2,2-bis-[4-(*m*-bromophenyl)-6-phenyl-pyrimidinyl] disulphide (XIVb), 2-amino-4-aryl-6-phenyl-pyrimidines (XVa, b), 2-acetamido-4-aryl-6-phenylpyrimidine (XVIa, b) and α-aroyl-β-benzylthiostyrenes (XVIIa, b) were prepared according to the methods previously reported by our group.[2-4] The results are reported in Table I.

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Studies on Carbon-13 Magnetic Resonance Spectroscopy. IX.[1] Carbon-13 Pulse Fourier Transform Nuclear Magnetic Resonance Chemical Shifts of 1-Substituted-3,4-dimethoxy- and -3,4-methylenedioxybenzene Derivatives

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C-13 nuclear magnetic resonance chemical shifts of 1-substituted-3,4-dimethoxy- and -3,4-methylenedioxybenzene derivatives were measured. Reliability of the additivity rule of the shielding parameters of monosubstituted benzenes, and the linear relations between the chemical shifts and shielding parameters or substituent constants were confirmed. Deviations from the additivity rule are mainly attributed to the *ortho* steric effect.

Keywords——C-13 NMR chemical shift; 1-substituted-3,4-dimethoxybenzenes; 1-substituted-3,4-methylenedioxybenzenes; substituent constants; additivity rule

Introduction

In the previous reports of this series,[3] carbon-13 chemical shifts of mono- (**1**) and disubstituted benzene derivatives were measured under the proton decoupled continuous wave mode, and the reliability of the additivity rule of the shielding parameters of monosubstituted benzenes was confirmed in the disubstituted series, and the correlations between the chemical shifts and substituent constants σ_i or σ_π,[4] as empirical parameters of σ- and π-electronic effects, were also acknowledged.

In this work, the reliabilities of the above rule were examined for 1-substituted-3,4-dimethoxy- (**2**) and -3,4-methylenedioxy benzene (**3**) series, and the relationships between the chemical shifts and shielding parameters and/or with the substituent constants were confirmed as the basis of the assignment of the chemical shifts of complex natural products.

Experimental

All monosubstituted benzenes were commercially available, whereas 1-substituted-3,4-dimethoxy- and -3,4-methylenedioxybenzene derivatives were prepared by the authentic methods from vanilline, piperonal, *etc.*

All spectra were measured at 22.63 MHz on a Hitachi R-22 type NMR spectrometer with a HITAC 10-II computer system under pulse Fourier transform mode. 99.8% $CDCl_3$ (CEA) solutions of samples

1) Part VIII: M. Sugiura and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **22**, 2988 (1976).
2) Location: *Yamadakami 133-1, Suita, Osaka 565, Japan.*
3) G. Miyajima, Y. Sasaki, and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **19**, 2301 (1971); *idem, ibid.*, **20**, 429 (1972).
4) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 873 (1965).

were prepared in a concentration range of 0.5 M with 1% TMS internal standard. Chemical shifts are given in ppm relative to TMS.

Conditions of measurements are as follows: pulse angle, 25 μsec; pulse location, 7300 Hz; decoupling powder, 8 watts; data points, 8 K; pulse interval, 5 or 3 sec; error, ±0.06 ppm.

Results and Discussion

Monosubstituted Benzene Derivatives

Carbon-13 chemical shifts of **1** in $CDCl_3$ are summarized in Table I.

These data are slightly different from our previous results[3] measured in the high concentration by the proton decoupled continuous wave mode. Chemical shifts at each positions

Table I. C-13 Chemical Shifts (ppm) of Monosubstituted Benzene Derivatives

Substituent	Position			
	ipso	*ortho*	*meta*	*para*
NH_2	18.04	−13.24	0.90	−9.83
OMe	31.35	−14.32	1.08	−7.70
OH	27.03	−12.89	1.38	−7.37
OCOMe	22.48	−6.77	1.08	−2.58
Br	−5.75	3.24	1.68	−1.50
Et	15.88	0	−0.47	−2.76
Me	9.53	0.72	−0.08	−3.00
H	0	0	0	0
CO_2Me	1.98	1.26	0	4.56
CHO	8.21	1.38	0.66	6.05
COMe	8.93	−0.06	0.24	4.68
CN	−15.70	3.84	0.86	4.44
NO_2	20.08	−4.85	0.96	6.17

Internal reference=TMS.
Concentration=0.5—0.6 M in $CDCl_3$.
C-13 chemical shifts of C_6H_6=+128.26 ppm from TMS.

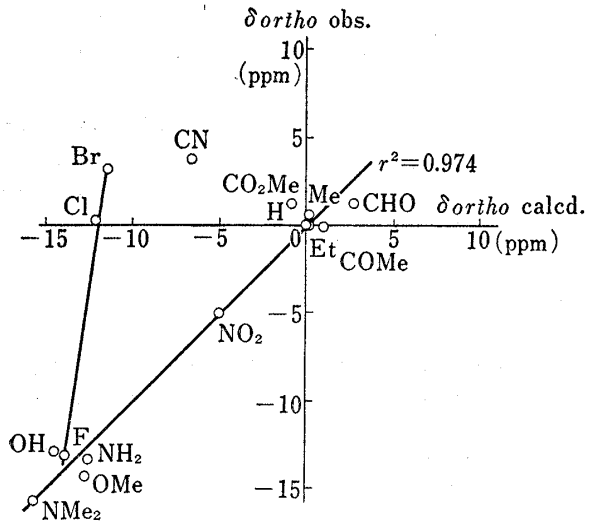


Fig. 1. Correlations between Observed and Calculated C-13 Chemical Shifts of *ortho* Positions of Monosubstituted Benzenes

$\delta_{ortho\ Calcd.}$ are calculated by $-31.3\,\sigma_I+26.5\,\sigma_\pi+0.5$
Factors are estimated by least square method.

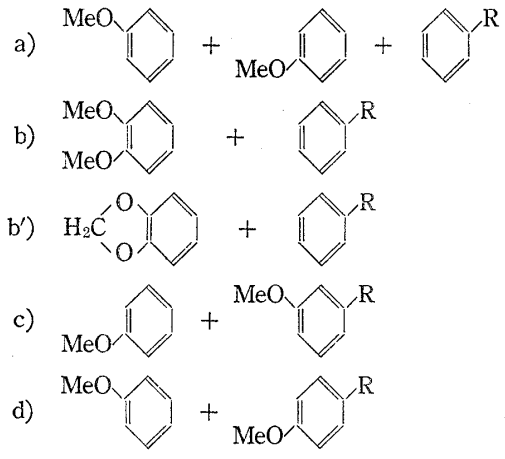


Chart 1

were tried to correlate with some parameters. Among them, δ_{ortho} —the shifts of *ortho* positions— are found to correlate with the linear combination of σ_i and σ_π, except CN and halogens (Fig. 1). The deviation of benzonitrile is ascribed to the dimer formation in solution,[5] and those of halogens to their heavy atom effects,[6] and roughly correlate with electronegativity.[7]

Additivity Rule

To predict the chemical shifts of **2** by the additivity rule, four treatments are proposed, namely, a) simple summation of three shielding parameters obtained from **1**, b) summation of shielding parameters of monosubstituted benzenes and veratrole, considering the *ortho* steric effect,[8] c) anisole and *meta*-substituted anisole series, and d) anisole and *para*-substituted anisole series,[9] respectively (*cf.* Chart 1). Of the four, method b) is the best one which leads to the least mean of |Δ value|, defined as the difference between the observed and calculated shifts. Observed and calculated shifts of **2** referred to benzene (128.26 ppm from TMS) and the |Δ values| are listed in Table II. With a few exceptions, |Δ values| are small enough to assign the shifts of related compounds using the additivity rule alone. Means of |Δ values| at each positions calculated by method a) and b), as well as the observed and calculated shifts

Table II. Calculated and Observed C-13 Chemical Shifts (ppm) of 1-Substituted 3,3-Dimethoxybenzene Derivatives

Substituent			C-1	Δ	C-2	Δ	C-3	Δ	C-4	Δ	C-5	Δ	C-6	Δ
NH_2	Calcd.	(a)	11.42	0.98	−26.48	0.91	17.93	3.76	7.20	6.76	−12.34	2.53	−19.86	1.96
		(b)	10.61	1.79	−30.02	2.63	21.76	0.07	11.03	2.93	−15.88	1.01	−20.67	1.15
	Obs.		12.40		−27.39		21.69		13.96		−14.87		−21.82	
OMe	Calcd.	(a)	24.73	1.40	−27.56	0.19	18.11	3.65	9.33	5.95	−12.16	3.90	−20.94	4.23
		(b)	23.92	2.21	−31.10	3.35	21.94	0.18	13.16	2.12	−15.70	0.36	−21.75	3.42
	Obs.		26.13		−27.75		21.76		15.28		−16.06		−25.17	
Me	Calcd.	(a)	2.91	0.77	−12.52	3.15	16.95	3.60	14.03	4.77	−13.32	3.43	−5.90	1.60
		(b)	2.10	0.04	−16.06	0.39	20.78	0.23	17.86	0.94	−16.86	0.11	−6.71	0.79
	Obs.		2.14		−15.67		20.55		18.80		−16.75		−7.50	
Br	Calcd.	(a)	−12.37	4.35	−10.00	3.31	18.71	2.87	15.53	4.61	−11.56	4.02	−3.38	1.47
		(b)	−13.18	3.54	−13.54	0.23	22.54	0.96	19.36	0.78	−15.10	0.48	−4.19	0.66
	Obs.		−16.72		−13.31		21.58		20.14		−15.58		−4.85	
CO_2Me	Calcd.	(a)	−4.64	0.81	−11.98	4.08	17.03	3.41	21.59	3.22	−13.24	4.56	−5.36	0.75
		(b)	−5.45	0	−15.52	0.54	20.86	0.42	25.42	0.61	−16.78	1.02	−6.17	1.56
	Obs.		−5.45		−16.06		20.44		24.81		−17.80		−4.61	
CHO	Calcd.	(a)	1.59	0.31	−11.86	5.96	17.69	3.71	23.08	3.18	−12.58	6.55	−5.24	3.60
		(b)	0.78	1.12	−15.40	2.42	21.52	0.12	26.91	0.65	−16.12	3.01	−6.05	4.41
	Obs.		1.90		−17.82		21.40		26.26		−19.13		−1.64	
COMe	Calcd.	(a)	2.31	0.03	−13.30	4.68	17.27	3.53	21.71	3.40	−13.00	5.22	−6.68	1.65
		(b)	1.50	0.84	−16.84	1.14	21.10	0.30	25.54	0.43	−16.54	1.68	−7.49	2.46
	Obs.		2.34		−17.98		20.80		25.11		−18.22		−5.03	
CN	Calcd.	(a)	−22.32	2.01	−9.40	4.80	17.89	3.09	21.47	3.16	−12.38	4.52	−2.78	0.92
		(b)	−23.13	1.20	−12.94	1.26	21.72	0.74	25.30	0.67	−15.92	0.98	−3.59	1.73
	Obs.		−24.33		−14.20		20.98		24.63		−16.90		−1.86	
NO_2	Calcd.	(a)	13.46	0.34	−18.09	3.61	17.99	2.63	23.20	3.05	−12.28	6.12	−11.47	0.62
		(b)	12.65	0.47	−21.63	0.07	21.82	1.20	27.03	0.78	−16.86	1.54	−12.28	1.43
	Obs.		13.12		−21.70		20.62		26.25		−18.40		−10.85	

5) M. Mishima, Ph. D. Thesis, Osaka University (1976).
6) G.E. Maciel, "Topics in Carbon-13 NMR Spectroscopy," Vol. I, ed. by G.C. Levy, John Wiley and Sons Inc., New York, 1974, p. 68.
7) H.O. Pritchard and H.A. Skiner, *Chem. Res.*, **55**, 745 (1955).
8) D.M. Grant and B.V. Cheney, *J. Am. Chem. Soc.*, **89**, 5315 (1968).
9) G.B. Savitsky, *J. Phys. Chem.*, **67**, 2723 (1963); D.W. Beistel and W.D. Edwards, *ibid.*, **80**, 2023 (1976).

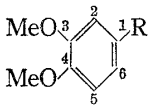
of veratrole are tabulated in Table III. The |Δ values| of about 3 ppm at C-3 and -4 of veratrole are revealed also at the same positions as the mean of |Δ values| by method a). The deviations by method a) are mainly ascribed to the effect of *ortho* disubstitution, and consequently, the reliance of additivity by the method b) including this effect is well promoted.

The observed chemical shifts of **3**, calculated shifts by method b'), and the shift differences (|Δ values|) are also listed in Table IV. The magnitudes of the |Δ values| are the same order as those of **2** by the method b), and the utility of the additivity rule is also confirmed.

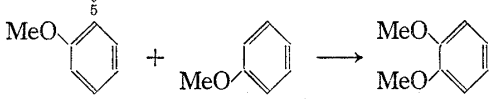
Table III. Comparison of Method a) and b) in Veratrole

Position[a)]		1	2	3	4	5	6
Mean of |Δ values|	Method a)	1.22	3.41	3.36	4.28	4.54	1.87
	Method b)	1.25	1.34	0.47	1.10	1.13	1.96
Veratrole	Calcd.[b)]	−6.62	−13.24	17.03	17.03	−13.24	−6.62
	Obs.	−7.43	−16.78	20.86	20.86	−16.78	−7.43
	[c)]	0.81	3.54	3.83	3.83	3.54	0.81

a)



b)



c) |Δ values| are expressed in ppm unit.

Table IV. Calculated and Observed C-13 Chemical Shifts (ppm) of 1-Substituted-3,4-methylenedioxybenzene Derivatives

		C-1	C-2	C-3	C-4	C-5	C-6
NH_2	Calcd.	11.33	−32.90	20.02	9.29	−18.76	−19.95
	Obs.	13.12	−30.27	19.90	11.98	−19.78	−21.46
	Δ	1.79	2.63	0.12	2.69	1.02	1.51
OMe	Calcd.	24.64	−33.98	20.20	11.42	−18.58	−21.03
	Obs.	26.91	−30.81	20.02	13.37	−20.44	−23.49
	Δ	2.27	3.17	0.18	1.95	1.86	2.46
Me	Calcd.	2.82	−18.94	19.04	16.12	−19.74	−5.99
	Obs.	3.12	−18.76	19.18	17.02	−20.26	−6.83
	Δ	0.30	0.18	0.14	0.90	0.52	0.84
Br	Calcd.	−12.46	−16.42	20.80	17.62	−17.98	−3.47
	Obs.	−15.22	−16.00	20.32	18.70	−18.76	−4.02
	Δ	2.76	0.42	0.48	1.08	0.78	0.55
CO_2Me	Calcd.	−4.73	−18.40	19.12	23.68	−19.66	−5.45
	Obs.	−4.02	−18.76	19.42	23.25	−20.38	−3.00
	Δ	0.71	0.24	0.30	0.43	0.72	2.45
COMe	Calcd.	2.22	−19.72	19.36	23.80	−19.42	−6.77
	Obs.	3.90	−20.30	19.85	23.48	−20.53	−3.57
	Δ	1.68	0.58	0.49	0.32	1.11	3.20
CHO	Calcd.	1.50	−18.28	19.78	25.17	−19.00	−5.33
	Obs.	3.90	−20.30	19.85	23.48	−20.53	−3.57
	Δ	2.40	2.02	0.07	1.69	1.53	1.76
CN	Calcd.	−22.41	−15.82	19.98	23.56	−18.80	−2.87
	Obs.	−23.20	−16.90	19.78	23.25	−19.18	−0.12
	Δ	0.79	1.08	0.20	0.31	0.38	2.75
NO_2	Calcd.	13.37	−24.51	20.08	25.29	−18.70	−11.56
	Obs.	14.38	−23.79	19.96	24.81	−20.74	−8.45
	Δ	1.01	0.72	0.12	0.48	2.04	3.11

Δ = chemical shifts difference expressed in an absolute value.

As to the corresponding positions, good correlations between 2 and 3 are observed at C-1, -2, -4, and -6 (Table V). The disagreements at C-3 and -5 are elucidated by the fact that chemical shifts at C-3 and -5 of **2** are expressed by the linear combination of σ_π and δ_{meta}, whereas those of **3** are not (cf. Table VI).

TABLE V

Position	Correlation coefficient **2** *vs.* **3**	Position	Correlation coefficient **2** *vs.* **3**
C-1	0.999	C-4	0.999
C-2	0.995	C-5	0.522
C-3	0.433	C-6	0.995

TABLE VI. Correlation Coefficient Chemical Shifts *vs.* Various Parameters

Position	Correlation for	**2**	**3**
1	δ_{ipso}	0.995	0.995
2	δ_{ortho}	0.969	0.986
3	δ_{meta}	0.519	0.609
	σ_π	0.573	0.015
	σ_I	0.000	0.311
	$-1.17\sigma_\pi+0.49\delta_{meta}$	0.892	
4	δ_{para}	0.998	0.997
	σ_π	0.992	0.969
5	δ_{meta}	0.145	0.141
	σ_π	0.812	0.094
	σ_I	0.131	0.006
	$-3.73\sigma_\pi+0.50\delta_{meta}$	0.874	
6	δ_{ortho}	0.953	0.936

δ_{ipso}, δ_{ortho}, δ_{meta}, δ_{para}: chemical shifts of monosubstituted benzenes.

The correlations between C-13 chemical shifts of **2** or **3** and some parameters such as shielding parameters (δ_{ipso}, δ_{ortho}, δ_{meta}, and δ_{para}), substituent constants σ_π and σ_I, or their linear combinations are summarized in Table VI, where C-1, -2, -4, and -6 showed good linear relations with the shielding parameters, but none of parameters were linear with chemical shifts at *meta*- like positions C-3 and -5.

The chemical shifts of C-3 and -5, corresponding to the *meta* positions of the substituent groups, are expected to correlate with the substituent constants σ_π, owing to the resonance interaction between C-1 substituents and C-4 OCH_3. Actually, C-5 chemical shifts are linear with the substituent constants σ_π (r^2=0.812). Methoxyl group at C-3 position disturbs 1,4-resonance interaction, and C-3 chemical shifts afforded poor interrelations with the substituent constants σ_π or *meta* shielding parameters. The correlation coefficients are promoted by the linear combination of σ_π and δ_{meta} (r^2=0.892 for C-3 and r^2=0.874 for C-5).