}J(C, H)$ values are 0.9—2.9 Hz larger than the corresponding ones extracted from the spectrum. For the other compounds, the calculation has only been made for 4-methylpyrimidine in $CF_3CO_2H$ for which the ratio $2\,\Delta\delta/^{1}J(C, H)$ is the least favourable (0.94 at 80 MHz). By analogy with the signs of coupling constants determined for monoprotonated pyrimidine in $H_2O$, all coupling constants were considered as positive, except $^{2}J$(C-4, 5-H), $^{2}J$(C-6, 5-H), and $^{4}J$(C-5, 2-H). Coupling constants are listed in Supplementary Publication No. SUP 23013 (5 pp.),* and the ranges of their values are summarized in Table 1.

The relative values of coupling constants *within* a compound follow some simple rules, whatever the populations of the two monoprotonated species may be: $^{1}J$(C-2, 2-H) > $^{1}J$(C-6, 6-H) > $^{1}J$(C-5, 5-H); $^{3}J$(C-2, 6-H) > $^{3}J$(C-6, 2-H) ⩾ $^{3}J$(C-4, 6-H); $^{4}J$(C-2, 5-H) ⩽

* For details of Supplementary Publications see Notice to Authors No. 7 in *J. Chem. Soc., Perkin Trans. 2*, 1979, Index Issue.

TABLE 1

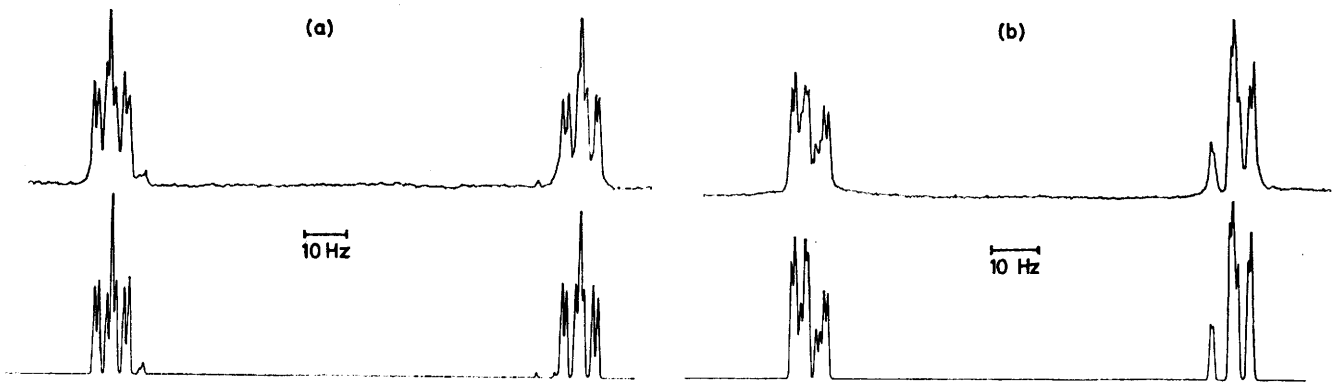
$J$(C,H) coupling constants for methyl- and amino-pyrimidines in $CF_3CO_2H$ (Hz) [a]

| | $^1J$ | | $^2J$ | | $^3J$ | | $^4J$ | |
|---|---|---|---|---|---|---|---|---|
| C-2 | $^1J$(C-2, 2-H) | 212.7—221.4 (10) | $^2J$(C-2, 2-Me) | 6.5—7.8 (3) | $^3J$(C-2, 4,6-H) | 6.3—10.0 (9) | $^4J$(C-2, 5-H) | ⩽0.5 (10) |
| | $^1J$(C-4, 4-H)<br>$^1J$(C-6, 6-H) | 189.6—196.1 (10) | $^2J$(C-4, 5-H) [b]<br>$^2J$(C-6, 5-H) [b] | −4.2 to −1.7(9) | $^3J$(C-4, 2-H)<br>$^3J$(C-6, 2-H) | 6.1—9.5 (11) | | |
| C-4<br>C-6 | | | $^2J$(C-4 4-Me)<br>$^2J$(C-6, 6-Me) | 5.7—6.8(7) | $^3J$(C-4, 6-H)<br>$^3J$(C-6, 4-H) | 3.4—6.9 (8) | | |
| | | | | | $^3J$(C-4, 5-Me)<br>$^3J$(C-6, 5-Me) | 4.4—6.6 (4) | | |
| C-5 | $^1J$(C-5, 5-H) | 174.7—185.3 (11) | $^2J$(C-5, 4,6-H)<br>$^2J$(C-5, 5-Me) | 2.8—6.6 (5)<br>5.9 (1) | $^3J$(C-5, 4,6-Me) | 2.8—4.3 (5) | $^4J$(C-5, 2-H) | −1.4 to 0 (5) |
| | $^1J$(2-Me) | 132.2—132.6 (5) | | | | | $^4J$(2-Me, 4,6-H) | ⩽0.5 (3) |
| | $^1J$(4-Me)<br>$^1J$(6-Me) | 131.1—131.9 (9) | | | $^3J$(4-Me, 5-H)<br>$^3J$(6-Me, 5-H) | 1.7—3.3 (5) | $^4J$(4-Me, 2-H)<br>$^4J$(6-Me, 2-H) | ⩽0.5 (4) |
| | | | | | | | $^4J$(4-Me, 6-H) | ⩽0.5 (4) |
| | $^1J$(5-Me) | 130.0—131.2 (3) | | | $^3J$(5-Me, 4,6-H) | 2.3—3.1 (2) | | |

[a] The number of compounds used for the determination of the range of values is given in parentheses. [b] This value is ⩽0.5 Hz for C-4 (C-6) substituted by an amino-group.

0.5 Hz; $^3J$(C-4, 2-H) ⩾ $^3J$(C-4, 6-H) > $^2J$(C-4, 5-H); $^3J$(C-6, 2-H) > $^2J$(C-6, 5-H).

Our data, along with some literature results,[1,5,6] suggest that these rules should be valid for the monoprotonated pyrimidine ring, in different media, and whatever the nature, number, and position of the substituents may be. It is important to note that these rules are different from the ones observed for the neutral pyrimidine ring.[1] Namely, the relations $^2J$(C-5, 6-H) > $^2J$(C-6, 5-H) and $^3J$(C-2, 6-H) > $^3J$(C-4, 2-H) are not valid any more. This is due to the dependence of the protonation effect on the site of protonation.




The fully coupled $^{13}C,^1H$ spectra of C-4, -6 (a) and C-5 (b) of pyrimidinium chloride in water. The upper trace is the observed spectrum and the lower the simulated spectrum

*Protonation Effect on Coupling Constants.*—In order to determine the protonation effect on coupling constants, it is important to take into account the solvent effect when monoprotonated and neutral species are studied in different media, since this latter effect is often not negligible, especially for $^1J$(C, H) coupling constants.[1]

A detailed study of these two effects has been carried out on pyrimidine and some methyl derivatives in $H_2O$ and trifluoroacetic acid. For pyrimidine and 5-methylpyrimidine, monoprotonation was achieved by addition of hydrochloric acid to the aqueous solution of these compounds and monitored by changes in their carbon chemical shifts. 4-Methylpyrimidinium chloride and 4,6-dimethylpyrimidinium bromide are partially deprotonated in $H_2O$. The extent of protonation was calculated from the p$K_a$ values of the compounds and the concentration of the solutions. This extent is 90.3% for 4-methylpyrimidinium chloride in $H_2O$ (*c* 1M, p$K_a$ 1.31) [9] and 97.2% for 4,6-dimethylpyrimidinium bromide in $H_2O$ (*c* 2.4M, p$K_a$ 2.7). The observed coupling constants were then corrected for the effect of deprotonation, using the values obtained for the neutral compounds in $H_2O$.[1]

For pyrimidinium chloride in $H_2O$ coupling constant values were obtained by iterative spectral analysis of the carbon lines only (see Figure). They all appeared to be positive except $^2J$(C-4, 6, 5-H) and $^4J$(C-5, 2-H).

The coupling constant values for monoprotonated pyrimidines are summarized in Table 2. The data for 4-methylpyrimidinium chloride in dimethyl sulphoxide [9] are also listed for the sake of comparison. Data for the neutral species have already been published.[1]

A similar study has been carried out on 2- and 4-methylpyridine. Although these compounds are complex spin systems, their carbon spectra have been analysed only on a first-order basis; the $^1J$(C, H) values

TABLE 2

$J$(C,H) coupling constants for some monoprotonated pyrimidines (Hz)

| Compound | Solvent | C-2 | | C-4 | | C-5 | | C-6 | | CH$_3$ | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| (1) | $H_2O$ | $^1J$(C-2, 2-H) | 219.1 | $^1J$(C-4, 4-H) | 194.4$_5$ | $^1J$(C-5, 5-H) | 181.0 | $^1J$(C-6, 6-H) | 194.4$_5$ | | |
| | | $^2J$(C-2, 4,6-H) | 8.5$_5$ | $^2J$(C-4, 5-H) | −1.10 | $^2J$(C-5, 4,6-H) | 5.6 | $^2J$(C-6, 5-H) | −1.10 | | |
| | | | | $^3J$(C-4, 2-H) | 7.21 | | | $^3J$(C-6, 2-H) | 7.21 | | |
| | | $^4J$(C-2, 5-H) | ≤0.5 | $^3J$(C-4, 6-H) | 5.55 | $^4J$(C-5, 2-H) | −1.4 | $^3J$(C-6, 4-H) | 5.55 | | |
| | $CF_3CO_2H$ | $^1J$(C-2, 2-H) | 220.0 | $^1J$(C-4, 4-H) | 196.1 | $^1J$(C-5, 5-H) | 178.6 | $^1J$(C-6, 6-H) | 196.1 | | |
| | | $^2J$(C-2, 4,6-H) | 8.5 | $^2J$(C-4, 5-H) | 1.7 | $^2J$(C-5, 4,6-H) | 6.6 | $^2J$(C-6, 5-H) | 1.7 | | |
| | | | | $^3J$(C-4, 2-H) | 6.5 | | | $^3J$(C-6, 2-H) | 6.5 | | |
| | | $^4J$(C-2, 5-H) | ≤0.5 | $^3J$(C-4, 6-H) | 5.1 | $^4J$(C-5, 2-H) | 1.2 | $^3J$(C-6, 4-H) | 5.1 | | |
| (2) | $Me_2SO$ [a] | $^1J$(C-2, 2-H) | 214.7 (211.4) | Poor resolution | | $^1J$(C-5, 5-H) | 179.6 (176.4) | $^1J$(C-6, 6-H) | 190.2 (187.8) | $^1J$(4-Me) | 130.8 (130.0) |
| | | | | | | Broad | | $^2J$(C-6, 5-H) | 3.6 (3.5) | | |
| | | $^3J$(C-2, 6-H) | 8.8 (9.3) | | | | | $^3J$(C-6, 2-H) | 7.3 (7.8) | $^3J$(4-Me, 5-H) | 2.1 (2.0) |
| | | $^4J$(C-2, 5-H) | ≤0.5 | | | | | | | | |
| | $H_2O$ [a] | $^1J$(C-2, 2-H) | 217.9 (216.6) | Poor resolution | | $^1J$(C-5, 5-H) | 180.8 (179.7) | $^1J$(C-6, 6-H) | 193.9$_5$ (192.8) | $^1J$(4-Me) | 130.8 (130.6) |
| | | | | | | Broad | | $^2J$(C-6, 5-H) | 2.2 (2.4) | | |
| | | $^3J$(C-2, 6-H) | 8.6 (8.8) | | | | | $^3J$(C-6, 2-H) | 7.1 (7.3) | $^3J$(4-Me, 5-H) | 2.4 (2.4) |
| | | $^4J$(C-2, 5-H) | ≤0.5 | | | | | | | | |
| | $CF_3CO_2H$ | $^1J$(C-2, 2-H) | 219.4 | | | $^1J$(C-5, 5-H) | 181.0 | $^1J$(C-6, 6-H) | 195.2 | $^1J$(4-Me) | 131.1 |
| | | | | | | | | $^2J$(C-6, 5-H) | 2.2 | | |
| | | $^3J$(C-2, 6-H) | 7.8 | Poor resolution | | Broad | | $^3J$(C-6, 2-H) | 6.8 | $^3J$(4-Me, 5-H) | 1.8 |
| (3) | $H_2O$ | $^1J$(C-2, 2-H) | 219.6 | $^1J$(C-4, 4-H) | 192.1$_5$ | | | $^1J$(C-6, 6-H) | 192.1$_5$ | $^1J$(5-Me) | 130.7 |
| | | | | | | $^2J$(C-5, 4,6-H) | 6.3 | | | | |
| | | $^3J$(C-2, 4,6-H) | 8.6 | $^2J$(C-4, 2-H) | 5.8 | $^2J$(C-5, 5-Me) | 6.3 | $^2J$(C-6, 2-H) | 5.8 | $^3J$(5-Me, 4,6-H) | 2.7 |
| | | | | $^3J$(C-4, 6-H) | 5.8 | | | $^3J$(C-6, 4-H) | 5.8 | | |
| | | | | $^3J$(C-4, 5-Me) | 5.8 | | | $^3J$(C-6, 5-Me) | 5.8 | | |
| | | | | | | $^4J$(C-5, 2-H) | 1.4 | | | | |
| | $CF_3CO_2H$ | $^1J$(C-2, 2-H) | 221.4 | $^1J$(C-4, 4-H) | 192.2 | | | $^1J$(C-6, 6-H) | 192.2 | $^1J$(5-Me) | 131.1 |
| | | | | | | $^2J$(C-5, 4,6-H) | 5.9 | | | | |
| | | $^3J$(C-2, 4,6-H) | 8.3 | $^2J$(C-4, 2-H) | 6.1 | $^2J$(C-5, 5-Me) | 5.9 | $^2J$(C,6, 2-H) | 6.1 | $^3J$(5-Me, 4,6-H) | 2.3 |
| | | | | $^3J$(C-4, 6-H) | 6.1 | | | $^3J$(C-6, 4-H) | 6.1 | | |
| | | | | $^3J$(C-4, 5-Me) | 6.1 | | | $^3J$(C-6, 5-Me) | 6.1 | | |
| | | | | | | $^4J$(C-5, 2-H) | 1.4 | | | | |
| (6) | $H_2O$ [a] | $^1J$(C-2, 2-H) | 215.9 (215.5) | | | $^1J$(C-5, 5-H) | 176.2 (175.9) | | | $^1J$(4,6-Me) | 130.7 (130.6) |
| | | | | $^2J$(C-4, 5-H) | 2.5 (2.5) | | | $^2J$(C-6, 5-H) | 2.5 (2.5) | | |
| | | | | $^3J$(C-4, 4-Me) | 7.0 (7.0) | | | $^3J$(C-6, 6-Me) | 7.0 (7.0) | | |
| | | | | $^3J$(C-4, 2-H) | 7.0 (7.0) | $^3J$(C-5, 4,6-Me) | 3.9 (3.9) | $^3J$(C-6, 2-H) | 7.0 (7.0) | $^3J$(4,6-Me, 5-H) | 2.4 (2.4) |
| | | $^4J$(C-2, 5-H) | ≤0.5 | | | $^4J$(C-5, 2-H) | 1.5 (1.5) | | | | |
| | $CF_3CO_2H$ | $^1J$(C-2, 2-H) | 218.4 | | | $^1J$(C-5, 5-H) | 176.2 | | | $^1J$(4,6-Me) | 131.7 |
| | | | | $^2J$(C-4, 5-H) | 2.6 | | | $^2J$(C-6, 5-H) | 2.6 | | |
| | | | | $^2J$(C-4, 4-Me) | 6.8 | | | $^2J$(C-6, 6-Me) | 6.8 | | |
| | | | | $^3J$(C-4, 2-H) | 6.8 | $^3J$(C-5, 4,6-Me) | 3.9 | $^3J$(C-6, 2-H) | 6.8 | $^3J$(4,6-Me, 5-H) | 2.4$_5$ |
| | | $^4J$(C-2, 5-H) | ≤0.5 | | | $^4J$(C-5, 2-H) | 1.0 | | | | |

[a] The coupling constants of the salts have been corrected for the effect of deprotonation in the solvent used, $Me_2SO$ or $H_2O$. The experimental values are given in parentheses.

TABLE 3

$^1J$(C,H) coupling constants for neutral and monoprotonated pyridines (Hz)

| Compound | Solvent | C-2 | C-3 | C-4 | C-5 | C-6 | CH$_3$ |
|---|---|---|---|---|---|---|---|
| 2-Methylpyridine | $Me_2SO$ [a] | | 161 | 163 | 163 | 177 | 127 |
| | $H_2O$ | | 163.7 | 163.8 | 165.8 | 177.4 | 127.2 |
| 2-Methylpyridinium | $H_2O$ | | 173.4 | 170.6 | 176.0 | 188.3 | 130.6 |
| | $CF_3CO_2H$ | | 173.6 | 171.2 | 176.9 | 189.7 | 131.4 |
| 4-Methylpyridine | $Me_2SO$ | 175 | 160 | | 160 | 175 | 127 |
| | $H_2O$ | 178.1 | 161.4 | | 161.4 | 178.1 | 127.7 |
| 4-Methylpyridinium | $Me_2SO$ | 190.4 | 172.2 | | 172.2 | 190.4 | 129.0 |
| | $H_2O$ | 190.9 | 172.5 | | 172.5 | 190.9 | 129.5 |
| | $CF_3CO_2H$ | 190.6 | 172.9 | | 172.9 | 190.6 | 130.0 |

[a] Y. Takeuchi, *Org. Magn. Reson.*, 1975, **7**, 181.

thus obtained are only approximate. They are summarized in Table 3.

*One-bond Coupling Constants* $^1J$(C, H).—To evaluate the protonation effect, only data obtained for monoprotonated and neutral compounds in the same medium can be taken into account. These effects depend on the position (α, β, or γ) of the carbons considered with respect to the site of protonation and are symbolized by $\Delta(^1J_\alpha)$, $\Delta(^1J_\beta)$, and $\Delta(^1J_\gamma)$.

For pyrimidine and its derivatives, they can be cal-

culated by relationships similar to those used for the carbon chemical shift protonation parameters; for 4-methylpyrimidinium chloride, the population of the 1-H species used in the calculation was 70%.[9] The values of these $\Delta(^1J)$ parameters obtained in $H_2O$ are listed in Table 4, along, for the sake of comparison, with the values for 2- and 4-methylpyridine.

TABLE 4

One-bond coupling constant protonation parameters $\Delta(^1J)$ for pyrimidines and pyridines in $H_2O$ (Hz)

| Compound | $\Delta(^1J_\alpha)$ | $\Delta(^1J_\beta)$ | $\Delta(^1J_\gamma)$ |
|---|---|---|---|
| (1) | 13.5 | 10.1 | 8.8 |
| (2) | 13.7 | 11.7 | 7.5 [a] |
| (3) | 13.9 | | 6.6 |
| (6) | 13.4 | 8.9 | |
| 2-Methylpyridinium | 10.9 | 10.2 (C-5) 9.7 (C-3) | 6.8 |
| 4-Methylpyridinium | 12.8 | 11.1 | |

[a] This value has been determined from the $\Delta(^1J_\alpha)$ value and the populations of the 1- and 3-H species of the corresponding compound in $H_2O$ (*cf.* ref. 9).

Data in Table 4 show that protonation induces large increases for all the one-bond coupling constants since $\Delta(^1J)$ parameters vary from 6.6 to 13.9 Hz. Furthermore this increase is larger, the closer the carbon considered is to the site of protonation: $\Delta(^1J_\alpha) > \Delta(^1J_\beta) > \Delta(^1J_\gamma)$.

These changes could be explained on the basis of variations in the effective nuclear charge [12] of the carbon atoms since protonation increases the eletronegativity of the nitrogen atom. Furthermore these results are similar to the changes observed in the $^1J$(C,H) coupling constant of benzene [13] when a methine group is replaced by a nitrogen atom: $\Delta^1J$(C-2, 2-H) 19.2, $\Delta^1J$(C-3, 3-H) 4.6, and $\Delta^1J$(C-4, 4-H) 4.0 Hz. This general trend was reproduced by a theoretical calculation [14] of these $\Delta^1J$(C, H) values (14.3, 3.6, and −0.6 Hz, respectively). Since only the Fermi contact term was taken into account in this calculation, the similarity of the results suggests that this term should be the main contribution to the changes observed in $^1J$(C, H) upon protonation.

It is interesting to note that the one-bond coupling constants of the methyl groups also increase slightly (2—3 Hz) upon protonation.

When the protonated and neutral compounds are in different media, solvent effects have to be considered, as mentioned above. Solvent effects on the $^1J$(C, H) coupling constants of monoprotonated species can be evaluated from the data in Table 2, with relationships analogous to those used for the chemical-shift study.[9] Since they can amount to a few Hz (see Table 2), these solvent effects appear to be far from negligible with respect to the $\Delta(^1J)$ protonation parameters. As an example, $^1J$(C-2, 2-H) for 4-methylpyrimidinium chloride varies from 214.7 (solvent $Me_2SO$) to 217.9 Hz (solvent $H_2O$). In fact, if they are not taken into account, they limit the conclusions about protonation effect, as shown by the data in Table 5.

Results obtained for substituted pyrimidines allow only the conclusion that the increases of $^1J$(C, H) upon protonation are greater for carbons α to the site of protonation. For 4-aminopyrimidines, the population of the 1-H species is *ca.* 95% [9] and the increases in $^1J$(C, H) are similar for C-2 and -6. These increases are greater than those observed for C-5 which is β to the sites of protonation: $\Delta^1J$(C-2, 2-H) (17.9—20.3 Hz) ≃ $\Delta^1J$(C-6, 6-H) (16.9—18.5 Hz) > $\Delta^1J$(C-5, 5-H) (14.6—15.3 Hz).

On the other hand, the population of the 1-H species is only *ca.* 70% for 4-methylpyrimidines. Consequently, the values observed for $\Delta^1J$(C, H) are smaller for C-6, as expected, than for C-2: $\Delta^1J$(C-2, 2-H) (18.0—19.3 Hz) > $\Delta^1J$(C-6, 6-H) (12.9—14.6 Hz) ≃ $\Delta^1J$(C-5, 5-H) (13.0—14.3 Hz).

For pyridines, determination of the $^1J$(C, H) coupling constants by first-order analysis of their spectra, together with neglect of the solvent effects, scrambles all the $\Delta^1J$(C, H) values. This makes it impossible to draw any conclusions other than that there is an increase of all the $^1J$(C, H) coupling constants upon protonation.

*Long-range Coupling Constants* $^iJ$(C, H).—Solvent effects on long-range coupling constants $^iJ$(C, H) of monoprotonated pyrimidines (as well as for neutral pyrimidines [1]) are very small, as shown in Table 2. It is

TABLE 5

Variations of the $^1J$(C,H) values of some pyrimidines and pyridines upon protonation (Hz) [a]

| Compound | Solvents: Protonated species | Solvents: Neutral species | C-2 | C-3 | C-4 | C-5 | C-6 | Ref. |
|---|---|---|---|---|---|---|---|---|
| Pyrimidine | $CF_3CO_2H$ | $H_2O$ | 14.4 | | 12.8 | 7.7 | 12.8 | |
| | $CF_3CO_2H$ | $Me_2SO$ | 17.1 | | 13.9 | 9.7 | 13.9 | |
| 4-Methylpyrimidines [b] | $CF_3CO_2H$ | $Me_2SO$ | 18.0—19.3 | | | 13.0—14.3 | 12.9—14.6 | |
| 4-Aminopyrimidines [c] | $CF_3CO_2H$ | $Me_2SO$ | 17.9—20.3 | | | 14.6—15.3 | 16.9—18.5 | |
| Pyridine | $CF_3CO_2H$ | Pure liq. | 13.4 | 11.1 | 11.0 | 11.1 | 13.4 | 2 |
| | $CF_3CO_2H$ | Pure liq. | 13 | 14 | 11 | 14 | 13 | 5 |
| | $CF_3CO_2H$ | $CDCl_3$ | 13 | 13 | 11 | 13 | 13 | 5 |
| 2-Methylpyridine | $CF_3CO_2H$ | $H_2O$ | | 9.9 | 7.4 | 11.1 | 12.3 | |
| | $CF_3CO_2H$ | $Me_2SO$ | | 13 | 14 | 8 | 13 | |
| 4-Methylpyridine | $CF_3CO_2H$ | $H_2O$ | 12.5 | 11.5 | | 11.5 | 12.5 | |
| | $CF_3CO_2H$ | $Me_2SO$ | 16 | 13 | | 13 | 16 | |

[a] These values represent both the monoprotonation and the solvent effects (see text). [b] These data are for 4-methyl-, 2,4-dimethyl-, and 4,5-dimethyl-pyrimidine. [c] These data are for 2-methyl-4-amino-, 4-amino-6-methyl-, 4,5-diamino-, and 4,5-diamino-6-methyl-pyrimidine.

then possible to evaluate the protonation effects on these coupling constants by comparison of the data obtained in trifluoroacetic acid for the monoprotonated pyrimidines with those obtained in dimethyl sulphoxide for the neutral compounds.[1]

The larger effects are observed for the three-bond coupling constants $^3J$(C, H) across a nitrogen atom. Data listed in Table 6 show that these coupling constants decrease when the nitrogen atom is protonated. The decreases depend on the position ($\alpha$, $\beta$, or $\gamma$) of the carbon and hydrogen atoms considered with respect to the site of protonation, therefore on the relative populations of the 1- and 3-H species. For example the change in $^3J$(C-6, 2-H) (−4.5 Hz) is larger than in $^3J$(C-4, 2-H) (−0.5 Hz) for 4,5-diamino-6-methylpyrimidine which exists mainly as the 1-H species when it is monoprotonated. This decrease in the $^3J(C_\alpha,H_{\alpha'})$ coupling constants across protonated nitrogen has already been observed for nicotinamide [3] and pteridine: [4] the changes amounted to −5 Hz. They agree with theoretical calculations of the three-bond coupling constants of pyridine [8] which predict a decrease of 8 Hz for $^3J$(C-2, 6-H) upon protonation.

This protonation effect on the $^3J$(C, H) coupling constants can be used to determine the site of monoprotonation.[4] Thus the changes observed in $^3J$(C-2, 6-H), $^3J$(C-6, 2-H) and $^3J$(C-4, 2-H) (−4.9, −4.4, and −1.3 Hz, respectively) for 4,5-diaminopyrimidine indicate that the monoprotonated compound exists mainly as 1-H species. This conclusion is confirmed by the similar changes obtained in these coupling constants for 4,5-diamino-6-methylpyrimidine for which the populations of the 1-H and 3-H forms have been calculated. Since the decreases of these $^3J$(C, H) coupling constants depend on the relative populations of the monoprotonated forms, the rule $^3J$(C-2, 6-H) > $^3J$(C-4, 2-H) observed for neutral compounds [1] is not always valid for monoprotonated pyrimidines.

For the two-bond $^2J$(C, H) coupling constants, some results (see Table 2 and ref. 1) indicate that monoprotonation decreases $^2J(C_\beta,H_\alpha)$ and increases $^2J(C_\alpha,H_\beta)$. For example, the changes observed in $^2J$(C-5, 6-H) and $^2J$(C-6, 5-H) for pyrimidine are −1.2 and 1.6 Hz, respectively. These protonation effects agree with data obtained for nicotinamide.[3] Thus the relationship observed [1] for neutral pyrimidines with no substituent on N-1, $^2J$(C-5, 6-H) > $^2J$(C-6, 5-H), does not apply for all the corresponding monoprotonated compounds.

Although the protonation effects on long-range coupling constants are smaller than on one-bond coupling constants, they proved to be more useful for the determination of the site of protonation since they are not very sensitive to solvent effects.

TABLE 6

Variations of $^3J$(C,H) values across nitrogen of pyrimidine and some derivatives upon protonation (Hz) [a]

| Compound | 1-H (%) [b] | $\Delta^3J$(C-2, 6-H) | $\Delta^3J$(C-4, 2-H) | $\Delta^3J$(C-6, 2-H) |
|---|---|---|---|---|
| (1) | 50 | −1.9 | −2.2 | −2.2 |
| (2) | 77 | −2.9 | Not resolved | −2.4 |
| (3) | 50 | −1.9 | −3.2 | −3.2 |
| (4) | 69 | −2.6 | | |
| (5) | 69 | −2.5 | Not resolved | −2.7 |
| (8) | 50 | −1.5 | | |
| (10) | 95 | | −1.0 | Not determined |
| (13) | | −3.1 | | |
| (15) | | −4.9 | −1.3 | −4.4 |
| (16) | 90 | | −0.5 | −4.5 |
| (17) | 50 | | −3.0 | −3.0 |

[a] Solvents for monoprotonated and neutral compounds are trifluoroacetic acid and dimethyl sulphoxide respectively. [b] The populations of the 1-H form are from ref. 9, except for (16) (this work).

## EXPERIMENTAL

The origins of the compounds studied have been previously reported.[9] Solutions were made up in dimethyl sulphoxide, water, or trifluoroacetic acid in the 0.8—2.8M concentration range.

$^{13}$C N.m.r. spectra were obtained with Varian CFT-20 or XL-100-12 spectrometers. Experimental conditions were: spectral width ⩽2 400 Hz; acquisition time ⩾1.7 s; pulse delay 1—3 s; flip angle 30°; number of acquisitions 15 000—60 000. The resolution was better than 0.6 Hz; however, the observed coupling constant values are accurate to ±0.2 Hz when they were determined from well resolved multiplets.

The $^{13}$C spectrum of pyrimidinium chloride in water was analysed as ABCDX (for C-4) and $AB_2CX$ (for C-5) spin systems using the iterative program LAME [15] on a CII Iris-80 computer.

The $^1$H spectrum of 4-methylpyrimidine coupled with $^{13}$C-6 in $CF_3CO_2H$ was analysed as an $ABCD_3X$ spin system. The difference between the experimental and calculated chemical shifts is less than the experimental error.

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