The Substituent Effect. V. NMR Chemical Shifts of Hydrogen-bonding Hydroxyl Proton of Phenols in DMSO

Mizue FUJIO, Masaaki MISHIMA, Yuho TSUNO,[1)]
Yasuhide YUKAWA* and Yoshio TAKAI*

Department of Chemistry, Faculty of Science, Kyushu University, Hakozaki, Fukuoka 812

**Institute of Scientific and Industrial Research, Osaka University, Yamada-kami, Suita, Osaka 565*

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The chemical shifts of the hydrogen bonded OH proton of *m*- and *p*-substituted phenols, and 4-substituted 2-cresols, 3-cresols, and 2,6-xylenols were determined in DMSO. The effects of substituents on the hydroxyl chemical shift of these series were correlated linearly with each other (correlation coefficient$>$0.999), except for the bulky planar substituents in the 3-cresol series which may be subject to the steric loss of their coplanarity with the benzene ring. The substituent effects were treated successfully with the equation, $\Delta\delta=\rho(\sigma^0+r^-\Delta\bar{\sigma}_R^-)$. The phenol series gave $r^-=0.673$ and $\rho=1.530$. The same r^- value appeared to be applicable to all the other series with negligible changes in the ρ value. Deviations from the correlation of particular substituents, in particular those having acidic hydrogen, were attributed to the modification of the electronic nature of substituents arising from the strong substituent-DMSO interaction.

Concerning the substituent effects, we discussed in detail the application of the LArSR Eq. (1) and LSFE Eq. (2)[2)] to the correlational analysis of the hydroxyl proton chemical shifts of *m*- and *p*-substituted phenols in DMF.[3)]

$$\log(k/k_0) \text{ or } P-P_0=\rho\bar{\sigma}=\rho(\sigma^0+r^+\Delta\bar{\sigma}_R^++r^-\Delta\bar{\sigma}_R^-) \quad (1)$$

$$\log(k/k_0)_p=\rho\bar{\sigma}_p=\rho(\sigma_i+q_r^+\sigma_\pi^++q_r^-\sigma_\pi^-) \quad (2)$$

$$\log(k/k_0)_m=\rho\bar{\sigma}_m=\rho(1.17\sigma_i+0.50\sigma_\pi^\pm) \quad (2')$$

The substituent chemical shifts of the hydrogen bonded hydroxyl proton were described in terms of inductive and resonance parameters derived from the chemical reactivity. This might be due to the fact that the hydrogen-bonding of phenols resembles the dissociation of phenols in the electronic situation. The results indicated that the electronic nature of substituents in DMF solution was effectively modified, in reference to those in aqueous solutions, by the particular substituent-solvent interactions. We tentatively derived a set of inductive and resonance substituent constants for such DMF-modified substituent groups. The validity of such a treatment should be verified for systems other than the substituted phenols in DMF solution. Further, the consistency of solvent-modified parameters therefrom should be verified in various systems whose resonance requirements with substituents differ; the constancy of parameters independent of the systems of different combinations of inductive-resonance effects should be examined. Since the chemical shifts of ordinary protons of substituted benzene derivatives are usually determined in non-aqueous aprotic solvents, similar modification of the substituent effect may be involved in these chemical shift data. In order to shed further light on these problems, we have studied substituent effects on the hydrogen-bonded proton NMR chemical shifts of various series of phenols, naphthols,[4)] anilines,[4)] and acetanilides[5)] in several aprotic solvents.

The proton resonance spectra of NH groups generally have a broadened line due to quadrupole of nitrogen, which hinders the ultimate accuracy of the chemical shift measurement of substituted anilines and acetanilides in DMF. However, such a difficulty due to broadening was found to be much reduced in measurements in DMSO solution. A similar improvement was also observed in the determination of OH chemical shifts of some hindered phenol systems such as substituted cresols and xylenols. DMSO is now being extensively used as a solvent and the substituent chemical shift data in DMSO solution have recently become available from our studies which include not only proton NMR but ^{13}C and ^{19}F NMR chemical shift data.[4)] Determination of the set of substituent parameters from the phenol substituent chemical shifts in the particular solvent thus becomes necessary as a reference for this series of studies. The phenol-hydroxyl chemical shifts in DMSO have been studied by several investigators[6-8)] and treated with σ^- constants. Our treatment stands on a different basis and appears to be more consistent.

The present paper gives brief discussions on our LArSR analysis of substituent effects on the chemical shifts of phenols in DMSO solution. A similar treatment of substituent chemical shifts of series of hindered phenols is included for comparison. A forthcoming paper[9)] will give the LSFE analysis and a comparison with relevant treatments of the same material by means of Taft[10)] and Swain and Lupton[11)] equations.

Experimental

The chemical shifts were measured from the low field ^{13}C–H satellite of dimethyl sulfoxide as an internal standard with a Hitachi-Perkin Elmer R-20 Spectrometer operating at 60 MHz.

Dimethyl sulfoxide was fractionally distilled from calcium hydride under reduced pressure and stored over molecular sieves.

All the phenols, cresols and xylenols were thoroughly purified by repeated fractionation or recrystallization from appropriate solvents, and for some phenols purification was effected by further sublimation of purified samples. Melting points and other physical constants agreed well with established values. The preparation of most *m*- and *p*-substituted phenols was previously described.[3)]

m- *and* p-*Hydroxyphenyltrimethylammonium Iodides* were prepared from corresponding aminophenols by exhaustive meth-

ylation with methyl iodide in aqueous sodium carbonate solution; *m*-$(Me)_3N^+I^-$ derivative, mp 198.5 °C, recrystallized from ethanol, lit,[12] mp 179 °C, and *p*-$(Me)_3N^+I^-$ derivative, mp 210.5 °C, recrystallized from ethanol, lit,[12] mp 195 °C.

m-*and* p-*Hydroxyphenyldimethylsulfonium Iodides* were prepared from methylmercaptophenols by methylation on heating with methyl iodide in a sealed tube at 110 °C for 12 hr; *m*-isomer, mp 79—80 °C, from methanol-ether, lit,[13] mp 97—98 °C; *p*-isomer, mp 127—128 °C, from ethanol-ether, lit,[14] mp 123—124 °C.

m-Methylmercaptophenol afforded m-*hydroxyphenyl methyl sulfoxide* on oxidation. The phenol was allowed to react with methanesulfonyl chloride in acetic anhydride for 24 hr at 0—−5 °C, to give the methanesulfonate (mp 36—37 °C, lit,[15] mp 38—39 °C). Oxidation of the sulfonate on standing the mixture with fuming nitric acid ($d=1.52$) in acetic anhydride for 24 hr at below 0 °C, yielded *m*-methylsulfinylphenyl methanesulfonate (mp 89—90 °C, lit,[15] mp 89—90 °C), which was hydrolyzed with 10% aq. sodium hydroxide solution at 50 °C for 24 hr to give the final product; mp 55—55.5 °C; from benzene-chloroform, lit,[15] mp 61—62 °C.

Several 3-cresols, available from commercial sources, were purified by appropriate methods; 3-*cresol*, bp 101 °C/20 mmHg, lit,[16] mp 202 °C; 3,4-*dimethylphenol*, mp 62—63 °C, from benzene-petroleum ether, lit,[16] mp 62.5 °C; 4-*chloro*-3-*cresol*, mp 63—63.5 °C, from *n*-hexane, lit,[17] mp 66 °C; 4-*nitro*-3-*cresol*, mp 133—133.5 °C, from ethanol-benzene, lit,[18] mp 129 °C; 4-*methylthio*-3-*cresol*, mp 56.8—57.2 °C, from benzene-*n*-hexane, lit,[12] mp 55—56 °C.

4-*Amino*-3-*cresol* was prepared from 4-nitro-3-cresol by reduction with stannous chloride in alcoholic hydrochloric acid and purified by sublimation under 1 mmHg at 120 °C (mp 180—181 °C, lit,[16] mp 179 °C), which was converted by acetylation with acetic anhydride-water into 4-*acetamino*-3-*cresol* (mp 132—133 °C, from aq. ethanol, lit,[16] mp 130 °C) and by methylation with methyl iodide into 2-*methyl*-4-*hydroxyphenyltrimethylammonium iodide*, mp 216—217 °C, from ethanol, lit,[12] mp 194.8—195 °C.

4-Dimethylamino-3-cresol was also derived from 4-amino-3-cresol. The aminocresol was converted into the methyl ether with diazomethane and then into *N,N,N*-trimethyl-4-methoxy-2-methylanilinium iodide with methyl iodide. The anilinium iodide was converted by the method given by Cope *et al.*,[19] reductive fission with lithium aluminum hydride in boiling THF, into 4-dimethylamino-3-methylanisole (bp 163 °C/26 mmHg), which yielded 4-*dimethylamino*-3-*cresol* (mp 89—89.2 °C, from ligroin. Found: C, 71.37; H, 8.57; N, 9.17%. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26%.) by the ether-fission with boiling hydroiodic acid.

4-Methoxy-3-cresol and 3-methylhydroquinone were prepared from 4-amino-2-cresol. 4-Amino-2-cresol was allowed to react with diazomethane to give 4-amino-2-methylanisole, which was diazotized in dil. sulfuric acid at 0 °C and decomposed at elevated temperature. The phenolic product gave two distillates, bp 120 °C/18 mmHg and bp 160 °C/18 mmHg, on fractionation. 4-*Methoxy*-3-*cresol*, mp 43.5—45.2 °C (lit,[20] mp 46 °C), was obtained from the former fraction by recrystallization from petroleum ether, and 3-*methylhydroquinone*, mp 131.5—132 °C, lit,[21] mp 124—125 °C, from the latter, by recrystallization from benzene.

Oxidation of 4-methylthio-3-cresyl acetate with hydrogen peroxide in acetic acid according to the method given by Bordwell and Boutan[15] gave 4-methylsulfonyl-3-cresyl acetate, which was hydrolyzed with 10% aq. potassium hydroxide solution to give 4-*methylsulfonyl*-3-*cresol* in good yield (mp 105.5—106.5 °C, from chloroform. Found: C, 51.38; H, 5.21; S, 17.28%. Calcd for $C_8H_{10}SO_3$: C, 51.60; H, 5.41; S, 17.22%.). 4-Methylthio-3-cresol was converted into 4-*methylsulfinyl*-3-*cresol* (mp 120.8—121 °C, from benzene-chloroform; Found: C, 56.28; H, 5.82; S, 18.70%. Calcd for $C_8H_{10}SO_2$: C, 56.44; H, 5.92; S, 18.84%.) *via* 4-methylthio-3-cresyl methanesulfonate, by the same oxidation procedure for *m*-hydroxyphenyl methyl sulfoxide. 4-*Hydroxy*-2-*tolyldimethylsulfonium iodide* (mp 113.5—114 °C, from ethanol-ether, lit,[12] mp 110—111 °C) was obtained by the same method as that for hydroxyphenyldimethylsulfonium iodide. 4-*Thiocyano*-3-*cresol* was prepared by the procedure given by Bordwell and Boutan[22] and was purified by recrystallization from benzene-ligroin; mp 79 °C, lit,[23] mp 76 °C.

4-*Acetyl*-3-*cresol* (mp 134 °C, from benzene, lit,[24] mp 128 °C) was obtained by the Fries rearrangement of 3-cresyl acetate with $AlCl_3$, being allowed to stand at room temperature for 24 hr in nitrobenzene.

4-*Bromo*-3-*cresol* was given by the bromination of *m*-cresol according to the reported method.[25] The bromination product obtained by the dropwise addition of bromine to *m*-cresol in chloroform was carefully fractionated to remove the 6-bromo derivative. The fraction, bp 140—145 °C at 20 mmHg, gave 4-bromo-3-cresol and purification was further effected by repeated recrystallization from petroleum ether; mp 59 °C, lit,[26] mp 58.5—59.2 °C and[25] 60—61 °C. 4-Bromo-3-cresol was converted into 4-*cyano*-3-*cresol* (mp 140—140.2 °C, from benzene. Found: C, 72.06; H, 5.21; N, 10.32%. Calcd for C_8H_7NO: C, 72.16; H, 5.30; N, 10.52%.) by the method given by Friedman and Shechter.[27] The 4-cyano derivative was hydrolyzed and esterified with methanol to give 4-*carbomethoxy*-3-*cresol*; mp 115.5—116 °C recrystallized from benzene (lit,[28] mp 109 °C).

2-*Cresol* (bp 128—129 °C/110 mmHg, lit,[16] bp 130 °C/112 mmHg) and 2,4-*xylenol* were obtained by purification of commercial products.

By the usual diazonium method, 4-chloro-2-toluidine was converted into 4-*chloro*-2-*cresol* (mp 48.5—49 °C, from petroleum ether, lit,[17] mp 49 °C), and 4-nitro-2-toluidine into 4-*nitro*-2-*cresol* (mp 95—95.5 °C, from benzene-ligroin, lit,[29] mp 94.4—95 °C).

4-Nitro-2-cresol was reduced with stannous chloride in alcoholic hydrochloric acid into 4-*amino*-2-*cresol* (mp 178 °C subl. at 100 °C/3.5 mmHg, lit,[16] mp 175 °C) which was followed by acetylation with aq. acetic acid and acetic anhydride into 4-*acetylamino*-2-*cresol* (mp 185—185.5 °C from aq. ethanol, lit,[16] mp 179 °C), and also by exhaustive methylation with methyl iodide into 4-*hydroxy*-3-*methyl phenyltrimethylammonium iodide* (mp 226.8—227 °C, from ethanol. Found: C, 40.84; H, 5.60; N, 4.70; I, 42.99%. Calcd for $C_{10}H_{16}ONI$: C, 40.97; H, 5.50; N, 4.78; I, 43.29%.).

4-*Dimethylamino*-2-*cresol* was prepared from 4-amino-2-methylanisole by same procedure as that for 3-cresol derivative, mp 84—85 °C, recrystallized from benzene-ligroin. Found: C, 71.20; H, 8.67; N, 8.98%. Calcd for $C_9H_{13}NO$: C, 71.49; H, 8.67; N, 9.26%.

4-Bromo-2-methylacetanilide was saponified to give 4-bromo-2-methylaniline, which was converted by the diazonium method into 4-*bromo*-2-*cresol*; mp 65—65.5 °C, from ligroin, lit,[16] mp 64 °C. Similarly, 4-*cyano*-2-*cresol* (mp 97.5—97.8 °C, from benzene-ligroin, lit,[16] mp 93 °C) was prepared from 4-cyano-2-methylaniline, and was converted by saponification and esterification into 4-*carbomethoxy*-2-*cresol*; mp125.8—126 °C, from ligroin-benzene. Found: C, 64.87; H, 5.98%. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07%.

4-*Acetyl*-2-*cresol* (mp 112—112.2 °C, from benzene, lit,[30] mp 104 °C) was obtained by the same method as that for 3-cresol.

4-*Methoxy*-2-*cresol* was synthesized according to the reported meth od[31]; 4-methoxyphenol was converted into 2-cresol by

direct introduction of 2-methyl group with dimethylamine and formaldehyde followed by hydrogenolysis (120 atom H_2, 200 °C, 16 hr) in the presence of CuCrO in dioxane; mp 72 °C, from benzene–ligroin, lit,[31] mp 70.5 °C.

4-*Thiocyano*-2-*cresol* was obtained by the same method as that for the 3-cresol derivative; mp 70.5—71 °C, from benzene–ligroin, lit,[23] mp 71 °C.

The following 4-substituted 2,6-xylenols were employed for measurements after repeated recrystallization of commercial products from appropriate solvents; 2,6-*xylenol*, mp 45—45.2 °C, from *n*-hexane, lit,[32] mp 46—47 °C; 2,4,6-*trimethylphenol*, mp 73.8—74.2 °C, from *n*-hexane, lit,[31] mp 70—71 °C; 4-*methylthio*-2,6-*xylenol*, mp 63 °C, from *n*-hexane, lit,[33] mp 62.5—64 °C.

4-*Nitro*-2,6-*xylenol* was prepared by the following procedure. 2,6-xylenol was converted into its methyl ether with dimethyl sulfate and then nitrated with nitric acid in acetic anhydride. 4-Nitro-2,6-xylenol methyl ether obtained was demethylated with hydrobromic acid–acetic acid mixture to give the final compound; mp 172.5—173 °C, from benzene, lit,[32] mp 170—172 °C. 4-*Hydroxy*-2,6-*xylenol* was obtained from the above 4-nitro-2,6-xylenyl methyl ether successively by reduction with tin in hydrochloric acid–ethanol, diazotization of the resulting aniline to give the phenol, and demethylation; mp 153—154 °C, sublimation 120 °C at 4 mmHg, lit,[16] mp 149—151 °C.

4-*Bromo*-2,6-*xylenol* was prepared[34,35] from 2,6-xylenol by bromination in acetic acid at 15°C and purified by recrystallization from *n*-hexane, mp 79—79.5 °C, lit,[35] mp 79 °C. The above 4-bromo compound was converted into 4-*cyano*-2,6-*xylenol* (mp 125 °C, from aq. ethanol, lit,[32] mp 124—125 °C) by the usual procedure[27] with cuprous cyanide in boiling DMF. 4-*Carbomethoxy*-2,6-*xylenol* was given by saponification of the 4-cyano compound and esterification of the 4-carboxylic acid with methanol–conc. sulfuric acid; mp 131.5—132 °C, from benzene, lit,[16] mp 130 °C.

4-*Acetyl*-2,6-*xylenol* was obtained by the Fries rearrangement of 2,6-xylenyl acetate and recrystallized from ethanol–benzene; mp 156—157 °C, lit,[32] mp 151—152 °C. 4-*Benzoyl*-2,6-*xylenol* was prepared by the same procedure from 2,6-xylenyl benzoate; mp 145 °C, from aq. ethanol, lit,[36] mp 142—142.5 °C.

4-*Methoxy*-2,6-*xylenol* was synthesized according to the procedure described for 4-methoxy-2-cresol; mp 78.2—78.5 °C, from ligroin, lit,[31] mp 77 °C.

4-*Hydroxy*-3,5-*dimethylphenyldimethylsulfonium iodide* was prepared from 4-methylthio-2,6-xylenol with methyl iodide by heating under reflux for 30 min; mp 130 °C, from methanol–ether. Found: C, 38.69; H, 5.10; S, 10.52; I, 40.51%. Calcd for $C_{10}H_{15}OSI$: C, 38.72; H, 4.87; S, 10.34; I, 40.91%.

4-*Methylsulfonyl*-2,6-*xylenol* was prepared from 4-methylthio-2,6-xylenol by oxidation by the same procedure as that for *p*-substituted cresol and recrystallized from chloroform–benzene–ethanol, mp 158—159 °C, lit,[37] mp 149—150 °C.

4-*Hydroxy*-3,5-*dimethylphenyl methyl sulfoxide* was prepared by the same procedure as that for *m*-hydroxyphenyl methyl sulfoxide; 4-methylthio-2,6-xylenol was converted into the corresponding methanesulfonate (mp 77—78.5 °C, from chloroform–*n*-hexane) which was oxidized with fuming nitric acid–acetic anhydride to 4-methanesulfoxy-3,5-dimethylphenyl methyl sulfoxide (mp 122.5—123.5 °C, from benzene–chloroform) and then followed by saponification to give the final compound, mp 76—77 °C, from benzene–chloroform–petroleum ether. Found: C, 58.56; H, 6.49; S, 17.23%. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56; S, 17.40%.

4-*Acetamino*-2,6-*xylenol* was prepared by reduction of 4-nitro-2,6-xylenol with stannous chloride in ethanolic hydrochloric acid, followed by direct acetylation of the aniline obtained with aqueous acetic acid–acetic anhydride mixture and recrystallized from benzene, mp 142.5—143 °C; Found: C, 66.84; H, 7.44; N, 7.56%. Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82%.

Results

In the hydroxyl chemical shift measurement in DMSO solution, relatively sharp and stable signals were obtained for various phenols even under conditions of highest possible dilution (about 0.065 M). The dilution shift was generally insignificant in this solvent, at most *ca.* 2 Hz on 4-fold dilution, and was practically negligible in the case of hindered phenols. Most phenols gave hydroxyl signals of half-height width within 1.5 Hz. Although Traynham[6] did not find the OH signal of *p*-aminophenol, we succeeded in observing a sharp signal of the OH proton with regular intensity by using the sample purified by repeated sublimation immediately before use. Fischer *et al.*[38] reported that 4-formyl- and 4-nitro-2,6-xylenols exhibited very broad peaks, especially the latter a peak of half-height width of 1.4 ppm. According to the present results, 2,6-xylenols generally gave slightly broader signals for the hydroxyl proton than unhindered phenols, but the nitro derivative gave a signal of width within 5 Hz, benzoyl and cyano derivatives 7 Hz, and at the worst, acetyl derivative 12—17 Hz.

The non-equivalent OH protons of 2-methyl- and 2,6-dimethyl-hydroquinones gave two separated signals of the ordinary half-height width in this solvent. This suggests that no rapid proton exchange occurs between the two OH groups. The assignment was made on the basis of correlations between substituent chemical shifts for different structural classes of phenols.

The hydroxyl proton chemical shifts extrapolated to the infinite dilution are summarized in Table 1. Since

Table 1. Chemical shifts of hydroxyl protons of phenols, cresols and xylenols in DMSO

No.	Subst.	Phenol		2-Cresol	2,6-Xylenol	3-Cresol
		$\Delta\delta_p^{TMS}$	$\Delta\delta_m^{TMS}$	$\Delta\delta_{2\text{-Me}}^{TMS}$	$\Delta\delta_{2,6\text{-Me}_2}^{TMS}$	$\Delta\delta_{3\text{-Me}}^{TMS}$
1	NO_2	10.963	10.353	10.907	9.782	10.717
2	CN	10.540	10.140	10.455	9.353	10.418
3	SO_2CH_3	10.510	10.160		9.295	10.367
4	$SOCH_3$	10.010	9.895		8.757	9.855
5	SCN	10.140		10.056		10.070
6	$SMe_2^+I^-$	10.665	10.352		9.513	10.557
7	$NMe_3^+I^-$	10.085	10.168	9.990		10.012
8	COC_6H_5	10.373	9.793		9.185	
9	$COCH_3$	10.250	9.703	10.175	9.047	10.050
10	$COOCH_3$	10.257	9.765	10.172	9.058	10.065
11	H	9.253		9.128	8.072	9.142
12	Br	9.623	9.813	9.515	8.418	9.497
13	Cl	9.600	9.810	9.480		9.468
14	SCH_3	9.370	9.425		8.160	9.252
15	NHAc	9.078	9.262	8.930	7.887	9.127
16	CH_3	9.002	9.140	8.865	7.822	8.885
17	OCH_3	8.828	9.295	8.660	7.617	8.695
18	OH	8.535	9.077	8.382	7.357	8.432
19	NMe_2	8.535	8.928	8.365		8.815
20	NH_2	8.267	8.755	8.078		8.200

the values for *m*- and *p*-substituted phenols were already reported,[3] the Table 1 includes only new data and those necessary for comparison with substituent shifts of other derivatives. The results for *m*- and *p*-substituted phenols are in good agreement with those reported by Traynham[6] and Ouellette[7] within ±0.01 ppm. The data for *p*-acetyl and *p*-trifluoromethyl derivatives are identical with Traynham's values but not with those of Ouellette. Socrates[8] also reported a set of data under the same conditions, differing from ours by more than ±0.1 ppm for 13 derivatives and more than ±0.3 ppm for 6 in 45 derivatives where comparisons are possible. The discrepancies appear to be out of the usual limit of conceivable errors when compared to the fact that the data of Tribble and Traynham differed from ours only at most by 0.03 ppm.

The chemical shifts of 4-substituted 2,6-xylenols are generally in good agreement with those reported by Fischer *et al.*[38]

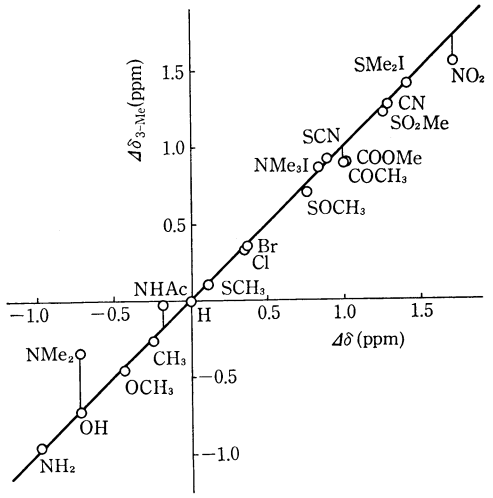

Fig. 1. The linear relation between the substituent chemical shifts of 3-cresols and phenols.

Discussion

In *m*- and *p*-substituted phenols, the electron attracting substituents gave a lower field shift and the releasing groups a higher field shift. This can be interpreted reasonably in terms of the stabilization or the dispersion of the acquired negative charge at the hydroxyl oxygen by the strong OH–DMSO hydrogen-bonding. The stronger hydrogen-bonding by the acid-strengthening substituents should bring about the greater shifts toward down field. Thus the substituent chemical shift may be in principle related to the Hammett-type substituent constants.

The substituent chemical shifts of 4-substituted 2-cresols correlate linearly to those of 4-substituted phenols with excellent precision (correlation coefficient 0.99995 and standard deviation ±0.009) by

$$\Delta\delta_{2\text{-Me}} = 1.047\Delta\delta - 0.008$$

Similarly 4-substituted 2,6-xylenols correlate with phenols by

$$\Delta\delta_{2,6\text{-Me}_2} = 0.999\Delta\delta - 0.009$$

with a correlation coefficient 0.9999 and a standard deviation ±0.013. Introduction of two methyl groups at both *ortho* positions to the phenol hydroxyl markedly shifts the correlation line to up field but does not affect the susceptibility of the hydroxyl chemical shift to changes in 4-substituent. 4-Substituted 3-cresols also give a good linear plot of the substituent chemical shifts against phenols, as shown in Fig. 1 with the slope= 1.000, except dimethylamino, acetamino, and nitro derivatives, deviations of which can of course be referred to the steric loss of coplanarity of substituents with the benzene ring.

Socrates[8] pointed out that the substituent chemical shifts of various phenols, including *ortho*-substituted derivatives, in DMSO solution were correlated linearly to the pK_a of corresponding phenols in water. Figure 2 shows a plot of the chemical shifts obtained in the present study against the corresponding pK_a values in water. Because of their leveling effect, strongly electron releasing substituents in the dissociation of

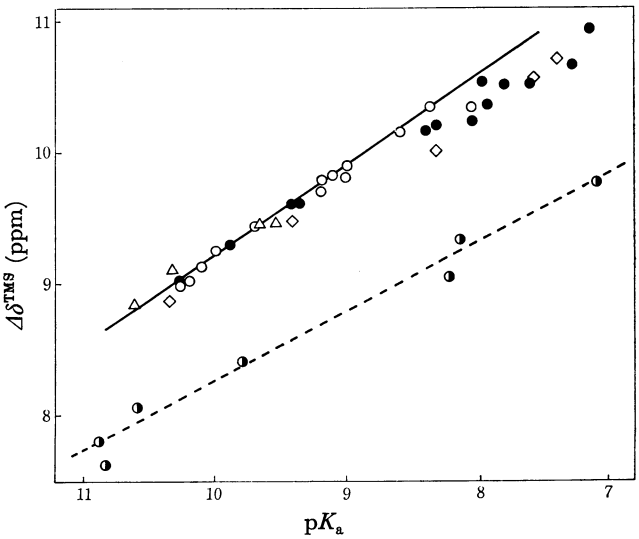

Fig. 2. The plot of the relative hydroxyl chemical shifts of phenols against the pK_a values: *m*-substituted ○, *p*-substituted ● phenols, 3-cresols ◇, 2-cresols△, and 2,6-xylenols ◑.

phenols could not be included in this comparison. *m*-Substituents appear to fall on a straight line and all +*R* class 4-substituted derivatives deviate substantially below the line. These systematic deviations should be significant in view of the excellent correlations of hydroxyl chemical shifts among different classes of phenols above. It is worthy to note that the 2,6-xylenols fall on a parallel line. Thus, Socrates' correlation does not seem to be an accurate description of the substituent effect on the hydroxyl chemical shift of various phenols in DMSO. The systematic deviations of *para* substituents evidently suggest that the resonance contribution (relative to the inductive contribution) of +*R* class *para* substituents is less important in the hydrogen-bonding hydroxyl chemical shifts with DMSO than in the dissociation of phenols in water.

The relative chemical shifts for 17 well-behaving *m*-substituents on phenol in DMSO give a linear Hammett correlation with the standard σ_m constants,[3]

$$\Delta\delta = 1.529\sigma_m - 0.004 \quad (3)$$

with standard deviation ±0.022 and correlation coefficient 0.9987.[39] Fischer *et al.* applied a similar treatment to each of three sets of literature data[6,7] to give ρ values of 1.4—1.53.[38] In Eq. (3) of *meta* derivatives, deviations are obvious for amino, hydroxyl, and acetamino groups which were not included in the calculation. *m*-Acetyl, *m*-carboalkoxy, and *m*-methoxy groups exhibited slightly less electron-attracting effects than expected from the standard σ_m values and are fitted closer to the correlation line by employing the $\bar{\sigma}$ values, 0.291, 0.31, and 0.06, respectively, which were derived from pK_a of corresponding benzoic acids in aqueous organic solutions.[40] All the results suggest the importance of the solvent-substituent interaction. Amino, acetamino, and hydroxyl groups act as effective hydrogen-bond donors to DMSO. The negative charge acquired at hydroxyl oxygen or amino nitrogen due to hydrogen bonding with an acceptor solvent can make these groups more electron releasing. The loss of hydrogen-bond donation in non-aqueous aprotic solution can explain the deviations of *m*-methoxy, *m*-acetyl, and *m*-carboalkoxy groups. The substituent parameters of a given group should change due to the modification of its electronic nature by the solvent-substituent interaction.[3] Since the ordinary substituent parameters were derived from the data in aqueous solutions where donative hydrogen bonding to substituents is highly important, they may not correlate well with the data in aprotic solvents. We have denoted the overall effect as "the solvent-modification of substituent effects" or "the effect of solvent-modified substituents."[3] There should be a number of possible causes for the deviations, but we assume that the deviations observed in the above correlation can be referred primarily to the effect of the solvent-modification of substituents. Thus, all substituents would be modified more or less in the present system. However, most *meta* substituents except for the few groups mentioned above follow Eq. (3) and the range of fitting covers chemical shift changes over 1.2 ppm. Accordingly the ρ value obtained above appears to be sufficiently reliable.

We see from Socrates' correlation (Fig. 2) that the conjugatively electron attracting (+*R*) *para* substituents exhibit more enhanced resonance effects than those estimated from corresponding σ_p^0 values. Traynham applied σ_p^- values for correlating these substituents and gave slightly different ρ values for *para* and *meta* derivatives.[6] From the systematic deviations in Fig. 2 it is evident that neither σ_p^0 nor σ_p^- could represent appropriately the effects of +*R para* substituents in this system with the same ρ value as *meta* substituents. In order to describe the effects of both *para* and *meta* substituents, an introduction of certain parameter weighting resonance contribution relative to the inductive or unexalted polar contribution appears to be necessary. The LArSR equation can be applied to this system as a useful approximation, giving a satisfactory correlation (for 30 *m*- and *p*-derivatives),

$$\Delta\delta = 1.530(\sigma^0 + 0.673\Delta\bar{\sigma}_R^-) - 0.004 \quad (4)$$

with standard derivation ±0.024 and correlation coefficient 0.9990.[41] This confirms that the substituent effect on the hydrogen-bonded hydroxyl chemical shift can be treated in the same way as that on chemical reactivities in terms of the Hammett-type substituent parameters. The −*R para* substituents appear to give a better fit to the σ_p than to σ_p^0 constants,[3,42] but the deviations due to the solvent-modification may also be expected for certain *para* substituents as observed in the *meta* correlation. When the −*R para* groups are correlated with the standard σ_p^0 values, the *p*-amino, hydroxy, acetamino and some other groups deviate from the correlation to a comparative extent as the *meta* analogues do. The +*R* groups generally satisfy Eq. (4), while carbonylamido and sulfonamido groups show significant derivations. Deviations of the trimethylammonium and dimethylsulfonium groups are remarkable. Nevertheless, it is evident from the satisfactory fit to Eq. (4) that modification of the electronic nature of substituents with DMSO is not significant at least as far as the ordinary +*R* substituents are concerned.

Table 2. Apparent substituent constants in DMSO

No.	Subst.	$\bar{\sigma}_p$				
		Phenols $\bar{\sigma}_m$	Phenols $\bar{\sigma}_p$	2-Cresols $\bar{\sigma}_{2\text{-Me}}$	2,6-Xylenols $\bar{\sigma}_{2,6\text{-Me}_2}$	3-Cresol $\bar{\sigma}_{3\text{-Me}}$
1	NO_2	0.722	1.121	1.118	1.128	1.033
2	CN	0.583	0.844	0.836	0.848	0.838
3	SO_2CH_3	0.596	0.825		0.809	0.804
4	$SOCH_3$	0.422	0.498		0.475	0.469
5	SCN		0.583	0.587		0.609
6	$SMe_2^+I^-$	0.721	0.926		0.952	0.928
7	$NMe_3^+I^-$	0.601	0.547	0.546		0.571
8	COC_6H_5	0.356	0.735		0.737	
9	$COCH_3$	0.297	0.655	0.661	0.647	0.596
10	$COOCH_3$	0.337	0.658	0.659	0.655	0.606
11	H		0.002	0.007	0.008	0.002
12	Br	0.369	0.244	0.249	0.236	0.235
13	Cl	0.367	0.229	0.227		0.216
14	SCH_3	0.115	0.079		0.066	0.074
15	NHAc	0.008	−0.112	−0.116	−0.113	−0.007
16	CH_3	−0.071	−0.162	−0.157	−0.155	−0.166
17	OCH_3	0.030	−0.276	−0.285	−0.290	−0.290
18	OH	−0.113	−0.467	−0.459	−0.457	−0.462
19	NMe_2	−0.210	−0.467	−0.469		−0.211
20	NH_2	−0.323	−0.643	−0.648		−0.614

The ρ values obtained by means of Eqs. (3) and (4) being identical, the apparent $\bar{\sigma}$ values of this system (Table 2) are calculated by using the ρ value of 1.529. The excellent linear correlations of the 4-substituent chemical shifts among phenols, 2- and 3-cresols, and xylenols indicate that these sets of data may give an identical set of apparent $\bar{\sigma}$ values for 4-substituents and that the degree of resonance exaltation of +*R* 4-substituents, r^-=0.673 in Eq. (4), remains practically constant. The ρ value for each structural class is obtained by 1.529 λ, where λ is the slope of the plot of $\Delta\delta$ for a respective system aganist those of the phenol system. The sets of apparent $\bar{\sigma}$ values for all 4-substituents derived from 2-cresols and 2,6-xylenols are

identical within experimental uncertainty with the values from the parent phenols (Table 2). The same $\bar{\sigma}$ values are also given from the 3-cresol system for most 4-substituents, excluding the bulky planar groups which require the coplanarity with the benzene ring for resonance.

The agreement of these values suggests that the deviations from the calculated set of apparent substituent constants with standard parameters are not due to the experimental error but are inherent to substituents. Apparent $\bar{\sigma}$ values for most substituents are slightly more electron releasing than σ_p^0 for $-R$ groups and the calculated $\bar{\sigma}$ values for $+R$ groups. This can be attributed to the decrease in the electron-attracting effect of substituents in aprotic DMSO due to the absence of hydrogen-bonding from water in which the standard substituent parameters were determined. Significant deviations are observed for the substituents carrying an active hydrogen such as NH_2, OH, $NHCOCH_3$, $CONH_2$ and SO_2NH_2, whose particularly enhanced electron-releasing effects may be explained as to be due to the effect of the negative charge gained through the hydrogen-bonding with DMSO, in addition to the regular enhancement. The decreased electron attraction of charged groups NMe_3^+ and SMe_2^+ should not be unreasonable if the difference in solvation between the charged and dipolar substituents in aprotic and protic solvents is considered. The effect of solvent modification of respective substituents may thus be estimated at least qualitatively by the difference of apparent $\bar{\sigma}$ from the calculated values. However, since the $\bar{\sigma}$ values for $+R$ groups should only measure the apparent effects in reference to a given intermediate r value of 0.673, they cannot be taken as a proper set of substituent parameters for the solvent-modified substituents with DMSO, unless they can be in some way referred to the standard σ^0 scale ($r=0$) or σ^- scale ($r=1.00$).

The effect of the 3-methyl group in the 3-cresol system remains constant regardless of changes in 4-substituents, and the additivity of substituent effects holds giving an apparent $\bar{\sigma}$ of -0.07 for the 3-methyl group, except for the case where the steric loss of resonance of 4-substituents exists. In the 2-cresol system, the effect of the *o*-methyl group is represented similarly in an additive manner giving an apparent -0.075 effect in σ unit for the methyl group, even though the ρ value 1.579 is slightly higher than that for the parent phenol system. Introduction of another *o*-methyl group also exhibits a constant additive effect throughout the series, but the apparent -0.77 effect in σ unit appears too large for it to be referred to the electronic effect of two methyl groups. The effect of the 2,6-dimethyl group would not arise from electronic modification of the system but predominantly from a certain non-electronic effect due to its proximity to the phenol hydroxyl functionality.

The phenomenon was ascribed to the steric loss of coplanarity of the DMSO-hydrogen bonding OH function with the benzene ring and consequently to the enhanced shielding due to an acquired negative charge at the oxygen atom.[6] Deviation from the coplanarity of the detection function should produce a marked decrease in the resonance interaction with $+R$ *para* substituents and this is reflected in the apparent $\bar{\sigma}$ values. However, the difference between the $\bar{\sigma}_p$ values for the hindered and unhindered phenol series is hardly detectable. Further information is obtained from results of the 4-substituted 3-cresol system. 4-Dimethylamino and 4-acetamino groups exhibit a significant loss of electron-releasing effect (Fig. 1), while the 4-hydroxyl group which is effectively stabilized through hydrogen bonding with DMSO shows none. This is in line with the fact that the *o*-cresols exhibit an up-field shift no more significant than expected from the additivity of substituent effects, and does not conflict with the above argument. On the other hand, the chemical shift difference 0.618 of the unhindered hydroxyl proton of 3,5-dimethylhydroquinone relative to 3,5-dimethylphenol provides an apparent $\bar{\sigma}$ value of -0.40 for the sterically hindered hydrogen-bonding 4-OH substituent in the 3,5-xylenol system, on the assumption $\rho=1.53$. The decrease of the $\bar{\sigma}$ value from -0.46 for unhindered systems (Table 2) is insignificant in contrast to the marked reduction observed in the case of the methoxy group from the ordinary value of -0.27 to -0.12 for the hindered one. Thus, the coplanarity of the hydrogen-bonding OH is not lost effectively, even in the presence of two *ortho* methyl groups. The proximity of the DMSO molecule will be determined by the steric effects in the neighborhood of the phenol site and the steric restriction of approach of DMSO to the site should be sufficient to cause a minor loss (*ca.* 10%) in the electron releasing effect of the hydroxyl group. The data appear to be insufficient to draw any decisive conclusion, but it is conceivable that the up-field shift of the hindered hydroxyl proton is caused largely by the change in the extent of transfer of hydrogen-bonding proton between the donor and acceptor molecules.

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