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Studies on ^{13}C Magnetic Resonance Spectroscopy. XII.[1] ^{13}C and ^{1}H NMR of 5-Substituted Pyrimidine Derivatives

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^{13}C and ^{1}H nuclear magnetic resonance chemical shifts of 5-substituted pyrimidine derivatives were measured. The linear correlations of the chemical shifts between 5-substituted pyrimidines *vs.* monosubstituted benzenes, 3-substituted pyridines or substituent constants were revealed, and the chemical shift of pyrimidine derivatives can be predicted by the additivity rule.

Keywords——^{13}C NMR chemical shift; ^{1}H NMR chemical shift; 5-substituted pyrimidines; 2,4-dichloro-5-substituted pyrimidines; substituent constants; additivity rule

Introduction

As for the practical utility of the nuclear magnetic resonance spectroscopy, it is significant and appropriate to predict the chemical shift from the chemical structure or from the empirical parameter.

In the case of heteroaromatic systems, the substituent chemical shift (SCS) of monosubstituted benzenes would be expected to be one of the most important substituent parameters accepted in the numerous reports.[3]

In the previous paper[4] of this series, carbon-13 nuclear magnetic resonance (^{13}C NMR) spectra of substituted pyridine derivatives were examined by refering to the monosubstituted benzene series. However, there are few papers on the heteroaromatic compound with two nitrogen atoms in one six-membered ring.

In this work, we have measured the carbon magnetic resonance (CMR) and proton magnetic resonance (PMR) spectra of 5-substituted pyrimidines (I) and 2,4-dichloro-5-substituted pyrimidines (II), and chemical shifts of these two series were compared with those of monosubstituted benzenes or substituent constants,[5,6] and the empirical correlations were examined.

Experimental

Measurement of NMR Spectra——The details of the CMR measurements are all the same as described in the previous report.[3d] All PMR spectra were measured with a Hitachi Perkin-Elmar Model R-22 type NMR spectrometer operating at 90 MHz. Spectra were taken in dil. $CDCl_3$ solution ($\sim 2.5 \times 10^{-1}$: PMR; $\sim 5 \times 10^{-1}$ mol: CMR) with tetramethylsilane (TMS) as an internal reference. Line positions were calibrated by the frequency counter with an accuracy of ±1.0 Hz.

Assignment of spectra was made by peak height and multiplicity argument, or by comparisons with the spectral data of substituted pyridines and benzenes.

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Materials——2,4-Dichloro-5-substituted Pyrimidines: R_5=N,N-$Me_2$$^{7)}$ was prepared by chlorination with phosphorous oxychloride after dimethylamination of 5-bromouracil.

R_5=$NH_2$$^{8)}$ was prepared by the method of Whittaker from 5-nitrouracil.

R_5=Me was prepared from thymine by the analogous procedure discribed for N,N-Me_2.$^{7)}$ Yield 74%, bp 117—118°/18—20 mmHg. *Anal.* Calcd. for $C_5H_4Cl_2N_2$: C, 36.84; H, 2.47. Found: C, 36.81; H, 2.53.

R_5=H$^{8)}$ was prepared from uracil.

R_5=NO_2 was prepared by chlorination$^{8)}$ after nitration of uracil.$^{9)}$

R_5=Br$^{10)}$ was prepared from 5-bromouracil by the method of Chesterfield.

5-Substituted Pyrimidines: R_5=H and Me were obtained commercially.

R_5=N,N-$Me_2$$^{7)}$ and $NH_2$$^{8)}$ were obtained by the dechlorination of corresponding 2,4-dichloro derivatives with H_2+Pd/C.

R_5=Br$^{11)}$ was prepared from 1,1,3,3-tetramethoxypropane by the method of Bredereck.

R_5=OMe$^{12)}$ was prepared from 5-bromopyrimidine and sodium methoxide.

Results and Discussion

Observed ^{13}C and ^{1}H chemical shifts and SCS of 5-substituted pyrimidines (I) and 2,4-dichloro-5-substituted pyrimidines (II) are summarized in Table I and Table II.

TABLE I. Chemical Shifts (δ)$^{a)}$ and SCS$^{b)}$—^{13}C and ^{1}H—of 5-Substituted Pyrimidines

Posotion R_5	C-2		C-4		C-5		H-2		H-4	
	δ	SCS	δ	SCS	δ	SCS	δ	SCS	δ	SCS
NMe_2	147.31	−11.75	140.07	−16.71	143.36	21.94	8.58	0.68	8.20	0.56
$NH_2$$^{c)}$	147.90	−11.16	142.35	−14.43	142.15	20.73	8.66	0.60	8.20	0.56
OMe	151.57	−7.49	143.12	−13.66	153.49	32.07	8.86	0.40	8.41	0.35
Me	156.42	−2.64	156.96	0.18	130.83	9.41	9.06	0.20	8.58	0.18
H	159.06	0.0	156.78	0.0	121.42	0.0	9.26	0.0	8.76	0.0
Br	156.54	−2.52	157.68	0.90	120.76	−0.66	9.12	0.14	8.81	−0.05

a) δ; ppm from TMS.
b) SCS=δ(X-R)−δ(X-H) [CMR]
=δ(X-H)−δ(X-R) [PMR].
c) Solv.; d_6-DMSO.

TABLE II. Chemical Shifts (δ)$^{a)}$ and SCS$^{b)}$—^{13}C and ^{1}H— of 2,4-Dichloro-5-substituted Pyrimidines

Position R_5	C-2		C-4		C-5		C-6		H-6	
	δ	SCS	δ	SCS	δ	SCS	δ	SCS	δ	SCS
NMe_2	154.27	−8.39	150.97	−10.07	143.36	23.08	148.93	−11.03	8.18	0.35
NH_2	147.91	−14.75	146.24	−14.80	137.13	16.85	144.50	−15.46	8.09	0.44
Me	157.92	−4.74	162.30	1.26	128.85	8.57	159.84	−0.12	8.42	0.11
H	162.66	0.0	161.04	0.0	120.28	0.0	159.96	0.0	8.53	0.0
Br	158.82	−3.84	161.40	0.36	118.78	−1.50	161.52	1.56	8.70	−0.17
COOMe	163.86	1.20	162.54	1.50	122.74	2.46	162.06	2.10	9.03	−0.50
NO_2	162.53	−0.13	155.58	−5.46	140.83	20.55	156.36	−3.60	9.15	−0.62

a) δ; ppm from TMS.
b) SCS=δ(X-R)−δ(X-H) [CMR]
=δ(X-H)−δ(X-R) [PMR].

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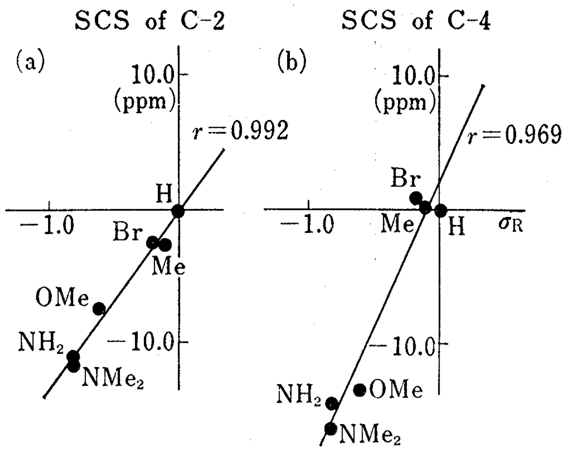

Fig. 1. Plots of (a) C-2 and (b) C-4 ^{13}C SCS of 5-Substituted Pyrimidines *vs.* Substituent Constants σ_R

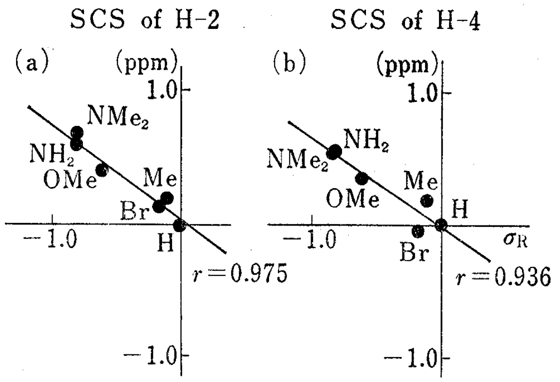

Fig. 2. Plots of (a) H-2 and (b) H-4 ^{1}H SCS of 5-Substituted Pyrimidines *vs.* Substituent Constants σ_R

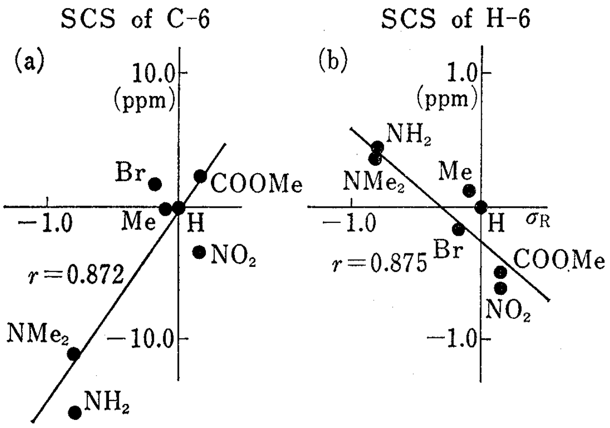

Fig. 3. Plots of (a) C-6 ^{13}C and (b) H-6 ^{1}H SCS of 2,4-Dichloro-5-substituted Pyrimidines *vs.* Substituent Constants σ_R

All ^{13}C SCS of I were tried to correlate with the Taft's substituent constants.[5] The results indicated the high degree of linearity among *ortho*, *para* and *ipso* shifts *vs.* σ_R, and agreed quite favorably with the results of Charton,[13] and the correlation of ^{1}H SCS with σ_R is also successful.

The effect of substitution at *ipso*, *ortho* and *para* positions of 5-substituted pyrimidines are appeared to be controlled by the mesomeric effect of the substituent. Of the correlations of SCS of II with the substituent constants, the same trends are quite evident.

The experimental data of 5-substituted pyrimidines are compared with the available results from 3-substituted pyridines[4,14] or monosubstituted benzenes,[3b,3d] and the correlation coefficients are summarized in Table III.

TABLE III. Correlation Coefficients (r) between I *vs.* Monosubstituted Benzenes and 3-Substituted Pyridines

I	C-2	C-4	C-5	H-2	H-4
Benzene	0.990	0.993	0.989	0.989	0.990
Pyridine	0.995	0.999 0.995	0.997		

As illustrated in Fig. 4, the substituent effects for the ^{13}C SCS of substituted pyrimidines are plotted against those of the corresponding carbons of the monosubstituted benzene series.

Linear combinations of SCS are found among them, and the solid lines, which represents the substituent effect in pyrimidines, are assumed to be equal to those of monosubstituted benzenes.

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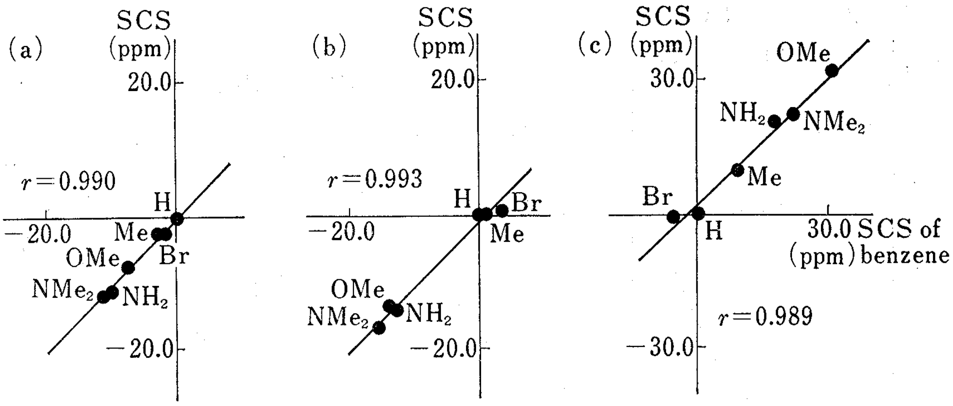
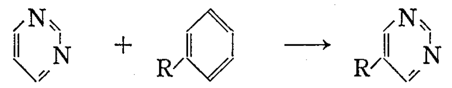


Fig. 4. Correlations between ^{13}C SCS of (a) *para*, (b) *ortho* and (c) *ipso* Position of 5-Substituted Pyrimidines and Monosubstituted Benzenes

Table III shows that the substituent effect in 5-substituted pyrimidines are parallel to that in 3-substituted pyridines, and thus the additional nitrogen at position 5 plays little effect in controlling the substituent effect. This implys that the nitrogen atom does not differ from carbon in the ability of the transmission of electronic effect of substituent.

The chemical shifts of I are estimated by the additivity of the shielding parameters of monosubstituted benzene derivatives, and the observed shifts were compared with those of calculated ones from the additivity the shielding parameters as follows.

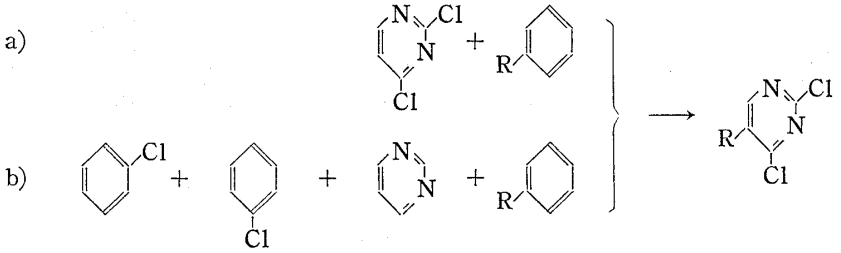


And the results are summarized in Table IV. Table IV shows that the differences between the observed and calculated values —|Δ|— are negligible with a few exceptions. The means of |Δ| values at C-2, C-4, C-5, H-2 and H-4 are ~0.5, 1.0, 1.5, 0.03 and 0.10 ppm, respectively. These magnitudes are small enough to assign the shifts of the related compounds using the additivity rule alone.

Table IV. |Δ Values| and Calculated Chemical Shifts of 5-Substituted Pyrimidines (ppm)

Position R_5	C-2 Calcd.	C-2 |Δ|	C-4 Calcd.	C-4 |Δ|	C-5 Calcd.	C-5 |Δ|	H-2 Calcd.	H-2 |Δ|	H-4 Calcd.	H-4 |Δ|
NMe_2	−11.69	0.06	−15.64	1.07	22.36	0.42	0.67	0.01	0.66	0.10
NH_2	−9.83	1.33	−13.24	1.19	18.04	2.69	0.64	0.04	0.76	0.20
OMe	−7.70	0.21	−14.32	0.66	31.35	0.72	0.43	0.03	0.48	0.13
Me	−3.00	0.36	0.72	0.54	9.53	0.12	0.22	0.02	0.21	0.03
H	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Br	−1.50	1.02	3.24	2.34	−5.75	5.09	0.05	0.09	−0.18	0.13
Mean of values		0.497		0.967		1.507		0.032		0.098

Also, to predict the chemical shifts of II by the additivity rule, two treatments are proposed, namely,



a)=summation of the shielding parameters of monosubstituted benzenes and 2,4-dichloropyrimidine, b)=summation of the shielding parameters of monosubstituted benzenes, pyrimidine and two chlorobenzene moieties.

The observed values are roughly agreed with the calculated ones from a and b, of which the former is more favorable. However, the linear relations between the SCS of II and monosubstituted benzenes are apparent ($r>0.9$).

From above result, we are able to conclude that the chemical shifts (^{13}C and ^{1}H)of substituted pyrimidines are obtained by the additivity rule.