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Reactions of Isopropyl Methylphosphonofluoridate with Substituted Phenols. II

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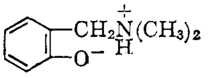
A previous study on the reactivity of isopropyl methylphosphonofluoridate (GB) with various phenolic anions indicated that the incorporation of a cationic site into the phenolic nucleus increased the reactivity of the anion relative to its basic strength. Further studies have been carried out on this "charge" effect, the classes of compounds investigated and reported in this paper being mono- and bisdimethylaminomethylphenols, -catechols, and -pyrogallols. At least in the hydroxybenzenes, the general phenomenon of the charge effect is established. The effect is demonstrated to be additive; that is, each cationic site contributes to an increase in reactivity, the magnitude of the increase being related to the distance of separation of the cationic and anionic sites. The charge effect is another factor, previously unrecognized, to be reckoned with in any discussion involving nucleophilic reactivity.

In a previously reported study[1] of the reactivity of the "nerve gas" isopropyl methylphosphonofluoridate (GB) with various phenols, it had been shown that phenolate ions possessing cationic groups exhibited higher reactivity than would be predicted from their basic strengths. Anions of *o*-substituted phenols of the above type, in particular the dipolar ions of the Mannich bases of phenol I and of salicylamine, showed an increase in reactivity over that of phenolate similar to that shown by the monocatecholate ion.[2] The increase in reactivity of I and of the monoanions of catechol over phenolates of like basic strength has been attributed to bonding by the hydroxyl hydrogen to the phosphonyl oxygen of GB, which aids in the formation of a transition state. In view of the similarities in the basicities and potential for hydrogen bonding of a monocatecholate anion and I, it would have been plausible to explain the anomalous activity of I in terms of hydrogen bonding. Yet, it was also shown that the reactivity of the anions of salicylamine and of I could be explained adequately on the basis that two effects, steric and electrostatic (neither of which involves hydrogen bonding), are operative; that the electrostatic effect, which was attributed to the presence of a cationic charge in the phenol, was responsible for the rate acceleration whereas the steric effect was decelerating; and that enhancement of the rate was found when the accelerating electrostatic effect was greater than the opposing steric effect (the case in compounds such as salicylamine and I). The explanation offered to account for the abnormal reactivity shown by salicylamine and I was that, in contrast to other substituted phenols, the pK_a of a cationic phenol was not a valid measure of the basicity of the dipolar phenolate ion to a neutral substrate (in this case, GB); that, in fact, the basicity to a neutral substrate is much greater than is indicated by the pK_a of the conjugate acid.



I

To help decide which of the two explanations is more acceptable, it was thought advisable to obtain data showing whether the behavior of I was more closely related to that of a phenolate or monocatecholate anion. In this connection, the slopes of the lines in the plots of log k_2 *vs.* pK_a (exponents in the Brønsted equation) for the GB-phenolate and GB-monocatecholate reactions are *ca.* 0.6[1] and 0.8[2]; the slope of the line in the plot of log k_2 *vs.* pK_a for the reaction between the anions of substituted Mannich bases of phenols with GB might be revealing. Also, a comparison of the effects on the reactivity produced by substitution *ortho* to the hydroxyl group in phenol, catechols, and I could indicate significant differences or similarities among the classes of compounds.

In the aforementioned study[1] it was shown that phenols possessing cationic groups in positions *meta* and *para* to the phenolic anion also showed significant rate enhancement (although not so great as in the case of *o*-phenolamines). The novelty of this effect made desirable a more general examination of this phenomenon. Studies are also reported herein on the reactivity of mono- and polydimethylaminomethylcatechols and pyrogallols with GB.

Experimental

Materials and Equipment.—Compounds not synthesized for these studies were procured from commercial sources (reagent grade) and used without further purification. The GB used in the experiments was supplied by the Chemical Research Division of the Chemical Research and Development Laboratories, Edgewood Arsenal. It was distilled once, then redistilled from triethylamine, and distilled again from sodium fluoride. Its analysis indicated 99.7% purity.

Mono(dimethylaminomethyl)phenols and the Mono(dimethylaminomethyl)methyl Ester of Gallic Acid.[3]—For the mono-Mannich bases of phenol, *p*-chlorophenol, *p*-methylphenol, *p*-methoxyphenol, *o*-methylphenol, *o*-ethylphenol, and methyl gallate, good yields were obtained by the following procedure[4].

To a cooled alcohol solution containing equimolar quantities of the appropriate phenol and dimethylamine was added an equimolar quantity of 40% formaldehyde slowly and with stirring. The solution was allowed to come to room temperature and then was refluxed for 3 hr. The solvent and unreacted volatile materials were then removed *in vacuo*, and the solution was acidified with 6 *N* HCl. After extraction of the acidic aqueous solution

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(1) J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Billington, Jr., and G. R. List, *J. Am. Chem. Soc.*, **86**, 3075 (1964).

(2) J. Epstein, D. H. Rosenblatt, and M. M. Demek, *ibid.*, **78**, 341 (1956).

(3) "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

(4) It is possible that this procedure would produce appreciable quantities of the *p*- as well as the *o*-substituted Mannich bases from the *o*-alkylphenols. Nuclear magnetic resonance and infrared studies on the final purified products revealed that these are *o*-substituted Mannich bases. For the n.m.r. studies, we are indebted to Mr. H. Klapper, Physico-Chemical Research Division, Chemical Research and Development Laboratories; for the infrared studies, to Mr. F. Block, Defensive Research Division, Chemical Research and Development Laboratories.

TABLE I

ANALYTICAL DATA FOR HYDROCHLORIC ACID SALTS^a OF MONO(DIMETHYLAMINOMETHYL)PHENOLS AND METHYL ESTER OF GALLIC ACID

	Calculated				Found			
	C,%	H,%	N,%	Neut. equiv.	C,%	H,%	N,%	Neut. equiv.
o-M^b-Phenol	57.8	7.5	7.5	187.7	56.9	7.6	7.6	186
o-M^b-*p*-Cl-Phenol	48.7	5.9	. . .	222.1	48.7	6.1	. . .	225
o-M^b-*p*-Methylphenol	59.5	7.9	. . .	201.7	59.6	8.0	. . .	196
o-M^b-*p*-Methoxyphenol	55.2	7.4	. . .	217.7	55.4	7.4	. . .	215
o-M^b-*p*-*t*-Butylphenol	61.0	8.3	6.5	215.7	60.1	8.6	6.2	214.5
o-M^b-*o*-Methylphenol	59.6	8.0	. . .	201.7	59.5	7.9	. . .	203
o-M^b-*o*-Ethylphenol	61.0	8.3	6.5	215.7	60.1	8.6	6.2	214.5
o-M^b-*o*-Methoxyphenol	55.2	7.5	. . .	217.7	55.4	7.6	. . .	215.5
M^b-Methyl gallate	47.4	5.8	. . .	277.7	47.4	5.8	. . .	281

^{a} One mole of HCl per mole of base. ^{b} M = $CH_2N(CH_3)_2$.

TABLE II

ANALYTICAL DATA FOR HYDROCHLORIC ACID SALTS^a OF BIS(DIMETHYLAMINOMETHYL)PHENOLS, CATECHOL, AND GALLIC ACID

	Calculated				Found			
Compound	C,%	H,%	N,%	Neut. equiv.	C,%	H,%	N,%	Neut. equiv.
2,6-Bis-M^b-4-methylphenol	52.8	8.2	. . .	295.3	52.4	8.2	. . .	318
2,6-Bis-M^b-4-fluorophenol	48.2	7.1	. . .	305.2	48.4	7.1	. . .	305
2,6-Bis-M^b-4-methoxyphenol	50.1	7.9	. . .	311.3	50.3	7.8	. . .	312
2,6-Bis-M^b-4-phenylphenol	60.5	7.3	7.8	353.7	60.7	7.4	7.7	370
2,6-Bis-M^b-4-*t*-butylphenol	56.9	9.0	8.3	337.3	54.0	9.5	7.9	340
2,6-Bis-M^b-4-chlorophenol	45.7	6.7	8.9	315.7	45.5	6.8	8.8	325
3,6-Bis-M^b-catechol	48.3	7.4	. . .	297.2	48.2	7.6	. . .	308
2,6-Bis-M^b-gallic acid	. .	. . .	. . .	357	. .	. . .	. . .	367

^{a} Two moles of HCl per mole of compound. ^{b} M = $CH_2N(CH_3)_2$.

with ether, the aqueous phase was concentrated; the solid was filtered off and recrystallized from alcohol or an alcohol–ether mixture. Analytical data for the mono-Mannich bases of different phenols and of methyl gallate are shown in Table I.

2,6-Bis(dimethylaminomethyl)phenols and 3,6-Bis(dimethylaminomethyl)catechol.—For the preparation of 2,6-bis(dimethylaminomethyl)phenols, 3,6-bis(dimethylaminomethyl)catechol, and 2,6-bis(dimethylaminomethyl)gallic acid, the same procedure was used as in the preparation of monosubstituted phenols except that the molar ratio of amine:formaldehyde:phenol (or catechol or pyrogallol) was 3:3:1. Analytical data for these compounds are given in Table II.

2,3-Dihydroxybenzylamine Hydrochloride.—2,3-Dimethoxybenzaldoxime, prepared from the commercially available corresponding aldehyde, was catalytically reduced (Pd–C catalyst) in a solution of hydrogen chloride in dry ethanol. The resulting product was heated with concentrated hydrochloric acid at 160° for several hours in a sealed tube to produce 2,3-dihydroxybenzylamine, m.p. 185°, lit.[5] 186°.

3,4-Dihydroxybenzylamine hydrochloride was prepared by the reduction of the corresponding oxime[6] over Pd–C catalyst in ethanolic dry HCl solution; m.p. 171° (lit.[5] 172°).

3-Dimethylaminomethylcatechol hydriodide was prepared by refluxing 0.1 mole of 6-dimethylaminomethylguaiacol (Table I) with constant boiling hydriodic acid. The product was recrystallized from acetone–ether solution; m.p. 143°.

Anal. Calcd. for $C_9H_{14}O_2NI$: C, 36.6; H, 4.74; N, 4.73. Found: C, 36.8; H, 4.80; N, 4.77.

3-Dimethylaminomethylcatechol Methiodide.—6-Dimethylaminomethylguaiacol (0.15 mole; Table I) was refluxed with 45 ml. of methyl iodide for 2 hr. After cooling, ether was added and the low-melting orange solid which precipitated was filtered off. After the solid was refluxed with constant boiling hydriodic acid for 20 hr., the volatiles were removed *in vacuo* and the remaining solid was recrystallized from acetone–ether solution; m.p. 182°.

Anal. Calcd. for $C_{10}H_{16}O_2NI$: C, 38.3; H, 5.17. Found: C, 38.9; H, 5.30.

2,3-Dihydroxyphenethylamine hydrochloride was prepared by the following sequence of reactions: 2,3-dimethoxybenzaldehyde (0.1 mole) in 250 ml. of ethanol containing 0.2 g. of ferric chloride was hydrogenated to the corresponding benzyl alcohol over PtO_2 catalyst according to standard procedures. The alcohol boiled at 119–120° (1 mm.). The alcohol was converted to the corresponding chloride (b.p. 87–89° (1.2 mm.)) by reaction with thionyl chloride at 50° for 2 hr. Conversion to the corresponding nitrile was achieved by stirring a solution of the chloride with an equimolar quantity of potassium cyanide in a small volume of water. The product boiled at 109–112° (45 mm.). The nitrile was reduced to 2,3-dimethoxyphenethylamine (m.p. of HCl salt 104–105°) with lithium aluminum hydride according to the procedure of Amundsen and Nelson.[7] Heating this phenethylamine in a sealed tube with concentrated hydrochloric acid for 2 hr. at 160°, concentration of the reaction mixture, precipitation, and recrystallization from alcohol–ether yielded a solid, m.p. 179°.

Anal. Calcd. for $C_8H_{12}O_2NCl$: C, 50.5; H, 6.31. Found: C, 49.8; H, 6.30.

3,5-Bis(dimethylaminomethyl)catechol dihydrochloride was prepared by permitting guaiacol to react with formaldehyde and dimethylamine (as described for the preparation of the bis(dimethylaminomethyl)phenols) and cleaving off the methyl group by heating with concentrated hydrochloric acid in a sealed tube at 160° for 2 hr.

Anal. Calcd. for $C_{12}H_{22}O_2N_2Cl_2$: C, 48.4; H, 7.4; N, 9.4. Found: C, 47.4; H, 7.6; N, 9.7.

4-Dimethylaminomethylpyrogallol Hydriodide.—2,6-Dimethoxy-4-(dimethylaminomethyl)phenol was prepared by treating 2,6-dimethoxyphenol with formaldehyde and dimethylamine in accordance with the preparation of mono(dimethylaminomethyl)phenols. The product was heated with constant boiling hydriodic acid in a sealed tube at 140° for 4 hr.; m.p. 177°.

Anal. Calcd. for $C_9H_{14}O_3NI$: C, 34.7; H, 4.5. Found: C, 34.4; H, 4.7.

Kinetic Measurements.—The techniques used to follow the rate of reaction of GB with the compounds shown herein has been described previously.[1,2] The colorimetric test for GB concentration[2] required the addition of 0.1 mmole of mercuric chloride when the anion associated with the Mannich bases was iodide. Bimolecular rate constants were calculated from the equation

$$k_2 = \frac{(k_{\text{obsd}} - k_{\text{hyd}})}{[\mathrm{C}_0]} \times \frac{[\mathrm{H}^+] + K_\mathrm{a}}{K_\mathrm{a}}$$

where k_{obsd} is the observed first-order rate constant, k_{hyd} is the spontaneous hydrolysis rate of GB at the pH of the test solution, K_a is the acid dissociation constant of the species whose anion is reactive (determined by potentiometric titration), and $[\mathrm{C}_0]$ is the initial total concentration of all species (of the phenol, catechol, or pyrogallol compound).

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(5) I. M. Heilbron, "Dictionary of Organic Compounds," Vol. I, Oxford University Press, New York, N. Y., 1943, p. 823.

(6) K. Hoesch and T. v. Zarzecki, *Ber.*, **50**, 462 (1917).

(7) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.*, **73**, 242 (1951).

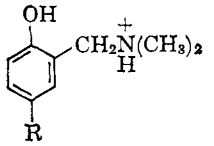
pK_a Determination.—pK_a values were determined in 0.1 N KNO_3 by potentiometric titration with 0.27 N $Ba(OH)_2$ under nitrogen.

Results

In Table III the pK_a and k_2 values for p- (to the phenolic hydroxyl group) substituted Mannich bases of phenol are given. The relationship of log k_2 to the pK_a of the phenol, excluding the p-methoxy compound, is linear,[8] conforming to the equation log $k_2 = 0.625\text{p}K_a - 3.538$. The abnormal behavior of the p-OCH_3 substituted Mannich base of phenol relative to the other Mannich phenols (the activity is 0.29 log unit greater than expected for its basicity) is similar to that found in studies with monosubstituted phenols. Thus, at least in respect to slope, the Mannich bases of phenol behave more like phenols (slope *ca.* 0.6) than catechols (slope 0.8).

TABLE III

pK_a AND k_2 VALUES FOR THE REACTION OF *para* SUBSTITUTED MANNICH BASES OF PHENOL WITH GB AT 25°, $\mu = 0.1$



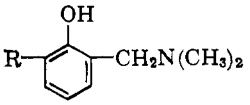
R	pK_1[a]	k_2,[b] l. mole^{-1} min.$^{-1}$
H	8.53	63.2 ± 1.2[c]
Cl	7.95	26.2 ± 2.0[d]
OCH_3	8.62	139.6 ± 2.0[c]
CH_3	8.70	79.0 ± 1.2[c]
$C(CH_3)_3$	8.59	70.9 ± 2.5[c]

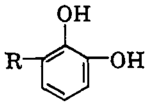
[a] Determined by potentiometric titration. [b] Calculated from equation: $k_2 = (K_{\text{obsd}} - K_{\text{hyd}})/[C_0] \times ([H^+] + K_a)/K_a$. [c] Average of 3 runs. [d] Average of 4 runs.

A comparison of the effects produced by substitution *ortho* to the hydroxyl groups in the Mannich bases of phenol and catechol is shown in Table IV. In contrast to the o-methoxyl group which appears to have little or no effect on the reactivity of a monocatecholate ion whose conjugate acid has a pK_a of 9.36, substitution in the position *ortho* to the phenolic hydroxyl by methyl, methoxyl, or ethyl in the Mannich base of phenol produces marked deactivation of the phenolate anion toward GB. In fact, the magnitude of the depression in rate, log (k found)/(k calcd.), is very similar to that found in the phenol series[1] for guaiacol, o-cresol, and o-ethylphenol.

TABLE IV

COMPARISON OF EFFECTS OF *ortho* SUBSTITUTION IN MANNICH BASES OF PHENOL AND CATECHOL ON THEIR RATES OF REACTION WITH GB AT 25°, $\mu = 0.1$





		k_2, l. mole^{-1} min.$^{-1}$			k_2, l. mole^{-1} min.$^{-1}$	
R	pK_a	Found	Predicted[a]	pK_a	Found	Predicted[b]
H	8.53	63.2 ± 1.2[c]	61.8	9.48	589[e]	582
CH_3	8.30	7.89 ± 0.01[d]	44.4			
OCH_3	8.42	5.78 ± .02[d]	52.7	9.36	473 ± 3[d]	463
C_2H_5	8.02	4.39 ± .24[c]	29.8			

[a] From the equation log $k_2 = 0.625\text{p}K_a - 3.538$. [b] From the equation log $k_2 = 0.806\text{p}K_a - 4.875$ (data in ref. 2). [c] Average of 3 runs. [d] Average of 2 runs. [e] From ref. 2.

Thus, again with respect to the steric effects produced by *ortho* substitution, the Mannich bases of phenol resemble the phenols rather than the catechols.

With the evidence mounting in favor of a similarity in behavior between the Mannich bases of phenols and ordinary phenols, there was reason to abandon hydrogen bonding as a reason for the abnormal reactivity of the phenolamines and to embrace the hypothesis[1] that the reactivity was a result of two opposing factors, *viz.*, a steric factor (decelerating) and an accelerating factor attributed to the presence of a cationic charge in the attacking nucleophile. The magnitude of the latter effect was shown to be inversely proportional to the square of the distance between the phenolate oxygen and the positive charge, and the explanation offered for the increased activity of the phenolamine anions relative to their basic strengths was that the dipolar anion exhibited a higher basicity to the neutral (as compared with the hydronium ion) substrate. With this in mind, we sought to increase the reactivity of the Mannich bases of phenols by adding a second dimethylaminomethyl group *ortho* to the phenolic hydroxyl. Implicit in our assumption was that *both the steric and the charge effects* would be additive in a simple arithmetic fashion and that the difference in reactivity between compounds containing one and two dimethylaminomethyl groups would be equal to the difference between phenol and the Mannich base of phenol (comparisons, of course, at similar basic strengths). Alternatively expressed, it had been shown[1] that the mathematical relationship for predicting the reactivity of an *ortho*-substituted cationic phenol with a phenol of the same pK_a was

$$\log \frac{k_2}{k_0} = \left[\log \frac{k_2}{k_0}\right]_s + \left[\log \frac{k_2}{k_0}\right]_e$$

where log k_2/k_0 is the difference in reactivity between an *ortho*-substituted cationic phenol and a phenol of the same pK_a; [log k_2/k_0]$_s$ is the difference in reactivity between an *ortho*-substituted phenol (the o-group being isosteric with the o-group in the cationic phenol, but possessing no charge) and a phenol of the same pK_a; and [log k_2/k_0]$_e$ is the difference in reactivity between a phenol containing a cationic group and a phenol of the same pK_a.

The last term will be related to the distance of charge separation as

$$\left[\log \frac{k_2}{k_0}\right]_e = \frac{c}{d^2}$$

where c is a constant, and d is the distance between the positively and negatively charged groups. On this basis log k_2/k_0 for the bis-Mannich compound should have been twice that of the mono-Mannich, since it was assumed that the value of each contributing factor (designated by [log k_2/k_0]$_s$ and [log k_2/k_0]$_e$) would be two times that of the monosubstituted compound. The data shown in Table V indicate that the enhancement given by a bissubstituted phenol falls short of

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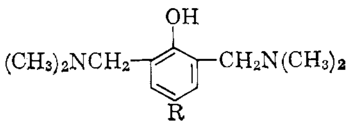
[8] In the equations given in the body of this report, the pK_a was determined potentiometrically. It is to be noted that the pK_a is *not* that of the active species, *viz.*, the dipolar ion, but rather the p($K_{11} + K_{12}$) as described in ref. 1. Although the absolute pK_1 and pK_2 values are different from those given in Table III, the relative positions of the compounds in a plot, and hence the slope of the equation, would not be significantly different from those given here.

TABLE V

REACTIVITY OF BIS-MANNICHS WITH GB AT 25°, $\mu = 0.1$



R	pK_1	k_2 (found), l. mole^{-1} min.$^{-1}$	$k_2{}^c$ (predicted for a mono-Mannich), l. mole^{-1} min.$^{-1}$
CH_3	6.45	2.94 ± 0.05^a	3.09
F	5.77	1.32 ± .08^a	1.20
OCH_3	6.33	4.31 ± .21^a	2.63
C_6H_5	5.65	1.13 ± .07^b	1.00
$C(CH_3)_3$	6.30	2.86 ± .11^a	2.51
Cl	5.20	0.62 ± .15^a	0.51

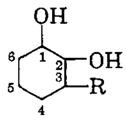
[a] Average of two runs. [b] Average of three runs. [c] Calculated from equation log $k_2 = 0.625\text{p}K_a - 3.538$ (see Fig. 1 and Table III).

expectations. The bimolecular rate constants[9] are of the same order as would be predicted for monosubstituted phenols (last column of Table V). Although the *p*-OCH_3 substituted bis(dimethylaminomethyl)-phenol shows a measurable degree of enhancement (log k_2 found/k_2 calcd. = 0.21), this may be attributed entirely to the methoxy rather than the dimethylaminomethyl group inasmuch it has been shown that a *p*-OCH_3 group, both in a series of phenols[1] and in the series of mono(dimethylaminomethyl)phenols (Table III), increases the reactivity by such a degree. In retrospect, however, it was thought possible that the steric effect of two bulky dimethylaminomethyl groups could be considerably larger than would be predicted by the arithmetic treatment shown above and that one could obtain results which showed no apparent increase in reactivity even though there was an additive accelerating effect attributed to the cationic substituents.

Because of this possibility, and since the results obtained with *o*-methoxycatechol (See Table IV) indicated that bulk steric effects might be absent in *ortho*-substituted catechols, a series of catecholamines was evaluated for reactivity with GB. These data are shown in Table VI.

TABLE VI

REACTIVITY OF CATECHOLAMINES



WITH GB AT 25°, $\mu = 0.1$

R	pK_1	k_2, l. mole^{-1} min.$^{-1}$ Found	Calcd.^{a}	log $\frac{k_2\text{found}}{k_2\text{calcd.}}$
3-$CH_2N^+H_3$	8.30	324^b ± 2	63.8	0.705
3-$CH_2N^+H(CH_3)_2$	8.01	244^b ± 2	38.1	.806
3-$NH_2N^+(CH_3)_3$	8.10	217^b ± 13	45.1	.682
3-$CH_2CH_2N^+H_3$	8.60	270	114	.374
4-$CH_2N^+H_3$	8.60	214 ± 17^d	114	.263
3,6-bis-$CH_2N^+H(CH_3)_2$	6.39	71.2 ± 5.2^d	1.88	1.578
3,5-bis-$CH_2N^+H(CH_3)_2$	7.22	63.4 ± 1.7^c	8.78	0.858
3,4,6-tris-$CH_2N^+H(CH_3)_2$	4.92	88.9 ± 3.3^c	0.123	1.865

[a] log $k_2 = 0.806\text{p}K_a - 4.875$ (data in ref. 2). [b] Two runs. [c] Three runs. [d] More than three runs.

From these data, the following conclusions and observations are cited: (a) Substitution in the 3-position by the group $-CH_2\overset{+}{N}R_3$ (R may be hydrogen or methyl) increases the reactivity of the aminomethylated catechol relative to a normal catechol of the same pK_a approximately 0.73 log unit (average of values 0.71, 0.81, and 0.68). (b) The increase in reactivity, as in the case of the phenols,[1] is related to the distance of separation of the cationic and anionic centers, the increase becoming larger as the distance is decreased. (c) The enhancement in reactivity given by the presence of a cationic site is additive, *i.e.*, the logarithmic difference in the rate between a catechol possessing several cationic sites and a catechol of the same pK_a having no cationic sites is equal to the sum of the logarithmic differences between the singly positively charged catechols and catechols of the same pK_a possessing no cationic charge. This may be seen more clearly from the following:

An increase in reactivity of *ca.* 0.73 log unit is found when there is a $-CH_2\overset{+}{N}R_3$ group in the 3-position of catechol, and an increase of 0.26 log unit is observed where there is a $-CH_2\overset{+}{N}H_3$ (and presumably a $-CH_2\overset{+}{N}R_3$) in the 4-position. The 3,6-bis-$CH_2\overset{+}{N}R_3$ catechol contains two groups in the 3-position and hence would be expected to increase the reactivity by approximately 1.46 log units; the increase found was 1.58 log units. Similarly, the 3,5-bis-$CH_2\overset{+}{N}R_3$ catechol contains one group in the 3-position (0.73 log unit increase) and a second in the 4-position (0.26 log unit increase). The expected increase is 0.99 log unit. An increase of 0.86 log unit was observed. Finally, the 3,4,6-tris-$CH_2\overset{+}{N}R_3$ catechol might be expected to show a 2(0.73) + (0.26) = 1.72 log units increase. The observed increase was 1.87 log units.

(d) There appears to be no bulk steric effect of the $-CH_2\overset{+}{N}R_3$ when *ortho* to the catechol hydroxyls. If there were, then one would expect a much lower reactivity for the 3-trimethylaminomethylcatechol than was observed[10] and a smaller increase in reactivity than was observed for the 3,6-bis-Mannich derivative of catechol.

Behavior similar to the catechols is shown by the pyrogallols (Table VII). The straight line, the equation of which was used to calculate the values shown in the fourth column, was constructed from the k_2 and pK_a data on only three compounds, pyrogallol, gallic acid, and methyl gallate. The accuracy of calculated rate constants of the others, therefore, is questionable (especially the k_2 values of log pK_a pyrogallols). Nevertheless, the pattern is clear and qualitatively quite similar to that observed for the catechols with respect to: (a) the effect of distance of separation of charges upon the increase in reactivity, (b) the additivity effect, and (c) the absence of bulk steric effect by *ortho*-substituted dimethylaminomethyl groups. The magnitude of the increase in reactivity is slightly less than that found in catechol series and may be related to the difference in the distance of separation of the cationic and anionic charges in the two compounds.

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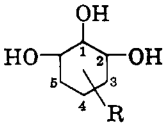
(9) At pH *ca.* 6, it was expected that the log $k_{2(\text{bis-Mannich})}/k_{2(\text{mono-Mannich})}$ would be between 0.7 and 1.0.

(10) *Cf.* phenol data, ref. 1; in the phenol series, the observed reactivity of *o*-trimethylammoniomethylphenol was only very slightly greater than a phenol of comparable pK_a, despite the presence of the rate accelerating cationic group close to the phenolate oxygen. The low reactivity has been ascribed to the bulk steric (decelerating) effect of the *o*-trimethylammoniomethyl group.

TABLE VII

REACTIVITY OF PYRAGALLOLS,  WITH GB,

$\mu = 0.1$

R	pK_a	k_2, l. mole^{-1} min.$^{-1}$ Found	k_2, l. mole^{-1} min.$^{-1}$ Calcd.[a]	log $\frac{k_2 \text{ found}}{k_2 \text{ calcd.}}$
H	9.12	1436 ± 30[b]	1415	..
4-CO-O$^-$	8.78[c]	817 ± 42[d]	792	..
4-CO-OCH$_3$	7.88	168.4 ± 2.0[d]	170	..
4-CH$_2$N$^+$H(CH$_3$)$_2$	8.26	724 ± 11[e]	324	0.35
3-CH$_2$N(CH$_3$)$_2$,4-COOCH$_3$	6.80	90.2 ± 2.8[f]	25.1	.56
3,5-bisCH$_2$N$^+$H(CH$_3$)$_2$,4-COO$^-$	6.95[c]	280.5	33.2	.93

[a] Calculated from equation log $k_2 = 0.758\text{p}K_a - 3.7$. [b] Average of three runs. [c] pK_a of the first hydroxyl group. [d] Average of 2 runs. [e] Average of 4 runs. [f] Average of 7 runs.

Discussion

The data presented herein on the reactivity of mono-Mannich phenols (slope in the Brønsted equation and effects on reactivity produced by substitution *ortho* to the phenolic hydroxyl) show that these compounds resemble phenols rather than catechols in their behavior toward GB. Although not conclusive, this would tend to strengthen the electrostatic–steric (in contrast to H-bonding) interpretation for anomalous reactivity of the *o*-phenolamines. The studies made with anions of catechols and pyrogallols possessing cationic groups show that their reactivities are much greater than would be predicted from their basicities and, as in the case of the phenols, that the increase in reactivity is related to distance of separation of the cationic and anionic charges. A very significant finding is that the increase in reactivity shown by a catechol or pyrogallol anion possessing multiple cationic sites is equal to the sum of the increases due to individual contributions of each cationic group. Finally, unlike the phenols, it appears that substitution in the position *ortho* to catechols and pyrogallols does not produce any bulk steric effects.

If one can assume that there are no steric effects in *ortho*-substituted catechols and pyrogallols (justifiable from the data in Tables VI and VII), then the increase in reactivity (log k_2/k_0) of catechols and pyrogallols containing the dimethylaminomethyl group in the 3- and 4-position over that expected from a catechol or pyrogallol of the same pK_a should be attributed solely to the "charge" effect. An estimation, then, of the distance of separation can be made from the magnitude of the increase, assuming, as in the phenols, that the increase is inversely related to the square of the distance of separation of the cationic and anionic groups. In this connection, it is of interest to compare the [log k_2/k_0]$_e$ values attributed to the presence of a cationic group in the phenols, catechols, and pyrogallols. These are shown in Table VIII.

TABLE VIII

[LOG k_2/k_0]$_e$ FOR PHENOLS, CATECHOLS, AND PYROGALLOLS

	Phenols[b]	Catechols	Pyrogallols
2-CH$_2$N$^+$H(CH$_3$)$_2$	1.85 (calcd.)	...	...
3-CH$_2$N$^+$H(CH$_3$)$_2$	0.315	0.806	0.555
4-CH$_2$N$^+$H(CH$_3$)$_2$	0.179	0.263[c]	0.35

[a] See Tables VI and VII system of numbering of groups. [b] Data from ref. 1. [c] Value for CH$_2$N$^+$H$_3$.

The distance (calculated from the data in Table VIII) between the opposite charges when the dialkylaminoalkyl group is in the 3-position is least in the catechol and greatest in the phenol. When the substituent is in the 4-position, the calculated distance is least in the pyrogallol and greatest in the phenol. In fact, the absolute values of the 4-substituted pyrogallol and the 3-substituted phenol are sufficiently close so as to suggest that, in the former compound, the center of high electron density is on either of the terminal oxygens of pyrogallol. It is of interest, in this connection, that phosphonylation of pyrogallol occurs on the terminal hydroxyl group.[11]

From the previously derived relationship [log k_2/k_0]$_e$ = c/d^2,[1] where c is a constant = 12.7 and d is the distance of separation of the cationic and anionic charges, the distances between the positive and negative groups in the anions of 3-substituted catechol, pyrogallol, and phenolamines shown in Table VIII are 4.0, 4.8, and 6.4 Å. If it is assumed that the spatial arrangement of the groups containing the positively charged substituent is similar among the compounds, and that the site of high electron density is localized on the phenolic oxygen in the phenolamine, then it must be concluded that the site of high electron density in the catechol (and also pyrogallol) resides *between* two oxygen atoms. The conclusions to be derived from the studies on the effect of substituents in the 4-position on the ionization constant of catechols by Corse and Ingraham,[12] whereby it was found necessary to assign values to the substituents which are an average of the accepted σ_m and σ_p values, is consistent with our postulation of the locus of high electron density in the catechols.

Also, a comparison of the k_2/k_0 values for the 4-substituted phenols and catechols indicates that the distance between cationic and anionic sites is closer in catechol than in the corresponding phenolic compound.

From the distances of separation between the cationic and anionic sites, one obtains a basis for explaining the presence or absence of steric (decelerating) effects. If the distance is approximately 4 Å. (as in the case of 3-di- or trimethylammoniomethylcatechol), no decelerating effect attributed to bulk is observed; if the distance is approximately 2.6 Å. (as in the case of trimethylammoniomethylphenol), then the effect is marked (see ref. 36 of ref. 1).

The effect of a cationic group on the reactivity of anions of the hydroxybenzenes in displacement reactions of the phosphonyl ester, GB, has now been established; we are now accumulating information on the "charge" effect on other displacement reactions and other classes of nucleophiles. In connection with the latter, we have found that the nucleophilicity of oximes to GB is increased by the incorporation of a cationic site.[13] The charge factor is another factor, previously unrecognized,[14] to be reckoned with in any discussion involving nucleophilic reactivity.

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[11] B. J. Jandorf, T. Wagner-Jauregg, J. J. O'Neill, and M. A. Stolberg, *J. Am. Chem. Soc.*, **74**, 1521 (1952). That the phosphonylation occurs on the terminal hydroxyl was confirmed by unpublished studies in our laboratory. The phosphonylated pyrogallol was separated by filter paper chromatography and identified.

[12] J. Corse and L. L. Ingraham, *J. Am. Chem. Soc.*, **73**, 5706 (1951).

[13] Unpublished data.

[14] See, *e.g.*, J. Bunnett, *Ann. Rev. Phys. Chem.*, **14**, 271 (1963).