

Short Communications

Thermodynamic Ionization Constants of Some *Ortho*-Substituted Guaiacol Derivatives

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Ortho-substituted methoxyl groups exert a definite influence on hydrogen bond formation by phenols;¹ whereas their influence on the acidity is not usually very pronounced.² In order to elucidate these findings further, we have determined the thermodynamic ionization constants of the four *ortho*-substituted guaiacols given in Table 1.

Experimental. The ionization constants were determined by potentiometric titration employing a glass electrode of the free acid with 0.1 N sodium hydroxide, or the sodium salt with 0.1 N hydrochloric acid at 25°C in water in the usual manner.³ The Radiometer PHM 4 pH-meter used was calibrated with standard buffers.⁴ The thermodynamic ionization constant was obtained after applying the usual Debye-Hückel correction for the ionic strength of the solution.

Results. The results and the melting points of the pure substances and the ionic strengths of the solutions are collected in Table 1. For reference and comparison, the value of p*K* of *o*-acetoguaiacone was also determined spectrophotometrically at 372 mμ, *i.e.* where the absorption by the phenolate ion is a maximum, using the

methods described earlier in Ref.⁵ and was found to agree with the potentiometric value within the limits of experimental error.

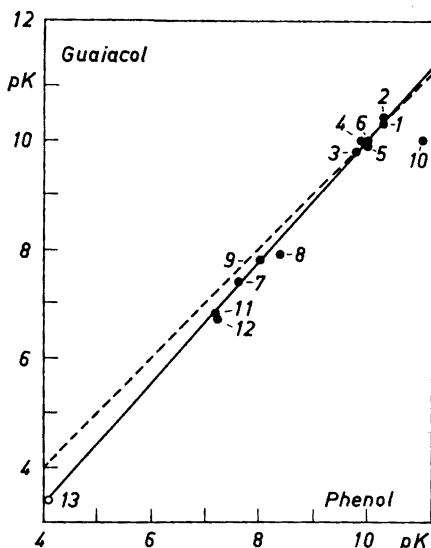


Fig. 1. Relationship between p*K*-values of *o*- and *p*-substituted guaiacols and corresponding phenols. 1. *p*-CH₃, 2. *o*-CH₃, 3. *p*-CH₂OH, 4. *o*-CH₂OH, 5. *o*-OCH₃, 6. *o*-H, 7. *p*-CHO, 8. *o*-CHO, 9. *p*-COCH₃, 10. *o*-COCH₃, 11. *p*-NO₂, 12. *o*-NO₂, 13. 4,6-dinitro, substituted guaiacol and phenol. The data not given in the present paper are taken from compilations and results in Refs.² and⁶.

Table 1. Melting points and thermodynamic ionization constants of *ortho*-substituted guaiacols in water at 25°C. *I* = ionic strength.

	m.p.	<i>I</i>	p <i>K</i>
2-Methoxy-6-methylphenol	41 - 42°	0.015	10.36 ± 0.02
2-Methoxy-6-methylolphenol	61.5 - 62°	0.01	9.97
2-Methoxy-6-acetylphenol (<i>o</i> -acetoguaiacone)	52 - 53°	0.01	10.00
2-Methoxy-4-methyl-6-formylphenol	73 - 75°	0.01	8.04

The influence of the methoxyl group on the acidity and charge distribution in phenols is illustrated by a plot of the pK 's of the substituted guaiacols against the pK 's of the corresponding phenols without the methoxyl group (cf. Fig. 1). It is of interest to note that the correlation for p -substituted guaiacols and phenols is almost linear (cf. also the correlation between the values of the Hammett function σ and the infra-red hydroxyl spectra in Ref.⁹); only a slight increase in acidity (difference between dotted and full line in Fig. 1) with increasing electronegativity of the substituent is evident.

However, the relationships are much more complex with the o -substituted compounds. When strong intra-molecular hydrogen bonds are formed, *i.e.* when a $-\text{NO}_2$, $-\text{CHO}$ or $-\text{COCH}_3$ group is in o -position relative to the phenolic hydroxyl, the methoxyl group, through charge displacement in the unionized guaiacol molecule, decreases the ionization tendency and consequently the acidity. This effect increases rapidly with decreasing electronegativity of the chelating group, *i.e.* in the order 4,6-dinitro $< o$ - $\text{NO}_2 < o$ -CHO $< o$ - COCH_3 .

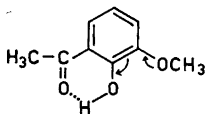


Fig. 2. Charge displacement in 2-methoxy-6-acetylphenol.

The strong effect of the o -acetyl group as compared with the formyl and nitro groups is especially noteworthy. In o -hydroxynaphthones the corresponding effect is markedly weaker⁷, which, however, is attributed to the deviation of the acetyl groups from the plane of the ring, resulting in the weakening of conjugation and hydrogen bonding simultaneously. It is evident that the large decrease in acidity in o -hydroxyacetophenones is in some way caused by the electron-donating methyl group, but a valid explanation can be obtained only by quantum mechanical calculation of the electron distribution, *cf.* Ref.⁸ In a later report these and related effects in phenolic compounds of the guaiacol type will be discussed with the aid of such calculations.

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Preparation of Pure Thyroglobulin

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For the study of thyroid proteins a new method for the purification of thyroglobulin was developed. Both hog and human thyroid tissue was used. The hog thyroid was obtained from the local abattoir and the human thyroid tissue from non toxic goitre patients by thyroidectomy. In one case radioactive iodine was administered 72 h before the operation.

The thyroid tissue was frozen at -20° and cut into slices about 1 mm thick. The slices were suspended in cold saline solution and left overnight at -4° . After shaking the solution was centrifuged and the supernatant brought to a volume of 15 ml