

ORIGINAL ARTICLE

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Predicting the hydroxymethylation rate of phenols with formaldehyde by molecular orbital calculation

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Abstract The rates (k) of hydroxymethylation of phenol, resorcinol, phloroglucinol, and several methylphenols in diluted 10% dimethylformamide aqueous alkaline solution were calculated based on the consumption of phenols and formaldehyde. The k values of phloroglucinol and resorcinol relative to that of phenol were about 62000 and 1200 times, respectively. The phenols that have methyl or hydroxyl groups at the C-3 or C-5 position (or both) have larger rate constants than phenols with substituents at other positions. Several kinds of atomic charge of the carbons on the aromatic ring of phenols were calculated using the semiempirical or *ab initio* method. The correlations between the average k (Ave. k) and average electrostatic charges (Ave. q) at the carbons were fairly good. Highest occupied molecular orbitals (HOMO) were observed. The best correlation between Ave. k and Ave. q was obtained when diphenols and triphenols were assumed to exist in solution as their respective di-anion.

Key words Chemical computation · *Ab initio* · Semiempirical · Phenolic compounds · Formaldehyde

Introduction

To utilize phenolic adhesive systems more effectively and to develop new phenolic adhesives, it is important to understand the reaction of phenolic compounds with formaldehyde. To date, analytical studies on phenolic adhesives have

concentrated mainly on kinetics.¹⁻⁵ These studies have dealt not only with calculating reaction rates but also with complex processes for isolating and identifying intermediates and reaction products. Recently, computational chemistry methods have been introduced that allow analysis of reaction mechanisms and prediction of the reactivity in synthetic chemistry and protein technology. Therefore, using computational chemistry to predict the reactivities of a wide variety of phenolic compounds with formaldehyde would make it possible to obtain new insight into the reaction mechanisms for curing phenolic adhesives. The correlation between charges and rate constants are discussed in this report. The charges were calculated by semiempirical molecular orbital and *ab initio* methods on reactive sites of phenolics. The rate constants were determined from the consumption of phenolics and formaldehyde.

Experimental

Reaction of phenols with formaldehyde under basic conditions

Phenols used were phenol, resorcinol, phloroglucinol, 2-methylphenol (2MP), 3-methylphenol (3MP), 4-methylphenol (4MP), 2,4-dimethylphenol (24MP), 2,5-dimethylphenol (25MP), and 2,6-dimethylphenol (26MP), as shown in Fig. 1. Phenols, formaldehyde, and sodium hydroxide were commercial products used without further purification.

Reaction of phenols with formaldehyde was conducted in a three-necked flask fitted with a condenser and thermometer. The reaction was run at 30°C. A phenol (2 mmol) and formaldehyde (2 mmol) were dissolved in 10% aqueous dimethylformamide (DMF) solution with stirring. Sufficient 10% sodium hydroxide solution was added so that the pH equaled the pK_a of the phenols. The solvent volume was adjusted to give a solid concentration of 1%.

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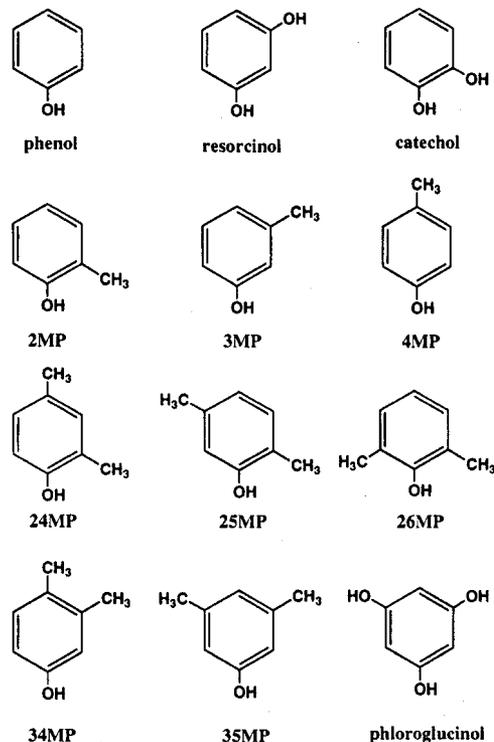


Fig. 1. Phenolic compounds used in this study

Determining phenol concentration by high performance liquid chromatography

Consumption of the phenols were analyzed by a Hewlett Packard 1050 series chromatograph with an inertsil ODS-3 column (25×0.46 cm). The mobile phase consisted of acetonitrile/0.01% trifluoroacetic acid (TFA)/water. An elution gradient of 5%–45% acetonitrile in 30 min was used for phloroglucinol and resorcinol analyses, of 10%–45% acetonitrile in 25 min for phenol, and of 30%–60% acetonitrile in 30 min for the methylphenols. The eluants were detected in the ultraviolet (UV) range at 273 nm.

Determining formaldehyde concentration using the hydroxylamine hydrochloride method

The concentration of formaldehyde remaining in the reaction mixture was determined by the hydroxylamine hydrochloride method.⁶ A 1-ml aliquot of the sample was taken from the reaction mixture and poured into a weighing jar containing 3 ml of 0.5N hydroxylamine hydrochloride solution adjusted to pH 4. The sample was then titrated to pH 4 with 0.02N sodium hydroxide solution using an autotitrator FMS-201 (Fluid Management Systems).

Isolation of reaction products from the reaction of 24MP or 26MP with formaldehyde

A precipitate appeared in the reaction mixture of 26MP with formaldehyde after 5 h of reaction. The filtrate was

collected on a glass filter. After drying *in vacuo*, the cream-colored powder product (26MP-1) was obtained.

The reaction of 24MP with formaldehyde was performed on a large scale to obtain the reaction products. Aliquots of 20 mmol of 24MP and 20 mmol of formaldehyde were dissolved in 20 ml of 50% aqueous methanol solution with stirring in a three-necked flask. Then 3.6 ml of 10% aqueous sodium hydroxide was added to the solution. The reaction was continued for 5 h at 50°C. The reaction mixture was separated by column chromatography over LH-20 gel with water as the solvent. Four fractions (Fr1–Fr4) were obtained. Fr3 was chromatographed over silica gel with toluene/ethylformate [1/1 (v/v)]. Fractions (1 ml) were collected with a fraction collector. Thin-layer chromatography (TLC) was used to monitor the fractionation. The major product (Fr3-a) was isolated from tubes 12–21. The addition of acetone to Fr1 resulted in a precipitate. The filtrate was chromatographed over silica gel with toluene/acetone [3/1 (v/v)]. Fractions (0.5 ml) were collected with a fraction collector. A minor product (Fr1-a) was isolated from tubes 25–31.

Identification of reaction products by ^{13}C - ^1H -NMR and GC-MS

High-resolution ^1H -nuclear magnetic resonance (NMR) and ^{13}C -NMR spectra in acetone- d_6 were recorded with a Bruker AVANCE DPX 250 spectrometer. The following conditions were used to record spectra: pulse angle 30° ($4\mu\text{s}$ ^1H , $2.2\mu\text{s}$ ^{13}C); digital resolution 0.244 Hz/pt (^1H) and 0.960 Hz/pt (^{13}C) corresponding to a spectral length of 4006 Hz (^1H) and 15723 Hz/pt (^{13}C) for a memory space of 16K (^1H , ^{13}C).

Bis(4-hydroxy-3,5-dimethylphenyl)methane (26MP-1)

^1H -NMR (250 MHz, acetone- d_6): **d**2.15 (12H, s, $4 \times \text{CH}_3$), 3.63 (2H, s, CH_2), 6.75 (4H, s, C-2, 6, 2', 6'). ^{13}C -NMR (62.9 MHz, acetone- d_6): 616.6 ($4 \times \text{CH}_3$), 41.0 (CH_2), 124.5 (C-3, 5, 3', 5'), 129.5 (C-2, 6, 2', 6'), 133.9 (C-1, 1'), 156.2 (C-4, 4'). Gas chromatography-mass spectrometry (GC-MS): m/z 256 (M^+ , 55), 241 ($\text{M}^+ - \text{CH}_3$, 100), 226 ($\text{M}^+ - 2\text{CH}_3$, 9), 211 ($\text{M}^+ - 3\text{CH}_3$, 11), 196 ($\text{M}^+ - 4\text{CH}_3$, 9), 135 [$\text{C}_6\text{H}_2\text{CH}_2(\text{CH}_3)_2\text{OH}$, 33], 91 ($\text{C}_6\text{H}_5\text{CH}_2$, 41), 77 (C_6H_5 , 17).

2-Hydroxymethyl-4,6-dimethylphenol (Fr3-a)

^1H -NMR (250 MHz, acetone- d_6): **d**2.13 (6H, s, $2 \times \text{CH}_3$), 4.75 (2H, s, CH_2), 6.70 (1H, d, $J = 2.2$ Hz, H-5), 6.80 (1H, d, $J = 2.2$ Hz, H-3). ^{13}C -NMR (62.9 MHz, acetone- d_6): 615.8 (CH_3 , C-2), 20.4 (CH_3 , C-4), 63.9 (CH_2), 125.1 (C-2), 126.0 (C-6), 126.3 (C-5), 128.5 (C-4), 131.1 (C-3), 152.9 (C-1). GC-MS: m/z 152 (M^+ , 19), 135 ($\text{M}^+ - \text{OH}$, 19), 121 [$\text{C}_6\text{H}_5\text{CH}_2(\text{CH}_3)_2$, 0.3], 106 (121- CH_3 , 41), 91 (121- 2CH_3 , 100), 77 (C_6H_5 , 16).

Computational methods

Semiempirical calculations were conducted on a Gateway 2000 PC at the RHF/PM3//RHF/PM3 level of theory using HyperChem and on a Macintosh Powerbook G3 at the RHF/PM3 level of theory using SPARTAN Plus. All *ab initio* calculations, except 3-21G, were performed on an IBM model 720 RISC/6000 Workstation using either GAMESS or Gaussian 98. The optimized structures obtained from HyperChem were used as the starting structures for calculations at the RHF/6-31g//RHF/6-31g level of theory using GAMESS. The GAMESS optimized structures were then used as the starting structures for calculating Mulliken, NBO, CHelp, CHelpG, and Merz-Kollman/Singh (MK) based charges at the RHF/6-31g//RHF/6-31g, RHF/6-31+g//RHF/6-31+g, and B3LYP/6-311+g(2d,p)//B3LYP/6-311+g(2d,p) level of theory using Gaussian 98. The electrostatic charges (ES) were calculated on a Macintosh Powerbook G3 at the RHF/3-21G level of theory using SPARTAN Plus.

Results and discussion

Hydroxymethylation of phenolics and formaldehyde and reaction products

The well-known reaction between a phenol and formaldehyde in alkaline solution leads to introduction of a hydroxymethyl group in the aromatic nucleus at positions *ortho* or *para* (or both) to the hydroxyl group. The hydroxymethylation rate is proportional to the anion concentration of the phenol.⁷ Therefore, for comparing the reactivity of phenols in alkaline media, the reactions were conducted at conditions where all the phenols had the same anion concentration (i.e., at a pH equivalent to the pKa of the individual phenol). The pKa was determined from the usual relation as follows: $\text{pKa} = \text{pH} - \log\{[A^-]/[AH]\}$, where $[A^-]$ is the concentration of the completely ionized salt, and $[AH]$ is the concentration of the acid. In this study, the reactions of the phenols with formaldehyde to form the hydroxymethylated derivatives were carried out at a pH such that $[A^-] = [AH]$.

For completely dissolving the methylphenols and phloroglucinol, a 10% aqueous DMF solution was needed. The pKa of phenolics determined in 10% aqueous DMF are shown in Table 1. The pKa determined in a solution containing organic solvent is generally higher than the pKa determined in water. The pKa values for phenol measured in water versus 10% DMF solution were 9.98 and 9.96, respectively. This indicates that DMF does not affect the ionization of phenol and therefore presumably does not affect ionization of the other phenols.

The high-performance liquid chromatography (HPLC) of phenol after 23h and of 26MP after 5h of reaction with formaldehyde are shown in Fig. 2. Two products and residual initial phenols are present in both reaction mixtures. The two products in the phenol reaction were identified as

Table 1. pKa value of phenolic compounds used in this study

Phenolic	pKa	
	This study ^a	Literature ^b
2MP	10.35	10.20
3MP	10.14	—
4MP	10.27	10.17
24MP	10.50	—
25MP	10.51	—
26MP	10.65	10.22
34MP	10.25	—
35MP	10.08	—
Phenol	9.96	9.98
Resorcinol	9.45	9.40
Catechol	9.49	9.40
Phloroglucinol	8.99	—

^aThe measurement was done in aqueous solution containing 10% dimethylformamide (DMF) by weight

^bThe phenol data were measured in water and the others in pyridine according to Abe and Ono⁸

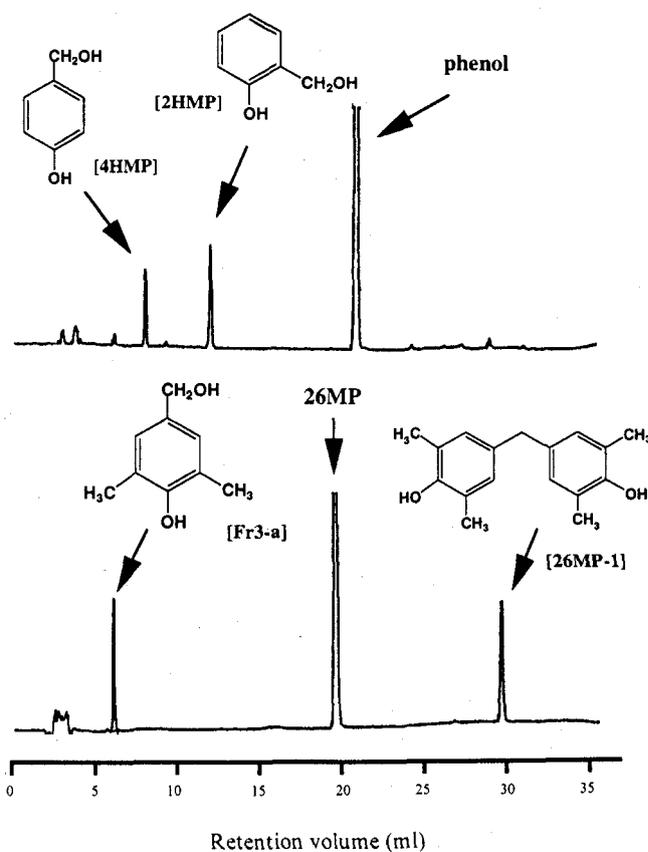


Fig. 2. High-performance liquid chromatography (HPLC) of reaction products of phenol or 26MP with formaldehyde. 4HMP, 4-hydroxymethylphenol; 2HMP, 2-hydroxymethylphenol; Fr3-a, 4-hydroxymethyl-2,6-dimethylphenol; 26MP, 2,6-dimethylphenol; 26MP-1, bis(4-hydroxy-3,5-dimethylphenyl)methane

2HMP and 4HMP by co-HPLC of authentic samples. In the case of the 26MP reaction, the two products appear in different regions of the chromatogram. Component 26MP-1, which was isolated as a powder after filtration and drying *in vacuo*, eluted later than 26MP. The GC-MS of 26MP-1 contained a molecular ion peak at 256 m/z. The existence of

four methyl groups was supported by peaks at 241, 226, 211, and 196 m/z, respectively. Furthermore, its ¹H-NMR showed one methylene group at 3.63 ppm and four equivalent aromatic protons at 6.75 ppm, indicating a symmetrical compound. Therefore, this compound was identified as bis(4-hydroxy-3,5-dimethylphenyl)methane. Component 26MP-2 eluted earlier than 26MP. Its GC-MS contained a molecular ion peak at 152 m/z. The 26MP-2 was presumed to be 4-hydroxymethyl-2,6-dimethylphenol because it should form with ease owing to the strong nucleophilicity of the *para* position of 26MP.

Rate of hydroxymethylation of phenolics with formaldehyde

According to the kinetic study by Zavitsas *et al.*,⁹ the effects of formaldehyde polymer equilibria and the dielectric constant can be ignored in solutions containing more than 95 mol% water. Thus, the base-catalyzed hydroxymethylation of phenol by formaldehyde in a diluted aqueous system is generally accepted to be a second-order ion molecular reaction of which the kinetics follow the general rate expression given by Eq. (1)

$$\text{Rate} = k[\text{P}^-][\text{F}] \quad (1)$$

where P⁻ is the phenoxy anion, and F is unreacted formaldehyde. Judging from the reaction products of phenol, it reacts with formaldehyde *via* simultaneous reactions. On the other hand, 26MP reacts *via* simultaneous-competitive reactions, as shown in Fig. 3. The rate for phenol can be expressed as follows:

$$-d[\text{P}^-]/dt = k_1[\text{P}^-][\text{F}] + k_2[\text{P}^-][\text{F}] = (k_1 + k_2)[\text{P}^-][\text{F}] \quad (2)$$

where $d[\text{P}^-]$ is the consumption of phenol anion; $[\text{P}^-]$ is the concentration of remaining phenol anion; $[\text{F}]$ is the concentration of unreacted formaldehyde; and k_1 and k_2 are rate constants. From Eq. (2), the rate constant for hydroxymethylation (k_{HM}) of phenol is given as

$$k_{\text{HM}} = k_1 + k_2 = -d[\text{P}^-]/dt * [\text{P}^-] * [\text{F}] \quad (3)$$

The rate of reaction of 26MP can be expressed as follows:

$$-d[26\text{MP}^-]/dt = k_3[26\text{MP}^-][\text{F}] + k_4[26\text{MP}^-][4\text{HM}26\text{MP}^-] \quad (4)$$

$$d[4\text{HM}26\text{MP}^-]/dt = k_3[26\text{MP}^-][\text{F}] - k_4[26\text{MP}^-][4\text{HM}26\text{MP}^-] \quad (5)$$

where $d[26\text{MP}^-]$ is consumption of 2,6-dimethylphenol anion; $[26\text{MP}^-]$ is the concentration of remaining 2,6-dimethylphenol anion; $[4\text{HM}26\text{MP}^-]$ is the concentration of 4-hydroxy-2,6-dimethylphenol anion; $d[4\text{HM}26\text{MP}^-]$ is consumption of 4-hydroxy-2,6-dimethylphenol; and k_3 and k_4 are rate constants. From Eqs. (4) and (5), the rate constant of hydroxymethylation in 26MP is given by Eq. (6)

$$k_{\text{HM}} = k_3 = \{d[4\text{HM}26\text{MP}^-] - d[26\text{MP}^-]\} / 2dt * [26\text{MP}^-] * [\text{F}] \quad (6)$$

Judging from the HPLC and GC-MS data of the products formed by the reactions of formaldehyde with the phenolic

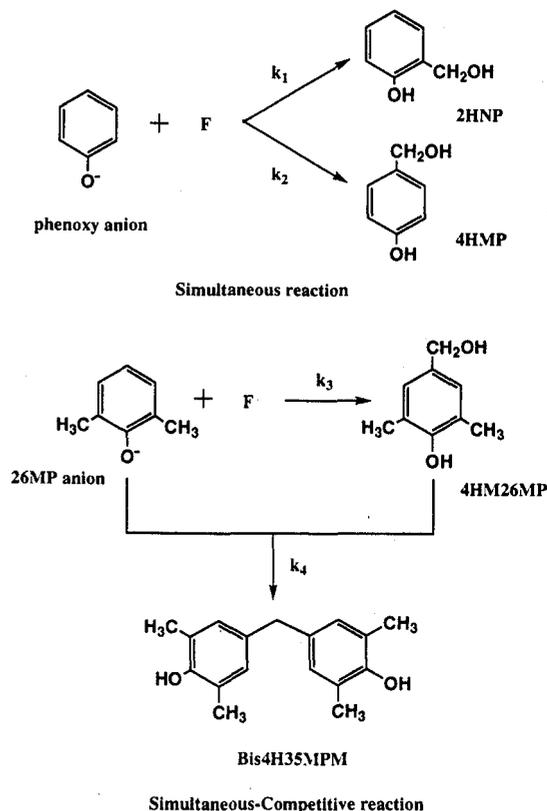


Fig. 3. Classification of composite reaction of the hydroxymethylation of phenol with formaldehyde. F, formaldehyde; 4HM26MP, 4-hydroxymethyl-2,6-dimethylphenol; Bis4H35MPM, bis(4-hydroxy-3,5-dimethylphenyl)methane

Table 2. Rate constant for hydroxymethylation of phenolics with formaldehyde

Phenolic	Class of reaction ^a	Relative k^b	Ave. k^c
2MP	S-C	0.52	0.26
3MP	S	10.29	3.43
4MP	S	0.62	0.31
24MP	S	2.46	2.46
25MP	S-C	14.20	7.10
26MP	S-C	0.85	0.85
34MP	S	4.23	2.12
35MP	S	50.10	16.70
Phenol	S	1.00	0.33
Resorcinol	S	1232.00	410.73
Phloroglucinol	S-C	62 118.00	20 706.04

^aS, simultaneous reaction; S-C, simultaneous-competitive reaction

^bRelative rate constant based on the rate constant of phenol

^cAverage (Ave.) constant is the relative rate constant divided by the number of reactive sites of phenolics with formaldehyde

compounds used in this study, all reactions are apparently grouped into simultaneous or simultaneous-competitive reactions. The relative rate constants for hydroxymethylation of the phenolics calculated with equations similar to Eq. (5) or (6) are shown in Table 2. The phenolics with methyl or hydroxyl groups at the C-3 or C-5 position (or both) show comparatively larger rate constants than phenolics with substituents at other positions. This is probably due to the

Table 3. Correlation coefficient (2) of the average rate constant on hydroxymethylation and average charge (Ave. S_q)

Atomic charge	Semiempirical: RHF/PM3	<i>Ab initio</i>			
		RHF/3-21G	RHF/6-31G	RHF/6-31+G	B3LYP/6-311+G(2d,p)
Mulliken	0.5099		0.6545	0.0030	0.0394
HOMO Pz	0.0641				
ES	0.8565	0.8833			
NBO			0.8776	0.8751	0.8531
Chelp			0.7964	0.8201	0.7752
CHelpG			0.8368	0.8414	0.7251
MK			0.8392	0.8385	0.6249

S_q was determined at various levels of computational theory using the indicated methods for calculating atomic charges. Correlation coefficients were determined from first-order regression of the log of the relative average rate constants for hydroxymethylation of phenolic compounds with formaldehyde

inductive effect of an electron-donating group (e.g., methyl or hydroxyl group) and by resonance delocalization with the *ortho* and *para* positions on the phenol ring. Thus, hydroxymethylation can occur at three possible positions on the phenol ring. The average rate constant (Ave. k) represents the relative k divided by the number(s) of unsubstituted *ortho* and *para* positions.

The reaction rates for resorcinol and phloroglucinol are much larger than that of phenol under the same conditions. This explains the difficulty controlling the reaction of condensed tannins having resorcinolic or phloroglucinolic substructures when they are used for the formulation of wood adhesives.

Correlations of the rate of hydroxymethylation and the charges on phenolic carbons in HOMO

The reaction of phenolics with formaldehyde corresponds to an electrophilic aromatic substitution. In basic media, it is known that the phenolics are present as phenolate anions in which the negative charge is stabilized by resonance delocalization at the *ortho* and *para* positions. Reaction with the partial positive charge on the carbon of formaldehyde can then occur at the *ortho* and *para* positions. According to the frontier molecular orbital theory, "only the highest occupied (HOMO) and lowest unoccupied (LUMO) molecular orbitals should be taken into account to explain the mechanism of reactions such as substitution reactions. The frontier orbitals have the strongest two-electron interactions because the HOMO is the occupied orbital usually closest in energy to the unoccupied LUMO. The more overlap between the HOMO of a phenoxy anion and the LUMO of formaldehyde, the greater its reactivity with formaldehyde. In addition, the larger the charges on the *ortho* and *para* positions of phenolics, the larger their reactivity.

Table 3 shows the correlation between average atomic charges calculated at semiempirical and *ab initio* levels of theory and the experimental average rate constant for hydroxymethylation. The ES values calculated by Mac SPARTAN at the RHF/3-21G level show a good correlation ($r^2 \sim 0.9$) with the reaction rate. In calculations at higher levels of theory, NBO, CHelpG, and MK charges also show excellent correlations, $r^2 = 0.80-0.85$.

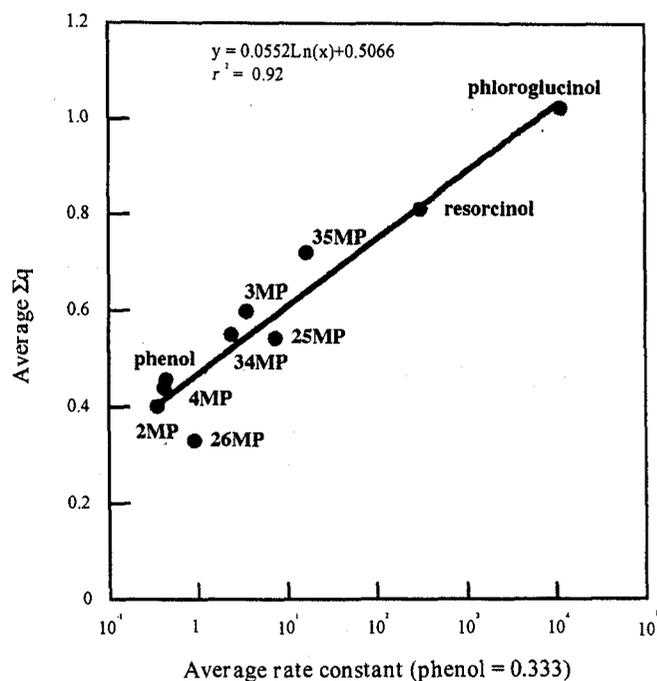


Fig. 4. Semilog plot of the relative average rate constant for hydroxymethylation of phenol with formaldehyde versus the absolute value for average S_q . S_q (ChelpG) was calculated at the RHF/6-31+G/RHF/6-31+G level of theory using Gaussian 98

Figure 4 shows the correlation of the average reaction constant (Ave. k) and CHelpG charges calculated at the RHF/6-31+G level, considering resorcinol and phloroglucinol to occur as di-anions. The correlation coefficients indicate excellent correlation compared to that obtained with mono-anions ($r^2 = 0.92$). The HOMO is distributed on carbons 2, 4, 6 of the mono-anion of resorcinol at the 3-21G level as determined by SPARTAN; on the other hand, that orbital scarcely exists at C-2 of the resorcinol di-anion despite a large negative charge at C-2. This explains why substitution to form hydroxymethyl groups in the reaction of resorcinol with formaldehyde under basic conditions does not take place at the C-2 position, only at the C-4 and C-6 positions.

The theory of superdelocalizability by Fukui¹¹ indicates that HOMO-1 and HOMO-2 as well as HOMO must be taken into consideration. Therefore, the charges and distribution of HOMO, HOMO-1, and HOMO-2 must also be taken into consideration to obtain a better understanding of the reactivities of phenolics.

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