Intramolecular Proton-transfer Catalysis of Nucleophilic Catalysis of Acetal Hydrolysis. The Hydrolysis of 8-Dimethylamino-1-methoxymethoxynaphthalene

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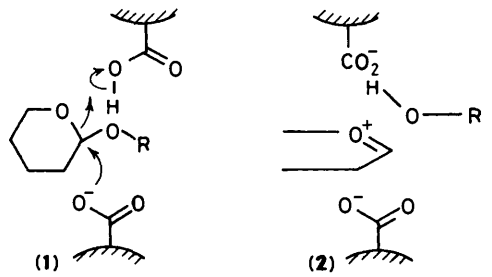
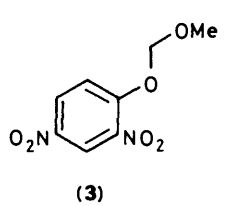
The cleavage of the conjugate acid of the title aryl methyl acetal is catalysed efficiently by the neighbouring Me_2NH^+ group, and also by added nucleophiles. Hydrolysis and nucleophilic catalysis involve a common mechanism, with obligatory but weak bonding to water or the added nucleophile in the transition state. The key to efficient intramolecular proton-transfer catalysis appears to be an intramolecular hydrogen bond between the general acid and the leaving-group oxygen which is strong in the product and transition states, but weak or absent in the ground state.

The catalytic roles of the two carboxy groups at the active site of lysozyme remain ill-defined, despite more than two decades of mechanistic work inspired by the problem.[1] There is broad agreement that glutamic acid-35, which is involved in the CO_2H form, acts as a general acid to assist glycoside cleavage. But although intramolecular general acid catalysis can be observed in model systems, it has proved extraordinarily difficult to reproduce anything like the remarkable efficiency of the enzyme reaction. A possible explanation[1] is that this depends crucially on the participation of the CO_2^- group of aspartic acid-52, although there is no agreement on exactly how this group is involved. Two 'extreme' possibilities—between which the truth may also lie—are: (i) that it acts as a nucleophile, so that the initial glycoside cleavage is a concerted general acid-catalysed nucleophilic substitution (**1**); and (ii) that the CO_2^- group provides electrostatic stabilisation of the developing oxocarbocation, which is a normal intermediate in acetal cleavage (**2**). Neither 'extreme' position is easy to sustain. The former because an intermediate acyl glycoside would normally be stable enough to detect; the latter because it is difficult to accept that the active-site structure could be rigid enough to prevent at least some bonding between a reactive



(1) (2)

oxocarbocation and an adjacent nucleophile. Nor does either mechanism have convincing precedent. Substantial electrostatic effects in particular are not normally observed in aqueous solution.[2] And although we have demonstrated nucleophilic catalysis of acetal hydrolysis in a particularly favourable case (**3**),[3a] we could detect none for the hydrolysis of the related acetal (**4**),[3b] in which the phenol oxygen acts as a good leaving group by virtue of intramolecular general acid catalysis by the neighbouring CO_2H group. The salicylic acetal system (**4**) is of special interest because it displays intramolecular catalysis that is uniquely efficient. General acid–base catalysis is normally characterised by an effective molarity (EM) which is <80 mol dm^{-3}, and often no more than 1 mol dm^{-3}. But the EM for



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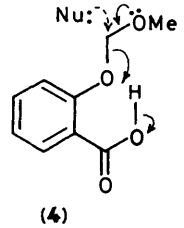
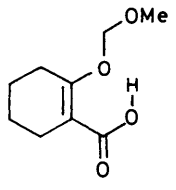


(4)

catalysis by the neighbouring CO_2H group in the hydrolysis of some salicylic acid derivatives can be as high[4] as 10^4 mol dm^{-3}, evidently reflecting special features of the mechanism of catalysis. This clearly differs from that for other, less efficient, reactions involving intramolecular general acid catalysis, and from the corresponding intermolecular reactions.[5] In particular, there is no convincing evidence that the key proton is in flight in the transition state, nor any corresponding intermolecular reaction for comparison. We use the less specific term 'proton-transfer catalysis' to distinguish this process from the classical general acid-catalysis mechanism.

This paper describes an investigation designed to isolate the factors responsible for this unique catalytic efficiency. The new system we have developed not only displays efficient catalysis of acetal hydrolysis,[6] but also shows intramolecular catalysis of attack by external nucleophiles, of the sort (**1**) suggested for the lysozyme reaction.

We set about isolating the structural factors associated with high catalytic efficiency in the salicylic acid system (**4**) by a process of elimination. High efficiency is retained in the tetrahydrosalicylic acid acetal (**5**), which is actually hydrolysed about twice as fast as (**4**) at 39 °C,[7] but disappears in the fully reduced system (**6**).[8] This is not simply because the leaving group is now an alkoxy, rather than an enol or phenol oxygen, because catalysis is also scarcely detectable in (**7**),[7] in which the leaving group is again an enol oxygen, as in (**5**).



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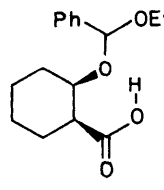

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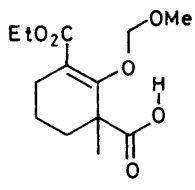

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Compounds (**4**) and (**5**) have in common two structural features which are absent in (**6**) and (**7**): (i) the leaving-group

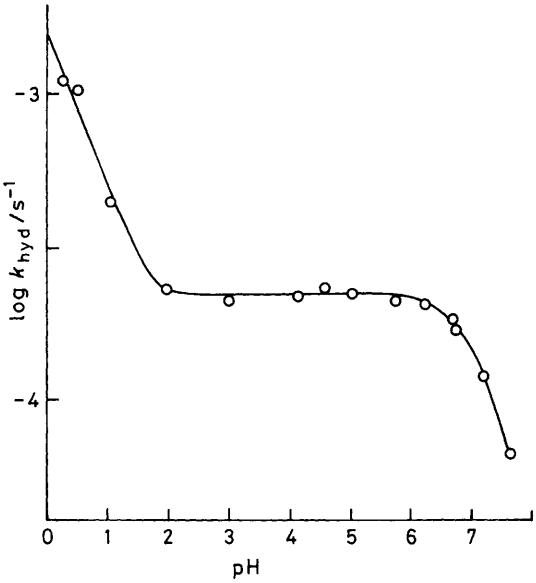
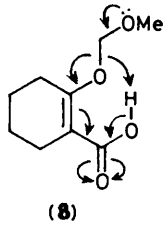


Figure 1. pH–Rate profile for the hydrolysis of (**10**), at 65 °C and ionic strength 1.0 mol dm^{-3}.

oxygen is conjugated with the catalytic CO_2H group, making possible an unusual sort of concerted process (**8**), which might conceivably be uniquely efficient;* and (ii) the product anion [*eg* (**9**) from a salicylic acid derivative] is stabilised by an intramolecular hydrogen bond so strong that it persists in water [and is responsible for the very high† p*K*a of (**9**)].



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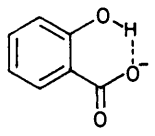
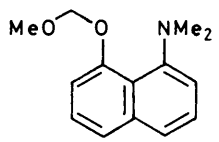
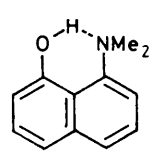


(**9**)

In the hope of choosing between these factors we prepared the acetal (**10**) of another system (**11**), the only other phenol or alcohol useful in this context known to be stabilised by a strong intramolecular hydrogen bond in water,‡ but where conjugation between catalytic (Me_2NH^+) and leaving group is not possible.



(**10**)



(**11**)

Experimental

The preparation of 8-dimethylamino-1-naphthol (**11**) (by a novel method), and of the acetal (**10**), are described elsewhere.[11] Reactions were followed at 65 °C and ionic strength 1.0 mol dm^{-3}, maintained with sodium perchlorate or chloride, in the thermostatted cell compartment of a Gilford 2600 spectrophotometer. Runs were initiated by injecting 1–5 mm^3 of a stock solution of (**10**) in dioxane into 280 mm^3 of buffer, and were followed for three half-lives, with end points taken after at least ten. Pseudo-first-order rate constants were calculated using a least-squares program written in BASIC for a BBC microcomputer by Dr. A. Sutkowski of this department. The release of (**11**) was generally followed at 240 nm, but at 330 nm for reactions with nucleophiles, some of which absorb strongly at the lower wavelength. Reactions with (sodium) halides and with thiourea were performed in 10% free base MES§ buffers: 60% free base was used for the azide reaction. Reactions with carboxylate salts and pyridine–pyridinium (perchlorate) were self-buffered (80% free base). Ionic strength was maintained with sodium chloride, except for the reactions of carboxylates and chloride itself, when perchlorate was used. pH values were measured using a Radiometer PHM 82 meter, fitted with a Russell CMAW 78 combination glass electrode.

Table 1. Rate constants for the hydrolysis of (**10**), at 65 ± 0.1 °C and ionic strength 1.0 mol dm^{-3} ($NaClO_4$).[a]

Hydrolysis conditions (concn./mol dm^{-3})	pH	$10^4 k_{obs}/s^{-1}$
HCl (0.5	0.24	10.52, 11.69
HCl (0.3)	0.48	10.38
HCl (0.1)	1.03	4.71
HDl (0.01)	1.94	2.31
HCl (0.001)	2.98	2.13
HCl (0.001) at 55, 60, 70, 75, 80, and 85 °C		0.65, 1.18, 4.06, 7.18, 11.69, 19.87
DCl	3.13[b]	1.26
Acetate (25% free base; 0.05)	4.11	2.17
Acetate (50% free base; 0.05)	4.56	2.34
Acetate (75% free base; 0.05)	5.01	2.25
Phosphate (25% free base; 0.05)	5.72	2.10
Phosphate (50% free base; 0.05)	6.20	2.05
Phosphate (75% free base; 0.05)	6.67	1.85
TRIS (25% free base; 0.05)	6.74	1.64
TRIS (50% free base; 0.05)	7.20	1.18
TRIS (75% free base; 0.05)	7.63	0.67

[a] $\Delta H^‡$ 109.2 ± 0.59 kJ mol^{-1} and $\Delta S^‡$ 6.65 ± 1.30 J K^{-1} mol^{-1} at 65 °C. [b] pD.

Results and Discussion

Hydrolysis.—The pH–rate profile (Figure 1) for the hydrolysis of (**10**) has been reported in our preliminary communication.[6] The full set of data is given in Table 1. The pK_a of the catalytic dimethylamino group (7.40 at 65 °C, from analysis of the pH–rate profile) compares well with the value measured by Awwal and Hibbert[10] for the methoxy derivative (**12**) (7.75 at 25 °C, ionic strength 0.1 mol dm^{-3}). The profile has the same general shape as those obtained for salicylic acid derivatives [and for 8-methoxymethoxy-1-naphthol (**13**), studied recently by Hibbert and Spiers[12]]. But it is dominated by the reaction of the conjugate acid as far as pH 7, demonstrating the catalytic advantage in this reaction of a weak general acid. At pH 7, (**10**)·H^+ is hydrolysed nearly 10^6 times faster than the extrapolated rate for the specific acid-catalysed reaction. This is one measure of the effectiveness of catalysis by the Me_2NH^+ group (see below). However, this comparison involves two very different mechanisms, and thus tells us little about the efficiency of intramolecular *versus* intermolecular catalysis.

Kinetic parameters for the hydrolysis of the conjugate acid of (**10**) are similar to those for the hydrolysis of the salicylic acid

* But which would clearly be irrelevant to the enzyme mechanism, because catalytic and substrate groups are in different molecules.
† 12.66 at 39 °C (see ref. 9).
‡ The p*K*a of the OH group of 8-dimethylamino-1-naphthol is 14.9.[10]
§ 4-Morpholine-ethane sulphonic acid.

Table 2. Second-order rate constants for the reactions of (**11**) with nucleophiles, in 10% MES buffers, pH 4.72–4.90, at 65 ± 0.1 °C, ionic strength[a] 1.0 mol dm^{-3}.

Nucleophile	Concn. range/ mol dm^{-3}	$k_2/10^{-4}$ mol^{-1} dm^3 s^{-1}
Chloride	0.1–0.9	2.48
Bromide	0.1–0.9	3.53
Bromide at 70, 75, 80, and 85 °C		4.80, 7.96, 13.33, 20.78
Iodide	0.3–0.9	6.10
Azide[b]	0.1–0.8	4.08
Thiourea	0.1–0.9	2.24, 2.35
Pyridine	0.1–0.5	≤0.05
Acetate	0.1–0.7	1.52
Methoxyacetate	0.1–0.7	1.97
Chloroacetate	0.1–0.7	1.64

[a] Maintained with NaCl ($NaClO_4$ for chloride and carboxylate reactions). [b] Azide 60% free base, pH 6.0.

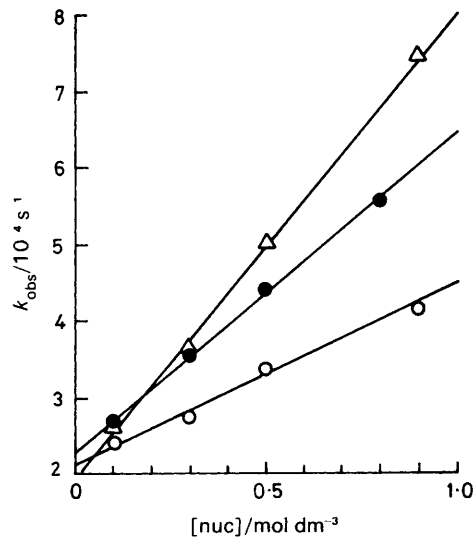
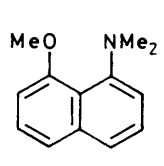


Figure 2. Second-order plots for the reactions of (**10**)·H^+ with selected nucleophiles, at 65 °C and ionic strength 1.0 mol dm^{-3}. Data are for thiourea (○), azide (●), and iodide (△).

derivative (**4**), and similarly are relatively uninformative. The activation parameters (Table 1) are consistent with a unimolecular process in both cases: $\Delta S^{\ddagger}$ = 6.65 J K^{-1} mol^{-1} for (**10**) and 32 J K^{-1} mol^{-1} for (**4**).[13] There is a small deuterium isotope effect: k_{H_2O}/k_{D_2O} = 1.69 at 65 °C for (**10**) and 1.61 at 39 °C for (**4**).[5]



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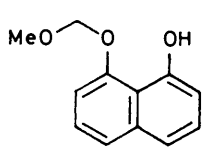

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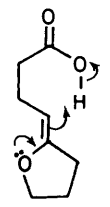
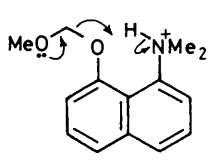


(**14**)

Isotope effects in this range are difficult to interpret with any confidence, since they appear to depend not only on the particular donor and acceptor atoms involved, and the degree of proton transfer in the transition state, but also on transition-state geometry. Thus Kresge[14] recently measured a very low solvent deuterium isotope effect (k_{H^+}/k_{D^+} = 1.33) for the hydrolysis of (**14**), which is otherwise a well behaved general acid-catalysed reaction (Brønsted α = 0.58). Intermolecular proton transfer to the vinyl ether carbon of (**14**) involves much larger isotope effects,[14] as appears generally to be the case.[15] Proton transfer in the intramolecular reaction occurs through a six-membered cyclic transition state, and thus must involve non-linear geometry at H. This is the case also with our derivatives, and in the salicylate system. Furthermore, Liotta[16] has provided evidence that 'acute transition-state geometry' may reduce primary isotope effects well below the expected values for proton transfers to and from carbanions.

Thus the low solvent deuterium isotope effect tells us little about the mechanism of hydrolysis of (**10**). But in the light of the large rate enhancement associated with the presence of the Me_2NH^+ group (Figure 1), and previous discussions of this type of reaction,[5] we can write a partial mechanism (**15**) for the hydrolysis of the conjugate acid of (**10**). This is similar to the



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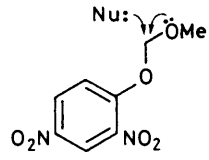


(**16**)

mechanism (**4**) written for the hydrolysis of the corresponding salicylic acid derivative, but the similarities conceal important differences. In particular, the hydrolysis of (**10**)·H^+ is catalysed by nucleophiles, while the evidence in the case of (**4**) is not convincing (see below).

Reactions with nucleophiles.—In previous work we characterised nucleophilic catalysis (**16**) of the hydrolysis of 1-methoxymethoxy-2,4-dinitrobenzene (**3**),[3] and Knier and Jencks[17] have reported similar reactions of the *N*-methoxymethyl-*N*,*N*-dimethylanilinium cation. A preliminary study on 2-methoxymethoxybenzoic acid at its pK_a (pH 3.77, at 39 °C, 0.1 mol dm^{-3} formate buffer, ionic strength made up to 1.0 mol dm^{-3} with various salts) showed no evidence for nucleophilic catalysis of hydrolysis.[3b] The observed first-order rate constants (7.28, 7.06, 9.18, and 9.87 × 10^{-4} s^{-1} for $NaClO_4$, KCl, NaSCN, and NaBr, respectively, with cation effects expected[3a] to be negligible), show no sensible dependence on nucleophilicity.

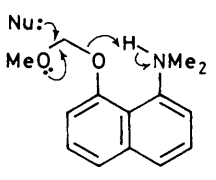
In contrast, the hydrolysis of (**10**) shows well-defined catalysis by added nucleophiles in the pH-independent region near pH 5. Data are shown in Table 2, and second-order plots for selected nucleophiles in Figure 2. The curvature which complicated the corresponding plots for the reactions of anions with the neutral acetal (**3**) is not a problem for (**10**)·H^+. For reactions with anions there is a good correlation (r = 0.970) with the Swain–Scott nucleophilicity parameter n (based on reactions with MeBr in water[18]), with a low sensitivity (slope) s = 0.24. This is identical within experimental error with the s value observed for the reactions (**16**) with nucleophiles of methoxymethoxy-2,4-dinitrobenzene,[3] and the plot shows similar negative deviations for the points for neutral nucleophiles, thiourea and water. [Pyridine, unaccountably, shows no reaction with (**10**)·H^+.] A log–log plot of observed second-order rate constants for the reactions of (**10**)·H^+ (at 65 °C) and (**3**) (at 39 °C) for the six nucleophiles (of both charge types) common to both studies shows an excellent linear correlation (r = 0.996) and unit slope (0.99). This indicates an identical response of the nucleophile to the electrophilic centre in the two transition states, and hence also similar degrees of bond-breaking to the leaving group.

This is convincing evidence that a nucleophile mechanism is involved: the alternative general base catalysis can be ruled out

with confidence because iodide, the weakest base, is the most effective catalyst. We did not attempt to isolate the initial product of nucleophilic attack, as we could in the reaction of 1-methoxymethoxy-2,4-dinitrobenzene.[3] Here this is expected to be a short-lived species in each case, so that true nucleophilic catalysis of hydrolysis is involved.

Thus the picture we developed earlier for (3),[3a] of a loose ('exploded') transition state, with bond breaking well advanced, but little bond formation to the nucleophile, applies also to the reactions of (10)·H$^+$. In particular, it must apply to the reaction with water. As mentioned above, this reaction shows a negative deviation from the Swain–Scott plot for reactions with anions; presumably a modest electrostatic effect. But if water were *not* involved as a nucleophile—because the simple unimolecular process (15) was faster—a positive deviation would be expected.[3a] This evidence is consistent with the conclusion of Young and Jencks[19] that the methoxymethyl cation is too unstable to exist in water. So our picture (17) of the hydrolysis reaction, like that with other nucleophiles, includes some, albeit weak, involvement of water as a nucleophile. $\Delta S^{\ddagger}$ for the second-order reaction with Br^- is 30 J K^{-1} mol^{-1}, smaller than that (Table 1) for the hydrolysis reaction: a similar difference is observed for the water and iodide-catalysed reactions of (3).[3] Of course, the main driving force for elimination of the leaving group, as expected for an acetal, remains the non-bonded electron pair on the remaining oxygen.

A similar mechanism (18) accounts for the reaction with carboxylate anions. We have few data (Table 2), but there is clearly a very low sensitivity to basicity also (Brønsted β close to zero): the most basic of the three carboxylate anions used (acetate) reacts no faster than the least basic (chloroacetate). This result is consistent with a preassociation–concerted mechanism,[17] but since reactivity towards (10)·H$^+$ does depend, albeit weakly, on conventional nucleophilicity towards saturated carbon, we prefer the picture with some bonding to the nucleophile in the transition state. On a mole for mole basis, carboxylate ions react with (10)·H$^+$ 30–40 times more rapidly than do molecules of water.



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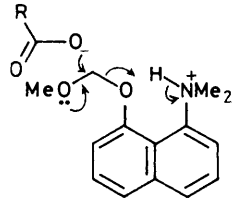

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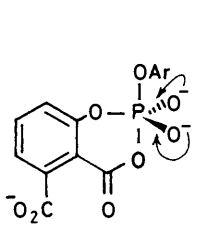
Efficiency of Catalysis.—We cannot calculate effective molarities[4] for the neighbouring CO_2H and Me_2NH^+ groups of acetals (4) and (10)·H$^+$ because intermolecular general acid catalysis is not detectable for the hydrolysis of formaldehyde acetals $MeOCH_2OAr$. This evidence itself sets a lower limit of 10–20 mol dm^{-3} on the EM, but it is not possible to be more precise. Next best as a measure of efficiency is to estimate the rate enhancements associated with the introduction of the catalytic groups, using available free-energy relationships for the spontaneous hydrolysis of the related compounds $MeOCH_2OX$.[20] This requires an estimate of what the pK_a of the leaving group—salicylate monoanion for (4), the naphthol (11) for (10)—would be in the absence of the intramolecular hydrogen bond. For (11) we use the measured pK_a (9.40) of 1-naphthol.[21] [We attempted to make the 8-trimethylammonium derivative of (11), as a better model for (10)·H$^+$, but it turned out to be very unstable.[11]] For salicylate the problem is more complicated, since the electronic effect of the *o*-CO_2H group cannot be neglected, nor can it be simulated by *o*-CO_2Me, since methyl salicylate itself shows significant intramolecular hydrogen bonding.[9]

We make two independent estimates, which turn out to be in good agreement. (i) From the product ratio observed for the breakdown of a series of pentacovalent intermediates (19), formed from aryl salicyl phosphate esters, salicylate has been shown to be lost at the rate expected for an exocyclic (ArO^-) group derived from a phenol of pK_a 8.52.[22] In this case the CO_2H proton is replaced by the more electrophilic phosphorus. Alternatively, (ii) we can compare data for the reactions of substituted pyridines ($\beta_{nuc.}$ = 0.21)[23] with salicyl phosphate dianion (20), and other phosphate ester dianions: the transition state for this reaction is closely similar to that for hydrolysis, which appears to involve no detectable proton transfer from CO_2H to the leaving group oxygen. Insofar as any proton



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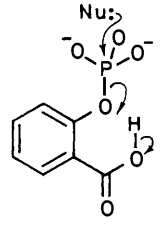


(20)

transfer has occurred—and unless a conformational change is entirely rate determining it seems inescapable that the process must at least have started, to account for the observed catalysis—any error in our estimate will be in the opposite direction to that based on reaction (19).

Direct and cross interaction coefficients[24] have been measured for phosphoryl transfer between substituted pyridines;[25,26] the few data that are available for phosphoryl transfer from arenolates to pyridines exhibit similar behaviour. The dianion of 2,4-dinitrophenyl phosphate undergoes a clean second-order reaction with pyridines which is independent of the basicity of the nucleophile (Brønsted $\beta_{nuc.}$ = 0).[27] The corresponding reaction with 4-nitrophenyl phosphate shows a small but significant $\beta_{nuc.}$ = 0.13.[28] Based on these two systems we can calculate a cross interaction coefficient p_{xy} = $d\beta_{nuc.}/dpK_L$ = 0.042 (significantly greater than p_{xy} = 0.014 observed for phosphoryl transfer between pyridines[25]). Using this value, and the observed $\beta_{nuc.}$ of 0.21, we can estimate pK_L = 9.0 for the almost non-hydrogen bonded salicylate monoanion. In view of the uncertainties involved, this represents better than hoped for agreement with estimate (i), and we use the mean value of 8.75 with some confidence as the appropriate pK_a for the OH group of salicylate with the H-bond opened. (This allows an estimate also, using the observed pK_a,[9] of 1.2 × 10^{-4} for the equilibrium constant for the opening of this H-bond, very close to an estimate of 1 × 10^{-4} made by Hibbert.[29])

Salomaa's data[30] for the spontaneous hydrolysis of the methoxymethyl esters of chloroacetic, formic and acetic acids at 35 °C gives an excellent linear correlation with the pK_a of the leaving group acid (β_{LG} = 0.78, r = 0.9999), which predicts accurately the known rate constant for the spontaneous hydrolysis of methoxymethoxy-3,4-dinitrobenzene[20] at 39 °C. We use this correlation to estimate spontaneous rates at 39 °C for the hydrolysis of other $MeOCH_2OAr$ compounds, with pK_{ArOH} of 8.75 and 9.40, as 1.4 × 10^{-8} and 4 × 10^{-9} s^{-1}, respectively. There is evidence of significant steric acceleration by an *o*-nitro group, worth just over an order of magnitude in rate, for the cleavage of methoxymethoxy-2,4-dinitrobenzene,[20]

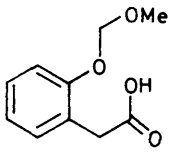
Table 3. Catalytic effects of neighbouring general acid groups on the hydrolysis of methoxymethyl acetals.

Compound	pK_{est}	k_{hyd}(est)	k_{obs}/s^{-1} (at 39 °C)	Catalysis
(**4**)	8.75	1.4×10^{-7}	1.43×10^{-3}	1×10^{4}
(**10**)·H^+	9.4	4.25×10^{-9}	8×10^{-6}	1.9×10^{3}
(**25**)	9.4	4.25×10^{-9}	$<4 \times 10^{-6}$ [a]	<900

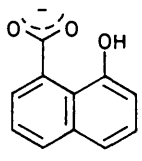
[a] The value of k_{obs} is about half that observed for (**10**) at 65 °C;[31] the ratio will thus be greater at 39 °C.

so our best estimate for the salicylic acid derivative is 1.4×10^{-7} s^{-1} (Table 3).

The salicylic acid systems remains the most efficient, though these comparisons take no account of the strength of the general acid involved [3.6 pK_a units stronger for (**4**) than for (**10**), which is over 100 times less reactive]. But all three systems in Table 3 are highly efficient compared with compounds like 2-methoxymethoxyphenylacetic acid (**21**),[31] (**6**) and (**7**) which all show little or no catalysis by neighbouring CO_2H groups. All three compounds in Table 3 are characterised by intramolecular hydrogen bonds between the leaving group OH and the conjugate base of the general acid in the products of hydrolysis; these are stronger for salicylate (**9**) and (**11**) than for (**22**) (which has a pK_a of 11.5 at 40 °C[32]).

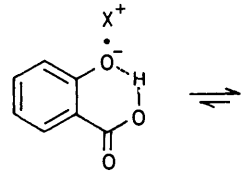


(**21**)

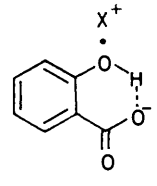


(**22**)

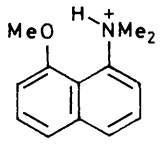
We conclude that a strong intramolecular hydrogen bond of this sort stabilises not only the product, but also the transition state leading to it, and thus confers a kinetic advantage on the derivatives of such systems in appropriate reactions. This is consistent with our previous conclusions about the transition states for the hydrolysis of salicylic acid derivatives (**23**), which are well advanced in terms of bond breaking, but not in terms of proton transfer to the leaving group,[5,23] simply requiring that the strength of the intramolecular H-bond be similar for both positions (**23**) ⇌ (**9**) of the proton in the leaving group.



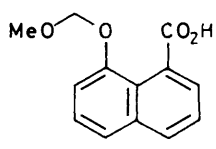
(**23**)



(**9**)



(**24**)



(**25**)

Specifically, catalytic efficiency should depend on the difference in hydrogen-bond strengths between ground and transition states. An *o*-alkoxy substituent has no significant effect on the pK_a in benzoic acid in aqueous media,[33] so we may presume that intramolecular hydrogen bonding is insignificant in the ground state for (**4**). On the other hand, Awwal and Hibbert[10] detected a weak hydrogen bond (K 2–5 × 10^{-2}) for the 8-methoxy compound (**24**), which has a similar pK_a to (**11**), which may be presumed to behave similarly. This would reduce the difference in hydrogen-bond strengths relative to (**4**), and perhaps explain the lower efficiency of catalysis in the former system.

Conclusions

There is a growing body of evidence that a key factor in the high efficiency of proton-transfer catalysis in systems such as those listed in Table 3 is the strong intramolecular hydrogen bond, involving the catalytic proton, in the products of reaction, which is weak or absent in the initial states. All three systems in Table 3 give products involving such a hydrogen bond, whereas inefficient systems [*e.g.* (**6**), (**7**), and (**21**)] do not. Of the three compounds in Table 3, the two most efficient [(**4**) and (**10**)] have the strongest product intramolecular H-bonds; the salicylic acid system (**4**) may be more efficient than (**10**) because there is already significant intramolecular H-bonding in the latter ground state, suggesting that the important parameter is indeed the difference in the strengths of the intramolecular hydrogen bonds in the starting materials and the transition states.

There is no reason to doubt that enzyme active-site structures are well able to provide the conditions for the formation of strong hydrogen bonds between suitable donor and acceptor groups. The two most successful model systems available for efficient proton-transfer catalysis [(**9**) and (**11**)] differ qualitatively, in that delocalisation in the salicylate monoanion may strengthen the hydrogen bond by allowing the basicities of the donor and acceptor oxygens to converge, whereas the strength of the H-bond in (**11**) depends primarily on the geometry of the system, and may therefore be a better model for an enzyme system. But in neither case is participation by external nucleophiles very effective: added 1 mol dm^{-3} carboxylate anion, for example, does not even double the rate of hydrolysis of (**10**)·H^+. We may have made some progress in developing a model for the lysozyme reaction with relatively efficient proton-transfer catalysis, but the role of the nucleophile in the model remains largely passive. Here lies the most obvious scope for improvement.

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