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LINEAR FREE ENERGY RELATIONSHIPS FOR CARBON-13 NMR CHEMICAL SHIFTS OF SUBSTITUTED BENZOIC ACIDS[1]

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Abstract - In order to examine ^{13}C-SCS of substituted benzoic acids, chemical shifts of the acid form (I) and the dissociated form (II) have been obtained separately. Single substituent parameters, σ° or σ^{+} are correlated with the shifts for the carboxyl (δ_{co}) or ipso carbons (δ_{ipso}), respectively. Among the available five equations which are developed for the analysis with dual (or divided) substituent parameters (DSP), the Swain–Lupton equation (eqn 3) and the Taft–Swain–Lupton equation (eqn 4) give much better correlations, not only for δ_{co} and δ_{ipso} but also for the results for ring carbons (C(2), C(5), C(6)), except for those attached to or neighboured by substituents. It is concluded that the SCS of aromatic compounds are best analyzed with substituent parameters derived from reactions or equilibria on the basis of linear free energy relationships.

Substituent induced chemical shifts (SCS)[2] of aromatic[3] compounds are subjects of topical interest. The theoretical interpretation of chemical shifts of NMR was initiated with Ramsey's formula,[4] which is composed of paramagnetic and diamagnetic terms. The Karplus–Pople equation[5] is often cited today for correlations of ^{13}C NMR chemical shifts whose nuclear shieldings are predominantly paramagnetic. However the theoretical equations contain various parameters, such as electron density, bond order and mean excitation energy whose estimation precise enough to identify subtle differences induced by different substituents on the aromatic ring is beyond the commonly used MO calculations. Thus only for certain systems, such as a series of aromatics of $(4n + 2)\pi$ electrons are the results well correlated with electron density, one of the important causative factors governing the chemical shifts.

On the other hand, the Hammett equation[6] on the basis of linear free energy (LFE) relationships has been used in hundreds of organic reactions and the resulting substituent constants have proved to be useful for correlation of NMR chemical shifts too.[7] In fact, the most comprehensive parameters applicable to the SCS of mono- and disubstituted benzenes so far reported are these substituent constants and the dual (or divided) substituent parameters (DSP).

Therefore it will be worthwhile to examine SCS of substituted benzoic acids from which the substituent constants were originally derived. Other research groups[8,9] have previously tested the series, but we wish to report a more detailed analysis.

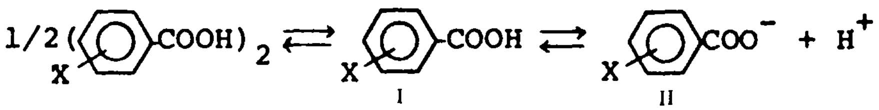
EXPERIMENTAL

All derivatives of benzoic acid were of chemical pure grade and used as purchased. The benzoic acids of 50–500 mg were dissolved in a mixture of perdeuterodimethyl sulfoxide (DMSO-d_6) and H_2O (4 to 1 in a volume ratio) of 3 ml. The pH of the solutions were adjusted to either 1.0 or less, or 13.0 or more by addition of either a few drops of conc HCl or one or two pellets of NaOH, respectively. The ^{13}C NMR spectra were measured on a Varian XL-100-15 spectrometer operating in the pulsed Fourier transform mode at 25.16 MHz under noise-modulated proton decoupled conditions with 2 KHz band width at 8 W for normal spectra, and with upfield irradiation by 500 Hz at 2 W for off-resonance spectra. The attached computer of 4 K data points printed out peak position in Hz units which were converted to normal chemical shifts (ppm from TMS) using the central signal of DMSO-d_6 (38.8 ppm).

RESULTS AND DISCUSSION

It would be erroneous to evaluate SCS of benzoic acids in organic solvents, because the degree of association and dissociation of the acids varies with their pK_a values and thermodynamic stabilities in the solvents. And further, protonation or deprotonation of substituents, such as hydroxyl, amino or carboxyl groups affects very much the chemical shifts of almost all the ring carbons and the carboxyl carbons.[10] We have shown the effect of association and dissociation on the chemical shifts of carboxyl carbon (δ_{co}) of benzoic acid are as much as *ca* 5 ppm and 9 ppm, respectively.[11] It is rather surprising that the previous workers[8,9] reported straight lines including hydroxyl and carboxyl substituents for a relationship between δ_{co} and pK_a values in DMSO.

In the present studies, the chemical shifts of the free acids (I) and the dissociated anions (II) have been obtained separately.



I II

(1)

Table 1. Chemical shifts[a] of substituted benzoic acids in DMSO-d_6/H_2O (4/1) at pH < 1.0 (for I) or pH > 13.0 (for II)

Substituent		CO	C(1)	C(2)	C(3)	C(4)	C(5)	C(6)
p-OCH_3	I	167.4	122.4	131.3	113.7	162.7	113.7	131.3
	II	170.8	131.5	130.7	112.5	160.1	112.5	130.7
p-CH_3	I	167.7	127.6	129.2	129.0	143.3	129.0	129.2
	II	171.3	135.8	128.0	129.1	139.0	129.1	128.0
p-F	I	166.7	126.8	131.9	115.4	164.8	115.4	131.9
	II	170.0	135.2	131.3	113.9	163.0	113.9	131.3
p-Cl	I	166.7	129.2	131.0	128.5	137.9	128.5	131.0
	II	170.0	137.4	130.8	127.3	134.2	127.3	130.8
p-NO_2	I	166.0	136.1	130.6	123.5	149.9	123.5	130.6
	II	168.8	147.8	129.9	122.6	145.0	122.6	129.9
H	I	167.7	130.5	128.7	128.3	133.1	128.3	128.7
	II	171.4	138.2	129.0	127.5	129.7	127.5	129.0
m-CH_3	I	167.7	130.3	129.5	137.9	133.4	128.3	126.4
	II	171.6	137.5	129.6	136.7	130.6	127.5	126.2
m-Cl	I	166.3	132.5	130.4	133.3	132.5	128.7	127.7
	II	169.8	140.5	129.4	132.3	129.4	128.7	127.4
m-NO_2	I	165.5	131.9	123.3	147.3	126.9	130.1	135.0
	II	168.1	140.9	123.8	147.2	123.3	129.0	135.2
m-COOH	I[12]	166.6	130.5	129.8	130.5	133.3	128.8	133.3
m-COO^-	II	171.0	138.4	126.2	138.4	129.9	129.6	129.9

a) ppm from TMS.

Taking into account the solubilities of benzoic acids, a solvent mixture of DMSO-d_6 and water in the ratio of 4 to 1, with addition of either conc hydrochloric acid (for I) or sodium hydroxide (for II) was used. The results are given in Table.

Peak assignments were made by off-resonance and calculation based on the assumption of additivity of two substituents. The additivity calculation had been well employed for benzene dicarboxylic acids.[12] Titration shifts also assisted the assignments.[11] Single parameters for linear plots were σ°[13] for δ_{co} (Fig. 1) and σ^+ for ipso carbons (δ_{ipso}) (Fig. 2) with correlation coefficients (r) of 0.94 for both lines in Fig. 1 and 0.93 and 0.92 for I and II, respectively in Fig. 2.

An inverse substituent effect[14] is indicated in Fig. 1. Alternation of induced charge[15] interprets relevantly the effects not only at side-chain carbons but also at ring carbons.[16] The correlation of δ_{co} with either σ° (Fig. 1) or σ (r = 0.91) agreed with small resonance

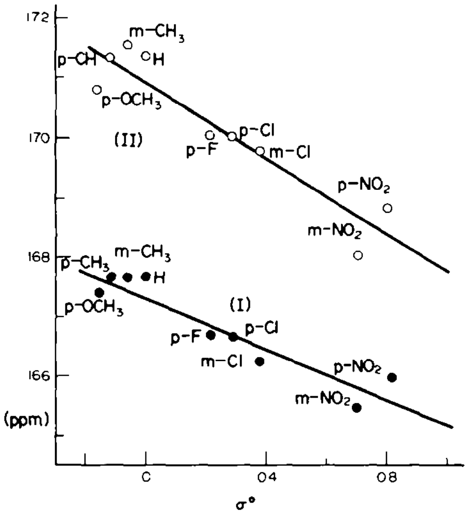


Fig. 1. Chemical shifts (δ_{co}) of the undissociated (I) or dissociated (II) carboxyl carbons of substituted benzoic acids vs Yukawa-Tsuno's σ°.

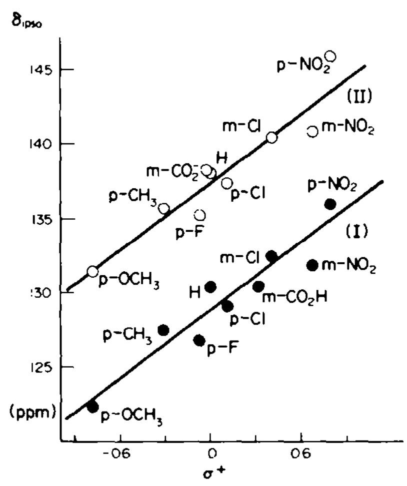


Fig. 2. Chemical shifts (δ_{ipso}) of ipso carbons of the undissociated (I) or dissociated (II) benzoic acids vs. Brown Okamoto's σ^+.

contributions, less than 20% by DSP analysis (vide post). This is probably because polar effects caused by strong interactions between carboxyl groups and either proton or hydroxide ion overrode the resonance effects of substituents.

The correlation of δ_{ipso} with σ^+ is normal in NMR where resonance factors are more important than in chemical reactions or equilibria. Levy *et al.*[17] first showed σ^+ is a better parameter than σ for para-carbons of monosubstituted benzenes.

Ratios of inductive or field effects and resonance effects can be obtained by the analysis with DSP. There are several equations for this purpose: Taft (eqn 2),[18] Swain Lupton (eqn 3),[19] Taft–Swain–Lupton combination (eqn 4),[20] Yukawa–Tsuno (eqn 5),[13,21] and Dewar (eqn 6)[22] equations where parameters of inductive (I) or field (F), resonance (R) or mesomeric field (M_I) with weighting factors (a, b, p, q, r) are involved.

$$\delta^c = a_2\sigma_I + b_2\sigma_R^0 + \text{constant} \quad (2)$$

$$\delta^c = f_3F + r_3R + \text{constant} \quad (3)$$

$$\delta^c = a_4\sigma_I + r_4R^0 + \text{constant} \quad (4)$$

$$\delta^c = a_5\sigma^0 + r_5\Delta\sigma_R^+ + \text{constant} \quad (5)$$

$$\delta^c = r_6F' + q_6M' + p_6M_I' \quad (6)$$

Alternatively various physical parameters have been applied to correlation for ^{13}C-SCS in limited cases. For instance, ipso and meta carbons of monosubstituted benzenes are correlated with electronegativity,[23,24] and ortho carbons with the Q value,[16] which includes polarity and ionization potential of substituent groups.[25]

On the other hand, there are abundant examples of excellent correlations with various DSP: *meta* and *para* carbons of simple monosubstituted benzenes[18,20] and all aromatic ring carbons of the compounds whose variable substituents (X) are insulated from aryl ring[20,26,27] have been reported. With a few exceptions,[16] SCS of disubstituted benzenes are also treated with either single parameters[28] or DSP.[20,27,29,30] While α or β carbons of either side-chain or ring linked to aryl ring are quite well correlated as is the corresponding SCS of proton NMR, successful DSP analysis for SCS of aryl carbons of disubstituted benzenes is usually limited to C(1) attached to the fixed substituents. It is often deduced that electron density is the most compelling factor for NMR chemical shifts, but electron density on each carbon calculated by CNDO/2 was useless for the present SCS.

Because of the above reasons, extensive analyses using eqns (2) (6) were conducted for all carbons of the benzoic acids, a kind of disubstituted benzenes. Goodness of fit was evaluated with correlation coefficients (r) in Table 2 except for eqn (6) from which r values were less than 0.85 (see also Ref. 27b) in multiple linear regressional analysis.

Such good correlations not only for carboxyl and C(1) but for other carbons (C(2), C(5) and C(6)) are obtained for the first time by applications of eqns (3) or (4). Theoretical ambiguity[31] of eqn (3) has recently

Table 2. Correlation coefficients (r)[a] of equations with divided substituent parameters for SCS of benzoic acids

	Eq. 2		Eq. 3		Eq. 4		Eq. 5
	meta	para	meta	para	meta	para	
n^b=	4	6	5	7	4	6	9
(I)							
CO	1.0	0.52	1.0	0.99	1.0	1.0	0.87
C(1)	0.99	0.88	0.96	1.0	1.0	0.98	0.95
C(2)	0.99	0.80	0.71	0.99	1.0	1.0	0.38
C(3)	0.74	0.72	0.60	0.87	0.78	0.75	0.98
C(4)	0.83	0.44	0.81	0.39	0.83	0.73	0.69
C(5)	0.98	0.72	0.93	0.87	0.99	0.75	0.94
C(6)	1.0	0.8	1.0	0.99	1.0	0.99	0.78
(II)							
CO	1.0	0.56	0.99	1.0	1.0	0.99	0.97
C(1)	0.99	0.86	0.94	0.99	0.99	1.0	0.92
C(2)	0.76	0.76	0.97	0.91	1.0	0.95	0.38
C(3)	0.84	0.73	0.73	0.85	0.81	0.77	0.60
C(4)	0.99	0.72	0.97	0.84	1.0	0.75	0.68
C(5)	1.0	0.73	0.63	0.85	1.0	0.77	0.73
C(6)	1.0	0.75	0.99	0.91	1.0	0.95	0.65

a) $r = \sqrt{R^2}$ where R^2 denotes coefficient of determination.

b) number of data sets.

been cleared.[30] Success with eqn (4) has also been demonstrated by Coulson.[20] Since all parameters through eqns (2)–(6) are derived from a variety of reaction rates or equilibria, DSP analysis can be a source of information additional to the reactions. In fact some of SCS[28] are now proposed as a quick and simple way to determine the parameter values of new substituents, otherwise difficult to determine.

Though the number of data sets in the meta series are small, all their DSP analyses with parameters covering a wide-range of values are good enough for us to conclude that DSP analysis would be the best approach to the SCS of, at least, meta and para positions to variable substituents (X). Lynch's empirical equation (eqn 7)[32] is profitable for C(3) and C(4) where X is neighboured or ortho position.

$$\delta^c = a_o + b\delta_o \qquad (7)$$

where a_o is the shift calculated for the parent species with X = H, the δ_o, the set of SCS for given position for monosubstituted benzenes with substituent (Y) of H, and b is the slope parameter.

Successful results suggest LFE relationships hold good for ^{13}C-SCS, but the ratio of polar and resonance effects of substituents will be changed with solvents. It is generally recommended to use nonpolar solvents in order to eliminate solute-solvent interactions which influence NMR chemical shifts more strongly than reactions. However if care is taken not to overlook the effect on the chemical shifts caused by H-bonding and/or dissociation, intramolecular electronic effects are sensed by for example proportionality between δ_c and δ_H. The solvent mixture (DMSO-d_6 and H_2O) used in the present studies enabled us to avoid the problems of solubility and association and the relative solvent induced chemical shifts seemed to be constant, probably owing to addition of either acid or base. Thus nearly equal slopes for species I and II of both δ_{co} and δ_{ipso} in Figs. 1 and 2 were obtained.

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