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NMR Study of the Benzoxazole Derivatives

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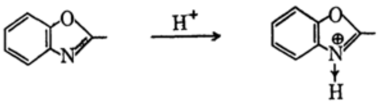
The PMR spectra of 5 benzoxazole derivatives were measured in CCl_4 (or $CDCl_3$) and CF_3COOH. It was found that, due to the magnetic anisotropy of heteroatoms and the electric-field effect, ring protons shift to a lower field than had been anticipated from the π-electron densities (in the case of 4-H, *ca.* 0.4 ppm). In acid media, the π-electron density distribution of benzoxazole is changed because of the protonation of the nitrogen atom, and these two effects vanish. Correcting the measured shifts with Pople's and Buckingham's expressions for these effects, the following relation has been found to hold between the corrected shifts and the π-electron densities calcultated with the Hückel LCAO MO method:

$$\tau - 2.95 = 3.37\ (\pi - 1)$$

Benzoxazoles are feeble bases and form salts in strong acids[1]:



Therefore, the π-electron density distributions in acids change from those in non-polar solvents.

The proton screening constant, σ, is defined as:

$$H = H_0(1 - \sigma)$$

where H_0=the magnitude of the applied field and H=the field actually experienced by the proton.

It is generally accepted[2] that σ can be divided into three terms, that is:

$$\sigma = \sigma_{loc.\ dia} + \sigma_{dis.\ other} + \sigma_{dis.\ int}$$

where $\sigma_{loc.\ dia}$=Lamb's correction for the diamagnetic current around the proton, $\sigma_{dis.\ other}$=the shielding effect due to the dia- or para-magnetic current of the other atoms in the molecule, and $\sigma_{dis.\ int}$=the effect due to the interatomic current in the molecule.

A number of studies[3] trying to correlate $\sigma_{loc.\ dia}$ with the calculated π-electron densities have appeared in the case of benzene derivatives. In this report, we have estimated the contribution of the magnetic anisotropy effects of nitrogen and oxygen atoms, as well as the influence of the electric field, on the proton chemical shifts. Attempts have also been made to correlate these shifts, in the case of benzoxazole derivatives in CCl_4 (or $CDCl_3$) and CF_3COOH, with the π-electron densities calculated by the Hückel LCAO MO method.

Experimental

Benzoxazole derivatives (2, 5-dimethylbenzoxazole, 2, 5, 7-trimethylbenzoxazole, 2, 5, 6-trimethylbenzoxazole, 2, 4, 5-trimethylbenzoxazole, and 2-methyl 5-chlorobenzoxazole) were synthesized from *o*-aminophenol derivatives according to standard procedures[1] by Dr. M. Tsujimoto of our laboratory. The purity of the benzoxazole derivatives was checked by means of their PMR spectra.

The chemicals employed as solvents were commercially available materials and were used without further purification. CCl_4, CH_3COOH, and HCOOH were from Wako Pure Chemical Ind., Ltd. (special grade), while CF_3COOH was from Tokyo Kasei Ind., Ltd. (G. R.); $CDCl_3$ was a Ciba, Ltd., "Solvent for NMR spectroscopy."

The NMR spectra of the benzoxazole derivatives were obtained in a 5% solution, using tetramethylsilane as an internal standard, at room temperature (23°C) with a 60 Mc NMR spectrometer (JNM 3H-60): they were calibrated by the usual sideband technique.

All the shifts are expressed in terms of the τ-values.

Results and Discussion

Chemical Shifts and π-Electron Densities. The NMR spectrum of each benzoxazole derivative was measured in CCl_4 (when insoluble, $CDCl_3$ was used), CH_3COOH, HCOOH, and CF_3COOH. The relation between the chemical shifts of 2, 5-dimethylbenzoxazole protons and the dissociation constants[4] of the acids in water

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[1] E. H. Rodd, "Chemistry of Carbon Compounds," Vol. 4, Elsevier Pub. Co., London (1957), p. 375.

[2] J. A. Pople, W. G. Schneider and H. J. Bernstein, "High-resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., New York (1959), Chap. 7.

[3] G. Fraenkel, R. E. Carter, A. McLachlan and J. H. Richards, *J. Am. Chem. Soc.*, **82**, 5846 (1960); A. Zweig, J. E. Lehnsen, J. E. Lancaster and M. T. Neglia, *ibid.*, **85**, 3940 (1963).

[4] R. A. Robinson and R. H. Stokes, "Electrolyte Solution," Rutterworth Sci. Pub., London (1955).

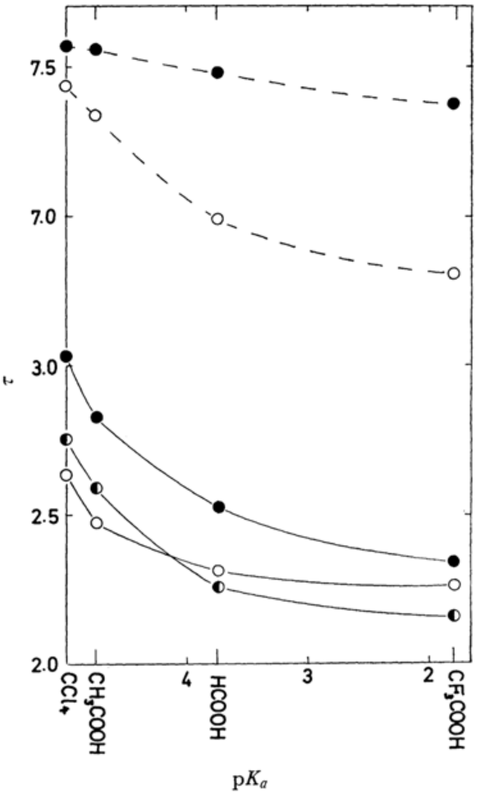

Fig. 1. Chemical shifts of 2,5-dimethylbenzoxazole protons in various acids.
– – ● 5-Me
– – ○ 2-Me
—— ○ 4H
—— ● 6H
—— ◐ 7H

TABLE 1. π-ELECTRON DENSITIES AND CHEMICAL SHIFTS

		π	τ	π^+	τ^+
2,5-Dimethyl-benzoxazole	1	1.820	—	1.781	—
	2	0.787	—	0.575	—
	3	1.341	—	1.686	—
	4	1.096	2.63	1.073	2.26
	5	0.895	—	0.889	—
	6	1.075	3.029	1.057	2.337
	7	0.997	2.751	0.996	2.153
	2Me	1.933	7.44	1.901	6.80
	5Me	1.954	7.57	1.953	7.37
2,5,7-Trimethyl-benzoxazole	1	1.822	—	1.782	—
	2	0.787	—	0.577	—
	3	1.342	—	1.686	—
	4	1.140	2.910	1.118	2.585
	5	0.892	—	0.886	—
	6	1.143	3.284	1.125	2.585
	7	1.953	—	0.882	—
	2Me	1.933	7.474	1.901	6.862
	5Me	1.954	7.653	1.953	7.441
	7Me	1.953	7.615	1.952	7.363
2,5,6-Trimethyl-benzoxazole	1	1.821	—	1.782	—
	2	0.805	—	0.586	—
	3	1.340	—	1.686	—
	4	1.092	2.724	1.072	2.401
	5	0.941	—	0.937	—
	6	0.955	—	0.938	—
	7	1.067	2.907	1.066	2.332
	2Me	1.935	7.473	1.902	6.888
	5Me	1.957	7.699	1.956	7.477
	6Me	1.957	7.699	1.956	7.477
2,4,5-Trimethyl-benzoxazole	1	1.822	—	1.782	—
	2	0.805	—	0.580	—
	3	1.337	—	1.686	—
	4	0.966	—	0.949	—
	5	0.959	—	0.950	—
	6	1.072	2.946	1.056	2.390
	7	1.044	2.846	1.042	2.390
	2Me	1.935	7.376	1.902	6.867
	4Me	1.956	7.510	1.956	7.416
	5Me	1.958	7.665	1.957	7.467
2-Methyl 5-chloro-benzoxazole	1	1.816	—	1.779	—
	2	0.787	—	0.570	—
	3	1.338	—	1.684	—
	4	1.001	2.402	0.983	2.171
	5	1.070	—	1.066	—
	6	1.005	2.770	0.984	2.261
	7	1.003	2.663	1.001	2.261
	2Me	1.933	7.375	1.900	6.861

(pK_a) are shown in Fig. 1 as an example; the figure clearly indicates that all the benzoxazole protons shift to a lower field according to the acid strength. This is mainly because the π-electron density distribution of benzoxazole derivatives in a non-polar solvent differs from that in acids.

The π-electron density distributions of the benzoxazole derivatives and the derivatives whose nitrogen atom is protonated (designated as π and π^+ respectively) were calculated by the Hückel LCAO MO method using Streitwieser's parameter$^{5)}$ (for the methyl group, the hetero-atom model was employed.)

For 2,5-dimethylbenzoxazole, 2,5,7-trimethylbenzoxazole, and 2,5,6-trimethylbenzoxazole, CCl$_4$ was used as a non-polar solvent, and 2,4,5-trimethylbenzoxazole and 2-methyl 5-chlorobenzoxazole were measured in CDCl$_3$. The chemical shifts measured in CCl$_4$ (or CDCl$_3$) (τ) and the shifts in CF$_3$COOH (τ^+) are tabulated in Table 1, along with the calculated π-electron densities, (π) and (π^+). The π-electron densities of benzoxazoles (π) are compared with those shifts measured in CCl$_4$ (or CDCl$_3$) (τ), and π-electron densities of benzoxazoles whose nitrogen atom is

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5) A. Streitwieser, Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley & Sons, New York (1961), p. 135.

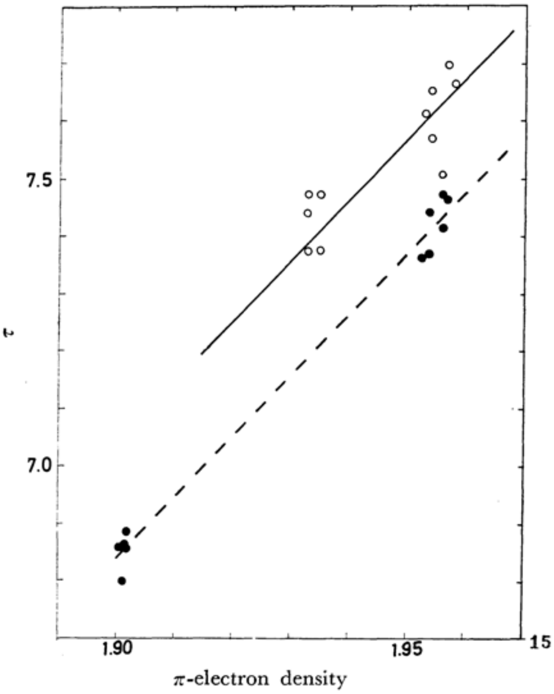

Fig. 2. Chemical shifts of Me group against π-electron density.
—— in CCl_4 or $CDCl_3$
$\tau+2.58=10.7\ (\pi-1)$ (1)
– – in CF_3COOH
$\tau^{+}+2.83=10.7\ (\pi^{+}-1)$ (2)

protonated (π^{+}), with the shifts in CF_3COOH (τ^{+}).

In Fig. 2, the chemical shifts of methyl groups are plotted against the calculated π-electron densities. The relation between the shifts and the calculated π-electron densities can be expressed as follows:

$$\tau+2.58=10.7\ (\pi-1) \tag{1}$$

$$\tau^{+}+2.83=10.7\ (\pi^{+}-1) \tag{2}$$

The slope of the least-squares line in CCl_4 (or $CDCl_3$) coincides with that in CF_3COOH.

Therefore, it may be deduced that, in acid media, the protonation occurs to the nitrogen atom, (this agrees with the well-known fact[6] that benzoxazole reacts with methyl iodide to give 3-methylbenzoxazolium iodide.) and changes the π-electron density distributions of the molecule, as well as the chemical shifts in CF_3COOH, from those in CCl_4 (or $CDCl_3$).

The difference in the solvent effect makes the shifts in CF_3COOH about 0.2 ppm lower; these lines should coincide without it.

The same relationship with benzene ring protons is shown in Fig. 3.

$$\tau-2.71=3.82\ (\pi-1) \tag{3}$$

$$\tau-2.38=3.50\ (\pi-1) \tag{4}$$

$$\tau^{+}-2.20=2.87\ (\pi^{+}-1) \tag{5}$$

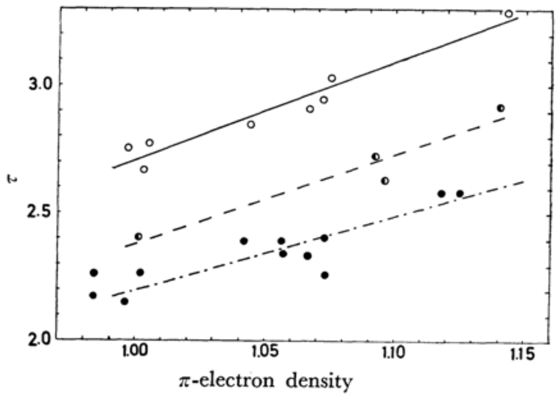

Fig. 3. Chemical shifts of ring protons against π-electron density.
—— ring protons except 4H in CCl_4 or $CDCl_3$
$\tau-2.71=3.82\ (\pi-1)$ (3)
– – 4H in CCl_4 or $CDCl_3$
$\tau-2.38=3.50\ (\pi-1)$ (4)
·—· in CF_3COOH
$\tau^{+}-2.20=2.87\ (\pi^{+}-1)$ (5)

The (3) and (4) lines show the relation of the shifts in CCl_4 (or $CDCl_3$), (3) for 6- and 7-H, and (4) for 4-H. The line for 4-H, (4), lies in a field about 0.3 ppm lower than the (3) line. On the other hand, in CF_3COOH all the benzene ring protons are on a single line, (5). The slopes of these three lines agree tolerably well. Thus, it can be concluded that π-electron densities essentially affect the shifts of ring protons. However, the fact that the relations between the shifts in CCl_4 (or $CDCl_3$) and the π-electron densities fall in two different lines can not be accounted for in terms of the π-electron density alone.

The differences in all the benzoxazole protons between the shift in CCl_4 (or $CDCl_3$) and that in CF_3COOH ($\tau-\tau^{+}$) are summarized in Table 2. Of benzene ring protons, 6- and 7-H show more than a 0.5 ppm low-field shift, but in 4-H the shift lower is only 0.2—0.3 ppm.

These facts suggest that, in CCl_4 (or $CDCl_3$), extra effects work on 4-H and shift it to a field lower by about 0.3 ppm, while in CF_3COOH these effects vanish. The difference ($\Delta\tau$), shown in Table 3, between the shift anticipated from the π-electron density (τ_{calcd}) and that measured in CCl_4 (or $CDCl_3$) (τ) may be attributed to the shift due to these extra effects. (τ_{calcd}) can be obtained by using expression (3), derived from (π) presented in Table 1. $\Delta\tau$ is considered to originate from the influence of magnetic anisotropy and the electric-field effect of N and O atoms.

We did not pay special attention to the ring-current effect ($\sigma_{dis.\ int}$), assuming that the influence of the ring current affects the ring protons

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[6] L. M. Clark, *J. Chem. Soc.*, **1926**, 233.

TABLE 2. THE VALUES OF LOW-FIELD SHIFT OF BENZOXAZOLE DERIVATIVE PROTONS BY PROTONATION ($\tau-\tau^+$)(ppm)

	2-CH_3	4-CH_3	5-CH_3	6-CH_3	7-CH_3	4H	6H	7H
2,5-Dimethylbenzoxazole	0.64	—	0.20	—	—	0.37	0.69	0.60
2,5,6-Trimethylbenzoxazole	0.59	—	0.22	0.22	—	0.32	—	0.58
2,5,7-Trimethylbenzoxazole	0.61	—	0.21	—	0.25	0.33	0.70	—
2,4,5-Trimethylbenzoxazole	0.51	0.09	0.20	—	—	—	0.56	0.46
2-Methyl 5-chlorobenzoxazole	0.51	—	—	—	—	0.23	0.51	0.40

TABLE 3. THE SHIFTS OF 4-H ATTRIBUTED TO ANISOTROPY EFFECT AND ELECTRIC FIELD EFFECT ($\Delta\tau=\tau-\tau_{cald}$)(ppm)

	π	τ_{cald}	τ	$\Delta\tau$
2,5-Dimethylbenzoxazole	1.096	3.08	2.63	−0.45
2,5,7-Trimethylbenzoxazole	1.140	3.25	2.91	−0.34
2,5,6-Trimethylbenzoxazole	1.092	3.06	2.72	−0.34
2-Methyl 5-chlorobenzoxazole	1.001	2.71	2.40	−0.31

equally. Moreover, it is found, from the π-electron density calculations, that protonation to the N atom causes less than a 1% decrease in the benzene ring current.

Influence of Magnetic Anisotropy of the N and O Atoms. When the local atomic susceptibility on the neighboring atom (X) is anisotropic, a proton (H) will experience a shielding effect. Suppose the three principal susceptibilities of X are χ_x^i ($i=1, 2, 3$) in directions which make angles, γ_i with the XH line; the mean contribution to the proton screening constant, $\Delta\sigma$, is then obtained from²⁾:

$$\Delta\sigma = \tfrac{1}{3}R^{-3}\sum_{i=1,2,3}\chi_x^i(1-3\cos^2\gamma_i)$$

where R=the distance between X and H.

A number of studies dealing with the magnetic anisotropy of the nitrogen atom have appeared. Dailey and Gawer⁷⁾ calculated the shifts due to the magnetic anisotropy of the N atom in the case of nitrogen heterocyclic molecules, including pyridine and quinoline, and found a rather large shift at the 8 position in quinoline. Their calculated values, however, can not be applied to benzoxazoles with a five-membered ring and two hetero-atoms.

We calculated the paramagnetic susceptibilities of the N and O atoms ($\chi_N{}^p$ and $\chi_O{}^p$) of 2,5-dimethylbenzoxazole by the method proposed by Pople,⁸⁾ assuming the oxazole ring of benzoxazoles to be a regular pentagonal structure and the N–C (like the O–C) bond to be a linear combination of an equal weight of N (or O) and C hybrid. As coordinate axes, y is taken along the lone-pair orbital, and z, perpendicular to the molecular plane. For an average excitation energy ΔE, we used 4.3 eV in the x-direction and 10 eV⁷⁾ in the y and z-directions.

The calculated susceptibilities and shifts are given in Tables 4 and 5.

TABLE 4. CALCULATED PARAMAGNETIC SUSCEPTIBILITIES OF N AND O ATOMS IN 2,5-DIMETHYLBENZOXAZOLE

$(Q_N)_x$	$(Q_N)_y$	$(Q_N)_z$	$(Q_O)_x$	$(Q_O)_y$	$(Q_O)_z$
2.32	3.22	2.00	1.59	2.68	2.00
$(\chi_N{}^p)_x$	$(\chi_N{}^p)_y$	$(\chi_N{}^p)_z$	$(\chi_O{}^p)_x$	$(\chi_O{}^p)_y$	$(\chi_O{}^p)_z$
17.4	10.4	6.5	11.9	8.7	6.5

The notations are the same as those in Ref. 8.

TABLE 5. CHEMICAL SHIFTS DUE TO THE MAGNETIC ANISOTROPY OF N AND O ATOM IN 2,5-DIMETHYLBENZOXAZOLE (ppm)

Position	due to N	due to O	Total
4	−0.40	−0.00	−0.41
6	−0.03	−0.04	−0.07
7	0.01	−0.20	−0.19

Influence of Electric Field. Buckingham⁹⁾ and Musher¹⁰⁾ have derived expressions for the electricfield effect by different methods. We used the former method to calculate the shifts due to this effect:

$$\sigma_E = -2\times10^{-12}E_z - 10^{-18}E^2$$

where E=the total electric field at the nucleus and E_z=its component along the z axis.

Because the measured dipole moments of furan, pyridine, and benzoxazole are 0.7, 2.2, and 1.5 Debye¹¹⁾ respectively, we assigned a dipole moment of 2.0 Debye to the nitrogen lone pair and one

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7) A. H. Gawer and B. P. Dailey, *J. Chem. Phys.*, **42**, 2658 (1965).

8) J. A. Pople, *J. Chem. Phys.*, **37**, 53, 60 (1962).

9) A. D. Buckingham, *Can. J. Chem.*, **38**, 300 (1960).

10) J. I. Musher, *J. Chem. Phys.*, **37**, 34 (1961).

11) L. E. Orgel, T. L. Cottrell, W. Dick and L. E. Sutton, *Trans. Faraday Soc.*, **47**, 113 (1951).

of 0.5 Debye to the oxygen lone pair from each atom at 1.0 A.[7] The calculated shifts are given in Table 6.

Correction for Magnetic Anisotropy Effects of Hetero-atoms and the Electric Field Effect. We corrected the measured shifts by adopting the values in Tables 5 and 6 as the shifts due to these effects.

TABLE 6. CHEMICAL SHIFTS DUE TO ELECTRIC FIELD EFFECT (ppm)

	4H	6H	7H
Assigned to N atom	−0.18	−0.03	−0.04
Assigned to O atom	−0.01	−0.01	−0.04
Total	−0.19	−0.04	−0.08

TABLE 7. CORRECTED CHEMICAL SHIFTS (τ_{corr}) AND π-ELECTRON DENSITIES (π)

Molecule	Position	π	τ_{corr}
2,5-Dimethyl-benzoxazole	4	1.096	3.23
	6	1.075	3.14
	7	0.997	3.02
2,5,7-Trimethyl-benzoxazole	4	1.140	3.51
	6	1.143	3.39
2,5,6-Trimethyl-benzoxazole	4	1.092	3.32
	7	1.067	3.18
2-Methyl 5-chloro-benzoxazole	4	1.001	3.00
	6	1.005	2.88
	7	1.003	2.93
2,4,5-Trimethyl-benzoxazole	6	1.072	3.06
	7	1.044	3.12

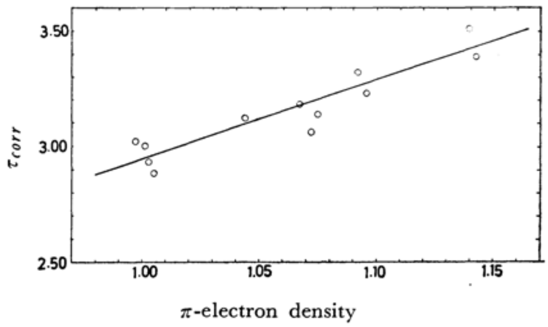

Fig. 4. Relation between the corrected shifts (τ_{corr}) and π-electron densities.
$\tau-2.95=3.37\ (\pi-1)$

In Table 7 and Fig. 4, the relation of the corrected shifts (τ_{corr}) to the calculated π-electron densities is presented. In this way, the following expression has been obtained to represent the relation by the least-squares method:

$$\tau_{corr}-2.95=3.37\ (\pi-1)$$

The slope of the line, 3.37 ppm/charge, is somewhat smaller than the values already reported[3] (∼10 ppm/charge). The line indicating the shifts in CF_3COOH lies in a field about 0.6 ppm lower than this corrected line. This may be attributed partly to an overestimation of the magnetic anisotropy and of the electric-field effect, and partly to the difference in solvent effect between CCl_4 (or $CDCl_3$) and CF_3COOH.

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