1969

The thermodynamic functions of ionisation of 4-substituted 2,6-dimethylphenols

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THE THERMODYNAMIC FUNCTIONS OF
IONISATION OF 4-SUBSTITUTED
2,6-DIMETHYLPHENOLS

A Thesis submitted for the partial fulfilment
of the requirements for the degree of
BACHELOR OF SCIENCE (HONOURS)

by

COLIN RICHARD PIDGEON

Supervisor: Dr. J. Ellis

Wollongong University College,
The University of New South Wales.
November, 1969.
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**Chapter**

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SUMMARY

Thermodynamic acidity constants of the ionisation of 4-methyl, 4-t-butyl, 4-bromo, 4-acetyl, 4-cyano, 4-formyl, 4-nitroso, 4-nitro 2,6-dimethylphenol, 2,6-dimethylphenol and p-hydroxyacetophenone have been measured by a combined e.m.f. - spectrophomometric technique within the temperature range 5 - 60°C. The standard thermodynamic functions: free energy, enthalpy, entropy and heat capacity have been calculated at 25°C.

The influence of substituents on the acidity of the phenols was found to be governed by two factors, neither of which predominates throughout the series. These factors are the ability of the substituent to delocalise the negative charge on the phenolate anion and the solute-solvent interaction hindered by the two ortho-methyl substituents. The enthalpy and entropy changes do not show linear correlations with substituent and there appears to be no relation between the variation of enthalpy with entropy.
CHAPTER 1.

INTRODUCTION AND DEFINITION OF THERMODYNAMIC FUNCTIONS.
INTRODUCTION

Thermodynamic data for the ionisation of weak acids and bases has been determined in the majority of cases using two techniques: (i) the direct calorimetric measurement of the heat of ionisation of the acid at some appropriate temperature (usually 25°C) and (ii) the measurement of thermodynamic ionisation constants over a range of temperature by spectrophotometric methods. Calorimetric methods directly determine the enthalpy, but for calculation of the other functions the pK_a of the acid must be known at the chosen temperature. For this reason almost all calorimetric measurements of thermodynamic data have been made at the one temperature 25°C.

The thermodynamic functions of ionisation of weak acids and bases can be accurately found spectrophotometrically by measuring the variation of pK_a with temperature. This has been made possible by the publication of acidity functions found with high precision for a range of buffer solutions. This project has yielded the thermodynamic functions for 4-substituted-2, 6-dimethylphenols. These results are discussed in terms of the influence of the electronic effects of the 4-substituents and the ortho-dimethyl groups on the thermodynamic properties of ionisation of the -OH group.

The principal aim of the research has been to obtain experimental data which will be useful for later deductions of relationships between acid strength and structure. The project was
undertaken as a continuation of studies to further knowledge of the heats and entropies of ionisation of phenols in aqueous solution. The data gained from this series of phenols will supplement that which has been accumulated by previous workers and it is hoped that it may assist later workers who will possibly attempt a detailed interpretation of the thermodynamics of the ionisation process of weak organic acids in terms of their structure, their anions and solute-solvent interactions.

The phenols used were 2, 6 - dimethylphenols substituted in the 4-position. There were nine substituted phenols available; the substituents being:

(i) methyl
(ii) t-butyl
(iii) hydrogen (i.e. 2, 6 - dimethylphenol itself)
(iv) bromo
(v) acetyl
(vi) cyano
(vii) formyl
(viii) nitroso
(ix) nitro

All compounds were made available by A. Fischer, G.J. Leary, R.D. Topsom and J. Vaughan of the University of Canterbury, Christchurch, New Zealand. These substituents show a wide range of possible inductive and conjugative effects which is most necessary for an evaluation of the effect of substituents on the ionisation process.

**THERMODYNAMIC FUNCTIONS**

There are four thermodynamic functions which can be calculated from the relationship between the acidity constant and the temperature.
They are free energy, enthalpy, entropy and heat capacity.

1. **Free Energy, G:**

   In most chemical processes neither the energy nor the entropy of the system remains constant throughout the reaction. The Gibbs free energy function $G$ describes how the enthalpy and entropy factors act together to drive a system to equilibrium.

   $$ G = H - T S $$

   for a free energy change

   $$ \Delta G = \Delta H - T \Delta S. $$

   A measure of the tendency of the process to proceed spontaneously at constant temperature is the decrease in the free energy.

   The thermodynamic standard free energy change, $\Delta G^\circ$, is given by

   $$ \Delta G^\circ = -RT \ln K_a $$

   where $K_a$ is the equilibrium acidity constant for the ionisation reaction. The unit of free energy is the calorie.

2. **Enthalpy, H:**

   The molar enthalpy or heat content ($H$) of a system is related to the molar energy ($E$), the pressure ($P$) and volume ($V$) by

   $$ H = E + P V. $$
The increase in enthalpy ($\Delta H$) of a system at constant pressure is equal to the heat absorbed. This extensive property of the system depends only on the initial and final states. It is a measure of the change in the energy content, dependent on an increase in the translational, rotational and vibrational energies as well as an expansion of the volume of the system. Enthalpy is measured in calories.

3. **Entropy, $S$:**

A structural or environmental change which affects the motion or vibration of a molecule, increasing its kinetic energy, will also increase the entropy (10b,11) of that molecule. Constraints on translational, rotational or internal molecular motions decrease entropy. If a molecule is confined into a smaller volume by solvation it will have a lower entropy. Molecules which become hindered in their movement, internal and overall rotation will also have lower entropies. The change of entropy depends upon the change of randomness or disorder of the system.

Actual entropy is not easily defined, but the change in entropy $dS$ is equal to the change in energy (or heat absorbed) $dq$ divided by the absolute temperature.

$$dS = \frac{dq}{T}$$

$$\Delta S = \int_{T_1}^{T_2} \frac{dq}{T}$$
The units of entropy are calories degree \(^{-1}\); sometimes the entropy unit (e.u.) is used.

Entropy is an extensive property, its value depends upon the amount of substance involved and upon the initial and final states. An increase in disorder (randomness) of a system leads to an increase in entropy. If \(\Delta S\) is positive, then the reaction will tend to proceed spontaneously. If \(\Delta S\) is negative, the reaction tends to proceed spontaneously in the opposite direction as indicated by the reaction.

4. Heat Capacity, \(C_p\):

The heat capacity \(^{(11)}\) represents the quantity of heat required to raise the temperature of the system by one degree, pressure remaining constant. The thermodynamic expression is

\[
C_p = \left( \frac{dH}{dT} \right)_p ; \quad \frac{C_p}{T} = \left( \frac{dS}{dT} \right)_p
\]

OR

\[
\Delta C_p = \left( \frac{d\Delta H}{dT} \right)_p
\]

That is, the heat capacity \((\Delta C_p)\) is the expression for the rate of increase of enthalpy with temperature.

Polar solvents are known to solvate charged species (ions) particularly strongly compared with the solvation of the neutral molecule. The effect of binding solvent molecules together around ions changes their freedom of motion which in turn affects the heat capacity of the system.
CHAPTER 2.

EXPERIMENTAL TECHNIQUE
AND CALCULATIONS
2, 6 - DIMETHYLPHENOLS

The phenols were obtained in a pure form from Fischer and co-workers (12), who described their preparation. These workers used the series for determination of acidity constants at 25°C by potentiometric titration. Before using any of the phenols their purity was tested by melting point determination, the results of which corresponded favourably with literature values as seen in table 1.

Table 1.

Melting Points of 2, 6 - Dimethylphenols:

<table>
<thead>
<tr>
<th>4-Substituent</th>
<th>Experimental Value</th>
<th>Literature Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH₃</td>
<td>71.5 - 72.5°C</td>
<td>69°C (13a)</td>
</tr>
<tr>
<td>C(CH₃)₃</td>
<td>80.0 - 80.5°C</td>
<td>80.5°C (14)</td>
</tr>
<tr>
<td>H</td>
<td>44.5 - 45.5°C</td>
<td>49°C (13b)</td>
</tr>
<tr>
<td>Br</td>
<td>77 - 78°C</td>
<td>79°C (12)</td>
</tr>
<tr>
<td>COCH₃</td>
<td>147.5 - 149°C</td>
<td>151°C (12)</td>
</tr>
<tr>
<td>CN</td>
<td>121.5 - 122°C</td>
<td>124°C (12)</td>
</tr>
<tr>
<td>CHO</td>
<td>113 - 113.5°C</td>
<td>114°C (12)</td>
</tr>
<tr>
<td>NO</td>
<td>168 - 169°C</td>
<td>171°C (12)</td>
</tr>
<tr>
<td>NO₂</td>
<td>166 - 167°C</td>
<td>170°C (13c)</td>
</tr>
</tbody>
</table>

It should be noted that the overall purity is not vitally important in spectrophotometric determinations of pK, provided any impurities present in the solution do not absorb at the chosen wavelength.

APPARATUS

Measurements of optical density were made using an Optica CF 4
spectrophotometer adapted to permit temperature variations of the solutions. The alterations described in detail by Hall and Reece (15) involved the replacement of the normal plastic cell under-carriage on which the cell holder rests by a hollow brass one through which thermostat liquid was circulated. Once the temperature of the solutions had stabilised they had a variation of $\pm 0.05^\circ\text{C}$, which is more than satisfactory for spectrophotometric measurements for the determination of enthalpy and entropy. For temperatures from ambient down to $5^\circ\text{C}$ a continuous stream of cold dry air was blown across the faces of the cells to prevent condensation on them.

The actual temperature of the solutions was found using a thermister probe, which dipped into one of the cells, connected to a digital thermometer capable of measurement to $\pm 0.01^\circ\text{C}$. Samples of water, the phenol in acid solution, in alkaline solution and in the appropriate buffer solution were contained in a matched set of four teflon-stoppered 2 cm cells. The stoppers prevented evaporation of the solvent at temperatures above ambient. Absorbance readings of the three phenol solutions were made against the reference water over the temperature range of $5 - 60^\circ\text{C}$. Readings were taken at about $5^\circ\text{C}$ intervals after the temperature of the solutions had stabilised. Acidity constants were than calculated at each temperature at which measurements were taken, making allowance for the absorbances of the blank acid, alkaline and buffer solutions.

**REASONS FOR CHOICE OF TECHNIQUE**

As was stated in chapter 1, calorimetric methods can be used
to determine the enthalpy change directly for a reaction. Other methods which can be used make use of empirically or thermodynamically derived forms of the van't Hoff equation.

\[
\frac{d (\ln K_a)}{dT} = \frac{\Delta H}{RT^2}
\]  \hspace{1cm} (1)

The free energy change can be calculated from the thermodynamic acidity constant.

\[
\Delta G = -RT\ln K_a
\]  \hspace{1cm} (2)

Calculation of the remaining thermodynamic function, the entropy change, can be done by substitution into equation (3).

\[
\Delta G = \Delta H - T. \Delta S
\]  \hspace{1cm} (3)

The van't Hoff equation (1), for the calculation of enthalpy, requires the measurement of acidity constants over a range of temperature. The slope of the resulting relationship yields the quantity \(\frac{\Delta H}{RT^2}\). Numerous methods are available for making these measurements, including:

(i) Potentiometric methods \(^{(16)}\), where the acid or base is titrated directly.

(ii) Conductiometric methods \(^{(17a,18)}\), in which the conductances of the weak acid or base are measured at various stoichiometric concentrations.
(iii) Spectroscopic methods \((4,5,6)\), where the ratio of the protonated to deprotonated forms of the acid is measured in a buffer of known acidity.

For the present work the spectroscopic method was chosen for the following reasons:

(i) Acidity constants were calculated from a formula involving acidity functions for buffer solutions. These functions \((7,8)\) are available for a range of buffers over temperatures from \(0 - 60^\circ\). pK\(_a\) values between \(-0.5\) and 10.9 calculated by this method have precision to \(\pm 0.001\) units.

(ii) The thermostat liquid controlled the temperature to \(\pm 0.05^\circ\) C which is better than satisfactory as extinction coefficients \((17b)\) for absorbing materials are not very sensitive to temperature. Control to within \(\pm 0.5^\circ\) C suffices, but to within \(\pm 0.1^\circ\) C is preferable.

(iii) Spectrophotometric methods \((17c)\) are relatively insensitive to the ionic environment, yet are highly sensitive to low concentrations of the absorbing species. Using 2 cm cells the phenol concentrations were in the order of \(3 \times 10^{-5}\) M. The exact solution concentrations need not be known but it is important to have the concentrations of the acidic, basic and buffered solutions identical.

All phenols were sufficiently soluble to give suitable absorbances (about 0.8). Except for 4 - \(t\) - butyl 2,6 - dimethylphenol,
the phenols were weighed out and dissolved in warm distilled water, then diluted to the required volume. The abovementioned phenol precipitated out of solution using this dissolution method. It was necessary to make a supersaturated solution of the 4-t-butylphenol which was then cooled to 3-5°C in an ice bath, seeded and allowed to stand for 20-40 minutes. The solution was filtered to remove all traces of undissolved phenol, this was then diluted to the required volume. The resulting concentration was fortunately sufficiently concentrated to give suitable absorbances without precipitating in the acidic solution.

(iv) The purity of the phenol was not critical provided impurities did not interfere with absorbances at the chosen wavelength.

**BUFFER SOLUTIONS**

The thermodynamic acidity constants \(K_a\) for the equilibrium ionisation of weak acids,

\[
HX + H_2O \rightarrow X^- + H_3O^+ ,
\]

is given by

\[
K_a = \frac{A_{X^-} \cdot A_{H_3O^+}}{A_{H_2O} \cdot A_{HX}}
\]

Since work was done in dilute solutions the activity \((17d)\) for the solvent \((A_{H_2O})\) in solution is virtually constant and equal to the activity of pure water.
Thus

$$K_a = \frac{A_{X^-} \cdot A_{H_3O^+}}{A_{HX}}$$  \hspace{1cm} (6)$$

From equation (6) we get

$$pK_a = pA_H - \log \frac{A_{X^-}}{A_{HX}}$$  \hspace{1cm} (7)$$

The acidity function $pA_H$ (i.e. pH) cannot be determined experimentally as such. Bates and Gary \(^{(7)}\) termed an "acidity function" as a useful experimental or operational quantity with exact thermodynamic meaning, the value of which is a function of the acidity of the medium. They introduced $p(A_H \gamma_{Cl})$ as such a thermodynamic acidity function. The value of the function was calculated from the electromotive force of cells of the type

Pt; $H_2$(1 atm) \hspace{1cm} Buffer containing chloride \hspace{1cm} AgCl; Ag.

$$p(A_H \gamma_{Cl}) = \frac{E - E^0}{2.303 \ RT/F} + \log M_{Cl}$$

where $E$ is the e.m.f. of the above cell.
$E^0$ is the standard potential of the cell.
$R$ is the gas constant.
$T$ is the absolute temperature.
$F$ is the faraday.
$M_{Cl}$ is the molal concentration of chloride ion.

$$pK_a = p(A_H \gamma_{Cl}) - \log \frac{A_{X^-}}{A_{HX}} + \log \gamma_{Cl^-}$$  \hspace{1cm} (8)$$

since $A = M. \gamma$ (i.e. activity = molality by activity coefficient)
\[ p_{K_a} = p\left( A_H \gamma_{\text{Cl}^-} \right) - \log \frac{M_{X^-}}{M_{HX}} + \log \frac{\gamma_{HX} \cdot \gamma_{\text{Cl}^-}}{\gamma_{X^-}} \] (9)

In solutions of low ionic strength \((I < 0.1)\) it is known \(^{(4)}\) that the activity coefficients of all ions of the same charge are very nearly identical (hence approximate cancellation \(\gamma_{\text{Cl}^-}\)) and that the activity coefficients of uncharged species approximate to unity. Confirmation that \(\gamma_X^- \approx \gamma_{\text{Cl}^-}\) and \(\gamma_{HX} \approx 1\) may be obtained by showing the constancy of the ionisation constant \((K_a)\) over a range of ionic strengths. For \(p\)-nitrophenol \(^{(4)}\) it has been shown that deviations from these approximations occur only at ionic strengths in excess of 0.1. These assumptions were also shown to be valid for 3,5-dichlorophenol \(^{(19)}\). \(4\)-nitroso 2,6-dimethylphenol was used to verify the assumptions for the present series of phenols. This was done using the phenol in the \(KH_2PO_4 - Na_2HPO_4\) buffer (table 11, ref. 7) at ionic strengths \(I = 0.02, 0.04, 0.08, 0.12\). It was clear that within experimental error the assumptions appeared to be valid over the whole temperature range. Thus the end right hand term of equation (9) approximates to unity.

Therefore \(p_{K_a} = p\left( A_H \gamma_{\text{Cl}^-} \right) - \log \frac{M_{X^-}}{M_{HX}}\) (10)

Bates and Schwarzenbach \(^{(20)}\) suggested a combination of electromotive force and spectrophotometric measurements for the calculation of acidity constants,

i.e. \(p_{K_a} = p\left( A_H \gamma_{\text{Cl}^-} \right) - \log \frac{A - A_a}{A_b - A}\) (11)
FIGURE 1

ABSORBANCE SPECTRA FOR SOLUTIONS OF 4-HYDROXY 3,5-DIMETHYLBENZONITRILE

WAVELENGTH (Millimicrons)

<table>
<thead>
<tr>
<th>Solution Type</th>
<th>Color</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basic Solution</td>
<td>Blue</td>
</tr>
<tr>
<td>Buffer Solution</td>
<td>Green</td>
</tr>
<tr>
<td>Acidic Solution</td>
<td>Red</td>
</tr>
</tbody>
</table>
where $A$, $A_a$ and $A_b$ are the absorbances of the buffered, acidic and basic phenol solutions.

In the buffered solution (c.f. Fig. 1) there is phenol and phenoxide ion shown by its extinction between that of the acidic and basic solutions. The most suitable buffer is one which produces equal concentrations of phenol ($M_{HX}$) and phenoxide ion ($M_{X^-}$), and in equation (10) $\log \frac{M_{X^-}}{M_{HX}} = 0$. This happens when $p(A_R \gamma C_1)$ for buffer = $pK_a$ for phenol. The concentration of phenol is proportional to the difference in absorbances of the basic and buffered solutions, i.e. $M_{HX} \propto A_b - A$. Likewise, the concentration of phenoxide ion is proportional to the difference in absorbances of the buffered and acid solutions, i.e. $M_{X^-} \propto A - A_a$. Hence the expression $\log \frac{M_{X^-}}{M_{HX}} = \log \frac{A - A_a}{A_b - A}$.

The buffers selected (7) must (i) have acidity functions differing no more than 1 unit from $pK_a$ for best results, and (ii) must not absorb light in the wavelength region where the useful bands of $X^-$ and $HX$ are located. In all cases suitable buffers were available from references 7 and 8. The following buffers were used, see table 2, each being prepared and stored as recommended.
Table 2.

Buffers used for pK<sub>a</sub> Determinations

<table>
<thead>
<tr>
<th>Substituent</th>
<th>pK&lt;sub&gt;a&lt;/sub&gt;</th>
<th>p(A&lt;sub&gt;H&lt;/sub&gt; ^&lt;Cl&gt; )</th>
<th>Buffer</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10.98</td>
<td>10.121&lt;sup&gt;(8)&lt;/sup&gt;</td>
<td>NaHCO&lt;sub&gt;3&lt;/sub&gt;- (8)</td>
</tr>
<tr>
<td>C(CH&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;3&lt;/sub&gt;</td>
<td>10.87</td>
<td>10.121&lt;sup&gt;(I = 0.04)&lt;/sup&gt;</td>
<td>Na&lt;sub&gt;2&lt;/sub&gt;CO&lt;sub&gt;3&lt;/sub&gt;</td>
</tr>
<tr>
<td>H</td>
<td>10.64</td>
<td>10.121</td>
<td></td>
</tr>
<tr>
<td>Br</td>
<td>9.85</td>
<td>10.121</td>
<td></td>
</tr>
<tr>
<td>COCH&lt;sub&gt;3&lt;/sub&gt;</td>
<td>8.22</td>
<td>8.251&lt;sup&gt;(7)&lt;/sup&gt;&lt;sup&gt;(I = 0.04)&lt;/sup&gt;</td>
<td>T.H.A.M.-HCl (21)</td>
</tr>
<tr>
<td>CN</td>
<td>8.22</td>
<td>8.251</td>
<td>table 15 ref.7</td>
</tr>
<tr>
<td>CHO</td>
<td>7.68</td>
<td>7.111&lt;sup&gt;(7)&lt;/sup&gt;&lt;sup&gt;(I = 0.01)&lt;/sup&gt;</td>
<td>KH&lt;sub&gt;2&lt;/sub&gt;P&lt;sub&gt;4&lt;/sub&gt;-Na&lt;sub&gt;2&lt;/sub&gt;HPO&lt;sub&gt;4&lt;/sub&gt; (22)</td>
</tr>
<tr>
<td>NO</td>
<td>7.60</td>
<td>7.040&lt;sup&gt;(I = 0.04)&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>NO&lt;sub&gt;2&lt;/sub&gt;</td>
<td>7.11</td>
<td>7.040</td>
<td>table 11 ref.7</td>
</tr>
</tbody>
</table>

**CALCULATIONS**

pK<sub>a</sub> values calculated from equation (11) were plotted manually against temperature for each run. When at least three consistent sets of data were obtained the curve of best fit was drawn. The curves had errors of ± 0.005, and at best ± 0.001 pK units. It was found that greatest errors were prevalent at the extremes of the temperature range (10 - 60°C).

At every 5° interval from 10 - 60° pK<sub>a</sub> values were taken from the line of best fit. These raw ionisation constants were corrected for the effect of the dissociation of the phenol on the p(A<sub>H</sub> ^<Cl> ) value of the buffer. The procedure was described by
Robinson and Kiang (23) which has often been used in the studies of phenols. Their equation is

\[
H_1 - H_2 = \frac{K_a M_p}{K_a + H_2} \frac{K (M_1 + M_2)}{K + H_2} + 1
\]  

(12)

where \(K_a\) and \(K\) are the dissociation constants of the phenol and buffer respectively. \(M_p\) is the concentration of the phenol. \(M_1\) and \(M_2\) are the respective concentrations of the weak acid and its sodium salt of the buffer solution. \(H_1\) and \(H_2\) are respectively the initial and corrected acidity functions. A more general method for the correction of the acidity function of the buffer, due to the contribution of protons from the dissociation of the acid, has been described by Bolton and Hall (19). These corrections were never greater than 0.003 pK units.

The thermodynamic functions of ionisation for each phenol were calculated from the corrected pK\(a\) values by the non-empirical method described by Clarke and Glew (24). For equilibrium constants over limited temperature ranges these workers developed the simple \textit{van't Hoff} equation (1). They assumed \(K_a\), \(\Delta G\), \(\Delta H\) and \(\Delta C_p\) were well behaved functions of \(T\). These quantities were related thus

\[
R \ln K_a = -\frac{\Delta G}{T} = \Delta S - \frac{\Delta H}{T}
\]

and

\[
\Delta C_p = \frac{d \Delta H}{dT}
\]
After numerous mathematical expansions and operations Clarke and Glew arrived at the relationship

\[ R \ln K = -\frac{\Delta G^\circ}{\Theta} + \frac{\Delta H^\circ}{\Theta} \left[ \frac{x}{1 + x} \right] + \Delta C_{p,\Theta} \left[ \chi^2 \sum_{n=1}^{\infty} \frac{n}{n-1} (-\chi)^{n-1} \right] \\
+ \frac{\Theta}{2} \left( \frac{d \Delta C_{p,\Theta}}{dT} \right)_0 \left[ \chi^3 \sum_{m=1}^{\infty} \frac{n}{n+2} (-\chi)^{n+1} \right] + \ldots \quad (13) \]

where \( \Theta = 298.15 \), the standard reference temperature for thermodynamic functions. \( x = \frac{T - \Theta}{\Theta} \), and \( T \) is the temperature of measurement of \( \ln K_a \).

A digital computer programme has been written \( (19) \) which fits equation (13) by least squares methods to the experimental \( pK_a \) values progressively as an equation in 1 to 5 temperature variables and at each stage tests the significance of the equation by means of a variance ratio F-test. It was found that the two variable equation gave the best fit to the experimental data for all phenols. The calculations of both (a) acidity function corrections, and (b) the thermodynamic functions of ionisation were carried out using an I.B.M. 1620 computer.
CHAPTER 3.

STRUCTURE AND ACIDITY
OF PHENOLS
The ionisation equilibrium for the phenols in aqueous solution is:

$$H_2O \rightleftharpoons H_3O^+ + A^-$$

where \( R \) = any of the nine substituents previously listed (c.f. table 1). This equilibrium may be represented in a more simple form as

$$HA + H_2O \rightleftharpoons A^- + H_3O^+.$$  

Ionisation of a molecular acid of the above type is an ionogenic reaction. It involves the transfer of the proton from the acid molecule to the solvent with the creation of ions; the electrical work required to separate the charged species is high (17e). The extent (17f) of proton transfer reactions studied in liquid solvents depends upon solvent properties: (i) its dielectric constant, (ii) its ability to solvate ions and molecules of the acid or base, and (iii) its own acidic or basic character. The protolysis reaction for phenols occurs between the solvent (\( H_2O \)) and the solute acid (HA). The dielectric force of the solvent expresses its affect on the electrostatic force between ions. The work of separating \( H_3O^+ \) and \( A^- \) ions varies inversely with the dielectric constant and since \( \kappa = 78 \) we would expect a reasonable degree of separation.
Water molecules being strongly polar in nature interact with the ions tending to stabilise them. This interaction is between the solvent dipoles and the positions of charge concentration on the solvated ion. Water may also stabilise the parent phenol and its ions through the mechanism of hydrogen bonding.

In the formation of a carbanion the three most important factors\(^\text{(25)}\) which control the ability of a carbon atom to accommodate the negative charge are:

(i) hybridisation of the orbitals carrying the negative charge,
(ii) \textit{delocalisation} of the charge by a conjugative mechanism, and
(iii) stabilisation by \textit{inductive} (or \textit{field}) effects. It would be considered that these factors similarly apply to the negative charge on the oxygen atom of the phenoxide anion. Substituents exert two different electronic effects\(^\text{(26,27)}\) capable of disturbing or stabilising molecular energies, they are inductive and resonance (conjugative) interactions.

\textbf{THE INDUCTIVE MECHANISM}\(^\text{(28,29)}\)

The electronegativity of an atom is a measure of the tendency to become negative, i.e. to attract electrons away from an atom linked to it. There is evidence\(^\text{(30)}\) that the attachment of a multiple linkage to an atom increases its effective electronegativity. An electron withdrawing group (e.g. a chlorine atom) attached to a chain of carbon atoms, may take a large share of the bonding electrons,
hence inducing a partial positive charge on the carbon atom to which it is attached. Since this positive charge will increase the electron-withdrawing power of the atom upon which it resides, the inductive effect will be relayed along the chain of atoms although with decreasing intensity. Kosower\(^{(25)}\) points out that the inductive effects are usually negligible if more than three bonds separate the substituent exerting the effect from the atom which must bear the charge.

Alkyl groups have a slight tendency to repel binding electrons when bound to unsaturated groups. Because of the +I effect of CH\(_3\) and C(CH\(_3\))\(_3\) groups we would expect a decrease in acid strength, in comparison with the parent phenol, due to the increase of the negative charge on the -O\(^-\) group of the phenoxide ion. The remaining substituents of the series all have -I effects, hence tending to stabilise the phenoxide ion, therefore increasing the acid strength. Whatever the effects of the substituents in the para-position they would not be expected to have marked inductive interactions with the -O\(^-\) group, as they are five bonds removed from the atom bearing the charge.

**THE CONJUGATIVE EFFECT\(^{(31)}\)**

Another factor of great importance in determining the acidity of aromatic acids is the degree of resonance stabilisation of the acid and its conjugative base. Resonance or conjugation is a second method of electron displacement. In this case, an electron pair may move from the condition in which it is binding two atoms, to that in which it is an unshared pair attached to one atom, i.e.
For example, p-cyanophenoxide ion has four possible resonance structures. The cyano substituent withdraws portion of the pi-electron cloud from the benzene ring, especially when it occupies the ortho- and para- positions. The structures II, III and IV indicate that the negative charge is not localised on the oxygen atom, but also resides partially on the ring and partially on the cyano group.
We would expect the most acidic phenols to be those with substituents capable of the greatest conjugative interaction, such substituents are the nitro, nitroso, cyano, aldehydo and acetyl groups.

Many workers have tried to divide polar interactions into inductive effects (the displacement of electrons along the molecular chain or ring) and direct or electrostatic field effects (which partially occur through the solvent). King\(^{(17g)}\) discourages the distinction as pointless because there is no way of estimating one interaction independently of the other.

**STERIC EFFECTS**

It is recognised\(^{(27)}\) that a substituent can influence a chemical reaction principally by its ability to occupy space. The phenomenon of steric hindrance is a situation where contact between reaction centres is made more difficult by interference of groups that do not otherwise participate. King\(^{(17g)}\) suggested the effects are small and hard to disentangle from other influences. Bulky substituents possibly have little effect on the direct loss of a proton because of its small size, but they may prevent solvent-solute interactions capable of stabilising the anion formed by dissociation. Comparison of the present series, having two methyl groups ortho to the -OH group, with para-substituted phenols shows that steric inhibition to solvation definitely weakens acid strength.

Intramolecular hydrogen bonding similar to that in salicylate ion I has a definite acid strengthening effect. It would
not be expected that there exists any intramolecular hydrogen bonding for ortho-methyl substituted phenols II, as this would involve bonds of the type $\text{C—H} \cdots \text{O}$, and these are unlikely when the hydrogen atom is in an alkyl group.

**THE HAMMETT EQUATION** $^{(32,33)}$

The effect of a substituent is evaluated by a measurement of how the introduction of the substituent into a substrate affects a physical or chemical property of the substrate. Hammett realised that certain extrathermodynamic relationships could provide much insight into the effects of substituents. He proposed a quantitative relationship between structure and reactivity. The Hammett equation relates structure to both equilibrium constants and rate constants for the reaction of meta- and para- substituted benzene derivatives. The original reaction series was benzoic acids, for which

$$\log K - \log K_0 = \sigma$$  \hspace{1cm} (14)

where $K$ and $K_0$ are the equilibrium constants for substituted and
unsubstituted benzoic acids respectively. The **substituent constant** \( (\sigma) \) represents the effect of the substituent on the ionisation of benzoic acid.

Considering the ionisation of another reaction series (e.g. phenylacetic acid), it was found that the effect of the substituent on this equilibrium was proportional to the effect of the substituent on the ionisation of benzoic acid. The **reaction constant** \((\rho)\) was introduced as a proportionality constant:

\[
\log \frac{K(X-\text{PhCH}_2\text{COOH})}{K_o(\text{PhCH}_2\text{COOH})} = \rho \log \frac{K(X-\text{PhCOOH})}{K_o(\text{PhCOOH})}
\]

i.e.

\[
\log \frac{K}{K_o} = \rho \cdot \sigma \quad (15)
\]

Shorter \((34)\) remarks that the Hammett linear free energy relationship is a useful one because the log of an equilibrium constant \((K)\) is proportional to the standard free energy of the reaction \((\Delta G^0)\). The Hammett equation describes the influence of polar *meta-* or *para-* substituents on side chain reactions of benzene derivatives.

**THE SUBSTITUENT CONSTANT \((\sigma)\)**

The sigma value is a measure of the polar effect of the substituent relative to hydrogen. Within substituent constant values \((25)\) there are the summed effects of the solvent on both the initial and final states, the temperature effect and the second order effect of the
substrate on the nature of the solvent around the molecule.

The \textit{para}-nitro group has a $\sigma_p$ value equal to 0.78 for the ionisation of benzoic acids, but in the ionisation of phenols and anilines

$$\text{X-} \text{C}_6\text{H}_4\text{-}\text{OH} + \text{H}_2\text{O} \rightleftharpoons \text{X-} \text{C}_6\text{H}_4\text{-}0^\ominus + \text{H}_3\text{O}^+$$

$$\text{X-} \text{C}_6\text{H}_4\text{-} \text{NH}_3^\ominus + \text{H}_2\text{O} \rightleftharpoons \text{X-} \text{C}_6\text{H}_4\text{-}\text{NH}_2 + \text{H}_3\text{O}^+$$

the p-NO$_2$ group needs an enhanced value of $\sigma_p^- = 1.27$. This is due to direct conjugation of the nitro group with the lone pair of electrons of the −OH or −NH$_2$ functional group. The nitro group is effectively more electron attracting than in \textit{p}-nitrobenzoic acid.

Sigma minus ($\sigma^-$) values are defined by the ionisation of phenols, and are used for reactions where electron withdrawal by the substituent is greater than can be accounted for by usual resonance interaction. For the present work $\sigma_p^-$ values were used for those substituents capable of conjugation with the aromatic nucleus; these were nitro, nitroso, formyl, cyano and acetyl substituents. The usual $\sigma_p$ values, derived from benzoic acids, can be used for the saturated groups (methyl, t-butyl, hydrogen and bromo). Effective sigma values ($\sigma_p^-$) used in this project were those derived from Biggs and
Robinson's \( (23,35) \) data from the thermodynamic ionisation constants of 4-substituted phenols in water at 25\(^\circ\)C. The substituent constants \( (\sigma^p) \) were calculated from their equation

\[
pK_a = 9.919 - 2.229 \sigma
\]

It is the opinion of Fischer et al. \( (12,14) \) and Cohen and Jones \( (36) \) that Biggs and Robinson's \( \sigma \) \textit{para} minus values are the most accurate available for phenols.

Elementary accounts of the Hammett equation often give the impression that the substituent constants are well understood qualitatively in terms of polar effects, which are the combined influence of inductive (\( +I \)) and resonance (\( +R \)) effects. To the contrary, Shorter \( (34) \) argues that this is very far from the case. The nature of that part of the polar effect which is not conjugative is by no means clear. Often the polarisation of bonds of the pi-electron system of benzene is invoked as an explanation. This has been shown to be unsatisfactory and now attention is paid to both field effects and polarisation of sigma- or pi-bonds.

It is recognised that substituent interactions are in accord with two qualitatively different mechanisms, the inductive and resonance effects, their magnitude depending on the particular reaction. There seems to be a different sigma value for the same substituent for almost every different reaction. Swain and Lupton \( (37) \) have found that the entire unhealthy collection of substituent constants may be replaced
by a single set of two constants for each substituent: $F$ (for field and inductive effects) and $R$ (for resonance). Non-resonance effects, i.e. pure field and inductive effects, are lumped together and called field effects. They avoid the assumption that meta and para field effects are equal for each substituent, as they were able to show this to be incorrect. Swain and Lupton also point out that different sigma values are not independent if a distinction between field and resonance can be made.

Using $f$ and $r$ as weighting constants all substituent constants can be defined or represented by a linear combination of $F$ and $R$:

$$\sigma = f.F + r.R$$

Field and resonance components of substituent effects are $\rho_f.F$ and $\rho_r.R$ respectively. The reaction constant ($\rho$) and the weighting constants ($f$ and $r$) are independent of the substituent. $F$ and $R$ parameters are independent of the reaction, the solvent and the temperature, and are characteristics only of the substituent.

It is interesting that Swain and Lupton show $\sigma$ and $\sigma^-$ values to have about the same "per cent resonance" ($%\ R$), 53 $\pm$ 0 and 56 $\pm$ 4 respectively, for para substitution. The enhanced substituent effect for phenol deprotonation for groups like $NO_2$ and $CN$ may come as much from field effects as from resonance interaction. The field effect $(26,37)$ of any group will be enhanced by resonance shifting of
electron density through the remainder of the system to the vicinity of the substituent; this factor may be the crucial characteristic of cases requiring $\sigma^-$.

THE REACTION CONSTANT ($\rho$)

Wells\(^{(38)}\) says that the understanding of the magnitude and sign of the Hammett rho-value depends upon the interpretation of the sigma values. The Hammett relationship yields the reaction parameter as a proportionality constant which is a measure of the sensitivity of the equilibrium constant of a particular reaction series to substituent changes relative to that of the standard reaction. Identification of sigma-values with measures of substituent polar effects allows the identification of the rho-value as the relative susceptibility of a particular reaction series to electrostatic and electronic effects. The following generalisations are evident from the meaning of the sigma-values; (i) Reactions aided by electron withdrawal, i.e. by acid strengthening substituents, will have positive rho-values. (ii) Reactions more sensitive to electronic effects than the ionisation of benzoic acids in aqueous solution will have rho-values of absolute magnitude greater than unity.

Wiberg\(^{(39)}\) suggests that reactions with a negative rho-value are those in which the carbon attached to the ring becomes relatively electron poor as a result of the reaction, and those having a positive rho produce a relatively electron rich carbon as a result of the reaction.
The magnitude of the reaction parameter gives information about the
degree of change of electron density but there is much about the
Hammett rho value which is not understood.

For a reaction series with structure I the variations in
equilibria caused by R may be correlated by the Hammett linear free
energy relationship. When a fixed substituent X is added ortho to Y
(the reaction centre), as shown in structure II, evidence has been
cited\(^{(33)}\) to suggest that the reaction constant is independent of the
nature of X.

\[ \begin{align*}
\text{I} & \quad \begin{array}{c}
\text{II} \\
\text{Y} & \text{X} \\
\text{R} & \text{X}
\end{array}
\end{align*} \]

On this basis rho for compounds of structure I should equal rho for
the same reaction compounds of structure II.

Chen and Laidler\(^{(6)}\) have measured the entropies of
ionisation of the cresols and xylenols in water, and they have
concluded that the 2-methyl substitution introduced no appreciable
steric requirement. Further evidence that supports this assumption
is contained in table 3 of rho-values for the ionisation of different
reaction series. It should be noted that Hancock and co-workers\(^{(40,41,42)}\)
use negative rho-values when Wells uses positive values. The convention used by Wells has been adopted for this project.

### Table 3.

<table>
<thead>
<tr>
<th>Reaction Series</th>
<th>Rho-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>para-monosubstituted phenols</td>
<td></td>
</tr>
<tr>
<td>4-substituted 2-nitrophenols</td>
<td>2.11(33); 2.23(35)</td>
</tr>
<tr>
<td>4-substituted 2-chlorophenols</td>
<td>2.16(40)</td>
</tr>
<tr>
<td>5-substituted 2-nitrophenols</td>
<td>2.22(41)</td>
</tr>
<tr>
<td>4-substituted 2,6-di-t-butylphenols</td>
<td>3.01(42)</td>
</tr>
<tr>
<td>4-substituted 2,6-dichlorophenols</td>
<td>3.50(36)</td>
</tr>
<tr>
<td>4-substituted 2,6-dimethylphenols</td>
<td>2.61(14)</td>
</tr>
<tr>
<td>4-substituted 2,6-dimethylophenols</td>
<td>2.70(12)</td>
</tr>
</tbody>
</table>

The series of 5-substituted 2-nitrophenols does not conform to the assumption. The electronic effects of the substituent are transmitted more effectively to the reaction site in this series than in the others above it in the table.

One would expect variation in $\rho$ to occur when the solvation of $Y$ is implicated in the property being measured (such as the degree of ionisation) and that the requirements for the solvation of $Y$ may vary with the nature of $R$. Whenever there is interaction between $X$ and $Y$ one might predict variation in rho. Such interaction may be steric hindrance to solvation of the anion of a phenol (III).
When \( X = \text{-} \text{t-Bu} \) the reaction constant for the dissociation of 4-substituted 2,6-di-t-butylphenols is +3.50\(^{36}\) which is 57% greater than that for the dissociation of unhindered phenols.

The requirements\(^{(12,36)}\) for the solvation of the functional group may vary with the substituent. A 4-nitro substituent attracts a large fraction of the negative charge, consequently the solvent sphere at the \(-O^-\) is smaller than that in the unsubstituted phenoxide ion. Steric inhibition to solvation due to the large \text{-} \text{t-butyl} groups in the ortho- positions is of greater consequence in the 2,6-di-t-butylphenoxide ion than in the 4-nitro 2,6-di-t-butylphenoxide ion. Thus there is a wider difference in the \( pK_a \) values of the hindered phenols compared with the corresponding phenols, i.e. \( p \) is larger for the dissociation of 2,6-di-t-butylphenols.

Fischer and co-workers\(^{(12)}\) reported the dissociation constants for the present series of 4-substituted 2,6-dimethylphenols in water at 25\(^\circ\)C. They suspected steric inhibition of solvation of the anion to be considerably less in the series than in the 2,6-di-t-butylphenols. This was borne out by their result of \( p = 2.70^{(12)} \), a 21% increase in the value for phenols. Again, Fischer and co-workers\(^{(14)}\) showed simple steric inhibition of solvation of the phenoxide anion by finding \( p = 2.61 \) for 4-substituted 2,6-dichlorophenols. This result also indicates that the observed enhancement for the 2,6-dimethyl and the 2,6-di-t-butyl series is not a consequence of polar rather than steric effects. If it were then the dichlorophenols should have had
a rho-value less than that for unhindered phenols because chloro- and methyl- groups have opposite electronic effects.
CHAPTER 4.

DISCUSSION OF RESULTS.
Table 4.
Experimental Results.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>Molal Concentration</th>
<th>Absorbance</th>
<th>Isobestic Points</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>molal/litre^-1</td>
<td>max. m.μ</td>
<td></td>
</tr>
<tr>
<td>CH3</td>
<td>3 x 10^-4</td>
<td>295</td>
<td>-</td>
</tr>
<tr>
<td>C(CH3)_3</td>
<td>3 x 10^-4</td>
<td>293</td>
<td>-</td>
</tr>
<tr>
<td>H</td>
<td>5 x 10^-4</td>
<td>287</td>
<td>-</td>
</tr>
<tr>
<td>Br</td>
<td>3 x 10^-4</td>
<td>297</td>
<td>-</td>
</tr>
<tr>
<td>COCH3</td>
<td>3 x 10^-5</td>
<td>342</td>
<td>236, 259, 306</td>
</tr>
<tr>
<td>CN</td>
<td>2 x 10^-5</td>
<td>290</td>
<td>232, 261</td>
</tr>
<tr>
<td>CHO</td>
<td>3 x 10^-5</td>
<td>345</td>
<td>234, 260, 310</td>
</tr>
<tr>
<td>NO</td>
<td>2 x 10^-5</td>
<td>385</td>
<td>265, 338</td>
</tr>
<tr>
<td>NO2</td>
<td>4 x 10^-5</td>
<td>431</td>
<td>246, 299, 406</td>
</tr>
</tbody>
</table>

Table 5.

pK_a Values of 4-X 2,6-Dimethylphenols.

<table>
<thead>
<tr>
<th>Substituent</th>
<th>pK_a</th>
<th>ref. pK_a</th>
<th>σ_p^-b.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH3</td>
<td>10.98</td>
<td>10.86; 10.89(43)</td>
<td>-0.15</td>
</tr>
<tr>
<td>C(CH3)_3</td>
<td>10.87</td>
<td></td>
<td>-0.14</td>
</tr>
<tr>
<td>H</td>
<td>10.64</td>
<td>10.59; 10.61(6)</td>
<td>0</td>
</tr>
<tr>
<td>Br</td>
<td>9.85</td>
<td>9.81</td>
<td>0.25</td>
</tr>
<tr>
<td>COCH3</td>
<td>8.22</td>
<td>8.22</td>
<td>0.84</td>
</tr>
<tr>
<td>CN</td>
<td>8.22</td>
<td>8.19; 8.27(44)</td>
<td>0.88</td>
</tr>
<tr>
<td>CHO</td>
<td>7.68</td>
<td>7.74</td>
<td>1.04</td>
</tr>
<tr>
<td>NO</td>
<td>7.60</td>
<td>7.56</td>
<td>1.10</td>
</tr>
<tr>
<td>NO2</td>
<td>7.11</td>
<td>7.07; 7.22(44)</td>
<td>1.24</td>
</tr>
</tbody>
</table>

(a) Ref. pK_a values from Fischer et.al. (12), unless otherwise stated.

(b) σ_p^- values calculated by Cohen and Jones (36), except for NO the value obtained from Fischer et.al. (12).
FIGURE 2
HAMMET CORRELATION

\[ pK_0 = \rho \sigma \]
There is satisfactory agreement between the present $pK_a$ values (column 2, table 5) and those obtained by Fischer et al.\,(12) (column 3, table 5) who used potentiometric titration. The $pK_a$ for 2,4,6-trimethylphenol found spectrophotometrically by Ko et al.\,(43) is in better agreement with our value. This also is the case for the value of 2,6-dimethylphenol obtained by Chen and Laidler\,(6) using spectrophotometry. The present values for 4-cyano and 4-nitro 2,6-dimethylphenols lie between the values obtained by Fischer et al.\,(12) and Wheland, Brownell and Mayo\,(44), both using potentiometric titration.

The recommended method\,(45) of evaluating rho-values is to fit a regression line to $\log K$ against $\sigma^*$ data for the meta-substituted and unsubstituted compounds. This cannot be applied to the present reaction series. The rho-value from the Hammett equation $\log K - \log K_o = \rho \sigma$ was found from a plot (Fig.2) of ($pK_o - pK$) against $\sigma$. This was done for the 4-X phenols as well as 4-X 2,6-dimethylphenols. The value of $\rho$ was calculated by the method of least squares and was found to be 2.75, with a correlation coefficient $r = 0.999$, a standard deviation $s = 0.056$ and a $pK_o = 10.56$ (for 2,6-dimethylphenol).

A comparison between the present 4-X 2,6-dimethylphenols (series A) and 4-X phenols (series B) can be made. For the dissociation of A the reaction parameter $\rho = 2.75$, whereas for B $\rho = 2.23$\,(35), this shows a 23% increase in rho in going from the unhindered series B
to the 2,6-dimethyl substituted series A. The steric inhibition of solvation, caused by the di-methyl groups ortho to the phenolate oxygen atom, is considered to be the reason for this increase. As can be seen from the changes of acid strength, in Fig.3, the requirements for solvation of the functional group vary with the substituent. In the phenoxide ion with saturated 4-substituents (methyl, t-butyl, hydrogen, bromo) the functional group carries the major portion of the negative charge. Thus it is the phenolate oxygen which must be stabilised by solvation. The presence of the ortho-methyl groups hinders this solvation and increases the pKₐ value, i.e. weakens the acid strength of the 4-X 2,6-dimethylphenols (series A, Fig.3). This explains the divergence of the two correlations for substituents with low sigma-values.

Those substituents (acetyl, cyano, formyl, nitroso and nitro) capable of direct conjugation take on portion of the negative charge themselves which in turn moves portion of the solvation sphere from the phenolate oxygen to the substituent.

The anion of 4-formylphenol will probably be closer in structure to I than II (R = H) whereas the hindered phenols (R = CH₃)
FIGURE 3

VARIATION OF pK_a WITH SUBSTITUENT
will have a greater tendency towards II. This arises because of the possibility of stabilisation by solvation of the charged oxygen atom in the aldehyde group when solvation of the phenolic oxygen is heavily hindered. The sum of the charges on both oxygens will be the same whether \( R = H \) or \( CH_3 \). If it is assumed that the total number of solvent molecules needed to solvate the negative charge is approximately constant with changing pK values, it is clear that the larger the \( \sigma^- \) value becomes the smaller will be the size of the solvent sphere around the phenolate oxygen. Although the steric effect of the methyl groups impedes solvation of the phenolic oxygen, the movement of negative charge to the aldehyde oxygen (II) along with portion of the solvent sphere ensures that the net change in solvation is probably small. If this argument is valid then the pK\(_a\) change on the introduction of two ortho-methyl groups to 4-X phenols (X capable of conjugative delocalisation of the negative charge) should contain an apparently negligible contribution from steric factors. The results for X = NO\(_2\), CHO, CN and COCH\(_3\) (Fig.3) are in agreement with the argument.

Cohen and Jones\(^{(36)}\) found that the Hammett plots of pK with \( \sigma^- \) for 4-X phenols and 4-X 2,6-di-t-butylphenols in water and in 50% ethanol intersected within the range of real sigma values. This has also occurred for the present work (Fig.3). Cohen and Jones suggested that the two bulky ortho-t-butyl groups may provide either steric hindrance or steric enhancement for ionisation, depending only
on the 4-substituent. They found that 4-nitro 2,6-di-\text{-}t\text{-}butylphenol to be more acidic than 4-nitrophenol. Rochester and Rossall\cite{47} believe that with increasing electron-withdrawing power of the 4-substituent steric inhibition to solvation by the \text{-}t\text{-}butyl groups would decrease whereas steric repulsion of the proton might be expected to increase. Thus for III (R = \text{-}t\text{-}butyl) X = methyl, \[ \begin{array}{c}
\text{R} \\
\text{R} \\
\text{OH} \\
\text{X}
\end{array} \]
\text{-}t\text{-}butyl or hydrogen steric inhibition to solvation would predominate whereas for X = NO\textsubscript{2} steric repulsion of the phenolic proton becomes predominant and steric inhibition to solvation minimal. The same argument would apply to our work (R = CH\textsubscript{3}) but with a lesser degree of steric hindrance and repulsion.

Normally $\sigma_p^-$ for nitroso = 1.60\cite{36}, but Fischer et al.\cite{12} found that the value of 1.10 was appropriate when the group occupied the 4-position of 2,6-dimethylphenol. This value was confirmed by the present work. The low sigma-value has been attributed\cite{12,36,48-51} to the tautomeric equilibrium between nitrosophenol (IV) and the quinone monoxime (V). The direction of the equilibrium between IV and V is solvent dependent\cite{49-51}.
The results of the thermodynamic ionisation functions calculated from the pKₐ data found by spectrophotometric methods during the project are tabulated below in table 6. The values of the thermodynamic functions of the ionisation of 4-substituted phenols have been collected from the literature and are listed in table 7 as a ready reference for comparison of the two reaction series.
Table 6.

Thermodynamic Functions of Ionisation of 4-X 2,6-Dimethylphenols

<table>
<thead>
<tr>
<th>4-Substituent</th>
<th>$\Delta G_{25}$</th>
<th>$\Delta H_{25}$</th>
<th>$\Delta S_{25}$</th>
<th>$\Delta C_{p25}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>14.98</td>
<td>5.29</td>
<td>-32.49</td>
<td>-69</td>
</tr>
<tr>
<td>C(CH$_3$)$_3$</td>
<td>14.87</td>
<td>5.43</td>
<td>-31.58</td>
<td>-51</td>
</tr>
<tr>
<td>H</td>
<td>14.52</td>
<td>5.18</td>
<td>-31.30</td>
<td>-57</td>
</tr>
<tr>
<td>Br</td>
<td>13.45</td>
<td>5.14</td>
<td>-27.84</td>
<td>-52</td>
</tr>
<tr>
<td>COCH$_3$</td>
<td>11.21</td>
<td>2.26</td>
<td>-30.01</td>
<td>16</td>
</tr>
<tr>
<td>CN</td>
<td>11.21</td>
<td>3.15</td>
<td>-27.04</td>
<td>23</td>
</tr>
<tr>
<td>CHO</td>
<td>10.49</td>
<td>2.92</td>
<td>-25.36</td>
<td>-40</td>
</tr>
<tr>
<td>NO</td>
<td>10.37</td>
<td>5.54</td>
<td>-16.20</td>
<td>-65</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>9.71</td>
<td>4.40</td>
<td>-17.80</td>
<td>-37</td>
</tr>
</tbody>
</table>

(a) Units are kcal mole$^{-1}$  (b) Units are cal deg$^{-1}$ mole$^{-1}$

Table 7.

Thermodynamic Functions of Ionisation of 4-X Phenols

<table>
<thead>
<tr>
<th>4-Substituent</th>
<th>$pK_{a,25}$</th>
<th>$\Delta G_{25}$</th>
<th>$\Delta H_{25}$</th>
<th>$\Delta S_{25}$</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>CH$_3$</td>
<td>10.28</td>
<td>14.02</td>
<td>5.50</td>
<td>-28.6</td>
<td>6</td>
</tr>
<tr>
<td>C(CH$_3$)$_3$</td>
<td>10.23</td>
<td>13.96$^d$</td>
<td>5.74</td>
<td>-23.5</td>
<td>36</td>
</tr>
<tr>
<td>H</td>
<td>9.95</td>
<td>13.57</td>
<td>5.74</td>
<td>-27.0</td>
<td>52</td>
</tr>
<tr>
<td>Br</td>
<td>9.33</td>
<td>12.74</td>
<td>5.74</td>
<td>-23.5</td>
<td>52</td>
</tr>
<tr>
<td>COCH$_3$</td>
<td>8.04</td>
<td>10.96</td>
<td>3.77</td>
<td>-24.1</td>
<td>e.</td>
</tr>
<tr>
<td>CN</td>
<td>7.96$^c$</td>
<td>10.87</td>
<td>4.92</td>
<td>-20.0</td>
<td>43</td>
</tr>
<tr>
<td>CHO</td>
<td>7.61$^c$</td>
<td>10.39</td>
<td>4.26</td>
<td>-20.6</td>
<td>2</td>
</tr>
<tr>
<td>NO$_2$</td>
<td>7.15</td>
<td>9.79</td>
<td>4.70</td>
<td>-16.9</td>
<td>1</td>
</tr>
</tbody>
</table>

(a) kcal mole$^{-1}$  (b) cal deg$^{-1}$ mole$^{-1}$  (c) Calculated from $\Delta G$
(d) Calculated from $pK_a$  (e) Present work.
Enthalpy and entropy values are derived from pK\textsubscript{a} values by differentiation, which always results in a loss of precision. Heat capacity values are found from the second derivative and will possess the least precision of all. King\textsuperscript{(17h)} calculated errors for the functions for pK\textsuperscript{+} 0.02 and pK\textsuperscript{+} 0.001, and by simple proportions the following errors can be expected for the present work:

<table>
<thead>
<tr>
<th>Error in pK\textsubscript{a}</th>
<th>ΔH\textsuperscript{+}</th>
<th>ΔS</th>
<th>ΔC\textsubscript{p}</th>
</tr>
</thead>
<tbody>
<tr>
<td>± 0.005</td>
<td>± 0.05 kcal mole\textsuperscript{-1}</td>
<td>± 0.08 cal mole\textsuperscript{-1} deg\textsuperscript{-1}</td>
<td>± 7 cal mole\textsuperscript{-1} deg\textsuperscript{-1}</td>
</tr>
</tbody>
</table>

Ives and Marsden\textsuperscript{(53)} consider the heat capacity (ΔC\textsubscript{p}) as the sum of two terms. The first (ΔC\textsubscript{r}\textsuperscript{p}) is a function of the "solute reaction proper" and is the contribution from the reaction.

\[ HA(aq) = H^+(aq) + A^-(aq) \]

The second (ΔC\textsubscript{h}\textsuperscript{p}) is attributed to the "associated solvent reaction" and is expected to be the larger contributor to ΔC\textsubscript{p}. It is furnished by the hydration reaction.

\[ xH_2O^{HA} + (y + z - x) H_2O^S = yH_2O^{H^+} + zH_2O^{A^-} \]

where H\textsubscript{2}O\textsuperscript{HA} is the hydration of HA molecules and H\textsubscript{2}O\textsuperscript{S} is the solvent water. The heat capacity is ΔC\textsubscript{p} = ΔC\textsubscript{r}\textsuperscript{p} + ΔC\textsubscript{h}\textsuperscript{p}.

Interpretations of ΔC\textsubscript{p} are complex and it is thought\textsuperscript{(53)} that ΔC\textsubscript{p} is likely to be specifically variable from one ionisation to another, particularly in its dependence on temperature. The positive values
for the acetyl- and cyano- substituted 2,6-dimethylphenols as opposed to the negative $\Delta C_p$ values for the remainder of the series substantiate this statement.

King$^{(17h)}$ reports that calorimetric measurements show $\Delta C_p$ to be a complex function of temperature, also that it is not constant as assumed by many people. Confidence in $\Delta C_p$ was tested by the curvature of the plot of $pK_a$ against $T$ within the experimental error of $pK_a$. Only slight changes in curvature produced dramatic changes in heat capacity (up to 20 cal mole$^{-1}$ deg$^{-1}$) indicating that this function is too susceptible to error, as calculated by the present method, to possess any physical meaning of any consequence.

Hepler and his co-workers$^{(1-3,54-57)}$ have assessed the influence of substituents on the thermodynamic functions of acid ionisation processes in water in terms of the equilibria.

$$HA_u(aq) = H^+(aq) + A^-_u(aq) \quad (1)$$

$$HA_s(aq) = H^+(aq) + A^-_s(aq) \quad (2)$$

$$HA_s(aq) + A^-_u(aq) = A^-_s(aq) + HA_u(aq) \quad (3)$$

$HA_s$ is a substituted acid and $HA_u$ the unsubstituted parent acid. The enthalpy and entropy changes for equilibrium (3) are considered to be the sum of internal and external contributions. Classical resonance and inductance effects are invoked to correlate heats of ionisation of a series of acids that occur within the acid as a result
of the loss of a proton and the gain of a negative charge. An equally important problem is the consideration and explanation of energy changes outside the acid due to changes in the acid-solvent and anion-solvent interaction energies.

\[ \Delta S = \Delta S_{\text{int.}} + \Delta S_{\text{ext.}} \]

The entropy of ionisation must also be considered in terms of differences within the acid and its anion and also the entropy changes due to differences in solute-solvent interaction.

\[ \Delta S = \Delta S_{\text{int.}} + \Delta S_{\text{ext.}} \]

Pitzer has shown that for a series of acids the "internal" entropies of the anion are less than those of the corresponding acids by an amount that is very nearly constant. Hepler and Fernandez conclude that because \( \Delta S_{\text{int.}} = 0 \) that differences in entropy of ionisation for acids are due to differences in solute-solvent interaction.

Feates and Ives and Ives and Marsden have discussed similar ideas in connection with cyanoacetic acid in water. They split extensive thermodynamic functions into a reaction part (water is not directly concerned) and a hydration part (where water is solely concerned), which are equivalent to Hepler's internal and external contributions.

Studies of the ionisation of phenols have suggested that the entropies of ionisation are primarily governed by solvation requirements of the phenoxide anions. Electron-withdrawing substituents attract portion of the negative charge of the phenolate oxygen atom and
thus reduce the overall solvation of the anion, decreasing the entropy of ionisation.

Theories concerned with explaining the effects of substituents on the acidity of phenols have been primarily developed for water as a solvent. Therefore, the auto-dissociation of water should be considered as a controlling factor in the strengths of organic acids. Hambly reveals that $\Delta H$ for the auto-dissociation of water varies from 14.88 kcal at 0°C to 11.86 kcal at 60°C, and $\Delta C_p = -51 \text{ cal deg}^{-1}$ calculated from the graph of $\Delta H$ against $T$. Hambly proved that for the dissociation of water many molecules are involved. The binding of solvent molecules to ions reduces their motion causing a negative $\Delta C_p$ value. The fall in $C_p$ for the ionisation of organic acids is usually in the range -25 to -50 cal deg$^{-1}$ and is generally smaller than that for water. This indicates that many solvent molecules are involved in the ionisation process of the organic acid.

It has been argued by Leffler and Grunwald that where a substituent causes a change in the free energy of a reaction process through a single interaction mechanism then any two of the quantities $\Delta G$, $\Delta H$, $\Delta S$ should be linearly related. $\Delta$ represents the change in going from an unsubstituted to a substituted state. Where more than one mechanism is in operation, yet one is dominant, then there exists a general trend towards linearity but with some scattering due to the minor mechanisms.
Figure 4

Correlation of Free Energy with Entropy

\[ \Delta G \text{ (kcal.deg.mole}^{-1}) \]

\[ - \Delta S \text{ (cal.deg.mole}^{-1}) \]

- \( t-Bu \)
- \( Me \)
- \( H \)
- \( Br \)
- \( NO \)
- \( NO_2 \)
- \( CN \)
- \( COMe \)
- \( CN \)
- \( COMe \)

4 - Substituted Dimethylphenols
4 - Substituted Phenols
FIGURE 5
CORRELATION OF FREE ENERGY WITH ENTHALPY

\[ \Delta G \text{ (kcal/mole)} \]

\[ \Delta H \text{ (kcal/mole)} \]

- **4-SUBSTITUTED 2,6 DIMETHYLPHENOLS**
- **4-SUBSTITUTED PHENOLS**
Substituent effects on the free energy change of ionisation are related mainly to changes in $\Delta S$. A high degree of linear proportionality between $\Delta G$, $\Delta H$ and $\Delta S$ exists for ortho- and para- substituted phenols but not for meta-substituted ones. The same dominant mechanism is thought to be present in ortho- and para- substituted series, but is only of minor importance for meta-substituted phenols. The mechanism is postulated as direct conjugation.

Figs. 4 and 5 represent any relation, if any, between the free energy and entropy, and free energy and enthalpy respectively. These plots do not show any linear proportionality, hence we suggest that the substituent effects on the ionisation of 4-substituted 2,6-dimethylphenols do not seem to show any one particularly dominant mechanism.

Hammett's equation was originally proposed to apply to isoentropic series but there appear to be more series where entropy varies than where it remains constant. Leffler(66) proposed that linear enthalpy-entropy relations could be correlated by Hammett's equation. Such relationships result from changes of substituents causing $\Delta H$ and $\Delta S$ to vary in the same direction. This is described by the "compensation effect"(66-68).

The commonly accepted method of correlating enthalpy with entropy of ionisation is to plot $\Delta H$ against $\Delta S$.

$$\Delta H = \Delta G_o + \beta \cdot \Delta S$$  \hspace{1cm} (1)

and

$$\Delta G = \Delta G_o + (\beta - T) \Delta S$$  \hspace{1cm} (2)
$\Delta G_o$ is the intrinsic free energy of ionisation. It is a standard state where $\Delta S = 0$. The intrinsic $\Delta G$ may be also written as the intrinsic enthalpy.

Extensions (38) have been made to the original single thermodynamic category for the Hammett equation, so as to include reaction series previously excluded. A source of failure was found in reaction series where direct conjugation between the substituent and the reaction center is possible, particularly series of anilines and phenols. To accommodate these two series enhanced sigma values (already discussed) were required. Wells (38) classified three broad thermodynamic behaviour types, each of which obeys the Hammett free energy relationship. Ritchie and Sager (69) also set up three exclusive classifications of thermodynamic behaviour. Their first two classes are incorporated in Wells' system and obey the Hammett equation but their third class does not obey the Hammett equation. The four broad classifications are:

(i) **Isoentropic Series:** where there is no change in entropy with substituent, \( \left( \frac{dS}{d\sigma} \right)_T = 0 \).

(ii) **Isoequilibrium Series:** $\Delta H$ and $\Delta S$ are linearly related by the compensation effect,

\[
\Delta H = \Delta H_o + \rho \cdot \Delta S.
\]

$\Delta H_o$ is the intercept of the $\Delta H - \Delta S$ plot. It is independent
of the substituent and has no physical significance. \( \beta \) is the slope of the isoequilibrium line.

(iii) **Random Series:** \( \Delta H \) and \( \Delta S \) vary apparently independently. As for classes (i) and (ii), this class also obeys the Hammett equation.

(iv) Non-obedience to the Hammett equation, but the series is an isoequilibrium one.

Classification (iii) has been thought by Ritchie and Sager\(^{(69)}\) to be the general rule for linear free energy correlations. They arrived at this conclusion after surveying much of the information available to them. Graphs were necessary to determine the correct classification for the present series of 4-substituted 2,6-dimethylphenols.

Everett and Wynne-Jones\(^{(70)}\) proposed that \( \Delta G, \Delta H \) and \( \Delta S \) at any temperature may be regarded as functions of \( \Delta H_o, T \Delta S_o \) and \( \Delta C_{po} \) (each at absolute temperature). Laidler\(^{(71)}\) put forward that polar substituent effects influences \( \Delta H_o \) only and leaves \( \Delta S \) unchanged. They preserve any additivity in \( \Delta G \) and \( \Delta H \). Steric and solvent effects influence both \( \Delta H \) and \( \Delta S \) in a compensating fashion. Such influences preserve additivity in \( \Delta G \) but that of \( \Delta H \) and \( \Delta S \) is lost. Laidler relates additivity to the prediction of the thermodynamic quantities for di-substituted compounds from the changes produced when single substituents are introduced separately.
FIGURE 6

CORRELATION OF ENTROPY WITH SUBSTITUENT

-ΔS (cal. deg.mole⁻¹)

4-SUBSTITUTED 2,6 DIMETHYLPHENOLS

4-SUBSTITUTED PHENOLS.
Fig. 6 shows that the entropy is dependent upon the substituent for the present series as well as the 4-substituted phenols. As \( \frac{dS}{d\sigma} \bigg|_{T} \neq 0 \) we conclude that the series do not fall into category (i). Also from Fig. 6 we see a general trend to higher \( \Delta S \) values (i.e. smaller \( -\Delta S \)) with increasing sigma values. This was to be expected as the need for solvation of the phenolate oxygen atom was considered (ch. 3) to be lowered by the delocalisation of the negative charge. The increase in \( \Delta S \) with sigma indicates greater motion and less solvation of those phenoxide ions with substituents capable of direct conjugation with the functional center.

Bolton and co-workers\(^{(52)}\) found that for para-substituted phenols the substituent effects appear to be dominated by entropy changes. This was indicated by a reasonably linear correlation of \( \Delta S_{25} \) with \( \sigma^n \) parameters\(^{(72)}\), which gave greater linearity than the correlation with \( \sigma_p^- \). Since their findings the thermodynamic functions of ionisation of para-hydroxyacetophenone have been determined (c.f. table 7). This was done during the present project. \( \Delta S_{25} \) for this phenol has been plotted against \( \sigma_p^- \) (Fig. 6) along with those entropy values known to Bolton et al. The \( \Delta S - \sigma_p^- \) point for the formyl group lies slightly away from a straight line through the points for the remaining groups. For the acetyl group this divergence is markedly increased and suggests that minor mechanisms other than entropy changes also appear as substituent effects on the ionisation of 4-substituted phenols.
CORRELATION OF ENTHALPY WITH SUBSTITUENT

$\Delta H$ (kCal. mol$^{-1}$)

$\sigma^p$

- 4-SUBSTITUTED 2,6 DIMETHYLPHENOLS
- 4-SUBSTITUTED PHENOLS
In the literature there has been little mention of isoenthalpic reaction series, in which \( \frac{d \Delta H}{d \sigma} \) = 0, hence we would not expect the present series to fall into this category. Fig. 7 shows this expectation to be correct and also verifies that polar effects, arising from inductive and resonance influences, affect the enthalpy. Laidler\(^{71}\) advances the idea that polar effects influence \( \Delta H \) but not \( \Delta S \) or \( \Delta C_p \), thus if only polar effects were involved in the ionisation process both \( \Delta H \) and \( \Delta G \) would be additive and linear free energy relationships would be obtained. Fig. 7 indicates that more than just polar effects are operating.

Classification (ii) is isoequilibrium series. To determine whether the present series lies in this group the enthalpy change was plotted against the entropy change and compared with a similar plot for 4-X phenols (Fig. 8).

If\(^{(69)}\) the free energies for dissociation in solution are strictly additive when \( \Delta H \) and \( \Delta S \) values are not, then this implies \( \Delta G \) is a simpler function than \( \Delta H \) or \( \Delta S \). A linear free energy (\( \Delta G \)) relationship and no such relationship for \( \Delta H \) and \( \Delta S \) implies that the latter functions are affected by factors which leave \( \Delta G \) unchanged. Since \( \Delta G = \Delta H - T \Delta S \), this can only be so if certain factors influence \( \Delta H \) and \( \Delta S \) in a compensating manner, leaving \( \Delta G \) relatively unchanged.

Steric effects arise from the ortho-methyl substituents and their interference on the ionisation of the functional group. All
FIGURE 8

CORRELATION OF ENTHALPY WITH ENTROPY

\[ \Delta H \text{ (Kcal.deg}^{-1}.\text{mole}^{-1}) \]

\[ -\Delta S \text{ (cal.mole}^{-1}.\text{deg}^{-1}) \]

- 4-\( \times \) 2,6 DIMETHYLPHENOLS
- 4-\( \times \) PHENOLS
thermodynamic functions \((\Delta H_o, \Delta S_o, \Delta C_{po})\) are considered to be affected\(^{(69)}\), therefore we expect complicated influences on \(\Delta G, \Delta H\) and \(\Delta S\). The result is that \(\Delta H\) versus \(\Delta S\) is not strictly linear, as is the case for the 4-substituted 2,6-dimethylphenols (Fig.8). We therefore reason that the present phenols do not act as an isoequilibrium series by virtue of the steric hindrance of the ortho-methyl groups.

\[ \Delta H \text{ and } \Delta S \text{ may be affected in a compensating fashion allowing } \Delta G \text{ to be an additive as well as a linear function for anilines and some unhindered phenols}^{(64)}. \]

The reaction series does not fit into classification (iv) because it does obey the Hammett equation. Therefore the conclusion is that the 4-substituted 2,6-dimethylphenols fit classification (iii) in which the enthalpy and entropy changes vary apparently independently (c.f. Fig.8).

Mitton and co-workers\(^{(26)}\) propose that a lack of regularity in \(\Delta S\) or \(\Delta H\) with substituent (Figs.4 and 5 respectively) and no relation in a plot of \(\Delta H\) against \(\Delta S\) (Fig.8) may be taken as an indication that more than a single interaction mechanism is contributing to the change in enthalpy and entropy of ionisation.

The entropies of ionisation can largely be explained in terms of the binding of water by the phenoxide ion produced by the reaction. The presence of the 2,6-dimethyl substitution introduces steric restriction to solvation near the functional group of the phenol.
The factors caused by the requirements of the methyl groups are dependent on the charge density of the phenolate oxygen atom. They become less significant with the increasing electron-withdrawing ability of the 4-substituent. Influences of the 4-substituent were found to be more important in the present series than in the unhindered phenols.

Hepler's theories for unhindered phenols in water suggest that the free energies of ionisation are largely determined by internal enthalpy changes and are only slightly affected by the compensating enthalpy and entropy changes caused by solute-solvent interactions. This cannot be so for the hindered phenols and it is concluded that solute-solvent interactions play an important part in determining the acidity \( pK_a \) of the hindered phenols.
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   (h) 194.


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ACKNOWLEDGEMENTS

The author wishes to thank his supervisor, Dr. J. Ellis, for suggesting the general outline and procedure of this project and for his guidance and discussion throughout. He would also like to express his appreciation to other members of the academic staff, in particular Mr. F.M. Hall, and research students of the Wollongong University College Chemistry Department for their help and advice. Gratitude is also expressed to the technical staff for their assistance.

The author is indeed grateful to his friends whose patience and assistance have made possible the final written work.

John R. Ridgeon