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Carbon-13 Nuclear Magnetic Resonance Spectroscopy. VI.[1] Studies on Carbon-13 Magnetic Resonance Spectra in Aromatic and Heteroaromatic Systems. (2). On the Chemical Shifts of Substituted Pyridine Derivatives[2]

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The carbon-13 chemical shifts of 2-, 3- and 4-substituted pyridine derivatives were examined in relation to those of monosubstituted benzene derivatives and the substituent constants σ_i and σ_π. The results are summarized as follows:

2-Pyridine derivatives

$\delta\,\text{C–R} = -20.0 + 0.62\delta\,\text{C–R/PhR}$

$\delta\,\textit{ortho} = +4.0 + 1.15\delta\,\textit{ortho}/\text{PhR}$

$\delta\,\textit{meta}(\text{C–4}) = -8.0 - 12.5(\sigma_i - 0.25\sigma_\pi)$

$\delta\,\textit{meta}(\text{C–6}) = -21.0 + 4.5(\sigma_i - 0.3\sigma_\pi)$

$\delta\,\textit{para} = +6.0 + \delta\,\textit{para}/\text{PhR}$

$= +5.8 - 22.0\sigma_\pi$

3-Pyridine derivatives

$\delta\,\text{C–R} = \delta\,\text{C–R/PhR}$

$\delta\,\textit{ortho}(\text{C–2}) = -22.0 + 0.88\delta\,\textit{ortho}/\text{PhR}$

$\delta\,\textit{ortho}(\text{C–4}) = -7.5 + \delta\,\textit{ortho}/\text{PhR}$

$\delta\,\textit{meta} = +5.0 - \delta\,\textit{meta}/\text{PhR}$

$= +4.5 - 5.0(\sigma_i - 0.3\sigma_\pi)$

$\delta\,\textit{para} = -20.0 + 1.10\delta\,\textit{para}/\text{PhR}$

$= -20.0 - 23.0\sigma_\pi$

4-Pyridine derivatives

$\delta\,\text{C–R} = -10.0 + \delta\,\text{C–R/PhR}$

$\delta\,\textit{ortho} = +3.0 + 1.15\delta\,\textit{ortho}/\text{PhR}$

$\delta\,\textit{meta} = -21.6 + 1.16\delta\,\textit{meta}/\text{PhR}$

$= -21.6 + 5.0\sigma_i$

Simple sum rules were also found to be applicable to symmetrical and unsymmetrical methyl substituted pyridine derivatives.

Introduction

In the preceding paper of this series,[1] the reliability of the simple sum rule of the carbon-13 shielding parameters of monosubstituted benzenes was confirmed with 1,3- and 1,4-disubsti-

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[1] Part V: G. Miyajima, Y. Sasaki and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **19**, 2301 (1971).

[2] This work was presented at the 23th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1970.

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tuted benzenes. The present work was undertaken to extend the conclusions in our previous paper[1] for substituted pyridines. A few years ago, Retocofsky and Friedel[4] measured the carbon-13 chemical shifts of numerous substituted pyridines, and suggested that both H-1 and carbon-13 chemical shifts of these systems were under the control of similar shielding mechanisms.

Experimental

Carbon-13 spectra are measured in an Hitachi Perkin-Elmer Type R-20A High Resolution nuclear magnetic resonance (NMR) Spectrometer equipped with a 15.085 MHz transmitter and a thermostatically controlled permanent magnet, with a proton external lock mode, which guarantees field and resolution stabilities over a long period. For normal scanning, the R-206C Carbon Attachment and A-1600 A Time Averaging Computer are used, and for the proton decoupling technique, the R-201 Spin Decoupler and R-208 Proton Wide Decoupler are operated at the same time. The signal positions read out from the A-1600 A Time Averaging Computer are calibrated as chemical shifts using the frequency counter in the frequency unit, or are taken directly from a precalibrated chart. Solid materials are made into solution, while liquids are examined directly with or without dilution. The fluids are placed in a normalized pyrex glass tube (8.0 mm *o.d.* and 7.0 mm *i.d.*), employing a plastic turbine driven by compressed air. Under these conditions, deviations in chemical shifts due to the sample tube are in the order of $\lesssim \pm 0.05$ ppm, even when an external reference is used. In this work, the signal positions of carbon-13 enriched MeI and C_6H_6, situated at 213.3 ppm and 65.2 ppm higher field than the CS_2 external reference, respectively, are used as references. The solvent effect observed in dimethylsulfoxide (DMSO) is $\lesssim 1.0$ ppm. 2-Fluoro, 3-iodo, 2-methoxy and 4-, 3- and 2-amino pyridines were purchased from Aldrich Chemical Co. Inc. Milwaukee, Wis., U.S.A. Other materials were obtained from Tokyo Kasei Chemical Co. Ltd. and were of the J.I.S. grade. The samples were used as neat liquids, unless otherwise stated.

Result and Discussion

General Treatment

The chemical shifts of substituted pyridine derivatives were estimated as the simple sum of the carbon-13 shielding parameters of monosubstituted benzene derivatives and those of the pyridine nucleus.[5] The observed shifts were compared with those calculated from the simple sum of the shielding parameters as described previously,[1] and the results are summarized in the following Tables (*cf.* Table I—III).

TABLE I. C-13 Chemical Shifts of 2-Substituted Pyridine Derivatives
Ref. C_6H_6 (ppm) (neat liquids)

R_2		2	3	4	5	6	
NH_2	obs.	−32.4	+19.0	−10.0	+14.9	−20.2	DMSO
	calcd.	−41.0	+17.2	− 9.0	+14.3	−23.2	
	Δ	+ 8.6	+ 1.8	− 1.0	+ 0.6	+ 3.0	
OH	obs.	−36.0	+21.5	− 8.1	+ 7.4	−14.3	DMSO
	calcd.	−48.9	+16.8	− 9.4	+11.3	−23.6	
	Δ	+12.9	+ 4.7	+ 0.7	− 3.9	+ 9.3	
OMe	obs.	−36.4	+17.4	− 9.8	+11.8	−18.9	
	calcd.	−53.9	+18.6	− 9.0	+11.9	−23.3	
	Δ	+17.5	− 1.2	− 0.8	− 0.1	+ 4.4	
Me	obs.	−30.2	+ 5.3	− 7.6	+ 7.7	−21.0	
	calcd.	−31.0	+ 3.8	− 7.4	+ 7.4	−21.6	
	Δ	+ 0.8	+ 1.5	− 0.2	+ 0.3	+ 0.6	

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[4] H.L. Retocofsky and R.A. Friedel, *J. Phys. Chem.*, **71**, 3592 (1967); *idem, ibid.*, **72**, 290 (1968); *idem, ibid.*, **72**, 2919 (1968).

[5] The carbon-13 chenical shifts of pyridine are: α −21.1 ppm, β+4.3 ppm and γ−7.7 ppm from benzene reference.

R_2		2	3	4	5	6
Et	obs.	−35.1	+6.4	−7.8	+7.4	−20.9
	calcd.	−37.5	+4.2	−7.2	+7.1	−21.4
	Δ	+2.4	+2.2	−0.6	+0.3	+0.5
F	obs.	−35.5	+19.0	−12.8	+7.0	−19.4
	calcd.	−56.9	+17.5	−9.0	+8.6	−23.3
	Δ	+21.4	+1.5	−3.8	−1.6	+3.9
Cl	obs.	−23.4	+3.6	−11.0	+5.5	−21.7
	calcd.	−27.1	+4.1	−9.1	+6.2	−23.3
	Δ	+3.7	−0.5	−1.9	−0.7	+1.6
Br	obs.	−14.4	−0.5	−11.0	+4.8	−22.5
	calcd.	−16.6	+0.8	−9.7	+5.5	−24.0
	Δ	+2.2	−1.3	−1.3	−0.7	+1.5
CHO	obs.	−24.6	+6.9	−9.0	+0.2	−21.8
	calcd.	−29.7	+3.0	−8.5	−1.7	−21.9
	Δ	+5.1	+3.9	−0.5	+1.9	+0.1
Ac	obs.	−25.4	+7.1	−8.4	+1.3	−20.8
	calcd.	−31.0	+4.2	−7.8	−0.2	−22.0
	Δ	+5.6	+2.9	−0.6	+1.5	+1.2
CN	obs.	−5.3	−0.7	−9.4	+0.7	−23.0
	calcd.	−6.0	−0.5	−8.7	−0.2	−22.9
	Δ	+0.7	−0.2	−0.7	+0.9	−0.1
NO_2	obs.	−29.1	+9.4	−13.2	−2.3	−21.5
	calcd.	−40.6	+9.6	−8.6	−1.9	−22.9
	Δ	+11.5	−0.2	−4.6	−0.4	+1.4

TABLE II. C-13 Chemical Shifts of 3-Substituted Pyridine Derivatives Ref. C_6H_6 (ppm) (neat liquid)

R_3		2	3	4	5	6	
NH_2	obs.	−9.2	−17.2	+6.5	+3.4	−10.3	DMSO
	calcd.	−9.0	−14.8	+5.2	+3.1	−11.9	
	Δ	−0.2	−2.4	+0.7	+0.3	+1.6	
OH	obs.	−10.4	−27.1	+4.5	+3.0	−12.5	DMSO
	calcd.	−9.4	−22.6	+4.8	+2.7	−14.9	
	Δ	−1.0	−4.5	−0.3	+0.3	+2.4	
Me	obs.	−22.4	−4.7	−7.9	+5.1	−18.8	
	calcd.	−22.5	−4.7	−8.2	+4.6	−20.9	
	Δ	+0.1	0	+0.3	+0.5	+2.1	
Et	obs.	−21.4	−10.7	−6.2	+4.6	−19.3	
	calcd.	−22.1	−11.2	−7.8	+4.8	−19.2	
	Δ	+0.7	+0.5	+1.6	−0.2	−0.1	
Cl	obs.	−20.8	−3.9	−7.5	+3.6	−19.7	
	calcd.	−22.2	−1.9	−8.0	+2.9	−20.0	
	Δ	+1.4	−2.0	+1.5	+0.7	+0.3	
Br	obs.	−23.2	+6.9	−10.6	+3.1	−20.2	
	calcd.	−18.0	+9.7	−11.3	+2.3	−20.7	
	Δ	−5.2	−2.8	+0.7	+0.8	+0.5	
I	obs.	−28.2	+32.7	−16.8	+1.9	−20.8	
	calcd.	−31.8	+36.9	−17.6	+1.7	−21.7	
	Δ	+3.6	−4.2	−0.8	+0.2	+0.9	
CHO	obs.	−23.5	−3.6	−7.7	+3.7	−26.5	
	calcd.	−22.4	−4.3	−9.0	+3.5	−27.1	
	Δ	−1.1	+0.7	+1.3	+0.2	+0.6	
Ac	obs.	−21.6	+4.6	−4.0	+7.0	−25.3	
	calcd.	−22.0	−4.7	−7.8	+4.3	−26.5	
	Δ	+0.4	+9.3	+3.8	+2.7	+1.2	
CN	obs.	−24.7	+18.0	−12.1	+3.7	−25.3	
	calcd.	−25.7	+20.2	−11.5	+3.3	−26.5	
	Δ	+1.0	−2.2	−0.6	+0.4	+1.2	

Table III. C-13 Chemical Shifts of 4-Substituted Pyridine Derivatives
Ref. C_6H_6 (ppm) (neat liquids)

R_4		2	3	4	
NH_2	obs.	−22.0	+18.1	−27.3	DMSO
	calcd.	−23.2	+17.2	−26.8	
	Δ	+ 1.2	+ 0.9	− 0.5	
Me	obs.	−21.6	+ 3.5	−18.5	
	calcd.	−21.6	+ 3.8	−16.7	
	Δ	0	− 0.3	− 1.8	
Et	obs.	−21.1	+ 4.6	−23.6	
	calcd.	−21.4	+ 4.2	−23.2	
	Δ	+ 0.3	+ 0.4	− 0.4	
Br	obs.	−24.1	+ 0.9	− 4.7	
	calcd.	−24.0	+ 0.8	− 2.3	
	Δ	− 0.1	+ 0.1	− 2.4	
CHO	obs.	−22.8	+ 4.9	−13.2	
	calcd.	−21.9	+ 3.0	−16.3	
	Δ	+ 0.9	+ 1.9	+ 3.1	
Ac	obs.	−22.7	+ 6.9	−14.5	
	calcd.	−20.0	+ 4.2	−16.7	
	Δ	− 0.7	+ 2.7	+ 2.2	
CN	obs.	−23.2	+ 2.1	+ 8.0	
	calcd.	−22.9	+ 0.5	+ 8.2	
	Δ	− 0.3	+ 1.6	− 0.2	

Carbon-13 Chemical Shift of Carbon Atoms with Substituent Groups

For 2-,3- and 4-substituted pyridine derivatives, the carbon-13 chemical shifts of carbon atoms with substituent groups were linearly related with those of monosubstituted benzene derivatives as shown in Fig. 1. From the gradients of the above correlations, the following empirical relations were deduced.

2-Pyridine $\delta\,\text{C–R} = -20.0 + 0.62\delta\,\text{C–R/PhR}$ ppm
3-Pyridine $\delta\,\text{C–R} = \delta\,\text{C–R/PhR}$ ppm
4-Pyridine $\delta\,\text{C–R} = -10.0 + \delta\,\text{C–R/PhR}$ ppm

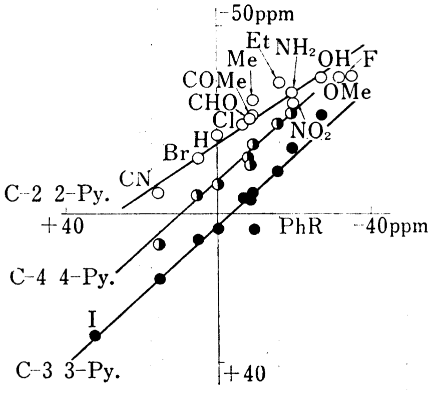

Fig. 1. Correlations between Carbon-13 Chemical Shifts of the Carbon Atoms with a Substituent Group of 2-, 3- and 4-Substituted Pyridines (vertical axis) and Those of Monosubstituted Benzenes (horizontal axis)

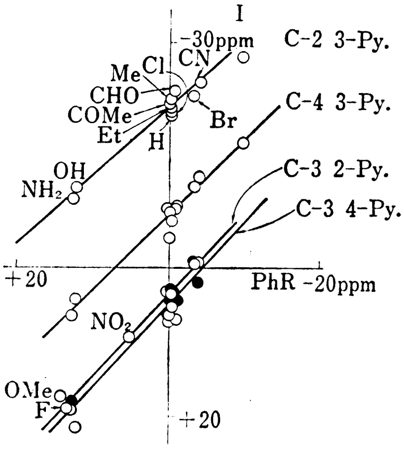

Fig. 2. Correlations between *ortho* Carbon-13 Chemical Shifts of 2-, 3- and 4-Substituted Pyridines (vertical axis) and Those of *ortho* Positions of Monosubstituted Benznes (horizontal axis)

●: C-3 carbon-13 chemical shifts of 4-pyridines where

δ C–R = carbon-13 chemical shift of carbon atom with a substituent group
δ C–R/PhR = carbon-13 chemical shift of carbon atom with a substituent group in monosubstituted benzenes

ortho Carbon-13 Chemical Shifts

In Fig. 2, the *ortho* carbon-13 chemical shifts of 2-, 3- and 4-substituted pyridine derivatives are compared with those of the *ortho* positions of monosubstituted benzene derivatives. The following relations were obtained.

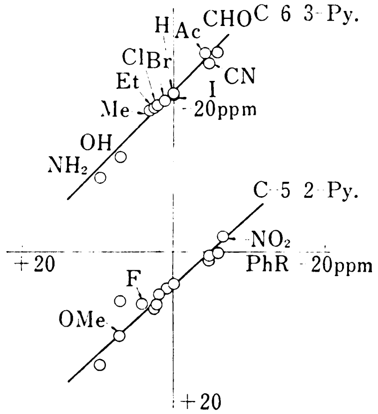

Fig. 3a. Correlations between *para* Carbon-13 Chemical Shifts of 2- and 3-Substituted Pyridines (vertical axis) and Those of *para* Positions of Monosubstituted Benzenes (horizontal axis)

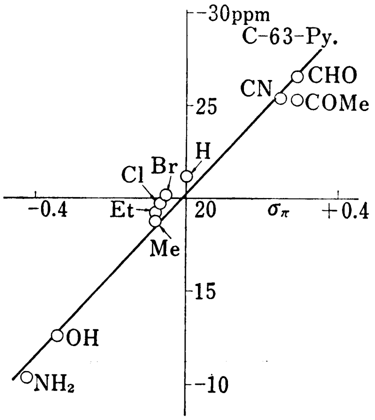

Fig. 3b. Correlation between Carbon-13 Chemical Shifts of the C-5 Positions of 2-Substituted Pyridines and Substituent Constants σ_π

2-Pyridine $\delta\, ortho = +4.0 + 1.15\delta\, ortho/\mathrm{PhR}$ ppm
3-Pyridine $\delta\, ortho\,(\mathrm{C–2}) = -22.0 + 0.88\delta\, ortho/\mathrm{PhR}$ ppm
$\delta\, ortho\,(\mathrm{C–4}) = -7.5 + \delta\, ortho/\mathrm{PhR}$ ppm
4-Pyridine $\delta\, ortho = +3.0 + 1.15\delta\, ortho/\mathrm{PhR}$ ppm

para Carbon-13 Chemical Shifts

As shown in Fig. 3a—c, the *para* carbon-13 chemical shifts of 2- and 3-substituted pyridines were both linearly related with those of the *para* positions of monosubstituted benzenes and the substituent constants σ_π.[6] The following relations were deduced from the results.

2-Pyridine $\delta\, para = +6.0 + \delta\, para/\mathrm{PhR}$ ppm
$= +5.8 - 22.0\sigma_\pi$ ppm
3-Pyridine $\delta\, para = -20.0 + 1.10\delta\, para/\mathrm{PhR}$ ppm
$= -20.0 - 23.0\sigma_\pi$ ppm

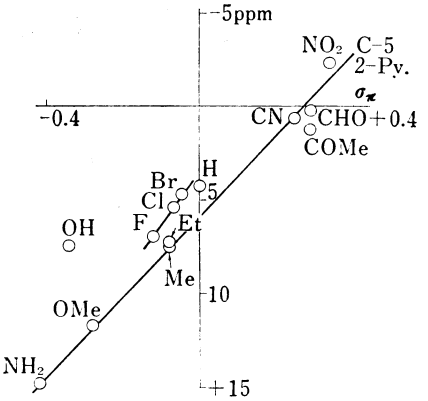

Fig. 3c. Correlation between Carbon-13 Chemical Shits of C-6 Positions of 3-Substituted Pyridines and Substituent Constants σ_π

meta Carbon-13 Chemical Shifts

The *meta* carbon-13 chemical shifts were compared with those of monosubstituted benzenes and the substituent constants σ_i and σ_π,[6] and the following results were obtained.

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[6] Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 873 (1965).

a. 2-Substituted Pyridine Derivatives——As shown in Fig. 4a, the C-4 chemical shifts of 2-substituted pyridines were fairly well correlated with the *meta* carbon-13 shifts of monosubstituted benzenes, whereas, as shown in Fig. 4c, those of C-6 positions deviate considerably in the electron releasing substituent group site. But, as shown in Fig. 4b and Fig. 4d, the formers are linear with σ_i—0.25 σ_π, and the latters are also with σ_i—0.3 σ_π, respectively, except in the case of the anisotropic substituent groups.

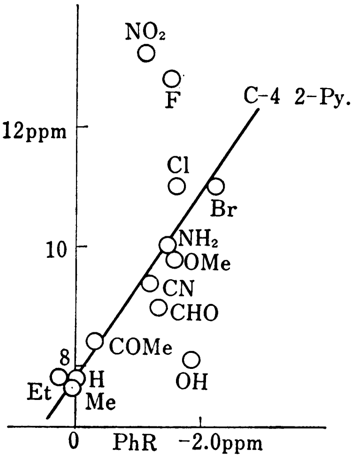

Fig. 4a. Correlations between C-4 Carbon-13 Chemical Shifts of 2-Substituted Pyridines (vertical axis) and Those of *meta* Positions of Monosubstituted Benzenes (horizontal axis)

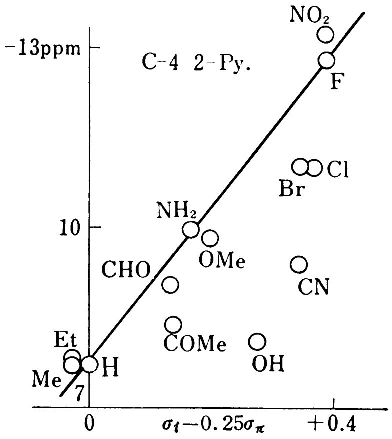

Fig. 4b. Corrlations between C-4 Carbon-13 Chemical Shifts of 2-Substituted Pyridines and Substituent Constants σ_i —0.25 σ_π

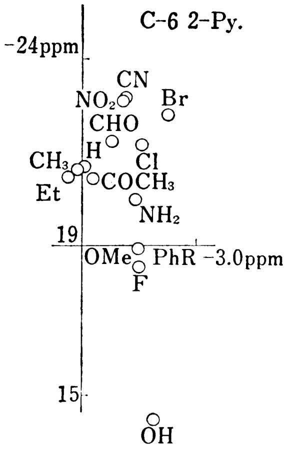

Fig. 4c. Correlations between C-6 Carbon-13 Chemical Shifts of 2-Substituted Pyridines (vertical axis) and Those of *meta* Positions of Monosubstituted Benzenes (horizontal axis)

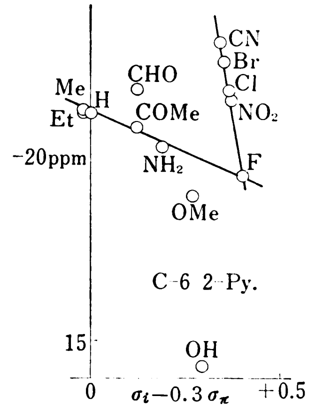

Fig. 4d. Correlations between C-6 Carbon-13 Chemical Shifts of 2-Substituted Pyridines and Substituent Constants σ_i —0.3 σ_π

$$\delta\, meta(\text{C-4}) = -8.0 - 12.5(\sigma_i - 0.25\sigma_\pi)\ \text{ppm}$$
$$\delta\, meta(\text{C-6}) = -21.0 + 4.5(\sigma_i - 0.3\sigma_\pi)\ \text{ppm}$$

b. 3-Substituted Pyridine Derivatives——As shown in Fig. 5a, the *meta* carbon-13 shifts of C-5 positions are linearly related with those of monosubstituted benzenes, as expressed in the following equation, and a linear relation was found between them and substituent constants $\sigma_i - 0.3\sigma_\pi$(*cf.* Fig. 5b)

$$\delta\, meta = +5.0 - \delta\, meta/\text{PhR ppm}$$
$$= +4.5 - 5.0(\sigma_i - 0.3\sigma_\pi)\ \text{ppm}$$

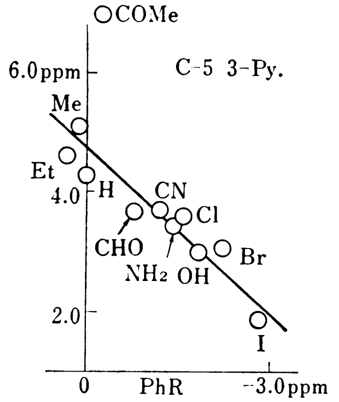

Fig. 5a. Correlations between C-5 Carbon-13 Chemical Shifts of 3-Substituted Pyridines (vertical axis) and Those of *meta* Positions of Monosubstituted Benzenes (horizontal axis)

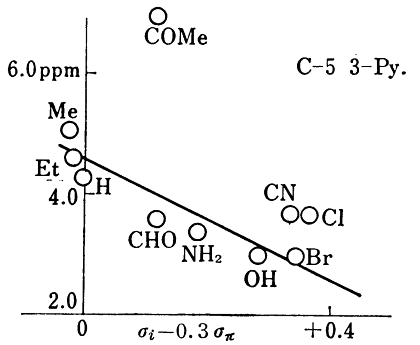

Fig. 5b. Correlations between C-5 Carbon-13 Chemical Shifts of 3-Pyridines and Substituent Constants $\sigma_i - 0.3\,\sigma_\pi$

c. 4-Substituted Pyridine Derivatives——In this series, the carbon-13 chemical shifts of of C-2 positions were correlated with the substituent constants σ_i and with *meta* carbon-13 chemical shifts of monosubstituted benzenes as shown in Fig. 6a—b, and the following empirical relations were obtained.

$$\delta\, meta = -21.6 + 1.16\delta\, meta/\text{PhR ppm}$$
$$= -21.6 - 5.0\sigma_i\ \text{ppm}$$

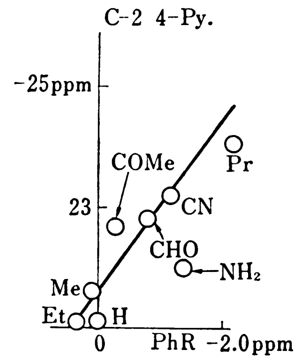

Fig. 6a. Correlations between C-2 Carbon-13 Chemical Shifts of 4-Substituted Pyridines (vertical axis) and Those of *meta* Positions of Monosubstituted Benzenes (horizontal axis)

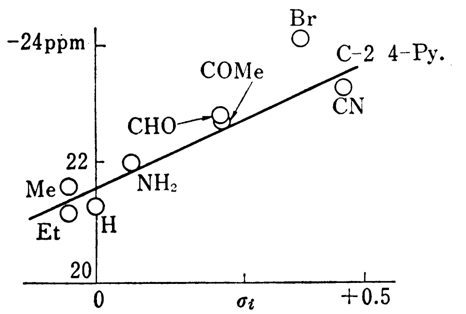

Fig. 6b. Correlations between C-2 Carbon-13 Chemical Shifts of 4-Substituted Pyridines and Substituent Constants σ_i

Methyl Pyridine Homologs

Results of symmetrically and unsymmetrically methyl substituted pyridine derivatives are summarized in Table IV. Results show that the simple sum rule is also valid with these systems.

Table IV. C-13 Magnetic Resonance Chemical Shifts of Methylpyridine Homologs (ppm) (neat liquids)

		2	3	4	5	6
2,3-di Me	obs.	−28.8	−2.8	− 8.4	+7.0	−18.4
		−29.6	−3.3	− 8.9	+7.0	−19.3
	calcd.	−31.7	−5.4	− 8.1	+7.5	−18.7
	Δ	+ 0.8	+0.5	+ 0.5	0	+ 0.9
		+ 2.9	+2.6	− 0.3	−0.5	+ 0.3
2,4-di Me	obs.	−30.0	+4.4	−18.3	+6.6	−21.4
		−30.8	+2.9	−16.6	+6.5	−21.6
	calcd.	−30.8	+3.1	−16.6	+6.6	−21.5
	Δ	+ 0.8	+1.5	− 1.7	+0.1	+ 0.2
		+ 0.8	+1.3	− 1.7	0	+ 0.1
2,5-di Me	obs.	−27.1	+5.9	− 8.2	−1.3	−21.4
		−27.8	+3.9	− 8.1	−1.6	−22.3
	calcd.	−28.1	+3.9	− 8.1	−1.8	−20.9
	Δ	+ 0.7	+2.0	− 0.1	+0.3	+ 0.9
		+ 1.0	+2.0	− 0.1	+0.5	− 0.5
2,6-di Me	obs.	−29.2	+8.6	− 8.0		
		−30.8	+6.5	− 7.4		
	calcd.	−30.9	+6.7	− 7.3		
	Δ	+ 1.6	+2.1	− 0.6		
		+ 1.7	+1.9	− 0.7		
3,5-di Me	obs.	−19.5	−3.9	− 8.4		
		−19.7	−4.6	− 9.1		
	calcd.	−19.6	−4.6	− 8.9		
	Δ	+ 0.2	+0.7	+ 0.7		
		+ 0.1	+0.7	+ 0.5		
3,4-di Me	obs.	−22.4	−4.1	−17.1	+3.3	−19.7
		−23.1	−3.3	−15.3	+2.1	−19.3
	calcd.	−22.4	−5.4	−17.4	+3.9	−20.8
	Δ	+ 0.7	−0.8	− 1.8	+1.2	− 0.4
		0	+1.3	+ 0.3	−0.6	+ 1.1
2,4,6-tri Me	obs.	−29.1	+7.6	−18.4		
		−30.6	+5.8	−16.3		
	calcd.	−30.7	+5.9	−16.4		
	Δ	+ 1.5	+0.8	− 2.1		
		+ 1.6	+0.7	− 2.0		

Conclusion

From the above results and discussions, we are able to deduce the following conclusions:

1) The substituent effect observed in the substituted pyridines are of the same extent or somewhat exaggerated when compared with those of the monosubstituted benzenes, especially in *ortho* and *para* positions.

2) The shift of *meta* carbon atom situated on the *meta* position from the substituent group is expressed by the linear combination of the substituent constants σ_ι and σ_π, and which signifies that the contribution from the delocalization is effective at *meta* positions.

3) For the C-2 carbon chemical shifts of 2-pyridines, the smaller coefficient of the empirical equation from Fig. 5 and the positive deviations observed in Table I are ascribed to the decreased $C_2 \rightarrow N$ bond polarisation which is opposed to that of the $C_2 \rightarrow$Substituent bond polari-

sation, and this fact is also consistent with the observed negative substituent effect on the C-6 carbon atom due to the decreased $C_6 \rightarrow N$ bond polarisation.

4) The anomalous shifts of 2-hydroxy pyridine in dimethyl sulfoxide solution are attributed to the contribution from 2-pyridone type structure or an inter- & intramolecular hydrogen bonding between OH and nitrogen lone pair. The experimental proof of the above tentatives will be presented in due time.