Electrophilic Catalysis of Sulphate ($-SO_3^-$) Group Transfer: Hydrolysis of Salicyl Sulphates assisted by Intramolecular Hydrogen Bonding

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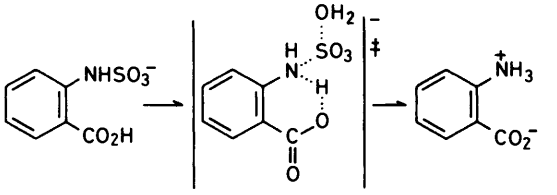
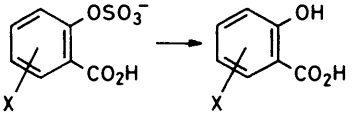
The hydrolysis of substituted salicyl sulphates has been measured over a range of pH values at 70 °C to obtain kinetic parameters for hydronium ion (k_H) and carboxylic acid (k_p) catalysis. A Jaffé treatment of the carboxy-catalysis parameter for a range of nuclear substituents yields ρ_{phenol} 1.51 ; $\rho_{carboxy}$ 0 indicates that the carboxy-function does not ionise on going from the ground- to the transition-state, consistent with hydrogen bonding rather than catalysis through proton transfer. The change in ' effective ' charge on the phenol oxygen on going from the ground- to the transition-state confirms less build up of negative charge than in the uncatalysed hydrolysis of aryl sulphates.

We recently provided substantial evidence that the hydrolysis of 2-carboxyphenylsulphamic acid involves a transition state with considerable proton transfer to the nitrogen from the *ortho*-carboxylic acid [equation (1)] relative to the ground state.[1] It may be argued that proton transfer is not required in the hydrolysis of the analogous salicyl sulphate [equation (2)] studied by Benkovic [2] as the phenolic oxygen should easily bear a negative charge whereas the sulphamic nitrogen is much less basic.[1] The possibility therefore exists that intramolecular catalysis of these analogous reactions takes a different form in each case, namely classical general acid catalysis in the sulphamic acid hydrolysis and electrophilic catalysis in the salicyl sulphate case.

The distinction between proton transfer and electrophilic catalysis by hydrogen bonding (without transfer of a proton) can be made by measuring the effect of substituents on the reaction transmitted through the carboxy-function. The Jaffé [3] approach is followed in this report for intramolecular carboxylic acid-catalysed hydrolysis of substituted salicyl sulphates [equation (2)] and this yields Hammett ρ values for transmission through the carboxy and phenol oxygens. Effective charges [4] on the phenol oxygen may also be estimated and these combine to give a complete charge picture of the reaction path relative to the standard charge change in the ionisation of phenols.



(1)



(2)

Experimental

Materials.—Salicyl sulphates were prepared by the following general procedure taken from Benkovic [2] and Burkhardt: [5] freshly distilled *NN*-dimethylaniline (15 ml) was cooled to 0 °C and chlorosulphonic acid (2.32 ml) slowly added with stirring to maintain the temperature below 10 °C. After addition, the mixture was allowed to warm to 35 °C slowly and then the appropriate salicylic acid (25 mmol) in *NN*-dimethylaniline (15 ml) added. The mixture was stirred for 2 h and then KOH (1.4 g) in water (20 ml; cold) was added to the cooled mixture. The product was extracted three times with ether and the pH adjusted to 1 with concentrated $HClO_4$. The acid solution was extracted with ether, filtered, and the aqueous layer basified with dilute potassium hydroxide solution to pH 8, extracted further with ether, filtered, and evaporated to yield the required dipotassium sulphate. Recrystallisation from water gave products with analyses agreeing with the proposed structures (Table 1) and m.p.s were not determined. I.r. (Perkin-Elmer model 297 spectrophotometer) and ^1H n.m.r. spectroscopy of the materials gave spectra consistent with the proposed structures. N.m.r. measurements were carried out on a JEOL 100 MHz instrument by Dr. D. O. Smith.

Buffer components were of analytical reagent grade and water used throughout the investigation was doubly distilled from glass.

Methods.—Kinetics were measured by adding a portion of a solution of the dipotassium salicylate (0.05 ml) to buffer (2.5 ml) in a silica cuvette in the thermostatted cell compartment of a Unicam SP 800 spectrophotometer. The wavelength was scanned during the reaction to determine the optimum wavelength for kinetic studies and rate constants were then measured at a constant wavelength (300—320 nm, see Table 2). The pseudo-first-order rate constants were calculated from plots of $A_t - A_\infty$ *versus* time on two cycle semi-logarithmic graph paper. The pH was measured (at 70 °C) in the cuvette after each kinetic run and the data discarded if the pH differed significantly from that for the stock buffer.

Potentiometric titration of the salicyl sulphates was carried out using a Radiometer pH-titration set comprising a recording titration assembly (REC 61/REA 60), pH-meter (PHM 62), and autoburette (ABU 11). Titration of the sample in 1M-KCl (5 ml) at 70 °C using 0.01M-HCl was corrected by titration of the background and the results fitted to the standard equation (3) where FB is the fraction of the basic form of the acid derived from the titration.

$$pK = pH + \log(1 - FB)/FB \quad (3)$$

Results

The reaction of the salicyl sulphates in HCl and chloroacetate buffers gave the corresponding salicylic acid as judged from the identity of the u.v. spectra of the products with those of

Table 1. Analytical data for dipotassium salicyl sulphates [b]

Substituent	Found (%) C	H	S	Formula	Calc. (%) C	H	S
None	28.3	1.3	10.7	$C_7H_4K_2O_6S$	28.5	1.4	10.9
5-Methyl	30.8	1.8	10.6	$C_8H_6K_2O_6S$	31.2	1.9	10.4
5-Chloro	25.8	0.9	9.4	$C_7H_3ClK_2O_6S$	25.6	0.9	9.7
4-Methoxy	30.0	1.8	10.1	$C_8H_6K_2O_7S$	29.6	1.9	9.9
4-Chloro	25.7	0.9	9.8	$C_7H_3ClK_2O_6S$	25.6	0.9	9.7
5-Bromo	22.9	0.9	8.6	$C_7H_3BrK_2O_6S$	22.6	0.8	8.6
5-Nitro [a]	25.1	1.0	9.3	$C_7H_3NK_2O_8S$	24.8	0.9	9.4
5-Iodo	20.5	0.8	7.7	$C_7H_3IK_2O_6S$	20.3	0.7	7.8

[a] Nitrogen: found 4.4%; calc. 4.1%. [b] Microanalyses were carried out by Mr. A. J. Fassam of this department using a Carlo Erba CHN analyser. Sulphur was analysed by combustion in oxygen followed by barium chloride titration.

Table 2. Hydrolysis of a series of substituted salicyl sulphates [a]

Substituent	λ/nm [b]	N [d]	10^3k_H [f]/ l mol^{-1} s^{-1}	10^4k_p/ s^{-1} [g]	pK [c,e]
None	320	12	7.6	3.1	3.50
5-Methyl	312	12	6.6	1.8	3.55
5-Chloro	312	11	8.5	7.2	3.12
4-Methoxy	317	13	11.5	5.0	3.60
4-Chloro	305	11	12.7	12.0	3.00
5-Bromo	320	13	10.9	7.1	3.15
5-Iodo	320	12	11.5	7.8	3.18
5-Nitro	310	10	50	202	2.85

[a] 70.0 °C, ionic strength maintained at 1M with KCl. [b] Wavelength for kinetics. [c] Thermodynamic pK. [d] Number of data points. [e] Obeys the Hammett equation: pK = $-0.82\sigma + 3.42$ (r 0.930). [f] Obeys the Brönsted equation: log k_H = -0.26pK + 0.46 (r 0.929). [g] The Jaffé plot has a slope 1.51 (ρ_{phenol}) and intercept -9.3×10^{-3} ($\rho_{carboxy}$) with r 0.997.

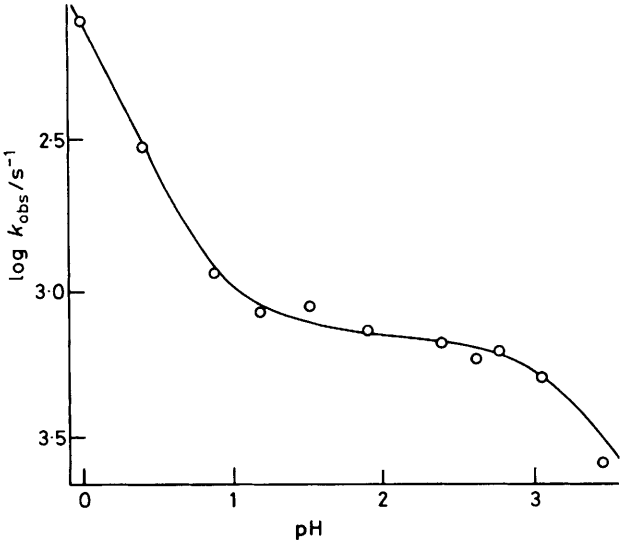


Figure 1. The dependence on pH of the hydrolysis of 5-chlorosalicyl sulphate at 70 °C and 1M ionic strength. The line is theoretical from equation (4) and parameters are from Table 2

authentic samples under the same conditions. Kinetic forms were accurately pseudo-first order up to *ca.* 90% of the total reaction and the rate depended on pH according to equation (4). Rate constants were independent of buffer concentration.

$$k_{obs} = (k_H a_H + k_p)/(1 + K_a/a_H) \quad (4)$$

Since the rate constants are very small at pH values above the pK of the carboxy-group the pK values were not measured kinetically. The thermodynamic pK was utilised to derive k_H and k_p from the data using equation (4). The pH-dependence of the hydrolysis of 5-chlorosalicyl sulphate is illustrated in Figure 1.

A simple Hammett equation correlates the pK of the salicyl sulphates (Table 2). The parameter k_H is analogous to that found by Burkhardt [6] for acid-catalysed hydrolysis of simple substituted phenyl sulphate anions; the Brönsted β_{lg} value for the present esters is 0.26 compared with Burkhardt's value of 0.26 at 48.6 °C and 0.21 at 78.7 °C.[6] The values of k_H are commensurate with Burkhardt's values for the simple esters.[6]

A Jaffé plot [equation (5)] must be used to correlate the parameter k_p as the substituent effect may be transmitted

$$\log k_p^X/k_p^H = \rho_{carboxy}\sigma_{carboxy} + \rho_{phenol}\sigma_{phenol} \quad (5)$$

through the carboxy or phenol oxygen to the reaction centre (the cleaving S–O bond). We may use the Jaffé approach to estimate the influence of carboxy on the reaction centre in this way. Care has to be exercised because a spuriously good Jaffé plot will result if there is a good correlation ($r > 0.900$) between the σ_m and σ_p values of the substituents employed.[3]

Application to the present substituents gives a correlation coefficient of 0.777 between σ_m and σ_p indicating that the results of a Jaffé plot will be significant. Equation (5) takes into account the two pathways for interaction by a particular substituent and the data can be correlated as in Figure 2. The parameters of equation (5) are recorded in Table 2; the value of $\rho_{carboxy}$ is very much less than the error in these measurements and is taken to be effectively zero. We used Hammett σ values in these correlations except that for the 5-nitro-substituent where σ^- is employed; the latter value gives a better correlation and its use is in accord with Burkhardt's finding [6] of a good correlation between k_H and pK of the corresponding phenol in phenyl sulphate hydrolysis. Equation (5) is rearranged so that a plot of $(\log k_p/k_p)/\sigma_{carboxy}$ against $\sigma_{phenol}^-/\sigma_{carboxy}$ is linear with a slope of ρ_{phenol} and intercept of $\rho_{carboxy}$.

Discussion

The Fate of the Proton in Spontaneous Hydrolysis of Salicyl Sulphate Monoanion.—Benkovic [2] showed that the hydrolysis of salicyl sulphate is catalysed by the participation of the *ortho*-carboxy-group whereas the carboxy-group in 4-carboxyphenyl sulphate has no effect on its hydrolysis over the pH range for ionisation of the acidic function. Mechanisms where

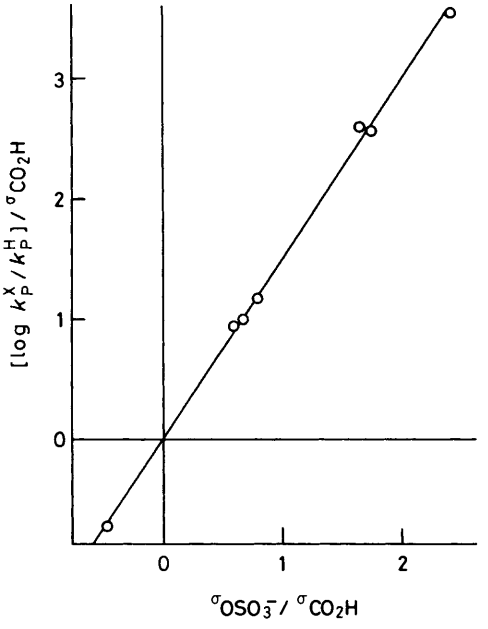
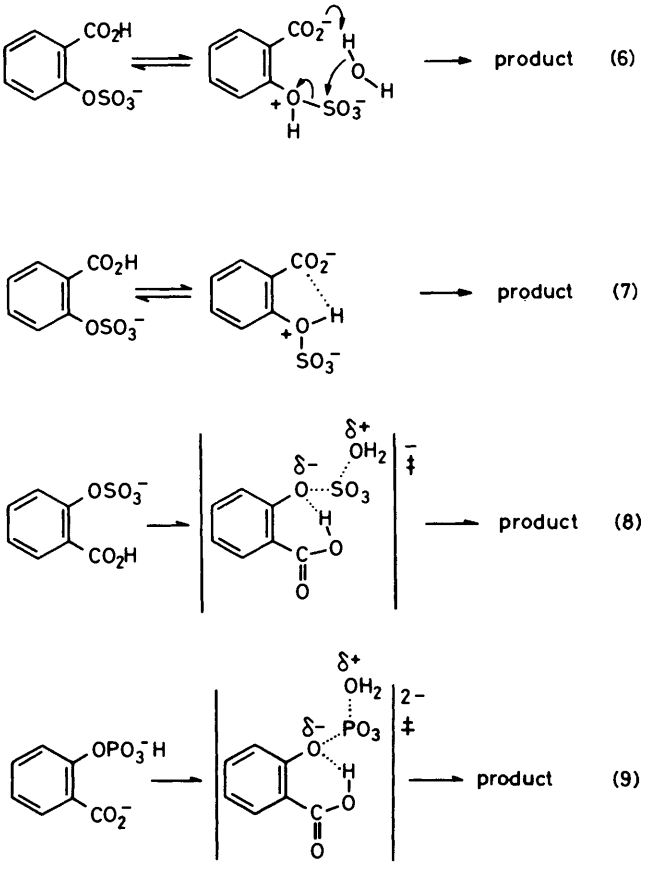


Figure 2. Jaffé plot for the spontaneous hydrolysis of salicyl sulphate monoanions (k_p). Line is theoretical from equation (5) and parameters are from Table 2

the sulphur is transferred to the carboxy-group have been eliminated as major pathways [1] by the observation that hydrolysis in ^{18}O-labelled water leads to salicylic acid with *no* ^{18}O-incorporation in the carboxy-group. Benkovic [2] excluded intramolecular general base catalysis [equation (6)] on the grounds of a low deuterium oxide solvent isotope effect for the plateau rate constant k_p (k_p^H/k_p^D 1.2). Benkovic [2] proposed that the low isotope effect is due to nearly complete proton transfer in the transition state relative to the ground state [equation (7)]. An alternative mechanism is that illustrated in equation (8) where the carboxylic acid stabilises the forming oxyanion by donation of a hydrogen bond. This mechanism can involve practically no transfer of the hydrogen in the transition state yielding little solvent isotope effect and yet still giving rise to effective catalysis. This mechanism has already been discussed by Bromilow and Kirby [7] for the corresponding phosphate hydrolysis.

Substituent effects on the reactivity transmitted through the carboxy-group should be essentially zero in the above formulation [equation (8)] as the bond between the hydrogen and the carboxy-oxygen is not effectively changed in going from ground- to transition-state. The formulation in equation (8) is not able to include solvation in the diagram. Effectively the carboxy-hydrogen changes its solvating agent from solvent water in the ground state to the forming anion in the transition state. This alteration is not likely to be ' seen ' by the substituents through the carboxy-group. Transmission of effects through the phenol oxygen will be more sensitive to solvation at this oxygen and the difference in solvation is ' seen ' by the substituents as shown later.

The mechanism of the catalysis is essentially that for hydrolysis of salicyl phosphate (dianion).[7] Bromilow and Kirby [7] found $\rho_{carboxy}$ −0.99 relative to that for the ionisation of the carboxy-group in salicyl phosphates (ρ −1.01); we find $\rho_{carboxy}$ 0 relative to that for ionisation of the salicyl sulphates (ρ −0.82). The difference in the two systems is traced to the ground states of the two reactions; the salicyl phosphate dianion involves mainly thei .onised carboxy-species so that the progress from ground- to transition-state

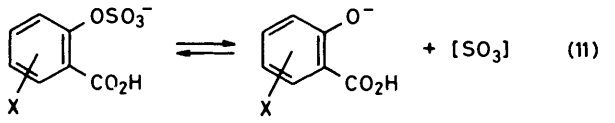


requires an effective transfer of the hydrogen from the phosphorus oxygen to that of the carboxylate [equation (9)]. Bromilow and Kirby [7] indicate a convincing mechanism for this transfer which must lead to a ρ value of *ca.* −1. Reference to equation (8) indicates that the ground state for the k_p parameter involves the proton already residing on the carboxy-group; there is thus no effect of substituent through the carboxy-route.

Effective Charge in the Transition State.—Electronic substituent effects on processes are essentially the manifestation of differences in stabilising effects of substituents on charge changes between two states. The concept of ' effective ' charge was developed to provide an experimental value for quantifying charge changes relative to those in a standard system.[4,8] In the present case we shall consider changes in ' effective ' charge on the phenolic oxygen of salicyl sulphate during its hydrolysis relative to the unit change in charge defined on a phenolic oxygen in the ionisation of phenols. In order to determine the change in effective charge we require the Brönsted β value for the transfer of sulphonate from the sulphate ester and this is known from previous studies from this laboratory.[9] Equation (10) illustrates a general reaction where the SO_3^- group is transferred to a general nucleophilic

$$ArOSO_3^- \underset{k_N}{\overset{k_L}{\rightleftharpoons}} ArO^- + [SO_3] \qquad (10)$$

acceptor. The β_{eq} value for this equilibrium is −1.74 and is independent of acceptor nucleophile. Thus the equilibrium [equation (11)] will have β_{eq} −1.74; although the mono-anionic form of salicyclic acid depicted in equation (11) is not the final product this form is the one produced in the rate-



(11)

controlling step. The β for the forward rate constant (effects transmitted through the phenol) is given by $-\rho_{phenol}/2.23 = -0.68$. The conversion factor 2.23 is the Hammett ρ value for the ionisation of phenols. The Leffler–Grunwald parameter ($\alpha = \beta_F/\beta_{eq} = 0.68/1.74 = 0.39$) is essentially a measure of the progress of the reaction along the reaction co-ordinate from ground- to product-state and the effective charge on the phenol oxygen in the transition state is given by equation (12) where $\varepsilon_{g.s}$, $\varepsilon_{p.s}$, and $\varepsilon_{t.s}$ are the effective charges in ground-

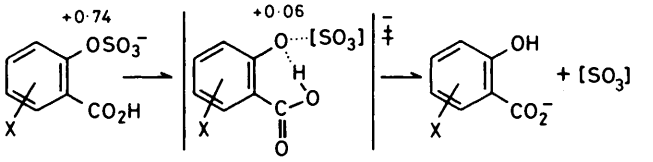
$$\varepsilon_{t.s} = \varepsilon_{g.s} + \alpha(\varepsilon_{p.s} - \varepsilon_{g.s}) = 0.74 - 0.39 \,.\, 1.74 = 0.06 \quad (12)$$

product-, and transition-state relative to the standardising ionisation. The change in effective charge from ground- to transition-state is thus −0.68. This change in effective charge may be compared with the change on the phenolic oxygen in the uncatalysed hydrolysis of the simple substituted mono-anionic aryl sulphates. The Leffler–Grunwald parameter for this reaction (1.2/1.74) requires an effective charge of −0.46 on the phenolic oxygen and a change in effective charge of −1.2. The increased negative charge in the uncatalysed system indicates that in the catalysed the charge is neutralised consistent with electrophilic interaction with the carboxy hydrogen.

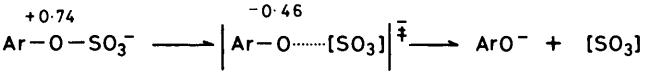
A very much smaller increase in negative charge is seen with proton-catalysed hydrolysis of the monoanion of the aryl sulphates.[6] The β_{lg} indicates that a change in charge of −0.26 occurs and this is fully in agreement with the conclusion of Kice and Anderson [10] of a full protonation of the phenolic oxygen prior to the rate-limiting decomposition. Effective charges are delineated in the Scheme for the above reactions. We have represented the SO_3 atoms in brackets in the transition state structures and also in the equilibrium of equation (11) for simplicity; there is probably bonding between the sulphur and the incoming nucleophile which is in this case water and we do not imply that sulphur trioxide becomes free at any stage.

Engberts and Kirby [11] showed that the proton is almost completely transferred from the carboxy-group to nitrogen in the hydrolysis of 2-carboxybenzenesulphonamides and we indicated that partial proton transfer occurs in the transition state for hydrolysis of 2-carboxyphenylsulphamate.[1] In the present study the lack of proton transfer to the forming phenolate ion is consistent with its being more stable than anilido or amido ion.

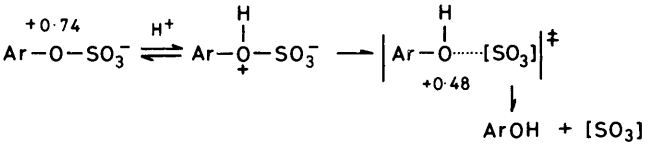
Control of Mechanism in Catalysis by the Carboxy-function.—The nature of the acyl function undergoing transfer determines whether the carboxy-group acts as a nucleophile or base (in its carboxylate ion form) or as an electrophile. Bromilow *et al.*[12] found that dialkyl and diaryl 2-carboxyphenyl phosphates are hydrolysed *via* attack of the carboxylate ion on the phosphorus atom. The hydrolysis of 2-carboxy-*NN*-dimethylbenzenesulphonamides [11] involves initial protonation of the nitrogen by the carboxylic acid followed by nucleophilic attack of the carboxylate on the sulphur. Substituted aspirins hydrolyse through either intramolecular general base catalysis of water attack at the carbonyl centre or through attack of the carboxylate directly.[13] The acyl functions in the above species are not charged and nucleo-



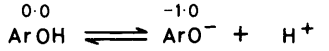
Salicyl sulphate monoanion (13)



Spontaneous hydrolysis of aryl sulphate monoanion (14)



Proton-catalysed hydrolysis of aryl sulphate monoanion (15)



Standardising equilibrium (16)

Scheme. Effective charges in the hydrolysis of some aryl sulphates

philic attack is much more efficient than in sulphate mono-anion or sulphamate [9] hydrolyses. Monophosphate dianion will also be less susceptible to nucleophilic attack on account of the negative charge and for this reason electrophilic catalysis by the carboxy-group is important in these reactions.

Enzymatic Sulphate ($-SO_3^-$) *Group Transfer.*—Reference to the work of Dodgson and his collaborators [14] indicates that the Class I arylsulphatase from *Aspergillus oryzae* has a good dependence of log k_{cat}/K_m on the pK of the leaving phenol for the hydrolysis of nine aryl sulphates (β_{lg} −0.23; r 0.919). Thus there is a change in ' effective ' charge of −0.23 units on the phenol oxygen from ground- to transition-state. This value is less than that for the salicyl sulphate case but approximately the same as that for proton-catalysed hydrolysis of aryl sulphate monoanions.[6] We are not able to discuss the data for the *Aerogenes metalcaligenes* enzyme as log k_{cat}/K_m obeys a non-linear function with the pK of the leaving phenol. The value k_{cat}/K_m is used here as it represents the effective bimolecular rate constant for transition from free enzyme and substrate in the ground- to the transition-state of the rate-limiting step.[14c]

The present results give quantitative data for the change in effective charge on the phenol oxygen in the enzymatic reactions; they are consistent with a considerable electron withdrawal from the oxygen.

We emphasise that the electrophilic nature of the catalysis was qualitatively understood some time ago.[14]

Acknowledgements

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References

1 A. Hopkins and A. Williams, *J. Org. Chem.*, 1982, **47**, 745.
2 S. J. Benkovic, *J. Am. Chem. Soc.*, 1966, **88**, 5511.
3 H. H. Jaffé, (*a*) *Science*, 1953, **118**, 246; (*b*) *J. Am. Chem. Soc.*, 1954, **76**, 4261.
4 See T. Deacon, C. R. Farrar, B. J. Sikkel, and A. Williams, *J. Am. Chem. Soc.*, 1978, **100**, 2525 for a definition of effective charge and references to previous work on this subject.
5 (*a*) G. N. Burkhardt and A. Lapworth, *J. Chem. Soc.*, 1926, 684; (*b*) G. N. Burkhardt, L. Horrex, and D. I. Jenkins, *ibid.*, 1936, 1649.
6 G. N. Burkhardt, W. G. K. Ford, and E. Singleton, *J. Chem. Soc.*, 1936, 17.
7 R. H. Bromilow and A. J. Kirby, *J. Chem. Soc., Perkin Trans. 2*, 1972, 149.
8 W. P. Jencks, *Cold Spring Harbor Symp. Quant. Biol.*, 1972, **36**, 1.
9 (*a*) A. R. Hopkins, R. A. Day, and A. Williams, *J. Am. Chem. Soc.*, 1983, in the press; (*b*) For previous references to this parameter see S. V. Hill, S. Thea, and A. Williams, *J. Chem. Soc., Chem. Commun.*, 1982, 547.
10 J. L. Kice and J. M. Anderson, *J. Am. Chem. Soc.*, 1966, **88**, 5242.
11 T. Graafland, A. Wagenaar, A. J. Kirby, and J. B. F. N. Engberts, *J. Am. Chem. Soc.*, 1979, **101**, 6981.
12 R. H. Bromilow, S. A. Khan, and A. J. Kirby, *J. Chem. Soc. B*, 1971, 1091.
13 A. R. Fersht and A. J. Kirby, *J. Am. Chem. Soc.*, (*a*) 1967, **89**, 4853, 4857; (*b*) 1968, **90**, 5818, 5826.
14 (*a*) K. S. Dodgson, B. Spencer, and K. Williams, *Biochem. J.*, 1956, **64**, 216; (*b*) K. S. Dodgson, D. Robinson, J. N. Suter, B. Spencer, and R. T. Williams, *ibid.*, 1952, **51**, 202; (*c*) A. Williams, *Biochemistry*, 1970, **9**, 3383.

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