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Deuterium Isotope Effects on Aromatic Carbon-13 Chemical Shifts. III. One-, Two-, and Three-Bond Isotope Effects on the ^{13}C Chemical Shifts of 3-Substituted Pyridines

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The one-, two-, and three-bond deuterium isotope effects ($^1\Delta$, $^2\Delta$, and $^3\Delta$) on the ^{13}C chemical shifts of 3-substituted pyridines are reported. $^1\Delta$, $^2\Delta$, and $^3\Delta$ are correlated with the ^{13}C chemical shifts of the observed carbons. $^1\Delta$ show a linear correlation with the ^{13}C chemical shifts with a positive slope. On the other hand, $^2\Delta$ and $^3\Delta$ show linear correlations with the negative slopes. They can thus be interpreted in terms of the π-electron density change by the substituent and the electron release effects by carbons one and two bonds apart from deuterium, respectively.

Even though the deuterium isotope effects on the NMR chemical shifts ($^n\Delta$, where n is the number of intervening bonds) have been known for a long time,[1] the true cause for $^n\Delta$ is still unclear. Since experimental data for $^n\Delta$ in π-systems are scarce, it is difficult to discuss them systematically.[2] Especially, only a few studies concerning the $^n\Delta$ of heteroaromatics have been reported.[2,3] Further studies are desired. We have shown that $^1\Delta$ and $^2\Delta$ for substituted benzenes are correlated with the π- and σ-electron densities, respectively.[4] In this study, we chose 3-substituted pyridines and here discuss their $^1\Delta$, $^2\Delta$, and $^3\Delta$. One of the reasons for our selection was that pyridine is an analogue of benzene. Additionally, the interaction between the nitrogen atom and the substituent seems to be small in a 3-substituted pyridine system.[5] It is therefore possible to estimate simply the substituent effect on the isotope shifts. In the present system, $^1\Delta$ were observed at the C_2, C_4, and C_6 positions, and $^2\Delta$ were observed at the C_3 and C_5 positions. The former values enable us to consider the mesomeric effects of the substituent. The latter values enable us to consider the inductive effects. Both $^1\Delta$ and $^2\Delta$ are correlated linearly with the ^{13}C chemical shifts of the observed carbons. The slope of a correlation line for $^1\Delta$ has a positive value. On the other hand, that for $^2\Delta$ is negative. This fact can be explained in terms of the π-electron density changes by the substituents and the electron-release effects due to the α-carbons (D-labelled carbons), respectively. In addition, $^3\Delta$ can be observed on alkyl side-chain carbons; they also show a linear correlation with δ_c. This can be explained in terms of electron release effects due to the β-carbons (*C–C–D).

Experimental

The samples were selected for ten 3-substituted pyridines and the unsubstituted pyridine. The substituents were 3-Me, 3-Et, 3-Bu^n, 3-Cl, 3-NH$_2$, 3-CH$_2$NH$_2$, 3-OH, 3-CH$_2$OH, 3,5-Me$_2$, and 3,5-Cl$_2$. Deuterium-labelled compounds were prepared with base-catalyzed proton–deuteron exchange reactions of the selected pyridines in either D_2O or 5—10 wt% NaOH–D_2O solutions. The starting materials used were commercially available and were used without further purification. The reaction vessels were Pyrex ampoules. A suitable amount of the starting material and a catalyst solution were sealed into an ampoule, and kept at 200—230 °C in an autoclave. H/D exchange reactions occurred at the 2-, 4-, and 6-positions of the pyridines. Therefore, $^1\Delta$ were observed at the C_2, C_4, and C_6 atoms, while $^2\Delta$ were observed at the C_3 and C_5 atoms. Although $^3\Delta$ could be observed on the carbons in the alkyl side chains, the long-range isotope shifts via more than three bonds were not observed on the ring carbons. Pyridine-4-d was prepared by a previously reported method.[6] The hydroxyl and amino hydrogens of the substituents exchanged with those in water, and could not be separately observed on the NMR time scale. Then, labelled substituents such as OD, NHD, or ND$_2$ showed no isotope effect on the ^{13}C chemical shifts. The NMR spectra were measured with a Varian XL-200 FT-NMR spectrometer at 50.3 MHz and a temperature of about 22 °C. The NMR samples were neat for liquid samples. For solid samples, they were dissolved in solvents having high solubility (see Tables 1 and 2). Peak assignments were carried out on the basis of their intensity changes occurring along with H/D exchange reactions, or on

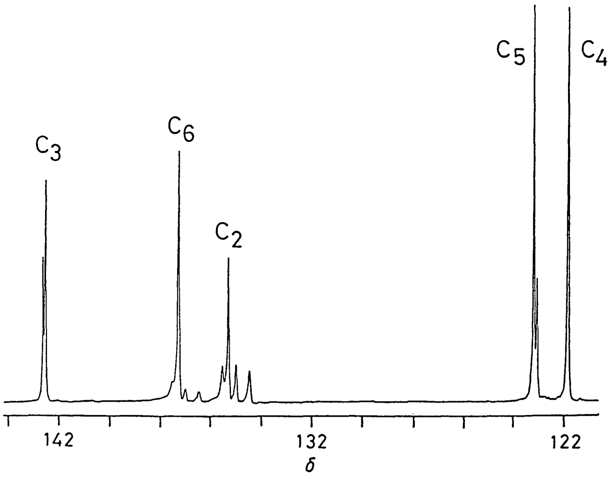


Fig. 1. ^{13}C NMR spectrum of 3-aminopyridine (a mixture of 2-D, 6-D, 2,6-D$_2$, and nondeuterated compounds).

the basis of splittings and/or broadenings by C–D couplings. An example of the ^{13}C spectra is shown in Fig. 1. In this figure two additional triplets at the C_2 and C_6 carbons are assigned to the signals coming from the deuterated species. The extent of deuteration proceeded fast at C_2, and slow at C_6. No triplet could be observed at C_4.

The isotope effects were evaluated from comparisons of the expanded spectra of these mixed species in the same sample tube, as described previously.[7] MNDO MO calculations were carried out using an NEC PC-9801 RA 32-bit personal computer with a "PASOCON MOPAC/386" program, which is based on the MOPAC (V3.1 QCPE No. 516) by Toray Systems Center.

Results and Discussion

All of the observed $^1\Delta$, $^2\Delta$, and $^3\Delta$ are listed in Tables 1, 2, and 3, respectively. The $^1\Delta$ are in a range from 252 to 363 ppb, while $^2\Delta$ are from 45 to 137 ppb. Their magnitudes are similar to those of the substituted benzenes.[4,7] All of the observed $^1\Delta$, $^2\Delta$, and $^3\Delta$ were toward the high field. The signs, however, are neglected in the tables. The substituents introduced to the pyridine ring usually decreased both $^1\Delta$ and $^2\Delta$. Particularly, large changes were observed at the ipso-positions of the substituents. $^3\Delta$ on alkyl side chains varied from 27 to 52 ppb. Correlations between isotope shifts and the chemical shifts have been reported in several articles.[7,8] We thus investigated them in the present system.

Table 1. α-Deuterium Isotope Shifts($^1\Delta$) of Pyridines in ppb[a)]

Substituent	Solvent	Observed carbon		
		C_2	C_4	C_6
—	Neat	351[b)]	296	351[b)]
3-Me	NaOH–D_2O[c)]	351	—[d)]	325
3-Et	Acetone-d_6	355[b)]	—	316
3-Bu^n	Neat	363	—	330
3-NH_2	D_2O	311	—	299
3-OH	CH_3OH	312[b)]	252[b)]	294[b)]
3-CH_2OH	NaOH–D_2O	316[b)]	308[b)]	339[b)]
3-CH_2NH_2	NaOH–D_2O	362	—	327
3-Cl	Neat	328	278	—
3,5-Cl_2	1,4-Dioxane	323	279	323
3,5-Me_2	Acetone-d_6	351[b)]	—	351[b)]

a) Errors are estimated to be within 4 ppb. b) With large errors (8 ppb). c) Neutralized after reaction. d) Not available.

Table 2. β-Deuterium Isotope Shifts($^2\Delta$) of Pyridines in ppb[a)]

Substituent	Solvent	Observed carbon			
		From 4-D		From 2-D or 6-D	
		C_3	C_5	C_3	C_5
—	Neat	106	106	129	129
3-Me	NaOH–D_2O[b)]	—[c)]	—	114	135
3-Et	Acetone-d_6	—	—	116	129
3-Bu^n	Neat	—	—	108	136
3-NH_2	D_2O	—	—	85	134
3-OH	CH_3OH	45	98	70	137
3-CH_2OH	NaOH–D_2O	—	106[d)]	—	136[d)]
3-CH_2NH_2	NaOH–D_2O	78[d)]	100	102	134
3-Cl	Neat	81	97	111	—
3,5-Cl_2	1,4-Dioxane	81	81	106	106
3,5-Me_2	Neat	—	—	110	110

a) Errors are estimated to be within 4 ppb. b) Neutralized after reaction. c) Not available. d) With large error (8 ppb).

Table 3. γ-Deuterium Isotope Shifts ($^3\Delta$) on Alkyl Side-Chain Carbons from 2-D in ppb[a)]

Substituent	Solvent	$^3\Delta$	δ/ppm
3-Me	NaOH–D_2O[b)]	49	18.34[c)]
3,5-Me_2	Acetone-d_6	52	18.19
3-Et	Acetone-d_6	43	26.90
3-Bu^n	Neat	40	32.17
3-CH_2OH	NaOH–D_2O	27	62.21

a) Errors are estimated to be within 3 ppb. b) Neutralized after reaction. c) Ref. 13.

$^1\Delta$ vs. δ_c. A linear correlation is found between the $^1\Delta$ and ^{13}C chemical shifts of the observed carbons, as shown in Fig. 2. $^1\Delta$ in ppb can be expressed as

$$^1\Delta\ (\text{ppb}) = 3.70\ \delta_c(\text{ppm}) - 211 \qquad (1)$$

The slope of the least-square line is positive and similar to that of para-substituted benzenes ($D{-}C_6H_4{-}X$), which was previously reported by Berger and Diehl.[8] For further discussions, the π-electron charges (Δq_π) of pyridine ring carbons were evaluated by an MNDO MO

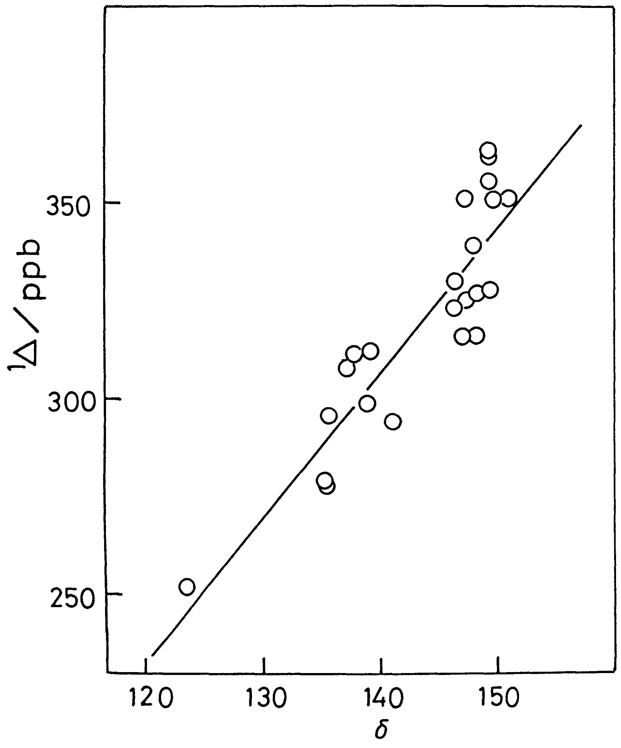


Fig. 2. Correlation between $^1\Delta$ (ordinate in ppb) and δ_c (abscissa in ppm) for 3-substituted pyridines with r=0.895 and a standard deviation of 13 ppb.

calculation. They are listed in Table 4. Plots between Δq_π and $^{1}\Delta$ are shown in Fig. 3. As can be seen, a linear correlation exists. The slope of the line is 642 ppb/electron unit, close to that of substituted benzenes (517 ppb/electron unit).$^{4)}$ Recent theoretical findings have established the isotope shifts' origin as discussed below.$^{2c)}$ The difference in the anharmonicities between the C–H and C–D bonds produce averaged bond-length changes in the NMR time-scale. Therefore, the time-averaged position of the C–D bonding electron should be different from that of the C–H bonding electron. The former will be nearer to the carbon atom than the latter. The D-labelled carbon would therefore be more shielded than the unlabelled carbon. Thus, upfield shifts $^{1}\Delta$ are observed. If we assume that the contribution of anharmonicity in shorter, stronger C–H bonds is small, the anharmonicity change on going from C–H to C–D is small. Therefore, in such a case, shielding changes of the carbon nuclei will be small. Thus, $^{1}\Delta$ will be diminished. We recently obtained several experimental results which strongly support this isotope shifts model. One is a correlation between $^{1}\Delta$ and ν_{CH} in the IR region for monosubstituted methane derivatives.$^{11)}$ The other is a correlation between $^{1}\Delta$ and the C–H bond lengths optimized by MNDO MO calculations for several aromatic compounds.$^{12)}$ From this information, a correlation between Δq_π and $^{1}\Delta$ is found to exist in the present system, and can be interpreted as discussed below. Electron release effects by substituents increase the π-electron densities at the ortho- and para carbons. For a sp^2 carbon, if it has a high π-electron density, its s-character increases. Its C–H bond length thus becomes shorter, and a smaller $^{1}\Delta$ is observed. Comparing $^{1}\Delta$ with the C–H bond lengths optimized by MNDO MO calculations (Table 5), increasing the C–H bond length roughly tends to increased $^{1}\Delta$.

Table 4. Calculated π-Electron Charges(Δq_π) of Pyridines$^{a)}$

Substituent	C_2	C_4	C_6
—	0.091	0.058	0.091
3-Me	0.099	0.064	0.095
3-NH_2	0.041	0.001	0.060
3-OH	0.047	−0.041	0.050
3-Cl	0.103	0.067	0.104
3,5-Me_2	0.103	0.070	0.103

a) Calculated by the MNDO MO method.

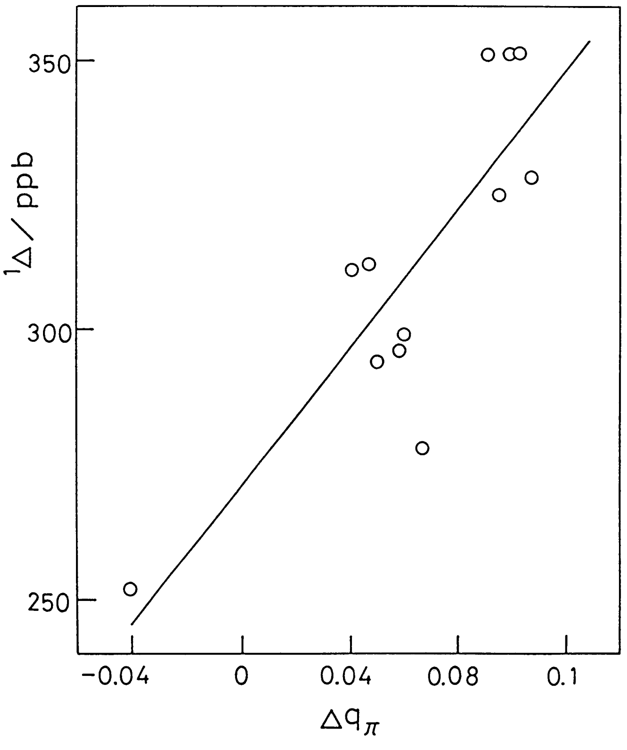
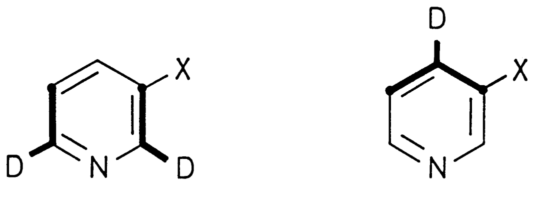


Fig. 3. Correlation between $^{1}\Delta$ and Δq_π. A correlated straight line is expressed as $^{1}\Delta = 642\ \Delta q_\pi + 271$ with $r = 0.842$.

$^{2}\Delta$ vs. δ_{C}. Correlations between the $^{2}\Delta$ and ^{13}C chemical shifts were also investigated. Different $^{2}\Delta$ values were obtained for the same carbons in the isotopomers; one was from the 2-D or 6-D isotopomer, and the other was from the 4-D isotopomer, as shown in Scheme 1. Typical expanded ^{13}C NMR spectra of C_3 and C_5 of the products obtained from an H/D exchange reaction of the 3-pyridinol are shown in Fig. 4. Since the reaction occurred at the 2-, 4-, and 6-positions, $^{2}\Delta$ are observed at C_3 and C_5. In the C_3 signals, the peaks can be assigned from left to right as follows: (a) 2-H, 4-H, (b) 2-H, 4-D, (c) 2-D, 4-H, (d) 2-D, 4-D isotopomers. From signal b, $^{2}\Delta$ was determined to be 45 ppb, and from signal c, 70 ppb. The value from signal d is consistent with the sum of 45 and 70 ppb. In each isotopomer, two kinds of $^{2}\Delta$ were differentiated as follows: $^{2}\Delta$ from 2-D or 6-D is always larger than that from 4-D for the isotopomers.

Table 5. Optimized C–H Bond Lengths of 3-Substituted Pyridines by the MNDO MO Method in Å

Substituent	C_2–H_2	C_4–H_4	C_6–H_6
—	1.095	1.090	1.095
3-Me	1.096	1.091	1.095
3-NH_2	1.096	1.091	1.094
3-OH	1.095	1.090	1.093
3-Cl	1.095	1.090	1.095
3,5-Me_2	1.096	1.092	1.096



2-D , 6-D 4-D

Scheme 1.

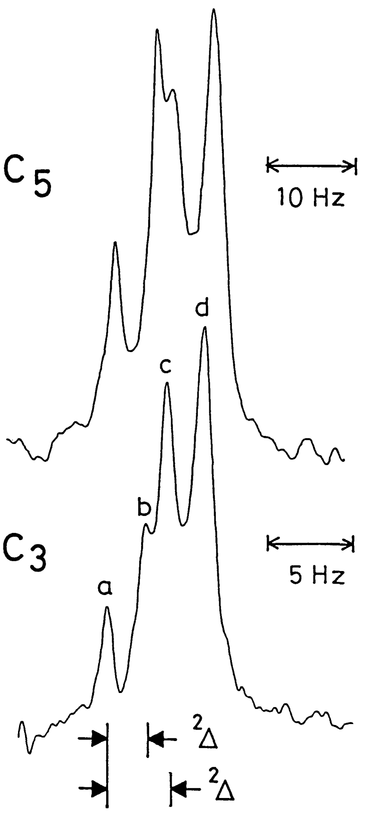


Fig. 4. ^{13}C NMR spectra of C_3 and C_5 of the products obtained from an H/D exchange reaction of 3-pyridinol. See text.

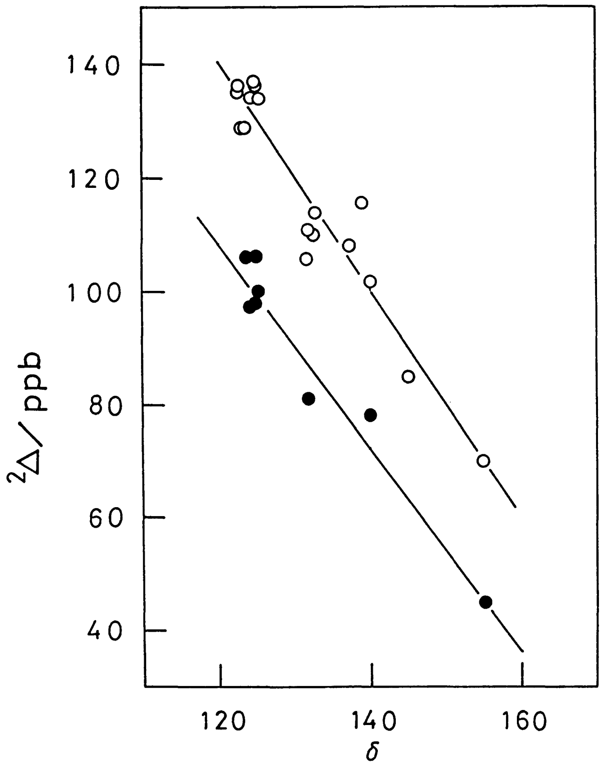


Fig. 5. Correlations between $^2\Delta$ (ordinate in ppb) and δ_C (abscissa in ppm) for 3-substituted pyridines. The white circles are for the 2-D or 6-D isotopomers. The black filled circles are for the 4-D isotopomers.

Since the difference between the two values is nearly constant, two good linear correlations between the $^2\Delta$ and ^{13}C chemical shifts of the observed carbons are obtained (Fig. 5). The two correlation lines have almost a parallel relationship with each other, and their slopes are very close to that of the substituted phenols.[7] These facts suggest that $^2\Delta$ can be explained in terms of electron release effects from the α-carbons (deuterium-labelled carbons).

It is well known that there are linear correlations between the electron densities and the NMR chemical shifts. We therefore evaluated the electron densities on $^2\Delta$-observed carbons by MNDO MO calculations. The calculated net atomic charges are given in Table 6. As shown in Fig. 6, plots between $^2\Delta$ and the net atomic charges (Δq_t) gave two parallel linear correlations. In our previous report, which is concerned with substituted benzenes, we proposed that there is a linear correlation between the $^2\Delta$ and σ-electron charges (Δq_σ).[4] In the present system, however, there are two better correlations between $^2\Delta$ and the total electron charges ($\Delta q_t = \Delta q_\sigma + \Delta q_\pi$) than $^2\Delta$ and Δq_σ, as shown in Fig. 6. The mean proportional coefficient of the two correlated lines is −372 ppb per unit charge. That for substituted benzenes is −355 ppb, which is calculated only for the ipso- and meta-carbons from previously reported data.[4] The present system is therefore similar to the substituted benzenes regarding the behavior of $^2\Delta$ and the charge densities.

In our previous report, we proposed a mechanism to explain $^2\Delta$.[4] The shielding of a D-labelled carbon, which directly reflects $^1\Delta$, is inductively transmitted to its adjacent carbon, whose $^2\Delta$ is dependent upon its net atomic charge (Δq_t) as shown in Fig. 6. However, $^2\Delta$ are not apparently correlated with $^1\Delta$.

As shown in Fig. 6, the almost constant difference between the two parallel correlated lines can be considered to be a part of $^2\Delta$ which is independent of the substituent. Therefore, $^2\Delta$ will be separated into two. One component is dependent on the substitutent and the other is independent of the substituent. The difference

Table 6. Calculated Electron Charges Δq_t (Δq_σ) of Pyridines[a)]

Substituent	C_3	C_5
—	−0.124	−0.124
	(−0.081	−0.081)
3-Me	−0.162	−0.128
	(−0.102	−0.081)
3-NH_2	−0.019	−0.098
	(0.003	−0.077)
3-OH	0.047	−0.084
	(0.050	−0.071)
3-Cl	−0.071	−0.122
	(0.033	−0.081)
3,5-Me_2	−0.166	−0.166
	(−0.103	−0.103)

a) Calculated by the MNDO MO method.

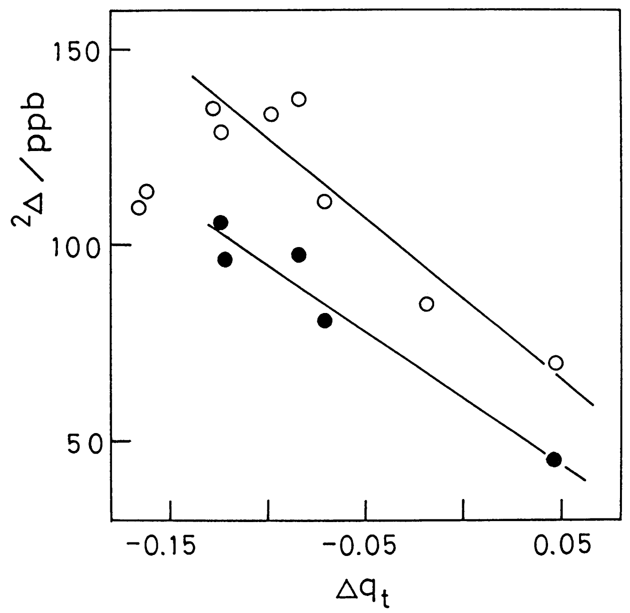


Fig. 6. Correlations between $^2\Delta$ and Δq_t. The white circles are for the 2-D or 6-D isotopomers. The black filled circles are for the 4-D isotopomers. The two correlated straight lines are expressed as $^2\Delta=-405\,\Delta q_t+87$ and $^2\Delta=-339\,\Delta q_t+61$, respectively, except for two points for 2-methyl- (and 3,5-dimethylpyridines.

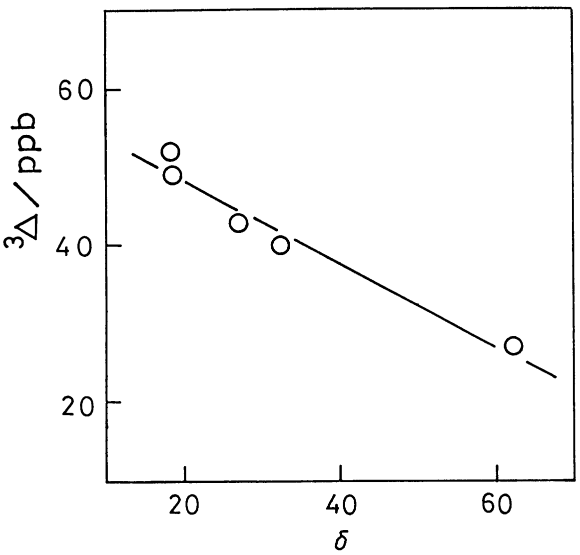
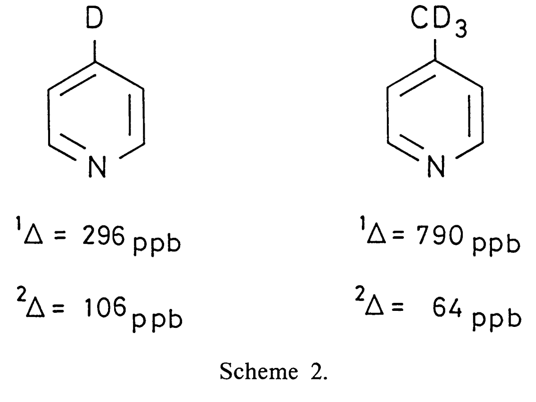


Fig. 7. Correlation between $^3\Delta$ (ordinate in ppb) on the alkyl side-chain carbons and δ_c (abscissa in ppm) for 3-substituted pyridines with r=0.980 and the standard deviation of 2.2 ppb.

mentioned before reflects the latter component. Therefore, $^2\Delta$ from 2-D or 6-D is always larger than that from 4-D for carbons in the isotopomers. In a sense, $^1\Delta$ of the D-labelled carbon will be transmitted to the adjacent $^2\Delta$-observed carbon. Then, $^2\Delta$ would be expected to reflect $^1\Delta$. This shows that $^1\Delta$ induced by 2-D or 6-D are always larger than $^1\Delta$ induced by 4-D for carbons in the isotopomers. These appear exactly in Table 1. However, $^2\Delta$ are strongly dependent upon the electron densities in the observed carbons.

It is considered that the magnitude of electron release effect from D-labelled carbon is controlled by the electron densities on the $^2\Delta$-observed carbon. A comparison of the data between the pyridine-4-*d* and the 4-(methyl-d_3)pyridine[10)] (Scheme 2) is also of interest in that two compounds with very large $^1\Delta$ and small $^1\Delta$ give almost similar $^2\Delta$. The transmitting route of the former case is C(sp^2)-C(sp^2); the latter one is C(sp^3)-C(sp^2). Thus, for $^2\Delta$, the transmitting route of the shielding change of the D-labelled carbon may play an important role. For $^2\Delta$ in the present system, however, all routes are similar in C(sp^2)-C(sp^2). Therefore, $^2\Delta$ will be mainly dominated by the electron densities in the $^2\Delta$-observed carbon.



Scheme 2.

$^3\Delta$ vs. δ_c. $^3\Delta$ on the ring carbons could not be observed. They can therefore be considered to be negligibly small. In contrast, $^3\Delta$ on the alkyl side-chain carbons could be observed, as shown in Table 3. Plots of $^3\Delta$ on the alkyl side-chain carbons and δ_c of the observed carbons give a linear correlation, such as in the cases of $^2\Delta$, as shown in Fig. 7. Since the least-square line has a negative slope, we can propose that $^3\Delta$ originates from the transmitted shielding change of the β-carbon ($^2\Delta$-observed carbon). That is to say, $^3\Delta$ is generated by an electron-release effect from the β-carbon. This mechanism is similar to that of $^2\Delta$.

Conclusion

$^1\Delta$ observed on the pyridine ring carbons are dependent upon the π-electron density changes originating from the substituents on the observed carbons. $^2\Delta$ arise as a result of transmitted shielding changes of the α-carbons. The transmitted shielding changes are controlled by the electron density changes in the observed carbons. $^3\Delta$ is generated by a mechanism similar to that for $^2\Delta$.

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