JOURNAL OF PHYSICAL ORGANIC CHEMISTRY
J. Phys. Org. Chem. 2004; **17:** 498–506
Published online in Wiley InterScience (www.interscience.wiley.com). DOI: 10.1002/poc.766

Free energy relationships and intramolecular general acid catalysis†,‡

Ian R. Greig and Anthony J. Kirby*

University Chemical Laboratory, University of Cambridge, Cambridge CB2 1EW, UK

Received 1 August 2003; revised 3 September 2003; accepted 3 September 2003

epoc ABSTRACT: Variations in reactivity of substituted salicylic acid derivatives are appraised in the light of the work of Jencks on transition-state structures, variations in transition-state structure and variations in reaction mechanism. The transition states for the intramolecular general acid-catalysed hydrolyses of a variety of compounds derived from salicylic acid are shown to be closely related to those for the corresponding spontaneous hydrolysis reactions of compounds derived from substituted phenols. Free energy relationships are used to estimate the potential benefits of improving intramolecular hydrogen bond geometry in an aqueous environment. Copyright © 2004 John Wiley & Sons, Ltd.

Additional material for this paper is available in Wiley Interscience

KEYWORDS: free energy relationships; transition-state structure; intramolecular general acid catalysis

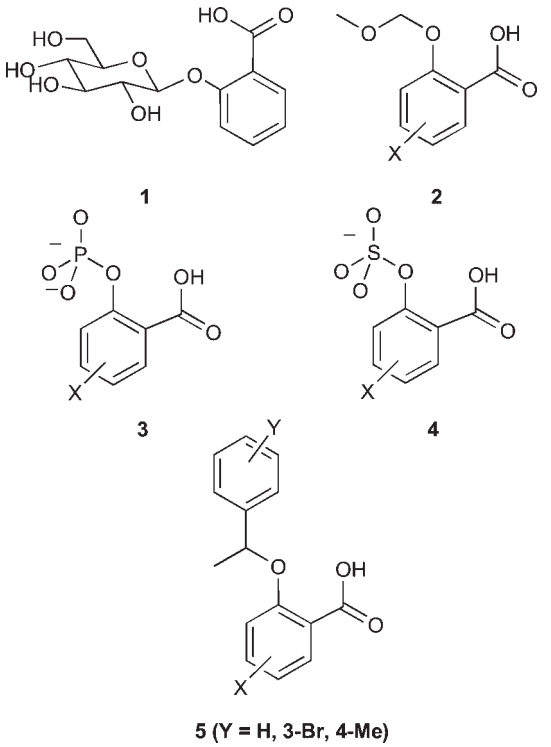
INTRODUCTION

The energetic coupling of proton transfers between heteroatoms and heavy atom rearrangements is one of the most widely used mechanisms by which enzymes achieve their remarkable rate accelerations. At pHs near neutrality, general acid- and general base-catalysed processes can provide competing reaction pathways of lower activation energy than spontaneous (water-catalysed), specific acid- or specific base-catalysed pathways for hydrolysis and other reactions. The quantitative description of transition-state structures and variations in structure for intermolecular general acid- and general base-catalysed reactions using free-energy relationships is well understood, thanks largely to the studies of Jencks and co-workers.[1,2] However, the systematic application of free energy relationship analysis to systems displaying intramolecular general acid or base catalysis has been relatively neglected. This is due in part to synthetic difficulties, and reflects also the problems that can arise when substituent effects do not act independently on reacting functionalities.[3–8] However, it represents a significant limitation in our understanding of intramolecular reactions, which seek to replicate the proximity in which reactive functionalities are held in enzyme Michaelis complexes, and provide a starting point for linking the studies of small molecule model reactions of bioorganic relevance and the reactivity of macromolecular enzyme mimics.[9,10]

Compounds derived from salicylic acid have long been used as enzyme models. Capon[11] and Piszkiewicz and Bruice[12] reported a significantly accelerated pH-independent rate of spontaneous hydrolysis in the cleavage of arylglycoside **1** (Scheme 1) at pH values below the pK_a value of the carboxyl group; however, their mechanistic interpretations of this behaviour differed. In principle the *ortho*-carboxyl/carboxylate group may act as an intramolecular general acid, general base or nucleophile, or as a source of electrostatic stabilization of an adjacent positively charged group. Analysis of the pH–rate profiles for the reactions of unsubstituted salicylic acid derivatives provides a clue to the role of the carboxyl group in catalysing the reaction of adjacent groups, but cannot distinguish between kinetically equivalent mechanisms, such as hydrogen bond-stabilized specific acid catalysis [in hydrogen bond-stabilized specific acid catalysis, proton transfer from the catalytic acid to the substrate (here the leaving group) is formally complete in the rate-determining transition state and the substrate conjugate acid is stabilized by hydrogen bonding to the conjugate base of the catalytic acid; for catalysis to be significant, the resultant increase in concentration of the conjugate acid must outweigh its stabilization] and general acid catalysis. Kirby, Williams and their co-workers have synthesized a range of substituted salicylic acid derived compounds **2–5** (Scheme 1) and analysed variations in their rates of hydrolysis to probe transition-state structure.[4,5,7,8]

Reactivity was varied by introducing substituents X into the two positions indicated in Scheme 1. These are *meta* and *para* to the catalytic carboxyl, but *para* and

**Correspondence to:* A. J. Kirby, University Chemical Laboratory, University of Cambridge, Cambridge CB2 1EW, UK.
E-mail: ajk1@cam.ac.uk
†Dedicated to the incomparable Bill Jencks.
‡Selected paper part of a special issue entitled 'Biological Applications of Physical Organic Chemistry'.



Scheme 1. Salicylic acid derivatives showing general acid catalysis of hydrolysis

meta to the phenolic oxygen. Thus a substituent X will alter both the leaving group ability of the phenolic oxygen and the acidity of the adjacent carboxylic acid. Following Jencks,[1] we define the two reaction coordinates as y' and x, respectively.[1] The reactivity of these compounds was originally analysed in terms of Jaffé's extended Hammett equation.[13] In this approach, the single substituent exerts (independent) influences on both carboxylic acid and phenolic centers according to the free-energy relationship given by

$$\log k_{xy'} = \rho_x \sigma_x + \rho_{y'} \sigma_{y'} + C \qquad (1)$$

This equation represents the simplest extension that may be made to the Hammett equation in an attempt to correlate structural perturbations that influence more than one reacting center. Just as the Hammett equation corresponds to a Taylor series expansion of the equation

$$\log k_x = f(\sigma_x) \qquad (2)$$

truncated at the first derivative terms, so Jaffé's extended Hammett equation truncates the Taylor series expansion of Eqn (3) at its first-derivative terms.

$$\log k_{xy'} = f(\sigma_x, \sigma_{y'}) \qquad (3)$$

A major contribution of Jencks and co-workers over a number of years has been the development and application of the higher order derivative terms in the Taylor series expansion of equations such as Eqn (3) in probing variations in transition-state structures and reaction mechanisms. The theoretical basis of this approach was established by Jencks and Jencks[14] and the principles later collated in the so-called 'BeMa HaPoThLe'.[1] Jencks and Jencks used the mathematical form of the potential energy surface given in Eqn (4) to analyse variations in transition-state structure.

$$\frac{\Delta G}{2.303RT} = ax^2 + by'^2 + cxy' + dx + ey' + f \qquad (4)$$

First-derivative terms in free energy relationships (such as ρ_x and $\rho_{y'}$) are related to coefficients d and e in Eqn (4); and define the position of a transition-state structure on a two-dimensional More O'Ferrall[15]–Jencks[16] diagram (see Fig. 1). The 'cross' second-derivative term ($\rho_{xy'} = \partial^2 k_{xy'}/\partial\sigma_x\partial\sigma_{y'}$) is related to coefficient c in Eqn (4) and may be used to explain variations in transition-state structure along the reaction coordinate (i.e. the curvature along the reaction coordinate). 'Direct' second-derivative terms (for example, $\rho_{xx} = \partial^2 k_{xy'}/\partial\sigma_x^2$) are related to coefficients a and b in Eqn (4) and represent variations in transition-state position (curvatures of the potential energy surface) parallel to the ordinates of the More O'Ferrall–Jencks diagram. The significance of quadratic terms in free-energy relationships has been the subject of comment and analysis by O'Brien and More O'Ferrall[17] and Dubois *et al.*[18] In recent times, Lee and co-workers have made extensive use of 'cross' second-derivative terms in analysing transition-state structures, noting that they often contribute more significantly to variations in reactivity than do the 'direct' second-derivative terms.[19,20]

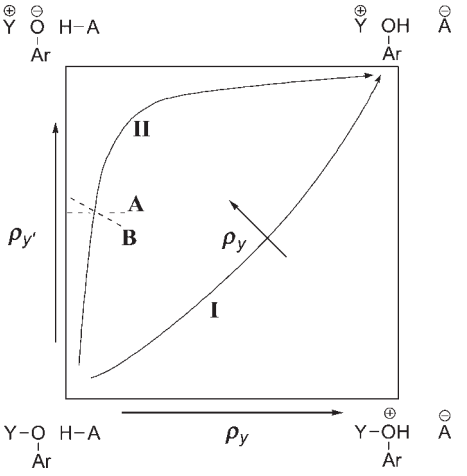


Figure 1. More O'Ferrall–Jencks diagram showing variations in transition-state structure

It the light of these findings, it has been noted that the extended Hammett equation of Jaffé cannot account for variations in the reactivity of a two-component (e.g. general acid and leaving group) system whose variation in transition-state position is governed by the reactivity–selectivity principle (RSP).[18] In the context of catalysis of hydrolysis in salicylic acid-derived compounds, a stronger general acid might be expected to elicit a lower sensitivity to leaving group ability. Indeed, just as the *minimum* Taylor series expansion of Eqn (2) is found to be sufficient in many cases for explaining the reactivity of one-component systems (in the absence of a change in mechanism or rate-determining step significant curvature in Brønsted plots is rarely observed), so the *minimum* Taylor series expansion of Eqn (3) capable of providing an RSP-consistent analysis of two component systems is that given in Eqn (5), in which the second-derivative cross-interaction term is included. This modification was originally introduced by Miller[21] and applied by Cordes and Jencks to the general acid-catalysed formation of semicarbazones.[22]

$$\log k_{xy'} = \left(\frac{\partial k_{x0}}{\partial \sigma_x}\right)_{y'} \sigma_x + \left(\frac{\partial k_{0y'}}{\partial \sigma_{y'}}\right)_{x} \sigma_{y'} + \left(\frac{\partial^2 k_{xy'}}{\partial \sigma_x \partial \sigma_{y'}}\right) \sigma_x \sigma_{y'} + C \tag{5}$$

In the spirit of the work of Jencks and his co-workers, we have re-examined the behaviour of the salicylic acid derived model compounds **2**–**5** to include an analysis of variations in transition-state structure and reaction mechanism.

METHODOLOGY

Kinetic data (see Supplementary material available in Wiley Interscience) from the original journal sources[4,5,7,8] were fitted to Eqns (6)–(9) using a least-squares analysis.[23] Standard σ values (σ^- for the 5-NO_2 substituent) were used[24] except for van Bekkum *et al.*'s recommended values of $\sigma_p = -0.111$ for the 5-MeO substituent.[25]

$$\log k_{xy'} = \rho_x \sigma_x + \rho_{y'} \sigma_{y'} + C \tag{6}$$

$$\log k_{xy'} = \rho_x \sigma_x + \rho_{y'} \sigma_{y'} + \rho_{xy'} \sigma_x \sigma_{y'} + C \tag{7}$$

$$\log k_{xy'} = \rho_x \sigma_x + \rho_{y'} \sigma_{y'} + \rho_{xx} \sigma_x^2 + C \tag{8}$$

$$\log k_{xy'} = \rho_x \sigma_x + \rho_{y'} \sigma_{y'} + \rho_{y'y'} \sigma_{y'}^2 + C \tag{9}$$

In each of these cases the value of $\log k_{xy'}$ is fitted to the expression shown rather than the value of $\log(k_{xy'}/k_{00})$ to the equivalent expression less the constant C. This ensures that each of the data points corresponding to a single compound (including that of the compounds X = H, reacting with a rate k_{00}) is given equal weight during the fitting procedure.

The extended Hammett equation originally used to describe the kinetic data and establish transition-state positions performed well in correlating rate data with substituent constants in many cases (the exceptions being the benzyl-ether derived compounds **5**). It was therefore important to establish the significance of the second-derivative terms as they will make only small contributions to observed variations in reactivity. This was achieved by applying the guidelines provided by Shorter.[26] Standard deviations associated with all parameters provide the most straightforward indication of the reliability of the reaction parameters calculated; in particular, relatively large errors may be expected in second-derivative parameters that are not significant in explaining observed variations in transition-state structure (i.e. deviations from behaviour as determined by Jaffé's extended Hammett equation). The significance of second-derivative terms in explaining deviations from behaviour according to Jaffé's extended Hammett equation may be quantified using partial correlation coefficients, $r_{14.23}^2$ [Eqn (10)], which quantify the additional fraction of the variance of the observed data from the model of Eqn (6) explained by the introduction of an additional parameter according to Eqns (7)–(9); F values for each fit provide similar information, with a significant increase in the F value associated with the fitted equation (i.e. beyond that of the extended Hammett equation), indicating that the additional parameter introduced has improved the significance of the fitted equation.

$$r_{14.23}^2 = \frac{R_{1.234}^2 - R_{1.23}^2}{1 - R_{1.23}^2} \tag{10}$$

($R_{1.234}^2$ is the correlation coefficient for observed data points 1, when explained using explanatory parameters 2, 3 and 4 (e.g. ρ_x, $\rho_{y'}$ and $\rho_{xy'}$), whereas $R_{1.23}^2$ is the correlation coefficient for observed data points 1 when explained using only the explanatory parameters 2 and 3 (e.g.ρ_x and $\rho_{y'}$).

A final method of testing the plausibility of the results obtained is pragmatic and chemical rather than statistical. Where similar intermolecular reactions have been studied, comparisons of the signs of second-derivative parameters determined for the intramolecular and the intermolecular reactions is important. Similar chemistries may be expected to display the same signs of both first and second derivative terms in the Taylor series expansion of Eqn (3).

RESULTS AND DISCUSSION

Table 1 provides the Hammett-type sensitivity parameters for acetal **2**, phosphate dianion **3** and sulfate **4** derived using the fitting procedures described above.

The mechanisms of hydrolysis of **2–4** are expected to be qualitatively similar. The methoxycarbenium ion derived from formaldehyde,[27,28] the metaphosphate monoanion[29] and sulfur trioxide[30,31] have all been shown to have lifetimes less than the dielectric relaxation time (τ_1) of the water molecule in water. Thus enforced S_N2 mechanisms are indicated, in which nucleophilic water is bound to the electrophilic carbon, phosphorus or sulfur at the transition state at least to some extent.[32,33] The tightness of the transition state (see later) will depend on the nature of the central atom.

The results presented in Table 1 support and reinforce the conclusions drawn in the original papers concerning the position of the transition state for intramolecular catalysis in these reactions. The transition states are characterized by appreciable charge build-up on the phenolic oxygen atom of the leaving group coupled to relatively small extents of proton transfer from the carboxylic acid group.[4,5,7] For **2–4** the inclusion of a term representing curvature (ρ_{xx}) at the transition state parallel to the ρ_x dimension (proton transfer) is uniformly insignificant in explaining variations in transition-state position. This is related to the small extents of proton transfer observed in all cases, the extent of proton transfer being zero in the case of sulfate **4**, $\sim$0.1 in the case of acetal **2** and $\sim$0.2 for phosphate dianion **3** [taking the values obtained from the most significant fit obtained using Eqns (7)–(9)]. (The ground-state form of the phosphate dianion **3** contains a negatively charged carboxylate group and a phosphate group also bearing a single negative charge. The hydrolysis reaction has been shown to occur via a general acid-catalysed mechanism which requires a pre-equilibrium transfer of a proton from the phosphate group to the carboxylate group prior to the rate-determining proton transfer from the resulting COOH group to the leaving group oxygen atom. The extent of negative charge build-up on the carboxylic acid group in the rate-determining step with respect to the preceding intermediate is therefore equal to $\rho_x + 1$.)

The addition of second-derivative terms $\rho_{xy'}$ and $\rho_{y'y'}$ (rows in bold in Table 1) proves better at describing variance from behaviour according to the extended Hammett equation than the term ρ_{xx}. Although in the case of acetal **2** the $\rho_{xy'}$ and $\rho_{y'y'}$ terms do not significantly improve the correlation with the observed rate data, the terms do prove useful in explaining variations in transition state positions for the phosphate dianion **3** and the sulfate **4**. The cross-interaction coefficient $\rho_{xy'}$ is shown to be negative in all cases (though significantly so only in the cases of phosphate dianion **3** and sulfate **4**). This indicates that variations in transition state position are in accordance with the RSP, with better leaving groups tending to elicit less assistance (i.e. less proton transfer in the transition state) from the general acid catalyst (Hammond behaviour). It is unfortunate that there are no reports of significant intermolecular catalysis in the hydrolysis of phosphate dianion monoesters and sulfate monoesters for comparison. Capon and Nimmo have, however, reported the general acid-catalysed hydrolysis of substituted phenyl methyl acetals derived from benzaldehyde[34] and their data may be analysed to yield an interaction coefficient, $\rho_{xy'}$, with a value of -0.447 ± 0.034.[19] The negative value obtained from the data of Capon and Nimmo[34] is consistent with the sign and magnitude of the values of $\rho_{xy'}$ obtained for the hydrolysis of **2–4**.

The hydrolyses of the ethers **5** could not all be followed at the same temperature (rates of hydrolysis of benzylic ethers are exceptionally sensitive to the stability of the resulting carbocation). The Hammett sensitivity parameter, ρ_y, is found to be -6.1 based on literature σ^+ values. If, however, the σ values are corrected for imbalanced polar and resonance effects according to the Yukawa–Tsuno equation,[35,36] using the value of $\rho^+ = 2.1$ determined by Richard and Jencks for similar reverse

Table 1. Parameters describing transition-state structures and variations in transition-state structures for **2–4**[a]

Compound	ρ_x	$\rho_{y'}$	$\rho_{xy'}$	ρ_{xx}	$\rho_{y'y'}$	F	$r^2_{14.23}$
Acetal **2**	0.09 ± 0.06	0.84 ± 0.04				582	
	0.11 ± 0.06	**0.91 ± 0.07**	**-0.12 ± 0.11**			**406**	**0.20**
	0.09 ± 0.07	0.84 ± 0.08		0.02 ± 0.21		324	0.00
	0.09 ± 0.06	**0.93 ± 0.07**			**-0.07 ± 0.05**	**455**	**0.29**
Phosphate dianion **3**	-0.95 ± 0.17	1.36 ± 0.13				62	
	-0.77 ± 0.10	**1.77 ± 0.11**	**-0.79 ± 0.17**			**152**	**0.75**
	-0.79 ± 0.20	1.45 ± 0.14		-0.43 ± 0.32		45	0.20
	-1.01 ± 0.11	**1.80 ± 0.15**			**-0.37 ± 0.10**	**107**	**0.65**
Sulfate **4**	-0.01 ± 0.05	1.43 ± 0.04				1963	
	-0.01 ± 0.04	**1.55 ± 0.06**	**-0.18 ± 0.08**			**2315**	**0.58**
	-0.00 ± 0.05	1.48 ± 0.08		-0.17 ± 0.21		1230	0.15
	-0.04 ± 0.04	**1.55 ± 0.06**			**-0.09 ± 0.04**	**2381**	**0.56**

[a] Parameters were obtained using the extended Hammett equation [Eqn (6), first row in each case], or including (separately) second derivative terms [Eqns (7)–(9), rows 2–4]. Rows for correlations involving $\rho_{xy'}$ and $\rho_{y'y'}$ are in bold. These descriptive terms produce similar ρ_x and $\rho_{y'}$ terms. For a detailed discussion, see the text.

reactions, a value of $\rho_y = 4.1$ is obtained.[37]) The rates of hydrolysis of the ethers with substituents Y = 3-Br and Y = 4-Me were followed over a range of temperatures for different X substituents and extrapolated to 39 °C (the temperature at which the hydrolysis of the unsubstituted benzylic, i.e. Y = H, series of compounds was followed).[8] The relative unreliability of this extrapolation procedure when used in the context of a small number of experimental points is illustrated for the substituted ethers with Y = 3-Br, using the rates extrapolated to 39 °C. In this case the best fits to Eqns (6)–(9) produce negative (and hence chemically meaningless) values of ρ_x. For small sample sizes any procedure including extrapolations made over a large range of temperatures therefore seem unreliable. As a result, the data for a given substituent Y for the three different benzylic carbocations were fitted at a temperature common to all X substituents. The parameters determined in this fashion were less accurate than those obtained for acetal **2**, phosphate dianion **3** and sulfate **4** (owing to the smaller number of data points obtained), yet an avoidable source of error was eliminated and useful values of sensitivity parameters and interaction coefficients obtained.

The data in Table 2 are largely consistent with those found in Table 1. The most reliable values of ρ_x obtained are small (although with large degrees of experimental uncertainty), suggesting relatively insignificant charge build-up on the carboxylic acid group at the transition state. Furthermore, the original paper indicated that the kinetically determined pK_a values of the carboxylic acid groups were correlated with the associated σ_x values with gradients that were in some cases substantially greater than 1, suggesting that the associated Brønsted α values might be substantially smaller than the values of ρ_x reported here.[8] As for **2–4**, addition of a parameter ρ_{xx} in ${\sigma_x}^2$ does not improve the correlations obtained to a significant extent. The introduction of the interaction coefficient $\rho_{xy'}$ or a term in $\rho_{y'y'}$ does seem to improve correlation with the experimental data. The negative values of $\rho_{xy'}$ obtained are consistent with Hammond-type variations in transition state position.

Of the reaction sensitivities obtained at the common temperature of 39 °C, we may have the greatest confidence in the results obtained for the substituents Y = H and 4-Me. Furthermore, these two series of data illustrate the potential importance of the inclusion of interaction coefficients in describing the reactivity of the systems involving multiple interacting components. [The signs of the cross-interaction parameters $\rho_{xyy'}$, ρ_{xy} and $\rho_{xy'}$ based on the data for Y = H and Y = 4-Me at 39 °C, are not well defined (Table 2). They are, however, consistent with the signs determined by Jencks and co-workers for the corresponding intermolecular reactions, for which the data are more reliable, since all three components x, y and y' could be varied independently.] The values of ρ_x, $\rho_{y'}$ and $\rho_{xy'}$ obtained from Eqn (7) may be used as a basis for an analysis of how these parameters vary with changing carbocation structure. Increasing the stability of the carbocation produced on hydrolysis of the ether by 4-methyl substitution (σ^+ for the 4-Me group is −0.250) is associated with an increase in ρ_x and a decrease in $\rho_{y'}$ and $\rho_{xy'}$. These changes in transition-state position may be expressed in terms of an additional axis in a three-dimensional description of the transition state structure (the additional dimension being that described by the ordinate ρ_y relating to the stability of the carbocation). The positive value of $\rho_{yy'} (= \partial\rho_{y'}/\partial\sigma_y)$ indicates a variation in transition-state position according to Hammond-type behaviour: the greater the stability of the carbocation generated the lower the sensitivity of the reaction to the

Table 2. Results describing transition-state structures and their variation for ethers **5**, using Eqns (6)–(9) (format as for Table 1)

Compound	ρ_x	$\rho_{y'}$	$\rho_{xy'}$	ρ_{xx}	$\rho_{y'y'}$	F	$r^2_{14.23}$
Ether (Y = H, 39 °C)	0.28 ± 0.25	0.62 ± 0.17				39	
	0.38 ± 0.11	**1.09 ± 0.17**	**−0.77 ± 0.25**			**137**	**0.90**
	0.27 ± 0.38	0.58 ± 1.04		0.12 ± 3.00		13	0.00
	0.26 ± 0.10	**1.10 ± 0.16**			**−0.39 ± 0.12**	**161**	**0.92**
Ether (Y = 3-Br, 39 °C)[a]	−0.70 ± 0.53	1.33 ± 0.36				13	
	−0.48 ± 0.19	**2.35 ± 0.29**	**−1.68 ± 0.42**			**75**	**0.94**
	−0.55 ± 0.69	2.41 ± 1.92		−3.19 ± 5.53		6	0.25
	−0.73 ± 0.20	**2.36 ± 0.32**			**−0.83 ± 0.23**	**62**	**0.93**
Ether (Y = 3-Br, 65 °C)	0.16 ± 0.37	0.67 ± 0.25				17	
	0.30 ± 0.25	**1.32 ± 0.38**	**−1.07 ± 0.56**			**27**	**0.79**
	0.12 ± 0.55	0.36 ± 1.51		0.90 ± 4.36		6	0.04
	0.14 ± 0.23	**1.34 ± 0.36**			**−0.54 ± 0.27**	**30**	**0.81**
Ether (Y = 4-Me, 39 °C)[a]	0.50 ± 0.32	0.37 ± 0.22				18	
	0.63 ± 0.02	**1.01 ± 0.03**	**−1.05 ± 0.04**			**5065**	**1.00**
	0.54 ± 0.47	0.69 ± 1.30		−0.92 ± 3.75		6	0.06
	0.47 ± 0.01	**1.03 ± 0.01**			**−0.52 ± 0.01**	**62598**	**1.00**
Ether (Y = 4-Me, 25 °C)	0.20 ± 0.27	0.40 ± 0.19				14	
	0.32 ± 0.03	**0.94 ± 0.05**	**−0.89 ± 0.07**			**905**	**0.99**
	0.23 ± 0.41	0.62 ± 1.12		−0.66 ± 3.23		5	0.04
	0.18 ± 0.02	**0.95 ± 0.03**			**−0.45 ± 0.02**	**2077**	**1.00**

[a] These data are from an extrapolation (see the text). The remainder are experimental.

ability of the leaving group. The negative value of $\rho_{xy}(=\partial\rho_x/\partial\sigma_y)$ indicates anti-Hammond behaviour in the position of the transition state with more stabilized carbocations eliciting more assistance from the general acid catalyst. A positive value of $\rho_{xyy'}(=\partial\rho_{xy'}/\partial\sigma_y)$ indicates that the energetic coupling (or the magnitude of $\rho_{xy'}$) between the leaving group and the general acid decreases for less stable carbocations.

Variations in transition-state positions for the general base-catalysed addition of alcohols to 1-phenylethyl carbocations by Jencks and co-workers constitute the key body of works in understanding transition-state structures, variations in transition-state structures and variations in reaction mechanism in such systems.[37–41] The reaction studied is effectively the intermolecular reverse reaction of the intramolecular general acid-catalysed cleavage of benzylic ethers described by Kirby *et al.*,[8] so the nature of the transition states described is expected to display similar sensitivities to variations in structure. This is indeed found to be the case. Cordes–Jencks interaction coefficients express variations in transition-state structure in terms of changes in β (the Brønsted parameter associated with a general base), pK_{nuc} (the pK_a value of nucleophile) and σ (the Hammett reaction constant associated with the benzylic carbocation) according to Eqns (11)–(13):

$$p_{xy'} = \frac{\partial\beta}{-\partial pK_{nuc}} = -a\rho_{xy'} \quad (11)$$

$$p_{xy} = \frac{\partial\beta}{-\partial\sigma_{cation}} = -b\rho_{xy} \quad (12)$$

$$p_{yy'} = \frac{\partial\beta_{nuc}}{-\partial\sigma_{cation}} = +c\rho_{yy'} \quad (13)$$

where a, b and c are positive constants.

Ta-Shma and Jencks[41] have reported a positive value of $p^*_{xyy'}$ [Eqn (14), where d is a positive constant] for the general base-catalysed addition of alcohols to benzylic carbocations, which is consistent with the positive value of $\rho_{xyy'}$ reported here for the salicylic acid-derived benzyl ether hydrolysis.

$$p^*_{xyy'} = \frac{\partial p_{xy'}}{-\partial\sigma_y} + d\rho_{xyy'} \quad (14)$$

Ta-Shma and Jencks[41] also carried out a systematic analysis of the significance of all possible third-derivative terms describing variations in transition state in the 1-phenylethyl carbocation system. A positive value of $\rho_{xyy'}$ is significant as it describes a mechanistic change that produces an uncoupling of the interaction between leaving group and general acid necessitated as decreasing carbocation stability drives the mechanism from one of general acid catalysis (pathway I, Fig. 1) to uncatalysed hydrolysis (pathway II, Fig. 1).

Across the range of compounds **2–5**, the salicylic acid group can be been seen to act in a consistent fashion in catalysing the departure of a phenolic leaving group: small extents of negative charge build-up on the carboxylic acid group are observed, indicating predominantly vertical reaction pathways at the transition state as expressed on the More O'Ferrall–Jencks diagram (Fig. 1). These predominantly vertical pathways are consistent with negligible contributions of ρ_{xx} terms to reactivity (implying that the level line[14] A in Fig. 1 is close to horizontal) and significant contributions of $\rho_{xy'}$ terms and of $\rho_{yy'}$ terms (implying that level line B in Fig. 1 falls close in orientation to that of line A). The uniform behaviour of the salicylic acid leaving groups in **2–5** is reflected in the relationships of these general acid-catalysed reactions with the corresponding spontaneous (or water-catalysed) hydrolyses of acetals, sulfates, phosphates and ethers with phenolic leaving groups. Table 3 summarizes Brønsted parameters ($\beta_{leaving\ group}$) for the spontaneous hydrolyses of **6–9** (corresponding to **2–5** without the carboxyl group) and for the general acid-catalysed hydrolyses of **2–5** (based on the values of the $\rho_{y'}$ terms in Tables 1 and 2, obtained using equations including a term in $\rho_{xy'}$). [These Brønsted parameters are obtained from the corresponding Hammett parameters by dividing by the sensitivity parameter for phenol ionization (-2.23).[42]] In cases where appropriate effective charges (derived from the Brønsted sensitivities of the equilibrium hydrolysis reaction) are available, the Brønsted coefficients thus obtained may be converted to Leffler parameters, or $\alpha_{y'}$ terms. These describe, on a scale from zero to one, the extent of negative charge build-up on the phenolic oxygen of the leaving group

Table 3. Brønsted and Leffler coefficients for the phenolic leaving groups in intramolecular general acid-catalysed (GAC) and spontaneous hydrolyses of acetals, phosphate monoester dianions, sulfates and ethers of salicylic acid

Compound type	Effective charge on phenolic O	$\beta_{y'}$ (GAC)	$\alpha_{y'}$ (GAC)	$\beta_{y'}$ (H_2O)	$\alpha_{y'}$ (H_2O)	$\alpha_{y'}$ (H_2O) $-\alpha_{y'}$ (GAC)
Acetals **2**, **6**	(+0.3, see text)	0.41	(0.32, see text)	0.82[43]	(0.63, see text)	(0.31, see text)
Phosphate dianions **3**, **7**	+0.36[44]	0.79	0.58	1.23[45]	0.90	0.32
Sulfates **4**, **8**	+0.7[46]	0.70	0.41	1.25[47]	0.71	0.30
Ethers **5**, **9** (Y = 4-Me)	+0.2[47,48]	0.45	0.38	0.95[8]	0.79	0.31

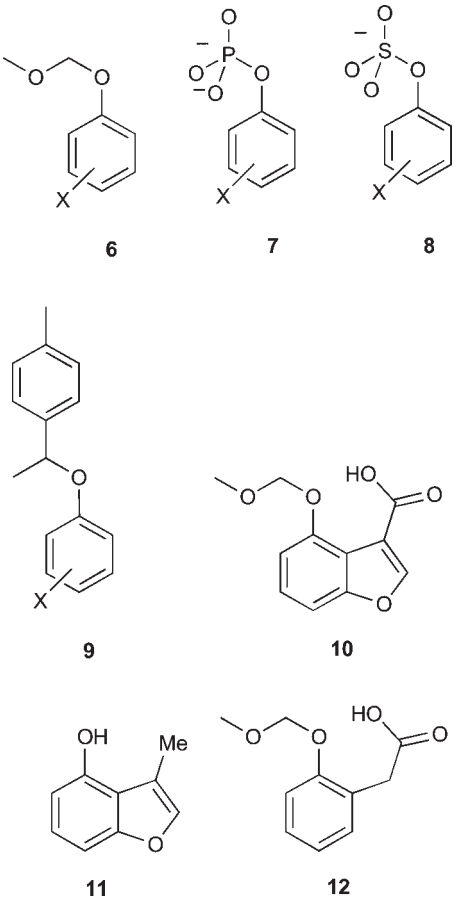
(which will be a function of both carbon—oxygen bond cleavage and the extent of proton transfer from the general acid).

Table 3 shows that for phosphate dianions **3**, sulfates **4** and ethers **5** the effect of the addition of the *o*-COOH of the salicylic acid leaving group on the transition-state position, with respect to the spontaneous reaction, is to bring the transition state forward (make it earlier) by around 0.3 Leffler units. No values of effective charge (derived from Brønsted β_{eq} values) for phenolic acetal oxygen atoms have been determined empirically to date, but we can estimate a value as follows. If we assume that the Leffler reaction parameters for the spontaneous and intramolecularly catalysed hydrolyses of acetals differ by 0.31 units (the mean and almost constant value determined for **3**, **4** and **5**), we can estimate the effective charge on the phenolic oxygen atom of *O*-methoxymethylphenols as +0.3 (equivalent to a Brønsted β_{eq} value of 1.3 for the hydrolysis of the *O*-methoxymethylphenols). This is consistent with the expectation that the effective charge will be larger than that found for phenolic ethers.[47]

INTRAMOLECULAR HYDROGEN BOND GEOMETRY AND REACTIVITY

The influence of hydrogen bond geometry on the rates of general acid-catalysed processes in constrained systems is of great interest, as it has a direct bearing on the question of whether enzymes achieve high catalytic efficiencies by the accurate positioning of acidic functionalities. Although salicylic acid-derived scaffolds provided the first means of placing a general acid near a leaving group heteroatom, other scaffolds based on benzofuran, benzisoxazole and naphthalene have been developed more recently.[49,50] The benzofuran scaffold (**10**, Scheme 2) is designed so that the intramolecular hydrogen bond obtained is close to linear. This optimized geometry is thought to contribute to preferential transition-state stabilization in the general acid-catalysed hydrolysis reaction.

The free energy relationships derived for acetal **2** may be used to estimate the extra transition-state stabilization derived from the benzofuran scaffold compared with the salicylic acid system, for the same reaction taking place under the same conditions. Differences in the pK_a values of the leaving group phenols and the carboxylic acids of benzofuran **10** and acetal **2** (X = H) can be used to predict the rate of reaction ($k_{predicted}$) for a compound with the salicylic acid framework of acetal **2** but the leaving group ability and catalyst acidity of benzofuran **6**. The ratio of this rate relative to rate for the hydrolysis of 2-methoxymethoxybenzoic acid **2**, is given by Eqn (15) {the cross term $[-0.054 \times \Delta pK_a(COOH) \times \Delta pK_a(phenol)]$ makes a negligible contribution (see above) and has therefore been omitted from Eqn (15)} (the coefficients are derived from the data for **2** in Table 1, line 2).



Scheme 2. Compounds used for comparisons of intermolecular and intramolecular reactivity

$$\Delta(\log k_{predicted}) = -0.11 \times \Delta pK_a(COOH) - 0.408 \times \Delta pK_a(phenol) \quad (15)$$

The value of $\Delta pK_a(COOH) = 0.07$ is obtained from the observed pH–rate profiles of **2** and **10**.[49,50] Our best estimate for ΔpK_a(phenol) is 0.43. [We have estimated previously a value of 8.52 for the effective pK_a of the salicylate leaving group.[50] Based on this figure, and a transmission coefficient of 0.4[51] to take account of the extra carbon atom in **10**, the replacement of the 3-methyl group of **11** (pK_a = 9.65 at 20 °C[52]) by COOH could lower the effective pK_a of the phenolic OH group by up to 0.7 units, to 8.95.] These differences substituted into Eqn (15) give a value of $k_{predicted}$ at 39 °C which is lower by a factor of 3.8 than the observed rate constant for the general acid-catalysed hydrolysis of **10** [$(3.55 \pm 0.15) \times 10^{-3}$ s^{-1} at 39 °C]. This difference between observed and predicted rates of reaction of benzofuran **10** corresponds to an energy difference of up to 3.4 kJmol^{-1} at 39 °C.

This figure is a measure of the stabilization of the transition state for the general acid-catalysed hydrolysis reaction by the benzofuran scaffold, relative to the salicyl framework. It includes changes in both through-ring and through-hydrogen bond interactions between the phenol and carboxylic acid groups in the transition state of both frameworks. It suggests that intramolecular general acid-catalysed processes involving phenolic leaving groups in an aqueous environment are relatively insensitive to geometric constraints, *once the conditions for the formation of a strong intramolecular hydrogen bond are fulfilled*. (Catalysis disappears when the rigid framework of **10** is removed, as in **12**.[53])

This low sensitivity is not surprising, in view of the relatively small extents of proton transfer from the carboxylic acid group and the substantial charge build-up of negative charge on the departing phenolic oxygen in the transition state. The effects of optimizing the geometry, and thus maximizing the strength of the developing hydrogen bond, will be more significant for the (relatively) earlier transition states involved in the reactions of typical biological acetals, with aliphatic oxygen leaving groups. So far only two such model systems have been identified[54,55] and further, detailed studies are needed to establish the potential magnitude of such effects. Of course medium effects (specifically those prevailing in the complicated microenvironment of an enzyme active site) will also be of major importance in determining the significance of constrained hydrogen bond geometry in general acid-catalysed processes (lower dielectric permittivities producing stronger hydrogen bonds and hence further scope for variations of strength with geometry).

Within certain limitations, our analysis suggests that the positioning of an effective catalytic general acid or base within an enzyme active site may tolerate a certain amount of flexibility. Mutagenesis studies carried out on general acids found within enzyme active sites [involving, for example, the interconversion of glutamic acid, aspartic acid and *S*-(carboxymethyl)cysteine residues] show a range of sensitivities to the positioning of general acids: in one case aryl glycoside hydrolysis was shown to be relatively insensitive to general acid position (3–23-fold decreases in the values of k_{cat}/K_M being observed)[56] whereas in the case of triose phosphate isomerase alteration of the length of the side-chain carrying the general base resulted in a 500-fold decrease in the value of k_{cat}/K_M.[57]

CONCLUSIONS

The structure-reactivity relationships developed by Jencks and co-workers are shown to be applicable to intramolecular general acid catalysis of the hydrolysis of a variety of substrates derived from salicylic acid. The correlations show the behaviour of salicylic acid as a leaving group to be consistent over a range of substrates with widely different reactivities, and provide some insight into the influence of hydrogen bond geometry in determining activation free energies for intramolecular general acid-catalysed hydrolyses.

Supplementary material

Kinetic data from the original journal sources[4,5,7,8] are available in Wiley Interscience.

Acknowledgements

The authors thank Professors A. Williams and J. P. Richard for helpful discussions. I.R.G. thanks the EPSRC for a studentship.

REFERENCES

1. Jencks WP. *Chem. Rev.* 1985; **85**: 511–527.
2. Jencks WP. *Bull. Soc. Chim. Fr.* 1988; 218–224.
3. Fersht AR, Kirby AJ. *J. Am. Chem. Soc.* 1967; **89**: 4853–4857.
4. Bromilow RH, Kirby AJ. *J. Chem. Soc., Perkin Trans. 2* 1972; 149–155.
5. Craze G-A, Kirby AJ. *J. Chem. Soc., Perkin Trans. 2* 1974; 61–66.
6. Buffet C, Lamaty G. *Recl. Trav. Chim. Pays-Bas* 1976; **95**: 1–6.
7. Hopkins AR, Green AL, Williams A. *J. Chem. Soc., Perkin Trans. 2* 1983; 1279–1283.
8. Barber SE, Dean KES, Kirby AJ. *Can. J. Chem.* 1999; **77**: 792–801.
9. Kirby AJ. *Angew. Chem. Int. Ed. Engl.* 1996; **35**: 707–724.
10. Kirby AJ. In *Stimulating Concepts in Chemistry*, Shibasaki M, Stoddart JFA, Vögtle F (eds). Wiley-VCH: Weinheim, 2000; 341–354.
11. Capon B. *Tetrahedron Lett.* 1963; **14**: 911–913.
12. Piszkiewicz D, Bruice TC. *J. Am. Chem. Soc.* 1968; **90**: 2156–2163.
13. Jaffé HH. *J. Am. Chem. Soc.* 1954; **76**: 4261–4264.
14. Jencks DA, Jencks WP. *J. Am. Chem. Soc.* 1977; **99**: 7948–7960.
15. More O'Ferrall RA. *J. Chem. Soc. B* 1970; 274–277.
16. Jencks WP. *Chem. Rev.* 1972; **72**: 705–718.
17. O'Brien M, More O'Ferrall RA. *J. Chem. Soc., Perkin Trans. 2* 1978; 1045–1053.
18. Dubois J-E, Ruasse M-F, Argile A. *J. Am. Chem. Soc.* 1984; **106**: 4840–4845.
19. Lee I. *Adv. Phys. Org. Chem.* 1992; **27**: 57–117.
20. Oh HK, Ku MH, Lee HK, Lee I. *J. Org. Chem.* 2002; **67**: 8995–8998.
21. Miller SI. *J. Am. Chem. Soc.* 1959; **81**: 101–106.
22. Cordes EH, Jencks WP. *J. Am. Chem. Soc.* 1962; **84**: 4319–4328.
23. *Scientist for Windows Version 1.03*. MicroMath, St Louis, Missouri, 1994.
24. Jaffé HH. *Chem. Rev.* 1953; 191–261.
25. van Bekkum H, Verkade PE, Wepster BM. *Recl. Trav. Chim. Pays-Bas* 1959; **78**: 815–850.
26. Shorter J. In *Correlation Analysis in Organic Chemistry: An Introduction to Linear Free-Energy Relationships*, Atkins PW, Holker JSE, Holliday AK (eds). Oxford University Press: Oxford, 1973.
27. Young PR, Jencks WP. *J. Am. Chem. Soc.* 1977; **99**: 8238–8248.
28. Amyes TL, Jencks WP. *J. Am. Chem. Soc.* 1989; **111**: 7888–7900.
29. Herschlag D, Jencks WP. *J. Am. Chem. Soc.* 1989; **111**: 7579–7586.
30. Guthrie JP. *J. Am. Chem. Soc.* 1980; **102**: 5177–5180.
31. Hopkins A, Williams A. *J. Chem. Soc., Chem. Commun.* 1983; 37–38.

32. Craze G-A, Kirby AJ, Osborne R. *J. Chem. Soc., Perkin Trans. 2* 1978; 357–368.
33. Jencks WP. *Acc. Chem. Res.* 1980; **13**: 161–169.
34. Capon B, Nimmo K. *J. Chem. Soc., Perkin Trans. 2* 1975; 1113–1118.
35. Yukawa Y, Tsuno Y. *Bull. Chem. Soc. Jpn.* 1959; **32**: 971–981.
36. Yukawa Y, Tsuno Y, Sawada M. *Bull. Chem. Soc. Jpn.* 1966; **39**: 2274–2286.
37. Richard JP, Rothenberg ME, Jencks WP. *J. Am. Chem. Soc.* 1984; **106**: 1361–1372.
38. Richard JP, Jencks WP. *J. Am. Chem. Soc.* 1984; **106**: 1396–1401.
39. Richard JP, Jencks WP. *J. Am. Chem. Soc.* 1984; **106**: 1373–1383.
40. Richard JP, Jencks WP. *J. Am. Chem. Soc.* 1984; **106**: 1383–1396.
41. Ta-Shma R, Jencks WP. *J. Am. Chem. Soc.* 1986; **108**: 8040–8050.
42. Bolton PD, Hall FM, Reece IH. *J. Chem. Soc. B* 1967; 709–712.
43. Craze G-A, Kirby AJ. *J. Chem. Soc., Perkin Trans. 2* 1977; 354–356.
44. Bourne N, Williams A. *J. Org. Chem.* 1984; **49**: 1200–1204.
45. Kirby AJ, Varvoglis AG. *J. Am. Chem. Soc.* 1967; **89**: 415–423.
46. Hopkins AR, Day RA, Williams A. *J. Am. Chem. Soc.* 1983; **105**: 6062–6070.
47. Williams A. *Adv. Phys. Org. Chem.* 1992; **27**: 1–55.
48. Bernasconi CF, Leonarduzzi GD. *J. Am. Chem. Soc.* 1982; **104**: 5133–5142.
49. Kirby AJ, Parkinson A. *J. Chem. Soc., Chem. Commun.* 1994; 707–708.
50. Kirby AJ, Percy JM. *J. Chem. Soc., Perkin Trans. 2* 1989; 907–912.
51. Exner O. In *Advances in Linear Free Energy Relationships*, Chapman NB, Shorter J (eds). Plenum Press: New York, 1972; 25.
52. Demerseman P, Reynaud R, Cheutin A, Lechartier J-P, Pène C, Laval-Jenatet A-M, Royer R, Rumpf P. *Bull. Soc. Chim. Fr.* 1965; 1464–1466.
53. Capon B, Smith MC, Anderson E, Dahm RH, Sankey GH. *J. Chem. Soc. B* 1969; **43**: 1038–1047.
54. Fife TH, Przystas TJ. *J. Am. Chem. Soc.* 1979; **101**: 1202–1210.
55. Hartwell E, Hodgson DRW, Kirby AJ. *J. Am. Chem. Soc.* 2000; **122**: 9326–9327.
56. Lawson SL, Wakarchuk WW, Withers SG. *Biochemistry* 1997; **36**: 2257–2265.
57. Straus D, Raines R, Kawashima E, Knowles JR, Gilbert W. *Proc. Natl. Acad. Sci. USA* 1985; **82**: 2272–2276.

