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39. Kazuo Tori and Masaru Ogata : Pyridazines. IX.*1 Proton Magnetic Resonance Studies of Pyridazine, Pyrazine, and Substituted Pyridazines.

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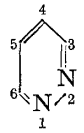
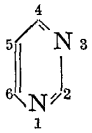
Much interest has been shown in the chemistry of pyridazines in recent years.[1] In previous papers of this series, we have also reported chemical and physical investigations of pyridazine N-oxides[2,3] and cinnoline N-oxides.*1,[4] Chemically, pyridazine (I) is known to undergo nucleophylic substitutions and to resist electrophylic attacks.[1]



I



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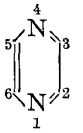

III

However, little is known of the physical properties of pyridazine, such as proton magnetic resonance, which is believed to give much information about this heterocyclic system. While pyrimidine (II) has already been studied in detail by this technique,[5,6] on the spectra of pyridazine only two data have been published.[7,8]

Proton magnetic resonance studies of several simple heteroaromatic compounds and their derivatives have been made by many workers to obtain complete sets of their proton magnetic resonance parameters,[9,10] or to reveal substituent effects.[5,11~13] Since spectra of simple heteroaromatic molecules exhibit rather simple signal patterns owing to their symmetrical structures in many cases, it is not easy to obtain complete sets of their proton magnetic resonance parameters. In order to make a complete analysis of such molecules as pyrimidine[5] and furan,[14] Reddy, *et al.* studied spectral patterns of C^{13}-satellites (in natural isotopic abundance) which can be analyzed by the first order theory, and succeeded in computing the normal spectrum of furan using the parameters obtained from the C^{13}-satellites.

Recently, a few efforts to correlate the carbon-hydrogen spin coupling constant $J_{C^{13}-H}$ to the τ-value have been done.[5,15,16] Matsuura and Goto[17] have attempted to correlate

*1 Part VIII. M. Ogata, H. Kano, K. Tori : This Bulletin, **11**, 1527 (1963).

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1) For example, R. C. Elderfield : "Heterocyclic Compounds," **VI**, 101 (1957), John Wiley & Sons, Inc., New York; E. H. Rodd : "Chemistry of Carbon Compounds," **IV-B**, 1201 (1959), Elsevier Publishing Co., New York.
2) M. Ogata, H. Kano : This Bulletin, **11**, 29, 35 (1963); H. Watanabe, M. Ogata, H. Kano : *Ibid.*, **11**, 39 (1963).
3) K. Tori, M. Ogata, H. Kano : *Ibid.*, **11**, 235 (1963).
4) M. Ogata, H. Kano, K. Tori : *Ibid.*, **10**, 1123 (1962); K. Tori, M. Ogata, H. Kano : *Ibid.*, **11**, 681 (1963).
5) G. S. Reddy, R. T. Hobgood, Jr., J. H. Goldstein : J. Am. Chem. Soc., **84**, 336 (1962).
6) W. Seiffert, H. Zimmerman, G. Scheibe : Angew. Chem., **74**, 249 (1962).
7) Y. Kawazoe, S. Natsume : Yakugaku Zasshi, **83**, 523 (1963).
8) T. Isobe : Bull. Chem. Research Inst. of Non-aqueous Solutions Tohoku Univ., **9**, 115 (1960).
9) For a review, see J. A. Pople, W. G. Schneider, H. J. Bernstein : "High-resolution Nuclear Magnetic Resonance," 266 (1959). McGraw-Hill Book Co., Inc., New York.
10) D. M. Grant, R. C. Hirst, H. S. Gutowsky : J. Chem. Phys. **38**, 470 (1963), and references cited therein.
11) G. S. Reddy, J. H. Goldstein : J. Am. Chem. Soc., **83**, 5020 (1961); S. Gronowitz, G. Sörlin, B. Gestblom, R. A. Hoffman : Arkiv Kemi, **19**, 483 (1962), and references cited therein.
12) G. S. Reddy, J. H. Goldstein : J. Phys. Chem., **65**, 1539 (1961).
13) S. Matsuura, T. Goto : J. Chem. Soc., **1963**, 1773.
14) G. S. Reddy, J. H. Goldstein : J. Am. Chem. Soc., **84**, 583 (1962).
15) N. A. Matwiyoff, R. S. Drago : J. Chem. Phys., **38**, 2583 (1963).
16) G. S. Reddy, J. H. Goldstein : *Ibid.*, **38**, 2736 (1963).

the *ortho* proton spin coupling constant J_{ortho} to the mean τ-value of the participating ring protons in heteroaromatic systems. On the other hand, it has been recognized that there is a proportional relationship between local π-electron charge densities on carbon atoms in aromatic molecules and chemical shifts of the corresponding ring protons if other factors contributing to the chemical shifts can be corrected.[6,18~22] Applicability of this relationship to nitrogen-containing heteroaromatic molecules has been discussed[22] in connection with the paramagnetic anisotropy effect arising from the n-π^* transition of the lone-pair electrons of the nitrogen atom.[23,24]

This paper deals with the proton magnetic resonance studies of pyridazine and its derivatives together with the spectrum of pyrazine (III) for comparison. Most of the spectra of these compounds were analyzable by the usual treatments.[25] However, in order to make complete analyses of the spectra of pyridazine and pyrazine, we had to study also their C^{13}-H spectra (in natural abundance) in the liquid state.

First, we discuss chemical shifts and coupling constants of the three diazine molecules. Next, substituent effects on chemical shifts of ring protons are described in comparison with other aromatic systems. Finally, we discuss the relationship of π-electron densities to the chemical shifts of the diazine molecules, taking account of the magnetic anisotropy of the nitrogen atoms.

Experimental

All the spectra were taken with a Varian model A-60 analytical NMR spectrometer system. Calibration of the spectrometer was checked by using the signal peaks of pure *p*-anisaldehyde (4% solution in carbon tetrachloride).[26] The spectra were observed on about 3 and 10% solutions (w/v) in $CDCl_3$ containing about 1% tetramethylsilane as an internal reference at room temperature. Effects of concentrations on the chemical shifts were ascertained about the ring protons. For studies of the electronic charge distributions, 5 mol. % solutions in cyclohexane were used.[6,19,22] The C^{13}-H spectra, except for pyrazine, were taken on the pure liquids, because these spectra were examined in the isotropically unenriched substances. In the case of pyrazine, a small quantity of $CDCl_3$ was added to dissolve its crystals. These spectra were used only as a source of values of coupling constants, which are believed to be insensitive to the medium.[27] All the chemical shifts are expressed in τ-values, and the coupling constants are in c.p.s. Accuracy limits are about $\pm 0.02\,\tau$ in chemical shifts, about ± 0.3 c.p.s. in J_{H-H} and about ± 0.5 c.p.s. in $J_{C^{13}-H}$.

All the pyridazine derivatives examined were synthesized by methods already reported.[2,28] Pyrazine (L. Light Co., Ltd.) and pyrimidine (Nutritional Biochemicals Corp.) were obtained commercially and used without further purification.

17) S. Matsuura, T. Goto : Presented at " the 2nd Symposium on Nuclear Magnetic Resonance (Japan)," in Tokyo, November (1962).
18) G. Fraenkel, R. E. Carter, A. McLachlan, J. H. Richards : J. Am. Chem. Soc., **82**, 5846 (1960).
19) H. Spiesecke, W. G. Schneider : Tetrahedron Letters, No. 14, 468 (1961).
20) A. Veillard, B. Pullman : Compt. rend., **253**, 2418 (1961).
21) B. P. Daily, A. Gawer, W. C. Neikam : Discussions Faraday Soc., **34**, 18 (1962).
22) T. Schaefer, W. G. Schneider : Can J. Chem., **41**, 966 (1963).
23) J. D. Baldeschwieler, E. W. Randall : Proc. Chem. Soc., **1961**, 303.
24) S. Matsuoka, H. Hattori, H. Suzuki, N. Nakagawa : presented at " Symposium on Electronic State in Molecule (Japan)", in Tokyo, October (1961).
25) For a review, see J. A. Pople, W. G. Schneider, H. J. Bernstein : " High-resolution Nuclear Magnetic Resonance " Chap. 6 (1959), McGraw-Hill Book Co., Inc., New York.
26) G. V. D. Tiers, D. R. Hotchkiss : J. Phys., Chem., **66**, 650 (1962).
27) N. Muller, D. E. Pritchard : J. Chem. Phys., **31**, 768, 1471 (1959).
28) A. Oppenheim : Ber., **34**, 4227 (1901); O. Poppenberg : *Ibid.*, **34**, 3265 (1901); S. Gabriel : *Ibid.*, **42**, 655 (1909); W. G. Overend, L. F. Wiggins : J. Chem. Soc., **1947**, 239; J. Druey, Kd. Meier, K. Eichenberger : Helv. Chim. Acta, **37**, 121 (1954); R. H. Mizzoni, P. E. Spoerri : J. Am. Chem. Soc., **76**, 2201 (1954); N. Takabayashi : This Bulletin, **5**, 229 (1957).

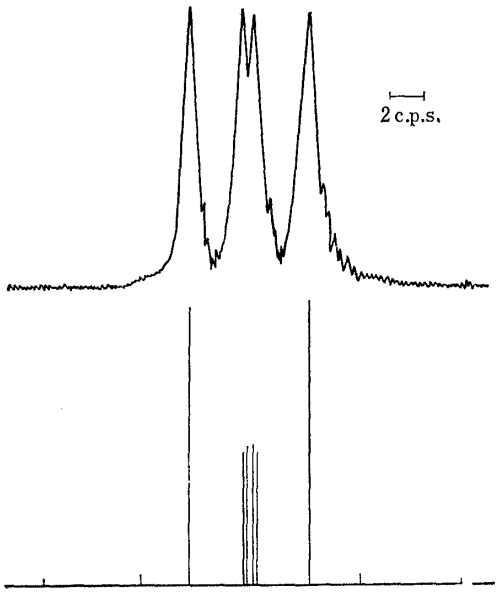

Fig. 1. Proton Magnetic Resonance Spectrum of Pyridazine in 10% Deuterochloroform at 60 Mc.p.s.

4,5-protons: The lower part is the calculated spectrum.

Results

The spectrum of pyridazine consists of two symmetrical quartets of an A_2X_2 type,[7,8,25] the high-field part of which is shown in Fig. 1. The spectra of 3-methyl- and 4-methylpyridazine (Figs. 2 and 3) as well as 3-chloropyridazine are somewhat more complex. They belong to ABX systems in which $J_{AB} \gg \tau_A - \tau_B \approx (J_{AX} - J_{BX})/2$.[29] However, the spectrum of 3-methoxypyridazine displays peaks of a normal ABX system,[25] which is easily analyzable. As expected, Figs. 1, 2, and 3 indicate that the higher part of the two quartets in the spectrum of pyridazine is arising from protons H_4 and H_5, and that the protons H_4 and H_5, like the protons H_3 and H_6, are magnetically equivalent. The signal patterns of pyridazine prove that J_{meta} and J_{ortho} are unequal in an A_2X_2 system.[14] To obtain a complete set of proton magnetic resonance parameters for pyridazine, we also examined

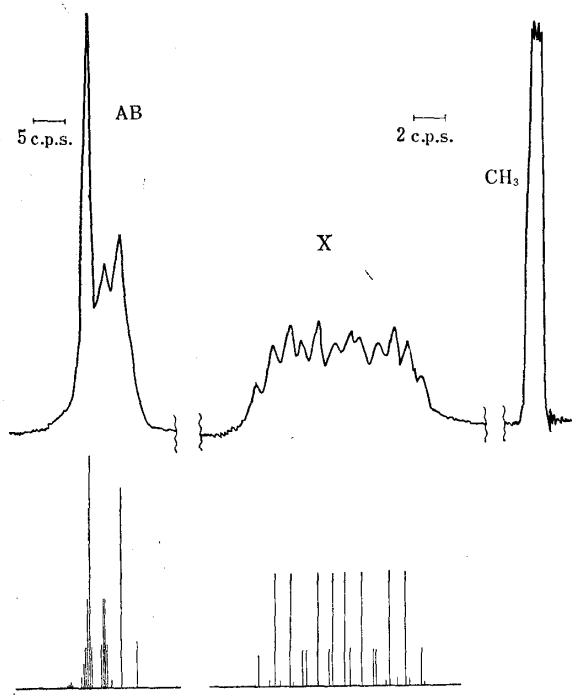

Fig. 2. Proton Magnetic Resonance Spectrum of 3-Methylpyridazine in 10% Deuterochloroform at 60 Mc.p.s.

AB: 4,5-protons.
X : 6-proton.
AB, X and CH_3 are not on the same scale.
The lower part is the calculated spectrum.

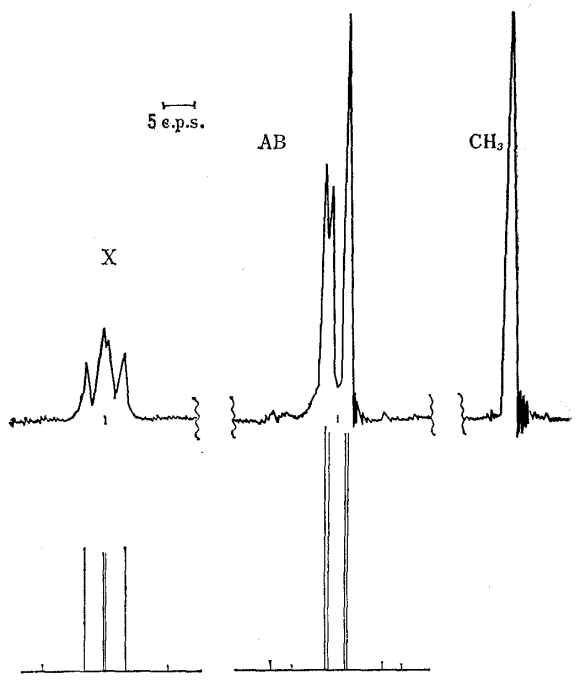

Fig. 3. Proton Magnetic Resonance Spectrum of 4-Methylpyridazine in 10% Deuterochloroform at 60 Mc.p.s.

AB: 3,6-protons.
X : 5-proton.
AB, X and CH_3 are not on the same scale.
The lower part is the calculated spectrum.

29) J. D. Roberts: "An Introduction to the Analysis of Spin-Spin Splitting in High-Resolution Nuclear Magnetic Resonance Spectrum," 77 (1961). W. A. Benjamin Inc., New York.

the C^{13}-satellites (in natural abundance) in the liquid state.[5,14] Fig. 4 shows the C^{13}-H spectra of pyridazine obtained; A is the low-field half of the H_3 and H_6 doublet and B is the high-field half of the H_4 and H_5 doublet. These spectra were easily analyzed by first order treatments. The coupling constants determined by the C^{13}-satellites are listed in Table I, together with the values of the chemical shifts obtained from the normal spectrum of pyridazine. The calculated frequencies and relative intensities based upon the parameters in Table I for pyridazine, the high-field part of which is shown in Fig. 1, are in good agreement with the data of the observed spectrum. This result is essentially different from that reached by Isobe,[8] who directly analyzed the normal spectrum as an A_2B_2 system.*3

Table I. Proton Magnetic Resonance Spectral Parameters for Diazines[a]
Chemical Shift (τ), Coupling Constant, J (c.p.s.)

Parameter	Pyridazine	Pyrazine	Pyrimidine[b]
τ_2	—	1.37	0.74
τ_3	0.76	1.37	—
τ_4	2.46	—	1.22
τ_5	2.46	1.37	2.64
τ_6	0.76	1.37	1.22
$J_{2,3}$	—	1.8	—
$J_{2,4}$	—	—	~0
$J_{2,5}$	—	1.8	1.5
$J_{2,6}$	—	~0.5	~0
$J_{3,4}$	4.9	—	—
$J_{3,5}$	2.0	~0.5	—
$J_{3,6}$	3.5	1.8	—
$J_{4,5}$	8.4	—	5.0
$J_{4,6}$	2.0	—	2.5
$J_{5,6}$	4.9	1.8	5.0
$J_{C^{13}-H_2}$	—	183	206
$J_{C^{13}-H_3}$	181.5	183	—
$J_{C^{13}-H_4}$	168.5	—	181.8
$J_{C^{13}-H_5}$	168.5	183	168
$J_{C^{13}-H_6}$	181.5	183	181.8

a) on 3% solution (w/v) in deuterochloroform, at room temperature.
b) ref. (5).

The spectrum of pyrazine which consists of a singlet peak gives no information about coupling constants. Therefore, the C^{13}-satellites of pyrazine in the liquid form were examined also. As shown in Fig. 5, the C^{13}-satellites consists of two broad triplets, which show that the J_{ortho} value and one of the J_{cross} values are very close. We assumed that the $J_{2,6}$ ($J_{3,5}$) is smaller than the $J_{2,5}$ ($J_{3,6}$), referring to the cases of pyridazine and pyrimidine.[5] The proton magnetic resonance parameters of pyrazine thus obtained are listed in Table I, in which those of pyrimidine reported by Reddy, *et al.*[5] are cited also for the purpose of comparison.*4

Since the methyl signal displays no splitting in the spectrum of 3-methylpyridazine, the coupling constants between the 3-methyl- and ring protons are presumably very small. This spectrum was analyzed as an ABX system by using the data obtained

*3 Isobe's result is as follows; $J_{3,4}=5.1$, $J_{4,5}=5.0$, $J_{3,5}=2.1$ and $J_{3,6}=1.3$ c.p.s.[8]
*4 All the coupling constants in heterocyclic compounds such as furan, pyrrole, thiophene, picoline and quinoline have proved to be of same sign.[30]
30) R. Freeman, D. H. Whiffen : Mol. Phys., **4**, 321 (1961); A. D. Cohen, K. A. McLauchlan : Discussions Faraday Soc., **34**, 132 (1962); B. D. N. Rao, J. D. Baldeschwieler : J. Chem. Phys., **37**, 2473 (1962); W. G. Paterson, G. Bigam : Can. J. Chem., **41**, 1841 (1963).

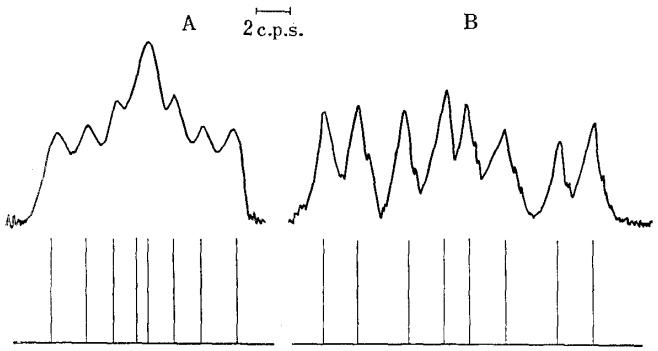

Fig. 4. C^{13}-H Spectra of Pyridazine

A : low-field part of 3,6-protons.
B : high-field part of 4,5-protons.
The lower parts are the calculated spectra.

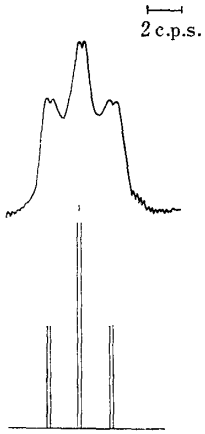

Fig. 5. C^{13}-H Spectrum of Pyrazine (low-field part)

The lower part is the calculated spectrum.

from the C^{13}-H spectra of the pure liquid. The peaks in the observed spectrum are very adequately reproduced in the calculated spectrum, as shown in Fig. 2. The proton magnetic resonance parameters of 3-methylpyridazine thus obtained are listed in Table II. Since the methyl signal in the spectrum of 4-methylpyridazine is split into a quartet as shown in Fig. 3, this spectrum was analyzed as an $ABXY_3$ system, where Y is the

TABLE II. Proton Magnetic Resonance Spectral Parameters for Pyridazine Derivatives.[a] Chemical Shift (τ), Coupling Constant, J (c.p.s.)

Substituent	Parameter											
	τ_3	τ_4	τ_5	τ_6	τ_{CH_3}	τ_{OCH_3}	$J_{3,4}$	$J_{3,5}$	$J_{3,6}$	$J_{4,6}$	$J_{4,5}$	$J_{5,6}$
None (I)	0.76 (0.76)	2.45 (2.46)	2.45 (2.46)	0.76 (0.76)	—	—	4.9	2.0	3.5	2.0	8.4	4.9
3-CH_3 (IV)	—	2.62 (2.65)	2.60 (2.63)	0.94 (0.95)	7.26 (7.26)	—	~0[b]	~0[b]	~0[b]	1.8	8.6	4.7
4-CH_3 (V)	0.92 (0.92)	—	2.67 (2.69)	0.96 (0.96)	7.60 (7.60)	—	~0.5[b]	2.2	3.0	~0[b]	1.0[b]	5.0
3-Cl (VI)	—	2.41 (2.44)	2.45 (2.48)	0.83 (0.83)	—	—	—	—	—	1.8	8.8	4.7
3-OCH_3 (VII)	—	2.98 (2.99)	2.59 (2.60)	1.12 (1.13)	—	5.92 (5.92)	—	—	—	1.7	9.0	4.5
3-CH_3, 6-Cl (VIII)	—	2.65 (2.66)	2.57 (2.58)	—	7.29 (7.29)	—	~0[b]	~0[b]	—	—	8.8	—
3-Cl, 4-CH_3 (IX)	—	—	2.58 (2.61)	1.01 (1.01)	7.54 (7.54)	—	—	—	—	~0[b]	1.0[b]	4.9
4-CH_3, 6-Cl (X)	1.01 (1.01)	—	2.60 (2.60)	—	7.59 (7.59)	—	~0.5[b]	2.2	—	—	1.0[b]	—
3-CH_3, 6-OCH_3 (XI)	—	2.74 (2.78)	3.10 (3.11)	—	7.38 (7.38)	5.88 (5.88)	~0[b]	~0[b]	—	—	8.8	—
3-Cl, 6-Cl (XII)	—	2.43 (2.48)	2.43 (2.48)	—	—	—	—	—	—	—	?	—
3-OCH_3, 6-Cl (XIII)	—	3.01 (3.02)	2.62 (2.63)	—	—	5.99 (5.99)	—	—	—	—	9.0	—
3-Cl, 4-CH_3, 6-Cl (XIV)	—	—	2.55 (2.57)	—	7.55 (7.55)	—	—	—	—	—	0.9[b]	—
3-CH_3, 5-Cl, 6-OCH_3 (XV)	—	2.67 (2.70)	—	—	7.40 (7.40)	5.82 (5.82)	~0[b]	—	—	—	—	—

a) on 10% (w/v) solution in deuterochloroform at room temperature. Values in parentheses are chemical shifts measured on 3% (w/v) solutions.
b) CH_3-H coupling.

methyl proton. It is difficult to interpret the C^{13}-satellites of the ring protons of 4-methylpyridazine because they are more complex owing to the couplings with the methyl protons. Assuming that $J_{4-CH_3,5}(J_{XY})=1.0$ c.p.s., $J_{4-CH_3,3}(J_{AY})=0.5$ c.p.s. and $J_{4-CH_3,6}(J_{BY})=0$ c.p.s., we computed the spectrum of 4-methylpyridazine to obtain a set of parameters of this molecule (in Table II), until the calculated and the observed spectra coincided. The spectrum of 3-chloropyridazine was analyzed in the same way used for 3-methylpyridazine. The spectra of other pyridazine derivatives show well-separated first order patterns. Table II summerizes their proton magnetic resonance parameters.

In the spectra of pyridazine and its derivatives, a small broadening is discernible in peaks arising from the protons H_3 and H_6, each of which is adjacent to a nitrogen atom. These broadenings can result from the spin coupling and the nuclear quadrupole relaxation effects of the N^{14} nucleus.[5,23] The values of chemical shifts in Table II show the expected trends with various substitutions as discussed later. The coupling constants vary relatively little from compound to compound. In this fact, we can amply justify the coupling constants determined for the pyridazine molecule.[14]

Discussion

Chemical Shifts and Coupling Constants

The chemical shifts of ring protons of diazine molecules are not easily compared directly to one another because the interpretation of chemical shifts may be affected by the location of nitrogen atoms in each diazine molecule. However, the chemical shift of the proton attached to a ring carbon atom adjacent to a nitrogen atom usually has a lower value in accordance with the expectation that this carbon has a lower electron density. This point will be discussed later.

In regards to the coupling constants, it is interesting to note that the $J_{3,6}$ has a fairly large value in pyridazine, which is even larger than that of the $J_{3,5}(J_{4,6})$. In pyrimidine, the $J_{2,5}$ also has a larger value than the $J_{2,4}(J_{2,6})$, even though the former is a J_{para}. A similar fact has been found in the $J_{2,4}$ of five-membered heteroaromatic ring systems such as furan[14] and pyrrole.[11] The magnitudes of the $J_{3,4}$ and the $J_{3,5}$ in pyridazine are comparable to those of the $J_{4,5}$ and the $J_{4,6}$ in pyrimidine, respectively. In pyrazine, the $J_{2,3}(J_{5,6})$, though it is a J_{ortho}, surprisingly has a small value. Further, it should be noted that 4-methyl protons in 4-methylpyridazine are appreciably coupled to the protons H_5 and H_3, whereas 3-methyl protons in 3-methylpyridazine are not coupled to other ring protons. A similar fact to the former has frequently been observed when a methyl group is attached to a carbon having a higher electron density in heteroaromatic molecules.[5,11,12] Electron density appears to be correlated to this coupling.

Recently, strong correlations have been found between electronegativities of various substituents and proton coupling constants in vinyl groups[31] and in benzene derivatives.[32] Matsuura and Goto[13] suggested that the very small value of the J_{ortho} in pteridine (1.7 c.p.s.) would be due to the electronegativity of nitrogen atoms. Among J's in the diazine molecules, the $J_{2,3}$ in pyrazine is such a case. On the other hand, the ring size of aromatic compounds was pointed out to affect their J_{ortho} because the five-membered aromatic heterocycles such as furan, selenophene and thiophene, have a smaller J_{ortho}.[8] Similar relation has been shown in the J_{cis} of cycloalkenes.[33] Therefore, at

31) For example, see T. Schaefer: Can. J. Chem., **40**, 1 (1962).
32) P. F. Cox: J. Am. Chem. Soc., **85**, 380 (1963).
33) O. L. Chapman: *Ibid.*, **85**, 2014 (1963); G. V. Smith, H. Kriloff: *Ibid.*, **85**, 2016 (1963); P. Laszlo, P. von R. Schleyer: *Ibid.*, **85**, 2017 (1963); K. Tori, R. Muneyuki, H. Tanida: Can. J. Chem., **41**, 3142 (1963).

present, it is difficult to correlate directly J_{ortho} with electronegativities or chemical shifts in heteroaromatic systems. However, it seems plausible that besides the electron density, J's in aromatic systems reflect the *s*-character of ring carbons, which varies with the ring size and the electronegativity of the adjacent atom.[34]

It is well known that $J_{C^{13}-H}$ is correlated with the percentage *s*-character of the carbon atomic orbital participating in the C-H bond,[27,35] and that it increases when electronegative atoms are bonded to the carbon.[15,27,34,35] In Table I are listed the observed values of $J_{C^{13}-H}$ in the diazine molecules. It is not surprising that $J_{C^{13}-H}$ of carbon atoms bonded to more electronegative nitrogen atoms have larger values than that in benzene (159 c.p.s.).[27] In diazines, very close values were obtained for the $J_{C^{13}-H}$ of the α-position to a nitrogen atom, $J_{C^{13}-H}(\alpha)$, from compound to compound. This is also the case with $J_{C^{13}-H}(\beta)$. Thus, the magnitude of $J_{C^{13}-H}$ for diazine molecule is in the order, $J_{C^{13}-H}(\beta)<J_{C^{13}-H}(\alpha)<J_{C^{13}-H}(\alpha,\alpha')$, where α,α' shows the α-position to both nitrogen atoms in pyrimidine. This fact implies that the percentage *s*-character of the carbon atomic orbital of diazines increases in each position, particularly in the α,α'-position. This increasing in the *s*-character can be due to the presence of two nitrogen atoms in diazine molecules. Similar increases have been observed in benzene derivatives having some strong electron-withdrawing substituents such as 1,3,5-trinitrobenzene.[36] Although the above order of the $J_{C^{13}-H}$ corresponds to the down-field trend in the chemical shifts of ring protons of the diazine molecules, $\tau_H(\beta)>\tau_H(\alpha)>\tau_H(\alpha,\alpha')$, as can be seen from Table I, all attempts to find an exact correlation between them were unsatisfactory. Furthermore, even the methyl shifts in the diazines were not found to be linear against the $J_{C^{13}-H}$ in the corresponding positions. Those discrepancies can not be explained without assuming the magnetic anisotropy effects arising from the nitrogen atoms.[23,24] A further discussion of this point will be given later. An attempt to correlate $J_{C^{13}-H}$ with J_{ortho} in aromatic molecules is now in progress.[37]

Substituent Effects on the Chemical Shifts in Pyridazine

In Table III are summerized the effects produced by a single substituent of various kinds upon the individual ring proton shift of pyridazines. The additivity of the substituent effect is easily found out from Table III. As expected from data on other aromatic systems,[11~13] a methyl or a chlorine makes a little effects on ring proton shifts, and a methoxyl group produces a large upfield shift. These substituent effects may be interpreted as the charge migration from a substituent to the ring or *vice versa* (the mesomeric and/or the inductive effect). A methoxyl group gives a large shift on the protons in *ortho*- and *para*-positions, but a little effects on the protons in *meta*-positions. This fact indicates that the mesomeric effect is predominant. In contrast, a methyl group gives an almost equal effect on each proton signal, as in the case of methylpyrimidines.[5] It was found that the total effects on all ring proton shifts produced by a single methyl group is about 0.75 p.p.m. in benzene, furan, pyrrole and thiophene, whereas in thiazole and pyrimidine it has a relatively reduced value of about 0.6 p.p.m.[5,11,12] As shown in Table III, the total effect by a methyl group is 0.58 p.p.m. in 4-methylpyridazine and is a somewhat smaller value of 0.50 p.p.m. in 3-methylpyridazine, in which the methyl group is attached to the carbon atom adjacent to the nitrogen atom. As pointed out by Reddy, *et al.*,[5] this difference in the total effect can result from the partial localization of the migration charge from a methyl group on the nitrogen atoms in the ring. Recently, Matsuura and Goto[13] have proposed that the total

34) H. A. Bent : Chem. Rev., **61**, 275 (1961).
35) N. Muller : J. Chem. Phys., **36**, 359 (1962); J. N. Shoolery : *Ibid.*, **31**, 1427 (1959).
36) H. M. Hutton, W. F. Reynolds, T. Schaefer : Can. J. Chem., **40**, 1758 (1962).
37) K. Tori, T. Nakagawa : to be published [presented at "the 3rd Symposium on Nuclear Magnetic Resonance (Japan)", in Osaka, November (1963)].

effect of a methyl group should be evaluated by taking account of the charge localization mentioned above. The total effect of the methyl group in the present case, as calculated by their equation,*[5] is obtained to be 1.08 p.p.m. as the mean value, This value falls in the normal aromatic range.[13]

Table III. Substituent Effects in Pyridazine[a]

Substituent	Compounds to be compared	Position 3	4	5	6	Sum
3-Methyl	IV-I	—	0.17	0.15	0.18	0.50
	VIII-VI	—	0.20	0.16	—	
	XI-VII	—	0.15	0.12	−0.04[b]	
4-Methyl	V-I	0.16	—	0.22	0.20	0.58
	X-VI	0.18	—	0.19	—	
	IX-VI	—	—	0.13	0.18	
	XIV-XII	—	—	0.12	—	
3-Chlor	VI-I	—	−0.04	0.00	0.07	0.03
	XII-VI	—	−0.02	0.02	—	
	VIII-IV	—	−0.03	0.03	0.03[b]	
	IX-V	—	−0.06[b]	−0.09	0.05	
	X-V	—	−0.07	−0.01[b]	0.05	
	XIV-IX	—	−0.03	0.01[b]	—	
	XIV-X	—	0.04[b]	−0.05	—	
	XIII-VII	—	0.04	0.03	0.07[b]	
4-Chlor	XV-XI	−0.06	—	−0.06	0.02[b]	
3-Methoxyl	VII-I	—	0.53	0.14	0.36	1.03
	IX-IV	—	0.50	0.12	0.12[b]	
	XIII-VI	—	0.56	0.21	—	

a) All values are the displacements of the proton shifts in p.p.m. relative to the same position in the unsubstituted ring.
b) shifts of methyl or methoxyl group.

Of incidental interest is the fact that the methyl group attached to the C_4-atoms always appears at a higher field than does the group on the C_3. Moreover, in pyridazines having both a methyl and a methoxyl group, the methyl shift is somewhat large owing to the electron-releasing effect of the methoxyl group. These facts indicate that the methyl shift reflects the electron charge density of the carbon atom to which the methyl group is attached, as in the cases of other aromatic rings, and that the charge density may be large in the order, $C_4 > C_3$, in the pyridazine molecule as expected.

Electronic Distributions in Diazine Molecules

It has frequently been reported that there is a quantitative relationship between the proton chemical shift referred to benzene, δ, and the local "excess" charge, $\Delta\rho$ (located on the carbon atom), in aromatic molecules,

$$\delta = k\Delta\rho \qquad \text{(A)}$$

where the constant k was found empirically to have a value about 10 p.p.m./electron.[6,18~22] Further, Spiesecke and Schneider[19] demonstrated the striking parallelism between the resonance shifts of C^{13} and that of the corresponding proton from the study of $C_5H_5^-$, C_6H_6, and $C_7H_7^+$. Thus, the π-electron distributions obtained from chemical shifts

5* The equation proposed by Matsuura and Goto[13] is as follows :

$$\text{Total effect of methyl group} = \frac{\text{Sum of ring proton shifts} \times \text{Number of ring atoms}}{\text{Number of ring carbon atoms bearing hydrogen atom}} = \sim 1.1 \text{ p.p.m (normal aromatic value)}$$

almost corresponds to those obtained from molecular orbital calculations in many compounds, if other factors contributing to the chemical shifts such as the ring current effect and the solvent effect can be corrected.[19~22] Although the above relationship (A) has been applied to such aromatic systems containing nitrogen atoms as pyridine,[18,21,22] quinoline,[21] isoquinoline,[21] pyrimidine,[6,21] pyridinium cation,[22,38] pyridazine N-oxide[3] and pyrazine N-oxide,[3] it is doubtful whether one can apply the equation (A) directly to heteroaromatic molecules because some factors originating from the heteroatom as adopted by Schug and Deck[39] can affect the ring proton chemical shifts besides the π-electron charge densities on the corresponding carbon atoms. First of all, the paramagnetic anisotropy effect due to the n-π^* transition of the lone-pair electrons of the nitrogen atoms[23,24] is probably of most importance in the present cases.

It is highly possible to assume this anisotropy. For instance, in the spectrum of quinoline[40,43] the signal of the proton H_8, the proton at the *peri*-position to the nitrogen atom, is found at a relatively low-field apart from other signals contrary to the anticipation from a Hückel MO calculation,[41] whereas in the spectrum of isoquinoline[40,43] the signal of proton H_8 is not found at the lower part of the spectrum, as expected.[41] Recently, Matsuoka, *et al.*[24] have estimated the magnitude of this anisotropic effect on the proton H_2 (H_6) in pyridine molecule to be -0.8 p.p.m., having employed its molecular orbitals and its ultraviolet absorption spectral data according to Pople's method.[42] A close value can also be derived from the result described by Schaefer and Schneider.[22] However, we now believe this value to be overestimated.[43]

Table IV. Proton Chemical Shifts and Local π-Electron Densities of Diazine Molecules

Compound	Proton position	Observed shift from benzene,[a] δ (p.p.m.)	Densities derived from signals,[b] $\rho_{exp.}$	Calculated densities from Hückel MO, $\rho_{calc.}$ $k_N=0.5\,\beta$	($k_N=0.4\,\beta$)	Anisotropic effect derived from $\rho_{exp.}$ and $\rho_{calc.}$,[b] δ' (p.p.m.)
Pyridazine	2, 6	-1.80	0.832	0.9230	(0.9392[c])	-0.98
	3, 4	$+0.04$	1.004	0.9534	(0.9628[c])	$+0.44$
Pyrazine	2, 3, 5, 6	-1.20	0.888	0.924[d]		-0.39
Pyrimidine	2	-1.85	0.827	0.842[e]	(0.8751[c])	-0.16
	4, 6	-1.30	0.879	0.873[e]	(0.8983[c])	$+0.06$
	5	$+0.21$	1.020	1.011[e]	(1.0073[c])	$+0.10$

a) in 5 mol. % solution in cyclohexane.
b) see text.
c) ref. (41).
d) M. Mataga, K. Nishimoto: Z. Phys. Chem. N.F., **13**, 140 (1959).
e) ref. (6).

In order to evaluate the local charge distributions in diazine molecules, we obtained their ring proton shift referred to benzene, δ, as given in Table IV, observing their spectra on 5 mol.% solution in cyclohexane.[6,19,22] According to Schaefer and Schneider,[22] the equation (A) with 10.7 p.p.m./electron as a k value was applied to δ to gain the experimental charge densities $\rho_{exp.}$, on each carbon. Here, we consider that the difference in the ring current effect due to the presence of the nitrogen atoms in the

38) I.C. Smith, W.G. Schneider: Can. J. Chem., **39**, 1158 (1961).
39) J.C. Schug, J.C. Deck: J. Chem. Phys., **37**, 2618 (1962).
40) J.A. Pople, W.G. Schneider. H.J. Bernstein: "High-resolution Nuclear Magnetic Resonance," 268 (1959). McGraw-Hill Book Co., New York.
41) H.F. Hameka, A.M. Liquori: Mol. Phys., **1**, 9 (1958).
42) J.A. Pople: Proc. Roy. Soc., **A239**, 541, 550 (1957); J. Chem. Phys., **37**, 53, 60 (1962).
43) M. Yamakawa, K. Tori: to be published [presented at "the 3rd Symposium on Nuclear Magnetic Resonance (Japan)," in Osaka, November (1963)].

ring is negligible.*6 Table Ⅳ also lists the electron densities, $\rho_{calc.}$, calculated by the Hückel MO method. As can be seen from Table Ⅳ, the $\rho_{exp.}$ values are almost consistent with the $\rho_{calc.}$ values without any correction in the case of pyrimidine, as quoted by Seiffert, *et al.*[6] Therefore, the anisotropic effects due to the nitrogen atoms in this molecule are believed to be relatively small. This result is due probably to the mutual cancellization of the effects of each nitrogen atom. The discrepancies are considerably larger in the cases of pyridazine and pyrazine. The signals of the protons H_3 and H_6 in pyridazine and of the protons in pyrazine are found at lower fields than those expected from the Hückel MO calculations. These down-field shifts can be ascribed to the anisotropy effect of the lone-pair electrons of the nitrogen atoms in these molecules, if the correct values were given for the charge densities by the MO calculation. Thus, we tentatively derived the paramagnetic anisotropy effect of the nitrogen atoms in each diazine molecule as a shift value, δ', from the difference between the $\rho_{exp.}$ and the $\rho_{calc.}$. The values of δ' obtained are almost consistent with the values theoretically derived according to the method of Matsuoka, *et al.*[24,43] However, the very large down-field shift of the α-protons of pyridazine can not be explained only as the anisotropic effect.[43] This is not apparent at present.

On the other hand, the MO calculation itself involves several questions to be solved. Recently, Matsuura and Goto showed in connection with their studies of pteridine[13] and purine[24] that a different order can be obtained for π-electron densities when a different calculation method is employed. In nitrogen-containing heteroaromatic molecules, the use of a different value for the parameter, k_N, leads to a different result. Further, in the calculation used for the pyridazine molecule, for example, a possible mutual interaction of the lone-pair electrons of each nitrogen atom was not taken into account. Therefore, it is a difficult problem to estimate electron distributions in aromatic molecules, particularly in heteroaromatic molecules. However, in even heteroaromatic molecules, it is almost certain that the proton magnetic resonance signal gives the order of electron distributions in the ring, as long as we take into account various effects such as the magnetic anisotropy and the ring current effect. More elaborate estimation of the anisotropy effect in many nitrogen-containing heteroaromatic molecules from the calculation according to Matsuoka, *et al.*[24] will be presented in a forthcoming paper.[43]

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Summary

Pyridazine, pyrazine and substituted pyridazines have been studied by proton magnetic resonance spectroscopy. The spectra of pyridazine and pyrazine were analyzed completely with the aid of information obtained from the C^{13}-satellites (in natural isotopic abundance), whereas the spectra of substituted pyridazines were analyzed easily by the usual treatments. The proton magnetic resonance parameters of diazines were discussed in connection with the electronegativity of the nitrogen atoms. Effects of some substituents upon the ring proton shifts of pyridazine were discussed. The total methyl effect on the ring protons of pyridazine (0.54 p.p.m.) falls in the normal aromatic range. Electronic charge distributions in diazine molecules were discussed by comparing the π-electron densities calculated by the Hückel MO method with those obtained from the ring proton chemical shifts. Discrepancies in these electronic densities were ascribed to the possible paramagnetic anisotropy effect arising from the n-π^* transition of the lone-pair electrons of the nitrogen atoms.

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*6 In the case of diazines, this ring current anisotropy difference has been estimated to be 0.95 as a ratio to the anisotropy of a benzene ring.[44]

44) G. G. Hall, A. Hardisson, L. M. Jackman: Discussions Faraday Soc., **34**, 15 (1962).