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# 28. Yasuo Makisumi, Haruyuki Watanabe, and Kazuo Tori : Studies on Azaindolizine Compounds. XVIII.*2 Proton Magnetic Resonance Spectra of *s*-Triazolo-[1,5-*a*]pyrimidine and its Derivatives.*3

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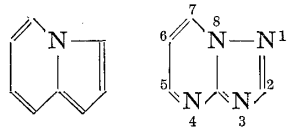
It has been known that indolizine and its derivatives show a well-developed aromatic character and that their characteristic reactivity[1] agrees with the results of theoretical considerations.[2]



indolizine I

Chart. 1

In previous papers of this series, one of the authors (Y. M.) reported on the reactivity of the derivatives of *s*-triazolo[1,5-*a*]-pyrimidine (I) possessing the indolizine skeleton. The results of this reactivity promoted some theoretical investigations on *s*-triazolo[1,5-*a*]pyrimidine.

It has been recognized that the proton resonance shift in aromatic molecules tends to reflect the $\pi$-electron density on the carbon atom to which the proton is bonded.[3] It is therefore of some interest to examine the possible quantitative aspects of such correlations and to what extent proton resonance shifts can provide useful information about the electron density distribution in aromatic systems.

In the present investigation, the nuclear magnetic resonance (NMR) spectra of a number of *s*-triazolo[1,5-*a*]pyrimidine derivatives were recorded to obtain some information on their reactivities and electronic structures by analyzing the chemical shifts and the methyl substituent effects on the ring protons.

## Experimental

All the NMR spectra were obtained with a Varian A-60 analytical NMR spectrometer on 10% (w/v) solutions in $CDCl_3$ containing about 1% tetramethylsilane as an internal reference. However, as 5- and 6-chloro-*s*-triazolo[1,5-*a*]pyrimidines (XIII and XIV) and 5- and 7-methoxy-*s*-triazolo[1,5-*a*]-pyrimidines (XVII and XVIII) are slightly soluble in this solvent, saturated solutions (about 6~8%) were used in these cases. Chemical shifts are expressed in p.p.m. on $\tau$-scale. The materials were prepared according to the already known procedures,[4,5] except for 6-methyl- and 5,6-dimethyl-*s*-triazolo-[1,5-*a*]pyrimidines (IV and VIII). The Bulow's method[5] was employed for the preparation of 5,6,7-trimethyl- and 2,5,6,7-tetramethyl-*s*-triazolo[1,5-*a*]pyrimidines (XI and XII), the structures of which were confirmed by their UV absorption spectra.

**6-Methyl-*s*-triazolo[1,5-*a*]pyrimidine (IV)**——To a solution of 2.3 g. of Na dissolved in 75 ml. of abs. EtOH, 17.4 g. of diethyl methylmalonate and 8.4 g. of 5-amino-*s*-triazole were added and the solu-

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*2 Part XVII. Y. Makisumi, S. Notzumoto, H. Kano : Ann. Rept. Shionogi Res. Lab., **13**, 37 (1963).

*3 The greater part of this work presented at the Kinki Branch Meeting of the Pharmaceutical Society of Japan, held at Kyoto in October 1962.

1) See Mosby : "The Chemistry of Heterocyclic Compounds," **15**, (Part I), 239 (1961). Interscience Publ. Inc., New York.

2) C. A. Coulson, H. C. Longuet-Higgins : Trans. Faraday Soc., **43**, 1433 (1947); K. Fukui, T. Yonezawa, C. Nagata, H. Shingu : J. Chem. Phys., **22**, 1433 (1954); A. Galbraith, T. Small, R. A. Barnes, V. Baekelheide : J. Am. Chem. Soc., **83**, 453 (1961).

3) See for examples, *a*) P. L. Corio, B. P. Dailey : J. Am. Chem. Soc., **78**, 3043 (1956); *b*) A. A. Bothner-By, R. E. Glick : J. Chem. Phys., **26**, 1651 (1957); *c*) H. Spiesecke, W. G. Schneider : *Ibid.*, **35**, 731 (1961); *d*) *Idem* : Tetrahedron Letters, No. 14, 468 (1961); *e*) B. P. Dailey, A. Gawer, W. C. Neikam : Discussions Faraday Soc., **34**, 18 (1962).

4) Y. Makisumi, *et al.* : This Bulletin, **7**, 903, 907 (1959); Y. Makisumi : *Ibid.*, **9**, 801, 808, 883 (1961), **11**, 845 (1963); K. Shirakawa : Yakugaku Zasshi, **79**, 903, 1482 (1959).

5) *a*) C. Bulow, K. Haas : Ber., **42**, 4638 (1909); *b*) *Idem* : *Ibid.*, **43**, 375 (1910).

tion was refluxed under stirring for 8 hr. After cooling, the precipitated Na salt was collected by filtration, dissolved in $H_2O$, treated with charcoal, and acidified with conc. HCl. The resulting precipitate was collected by filtration, washed with $H_2O$, and dried to give 5.9 g. of white crystalline product, m.p. 279° (decomp.). Recrystallization from 60% EtOH gave 6-methyl-*s*-triazolo[1,5-*a*]pyrimidine-5,7-diol as colorless needles, m.p. 291° (decomp.). *Anal.* Calcd. for $C_6H_6O_2N_4$ : C, 43.37; H, 3.64; N, 33.73. Found : C, 43.33; H, 3.91; N, 33.46. UV : $\lambda_{max}^{EtOH}$ 271.5 mμ (log ε 4.11).

This compound (5 g.) was heated with 30 ml. of $POCl_3$ at 100° for 4 hr. and the excess of $POCl_3$ was removed under reduced pressure. The residual syrup was poured into ice $H_2O$, neutralized with conc. $NH_4OH$, and extracted with $CHCl_3$. The extract was dried over $MgSO_4$ and evaporated to dryness to leave 5.35 g. of crude product, m.p. 133~136°. Recrystallization from benzene-petr. benzin gave 6-methyl-5,7-dichloro-*s*-triazolo[1,5-*a*]pyrimidine as colorless pillars, m.p. 150~150.5°. *Anal.* Calcd. for $C_6H_4N_4Cl_2$ : C, 35.49; H, 1.98; N, 27.59. Found : C, 35.38; H, 2.32; N, 27.32.

A solution of 5 g. of this dichloro compound in 200 ml. of abs. EtOH was hydrogenated over 2 g. of 5% Pd-C and 4.04 g. of AcONa. Two moles of $H_2$ was absorbed during 40 min. After removal of the catalyst, the filtrate was evaporated to dryness under reduced pressure and the residue was dissolved in $H_2O$ and extracted with $CHCl_3$. Evaporation of the solvent from the extract gave 2.1 g. of a white solid, which was recrystallized from benzene-petr. benzin to give colorless pillars (Ⅳ), m.p. 157~158°. *Anal.* Calcd. for $C_6H_6N_4$ : C, 53.72; H, 4.51; N, 41.77. Found : C, 53.37; H, 4.69; N, 41.74. UV : $\lambda_{max}^{EtOH}$ 282 mμ (log ε 3.59).

**5,6-Dimethyl-*s*-triazolo[1,5-*a*]pyrimidine (VIII)**——A solution of 0.91 g. of 7-chloro-5,6-dimethyl-*s*-triazolo[1,5-*a*]pyrimidine in 60 ml. of abs. EtOH was hydrogenated over 0.3 g. of 5% Pd-C and 0.6 g. of AcONa. After absorption of 1 mole of $H_2$, the reaction mixture was treated as above to yield 0.6 g. of a white solid. Recrystallization from benzene gave colorless scales, m.p. 182~183° (m.p. 178~178.5°[6]). *Anal.* Calcd. for $C_7H_8N_4$ : C, 56.74; H, 5.44; N, 37.82. Found : C, 57.08; H, 5.46; N, 37.67. UV : $\lambda_{max}^{EtOH}$ 278 mμ (log ε 3.64).

**5,6,7-Trimethyl-*s*-triazolo[1,5-*a*]pyrimidine (XI)**——This compound was prepared from 2-methylacetylacetone and 5-amino-*s*-triazole by the method of Bulow and Haas.[5a] Recrystallization from benzene-petr. benzin gave colorless pillars, m.p. 141~142° (m.p. 135~136°[5a]). *Anal.* Calcd. for $C_8H_{10}N_4$ : C, 59.24; H, 6.21; N, 34.55. Found : C, 59.35; H, 6.39; N, 34.41. UV : $\lambda_{max}^{EtOH}$ 278 mμ (log ε 3.72).

**2,5,6,7-Tetramethyl-*s*-triazolo[1,5-*a*]pyrimidine (XII)**——This compound was also prepared by Bulow's method[5b] from 2-methylacetylacetone and 3-methyl-5-amino-*s*-triazole. Recrystallization from benzene-petr. benzin gave colorless needles, m.p. 124~125° (m.p. 116~117°[5b]). *Anal.* Calcd. for $C_9H_{12}N_4$ : C, 61.34; H, 6.86; N, 31.80. Found : C, 61.33; H. 6.94; N, 31.67. UV : $\lambda_{max}^{EtOH}$ 282 mμ (log ε 3.76).

## Results

All the spectra of *s*-triazolo[1,5-*a*]pyrimidine derivatives except that of 2-methyl

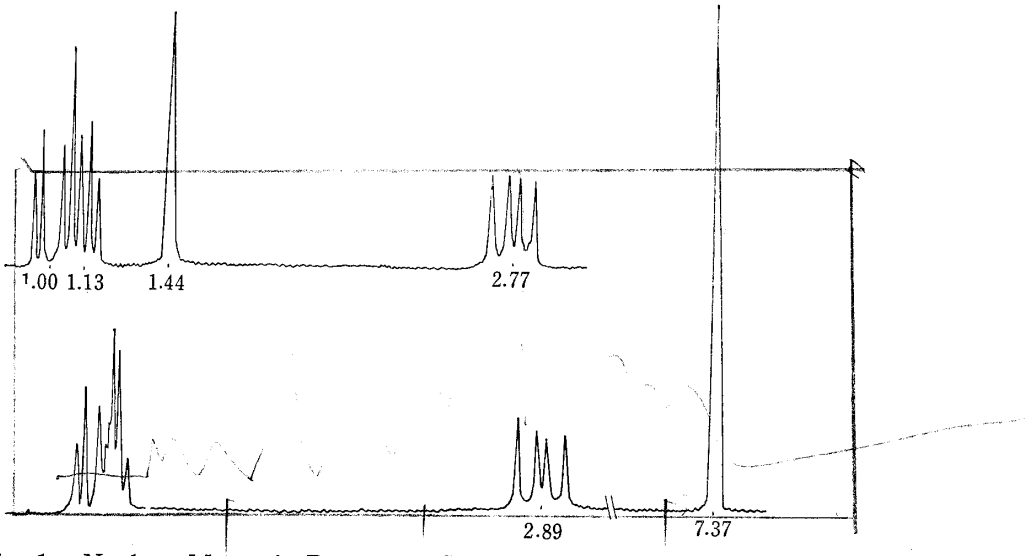


Fig. 1. Nuclear Magnetic Resonance Spectra of *s*-Triazolo[1,5-*a*]-pyrimidine (Ⅰ) (top) and its 2-Methyl Derivative (Ⅱ) (bottom)

6) C.F.H. Allen, H.R. Beilfuss, D.M. Burness, G.A. Reynolds, J.F. Tinker, J.A. VanAllan : J. Org. Chem., **24**, 796 (1959).

derivative (II) were simple first order patterns, which made it possible to compute all chemical shifts and spin coupling constants with sufficient accuracy by a first order analysis. Fig. 1 shows a reproduction of the spectra of *s*-triazolo[1,5-*a*]pyrimidine (I) and II. Similar NMR spectra were recorded for a number of methyl, chloro, methoxyl, and ethoxycarbonyl derivatives to make a complete assignment of their proton signals by comparison to each other. The chemical shifts and spin coupling constants for these protons bonded to the ring are summarized in Table I, where additional signals arising from the methyl substituents, which appear in higher field, are shown in parentheses.

## Assignment

**The Proton at 2-Position ($H_2$)**——The assignment of the signal from the proton attached to $C_2$ is straightforward, because the $H_2$ is five bonds removed from the nearest $H_7$ and can be expected to give rise to a singlet. The spectra of *s*-triazolo[1,5-*a*]pyrimidines possessing the $H_2$ show the singlet signals in a narrow region of 1.4 to 1.7 in $\tau$-value, whereas this singlet signal disappears in the 2-substituted derivatives.

**The Proton at 6-Position ($H_6$)**——Both the spectra represented in Fig. 1 show quartet signals which are distinctly separated from all other peaks and centered at 2.77 and 2.89 $\tau$, respectively. This signal disappears in 6-substituted derivatives, turns into a doublet by introducing a substituent into $C_5$ or $C_7$, and becomes a singlet in 5,7-disubstituted derivatives. In addition, the spin coupling constants observed in the quartet of I were 4.4 and 6.7 c.p.s., which suggest that this signal is due to a proton adjacent to two protons. Therefore, for all *s*-triazolo[1,5-*a*]pyrimidine derivatives possessing the $H_6$, the proton responsible for this signal must be that at $C_6$ (on the basis of these facts, one can unequivocally assign the signals in this region to the proton bonded to $C_6$, $H_6$).

**The Protons at 5- and 7-Positions ($H_5$ and $H_7$)**——The pair of doublet signals of equal intensity and spacing were assigned to the $H_5$ and the $H_7$. Although individual assignments cannot be made with certainty on the basis of chemical shifts, the high-field components (doublet) are assigned to the $H_5$ by comparing their spin coupling constants $J_{5,6}$ and $J_{6,7}$ with those observed in the spectra of the 5- and 7-substituted derivatives. The spin coupling constants, $J_{5,6}$ observed in the $H_6$ signals of the 7-substituted derivatives (V, VII, XV, and XVIII) are 4.4, 4.5, 4.7, and 5.3, c.p.s., while $J_{6,7}$ of the 5-substituted derivatives (III, VI, XIII, and XVII) are 7.0, 6.8, 7.0, and 7.3 c.p.s., respectively. Thus, it is natural to assign the doublet signal of I in Fig. 1 with the spacing of 4.4 c.p.s. to the proton at $C_5$.

The pattern arising from the $H_5$ and the $H_7$ of II represented an ABX system as shown in Fig. 1 where X corresponds to the $H_6$. In order to determine the chemical shifts and spin coupling constants of the protons $H_5$ and $H_7$, it was treated entirely by trial-and-error methods until the calculated spectrum gives the best fit to the observed one. The best set of parameters are listed in Table I.

Surveying the methyl signals of all the samples leads to three criterions concerning the methyl-ring proton spin coupling applicable for methyl signal assignments: (1) neither the methyl group at $C_2$ nor that at $C_5$ can couple with any ring proton in an appreciable manner, (2) the methyl group at either $C_6$ or $C_7$ couples with the ring proton $H_7$ or $H_6$, (3) the methyl group at $C_6$ couples with the ring proton $H_5$ in an inappreciable manner. On the basis of these criterions, one can easily make a reasonable assignment of methyl signals for all the methyl derivatives as shown in Table I, except those for 2,5-dimethyl and 5,6,7-trimethyl derivatives (VI and XI) which contain more than one methyl signal without any splitting due to a ring proton.

In the above exceptional examples, the singlet methyl signals were tentatively assigned as shown in Table I by assuming their relative chemical shifts in $\tau$-value to be in the order of 6-methyl>2-methyl>5-methyl>7-methyl, which is consistent with the order of ring protons and holds in the methyl signal assignments based on the above criterions. These assignments of the methyl signals are supported by the observation that the effect of methyl substitution at $C_2$ on chemical shifts of the remaining methyl groups are kept nearly constant when assigned as shown in Table I; *i.e.*, based on the above-mentioned order. The substituent effect will be discussed in the next section.

Table I. Nuclear Magnetic Resonance Spectral Parameters for *s*-Triazolo[1,5-*a*]pyrimidine Derivatives

| Compd. No. | Substituent | Chemical shift ($\tau$) | | | | Coupling constant J (c.p.s.) | | |
|---|---|---|---|---|---|---|---|---|
| | | $H_2$ | $H_5$ | $H_6$ | $H_7$ | $J_{5,6}$ | $J_{5,7}$ | $J_{6,7}$ |
| I | None | 1.44 | 1.13 | 2.77 | 1.00 | 4.4 | 2.0 | 6.7 |
| II | 2-$CH_3$ | (7.37) | 1.24 | 2.89 | 1.15 | 4.4 | 2.0 | 6.4 |
| III | 5-$CH_3$ | 1.57 | (7.27) | 2.96 | 1.23 | ~0[a] | ~0[a] | 7.0 |
| IV | 6-$CH_3$ | 1.53 | 1.29 | (7.50) | 1.29 | ~0[a] | ~0 | 0.5[a] |
| V | 7-$CH_3$ | 1.49 | 1.28 | 2.96 | (7.11) | 4.4 | ~0[a] | 0.8[a] |
| VI | 2,5-di-$CH_3$ | (7.41) | (7.32) | 3.07 | 1.36 | ~0[a] | ~0[a] | 6.8 |
| VII | 2,7-di-$CH_3$ | (7.36) | 1.38 | 3.09 | (7.17) | 4.5 | ~0[a] | 0.6[a] |
| VIII | 5,6-di-$CH_3$ | 1.64 | (7.35) | (7.60) | 1.44 | ~0[b] | ~0[a] | 0.9[a] |
| IX | 5,7-di-$CH_3$ | 1.59 | (7.34) | 3.14 | (7.19) | ~0[a] | ~0[b] | 0.8[a] |
| X | 2,5,7-tri-$CH_3$ | (7.40) | (7.39) | 3.26 | (7.25) | ~0[a] | ~0[b] | 0.8[a] |
| XI | 5,6,7-tri-$CH_3$ | 1.66 | (7.37) | (7.66) | (7.19) | ~0[b] | ~0[b] | ~0[b] |
| XII | 2,5,6,7-tetra-$CH_3$ | (7.42) | (7.40) | (7.69) | (7.24) | ~0[b] | ~0[b] | ~0[b] |
| XIII | 5-Cl | 1.47 | — | 2.79 | 1.15 | — | — | 7.0 |
| XIV | 6-Cl | 1.46 | 1.19 | — | 1.01 | — | 2.5 | — |
| XV | 7-Cl | 1.38 | 1.19 | 2.68 | — | 4.7 | — | — |
| XVI | 5,7-di-Cl | 1.43 | — | 2.67 | — | — | — | — |
| XVII | 5-$CH_3O$ | 1.69 | (5.87) | 3.38 | 1.40 | — | — | 7.3 |
| XVIII | 7-$CH_3O$ | 1.50 | 1.23 | 3.45 | (5.70) | 5.3 | — | — |
| XIV | 5,7-di-$CH_3O$ | 1.70 | (5.88) | 4.07 | (5.78) | — | — | — |
| XX | 5-$CH_3$,6-$COOC_2H_5$ | 1.43 | (6.99) | — | 0.53 | — | 0[a] | — |
| XXI | 7-$CH_3$,6-$COOC_2H_5$ | 1.40 | 0.67 | — | (6.72) | — | 0[a] | — |

*a*) $CH_3$-H coupling
*b*) $CH_3$-$CH_3$ coupling

## Discussion

Reddy and Goldstein have made extensive investigations of the methyl substituent effect on the ethylenic[7] and aromatic protons,[8,9] and found the effects on the proton chemical shifts to be approximately constant. Further, they found the total effect of a single methyl substitution on ring proton shifts in aromatic compounds to be about 0.75 p.p.m., regardless of the substituting position in the ring, and the distribution of the effect around the ring to be in general parallel with the order of aromaticity inferred from some other criteria. In this connection, it seems interesting to examine the methyl substituent effect of *s*-triazolo[1,5-*a*]pyrimidine by a similar way in order to evaluate the aromaticity of this ring.

7) G.S. Reddy, J.H. Goldstein : J. Am. Chem. Soc., **83**, 2045 (1961).
8) *Idem* : *Ibid.*, **83**, 5020 (1961).
9) G.S. Reddy, R.T. Hobgood, Jr., J.H. Goldstein : *Ibid.*, **84**, 336 (1962).

The effect of the methyl group on each ring proton shift is obtained by substracting the corresponding values for each parent ring compound. The results are summarized in Table II. The positive sign means a high-field shift by the introduction of a methyl group.

TABLE II. Methyl Substituent Effects in *s*-Triazolo[1,5-*a*]pyrimidine Derivatives

| (Substituted) — (Reference) | Position of proton | | | |
|---|---|---|---|---|
| | 2 | 5 | 6 | 7 |
| The effect due to 2-methyl | | | | |
| II — I | — | 0.11 | 0.12 | 0.15 |
| VI — III | — | (0.05) | 0.11 | 0.13 |
| VII — V | — | 0.10 | 0.13 | (0.06) |
| X — IX | — | (0.05) | 0.12 | (0.06) |
| XII — XI | — | (0.03) | (0.03) | (0.05) |
| The effect due to 5-methyl | | | | |
| III — I | 0.13 | — | 0.19 | 0.23 |
| VI — II | (0.04) | — | 0.18 | 0.21 |
| VIII — IV | 0.11 | — | (0.10) | 0.15 |
| IX — V | 0.10 | — | 0.18 | (0.07) |
| X — VII | (0.04) | — | 0.17 | (0.08) |
| The effect due to 6-methyl | | | | |
| IV — I | 0.09 | 0.16 | — | 0.29 |
| VIII — III | 0.07 | (0.08) | — | 0.21 |
| XI — IX | 0.07 | (0.03) | — | (0.00) |
| XII — X | (0.02) | (0.01) | — | (−0.01) |
| The effect due to 7-methyl | | | | |
| V — I | 0.05 | 0.15 | 0.19 | — |
| VII — II | (−0.01) | 0.14 | 0.20 | — |
| IX — III | 0.02 | (0.07) | 0.18 | — |
| X — VI | (−0.01) | (0.07) | 0.19 | — |
| XI — VIII | 0.02 | (0.02) | (0.06) | — |

The shifts of the methyl substituent are shown in parentheses.

The values listed in Table II show that the total methyl substituent effects in the 2-, 5-, 6-, and 7-methyl derivatives are 0.38, 0.55, 0.54, and 0.39 p.p.m., respectively. These values appear to be somewhat smaller than the value 0.75 p.p.m. that was previously observed in ethylene[7] and in some aromatic compounds.[8,9] Although many discussions have been made on the total effect of a methyl substituent which was sometimes understood to suggest the degree of aromaticity in the ring,[10] it seems to be difficult to derive fruitful information on the ring aromaticity from the total effect alone, because the total effect depends upon the number of ring protons, the number and species of heteroatoms in the aromatic ring, the position of the substitution, etc.

Another important factor of the methyl substituent effect is, as Reddy and Goldstein have already suggested, the distribution of this effect among the ring protons. It can be expected to provide detailed information about the electronic structure of these compounds, as well as the effects of substituents on it.

From the values listed in Table II, it is seen that the substitution in either ring by methyl groups shifts the ring proton signal to the high-field side by a small amount approximately constant and characteristic of each position, and which fact shows that the charge densities at the various ring positions change in an inappreciable manner with methyl substitution. Similar constancies of substituent effect have already been described on many aromatic compounds.[3a,8,10~12] In furan, pyrrole, and thiophene, it was

10) E.B. Baker: J. Chem. Phys., **23**, 1981 (1955).
11) H.J. Bernstein, W.G. Schneider: *Ibid.*, **24**, 469 (1956).
12) H.S. Gutowsky, D.W. McGarvey, L.H. Meyer: J. Am. Chem. Soc., **74**, 4809 (1952).

found that distribution of the methyl substituent effect on various ring protons is less uniform around the ring than is in the case of toluene as compared to benzene. Thus, it is not unreasonable to suppose that the more aromatic the ring is the more uniform the effect should be, as suggested by Reddy and Goldstein[8] when comparing 2-methylthiophene with 2-methylfuran. Further, it may be reasonably expected that there exists some simple relation between the methyl substituent effect and the $\pi$-bond order of the bond through which the effect is transmitted. This expectation is based on the following observations. The methyl proton shift in propane is 0.04 p.p.m. higher than that of ethane, *i.e.*, a very slight high-field shift for protons at the $\beta$-position occurs with methyl substitution in ethane, while the changes of $\beta$-proton shifts produced by a methyl substitution in ethylene are 0.41 p.p.m. for a *trans* and 0.32 p.p.m. for a *cis* proton. These two results illustrate two extreme cases on the effect over a single and double bond. In benzene, which is considered as a typical aromatic ring with a $\pi$-bond order of 0.66, the methyl effect upon the two *ortho*-protons is the same to each one and about 0.25 p.p.m.[13] It is also found that in 3-methylthiophene, the methyl effect shifts the signal due to the proton $H_2$ by 0.44 p.p.m. to high-field and that due to the proton $H_4$ by 0.22 p.p.m. This fact can be interpreted as due to the difference between the $\pi$-bond character in $C_2$-$C_3$ and that in $C_3$-$C_4$ as illustrated in Chart. 2.[8]

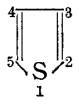

Chart 2.

These observations and rationalizations led to a working assumption that the methyl substituent effect can be transmitted more easily through a $\pi$-bond than a $\sigma$-bond, *i.e.*, the more the double bond character, the more profoundly the methyl substituent effect is transmitted. Although further work is in progress on this assumption and will be reported at a later date, it becomes considerably easier to understand the distribution of the methyl substituent effect listed in the present series of compounds if this assumption is accepted.

Turning to the *s*-triazolo[1,5-*a*]pyrimidine derivatives, the methyl substituent effect listed in Table II shows less uniform distribution around the various ring protons and subsequently less aromaticity of the ring. This lack of uniformity gives promise of supplying other interesting information about the electronic structure of the ring. Of the data in Table II, 6-mehyl-*s*-triazolo[1,5-*a*]pyrimidine (IV) provides the most important and reliable data for comparison of the substituent effect on the protons $H_5$ and $H_7$. The difference in the substituent effect between the protons $H_5$ and $H_7$ can be attributed to a resonance effect only, because these two protons are both *ortho* to the 6-methyl substituent and the magnetic anisotropy effect as well as the inductive effect of the methyl group are the same on these two protons. The methyl substituent effect on the protons $H_5$ and $H_7$ is 0.16 and 0.29 p.p.m. respectively, which indicates that the double bond character of $C_6$-$C_7$ is larger than that of $C_5$-$C_6$, if the assumption is valid, and accordingly that the structure shown in Chart 1 is exerting the most important contribution to the ground state of *s*-triazolo[1,5-*a*]pyrimidine ring.

It should be noticed that the 2-methyl substituent exerts a considerable effect (ca. 0.15 p.p.m.) upon the proton $H_7$ whereas the 7-methyl substituent affects the $H_2$ shift in an inappreciable manner through an inverse course. Although this fact must reflect the electronic structure of the *s*-triazolo[1,5-*a*]pyrimidine ring, the explanation for this is not immediately obvious.

A number of investigators have reported that the proton chemical shifts of conjugated molecules correlate most intimately with the local $\pi$-electron density on the

13) J. A. Pople, W. G. Schneider, H. J. Bernstein: "High-resolution Nuclear Magnetic Resonance," 263 (1959). McGraw-Hill Book Co., Inc., New York.

carbon atoms to which the proton in question is attached, and are approximately proportional to the theoretically calculated $\pi$-electron densities. Fraenkel, *et al.*[14] and Spiesecke and Schneider[3d] proposed a linear relationship

$$\delta = a\Delta\rho$$

where $\delta$ is the proton chemical shift relative to an appropriate reference, $\Delta\rho$ is the excess number of $\pi$-electrons on the carbon atom, and $a$ is a constant of the order of 10 p.p.m./electron. But there are still some factors which can affect the ring proton shifts, *e.g.*, (1) magnetic anisotropies of substituents and nitrogen atoms in the *s*-triazolo[1,5-*a*]pyrimidine ring, (2) ring current effects, (3) solvent effects, and (4) polarization of $\sigma$-bond.

The main difficulty in employing proton resonance shifts to evaluate the electron density on the *s*-triazolo[1,5-*a*]pyrimidine ring arose from the magnetic anisotropy of two types of nitrogens. The anisotropy of the pyrrole type nitrogen, $N_8$, will undoubtedly make some contribution to the measured proton shifts, but the magnitude of this contribution has not yet been discussed, and can not be reliably estimated. The lone-pair of the $N_8$ now get a considerable $\pi$-character and it is accordingly conceivable that the lone-pair anisotropy effect is greatly reduced to give, instead, rise to $\pi$-electronic anisotropy effect which may be estimated to be equivalent to that of $sp^2$ carbon atoms in this ring, *i.e.*, it is not necessary to take into account the anisotropy effect of the lone pair.

The magnitude of the anisotropy effect of a pyridine type nitrogen[15a] was estimated by Nakagawa, *et al.*[15b] as about 0.8 p.p.m., whereas one of the authors (K. T.) proposed a value of about 0.35 p.p.m.[16] These are the only two available data and it appears that the magnitude can not be estimated with sufficient accuracy to make a satisfactory correction to the observed shifts. By examining the degree to which the data can be matched, the present data lend some support to the latter value, the value of 0.25 p.p.m. giving the best fitting to the linear relation in conjunction with the correction of ring current effect mentioned below.

The second factor that makes the reliable charge density difficult to estimate from the chemical shifts is the ring current anisotropy effect in this ring. The resonance shifts of the protons $H_2$ and $H_7$ must be corrected for the ring current of the neighboring ring to bring the shift in line with the protons $H_5$ and $H_6$, which can be regarded as being affected to the same amount and suitable for a reference in comparing the relative chemical shifts. Though a more precise calculation is possible by quantum mechanical treatment of the diamagnetic anisotropy due to the ring current of $\pi$-electrons after London[17] and McWeeny,[18] there is, at present, no wholly reliable MO's which can be used for calculation of the anisotropy. The corrections were, therefore, roughly approximated with the values obtained for the indenyl ion by Schaefer and Schneider[19] in which a simple dipole model due to Pople[20] was employed to give 0.09

14) G. Fraenkel, R.E. Carter, A. McLachlan, J.H. Richards: J. Am. Chem. Soc., **80**, 3497 (1958); C. Maclean, E.L. Mackor: Mol. Phys., **4**, 241 (1961).
15) *a*) J.D. Baldeschwieler, E.W. Randall: Proc. Chem. Soc., **1961**, 303; *b*) N. Nakagawa, Y. Kawazoe, H. Hotta, M. Ito: presented at Symposium on Nuclear Magnetic Resonance (Japan), in Tokyo, November 1961.
16) *a*) K. Tori, M. Ogata, H. Kano: This Bulletin, **11**, 235 (1963); *b*) M. Yamakawa, K. Tori: presented at the 3rd Symposium on Nuclear Magnetic Resonance (Japan), in Osaka, November 1963.
17) F. London: J. Phys. radium. **8**, 397 (1937).
18) R. McWeeny: Mol. Phys., **1**, 311 (1958).
19) T. Schaefer, W.G. Schneider: Can. J. Chem., **41**, 966 (1963).
20) J.A. Pople: J. Chem. Phys., **24**, 1111 (1956).

and 0.28 p.p.m. for the protons $H_2$ and $H_7$, respectively, relative to the protons $H_5$ and $H_6$.

The correction of the third and fourth effects may be expected to be small as compared with the uncertainty of the former two corrections, and neglected here. The total corrections yielded the following $\tau$-values; 0.59 p.p.m. for the $H_2$, 0.25 for the $H_5$, and 0.28 for the $H_7$. These are brought together for ready comparison in Table Ⅲ along with the calculated charge densities derived from them and from simple Hückel molecular orbital (HMO) method. The experimental electron densities were calculated by putting the difference between the corrected $\tau$-value and an appropriately chosen $\tau$-value of 2.42 for $\delta$ in the equation, the coefficient a being taken as 10.7 p.p.m./electron.[19]

The theoretical densities included in Table Ⅲ for comparison with the densities derived from NMR data were calculated for the present purpose by HMO method, using the following set of parameters[21] :

$$\alpha_N=\alpha+0.5\beta,\ \alpha_{N_8}=\alpha+1.5\beta,\ \rho_{CN}=\rho=1$$

where $\alpha_N$, $\alpha_{N_8}$, and $\alpha$ are Coulomb integrals of pyridine type nitrogen, pyrrole type nitrogen and carbon atoms, respectively, $\beta$ is the exchange integral between two carbon atoms in benzene, and $\rho_{CN}$ and $\rho$ are the exchange integrals of C-N and C-C bonds in $\beta$ unit, respectively. Here, the inductive effect and overlap integrals were neglected.

Although various advanced methods of calculation[22] have been proposed to approach the true molecular orbitals, no wholly reliable method is yet available for the evaluation of charge density, and the absolute values of the calculated charge densities depend on the type of approximation employed. But the general trend of the electron density distribution and the alternation of the densities within the molecule is broadly similar in the various approximations.[22] Both the original and the corrected chemical shifts show good correspondence with the theoretical $\pi$-electron densities calculated by the HMO method. While a quantitative comparison with the NMR data may not be too meaningful, it is interesting to note that the electron densities calculated using the HMO method give in general too large alternations around the ring and the advanced MO methods tend to reduce the magnitude of the HMO charge densities without changing the general pattern. Hence, an advanced MO treatment may improve the fitting of theoretical charge densities for the experimental ones. The $\pi$-electron moment of *s*-triazolo[1,5-*a*]pyrimidine is calculated by assuming a regular hexagon and pentagon with bonds of 1.4 Å to give 6.4D., which is too large as compared with the observed value, 4.11D.[23] Neglecting the small $\sigma$-moment and multiplying the factor of 4.11/6.4, one can obtain better absolute charge densities as shown in the last column of Table Ⅲ.

Table Ⅲ. Proton Chemical Shifts, Subsequent Electron Densities, and Calculated Electron Densities of *s*-Triazolo[1,5-*a*]pyrimidine

| Position | Chemical shift ($\tau$) | Ring current correction (p.p.m.) | N Anisotropy correction (p.p.m.) | Corrected $\tau$-value | Charge density | | |
|---|---|---|---|---|---|---|---|
| | | | | | Exp. | HMO | Corrected MO |
| 2 | 1.44 | 0.09 | 0.5 | 2.03 | +0.036 | +0.075 | +0.048 |
| 5 | 1.13 | 0 | 0.25 | 1.38 | +0.097 | +0.136 | +0.087 |
| 6 | 2.77 | 0 | 0 | 2.77 | −0.032 | −0.050 | −0.032 |
| 7 | 1.00 | 0.28 | 0 | 1.28 | +0.107 | +0.157 | +0.101 |

21) A. Streitwieser, Jr. : "Molecular Orbital Theory for Organic Chemists," 135 (1961). John Wiley & Sons, Inc., New York.
22) See reference 21, p. 456.
23) Y. Makisumi, H. Watanabe : unpublished data.

Thus the charge densities determined from proton shifts show a remarkable good correspondence with the HMO charge distributions to indicate that the HMO is valid in predicting the reactivities of the ring protons.

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## Summary

Proton magnetic resonance spectra of the *s*-triazolo[1,5-*a*]pyrimidine derivatives are recorded to give the positional order of $H_6 > H_2 > H_5 > H_7$ for the ring proton chemical shifts in $\tau$-value. The methyl substituent effect on the proton chemical shifts and the correlation between the proton chemical shift and the local $\pi$-electron density on the carbon atom to which the proton is bonded, are discussed. Thus the charge densities determined from proton chemical shifts show a remarkably good correspondence with the charge distributions calculated by the simple Hückel MO method.

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**29. Shin-ichi Ueda :** Studies on the Dibenzo-*p*-dioxin (Diphenylene Dioxide) Derivatives. XL.*1 Electron Spin Resonance Spectra of Dibenzo-*p*-dioxin-2,7-dicarboxylic Acid and 2,7-Disulfonic Acid.

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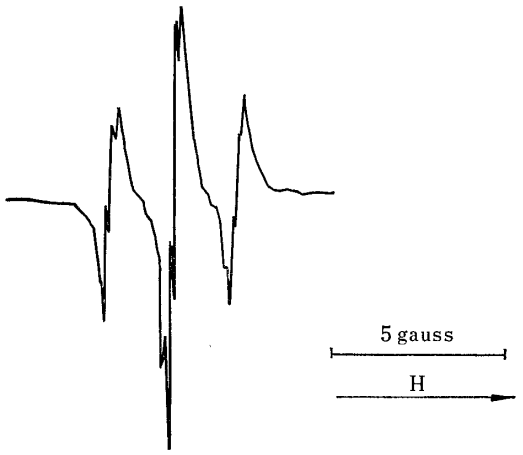


Fig. 1. Electron Spin Resonance Spectrum of Dibenzo-*p*-dioxin-2,7-disulfonic Acid (II) in conc. Sulfuric Acid with Potassium Nitrate

The author previously reported that dibenzo-*p*-dioxin (I) derivatives in concentrated sulfuric acid with an oxidizing agent such as potassium nitrate gave electron spin resonance (ESR) absorption spectra.*1,1) Dibenzo-*p*-dioxin-2,7-disulfonic acid (II)2) in concentrated sulfuric acid gave no color and no ESR absorption, while after the addition of potassium nitrate into the sulfuric acid solution, it colored blue and the ESR spectrum gave a triplet with the intensity ratios of 1:2:1, indicating a coupling of an unpaired electron spin with a set of two equivalent hydrogen nuclei. The g-value was 2.0038 (Fig. 1).

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*1 This paper constitutes Part XL of the series entitled "M. Tomita : Studies on the Dibenzo-*p*-dioxin Derivatives." Part XXXIX. M. Tomita, S. Ueda : This Bulletin, **12**, 40 (1964).

*2 Yoshida-konoe-cho, Sakyo-ku, Kyoto (上田伸一).

1) M. Tomita, S. Ueda, Y. Nakai, Y. Deguchi, H. Takaki : Tetrahedron Letters, No. 18, 1189 (1963); M. Tomita, S. Ueda : This Bulletin, **12**, 33 (1964).

2) M. Tomita, S. Ueda : Yakugaku Zasshi, **80**, 796 (1960).