

Studies on ^{13}C Magnetic Resonance Spectroscopy. XV.¹⁾
Correlation between ^{13}C NMR Chemical Shifts and
Charge Densities of Diaza-Benzenes

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Charge densities of diaza-benzenes—2-substituted pyrazines, 5-substituted pyrimidines and 4-substituted pyridazines—were calculated by the MINDO/2 method.

The correlations of the substituent-induced ^{13}C chemical shifts (^{13}C SCS) values of these three diaza-benzenes with total charge densities were determined, and linear relations between the two parameters were found even at the *ipso* position, whereas the correlations of the *ipso* SCS with a linear combination of substituent constants were poor.

Keywords— ^{13}C NMR chemical shift; charge density; HMO; MINDO/2; substituent constant; 2-substituted pyrazines; 5-substituted pyrimidines; 4-substituted pyridazines

Introduction

In aromatic systems it is useful to predict the chemical shift from the chemical structure or from an empirical parameter, of which the substituent constant³⁾ is the most important and expedient.

In the previous papers of this series,^{4,5)} ^{13}C chemical shifts have been reported for various diaza-benzenes, namely, 2-substituted pyrazines (I), 5-substituted pyrimidines (II) and 4-substituted pyridazines (III). The results of such studies can often be correlated with the ^{13}C chemical shifts of monosubstituted benzenes and pyridines and/or substituent constants.

Many studies⁶⁾ have sought to correlate the substituent-induced ^{13}C chemical shifts (SCS) of aromatic compounds with charge densities, but little work has been done on diaza-benzenes.

In this work, we investigated the relation between the ^{13}C chemical shifts of these three series of diaza analogs and linear combinations of the substituent constants σ_i and σ_π or of the charge densities calculated by the MINDO/2 method, including electronic interaction between substituents and the σ - or π -framework.

Experimental

Parametrizations of the simple HMO and MINDO/2 methods using modified programs based upon those of Kikuchi⁷⁾ were carried out on a NEAC 2200 computer, model S800, at the Computation Center of Osaka University.

- 1) Part XIV: H. Takai, A. Odani, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **27**, 1780 (1979).
- 2) Location: Yamadakami 133-1, Suita, Osaka 565, Japan.
- 3) For example; a) Y. Yukawa and Y. Tsuno, *Nippon Kagaku Zasshi*, **86**, 873 (1965); b) Y. Yukawa, "Riron Yuki Kagaku," Kagaku-Dojin, Kyoto, 1974, p. 89.
- 4) T. Tsujimoto, C. Kobayashi, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **27**, 691 (1979).
- 5) T. Tsujimoto, T. Nomura, M. Iifuru, and Y. Sasaki, *Chem. Pharm. Bull.* (Tokyo), **27**, 1169 (1979).
- 6) For example; a) P. Lazzeretti and F. Taddei, *Org. Magn. Reson.*, **3**, 283 (1971); b) T.K. Wu and B.P. Dailey, *J. Chem. Phys.*, **41**, 2796 (1964).
- 7) O. Kikuchi, "Bunshi-Kido-Ho," Kodansha, Tokyo, 1971.

Streitwieser's parameters⁸⁾ were used for the simple HMO parametrization.

The molecular geometries were estimated on the bases of data for pyrazine,⁹⁾ pyrimidine¹⁰⁾ and pyridazine,¹¹⁾ as well as for the corresponding monosubstituted benzene and pyridine derivatives.¹²⁾

The more stable molecular geometry was employed when two different substituent conformations could be considered.

Results and Discussion

Calculated total-, π - and σ -charge densities of the ring carbons of the diaza-benzene series are summarized in Table I—III.

The correlation coefficients of the SCS of these series with several empirical parameters are summarized in Table IV.

1) 2-Substituted Pyrazines (I)

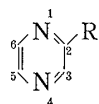
The ¹³C SCS values of I correlate linearly with $\alpha\sigma_i + \beta\sigma_\pi$ (α, β =empirical factors) except at the *ipso* and *meta* positions.

The poor correlation at the *meta* position may be mainly attributable to the narrow range of distribution of chemical shifts, causing them to be relatively more sensitive to experimental error or to second order effects.⁵⁾ These correlations indicate that a linear combination of substituent constants is preferable to their individual use.^{4,5)}

TABLE I. Charge Densities of 2-Substituted Pyrazines^{a)} calculated by the MINDO/2 Method

	C-2			C-3			C-5			C-6		
	Total-	π -	σ -	Total-	π -	σ -	Total-	π -	σ -	Total-	π -	σ -
NMe ₂	3.5306	0.8185	2.7121	3.9046	1.0420	2.8627	3.8737	1.0393	2.8344	3.7619	0.9107	2.8513
NH ₂	3.5076	0.8343	2.6733	3.8940	1.0376	2.8564	3.8643	1.0226	2.8418	3.7597	0.9101	2.8496
OMe	3.3824	0.8099	2.5726	3.8901	1.0284	2.8618	3.8576	1.0279	2.8297	3.7533	0.9169	2.8363
Me	3.7023	0.8777	2.8246	3.8201	0.9803	2.8398	3.8194	0.9843	2.8351	3.7711	0.9306	2.8405
H	3.7891	0.9436	2.8455	3.7891	0.9436	2.8455	3.7891	0.9436	2.8455	3.7891	0.9436	2.8455
COOMe	3.9558	1.0144	2.9414	3.7408	0.8911	2.8496	3.7941	0.9051	2.8591	3.8106	0.9573	2.8534

a) The numbering is as follows:



- 8) A. Streitwieser Jr., "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, 1961.
- 9) P.J. Wheatley, *Acta Cryst.*, **10**, 182 (1957).
- 10) F. Török, A. Hegedüs, and P. Pulay, *Theoret. Chim. Acta*, **32**, 145 (1973).
- 11) A. Almenningen, J. Bjørnsen, T. Ottersen, R. Seip, and T.G. Strand, *Acta Chem. Scand. (A)*, **31**, 63 (1977).
- 12) 2-Substituted Pyrazines—*a)* N,N-Me₂: i) P.Y. Delugeard and J.C. Messenger, *Acta Cryst.*, **B31**, 2809 (1975); ii) M. Chao, E. Schempp, and R.D. Rosenstein, *Acta Cryst.*, **B32**, 288 (1976); *b)* NH₂: *Idem, ibid.*, **B32**, 288 (1976); *c)* OMe: D.R. Carter and F.P. Boer, *J. Heterocycl. Chem.*, **9**, 335 (1972); *d)* Me: J.V. Barve and L.M. Pant, *Acta Cryst.*, **B27**, 1158 (1971); *e)* COOMe: i) F. Takusagawa, T. Higuchi, A. Shimada, C. Tamura, and Y. Sasada, *Bull. Chem. Soc. Jpn.*, **47**, 1409 (1974); ii) D.L. Hughes and J. Trotter, *J. Chem. Soc.*, 2358 (1971).
- 5-Substituted Pyrimidines—*a)* N,N-Me₂: i) F. Török, A. Hegedüs, and P. Pulay, *Theoret. Chim. Acta*, **32**, 145 (1973); ii) M. Chao, E. Schempp, and D. Rosenstein, *Acta Cryst.*, **B33**, 1820 (1977); *b)* NH₂: *Idem, ibid.*, **B31**, 2922 (1975); *c)* OMe: i) M.G. Takwale and L.M. Pant, *ibid.*, **B27**, 1152 (1971); ii) H.M. Seip and R. Seip, *Acta Chem. Scand.*, **27**, 4024 (1973); *d)* Me: M.G. Takwale and L.M. Pant, *Acta Cryst.*, **B27**, 1152 (1971).
- 4-Substituted Pyridazines—*a)* N,N-Me₂: P.Y. Delugeard and J.C. Messenger, *Acta Cryst.*, **B31**, 2809 (1975); *b)* NH₂: D.G. Lister, J.K. Tyler, J.H. Hog, and N.W. Larsen, *J. Mol. Struct.*, **23**, 253 (1974); *c)* OMe: H.M. Seip and R. Seip, *Acta Chem. Scand.*, **27**, 4024 (1973); *d)* Me: J.V. Barve and L.M. Pant, *Acta Cryst.*, **B27**, 1158 (1971); *e)* COOMe: i) D.L. Hughes and J. Trotter, *J. Chem. Soc.*, 2358 (1971); ii) N. Tanaka, T. Ashida, Y. Sasada, and M. Kakudo, *Bull. Chem. Soc. Jpn.*, **40**, 2717 (1967).

At the *ipso*, *ortho* or *meta* positions, the correlations of ^{13}C SCS of I with π -electron charge density— ρ_π —determined by the simple HMO method lack consistency and are poor even at the *para* position.

In the next step, ^{13}C SCS of I was compared with the total-electron charge density— ρ_{total} —calculated by the MINDO/2 method.

TABLE II. Charge Densities of 5-Substituted Pyrimidines^{a)} calculated by the MINDO/2 Method

	C-2			C-4			C-5		
	Total-	π -	σ -	Total-	π -	σ -	Total-	π -	σ -
NMe ₂	3.4288	0.7559	2.6279	3.7101	0.8529	2.8572	3.9018	1.0468	2.8550
NH ₂	3.4141	0.7420	2.6721	3.6718	0.8271	2.8447	3.9449	1.0759	2.8690
OMe	3.4185	0.7465	2.6720	3.6969	0.8332	2.8637	3.8220	1.0635	2.7585
Me	3.3882	0.7186	2.6696	3.6070	0.7789	2.8281	4.1948	1.1284	3.0664
H	3.3760	0.7014	2.6746	3.5836	0.7512	2.8324	4.2130	1.1732	3.0398

a) The numbering is as follows:

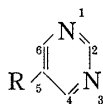


TABLE III. Charge Densities of 4-Substituted Pyridazines^{a)} calculated by the MINDO/2 Method

	C-3			C-4			C-5			C-6		
	Total-	π -	σ -	Total-	π -	σ -	Total-	π -	σ -	Total-	π -	σ -
NMe ₂	3.8611	0.9894	2.8717	3.7203	0.8563	2.8640	4.1468	1.1162	3.0306	3.7159	0.8679	2.8480
NH ₂	3.8335	0.9646	2.8689	3.7266	0.8785	2.8481	4.1016	1.0749	3.0267	3.7281	0.8802	2.8479
OMe	3.8592	0.9835	2.8757	3.5984	0.8487	2.7497	4.1591	1.1096	3.0495	3.7184	0.8696	2.8488
Me	3.7899	0.9409	2.8490	3.9197	0.9057	3.0140	4.0595	1.0364	3.0231	3.7426	0.8910	2.8516
H	3.7616	0.9091	2.8525	4.0053	0.9757	3.0296	4.0053	0.9757	3.0296	3.7616	0.9091	2.8525
COOMe	3.7062	0.8670	2.8392	4.1742	1.0403	3.1339	3.9601	0.9172	3.0429	3.7802	0.9278	2.8524

a) The numbering is as follows:

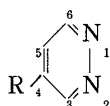


TABLE IV. Correlation Coefficients (γ) of Chemical Shifts of Diaza-Benzenes with Various Parameters

		$\alpha\sigma_i + \beta\sigma_\pi^a)$	$\rho_\pi^b)$	$\rho_{\text{total}}^c)$	$\rho_\pi^c)$	$\rho_\sigma^c)$
I	C-2	0.775	0.840	0.947	0.945	0.917
	C-3	0.967	0.794	0.929	0.896	0.860
	C-5	0.975	0.879	0.986	0.965	0.720
	C-6	0.823	0.137	0.838	0.841	0.305
II	C-2	0.989	0.911	0.947	0.944	0.569
	C-4	0.955	0.830	0.967	0.963	0.879
	C-5	0.771	0.888	0.962	0.917	0.940
III	C-3	0.984	0.711	0.838	0.803	0.889
	C-4	0.845	0.793	0.947	0.894	0.947
	C-5	0.995	0.753	0.863	0.841	0.178
	C-6	0.290	0.794	0.026	0.056	0.287

a) α, β = empirical factors.

b) Calculated by the simple HMO method.

c) Calculated by the MINDO/2 method.

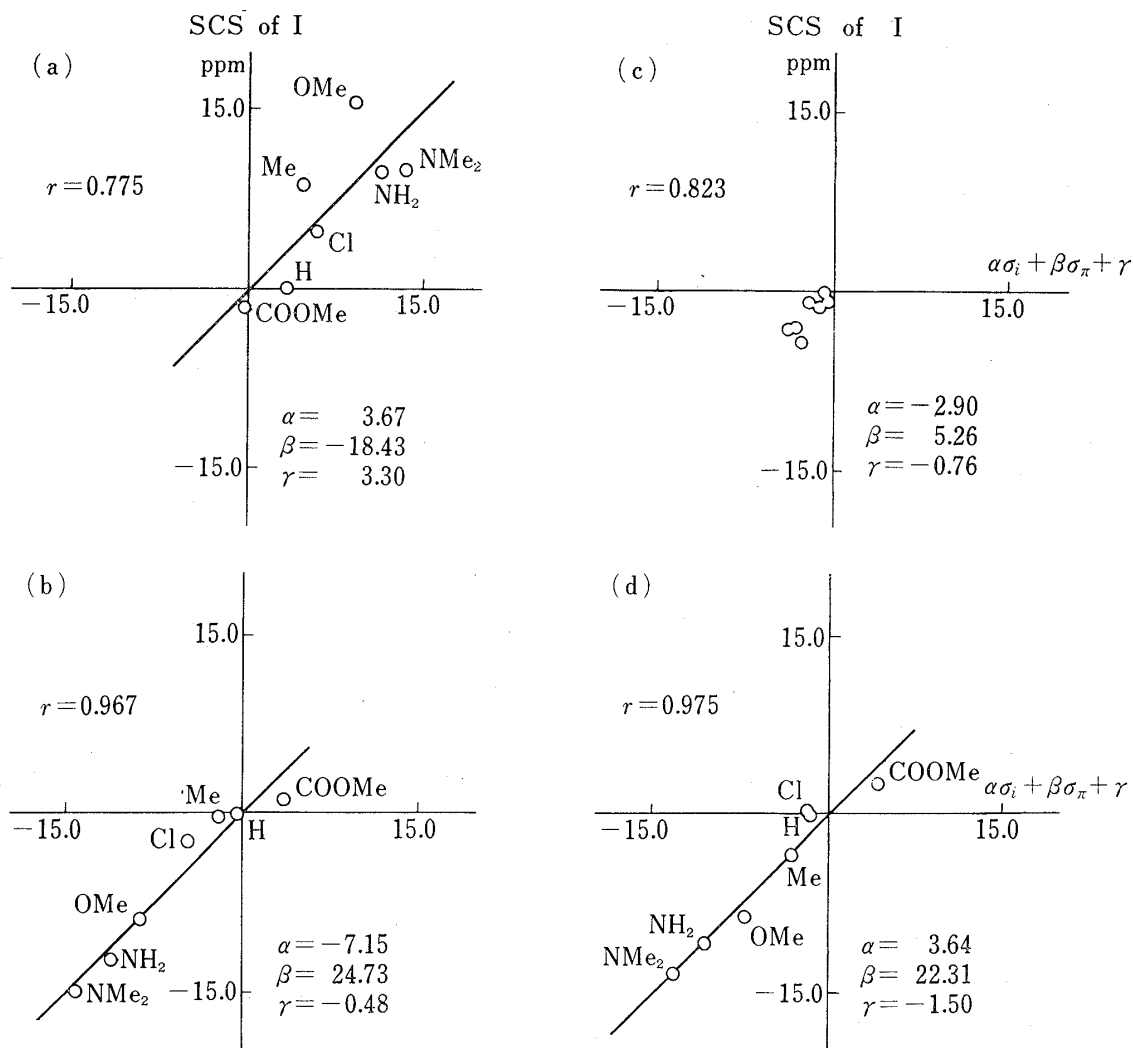


Fig. 1. Plots of ^{13}C SCS at (a) *ipso*, (b) *ortho*, (c) *meta* and (d) *para* Positions of 2-Substituted Pyrazines (I) vs. a Linear Combination of Substituent Constants

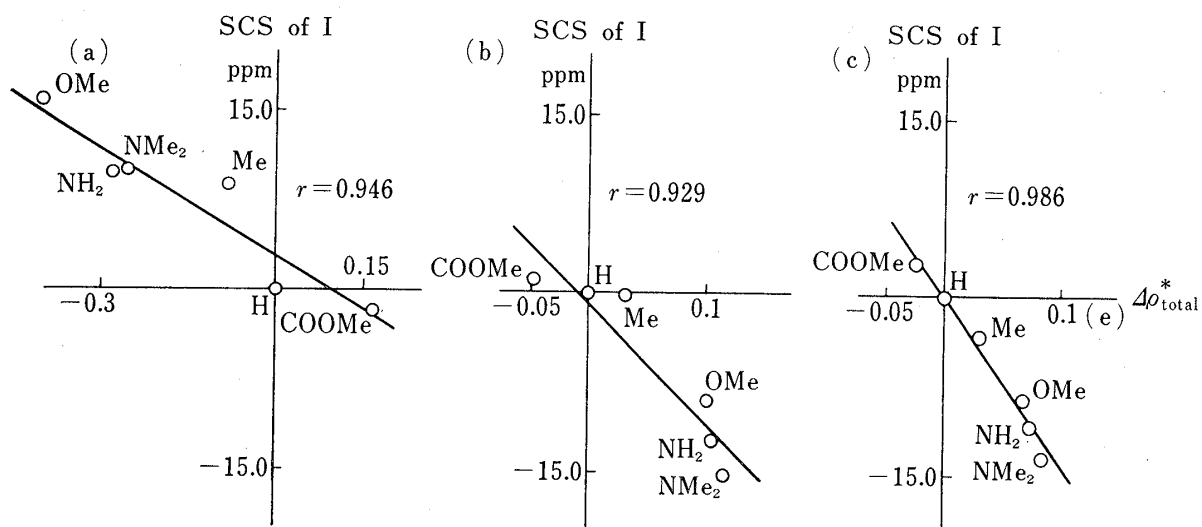


Fig. 2. Plots of ^{13}C SCS at (a) *ipso*, (b) *ortho* and (c) *para* Positions of 2-Substituted Pyrazines (I) vs. Total Charge Density calculated by the MINDO/2 Method

* $\Delta\rho = \rho(\text{X-R}) - \rho(\text{X-H})$.

In the first place, the relationship between ^{13}C SCS and ρ_π determined by MINDO/2 for I gives relatively high linearity except at the *meta* position (cf. Table IV), and attempts to correlate the SCS with ρ_{total} gave excellent results at the *ipso*, *ortho* and *para* positions, as illustrated in Fig. 2 (cf. Table IV).

As for the contribution of charge density, the slopes (e/ppm) of ρ_σ and ρ_π at the *ipso*, *ortho* or *para* positions—the relation of charge density vs. ^{13}C SCS of I—are -0.0184 , -0.0115 at the *ipso*, -0.0011 , -0.0077 at the *ortho* and 0.0012 , -0.0081 at the *para* position, respectively (cf. Table V). The ratios of ρ_σ/ρ_π are 1.60, 0.14 and -0.15 , and this agrees well with the observed trends for monosubstituted benzenes.

These results indicate that the effect of π -charge as well as σ -charge must be considered for the *ipso* position, and ^{13}C SCS at the *ipso* or *ortho* positions corresponded to the total charge density calculated by the MINDO/2 method, whereas σ_i and σ_π or their linear combinations are unsuccessful for the *ipso* position.

TABLE V. Slope (e/ppm) of the Plot of Charge Density vs. SCS for Monosubstituted Benzenes and Diaza-Benzenes

		ρ_π	ρ_σ	ρ_σ/ρ_π	ρ_i/ρ_σ
R-C ₆ H ₅ ^{a)}	C-1	-0.0048	-0.0115	2.40	0.42
	C-2	-0.0082	-0.0007	0.09	11.71
	C-4	-0.0073	0.0018	-0.25	-4.06
I	C-2	-0.0115	-0.0184	1.60	0.63
	C-3	-0.0077	-0.0011	0.14	7.00
	C-5	-0.0081	0.0012	-0.15	-6.75
II	C-2	-0.0041	0.0022	-0.54	-1.86
	C-4	-0.0049	-0.0016	0.33	3.06
	C-5	-0.0041	-0.0095	2.32	0.43
III	C-3	-0.0062	-0.0021	0.34	2.90
	C-4	-0.0057	-0.0106	1.86	0.54
	C-5	-0.0063	-0.0002	0.03	31.50

a) Monosubstituted benzenes; C-1=*ipso* position Unpublished data by H. Takai, A. Odani, and Y. Sasaki.

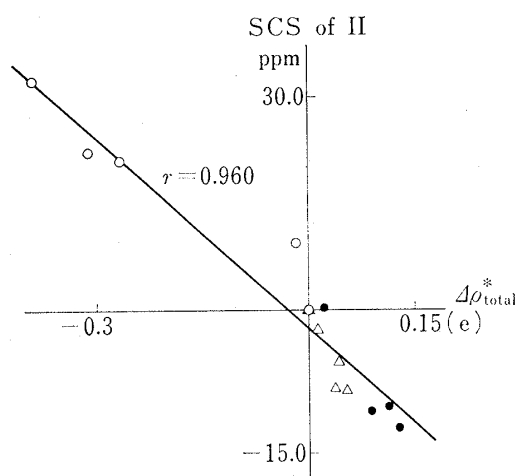


Fig. 3. Plots of ^{13}C SCS** of 5-Substituted Pyrimidines (II) vs. Total Charge Density calculated by the MINDO/2 Method

* $\Delta\rho = \rho(\text{X-R}) - \rho(\text{X-H})$.

** ○, *ipso*; ●, *ortho*; △, *para* position.

TABLE VI. π -Bond Order of 4-Substituted Pyridazines

Subs.	Bond	
	C ₃ -C ₄	C ₄ -C ₅
NMe	0.523	0.688
NH ₂	0.541	0.712
OMe	0.527	0.695
Me	0.555	0.728
H	0.573	0.743
COOMe	0.562	0.722

2) 5-Substituted Pyrimidines (II)

The ^{13}C chemical shifts of II show an excellent correlation with a linear combination of the substituent constants, and this treatment can be extended to the *ortho*, but not the *ipso* position; the correlation coefficients of both positions are improved by the use of a linear combination of the substituent constants.

For the *para* position, as shown in Table IV, a high degree of linearity is seen between ^{13}C SCS of II and ρ_π determined by the simple HMO method.

The correlation of ^{13}C SCS of II with ρ_{total} is successful at all positions; throughout all positions $r=0.960$ (cf. Fig. 3).

These results are consistent with those for I.

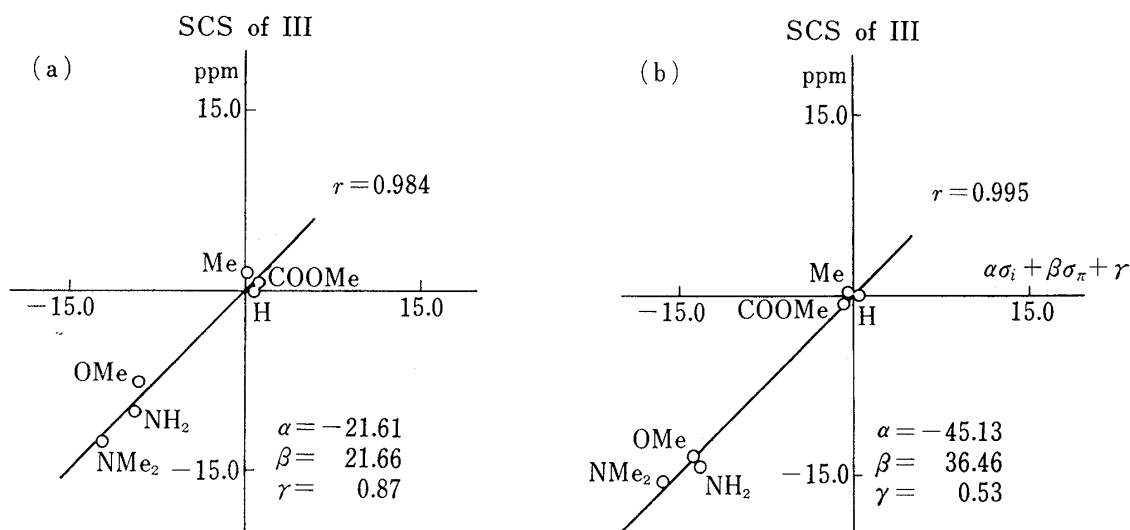


Fig. 4. Plots of ^{13}C SCS at (a) C-3 and (b) C-5 of 4-Substituted Pyridazines (III) vs. Linear Combinations of Substituent Constants

3) 4-Substituted Pyridazines (III)

As illustrated in Fig. 4, good linearities for the two *ortho* positions (C-3 and -5) were observed for the ^{13}C SCS of III and a linear combination of the substituent constants.

The correlations between ^{13}C SCS of III and ρ_{total} determined by the MINDO/2 method are only passable for all positions except *meta*, although the plots are roughly linear and the correlation coefficients (r) of the *ortho* positions are 0.838 and 0.863 at C-3 and -5, respectively, and the ratios of ρ_π/ρ_σ are 2.90 at C-3 and 31.50 at C-5.

This result suggests that the contribution of π -charge density is dominant at C-5, and this is consistent with the bond order calculated by the MINDO/2 method (cf. Table VI).