Polar Substituent Effects and the Ionization of Acids

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1 Introduction

Substituent effects on ionization of acids have long been investigated because of direct interest in the acidities of various compounds and also because of interest in sometimes elusive relationships between structure and reactivity. Arrhenius, Ostwald, van't Hoff, and other early investigators were primarily concerned with establishing and applying the principles of chemical equilibrium to acid ionizations (and other reactions) and therefore only incidentally investigated what we now call substituent effects. Following these pioneers were Vorländer (1902), Wegscheider (1902), Flürscheim (1909–1910), Derick (1911), and others who were explicitly concerned with substituent effects. Contributions of these early workers have been reviewed by Branch and Calvin,[1] Ingold,[2] and Hammett.[3]

Hammett[3] has described developments leading to what we now call physical organic chemistry in terms of gradual rejection of six obsessively held convictions, including the belief that 'there cannot possibly under any conditions be any relation between the rates of a group of reactions and the equilibria of the same group.' He also noted that the conviction that 'entropy effects can be neglected in problems of structure and reactivity' is still not quite dead. Investigations of acidities of series of related acids (such as substituted benzoic acids) and rates of reactions involving these acids or related compounds, led Brønsted and Pederson (1924), Pfluger and Hammett (1933), and especially Burckhardt (1935) and Hammett (1935) to recognize the ubiquity of relationships between equilibria and rates. Burckhardt (1935) and Hammett (1935) found 'a whole flock of linear free energy relationships' that were later summarized by Hammett[4] in the form of the rho-sigma equation that we now call the Hammett equation.

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[1] G. E. K. Branch and M. Calvin, 'The Theory of Organic Chemistry', Prentice-Hall, New York, 1941.

[2] C. K. Ingold, 'Structure and Mechanism in Organic Chemistry', 2nd edn., Cornell University Press, Ithaca, 1969.

[3] L. P. Hammett, *J. Chem. Educ.*, 1966, **43**, 464.

[4] L. P. Hammett, 'Physical Organic Chemistry', McGraw-Hill, New York, 1940.

Although Hammett has correctly emphasized the empirical basis for the rho-sigma linear free energy relationship, it has also proven worthwhile to interpret the empirical values of rho and sigma parameters in terms of properties of the solvent and various reacting species. These interpretations are implicitly or occasionally explicitly based on some theoretical justification for the empirical success of the Hammett equation. One fruitful approach that we describe has evolved from experimental investigation and theoretical consideration of the thermodynamics of ionization of acids.

Many interpretations of substituent effects on chemical reactivity as specifically illustrated by 'acidity' are based on pK_a or free energy of ionization values, which have been traditionally interpreted in terms of various polar and steric effects. In most discussions of substituent effects on chemical reactivity in terms of these classical concepts, the situation has been implicitly reduced to consideration of the reacting molecules and ions as isolated species. In this review we demonstrate that substituent effects on the ionization of acids can only be understood when we consider the reaction environment together with the 'internal' polar and steric effects of substituents. For this demonstration it is necessary to consider enthalpy and entropy effects as well as the more commonly considered free energies derived directly from pK_a values.

2 Thermodynamics of Ionization

Since principles of thermodynamics that are applicable to reactions in solution have been developed in many texts, we merely summarize the results.

The Gibbs free energy (relevant to systems maintained at constant pressure) is related to the enthalpy (heat) and entropy by

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{1}$$

in which the superscript zero indicates that the thermodynamic functions apply to species in some standard state. All quantities cited in this review refer to the hypothetical one molal standard state that is used in compilations[5,6] and defined clearly by King.[7] The standard free energy change associated with a reaction is related to the equilibrium constant by

$$\Delta G^\circ = -RT\ln K \tag{2}$$

These equilibrium constants must be calculated in terms of activities based on molalities in order to be consistent with the standard states for the thermodynamic functions in equation (1).

The variation of the equilibrium constant with temperature is given by

$$\mathrm{d}\ln K/\mathrm{d}T = \Delta H^\circ/RT^2 \tag{3}$$

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[5] R. M. Izatt and J. J. Christensen, 'Handbook of Biochemistry', ed. H. A. Sober, The Chemical Rubber Co., Cleveland, 1968.

[6] J. W. Larson and L. G. Hepler, 'Solute–Solvent Interactions', eds. J. F. Coetzee and C. D. Ritchie, Marcel Dekker, New York, 1969.

[7] E. J. King, 'Acid–Base Equilibria', Pergamon, New York, 1965.

and that of the enthalpy or heat of reaction by

$$\mathrm{d}\Delta H^\circ/\mathrm{d}T = \Delta C_p^\circ \tag{4}$$

Thus, if values for the equilibrium constant at several temperatures are available, successive differentiations yield values for ΔH° and ΔC_p°. Further use of equations (1) and (2) permits evaluation of ΔG° and ΔS°. Procedures for these calculations and uncertainties associated with them have been reviewed.[6,8] Conversely, if one has values for K and ΔH° at one temperature and for ΔC_p° (often nearly constant) over the temperature range of interest, it is possible to calculate the other thermodynamic functions over the same range of temperature.

To represent ionisation of an acid in aqueous solution we write

$$\mathrm{HA}^z(\mathrm{aq}) = \mathrm{H}^+(\mathrm{aq}) + \mathrm{A}^{z-1}(\mathrm{aq}) \tag{5}$$

for which we have thermodynamic functions represented by K_{HA}, $\Delta G^\circ_{\mathrm{HA}}$, *etc.* It is useful to compare these functions for HA with those for a reference acid HR in terms of the proton transfer reaction:

$$\mathrm{HA}^z(\mathrm{aq}) + \mathrm{R}^{z-1}(\mathrm{aq}) = \mathrm{A}^{z-1}(\mathrm{aq}) + \mathrm{HR}^z(\mathrm{aq}) \tag{6}$$

Thermodynamic functions for (6) are obtained as

$$K_s = K_{\mathrm{HA}}/K_{\mathrm{HR}} \tag{7}$$

and

$$\delta\Delta X^\circ = \Delta X^\circ_{\mathrm{HA}} - \Delta X^\circ_{\mathrm{HR}} \tag{8}$$

We now turn to general discussion of substituent effects represented by K_s and the related thermodynamic functions represented by $\delta\Delta X^\circ$. The next section of this review is devoted to applications of these general principles to specific acids.

The best known and most widely used correlation of substituent effects is the Hammett equation that we write as

$$\log K_s = \rho\sigma \tag{9}$$

The constant σ is intended to depend only on the substituent, while the parameter ρ depends on the reaction, solvent, and temperature. Differentiation of (9) with respect to temperature leads[6,9] to

$$\delta\Delta H^\circ = [2{\cdot}3RT^2(\mathrm{d}\rho/\mathrm{d}T)]\sigma = -(\mathrm{dln}\rho/\mathrm{dln}T)\delta\Delta G^\circ \tag{10}$$

and

$$\delta\Delta S^\circ = 2{\cdot}3R[\rho + T(\mathrm{d}\rho/\mathrm{d}T)]\sigma = -[(1/T) + (\mathrm{dln}\rho/\mathrm{d}T)]\delta\Delta G^\circ \tag{11}$$

Further differentiation leads to $\delta\Delta C_p^\circ$ proportional to $\delta\Delta S^\circ$. Thermodynamic

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[8] P. D. Bolton, *J. Chem. Educ.*, 1970, **47**, 638.

[9] J. W. Larson and L. G. Hepler, *J. Org. Chem.*, 1968, **33**, 3961. Note that eq. 17 should be printed as a fraction that reduces to ~0/0.

data[5,6] for ionisation of many acids support the predicted proportionalities. On the other hand, there are many acids for which the Hammett equation is successful in correlating free energies (equilibrium constants or rate constants), but which do not exhibit the other predicted proportionalities. One problem we therefore face is explaining why the Hammett equation is more general than 'it ought to be'.

Hammett and others[10,11] recognised long ago that it is useful to interpret the ionisation of acids in terms of temperature dependent properties of the solvent and temperature independent properties of the solute species. Most earlier investigations were based on electrostatic calculations and some particular algebraic representation of the dielectric constant of the solvent as a function of temperature, but we now find it more useful to follow the dichotomized enthalpy–entropy approach suggested by Hepler and O'Hara[12] and extended in later papers.

We now explicitly consider the thermodynamic functions to be associated with substituent effects in terms of

$$\delta \Delta H^\circ = \delta \Delta H_{\mathrm{int}} + \delta \Delta H_{\mathrm{env}} \tag{12}$$

and

$$\delta \Delta S^\circ = \delta \Delta S_{\mathrm{int}} + \delta \Delta S_{\mathrm{env}} \tag{13}$$

The subscripts int and env are used to indicate 'internal' and 'environmental' contributions to the total thermodynamic functions for substituent effects represented by the symmetrical reaction (6). As King[7] has clearly written:

'*Internal effects* are those intrinsic to the molecules and ions of the acid and base. *Environmental effects* are those which result from interaction of the molecules of the acid and base with the solvent.'

Several investigations[6,9,12,13] have shown that $\delta \Delta S_{\mathrm{int}} \simeq 0$ for most symmetrical reactions of type (6) and have suggested that $\delta \Delta H_{\mathrm{env}}$ is proportional to $\delta \Delta S_{\mathrm{env}}$ as indicated by

$$\delta \Delta H_{\mathrm{env}} = \beta_{\mathrm{e}} \delta \Delta S_{\mathrm{env}} = \beta_{\mathrm{e}} \delta \Delta S^\circ \tag{14}$$

Combination of equations leads to

$$\delta \Delta G^\circ = \delta \Delta H_{\mathrm{int}} + (\beta_{\mathrm{e}} - T) \delta \Delta S^\circ \tag{15}$$

Evidence from several investigations[12–18] indicates that $\beta_{\mathrm{e}} \simeq 300$ K for aqueous

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[10] E. C. Baughan, *J. Chem. Phys.*, 1939, **7**, 951.

[11] R. W. Gurney, 'Ionic Processes in Solution', McGraw-Hill, New York, 1953; and Dover, New York, 1962.

[12] L. G. Hepler and W. F. O'Hara, *J. Phys. Chem.*, 1961, **65**, 811.

[13] L. G. Hepler, *J. Amer. Chem. Soc.*, 1963, **85**, 3089.

[14] M. G. Evans and M. Polanyi, *Trans. Faraday Soc.*, 1936, **32**, 1333.

[15] D. J. G. Ives and P. D. Marsden, *J. Chem. Soc.*, 1965, 649.

[16] C. D. Ritchie and W. F. Sager, 'Progress in Physical Organic Chemistry', Interscience, New York, 1964, Vol. 2.

[17] P. D. Bolton, F. M. Hall, and J. Kudrynski, *Austral. J. Chem.*, 1968, **21**, 1541.

[18] P. D. Bolton and F. M. Hall, *J. Chem. Soc.* (*B*), 1969, 259.

solutions near room temperature and more generally that $\beta_e \cong T$. We therefore obtain

$$\delta\Delta G^\circ \cong \delta\Delta H_{\text{int}} \qquad (16)$$

from (15) and then relate (16) to the Hammett equation to obtain

$$\rho\sigma = -\delta\Delta H_{\text{int}}/2{\cdot}3RT = (C/2{\cdot}3RT)(-\delta\Delta H_{\text{int}}/C) \qquad (17)$$

in which we identify $(C/2{\cdot}3RT)$ with ρ and $(-\delta\Delta H_{\text{int}}/C)$ with σ.

Data[19] confirm that ρ varies linearly with $1/T$ for most reactions, and it has also been found that $\delta\Delta H_{\text{int}}$ values calculated from $\delta\Delta H_{\text{int}} = \delta\Delta H^\circ - \beta_e\,\delta\Delta S^\circ$ with $\beta_e \cong T$ are proportional to σ values. This latter proportionality is no surprise, since σ values are defined in terms of $\delta\Delta G^\circ$ values and we have $\delta\Delta G^\circ \cong \delta\Delta H_{\text{int}}$ in (16).

This treatment (eq. 12—17) is useful in that it shows how compensation of $\delta\Delta H_{\text{env}}$ and $T\delta\Delta S_{\text{env}}$ with $\beta_e \cong T$ leads to $\delta\Delta G_{\text{env}} \cong 0$ and thence to (16) and the Hammett equation. There are, however, deficiencies. If we have nearly complete compensation so that $\delta\Delta G_{\text{env}} \cong 0$, it follows that ρ should be independent of the solvent, which is untrue.[19] Furthermore, differentiation of (16) as an equality leads to $\delta\Delta S^\circ = 0$, which is not in accord with (11) from the Hammett equation or with many entropies of ionization.[5,6]

The relationship between $\delta\Delta H_{\text{env}}$ and $\delta\Delta S_{\text{env}}$, approximated by (14) with the 'environmental' parameter β_e, should ultimately be described in terms of details of interactions between solutes and solvent, which in turn involves structures of the molecules. Since ΔH_{int} values are also related to structures of solute species, it has been suggested[6,9] that the relationship between $\delta\Delta H_{\text{env}}$ and $\delta\Delta S_{\text{env}} \cong \delta\Delta S^\circ$ and consequent incomplete compensation can be represented by

$$\delta\Delta H_{\text{env}} - \beta_e\delta\Delta S^\circ = \gamma\delta\Delta H_{\text{int}} \qquad (18)$$

in which γ is a parameter that depends on the solvent.

We now proceed as before to obtain the following:

$$\delta\Delta G^\circ = \delta\Delta H_{\text{int}}(1+\gamma) + (\beta_e - T)\,\delta\Delta S^\circ \qquad (19)$$

$$\delta\Delta G^\circ \cong \delta\Delta H_{\text{int}}(1+\gamma) \qquad (20)$$

$$\rho\sigma = [C(1+\gamma)/2{\cdot}3RT](-\delta\Delta H_{\text{int}}/C) \qquad (21)$$

which now properly predicts the $1/T$ dependence of ρ and allows ρ to depend on the solvent. Differentiation of (20) as an equality leads[6,9] to proportionalities similar to (10) and (11) already obtained from the Hammett equation. As noted before, data for many (not all) acids are in accord with these predicted proportionalities, which can also be derived from electrostatic models. Further differentiation also leads[6,9] to

$$\delta\Delta C_p{}^\circ = \delta\Delta S^\circ\,[\mathrm{d}\beta_e/\mathrm{d}T) - 1]/[1 - (\beta_e/T)] \qquad (22)$$

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[19] P. R. Wells, *Chem. Rev.*, 1963, **63**, 171.

Since $\beta_e \cong T$, the terms in brackets are both close to zero and we expect no well-defined relationship between $\delta\Delta C_p°$ and $\delta\Delta S°$. Bell[20] has shown that an electrostatic model leads to a contrary prediction that $\delta\Delta C_p°$ should be proportional to $\delta\Delta S°$ and has also noted that 'there is no sign of such regularity'.

This most recent treatment (equations 18—22) is successful in several ways, which we summarize as follows. In addition to the general linear free energy relationship that is consistent with the Hammett equation, we also find derived proportionalities of thermodynamic quantities similar to equations (10 and 11) from the Hammett equation and can account for both the $1/T$ and solvent dependence of ρ. This treatment also accounts for the absence of general correlation between $\delta\Delta C_p°$ and $\delta\Delta S°$ and is in this sense superior to the Hammett equation and electrostatic models. In combination with the work of Ives and Marsden,[15] this treatment probably provides the best available understanding of (partial) compensation of enthalpies and entropies of ionization. And for purposes of much of the rest of this review we also have equation (20) as justification for the useful idea that $\delta\Delta G°$ values (and thence δpK_a values) are proportional to the $\delta\Delta H_{int}$ values that are most directly pertinent to understanding the connection between structure and reactivity in relation to substituent effects.

As King[7] has pointed out, it is difficult for approximate relationships (such as the Hammett equation or our equation 20) to stand differentiation. It is therefore not surprising that there are specific exceptions to the general correlations that are predicted and often observed involving enthalpies and entropies. Although we are presently able to account for many of these 'deviant' entropies and can use entropy data to obtain useful information, there is still need for improvements in the theory. It may be that the most fruitful approach will involve application of the methods of Leffler and Grunwald[21] to the approach described here. There is also the problem of obtaining better understanding of the parameter γ, which can be approached by way of thermodynamic data for reactions of type (6) in different solvent systems.

It should be noted that the 'environmental' proportionality constant β_e used here (formerly represented by b or β) is not generally equal to the 'isokinetic' or 'isoequilibrium' temperature β (which should perhaps be represented by β_i) that has been discussed by Leffler and Grunwald.[21] Relationships between β_e, β_i, and the temperature dependence of ρ are discussed elsewhere.[22]

3 Polar Effects on Free Energies of Ionization

Polar effects are usually sub-divided into inductive, conjugative, and hyperconjugative effects. We shall regard inductive effects as displacements of σ-electrons, caused by different electronegativities of the atoms involved. Electron-attracting substituents are denoted by $-I$, while $+I$ substituents are those which release electron density to the reaction centre. Conjugative (also called resonance

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[20] R. P. Bell, 'The Proton in Chemistry', Cornell University Press, Ithaca, 1959.

[21] J. E. Leffler and E. Grunwald, 'Rates and Equilibria of Organic Reactions', J. Wiley and Sons, Inc., New York, 1963.

[22] L. G. Hepler, *Canad. J. Chem.*, in the press.

or mesomeric) effects are those polar effects arising from the interaction and linkage of π-electron systems within the molecule and the resulting variations in electron density. They are, therefore, expected to be important only when both the reaction centre and the substituent affecting it have a π-electron system or available p-electrons or orbitals, so that conjugation between the two is possible. We follow common practice in using the abbreviation 'R effect' with the convention that a $+R$ substituent is one that releases π-electron density and a $-R$ substituent withdraws electron density from the system.

It has long been recognized that hydrogen atoms bonded to carbon atoms *alpha* to a π-electron system often appear to have a particular (small) stabilizing effect. An alternative expression of this observation is to say that alkyl groups having such hydrogen atoms appear to show a small $+R$ effect although they have no available p- or π-electrons. Because these hyperconjugative effects are small, it is only in favourable cases that any reasonable attempt can be made to separate them from other larger substituent effects.

We now turn to consideration of free energies of ionization of particular acids chosen to illustrate the various effects discussed above. Except in cases where the substituent is close to the reaction centre and can interact significantly through the solvent (in contrast to 'through the bonds' inductive effect interactions), all of these effects are proportional to what we have called $\delta\Delta H_{\mathrm{int}}$. It is worth emphasizing once again that it is because of 'compensation' referred to earlier that we have these polar substituent effects and $\delta\Delta H_{\mathrm{int}}$ both proportional to $\delta\Delta G^\circ$ as in equation (20), and thence also proportional to $\delta \mathrm{p}K_{\mathrm{a}}$. Data for all of our examples are taken from recent compilations,[5,6] except where other references are explicitly cited.

Clear illustrations of inductive effects are provided by certain acids having charged substituents. A positively-charged substituent is expected to exert a powerful $-I$ effect and is therefore an acid-strengthening group that decreases $\mathrm{p}K_{\mathrm{a}}$. Conversely, negatively-charged substituents exert a $+I$ effect and cause an increase in $\mathrm{p}K_{\mathrm{a}}$.

Examples to support and extend this general argument are provided by the $\mathrm{p}K_{\mathrm{a}}$ values in Table 1, which exhibit the decreases in $\mathrm{p}K_{\mathrm{a}}$ predicted for positively-charged substituents. Because of the localized character of σ-electrons, inductive

Table 1 *Thermodynamic data* (25 °C) *for ionization of amino-acids relative to acetic acid*

Acid	$\mathrm{p}K_{\mathrm{a}}$	$\delta\Delta G^\circ$ kcal mol^{-1}	$\delta\Delta H^\circ$ kcal mol^{-1}	$\delta\Delta S^\circ$ cal deg^{-1} mol^{-1}
$MeCO_2H$	4·76	0	0	0
$^+H_3NCH_2CO_2H$	2·35	−3·28	1·07	14·5
$^+H_3N(CH_2)_2CO_2H$	3·55	−1·65	1·16	9·4
$^+H_3N(CH_2)_3CO_2H$	4·03	−0·99	0·50	5·0
$^+H_3N(CH_2)_4CO_2H$	4·23	−0·72	0·26	3·3
$^+H_3N(CH_2)_5CO_2H$	4·37	−0·53	0·10	2·1

effects diminish considerably with increased distance of separation of substituent and reaction centre, as shown by the pK_a values given in Table 1. It should be noted that the $\delta\Delta G°$, $\delta\Delta H°$, and $\delta\Delta S°$ values in Table 1 also show a steady diminution and converge toward zero as expected when the $^+NH_3$ group is moved further from the reaction centre.

Ionization constants for aliphatic carboxylic acids with negatively-charged substituents (such as $^-O_2SeRCO_2H$) are in accord with the expected increase in pK_a accompanying a $+I$ effect.

In the case of the amino-carboxylic acids considered above, we have examples of one kind of substituent effect being so much more powerful than any others that it largely swamps these others, thus permitting us to interpret changes in pK_a values in terms of the single large inductive effect. In many other cases the total substituent effect that is observed must be attributed to complex combinations of two or more effects of comparable magnitude. Therefore it is often necessary to 'isolate' the effects of particular interest by means of careful choices of pairs of acids whose thermodynamic functions are to be compared.

Chloroacetic acid (pK_a = 2·86) is a considerably stronger acid in aqueous solution than is acetic acid (pK_a = 4·76). A traditional explanation is identical with that given above for charged substituents in that the $-I$ inductive effect of chlorine relative to the hydrogen it has replaced makes it 'easier' for the $-CO_2H$ reaction centre to ionise. Although this explanation is surely roughly correct, more careful analysis suggests that the comparison of chloroacetic acid with acetic acid may not be the best one for isolation of the inductive effect of present interest. Conjugative effects are properly considered to be of negligible importance in this case, but substitution of chlorine for hydrogen in acetic acid changes the number of α-hydrogen atoms and may also lead to a significant steric effect. Thus the observed change in pK_a, is, in principle, due to a combination of inductive, steric, and hyperconjugative influences.

We therefore compare chloroacetic acid with propionic acid, whereby we consider substitution of chlorine for a methyl group. In this case there is no change in number of α-hydrogen atoms and thence no concern with hyperconjugative effects. Because Me and Cl have nearly the same van der Waals radii, steric effects should make no substantial contribution to the difference in pK_a values for these two acids. We are therefore left with only the inductive effect as significant contributor to the difference between these pK_a values. Similarly, the difference between pK_a values for isobutyric acid and dichloroacetic acid should be almost entirely due to changes in inductive effect associated with replacing two Me by two Cl.

Qualitative conclusions concerning the I effect to be associated with the Cl substituent are seen to be the same from comparison of the pK_a values (Table 2) for $ClCH_2CO_2H$ and Cl_2CHCO_2H with acetic acid or the other suggested reference acids chosen to eliminate concern with steric and hyperconjugative effects. On the other hand, the magnitudes of the substituent effects and consequent tests of additivity relations do depend on the choice of reference acid. It must also be recognized that the price we pay for eliminating steric and hyper-

Table 2 *Thermodynamic data* (25 °C) *for ionization of chloroacetic acids and reference acids*

Acid	pK_a	ΔG° kcal mol^{-1}	ΔH° kcal mol^{-1}	ΔS° cal deg^{-1} mol^{-1}
$MeCO_2H$	4·76	6·49	−0·10	−22·1
$MeCH_2CO_2H$	4·88	6·67	−0·16	−22·9
$ClCH_2CO_2H$	2·87	3·90	−1·14	−16·9
Me_2CHCO_2H	4·85	6·61	−0·78	−24·8
Cl_2CHCO_2H	1·36[a]	1·86	−1·8[a]	−12[a]

[a] Values given here, which differ significantly from those reported earlier,[6] have been calculated from results of J. L. Kurz and J. M. Farrar, *J. Amer. Chem. Soc.*, 1969, **91**, 6057.

conjugative effects by comparison of chloroacetic acid with propionic acid is that we obtain information about the *I* effect of chlorine relative to methyl rather than relative to hydrogen.

Further application of this line of reasoning illustrates the difficulty in understanding small changes in pK_a or other thermodynamic properties. For example, how much of the observed 0·12 difference in pK_a values for acetic and propionic acids is due to the small inductive effect of methyl as compared to hydrogen, and how much is due to small steric and hyperconjugative effects? We must also recognize that the small difference in pK_a values for these and many other acids is somewhat temperature dependent and that the important relationship in (20) contains $\cong$ rather than $=$. As Bell[20] and others have warned, it is necessary to be very cautious in interpreting small differences in pK_a values.

In the aromatic acids the rigidity of the benzene ring ensures that *meta*- and *para*-sustituents are held sufficiently far away from the reaction centre that steric effects are generally of little importance. Thus, the effects of such substituents on the ionization of aromatic acids should be indicative only of polar influences. Here, however, unlike the aliphatic acids considered earlier, we expect to find both inductive and conjugative effects. Furthermore, we can expect to find marked variations in entropies of ionisation as a result of the considerable variations in distribution of charge density between substituents and reaction centres. In spite of these variations in ΔS° that are indicative of differences in solute–solvent interactions, we can still confidently relate substantial *I* and *R* effects on $\delta\Delta H_{\text{int}}$ to $\delta\Delta G^\circ$ and δpK_a values because of the compensation that led to (20).

In Table 3 we list pK_a values and other thermodynamic functions for ionization of phenol and some substituted phenols in which there are charged substituents. It is easily seen that the NMe_3^+ substituent leads to the increased ionization and smaller pK_a that is expected to accompany the $-I$ effect. Further, the effect is larger for the *meta*-substituent than it is for the *para*-substituent that is more distant from the reaction centre. We also see that there is no simple, easily interpreted relationship between ΔH° values and substituent effects.

The pK_a values (Table 3) for SO_3^- and CO_2^- substituted phenols present us

Table 3 *Thermodynamic data* (25 °C) *for ionization of aqueous phenols* (*charged substituents*)

Substituent	pK_a	$\Delta G°$ kcal mol^{-1}	$\Delta H°$ kcal mol^{-1}	$\Delta S°$ cal deg^{-1} mol^{-1}
H (phenol)	9·97	13·60	5·48	−27·2
m-NMe_3^+	8·06	10·99	5·93	−17·0
p-NMe_3^+	8·35	11·39	5·30	−20·4
p-SO_3^-	9·06	12·36	4·04	−27·9
p-CO_2^-	9·23	12·62	3·4	−31

with a new problem. Negatively-charged substituents are expected to *increase* pK_a values as a result of their $+I$ effects, but Table 3 shows that these substituents actually *decrease* pK_a values by fairly substantial amounts. We can only conclude that the $+I$ effects of these substituents are overcome by some larger effect that is acid strengthening. As we shall see in the next section, the entropies of ionization provide support for the suggestion that there are in fact substantial $-R$ effects that are responsible for the net acid strengthening effect of these substituents.

Ionization data for several other substituted phenols are given in Table 4.

Table 4 *Thermodynamic data* (25 °C) *for ionization of aqueous phenols* (*uncharged substituents*)

Substituent	pK_a	$\Delta G°$ kcal mol^{-1}	$\Delta H°$ kcal mol^{-1}	$\Delta S°$ cal deg^{-1} mol^{-1}
H (phenol)	9·97	13·60	5·48	−27·2
m-Cl	9·13	12·46	5·3	−24·0
p-Cl	9·41	12·85	5·68	−24·1
m-NO_2	8·35	11·40	4·85	−22·0
p-NO_2	7·15	9·75	4·65	−17·1
m-CN	8·57	11·69	5·04	−22·3
p-CN	7·97	10·87	4·76	−20·5

Data given here are from ref. (6) and P. D. Bolton, F. M. Hall, and I. H. Reece, *J. Chem. Soc.* (*B*), 1967, 709; P. D. Bolton, F. M. Hall, and J. Kudrynski, *Austral. J. Chem.*, 1968, 21, 1541.

The pK_a values are in accord with the expectation that each of these substituents exerts a $-I$ effect and is therefore acid strengthening. For the *p*-Cl substituent this effect is observed to be smaller than for the *m*-Cl substituent as expected for substituents that act largely by way of inductive effects. On the other hand, both *p*-NO_2 and *p*-CN substituents have larger acid-strengthening effects than the corresponding *meta*-substituents. It might therefore be inferred on this basis alone that there are also substantial $-R$ effects to be associated with these latter *para*-substituents. Confirmation of this idea, and some of the original evidence for it, came from the observation that *p*-NO_2 and *p*-CN require 'special' Hammett σ-values for application to phenol (and aniline) as compared to benzoic acid.[19] We shall see in the next section that ΔS° values are also pertinent to this question.

4 Entropies of Ionization

It has already been noted that ΔH° and $\delta\Delta H^\circ$ values are frequently difficult to interpret because these quantities are sums of ΔH_{int} and ΔH_{env} components. On the other hand, ΔG° and pK_a values are relatively easy to interpret because of their being proportional to ΔH_{int} values. Similarly, $\delta\Delta S^\circ$ values can frequently be interpreted in useful fashion because they are generally due almost entirely to differences in solute–solvent interaction that arise largely from variations in charge distributions within solute species.

It has often been stated that the greater conjugative stabilization of the anion of *p*-nitrophenol as compared to the anion of *m*-nitrophenol is sufficient to overcome the greater inductive effect of the *m*-NO_2 substituent and accounts for *p*-nitrophenol being a stronger acid than *m*-nitrophenol. If these 'internal energy' (or ΔH_{int}) effects were all that needed consideration, we might predict that differences in ΔG° and thence pK_a values for ionization of phenol and the nitrophenols would be entirely due to differences in ΔH° values. The data in Table 4 are clearly inconsistent with this simple idea, but can be understood[13] in terms of the dichotomized enthalpy–entropy approach described earlier.

We conclude[13] from the entropies of ionization that the anion of *p*-nitrophenol is less effective than is the anion of *m*-nitrophenol at orienting neighbouring water molecules. The greater orienting effectiveness of the *m*-nitrophenol anion results from a greater localization of the negative charge as compared to the delocalized charge on the *p*-nitrophenol anion, which is entirely consistent with traditional ideas about conjugative stabilization. Similar reasoning is applicable to the entropies of ionization of the cyanophenols.

The proposed $-R$ effects of the *p*-SO_3^- and *p*-CO_2^- substituents would be expected to make the charges on the *p*-SO_3^- and *p*-CO_2^- groups slightly more negative than their formal -1 charge. This 'extra' negative charge contributes more than enough to extra orientation of neighbouring water molecules to balance the decreased orientation near the slightly diminished negative charge on the phenolic oxygen, and thus accounts for the observed ΔS° values being more negative than that for phenol.

Evidence has been presented on both sides of the question as to the possibility of conjugative stabilization and charge delocalisation for *p*-chlorophenol. Because the entropies of ionisation of *p*-chlorophenol and *m*-chlorophenol (Table 4) are nearly identical in contrast to those for the nitro- and cyanophenols, we conclude that the *p*-Cl substituent does not permit greater charge delocalization in the anion than does the *m*-Cl substituent. Thus we also conclude that the *p*-Cl substituent exerts the expected $-I$ effect, with nearly zero R effect.

Earlier considerations[6,7,13,15] of entropies of ionization have contributed to our understanding of electron distributions within solute species, have permitted classification of certain acids as largely zwitterionic in solution, have yielded information about intramolecular hydrogen bonding in some acids, and have contributed to our understanding of ionisation of various protonated amines.

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