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Kinetic Studies by Means of the NMR Techniques. I. Acid-Catalyzed Proton-Exchange Reactions of Some Substituted Phenols

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A kinetic study was conducted on the acid-catalyzed proton-deuteron-exchange reactions of several substituted phenols. The rates of the exchange were determined by using the two-bond isotope shifts ($^2\Delta$) on the carbons and the pattern-fitting analyses for the ^{13}C NMR signals. The observed reaction rates can be expressed additively with substituent parameters. The parameters of the para positions are linearly correlated to the σ_p^+ with ρ=−3.6.

The proton-deuteron-exchange reaction is a typical ionic reaction. Therefore, its study can provide useful indices for various ionic reactions. In the cases of the title reactions, the reactions proceed through the σ-complex, whose formation is a rate-determining step. Katritzky et al. reviewed such acid-catalyzed hydrogen-exchange reactions.[1)]

In studies of hydrogen-exchange reactions, knowledge of the isotopic fractionation (*D* in %) is necessary. This fractionation can be obtained by various methods, such as IR,[2)] ^{1}H NMR,[3)] ^{2}H NMR,[4)] MS,[4)] and ^{13}C NMR.[4–8)] The organic reaction rates have been discussed in terms of the substituent parameters presented by Hammett[9)] and extended by Brown-Okamoto,[10)] Taft,[11)] and Yukawa-Tsuno.[12)] The Hammett equation has been applied to many reaction rates of the meta- and para-substituted benzenes.[13)] However, its application is limited in the cases of multiply substituted benzenes. Therefore, the parameters must be considered with regard to steric or mutual interactions between substituents.

In the present article, we present a method to evaluate simultaneously the title reaction rates for different sites of the substituted benzenes. The rates were obtained for thirty-eight sites of twenty unsubstituted and substituted phenols.

Experimental

The materials used were commercially available and were used without further purification. The reaction vessels were hand-made Pyrex ampules. A sample consisting of 0.01 mol of phenol was added to 1 g of a HCl/D_2O (0.1 wt%) solution, and the mixture was sealed into the Pyrex ampule with a stirring bar. The ampule was then kept at 80±1 °C in a DN-42 oven (Yamato Scientific Co.,Ltd.). The solution was stirred to produce the reaction. After the reaction had reached an extent of about 5—50 *D*%, the sample was cooled by immersing it in water; the contents were then separated into aqueous and oily (or solid) phases. The latter phase was used for the NMR measurement. The concentration of the NMR sample solution was neat for the liquid sample and ca. 50 wt% in dioxane for the solid sample. The samples were not degassed, since the presence of oxygen made T_1 short, which reduced the time needed to repeat its NMR measurement. The ^{13}C and ^{2}H NMR spectra were obtained with a Varian XL-200 FT-NMR spectrometer operating at 50.31 and 30.71 MHz respectively. The ^{13}C NMR spectra were measured by using the gated decoupling technique with no NOE pulse sequence. Data acquisition was carried out under the following conditions: flip angle of pulse, 45°: number of transients, 24—128: data points, 32000: delay time, 40 s, and spectral width, 2600—3500 Hz. The isotopic fractionation was obtained by the use of the Lorentzian lineshape-fitting procedure within an accuracy of ±0.5%. The computer-assisted lineshape simulations were run on a Sharp personal computer MZ-80B with a BASIC program, while the linear regressions were run on a Hitachi M-260H computer in our Institute using a FORTRAN program with double precision.

Results and Discussion

NMR Spectra. The NMR signal intensities of the deuterons meta to the hydroxyl or within the methyl group(s) did not change: that is, the natural abundance intensities remained even after the title reactions had been carried out for 200 h under the experimental conditions used. Those of the deuterium at the ortho and para positions were clearly observed with an increased intensity, but not separately, because of the broadening caused by the quadrupole interactions. In this system especially, the large solvent signal of D_2O sometimes interferes with the signals of the products. Therefore, the ^{2}H NMR signals of the products were not convenient for the product analyses. The NMR observation in the present study was, then, carried out only for the ^{13}C NMR spectra in the region of the aromatic carbons.

Figure 1 shows a typical ^{13}C NMR spectrum, which was observed for a solution obtained for 2-methylphenol. In this case, there are two reactive sites, C_4 and C_6, whose labeled carbon signals overlap with the unlabeled ones. The signal of the labeled carbon splits into three lines with coupling to deuterium, as may be seen in Fig. 1. It is also more shielded than that of the unlabeled carbon because of the so-called one-bond isotope shift, $^1\Delta$. The carbon atoms adjacent to the labeled one also suffer a high-field shift from the two-

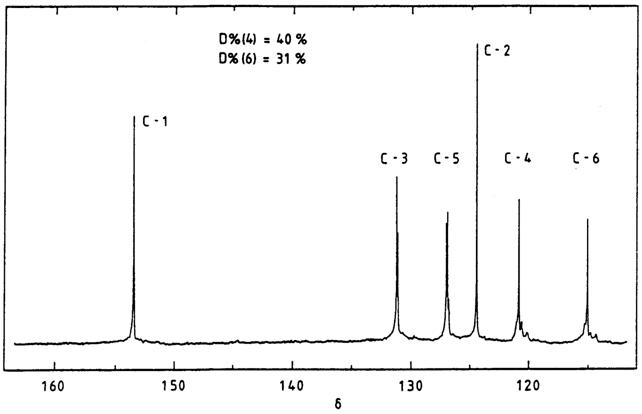


Fig. 1. The aromatic carbon regions of the 50.3 MHz ^{13}C NMR spectrum of the reaction mixtures of 2-methylphenol in the D_2O-HCl system. The spectrum was measured with the parameters of SW=2600 Hz, 32 k data points, AT=6.154s, D1=40s, and 64 aquisitions (NT).

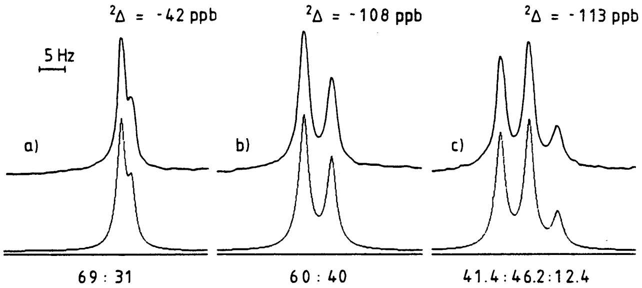


Fig. 2. ^{13}C NMR Spectra of (a) the C_1, (b) the C_3, and (c) the C_5 regions partly expanded from the spectrum of Fig. 1. The upper value gives the two-bond isotope shift and the lower one gives the intensity ratio of the signals. Data points were 427 points and half-height widths were 1.8, 2.3, and 2.4 Hz for a, b, and c, respectively.

bond isotope shift ($^2\Delta$). Therefore, both the C_1 and C_3 signals appear as two lines, and the C_5 signal, as three lines, as is shown in Fig. 2, though the C_2 signal does not split because it has no adjacent labeled carbon. The intensities of the signals are consistent with those obtained in each site, within an error of 1%.

Determination of *D* (%). In this article, the deuterium atom% is expressed as *D* (%). Reuben has reported a method of evaluating the deuterium/protium ratio by using the two-bond isotope shifts ($^2\Delta$).[6] His examples contain several equivalent labeled sites. However, in our cases, where the site in question has two nonequivalent adjacent site, its ^{13}C signal appears as three lines. This phenomenon may be ascribed to similar contributions from the two labeled deuterium atoms. In the cases of the method described here, the signals were sharp enough for the line separation to be observed and the D(%) could be determined accurately. As only the ortho and para protons of a phenol derivative undergo exchange reaction, the ^{13}C signals of C_1, C_3, and C_5 split into three or two lines only by means of adjacent labeled carbons. Thus, when the *D* (%) on the C_2, C_4, and C_6 of a phenol derivative are expressed as p, q, and r, the C_1, C_3, and C_5 signals split as follows:

$$C_1;\ (100-p)(100-r):(100-p)r+p(100-r)\ :pr$$
$$C_3;\ (100-p)(100-q):(100-p)q+p(100-q):pq$$
$$C_5;\ (100-q)(100-r):(100-q)r+q(100-r)\ :qr$$

If any one of C_2, C_4, or C_6 has a substituent, the D(%) of the substituted carbon is defined as zero. Then, in the case of 2-methylphenol, the D(%) of C_2 is equal to zero. Therefore, the two C_1 singlets have an intensity ratio of $(100-r):r$, while the two C_3 singlets have a ratio of $(100-q):q$. The three C_5 singlets have a ratio of $(100-q)(100-r):(100-q)r+q(100-r):qr$. Using these theoretical ratios, the pattern-fitting analyses were made for the experimental pattern, as is shown in Fig.2, by assuming that each signal fits the Lorentzian lineshape. The analyses need a parameter concerned with line widths. This is determined by a visual fitting of the calculated and observed spectra. The deuterium isotope shifts were determined from the spectra without any window function. As these parameters were determined independently, the D(%) of the sample can be obtained within an error of ±0.5% by means of the pattern-fitting analyses used. The values of p, q, and r can be determined by this method.

Evaluation of Reaction-Rate Constants. The exchange reaction between two reactants, AX and BX*, can be expressed as follows:

$$AX + BX^* \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} AX^* + BX, \tag{1}$$

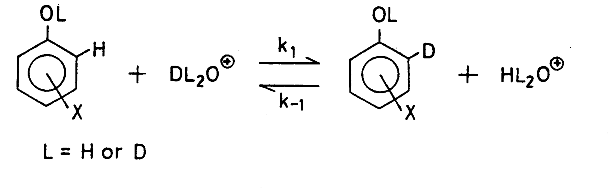
where X* represents a labeled X atom. The reaction is first-order with respect to the concentration of the isotope X*. Let the concentrations be: $[AX]+[AX^*]=a$, $[AX^*]=x$, $[BX]+[BX^*]=b$, $[BX^*]=y$, and $x+y=z$ (constant). Then, the rate will be expressed as:

$$\ln(x_0-x_e)-\ln(x-x_e)=kt((a+b)/ab) \tag{2}$$

where x_0 and x_e are the values of x at $t=0$ and ∞ respectively and where

$$x_e=az/(a+b). \tag{3}$$

The total exchange rate k is equal to the sum of k_1 and k_{-1}. Equation 2 has been named McKay's equation.[14] In this article, the hydrogen-deuterium-exchange reactions of the substituted phenols proceed as follows (Scheme 1):



Scheme 1.

Table 1. ^2H Distributions and Reaction Rates as Calculated from ^{13}C NMR Lineshape Analyses of 3-Methoxyphenol in $HCl-D_2O$ at 80 °C

Run No.	Time	HCl	$D/\%$			$D_e/\%$
	h	mmol dm^{-3}	C-2	C-4	C-6	
1	2.00	8.85	7 (1.61)[a]	29 (8.14)	32 (9.31)	71.6
2	3.00	15.9	18 (1.60)	57 (8.33)	59 (9.03)	74.9

a) The values in parentheses are the reaction rates (k) calculated from Eq. 4 in the text: they are divided by the concentration of HCl and are given in units of $10^{-3}\ s^{-1}\ dm^3\ mol^{-1}$.

Table 2. Exchange Rate Constants (k_1) Observed for the Reactions in $HCl-D_2O$ at 80 °C in Units of $10^{-6}\ dm^3\ mol^{-1}\ s^{-1}$

Compd. No.	Substituent	Site of exchange		
		H-2	H-4	H-6
1	H	8.97	16.7	8.97
2	$2-CH_3$	—	7.51	5.83
3	$3-CH_3$	53.5	156	77.0
4	$4-CH_3$	7.94	—	7.94
5	$2-OCH_3$	—	0.250	0.153
6	$3-OCH_3$	823	4120	4580
7	$4-OCH_3$	2.65	—	2.65
8	$2\text{-}t\text{-}C_4H_9$	—	1.23	2.12
9	$3\text{-}t\text{-}C_4H_9$	13.6	43.7	32.2
10	$4\text{-}t\text{-}C_4H_9$	1.60	—	1.60
11	2-Cl	—	0.019	0.019
12	3-Cl	1.56	2.64	2.43
13	4-Cl	0.235	—	0.235
14	$2,3-(CH_3)_2$	—	133	94.3
15	$2,4-(CH_3)_2$	—	—	6.45
16	$2,5-(CH_3)_2$	—	77.1	38.2
17	$2,6-(CH_3)_2$	—	0.668	—
18	$3,4-(CH_3)_2$	53.7	—	61.3
19	$3,5-(CH_3)_2$	546	1370	546
20	$2,3-(OCH_3)_2$	—	132	87.6

When the concentrations of the reactants are expressed by $D(\%)$, 0, D_e, and D can be substituted for x_0, x_e, and x in Eq. 2. Then, it is shown as follows:

$$((a+b)/ab)kt = \ln(D_e/(D_e-D)) = -\ln(1-(D/D_e)). \quad (4)$$

If k_1 is equal to k_{-1}, D_e can be calculated from the initial concentrations of the reactants. However, if k_1 is not equal to k_{-1}, where the reaction has the kinetic isotope effect (KIE), K ($=k_1/k_{-1}$) and D_e must be observed directly. In this case,

$$k_1 = k/(1+1/K),\ k_{-1} = k_1/K. \quad (5)$$

In the reactions studied for the 19 substituted phenols, no kinetic isotope effects (KIE) were observed except for that of 3-*t*-butylphenol. One reason seems to be the high reaction temperature used (80 °C). Two examples of evaluations of $D(\%)$ and the reaction rates are shown in Table 1. The error of $\log k$ is considered to be within ±0.03. The first-order rate constants evaluated for thirty-eight different sites of twenty phenols are given in Table 2. From the data in Table 2, it must be said that the rates of all the 3-substituted phenols are larger than those of the corresponding 2- or 4-substituted ones and that of the unsubstituted one. However, the rates of the 2- or 4-substituted phenols are smaller than that of phenol. These trends are to be expected from the electronic properties of the substituents. KIE was observed for the case of 3-*t*-butylphenol (**9**: hereafter compounds will be referred to using the numbers given in Table 2), and the K's were determined to be 0.0671, 0.206, and 0.119 for the 2-, 4-, and 6-positions respectively.

Substituent Parameters. The reaction rates for the substituted phenols are assumed to be expressed as the sum of the substituent parameters as follows:

$$\log k_X = \log k_H + \sum n_i S_i + \sum n_{jab} S_{jab}, \quad (6)$$

where k_X's are the observed rate constants k_1's for unsubstituted or substituted phenols. The value of $\log k_H$ on the right hand side of Eq. 6 can be determined as a parameter in a regression analysis of the parameters in Eq. 6. $S_i(X)$ (for example, S_o, S_m, or S_p) is a substituent parameter for the i-position with respect to the substituent X. The notation of $S_{jab}(X,Y)$ is used to express an interaction effect of the a- and b-positioned substituents, X and Y, to the j-positioned rate. These are correction terms for the interactions between the substituents, and n_i or n_{jab} is a weight factor for S_i or S_{jab}. For example, in the case of 3,5-dimethylphenol, the rates for two different sites can be calculated from Eq. 6 as follows:

2-position; $\log k_1 = \log k_H(\text{ortho}) + S_o + S_p + S_{213}$;
4-position; $\log k_1 = \log k_H(\text{para}) + 2S_o + S_{435}$.

A correction term, S_{213} or S_{435}, appears in the case where the observed site is sandwiched with two substituents, OH and X, or X and X, as in the present example. In the case of 3-methylphenol, the rates can be expressed as follows:

2-position; $\log k_1 = \log k_H(\text{ortho}) + S_o + S_{213}$;
4-position; $\log k_1 = \log k_H(\text{para}) + S_o$;
6-position; $\log k_1 = \log k_H(\text{ortho}) + S_p$.

In the case of 4-methylphenol, the rates can be expressed as follows:

2-(or 6-)position; $\log k_1 = \log k_H(\text{ortho}) + S_m$.

The observed data in Table 2 were analyzed except for those of Compounds **14**, **17**, and **20**, where three sub-

Table 3. Substituion Parameters of Eq. 6 Evaluated for the Reactions in $HCl-D_2O$

Parameter	Substituent			
	CH_3	CH_3O	t-C_4H_9	Cl
$S_o(X)$	0.991	2.403	0.429	−0.791
$S_m(X)$	−0.031	−0.510	−0.730	−1.563
$S_p(X)$	0.941	2.727	0.574	−0.549
$S_{213}(OH,X)$	−0.171	−0.421	−0.228	0.052
$S_{435}(X,X)$	−0.055	—	—	—
$S_{412}(OH,X)$	−0.295	−1.303	−0.393	−1.382
$S_{612}(OH,X)$	−0.113	−1.239	0.124	−1.103

log k_H(ortho)=−5.066. log k_H(para)=−4.788. Standard deviation=0.096. Probable error=0.011. Calculated from 33 data with 27 parameters.

stituents are adjacent to each other. Corrections for such three adjacent substituents can not be determined at the present stage. The $S_i(X)$ and $S_{jab}(X,Y)$ parameters thus obtained are given in Table 3. The parameters of log k_H in Eq. 6 were evaluated to be −5.066 and −4.788 for the two sites, ortho and para respectively. The values of log k_H(ortho) and log k_H(para) are in good agreement with the experimentally observed rates of phenol, within the limits of probable error. These parameters express S_o and S_p for the OH group. This group's k_H(ortho):k_H(para) ratio was obtained as 0.527:1. Thirty-three experimental data in Table 2 were correlated with 27 parameters with a standard deviation of 0.096. The reaction rates, log k_I, can be calculated within an error of ±0.03. S_o contains three contributions from the mesomeric, inductive, and steric effects of the substituents. S_m is evaluated from the data of the p-substituted phenols; it contains two contributions from the mesomeric and inductive effects of the substituents. S_p is essentially similar to Hammett's σ_p^+ and contains two contributions from the mesomeric and the inductive effects of the substituent. S_{213} appears in the cases of the meta-substituted phenols in which the two substituents interact sterically with each other in their activated states. As has been shown before in the example of 3-methylphenol (**3**), the log k_I's of the 2- and 4-positions of 3-substituted phenols are the same if S_{213} is not taken into consideration. The k_I's of phenol (**1**) are different for the two sites, the 2- and 4-positions. Therefore, the k_I's of 3-substituted phenols must be compared with each other after they have been divided by the corresponding k_I's of **1**. As a matter of fact, the k_I's of the 2-position are smaller than those of the 4-position except for one example. The ratios are, then, 0.579, 0.372, 0.639, and 1.100 for the 3-substituents of t-C_4H_9, CH_3O, CH_3, and Cl respectively. The bulkiness of the substituents is considered to be t-C_4H_9>CH_3O>CH_3>Cl, but the S_{213} of a methoxyl group shows a larger negative value than that of the t-C_4H_9 group. However, no details are known at present. The S_{435} appears in the case of the 4-position of **19**, much as with S_{213}. However, the S_{435} values of the two methyl groups are nearly zero. This shows that the hydoxyl group is more sterically effective than the methyl group in the present reaction. This is consistent with the fact that the methoxyl group is more effective than the t-butyl group for S_{213}. It is also considered that the presence of oxygen atom in the group has some effect. S_{412} and S_{612} appear in the cases of 2-substituted phenols. The two k_I's of the 4- and 6-positions of 2-substituted phenols must be compared with each other after the k_I's are divided by those of **1**. Their ratios are 0.692, 0.878, 0.312, and 0.537 for CH_3, CH_3O, t-C_4H_9, and Cl respectively. The k_I's at the 4-positions are affected more than those at the 6-positions by the introduction of 2-substituents. As may be seen in Table 3, the S_{412} and S_{612} values are especially large for the CH_3O and Cl groups. This contribution is probably due to the interference of the resonance effect of the hydroxyl group with the 2-substituents.

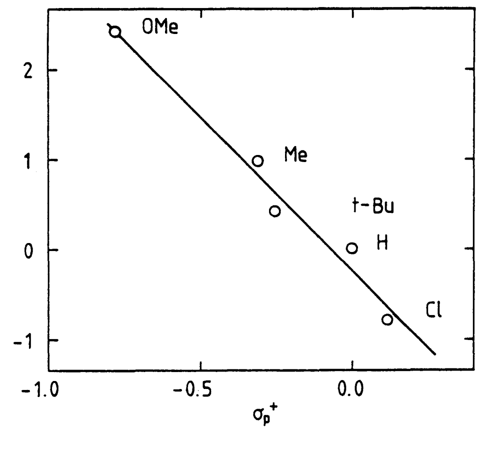


Fig. 3. Plot of S_o based on the σ_p^+ constants.

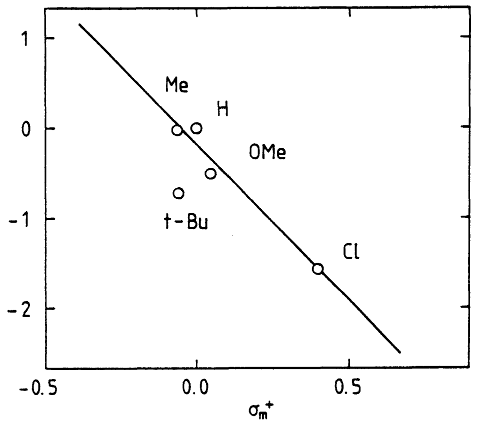


Fig. 4. Plot of S_m based on the σ_m^+ constants.

Correlation between Substituent Parameters and Hammett's Constants. The substituent parameters, S_o, S_m, and S_p, can be correlated with Hammett's constants, as is shown in Figs. 3—5. The S_o's are, however, plotted on a straight line with the σ_p^+ in Fig. 3, because no σ_o's are given in the Hammett relation. The straight line shows S_o=−3.4 σ_p^+−0.2, (r=0.986). In

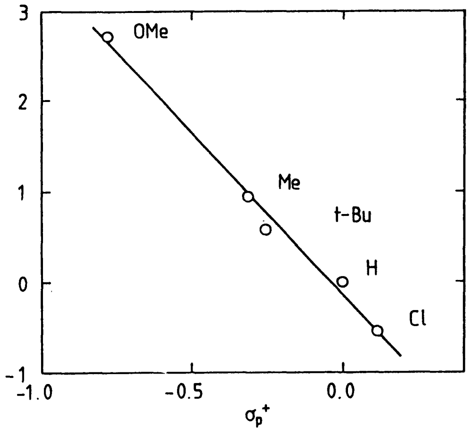


Fig. 5. Plot of S_p based on the σ_p^+ constants.

Fig. 4, the S_m of the *t*-butyl group is beneath the straight line. The straight line shows $S_m=-3.4\sigma_m^+-0.2$ ($r=0.979$) except for the point of the *t*-butyl group. In the case of S_p, all the values are correlated well with σ_p^+ by the use of the relation $S_p=-3.6\sigma_p^+-0.1$ ($r=0.995$), as is shown in Fig. 5. These values may be compared with that of $\rho=-3.51$ observed for similar reactions of 4-substituted anilines.[15)]

It may be concluded that the method used in this article can be applied to ascertain the reaction rates in similar hydrogen-deuterium-exchange reactions with a good precision and with simplicity.

The substituent parameters can be expressed with the Hammett relation. Especially, it must be said that the additive relation can be applied even to ortho-substituted phenols with small deviations. This may be ascribed to the small size of the reagent, that is, a proton or deuteron, in the hydrogen-deuterium exchange reaction.

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