# Chemistry of Pyrimidine. Proton Magnetic Resonance Study of Covalent Hydration Across the 3,4-Carbon-Nitrogen Bond of 5-Substituted Pyrimidines



Thomas J. Kress

The Lilly Research Laboratories, Eli Lilly and Company,
Indianapolis, Indiana 46285

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Pyrimidines containing 5-substituents which are weakly or strongly electron withdrawing undergo covalent hydration across the 3,4-carbon-nitrogen bond in aqueous acid. The degree of hydration was measured by proton magnetic resonance spectroscopy and was found to be dependent on the strength of the acid media and the electron withdrawing power of the 5-substituent.

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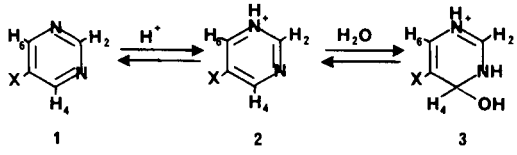
The phenomenon of covalent addition of water across the 3,4-carbon-nitrogen bond of pyrimidines bearing strongly electron withdrawing substituents in the 5-position has been firmly established [1]. Pyrimidines containing substituents such as 5-nitro [2], 5-methylsulfonyl [3], and 5-methyl sulfinyl [3] exist in aqueous acidic solution primarily as the hydrated cations **3**. Recently [4], three additional 5-substituted pyrimidines with electronegative groups ($CO_2H$, $CO_2CH_3$, and CN) have been shown to prefer the hydrated cation structure **3**.



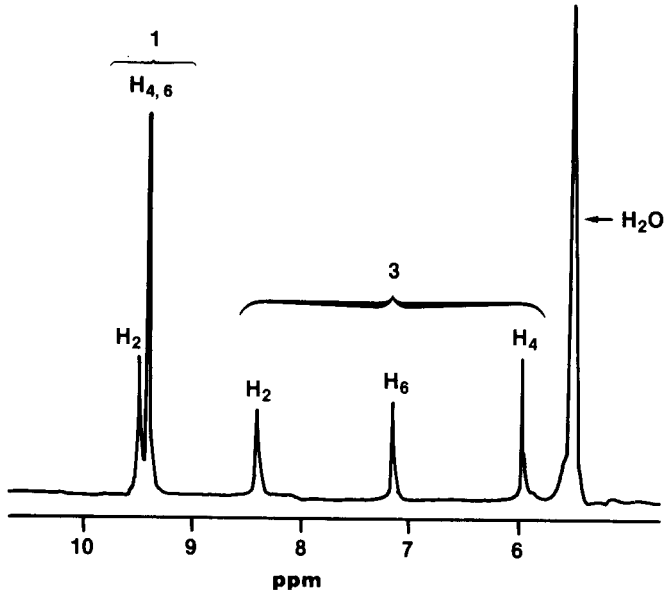

1 2 3

During the course of our work, we have discovered that covalent hydration of pyrimidine cations is indeed a very general reaction and occurs not only when the 5-substituent is strongly electron withdrawing; but also when it is weakly electron withdrawing (**1**, X = Cl, Br) [5] or even electron donating [6]. In addition, we have found the equilibria depicted in Scheme I are dependent on acid concentration, and can be measured using proton magnetic resonance spectroscopy.

## Results and Discussion.

Measurements of the proton magnetic resonance spectra using 5-bromopyrimidine (**1**, X = Br) as an example of a moderately electron withdrawing substituent in deuterium oxide and in increasing concentrations of deuterium chloride in deuterium oxide are listed in Table I. No covalent hydration was observed in deuterium oxide alone. However, in 0.1*N* deuterium chloride-deuterium oxide, an equilibrium mixture containing 5% hydrated cation **3** (X = Br) was evident by the appearence of three new upfield peaks corresponding to H-2, 4 and 6 of the now unsymmetrical species **3** (see Figure 1). The structure **3** was further

**Figure 1**
**90 MHz H Spectrum of**
**5-Bromopyrimidine at Equilibrium in 2N DCl-$D_2O$**




substantiated by the observation of coupling (J = 0.9 Hz) between H-2 and H-6. The equilibrium was found to be reversible, since neutralization regenerated the spectrum recorded in deuterium oxide alone. Also, the degree of hydration was **not** dependent on substrate concentration in a given acid strength. The degree of hydration reaches a maximum of 43% at about 4*N* deuterium chloride-deuterium oxide and descreases at higher acid concentrations. A similar result of decreasing hydration at very high acidities was observed during hydration studies on quinazoline [7] and was attributed to the decrease in the amount of free water remaining in the medium. It was also of interest to note that the chemical shifts of the ring protons in the hydrate remain virtually constant with increasing acid concentration which suggests that the covalent hydrate ex-

Table I

$^1$H NMR Spectra of 5-Bromopyrimidine

| | Chemical Shifts (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | **1** ⇌ **2** (X = Br) | | **3** (X = Br) | | | Ratio [a] |
| Solvent | H-2 | H-4,6 | H-2 | H-4 | H-6 [b] | 1-2/3 |
| Deuterium oxide | 9.08 | 8.93 | N.O. [c] | N.O. | N.O. | 100/0 |
| 0.1*N* Deuterium chloride/deuterium oxide | 9.10 | 8.96 | 8.39 | 5.92 | 7.12 | 95/5 |
| 1.0*N* Deuterium chloride/deuterium oxide | 9.28 | 9.18 | 8.39 | 5.92 | 7.12 | 70/30 |
| 2.0*N* Deuterium chloride/deuterium oxide | 9.50 | 9.42 | 8.39 | 5.94 | 7.14 | 59/41 |
| 4.0*N* Deuterium chloride/deuterium oxide | 9.60 | 9.53 | 8.39 | 5.91 | 7.14 | 57/43 |
| 6.0*N* Deuterium chloride/deuterium oxide | 9.63 | 9.53 | 8.39 | 5.92 | 7.10 | 73/27 |
| 9.0*N* Deuterium chloride/deuterium oxide | 9.65 | 9.55 | 8.39 | 5.92 | 7.14 | 86/14 |

[a] The percentage ratios of **1** to **3** were calculated by integration. [b] Across nitrogen coupling was observed in **3**, J-2, 6 = 0.90 Hz. [c] Not observable (N.O.).

Table II

$^1$H NMR Spectra of 5-Cyanopyrimidine

| | Chemical Shifts (ppm) | | | | | |
|---|---|---|---|---|---|---|
| | **1** ⇌ **2** (X = CN) | | **3** (X = CN) | | | Ratio |
| Solvent | H-2 | H-4,6 | H-2 | H-4 | H-6 | 1-2/3 |
| Deuterium oxide | 9.38 | 9.22 | N.O. [a] | N.O. | N.O. | 100/— |
| 0.1*N* Deuterium chloride/deuterium oxide | 9.39 | 9.23 | 8.57 [b] | 6.02 | 7.65 | 82/18 |
| 1.0*N* Deuterium chloride/deuterium oxide | 9.39 | 9.22 | 8.56 | 6.01 | 7.63 | 7/93 |
| 2.0*N* Deuterium chloride/deuterium oxide | 9.39 | 9.22 | 8.57 | 6.02 | 7.64 | 3/97 |
| 4.0*N* Deuterium chloride/deuterium oxide | N.O. | N.O. | 8.56 | 6.03 | 7.63 | —/100 |
| 6.0*N* Deuterium chloride/deuterium oxide | N.O. | N.O. | 8.57 | 6.05 | 7.63 | —/100 |
| 9.0*N* Deuterium chloride/deuterium oxide | N.O. | N.O. | 8.57 | 6.02 | 7.64 | —/100 |

[a] Not observable (N.O.). [b] Across nitrogen coupling was observed in **3** (X = CN), J-2, 6 = 0.73 Hz.

Table III

$^1$H NMR Spectra of 5-Substituted Pyrimidines

| | | Chemical Shifts (ppm) | | | | | |
|---|---|---|---|---|---|---|---|
| | | **1-2** | | **3** | | | Ratio % |
| Substituent X | Solvent | H-2 | H-4,6 | H-2 | H-4 | H-6 | 1/3 |
| -Cl | Deuterium oxide | 8.95 | 8.73 | N.O. [a] | N.O. | N.O. | |
| | 2*N* Deuterium chloride/deuterium oxide | 9.41 | 9.26 | 8.40 | 5.91 | 7.05 | 60/40 |
| $-CON(CH_3)_2$ [b] | 2*N* Deuterium chloride/deuterium oxide | 9.67 | 9.44 | 8.47 | 6.03 | 7.00 | 55/45 |
| $-OCH_3$ [c] | 2*N* Deuterium chloride/deuterium oxide | 9.27 | 9.08 | N.O. | N.O. | N.O. | |
| -H [d] | 2*N* Deuterium chloride/deuterium oxide | 9.72 | 9.44 | N.O. | N.O. | N.O. | |

[a] Not observable (N.O.). [b] The methyl groups appeared at 3.17 and 3.18. [c] Methyl shift at 4.15. [d] The 5-proton appeared at 8.32.

ists always in the protonated form **3**. At the same time, the chemical shifts of the unhydrated species become more deshielded until the acid concentration reaches about 4*N* deuterium chloride-deuterium oxide. We have attributed this trend to the shift in equilibrium between **1** and **2** with the anhydrous cation **2** being the predominant form in solution at ≥4*N* deuterium chloride-deuterium oxide.

The equilibria shown in Scheme I have also been determined for 5-cyanopyrimidine (**1**, X = CN) and are listed in Table II. Similar to 5-bromopyrimidine **1** (X = Br), no hydration was observed in deuterium oxide alone. With increasing acid strength, however, the effect of the cyano group on covalent hydration is greatly more pronounced than with the bromo substituent. For example, in 4.0*N* deuterium chloride (see Tables I and II) 100% of **1** (X = CN) was hydrated compared to 43% in **1** (X = Br). The fact that there was no change in the chemical shifts of the ring protons in **1** (X = CN) with increasing acid concen-

tration may reflect its lower basicity compared to **1** (X = Br).

The proton nmr spectra of several other pyrimidines measured in 2*N* deuterium chloride are listed in Table III. Both the chlorine (**1**, X = Cl) and *N,N*-dimethylcarboxamide (**1**, X = $CON(CH_3)_2$) substituents produce about 40-45% covalent hydration which was similar to the effect of bromine (**1**, X = Br). Although no covalent hydration was measurable when the 5-substituent was methoxy (**1**, X = $OCH_3$) or hydrogen (**1**, X = H), the existence of a finite amount of covalent hydration has been strongly inferred with these substances [6].

In summary, the degree of hydration can readily be measured by nmr spectroscopy and appears to be proportional to the electron withdrawing strength of the 5-substituent.

## EXPERIMENTAL

Proton nmr spectra were determined on a JEOL FX-90Q Fourier transform spectrometer. The parameters were: pulse angle 30°, acquisition time 4.09 seconds, interpulse delay 2.5 seconds. Melting points were determined on a Thomas-Hoover apparatus and are uncorrected. All nmr spectra were run at 5% w/w and the chemical shifts are relative to sodium 2,2-dimethyl-2-silapentane-5-sulfonate as internal standard. Elemental analyses were performed at Eli Lilly and Company.

Starting Materials.

5-Chloropyrimidine [8], 5-bromopyrimidine [8], 5-cyanopyrimidine [9], 5-methoxypyrimidine [10], and pyrimidine [11] were prepared by literature procedures.

*N,N*-Dimethyl-5-pyrimidinecarboxamide (**1**, X = $CON(CH_3)_2$).

Pyrimidine-5-carboxylic acid [12] (6.7 g, 54 mmoles) was refluxed for 2.5 hours with 20 ml of thionyl chloride affording a clear amber solution. The excess thionyl chloride was removed *in vacuo*, and the residue dissolved in 100 ml of chloroform and added dropwise to a vigorously stirred chilled solution of 40% aqueous dimethylamine. After stirring for twelve hours, the organic layer was separated and the aqueous phase was extracted with (2 × 50 ml) chloroform. The combined chloroform fractions were dried over magnesium sulfate, filtered, and the solvent removed *in vacuo* affording 6.4 g (78%) of crystalline solid. Two crystallizations from cyclohexane gave fine white needles, mp 75-77°; ir (chloroform): 1650 $cm^{-1}$ (amide C=O); ms: m/e 151 ($M^+$).

*Anal.* Calcd. for $C_7H_9N_3$: C, 55.62; H, 6.00; N, 27.80. Found: C, 55.39; H, 5.71; N, 27.52.

## REFERENCES AND NOTES

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[5] Our results on 5-bromopyrimidine differ from those in a recent report (see reference 4) which claims that 5-substituted pyrimidines bearing weakly electron withdrawing substituents form normal cations in aqueous acidic solutions.

[6] The following paper in this series presents evidence that strongly suggests the controlling factor in the outcome of the chemistry of these pyrimidines involves a covalent hydrate as a reaction intermediate.

[7] See ref [1], pp 10-11.

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