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Correlation Analysis of the pK_a Values of Mono- and Di-ortho-Substituted Benzoic Acids

Tomoko SOTOMATSU, Masao SHIGEMURA,
Yoshiyuki MURATA, and Toshio FUJITA*
Department of Agricultural Chemistry, Kyoto University, Kyoto 606-01

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The pK_a values of 10 benzoic acids occupied simultaneously at the 2- and 6-positions by various substituent combinations were newly measured in water at 25 °C. The effects of the substituents were analyzed quantitatively with regression analysis and free-energy-related parameters of the Hammett–Taft type. The results were compared with those of the analysis of the pK_a of mono-ortho-substituted acids cited in the literature. The resonance effect of substituents in di-ortho-substituted compounds was insignificant, but the electronic effect of the through-space inductive type in terms of the Charton σ_I and the steric effect in terms of the Taft–Kutter–Hansch E_s were not. The overall effects were additive for two substituents. In mono-ortho-substituted acids, a "regular" electronic effect of ortho substituents similar to that of the corresponding para substituents including the resonance effect component was indicated to work in addition to the steric and the through-space inductive effects. The steric and through-space inductive effects of a substituent were almost unchanged regardless of whether the substituent was involved in mono- or di-ortho substitution. A possible rationale integrating the results for mono- and di-ortho-substituted acids was to assume an intermediate formation for the dissociation process in which the carboxyl group is partly ionized and more easily twisted than the nonionized carboxyl group in the initial state.

The effect of ortho substituents in aromatic systems has been dealt with quantitatively by variations of the extended Hammett–Taft correlation analyses.[1] Our own procedure[2] is to simulate the proximity effects of ortho substituents by an inductive (field) electronic parameter such as the Swain–Lupton–Hansch F[3] and the Charton σ_I[4] and a steric parameter such as the Taft–Kutter–Hansch (TKH) E_s value.[5] Highly significant correlation equations have been formulated for the reactivity and equilibrium data sets of a number of mono-ortho-substituted compounds.[2,6,7] As an extension of our project, we set out to analyze the di-ortho substituent effects with use of the Hammett–Taft type parameters, and to compare the results with those for the mono-ortho substituent-effects. Di-ortho-substituted compounds are generally not very reactive owing mainly to steric factors. Thus, we selected the dissociation constant, pK_a, of benzoic acids as an index with which di-ortho-substituent effects could be analyzed. The pK_a value is a fundamental quantity in physical organic chemistry that can be precisely measured even for di-ortho-substituted derivatives.

Experimental

Data Set and Compounds. The pK_a values for ten 2,6-disubstituted benzoic acids were newly measured. The values for a number of 2,6-disubstituted benzoic acids have been published,[8] some of which, however, are different from our newly measured values. So, we generally used only our values for the di-ortho-substituted acids. Unless noted, other values for unsubstituted, mono-ortho, and other types of disubstituted compounds are cited from the work of Bijloo and Rekker,[9] in which they selected reliable data from an IUPAC publication.[10] Some 2,6-disubstituted benzoic acids were obtained commercially. 2-Chloro-6-nitrobenzoic acid was synthesized by the oxidation of 2-chloro-6-nitrotoluene by magnesium peroxide in water.[11] 2-Amino-6-methylbenzoic acid was purchased and converted to the corresponding acetamide derivative by acetylation with acetic anhydride, or to 2-hydroxy-6-methylbenzoic acid by diazotization followed by heating of the reaction solution.[12] 2-Chloro-6-methylbenzonitrile was hydrolyzed with sulfuric acid to the corresponding benzamide,[13] and further hydrolyzed with sodium nitrite in sulfuric acid[14] to give 2-chloro-6-methylbenzonic acid. Each compound was purified by recrystallization from an ether–hexane mixture. The 2-NHAc-6-Me compound is new; mp 184—187 °C, Anal. ($C_{10}H_{11}NO_3$) C, H, N.

Measurement of the Dissociation Constant. All measurements were made at 25±0.2 °C in aqueous solution (carbon dioxide-free water). Potentiometric titration was used for compounds with substituents that are charged in either highly basic or acidic solution, and the spectrophotometric procedure was used for other benzoic acids.[15] Standard (1 equiv) hydrochloric acid and sodium hydroxide solutions were used after appropriate dilution for titration as well as for preparation of aqueous solutions of various pHs.

The potentiometric titrations were made under a nitrogen atmosphere with an automatic titrator (AT-118, Kyoto Electronics) equipped with a glass combination electrode (C-111) and a temperature compensation electrode (T-111). The pH meter was standardized with standard aqueous buffers before the measurements. The initial concentration of each benzoic acid was 1—5 mM (1 M=1 mol dm^{-3}). The pK_a values were corrected by the Debye–Hückel limiting law for the ionic strength of solutions.[15] The standard deviation of the pK_a value of two to four repeats was ±0.03. In the spectrophotometric measurement, the absorbance of each substrate at 0.5 mM was measured in a pH range covering the half-ionization point with a Shimadzu UV360 spectrophotometer. An appropriate control solution was used in the reference cell. The pK_a values were averaged over two to four experimental runs for each compound, the accuracy being ±0.02.

Results

Table 1 lists the pK_a values and relevant substituent parameters. The σ values are from the paper of McDaniel and Brown.16) σ_I and the resonance parameter σ_R are from the compilation of Charton.4) The reference of the E_s parameter has been shifted to that of hydrogen.

Mono-ortho-Substituted Benzoic Acids. For the unsubstituted compound and the 10 mono-ortho-substituted compounds, Eq. 1 was formulated. The ortho-OH acid capable of intermolecular hydrogen bonding formation17) and the ortho-NH_2 acid capable of zwitter ionizing18) via internal hydrogen bonding19) as a neutral molecule were not included.

$$\mathrm{p}K_a = -1.000\sigma - 1.297\sigma_I + 0.442E_s + 4.235 \quad (1)$$
$$(0.195) \quad (0.229) \quad (0.075) \quad (0.104)$$

$$n = 11, \quad s = 0.049, \quad r = 0.998, \quad F_{3,7} = 524$$

In this and the following equations, n is the number of compounds, s is the standard deviation, r is the correlation coefficient, and F is the ratio between regression and residual variances. The figures in parentheses are the 95% confidence interval of the regression coefficients and intercept. Equation 1 was improved over the equation derived previously2) with use of the Taft σ_I. The E_s values of ortho NO_2 group estimated for the minimum dimension from the half-thickness5) was better than that from the half-width. For OMe and for NH_2 and NHAc, the E_s value was estimated from the van der Waals radii of oxygen and nitrogen atoms, respectively.5)

In Eq. 1, the σ value of the corresponding para substituents was used to simulate the "regular" electronic effect of ortho substituents.2) The σ_I term indicates that the electronic effect of ortho substituents is underestimated by such simulation, and its function in Eq. 1 is to compensate for the underestimation of the inductive (field) effect. The positive E_s term indicates that the bulkier the substituent, the easier the dissociation.

The statistics with 11 compounds and three independent variables seemed not to be reliable. So we incorporated four disubstituted benzoic acid9,10) in which one of the substituents was in the ortho position (2,5-

Table 1. pK_a Values of Benzoic Acids and Substituent Parameters

Substituents	$(\Sigma)\sigma$ a)	$(\Sigma)\sigma_I^{\mathrm{ortho}}$ b)	E_s (L) c)	E_s (S) c)	$(\Sigma)E_s^{\mathrm{ortho}}$ c)	σ_R b,d)	pK_a			
							Obsd e)	Eq. 2(7) f)	Eq. 10	Eq. 11
H	0	0	0	0	0	0	4.20	4.25(4.32)	4.37	4.22
2-Me	−0.17	−0.01	−1.24	0	−1.24	−0.16	3.91	3.89	3.92	3.88
2-Et	−0.15	−0.01	−1.31	0	−1.31	−0.14	3.79	3.84	3.87	3.83
2-*i*-Pr	−0.15	0.01	−1.71	0	−1.71	−0.16	3.64	3.63	3.64	3.63
2-OMe	−0.27	0.30	−0.55	0	−0.55	−0.58	3.90	3.86	3.85	3.78
2-F	0.06	0.54	−0.46	0	−0.46	−0.48	3.27	3.26	3.22	3.14
2-Cl	0.23	0.47	−0.97	0	−0.97	−0.25	2.91	2.97	2.94	2.88
2-Br	0.23	0.47	−1.16	0	−1.16	−0.25	2.87	2.89	2.85	2.80
2-I	0.18	0.40	−1.40	0	−1.40	−0.16	2.86	2.93	2.88	2.85
2-NO_2	0.78	0.67	−1.01	0	−1.01	0.10	2.19	2.16	2.13	2.03
2-NHAc	0.00	0.28	−0.61	0	−0.61	−0.35	3.65	3.61	3.62	3.54
2,5-Me_2	−0.24	−0.01	−1.24	0	−1.24		4.02	3.95	3.98	3.94
2,4-$(NO_2)_2$	1.56	0.67	−1.01	0	−1.01		1.42	1.41	1.46	1.30
2,3-Cl_2	0.60	0.47	−0.97	0	−0.97		2.67	2.62	2.62	2.53
2,4-Cl_2	0.46	0.47	−0.97	0	−0.97		2.72	2.75	2.74	2.66
2,6-F_2	0.12(0)	1.08	−0.46	−0.46	−0.92		2.27 g)	(2.14)	2.18	2.17
2-Cl-6-F	0.29(0)	1.01	−0.97	−0.46	−1.43		1.95 g)	(2.02)	2.04	2.07
2,6-Cl_2	0.46(0)	0.94	−0.97	−0.97	−1.94		1.82 g)	(1.90)	1.90	1.96
2,6-Me_2	−0.34(0)	−0.02	−1.24	−1.24	−2.48		3.25 g)	(3.20)	3.18	3.21
2-Cl-6-Me	0.06(0)	0.46	−1.24	−0.97	−2.21		2.43 g)	(2.55)	2.54	2.59
2-Cl-6-NO_2	1.01(0)	1.14	−1.01	−0.97	−1.98		1.48 g)	(1.55)	1.56	1.63
2-Me-6-NO_2	0.61(0)	0.66	−1.24	−1.01	−2.25		2.21 g)	(2.21)	2.20	2.26
2-OH-6-Me	−0.54(0)	0.23	−1.24	−0.55	−1.79		3.21 g)	(3.12)	3.12	3.12
2-NH_2-6-Me	−0.83(0)	0.16	−1.24	−0.61	−1.85		3.20 g)	(3.20)	3.20	3.20
2-NHAc-6-Me	−0.17(0)	0.27	−1.24	−0.61	−1.85		3.01 g)	(3.03)	3.02	3.03
2,6-$(NO_2)_2$	1.56(0)	1.34	−1.01	−1.01	−2.02		1.14 h)	(1.21)	1.21	1.31
2-OH-6-NO_2	0.41(0)	0.91	−1.01	−0.55	−1.56		2.23 i)	(2.12)	2.13	2.16
2-Cl-6-OH	−0.14(0)	0.71	−0.97	−0.55	−1.52		2.63 i)	(2.46)	2.48	2.49

a) From Ref. 15; σ (ortho) was simulated by σ (para). In Eqs. 8—11, $(\Sigma)\sigma=\Sigma\sigma^{\#}$ for mono-ortho, and 2,3-, 2,4-, and 2,5-disubstituted compounds, and $(\Sigma)\sigma=\Sigma\sigma^{\#}=0$ as shown in parentheses for di-ortho-substituted compounds. b) From Ref. 4. Σ is for the di-ortho compounds. c) From Ref. 5; the reference is shifted to H. d) Only for mono-ortho compounds. e) Unless noted from Refs. 9 and 10. f) Values in parentheses are calculated by Eq. 7. g) Newly measured value. h) From Ref. 22. i) From Ref. 17.

Me_2, 2,4-$(NO_2)_2$, 2,3-Cl_2, and 2,4-Cl_2) to give Eq. 2.

$$\mathrm{p}K_a=-\underset{(0.093)}{0.955}\sum\sigma-\underset{(0.179)}{1.357}\sigma_I+\underset{(0.070)}{0.438}E_s+\underset{(0.092)}{4.254} \tag{2}$$

$$n=15,\quad s=0.049,\quad r=0.998,\quad F_{3,11}=1156$$

Equation 2 coincides with Eq. 1 within the 95% confidence interval. The calculated pK_a values are listed in Table 1.

Because the σ(para) value is the composite of σ_I and σ_R, Eq. 1 was reanalyzed to give Eq. 3.

$$\mathrm{p}K_a=-\underset{(0.152)}{0.995}\sigma_R-\underset{(0.116)}{2.293}\sigma_I+\underset{(0.060)}{0.421}E_s+\underset{(0.084)}{4.211} \tag{3}$$

$$n=11,\quad s=0.038,\quad r=0.999,\quad F_{3,7}=839$$

By definition, $\sigma(\text{para})=\sigma_I+\sigma_R$,[4] so the slope of the σ_R term should be equivalent to that of the σ term in Eq. 1. The slight difference is due to collinearity among these parameters and to slight discrepancies in σ(para), σ_I, and σ_R values among the references from which the values are cited. The collinearity between σ_I and σ_R values in Eq. 1 is high (r^2=0.58), but that between σ_I and σ_R in Eq. 3 was low (r^2=0.02). The E_s value is nearly orthogonal with σ, σ_I, and σ_R. That the E_s term and intercept are practically identical between Eqs. 1 and 3 and that the σ_I term in Eq. 3 is more negative than that in Eq. 1 by almost one were taken to indicate the reliability of Eq. 1 and 2 as well.

The slope of the σ term for pK_a values of meta- and para-substituted compounds is -1 by definition, so the slopes of the σ terms in Eqs. 1 and 2 as well as the slope of the σ_R term in Eq. 3 all being almost equal to -1 indicate that the resonance effect and the coplanarity of mono-ortho substituents were not much different from those of the corresponding para substituents as far as the substituents included in Eq. 1 are concerned. The carboxyl group is probably not entirely coplanar with the benzene ring, because of the steric effect of ortho substituents. The unsubstituted coplanar acid could be included in Eqs. 1—3, so the above arguments suggest that the resonance interaction between the carboxyl group and the benzene ring would not be affected by the extent of the twisting of the carboxyl group, at least until the size of the ortho substituent in terms of $-E_s$ reaches that of the *i*-Pr group, the largest one studied here.

Di-ortho-Substituted Benzoic Acids. The pK_a values for the unsubstituted compound and the 10 newly measured di-ortho-substituted benzoic acids were analyzed in a similar way to give Eq. 4 with simple summation of parameters for two substituents.

$$\mathrm{p}K_a=-\underset{(0.182)}{0.127}\sum\sigma-\underset{(0.217)}{1.514}\sum\sigma_I+\underset{(0.089)}{0.447}\sum E_s+\underset{(0.195)}{4.224} \tag{4}$$

$$n=11,\quad s=0.084,\quad r=0.996,\quad F_{3,7}=304$$

The $\sum\sigma$ term is insignificant above the 95% level, so deletion of this term afforded Eq. 5.

$$\mathrm{p}K_a=-\underset{(0.151)}{1.628}\sum\sigma_I+\underset{(0.096)}{0.448}\sum E_s+\underset{(0.191)}{4.280} \tag{5}$$

$$n=11,\quad s=0.092,\quad r=0.995,\quad F_{2,8}=375$$

The addition of the $\sum\sigma_R$ term into Eq. 5 did not improve the correlation.

The carboxyl group sandwiched between two ortho substituents probably twists much from the benzene ring plane. Mono-ortho OH and NH_2 compounds were not included in Eq. 1, but such di-ortho-substituted acids as 2-Me-6-OH and 2-NH_2-6-Me were accommodated in Eq. 5. This indicates that internal hydrogen bonding and zwitterionization did not occur in these di-ortho-substituted acids and was taken as evidence of the twisting of the carboxyl group in di-ortho-substituted acids in general.

The inclusion of the planar unsubstituted benzoic acid in Eq. 5 might be irrelevant. However, the deletion of the unsubstituted compound afforded Eq. 6.

$$\mathrm{p}K_a=-\underset{(0.154)}{1.734}\sum\sigma_I+\underset{(0.150)}{0.588}\sum E_s+\underset{(0.342)}{4.612} \tag{6}$$

$$n=10,\quad s=0.071,\quad r=0.991,\quad F_{2,7}=371$$

The intercept could correspond to the pK_a value of an imaginary "twisted" benzoic acid. Because resonance interaction of the carboxyl group with the benzene ring is prohibited here, the pK_a value was expected to be lower than that of the "real" benzoic acid. In fact, the intercept of Eq. 6 was higher. This is probably due to a statistical artifact such as differences in the collinearity between the $\sum\sigma_I$ and $\sum E_s$ values in Eq. 5 (r^2=0) and Eq. 6 (r^2=0.28). A part of the $\sum\sigma_I$ term in Eq. 5 may be transferred into the $\sum E_s$ term in Eq. 6. Because the $-\sum E_s$ value is larger than the $\sum\sigma_I$ value for most compounds, the higher intercept in Eq. 6 could compensate for this more negative estimation of the $\sum E_s$ term. The size of each term and intercept overlaps within the 95% confidence interval, so Eq. 6 is regarded as being almost equivalent to Eq. 5.

Equations 5 and 6 show that the resonance effect of substituents is insignificant in di-ortho-substituted compounds. This might be taken to indicate that the π-bonded planar (NO_2), hydroxyl (OH), and amino (NH_2 and NHAc) substituents, capable of resonance interaction with the ring, are twisted from the ring plane in these congested systems. The twisting can be ignored, however, for symmetrical-top and monoatomic substituents such as Me and halogens. Therefore, the insignificance of the resonance component of the electronic effect in Eqs. 5 and 6 is not related to the twisting of the substituents. The pK_a value of di-ortho-substituted benzoic acids is not dependent on the twisting of substituents from the ring plane. Because the resonance component of the electronic effect of Me and halogen substituents is not significantly reduced in any case, the addition of the $\sum\sigma^{\circ}$ term for compounds substituted by combinations of Me and halogens was examined. It did not, however, improve the already excellent correlation represented by Eq. 5. The σ° is the substituent parameter applicable when the resonance interaction of the functional group, but not the substituents, does not occur with the benzene ring.[1,4]

These arguments suggest that the through-bond electronic effect of substituents, if any, is not significant in series of 2,6-disubstituted benzoic acids. Although direct evidence is lacking, the $\sum\sigma_{\mathrm{I}}$ term in Eqs. 5 and 6 seemed to mostly represent the electronic effect of the through-space type. That the unsubstituted benzoic acid could be incorporated into Eq. 5 also supports this suggestion. In the unsubstituted compound, the value of the through-space effect parameter for two ortho hydrogens, regardless of whether it is σ_{I} itself or a part of σ_{I}, is defined as being zero irrespective of the extent of the twisting of the carboxyl group.

To evaluate Eq. 5, we surveyed published pK_a values for other 2,6-disubstituted benzoic acids, preferably the values measured under consistent conditions in a single laboratory.[20] Among others, we selected the pK_a values from the publication of Dippy and co-workers,[21] because our newly measured values were either equivalent or close (±0.15) to their corresponding values for the 2,6-$\mathrm{Me_2}$ (3.25), 2-Cl-6-$\mathrm{NO_2}$ (1.34), and 2-OH-6-Me (3.32) derivatives with an exception for the 2,6-$\mathrm{Cl_2}$ (1.59). By inclusion of their values for the 2,6-$(\mathrm{NO_2})_2$,[22] 2-OH-6-$\mathrm{NO_2}$,[17] and 2-Cl-6-OH[17] derivatives, Eq. 7 was formulated for the 14 compounds; it is almost equivalent to Eq. 5.

$$\begin{aligned} \mathrm{p}K_a = &-1.622\textstyle\sum\sigma_{\mathrm{I}} + 0.464\textstyle\sum E_s + 4.320 \\ &\;\;(0.139) \qquad\;\; (0.101) \qquad (0.196) \end{aligned} \tag{7}$$

$$n=14,\quad s=0.103,\quad r=0.993,\quad F_{2,11}=400$$

Internal hydrogen-bond formation between the carboxylato and OH groups was unlikely in these additional compounds. The calculated values are listed in Table 1.

Mono- and Di-ortho-Substituted Benzoic Acids. Comparison of Eqs. 1 and 2 for mono-ortho derivatives with Eqs. 5 and 7 for di-ortho compounds indicated that the $(\sum)\sigma_{\mathrm{I}}$ terms are close and the $(\sum)E_s$ terms are almost equivalent. We first tried to differentiate the steric effect of two ortho substituents in di-ortho-substituted acids by classifying substituents so that the substituent with the more negative E_s value was larger than the other. The use of E_s(large) and E_s(small) as two independent steric parameters did not, however, give reasonable results for the compounds included in Eqs. 5 and 7, because of high collinearity between the two E_s values (r^2=0.465 for 14 compounds in Eq. 7). To reduce the collinearity, we analyzed the combined set of data included in Eqs. 2 and 7 to afford Eq. 8.

$$\begin{aligned} \mathrm{p}K_a = &-0.918\textstyle\sum\sigma^{\#} - 1.474\sigma_{\mathrm{I}}(\mathrm{mono}) - 1.609\textstyle\sum\sigma_{\mathrm{I}}(\mathrm{di}) \\ &\;\;(0.138) \qquad (0.254) \qquad\qquad (0.103) \\ &+ 0.478E_s(\mathrm{S}) + 0.466E_s(\mathrm{L}) + 4.321 \\ &\;\;(0.116) \qquad (0.100) \qquad (0.130) \end{aligned} \tag{8}$$

$$n=28,\quad s=0.079,\quad r=0.996,\quad F_{5,22}=600$$

In this equation, $\sum\sigma^{\#}$ is a composite parameter for the "regular" electronic effect, that is, $\sum\sigma$ for derivatives in which one of the ortho positions is occupied, and zero for di-ortho-substituted compounds. In this combined set, the E_s(S) value for mono-ortho derivatives is always zero (E_s of H), so the collinearity between E_s(S) and E_s(L) is insignificant (r^2=0.04). As anticipated, the sizes of the two E_s terms were practically identical, indicating that the differentiation of the steric effect between two ortho substituents was not necessary. By combining the two E_s terms, Eq. 9 was formulated.

$$\begin{aligned} \mathrm{p}K_a = &-0.918\textstyle\sum\sigma^{\#} - 1.472\sigma_{\mathrm{I}}(\mathrm{mono}) - 1.613\textstyle\sum\sigma_{\mathrm{I}}(\mathrm{di}) \\ &\;\;(0.135) \qquad (0.246) \qquad\qquad (0.083) \\ &+ 0.471\textstyle\sum E_s + 4.325 \\ &\;\;(0.065) \qquad (0.114) \end{aligned} \tag{9}$$

$$n=28,\quad s=0.077,\quad r=0.996,\quad F_{4,23}=783$$

In Eqs. 8 and 9, the σ_{I}(mono) and $\sum\sigma_{\mathrm{I}}$(di) terms are used separately. The overall inductive (field) effect of the mono-ortho substituents comprises not only the σ_{I} (mono) term but also the σ_{I} component of the regular σ, as indicated by Eq. 3. Originally, the σ_{I}(mono) term was added to compensate for underestimation of the electronic effect of mono-ortho substituents by simulating it by the regular σ value of the corresponding para substituents. The negative size of the σ_{I}(mono) term was lower than that of the $\sum\sigma_{\mathrm{I}}$(di) term, but the difference was marginal. That the slope of the σ_{I}(mono) term is similar to that of the $\sum\sigma_{\mathrm{I}}$ term for di-ortho substituents was taken to suggest that the σ_{I} component correcting the overall electronic effect of mono-ortho substituents is mostly of the through-space type. We combined the σ_{I}(mono) and $\sum\sigma_{\mathrm{I}}$(di) terms together to give Eq. 10, without much change in the statistical quality.

$$\begin{aligned} \mathrm{p}K_a = &-0.856\textstyle\sum\sigma^{\#} - 1.616\textstyle\sum\sigma_{\mathrm{I}}^{\mathrm{ortho}} + 0.494\textstyle\sum E_s^{\mathrm{ortho}} \\ &\;\;(0.089) \qquad (0.084) \qquad\quad (0.054) \\ &+ 4.374 \\ &\;\;(0.084) \end{aligned} \tag{10}$$

$$n=28,\quad s=0.078,\quad r=0.996,\quad F_{3,24}=1017$$

The calculated pK_a values are shown in Table 1. The negative slope of the $\sum\sigma^{\#}$ is significantly lower than unity. This is primarily due to the high collinearity

(r^2=0.55) between $\sum\sigma^{\#}$ and σ_I(mono) values in Eq. 9, and to the σ_I(mono) being used as the $\sum\sigma_I^{\text{ortho}}$ value for mono-ortho substituents in Eq. 10.

Discussion

The analysis above should provide suggestion about the mechanism of dissociation of mono- and di-ortho-substituted benzoic acids. Differentiation of the steric effect between substituents (including H) at the two ortho positions was not necessary. This indicates that a substituent has an almost identical steric effect on the carboxyl group, regardless of whether it is in a mono- or di-ortho compound, and that the effect is additive. Because the planar carboxyl is nonsymmetric with regard to the two ortho positions, the most plausible assumption is that the steric effect operates on a twisted or almost perpendicular carboxyl group which is symmetric with respect to the two ortho positions even in mono-ortho-substituted compounds. The σ_I(mono) term for mono-ortho substituents was close to the $\sum\sigma_I$ term for di-ortho substitutions and they were combined together in Eq. 10. Similar to the steric effect, the through-space inductive effect of substituents may be exerted on the twisted carboxyl group in mono- as well as di-ortho-substituted compounds.

Because the carboxyl group in mono-ortho-substituted acids is not much twisted from the benzene ring in the initial state, the above discussion suggests that the acid dissociation occurs via an intermediate, $\text{ArCOO}^{\delta-}\cdots\text{H}^{\delta+}$, in which the carboxyl group is partially ionized. In the ionized carboxylato group, the delocalization of the negative charge between the two equivalent oxygen atoms is significant at the cost of loss of resonance interaction with the benzene ring, which leads to ease of rotation.[23] Even in a partially ionized state, the carboxyl group could be twisted more easily to take the "perpendicular" conformation than in the initial neutral state. The partially ionized carboxyl group in mono-ortho-substituted derivatives could take a conformation with relative ease similar to that in di-ortho-substituted acids in which the carboxyl group is ultimately much twisted.

The positive E_s and $\sum E_s$ terms in our correlation equations indicated that the bulkier the ortho substituents, the easier the dissociation. The hydration of the partially ionized carboxyl group is more readily destabilized by the bulk of ortho substituents than the hydration of a completely ionized carboxylato group, even though the hydration strength of the carboxylate is higher than that of the partially ionized form. The twisting of the partially ionized carboxyl group is of course due to the presence of the ortho substituents in mono-ortho-substituted acids, but the extent of the twisting may not be much influenced by the E_s parameter of substituents.

The "regular" eletronic effect in terms of ($\sum$)σ in Eqs. 1 and 2 could be operative as such on the inital state to form the intermediate for mono-ortho-substituted compounds. For the di-ortho-substituted compounds, the electronic effect on intermediate formation may not be important if it indeed exists. For the meta and para substituted benzoic acids, the intermediate is not necessarily in the twisted conformation. The electronic effect on intermediate formation is represented by the regular σ term and the dissociation process is not susceptible to proximity substituent effects.

The di-ortho-substituted compounds used in this work would be regarded as being biased so that the proportion of compounds occupied by the NO_2 group in the set was high (4 out of 13). Therefore, to substantiate the above analyses and discussions further, the measurement should be required for a variety of compounds having various combinations of unsymmetric top-type substituents capable of resonance interaction with the ring such as acyl, carbalkoxyl, alkoxyl, and *N*,*N*-dialkylamino groups. Unfortunately, however, there is a limitation in the selection of substituents to synthesize this type of congested compounds. In addition, even though some of these compounds could be synthesized and measured, the assignment of the E_s value for substituents would not be simple. In this situation, the present analyses could be considered as being made as best as one can, if not complete.

Because the negative size of the $\sum\sigma^{\#}$ term in Eq. 10 is close to unity and the intercept is close to the pK_a value of unsubstituted benzoic acid, 4.20, we could incorporate meta- and para-substituted benzoic acids in this equation by setting as $\sum\sigma_I^{\text{ortho}}=\sum E_s^{\text{ortho}}=0$. The addition of 45 compounds[9,10] substituted by alkyl, halogen, OH, alkoxyl, CN, NO_2, Ac, NHAc, and COOH at meta and para positions, singly or with various combinations, afforded Eq. 11.

$$\begin{array}{llll} \text{p}K_a = -0.938\sum\sigma^{\#} & -\ 1.542\sum\sigma_I^{\text{ortho}} & +\ 0.420\sum E_s^{\text{ortho}} & \\ \qquad (0.042) & \quad (0.069) & \quad (0.031) & \\ \qquad +\ 4.224 & & & (11) \\ \qquad (0.022) & & & \end{array}$$

$$n=73,\quad s=0.072,\quad r=0.997,\quad F_{3,69}=3346$$

The collinearity between $\sum\sigma^{\#}$ and $\sum\sigma_I^{\text{ortho}}$ values for the 73 compounds is not significant (r^2=0) in Eq. 11 and the negative slope of the $\sum\sigma^{\#}$ term is now closer to unity than in Eq. 10. Because the pK_a values calculated by Eq. 11 were close to the corresponding observed values, the results of calculation are shown in Table 1 for mono- and di-ortho compounds only.

In summary, our analysis shows that the pK_a value of a variety of benzoic acids with substituents at ortho-, meta-, and para-positions, singly or in combination, can be analyzed and predicted by a single correlation equation, unless the internal hydrogen-bond formation occurs or substituents are enormously large.

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