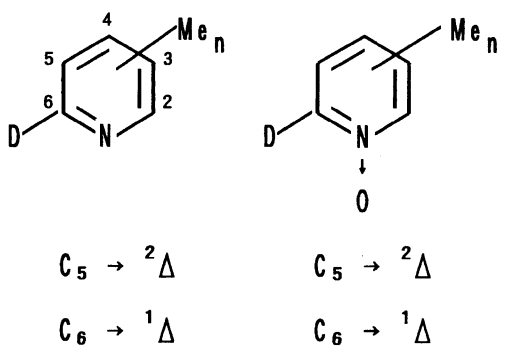
Deuterium Isotope Effects on Aromatic ^{13}C Chemical Shifts. V. Nonadditivity of Methyl Substituent Effects on One-Bond Isotope Shifts for Methylpyridine *N*-Oxides

Yasuki NAKASHIMA,† Moritaka FUKUNAGA, Keiko SUZUKI, and Kensuke TAKAHASHI*
Department of Applied Chemistry, Nagoya Institute of Technology, Gokiso-cho, Showa-ku, Nagoya 466
†Material Development Department, R & D Division, Menicon Co., Ltd., Biwajima-cho, Nishi-ku, Nagoya 451
(Received November 30, 1992)

One- and two-bond deuterium isotope effects ($^1\Delta$ and $^2\Delta$) on ^{13}C chemical shifts for methylpyridines and their *N*-oxides were investigated. The $^1\Delta$ values for methylpyridines agree with the calculated values, which are based on a simple additive rule of the methyl substituent effects. On the other hand, the additive rule was not satisfied in $^1\Delta$ for their *N*-oxides. This is attributed to a steric interaction between the substituent and the *N*-oxide group.

Even though deuterium isotope effects on NMR chemical shifts ($^n\Delta$ where n is the number of intervening bonds) have been known for a long time, the true causes for $^n\Delta$ are still unclear. They are currently under intensive discussions.[1] If the causes for $^n\Delta$ can be clarified, $^n\Delta$ will have new molecular parameters which can be used to characterize molecular structures and chemical bonds. We have systematically studied $^n\Delta$, and have reported on the additivities of substituent effects,[2,3] the dependence of $^n\Delta$ on the electron densities of the related carbons,[3,4] and the sensitivities of $^n\Delta$ on substituent-substituent steric interactions.[5] Further, we have found a dependency of $^1\Delta$ on the C–H bond lengths.[6,7] In this study, $^1\Delta$ and $^2\Delta$ on the ^{13}C chemical shifts of methylpyridines and their *N*-oxides were measured. Twenty methylated pyridines and their *N*-oxides were chosen (Scheme 1). They are substituted at the 6-position by deuterium. For methylated benzenes, which are analogues to the present working system, an increment system for $^n\Delta$ on ^{13}C chemical shifts has already been reported by Berger and Diehl.[8] Therefore, their data are compared with ours. $^1\Delta$ and $^2\Delta$ observed on the C_6 and C_5 can be explained in terms of δ_C and $^1J_{CH}$. Further, the additive effects of methyl substituents on $^1\Delta$ and $^2\Delta$ were investigated, and are discussed.



Scheme 1.

Experimental

Preparation and Deuteration of Dimethylpyridine *N*-Oxides. Dimethylpyridine *N*-oxides were prepared from the corresponding dimethylpyridines by a method described in the literature.[9] Their structures were identified by ^1H and ^{13}C NMR.

Deuterium-labelled compounds were prepared with base-catalyzed proton–deuteron exchange reactions of the corresponding compounds in 0.1—5 wt% NaOH–D_2O solutions. The reaction vessels were commercially available Pyrex ampoules. A suitable amount of the starting material and a catalyst solution were sealed into an ampoule, and then kept at 150—200 °C in an autoclave or kept at 80—90 °C in a thermostatted air oven. H/D exchange reactions occurred at the unsubstituted 2- or 6-position. Reactions also occurred at the methyl protons. However, the isotope shifts on the ring carbons were not influenced by deuteration of the methyl groups.

NMR Measurements. The ^{13}C chemical shifts and $^1J_{CH}$ were measured with a Varian XL-200 or Gemini-300 FT-NMR spectrometer at 50.3 or 75.8 MHz at about 22 °C. The δ_C values were determined in $CDCl_3$ solutions using the center peak of the solvent as an internal standard (77.0 ppm). The one- and two-bond deuterium isotope shifts were measured with a digital resolution better than 3 ppb/point (the spectral width is 2500 Hz and the number of data points is 32 K). The solvents are listed in Tables 1 and 2. The NMR samples were served as a mixture of H- and D-compounds, which is most suitable for a precise comparison of the isotope shifts.

MO Calculations. MNDO MO calculations were carried out using an NEC PC-9801 RA 32-bit personal computer with the program "PASOCON MOPAC/386", which was based on MOPAC (V 3.1 QCPE No. 516) by Toray systems Center.

Results and Discussion

All of the $^1\Delta$ and $^2\Delta$ obtained are given in Tables 1 and 2. They are all upfield shifts. Therefore, although they become negative values based on the definition of the chemical shifts, their signs are reversed in Tables 1 and 2. This means that a positive $^1\Delta$ and $^2\Delta$ implies a greater screening in the deuterated compound. The $^1\Delta$ values of pyridines ranged from 325 to 351 ppb, and

Table 1. One-Bond Deuterium Isotope Effects on ^{13}C NMR Chemical Shifts ($^1\Delta$) of the C-6 for Methylpyridines-6-*d* and Methylpyridine-6-*d* *N*-Oxides in ppb[a)]

No.[b)]	Substituent	Pyridine	Solvent	Pyridine *N*-oxide	Solvent
1	—	327	D_2O	268	1% NaOH–D_2O
2	2-Me	327	Neat	298	5% NaOH–D_2O
3	3-Me	325	Neat	255	5% NaOH–D_2O
4	4-Me	328	Neat	266	0.1% NaOH–D_2O
5	5-Me	351	Neat	282	5% NaOH–D_2O
6	2,3-Me_2	325	Neat	266	5% NaOH–D_2O
7	2,4-Me_2	327	Neat	267	5% NaOH–D_2O
8	2,5-Me_2	351	Neat	304	5% NaOH–D_2O
9	3,4-Me_2	325	Neat	261	5% NaOH–D_2O
10	3,5-Me_2	351	Neat	277	5% NaOH–D_2O
11	4,5-Me_2	349	Neat	285	5% NaOH–D_2O
12	2-Et	332	Neat	280	5% NaOH–D_2O

a) Digital resolutions are better than 3 ppb. Positive values show greater screening in the deuterated compounds with respect to the corresponding hydrido compounds.
b) The numbers are referred to those in Fig. 1.

Table 2. Two-Bond Deuterium Isotope Effects on ^{13}C NMR Chemical Shifts ($^2\Delta$) of the C-5 for Methylpyridines-6-*d* and Methylpyridine-6-*d* *N*-Oxides in ppb[a)]

No.[b)]	Substituent	Pyridine	Solvent	Pyridine *N*-oxide	Solvent
1	—	129	Neat	129	1% NaOH–D_2O
2	2-Me	137	Neat	133	5% NaOH–D_2O
3	3-Me	135	Neat	134	5% NaOH–D_2O
4	4-Me	118	Neat	131	0.1% NaOH–D_2O
5	5-Me	114	Neat	91	5% NaOH–D_2O
6	2,3-Me_2	137	Neat	125	5% NaOH–D_2O
7	2,4-Me_2	133	Neat	125	5% NaOH–D_2O
8	2,5-Me_2	114	Neat	113	5% NaOH–D_2O
9	3,4-Me_2	130	Neat	121	5% NaOH–D_2O
10	3,5-Me_2	110	Neat	c)	5% NaOH–D_2O
11	4,5-Me_2	103	Neat	104	5% NaOH–D_2O
12	2-Et	137	Neat	133	5% NaOH–D_2O

a) Digital resolutions are better than 3 ppb. Positive values show greater screening in the deuterated compounds with respect to the corresponding hydrido compounds.
b) The numbers are referred to those in Fig. 3. c) Not available.

those of pyridine *N*-oxides from 255 to 304 ppb. The $^2\Delta$ values of the former ranged from 103 to 137 ppb, and those of the latter from 91 to 134 ppb. Generally, both $^1\Delta$ and $^2\Delta$ of the *N*-oxides are smaller than those of the corresponding pyridines, respectively.

It is possible to evaluate the methyl substituent effects from the differences between $^1\Delta$ or $^2\Delta$ of methylsubstituted compounds and the unsubstituted one. They are given in Table 3. These effects (we call them 'SIS', for Substituent Isotope Shifts[2,3]) can be used to calculate $^1\Delta$ and $^2\Delta$ for dimethyl compounds. For later discussion, the ^{13}C chemical shifts and $^1J_{CH}$ of the carbons in nondeuterated compounds are also given in Tables 5 and 6, respectively.

Interaction Effect between Methyl and *N*-Oxide Groups on $^1\Delta$. As shown in Table 3, the ^1SIS were evaluated for pyridines and their *N*-oxides. Methyl-substituent effects on the $^1\Delta$ of methylpyridines seem to be negligibly small, with the exception of the ortho effect. On the other hand, those of the pyridine *N*-oxides show a quite different behavior. For example, the 2-methyl group, which exists at the meta-position to the $^1\Delta$-observed carbon, increases $^1\Delta$ by 30 ppb. This is the largest effect for $^1\Delta$. In contrast, the 4-methyl effect is negligibly small in spite of existing at a similar meta-position, compared with the 2-methyl effect. The 2-ethyl group also increases $^1\Delta$.

$^1\Delta$ in methylpyridines and their *N*-oxides can be compared with those in methylbenzenes.[8)] A comparison of the differences between the methylpyridines and methylbenzenes, or between the methylpyridines and their *N*-oxides, shows the existence of an interaction between a methyl group and an *N*-oxide group. They are listed in Table 4. The differences between the methylpyridines

Table 3. Substituent Effects on $^1\Delta$ and $^2\Delta$

Substituent	Pyridine	Pyridine *N*-oxide	Benzene[a]
for $^1\Delta$ on C-6			
2-Me	0	+30	−3
3-Me	−2	−13	−7
4-Me	+1	−2	−3
5-Me	+24	+14	+29
2-Et	+5	+12	b)
for $^2\Delta$ on C-5			
2-Me	+8	+4	−1
3-Me	+6	+5	−1
4-Me	−11	+2	−5
5-Me	−15	−38	−25
2-Et	+8	+4	b)

a) Evaluated from the data in Ref. 8. b) Not available.

and methylbenzenes (*Dif 1*s) ranged from 39 to 52 ppb. They seem to be almost constant. Therefore, the interaction between the substituent and the nitrogen atom in methylpyridines seems to be almost constant. On the other hand, among the differences between methylpyridines and their *N*-oxides (*Dif 2*s), an extremely irregular value was obtained for the 2-methyl derivative. The value is the smallest one in the third column of Table 4. In addition, three small values among the *Dif 2*s are all concerned with the 2-substituted compounds. It therefore suggests that in the 2-methyl derivatives the methyl group interacts specifically with the *N*-oxide group. It has been reported that there is a steric interaction between the oxygen atom and the 2-methyl group in 2-methylpyridine *N*-oxide.[10] To investigate this "steric" interaction more closely, MNDO MO calculations were carried out for 2-methylpyridine and its *N*-oxide. The heats of formation accompanying the rotation of the methyl group were calculated as shown in Fig. 4. There is evidently an energy change between 2-methylpyridine and its *N*-oxide accompanied by methyl rotation. A similar potential curve was also calculated for the 2-ethyl derivative. Therefore, the peculiar 2-methyl or 2-ethyl effect on $^1\Delta$ is explained in terms of the above-mentioned steric interaction. As shown in Table 3, both the 2-methyl and the 2-ethyl groups increase $^1\Delta$. The 2-ethyl effect, however, is smaller than the 2-methyl effect. The $^1\Delta$ value in 1-deuterio-2,3-dimethylbenzene shows a similar behavior. The interaction between the two methyl groups increases $^1\Delta$ by 6.9 ppb.[8]

Table 4. Differences of $^1\Delta$ between Pyridine and Benzene, and between Pyridine and Pyridine *N*-Oxide in ppb

Substituent	*Dif1*[a]	*Dif2*[b]
—	44	59
2-Me	47	29
3-Me	49	70
4-Me	48	62
5-Me	39	69
2,3-Me_2	51	59
2,4-Me_2	48	60
2,5-Me_2	47	47
3,4-Me_2	51	64
3,5-Me_2	52	74
4,5-Me_2	40	64
2-Et	c)	52

a) *Dif1* = $^1\Delta$(pyridine) − $^1\Delta$(benzene). b) *Dif2* = $^1\Delta$(pyridine) − $^1\Delta$(pyridine *N*-oxide). c) Not available.

Additivity of Methyl Substituent Effects on $^1\Delta$. If two methyl substituents are independent of each other, $^1\Delta$ may be calculated using the following equation:

$$^1\Delta_{calc} = {}^1\Delta_0 + \Sigma^1 SIS, \quad (1)$$

where $^1\Delta_0$ means $^1\Delta$ observed for the unsubstituted compound. Since this type of equation may also be applied to $^2\Delta$, the following equation is obtained:

$$^2\Delta_{calc} = {}^2\Delta_0 + \Sigma^2 SIS. \quad (2)$$

In the above equations, ^1SIS and ^2SIS are the values given in Table 3. If it is assumed that there is no serious interaction between the two methyl groups in dimethylpyridine, the additivity of the methyl-substituent effects is well established as shown by the white points in Fig. 1. On the other hand, the additivity was not successful for a series of dimethylpyridine *N*-oxides. As shown by the black points in Fig. 1, the points of 2, 3-, 2,4-, and 2,5-dimethylpyridine *N*-oxides (6,7, and 8) show large deviations from the correlated straight line. However, the points for 3,4-, 3,5-, and 4,5-dimethylpyr-

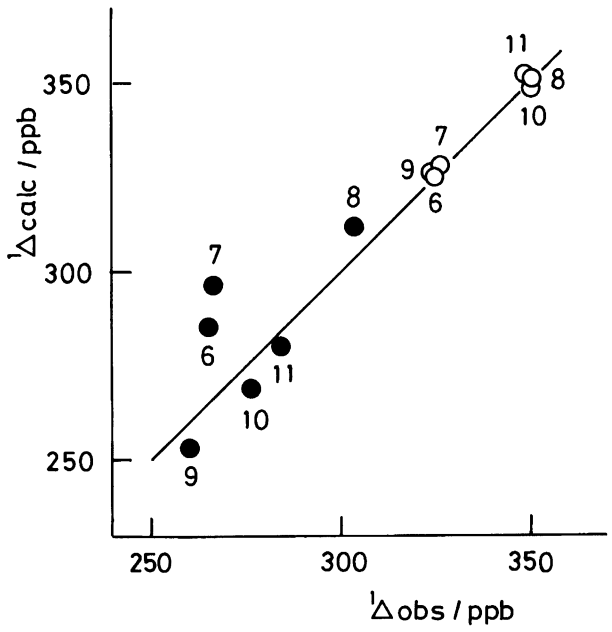


Fig. 1. Plots of $^1\Delta_{calc}$ (calculated using Eq. 1 in the text) vs. the observed ones for the dimethylpyridines (○) and their *N*-oxides (●). The slope and intercept of the straight line are 1.0 and 0.0, respectively.

Table 5. ^{13}C NMR Chemical Shifts of Methylpyridines and Their *N*-Oxides in $CDCl_3$ in ppm[a)]

Substituent	C_2	C_3	C_4	C_5	C_6	CH_3	
(for Methylpyridines)							
—	148.64	122.52	134.64	122.52	148.64	—	
2-Me	157.05	122.02	134.98	119.49	147.86	23.16	
3-Me	149.19	131.94	135.23	122.04	145.85	17.23	
4-Me	148.40	123.48	145.75	123.48	148.40	19.69	
2,3-Me_2	155.66	129.96	135.59	119.89	145.15	21.22	17.74
2,4-Me_2	157.04	123.13	146.14	120.76	147.91	23.27	19.84
2,5-Me_2	153.95	121.43	135.55	128.50	148.17	22.62	16.65
2,6-Me_2	156.48	119.04	135.38	119.04	156.48	23.41	
3,4-Me_2	149.07	131.14	144.47	123.57	146.42	15.29	18.01
3,5-Me_2	146.32	131.33	135.92	131.33	146.32	17.06	
2,4,6-Me_3	156.30	120.19	146.39	120.19	156.30	23.22	19.72
(for Methylpyridine *N*-oxides)							
—	138.97	125.61	125.85	125.61	138.97	—	
2-Me	148.70	126.25	125.35	123.29	139.01	17.47	
3-Me	136.98	134.89	124.70	123.66	134.35	15.94	
4-Me	137.26	125.71	136.40	125.71	137.26	18.96	
2,3-Me_2	146.91	133.90	126.34	121.07	135.79	12.49	18.24
2,4-Me_2	147.34	126.49	136.74	123.69	137.85	16.91	19.44
2,5-Me_2	144.57	124.81	125.79	132.88	137.85	16.09	16.71
2,6-Me_2	148.04	123.29	123.86	123.29	148.04	17.50	
3,4-Me_2	136.85	134.08	136.39	125.13	134.50	14.91	16.52
3,5-Me_2	134.67	134.50	127.08	134.50	134.67	16.29	
2,4,6-Me_3	147.70	124.33	136.10	124.33	147.70	17.64	19.69

a) Errors are estimated to be within 0.02 ppm.

Table 6. $^1J_{CH}$ in ^{13}C NMR of Methylpyridines and Their *N*-Oxides in Hz[a)]

Substituent	C_2	C_3	C_4	C_5	C_6
(for Methylpyridines)					
—[b)]	177.37	162.59	161.13	162.59	177.37
2-Me	(126.7)[c)]	160.3	162.9	163.9	176.7
3-Me	175.3	(127.1)	161.1	162.9	177.9
4-Me	176.9	160.8	(127.2)	160.8	176.9
2,3-Me_2	(126.5)	(126.7)	159.6	163.5	176.7
2,4-Me_2	(126.5)	158.8	(127.2)	162.0	175.8
2,5-Me_2	(126.6)	161.5	159.5	(126.9)	174.4
2,6-Me_2	(126.6)	160.3	159.1	160.3	(126.6)
3,4-Me_2	174.2	(126.9)	(127.0)	159.8	177.1
3,5-Me_2	175.4	(126.8)	156.7	(126.8)	175.4
2,4,6-Me_3	(126.5)	159.2	(126.9)	159.2	(126.5)
(for Methylpyridine *N*-oxides)					
—	189.4	165.7	172.1	165.7	189.4
2-Me	(130.5)	170.7	168.3	169.1	188.3
3-Me	189.6	(128.4)	167.3	166.9	188.0
4-Me	186.5	161.5	(128.0)	161.5	186.5
2,3-Me_2	(129.8)	(128.0)	166.0	167.1	186.8
2,4-Me_2	(130.1)	161.8	(127.9)	166.5	184.6
2,5-Me_2	(129.9)	164.8	165.7	(128.3)	183.9
2,6-Me_2	(129.8)	165.2	167.2	165.2	(129.8)
3,4-Me_2	184.9	(128.5)	(127.8)	164.6	186.8
3,5-Me_2	185.1	(128.3)	164.4	(128.3)	185.1
2,4,6-Me_3	(129.9)	162.6	(127.7)	162.6	(129.9)

a) Errors are estimated to be within 0.5 Hz. b) Ref. 12. c) The values in parentheses are those of the methyl carbons.

idine *N*-oxides (9, 10, and 11) show small deviations. In the former group containing the 2-methyl substituent, $^1\Delta$ are smaller than $^1\Delta_{calc}$. This fact can be explained as follows. The interaction between the 2-methyl and *N*-oxide groups becomes smaller when another methyl group is introduced at the 3-, 4-, or 5-position. This additional methyl group influences the electronic structure of the molecule. As a result, the interaction between the 2-methyl and *N*-oxide groups becomes smaller. In addition, the $^1\Delta$ values in methylpyridines show a rough correlation with $^1J_{CH}$ (Fig. 2) (Table 6). As shown in Fig. 2, whenever a small $^1J_{CH}$ is concerned, a large $^1\Delta$ is observed in the methylpyridines. A similar correlation appeared for those in the methylbenzenes.[8] The slope of the correlated straight line between $^1\Delta$ and $^1J_{CH}$ in Fig. 2 is close to that between $^1\Delta$ and $^1J_{CD}$ measured in the methylbenzenes, although the slope must be compared after multiplication by the magnetogyric ratios of the proton and deuteron.[8] On the other hand, there is only a divergent distribution for the black points from the pyridine *N*-oxides in Fig. 2. When there exists a notable interaction between the substituents, as shown in the case of 2-methylpyridine *N*-oxides, the perturbations to the $^1\Delta$-observed carbons from the methyl groups cannot be independent of each other. The additivity of the substituent effects on $^1\Delta$ will thus fail in the methylpyridine *N*-oxides. The correlation between $^1\Delta$ and $^1J_{CH}$ cannot also be obtained.

Two-Bond Isotope Shifts, $^2\Delta$. The $^2\Delta$ in the present system ranged from 91 to 137 ppb. The magnitude is not much different for both the pyridines and their *N*-oxides. The largest effect on $^2\Delta$ was observed at the carbon adjacent to the methyl groups in both the methylpyridines and their *N*-oxides. This effect is similar to those of the methylbenzenes. In addition, the 4-methyl (ortho) effect was large in pyridine. In the *N*-oxides, the ortho, meta, and para effects (4-, 3-, and 2-Me effects, respectively) are negligibly small. These are similar to those in benzene. In several systems the

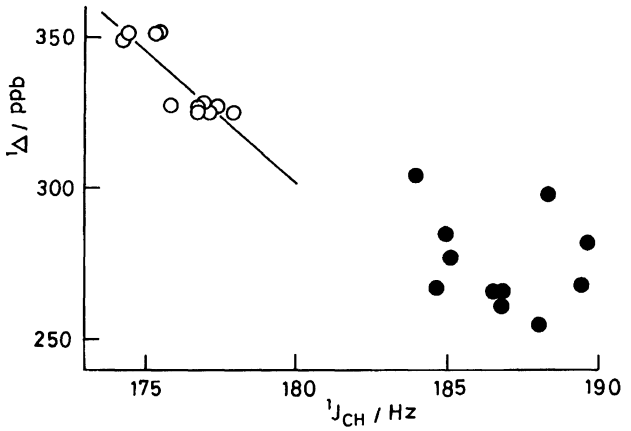


Fig. 2. Plots of $^1J_{CH}$ vs. $^1\Delta$ for the methylpyridines (○) and their *N*-oxides (●).

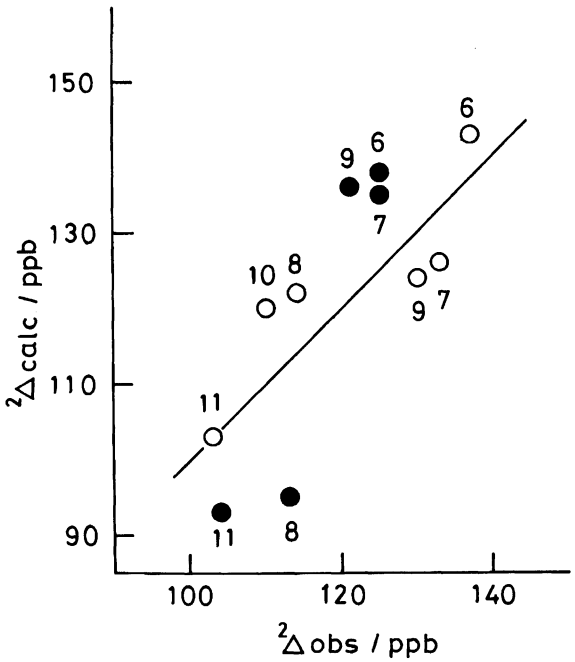


Fig. 3. Plots of $^2\Delta_{calc}$ (calculated using Eq. 2 in the text) vs. the observed ones for the dimethylpyridines (○) and their *N*-oxide (●). The slope and the intercept of the straight line are 1.0 and 0.0, respectively.

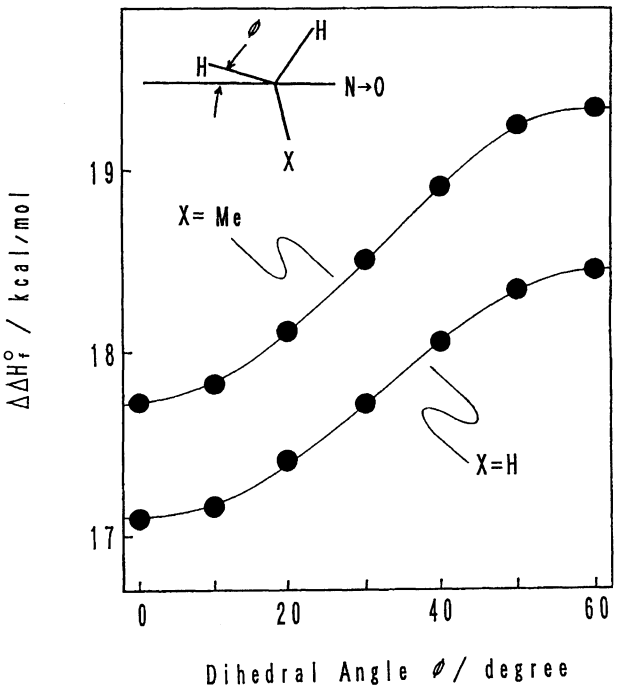


Fig. 4. Heat-of-formation difference accompanied by the rotation of the methyl or methylene group for 2-methyl-, or 2-ethylpyridine and their *N*-oxides. $\Delta\Delta H_f^\circ$ is defined as follows: $\Delta\Delta H_f^\circ = \Delta H_f^\circ$(*N*-oxide) $- \Delta H_f^\circ$ (methylpyridine or ethylpyridine). ΔH_f° means the heat of formation.

$^2\Delta$ values are correlated with δ_C.[2—4] Therefore, the $^2\Delta$ are considered to be sensitive to any electron-density changes on related carbons. In the present system, a rough correlation between $^2\Delta$ and δ_C was obtained. The slopes of the least-square lines[11] were very close to those of the reported values for other aromatic compounds.[2—4] Therefore, the electron dinsities of the observed carbons are important for $^2\Delta$. The $^2\Delta$ values observed for dimethyl compounds do not agree with the values calculated using Eq. 2. The calculated $^2\Delta$ vs. the observed ones are plotted in Fig. 3. The black and white points show a large dispersion both above and below the correlated straight line. The disagreement between the two is considered to be as follows. The $^2\Delta$ values depend on the electron densities of the observed carbons. The interactions between the nitrogen atom and the methyl groups or between the *N*-oxide and the methyl groups in the methylpyridines and their *N*-oxides may exist, respectively. Such interactions influence the electron densities on the $^2\Delta$-observed carbons. Therefore, the $^2\Delta$ for the methylpyridines and their *N*-oxides cannot be explained simply.

Conclusion

The methyl-substituent effects on $^1\Delta$ for the methylpyridines show a simple additivity. The $^1\Delta$ values for their *N*-oxides, however, cannot be explained in terms of the additivity. This can be attributed to a steric interaction between the 2-methyl and the *N*-oxide groups.

References

1) For recent reviews, see: a) P. E. Hansen, *Ann. Rep. NMR Spectrosc.*, **15**, 105 (1983); b) D. A. Forsyth, in "Isotope in Organic Chemistry," ed by E. Buncel and C. C. Lee, Elsevier, New York (1984), Vol. 6, Chap. 1.1; c) C. J. Jameson and H. J. Osten, *Ann. Rep. NMR Spectrosc.*, **17**, 1 (1985); d) S. Berger, "Isotope Effects in NMR Spectroscopy," ed by H. Günther, Springer, Berlin (1990), Vol. 22, p. 1; e) P. E. Hansen, *Prog. Nucl. Magn. Reson. Spectrosc.*, **20**, 207 (1988).

2) Y. Nakashima, A. Yoshino, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **62**, 1401 (1989).

3) Y. Nakashima, H. Nakane, S. Ban, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **63**, 2025 (1990).

4) Y. Nakashima, S. Ban, S. Itoh, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **64**, 3694 (1991).

5) Y. Nakashima, K. Suzuki, M. Fukunaga, and K. Takahashi, under preparation.

6) Y. Nakashima, H. Kanada, M. Fukunaga, K. Suzuki, and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **65**, 2894 (1992).

7) Y. Nakashima and K. Takahashi, *Bull. Chem. Soc. Jpn.*, **64**, 3166 (1991).

8) S. Berger and B. W. K. Diehl, *Magn. Reson. Chem.*, **24**, 1073 (1986).

9) K. Thomas and D. Jerchel, *Angew. Chem.*, **70**, 719 (1958).

10) R. J. Cushley, D. Naugler, and C. Oritz, *Can. J. Chem.*, **53**, 3419 (1975).

11) For pyridines: $^2\Delta = -2.14\,\delta_C + 390$, $r = 0.913$, S. D. = 5 ppb; for *N*-oxides: $^2\Delta = -2.21\,\delta_C + 402$, $r = 0.867$, S. D. = 7 ppb.

12) H. Günther, H. Seel, and H. Schmickler, *J. Magn. Reson.*, **28**, 145 (1977).