Highly Efficient Intramolecular General Acid Catalysis of Enol Ether Hydrolysis, with Rapid Proton Transfer to Carbon

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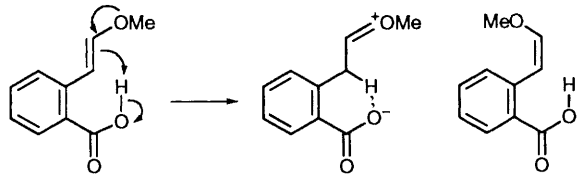
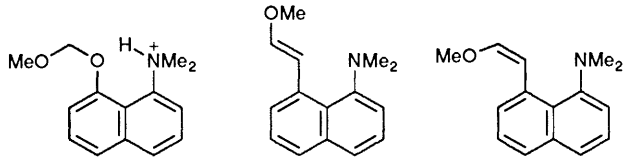
The hydrolysis of *E* and *Z* enol ether groups in the 8-position of 1-dimethylaminonaphthalene is catalysed by the neighbouring dimethylammonium group with remarkable efficiency. Similar compounds lacking a neighbouring general acid have been studied in strong acid, but the half-lives of **4***Z* and **4***E* below pH 3 are of the order of 10 s at 39 °C and external acid catalysis cannot be detected. The effective molarity is estimated as >60 000 M, the highest known for proton-transfer catalysis. This is ascribed to effective hydrogen-bond stabilisation of the in-flight proton. So efficient is proton transfer to carbon that the rate-determining step is probably not proton transfer to carbon but opening of the intramolecular hydrogen bond of the oxocarbocation intermediate **7**. The tight intramolecular H-bonding responsible for the high efficiency of catalysis prevents significant H/D exchange with solvent D_2O.

The hydrolysis of enol ethers **1***E* and **1***Z* is subject to highly efficient intramolecular general acid catalysis by the neighbouring carboxy group.[1] The effective molarity (EM[2] *ca.* 2000 M) of the carboxy group of **1***Z* in this reaction[1] is the highest yet measured for proton transfer to carbon, and we have explained it in terms of strong hydrogen bonding of the in-flight proton in the transition state. Hydrogen bonding between the carboxylic acid proton and the relevant H–C bond is negligible in the ground state, but presumed to be very strong in the initial product (**2**) of the reaction, which has a strongly acid C–H in the correct position to form a hydrogen bond with the carboxylate group. We believe that this strong, intramolecular hydrogen bonding has developed sufficiently to stabilise the transition state, and thus account for the high efficiency of general acid catalysis in this system. The structural features necessary for the formation of strong hydrogen bonds are readily available in enzyme active sites, and there is a strong presumption that such strong hydrogen bonding is a key factor in proton-transfer catalysis in relevant enzyme reactions. In an efficient enzyme-catalysed process such hydrogen bonding would be stronger in transition states than in ground or product states, and we are developing model systems which show this property.



1*E* **2** **1***Z*

The general base involved in enzyme-catalysed enolisations is often imidazole. It is not easy to predict how the change from a negatively charged (as in **2**) to a neutral general base will affect the strength of intramolecular hydrogen-bonding in the transition state, so we have examined a model system designed to show highly efficient general acid catalysis by a neighbouring NH^+ group of the reverse, ketonisation process. The pK_a of the dimethylammonium group of the acetal **3**, which shows a very high EM as a general acid in the hydrolysis of the acetal group,



3 **4***E* **4***Z*

is close to 7,[3,4] similar to that of imidazole. So we have examined the hydrolysis of the *E* and *Z* isomers **4***E* and **4***Z* of the enol ether derived from 8-dimethylamino-1-naphthylacetaldehyde.

Results and Discussion

Synthesis.—The parent naphthyl enol ethers **5***E* and **5***Z*, required for the determination of the EM, were prepared by Wittig olefination of 1-naphthaldehyde.‡ The mixture of *cis* and *trans* isomers obtained could be separated by either PLC or preparative HPLC. However, the corresponding mixture of isomers obtained from 8-dimethylamino-1-naphthaldehyde could not be separated, so **4***Z* and **4***E* were prepared separately, by the elimination of diphenylphosphinate from the separated intermediate diastereoisomeric adducts **6a** and **6b** according to Earnshaw *et al.*[5]

Reactivity.—The hydrolysis of the enol ethers **4***Z* and **4***E* is a remarkable reaction in several respects. (*E*)- and (*Z*)-PhCH=CHOMe were described by Chiang *et al.*[6] as 'too unreactive to be hydrolysed at convenient rates in dilute aqueous acid', and were studied by these authors in 10–55% $HClO_4$ (at 25 °C). Below pH 3 the half-lives of both **4***Z* and **4***E* are 13 and 10 s, respectively, at 39 °C. Moreover, within the pH-range the reactions are pH-independent, although the hydrolysis of an enol ether is normally exclusively acid catalysed: for the reactions of **4***Z* and **4***E* we find no significant acid catalysis even in 4 mol dm^{-3} HCl, and so can set only an upper limit on the rate of the acid-catalysed hydrolysis. Finally, the two isomers are hydrolysed at closely similar rates (ratio $k_0^{4Z}/k_0^{4E} = 1.33$), although the *Z* isomers of enol ethers are generally hydrolysed more rapidly—typically by a factor of about 4.[6,7] For example,

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‡ The trimethylammonium derivatives of **4**, which would be the first choice of compounds for comparison, are not available in these systems.[4]

Table 1 Kinetic parameters for the hydrolysis reactions of enol ethers studied in this work, at 39 °C and ionic strength 1.0 mol dm^{-3} (KCl)

	4Z	4E	5Z	5E
$k_H/dm^3\ mol^{-1}\ s^{-1}$	$(<5 \times 10^{-2})$	$(<2.5 \times 10^{-3})^a$	$1.68 \pm 0.1 \times 10^{-2}$	$4.50 \pm 0.26 \times 10^{-3}$
k_0/s^{-1}	$6.87 \pm 0.32 \times 10^{-2}$	$5.16 \pm 0.13 \times 10^{-2}$		
K_a		$9.76 \pm 1.6 \times 10^{-5}$		
pK_a		4.01 ± 0.08		

[a] Least-squares analysis of rate constants for the hydrolysis of **4E** at eight different HCl concentrations from 0.025 to 3.0 mol dm^{-3} gives $k_H = 1.3 \pm 0.9 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$.

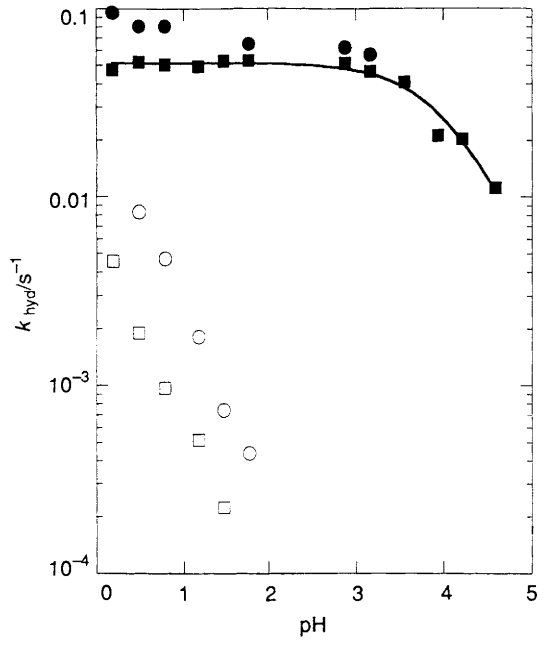
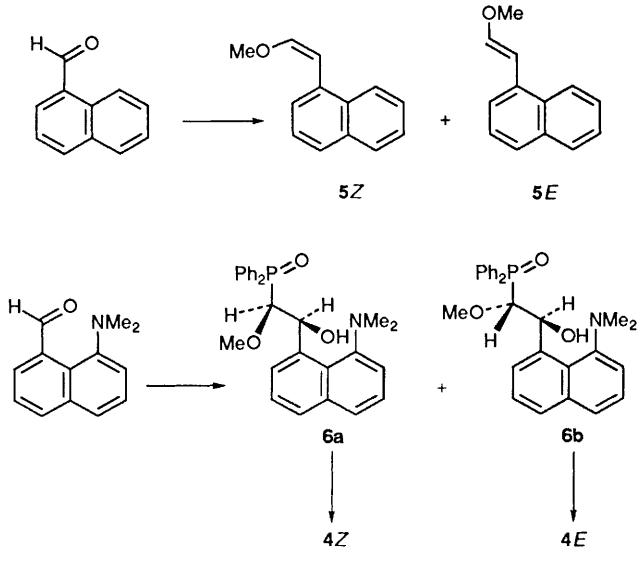


Fig. 1 pH–rate profiles for the hydrolysis of enol ethers **4E** (■) and **4Z** (●) and the corresponding 1-naphthyl derivatives **5E** (□) and **5Z** (○), at 39 °C and ionic strength 1.0 mol dm^{-3} (KCl). The points are experimental, the curve calculated, for the reaction of **4E**, using the rate and dissociations given in Table 1.

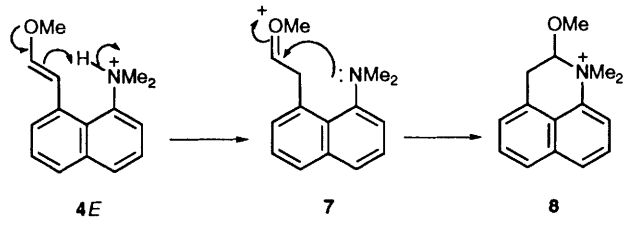


5Z is hydrolysed 3.7 times faster than **5E**, in a typical acid-catalysed reaction, while the rate ratio (k_0^{1Z}/k_0^{1E}) for the related enol ethers **1** described in the previous paper [1] is 12.5.

This behaviour is illustrated for the four compounds discussed in this paper by the pH-rate profiles shown in Fig. 1. The curve drawn for **4E** follows the ionisation of the dimethylammonium group, indicating that the exceptional reactivity is associated with the presence of this group. External acid catalysis is not observed simply because it is negligible—even in quite strong acid—compared with the effect of the neighbouring dimethylammonium group. Analysis of the data for **4Z** and **4E** allows us to set upper limits on the rate constants for H_3O^+-catalysed hydrolysis of 5×10^{-2} and $2.5 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$, respectively: consistent with values of 1.7×10^{-2} and $4.5 \times 10^{-3}\ dm^3\ mol^{-1}\ s^{-1}$ observed for the hydrolysis of **5Z** and **5E** under the same conditions. These data are summarised in Table 1.

The pK_a of the dimethylammonium group of **4E**, at 4.01, is—unexpectedly—normal for an aniline, and thus lower by some 3 units than the value near 7 found for the acetal **3**.[3,4] We attributed this increase in basicity of the dimethylamino group of the conjugate base of **3** to the steric effect of the *peri*-substituent, preventing it from lying in the plane of the aromatic system and thus interrupting the π-delocalisation which lowers the basicity of an aniline.[3] Since this factor should be no less important for **4** the effect which raises the pK_a of **3** to 7 must have a different origin: stabilisation of the protonated form of **3** by strong intramolecular hydrogen-bonding seems most likely.

Stereochemistry and Mechanism.—Though we have referred to the disappearance of the enol ether function in aqueous acid as hydrolysis, the rapid reaction of **4Z** and **4E** in aqueous solution at pH < 3 actually gives mainly the product (**8**) of addition of the dimethylammonium group to the double bond. [Smaller amounts of a hydrolysis product (**9**) are also formed, as discussed below.]



The reaction undoubtedly involves the two steps shown: since there is no catalysis by external general acids, and no significant amount of free dimethylamino group present at low pH a mechanism involving nucleophilic attack on the double bond by nitrogen—not unprecedented in systems with high EM [8]—can safely be ruled out.

For any normal enol ether little more discussion of mechanism would be necessary: the hydrolysis of simple enol ethers has been found, without exception,[9] to proceed by rate-determining proton transfer to carbon. The rate-determining step in the reaction of **4** should then be the proton transfer to give **7**, followed by the rapid capture of the oxocarbocation by the neighbouring dimethylamino group, competing favourably with attack by water by virtue of its high EM as well as its greater nucleophilicity. However, the proton-transfer step in this system is designed to be exceptionally fast: the de-protonation of **7** to regenerate starting material will therefore

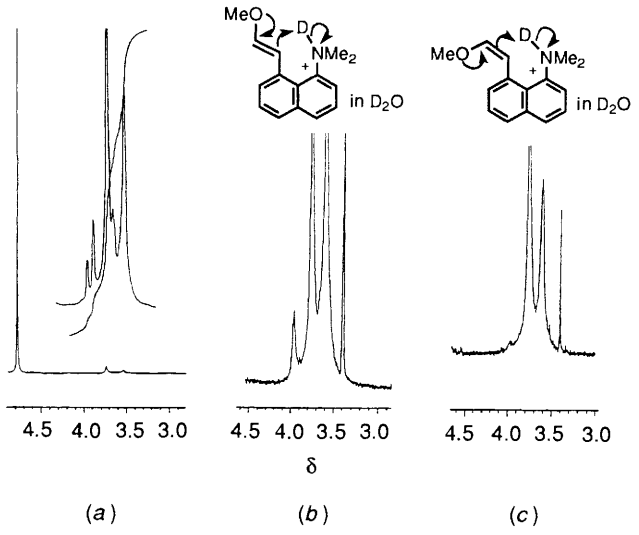


Fig. 2 Part ^{1}H NMR spectra of the reaction products (250 MHz, D_2O) from **4***E* and **4***Z*: (*a*) product from **4***E* (or **4***Z*) in H_2O; (*b*) from **4***E* in D_2O; (*c*) from **4***Z* in D_2O. The stronger signals represent the Me_2N^+ and OMe groups of the product **8**, and the sharp signal at δ 3.4 the small amount of methanol formed [absent from spectrum (*a*) because MeOH was removed with H_2O by evaporation]. See the text.

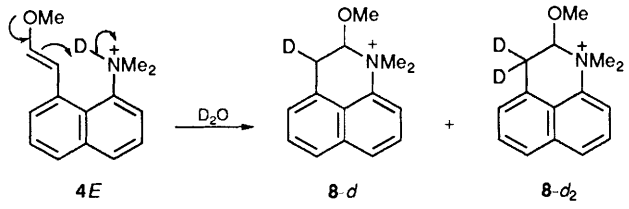
be highly favourable kinetically (high EM) as well as thermodynamically (the difference in the pK_as of the Me_2NH^+ and C–H groups may be as large as 9–10). Conditions for reversibility of the proton transfer step are therefore particularly favourable, and the forward reactions of the intermediate **7** are also relatively slow (see below).

The experimental evidence is not conclusive, but suggests that if a single step is rate determining, it is not the initial proton transfer to the enol ether carbon.

(1) *The rates of disappearance* for **4***Z* and **4***E* are closely similar, even though **4***Z* would be expected to be more reactive, as discussed above. (A particularly telling comparison is of the reactivities of the *E* and *Z* isomers of **4** with those of **1**, shown[1] to be hydrolysed with efficient intramolecular general acid catalysis, but with proton transfer to carbon rate determining in the usual way for enol ethers. **4***E* is hydrolysed 30 times faster than **1***E*, but **4***Z* only 3 times faster than **1***Z*.) A possible explanation would be that **4***Z* and **4***E* are interconverting by way of **7**, and that the observed rate corresponds more closely to that of the predominant isomer. Rapid equilibration can however be ruled out because the rates of disappearance of **4***Z* and **4***E* are measurably different. Kresge[10] has described the intermediate situation, with deprotonation and (in this case) cyclisation occurring at comparable rates. This would give different rates for each isomer, at least initially, and be characterised by kinetic behaviour which deviated significantly from strictly first order for the first one or two half-lives. After this period both isomers should settle down to give well behaved reactions showing identical rate constants corresponding to that of the equilibrium mixture of isomers present under the reaction conditions. An examination of the initial rate of disappearance of **4***Z* (*i.e.*, over the first second or so of reaction) showed no sign that the rate decreases over the course of the reaction.

(2) *Low solvent deuterium isotope effects* of 1.76 and 1.86 (in 0.03 mol dm^{-3} DCl in D_2O) are observed for the cyclisations of **4***Z* and **4***E*, respectively. These values are the lowest observed for enol ether hydrolysis.* Rate-determining proton transfer in such reactions is normally characterised by a primary deuterium isotope effect in the region of 3[11] (the rapid intramolecular reaction described in the previous paper[1] is a case in point); an inverse effect is expected where there is full reversibility. The values observed in the present case probably† rule out full reversibility, but are consistent with either an intermediate situation, or with strong hydrogen-bonding of the in-flight proton in the transition state.

(3) *Deuterium exchange experiments: mass spectra.* Because of the expected primary isotope effect on C–H cleavage, rapid deprotonation of **7** would favour removal of protium, so that reprotonation would introduce a second deuterium atom. If proton transfer were irreversible, on the other hand, only a single deuterium would be incorporated into the final product.



The mass spectrum of the product obtained from **4***Z* in D_2O provides evidence for the formation of small amounts of **8***d*$_2$. A strong peak at *m*/*z* 229 corresponds to M^+ for the tricyclic cation **8**-*d*. The *M* + 1 peak at 230 is too intense to be accounted for solely as the ^{13}C peak. The observed relative intensity of this peak is 32% of the molecular ion peak, compared with the 16.9% expected for the monodeuterio compound. This suggests that a small amount of **8**-*d*$_2$ is formed. The mass spectrum of the product from **4***E* did not show this enhancement of the *M* + 1 peak.

(4) *Deuterium exchange experiments.* ^{1}H *NMR.* The relevant part of the 250 MHz spectrum of the cyclic product **8** is shown in Fig. 2(*a*). The signals of the methylene group of interest appear as a partially concealed AB system with a geminal coupling constant of 18 Hz. Vicinal coupling is not apparent in the better-resolved low-field doublet,‡ suggesting that this represents the proton *anti* to the methoxy group, expected to appear at lower field if the methoxy group were pseudoequatorial in the heterocyclic ring (see Scheme 1 below). This doublet is not present in the spectrum [Fig. 2(*c*)] of a sample of **8** prepared by treatment of **4***Z* with 0.01 mol dm^{-3} DCl in D_2O. Possible explanations are the stereospecific substitution of the lower field proton by deuterium with consequent collapse of the remaining proton signal to a broad singlet (masked in this case by the signals of the $^+NMe_2$ and OMe groups): or the replacement of both hydrogens by deuterium. The same experiment on **4***E* shows that the former explanation is correct: the spectrum [Fig. 2(*b*)] shows the lower field proton signal, but as a broad singlet, indicating that the major product at least is the mono-deuterio compound **8**-*d*. These results do not rule out the possibility that some di-deuterio compound **8**-*d*$_2$ is formed. They do show clearly that the formation of **8**-*d* is close to stereospecific: based on the assignment of the lower field signal of the AB system to the proton *anti* to the OMe group the addition of the Me_2NH^+ group is *syn* (**10**→**11**, below).

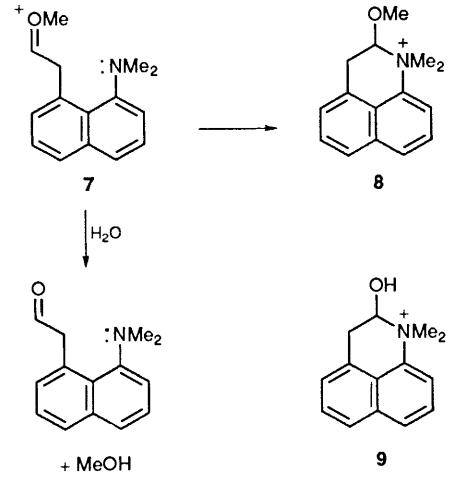
A signal at δ 5.45, assigned to the anomeric proton of **8**, is a

* Note that these values, measured in the pH-independent region, represent direct measurements of k_H/k_D, and are not reduced by the isotope effect on the pK_a, as are measurements made at pH > pK_a.

† The status of the proton or deuteron in the strong intramolecular C–H · · · N hydrogen bond we believe to be formed in the initial proton transfer step is not well-enough defined to allow us to estimate an equilibrium isotope effect with confidence.

‡ Spectra at 500 MHz did not improve the resolution significantly, but at 250 MHz it was possible to measure a coupling constant of 5.6 Hz on one leg of the partially concealed higher field part of the AB system.

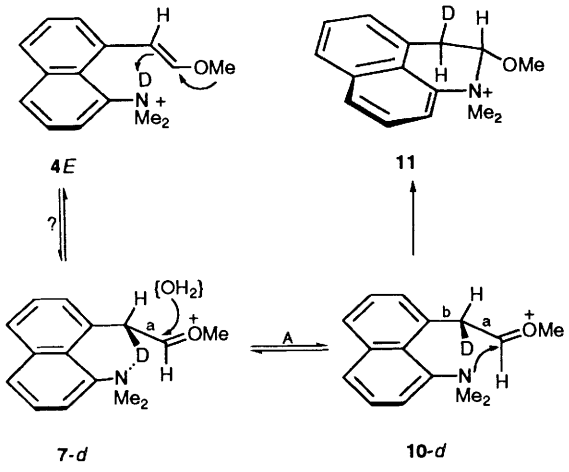
broad singlet at 250 MHz showing no significant coupling to either proton of the methylene group. A second signal at δ 5.65 indicates that a second product is formed. This peak is present in all product ^{1}H NMR spectra, and is accompanied in the product mixture by a sharp singlet of threefold higher intensity at δ 3.4, as expected for methanol. This identifies the minor product as **9**. It is clearly a kinetic product: from the NMR peaks the product ratio **8**:**9** is 5–6:1 from **4Z**, and 6:4 from **4E**, and these ratios do not change over 1–100 half-lives for the cyclisation. The formation of **9** complicates the interpretation of the deuterium incorporation experiments, because the signals of the CH_2 protons of interest in **8** and **9** are not resolved.



(5) *Deuterium exchange experiments:* ^{2}H *NMR.* Both isomers give two singlets in the positions (δ 3.9 and 3.6) corresponding to the original methylene doublets, thus giving access to information not available from the ^{1}H spectrum. Each represents one diastereoisomer of the mono-deuterio compound. **4***E* gives a *ca.* 2:3 ratio of products (low field : high field deuterium signal) whereas this increases to *ca.* 4:1 for **4***Z*. This selectivity can be explained by predominant *syn* addition, *via* the shortest pathway for ring closure (Scheme 1); diluted by the formation of significant amounts of **9** (the AB systems of the CH_2 groups of **8** and **9** are not resolved in the ^{1}H NMR spectrum), and by any **8**-d_2 present.

Kinetics and Mechanism.—The key product-determining steps of the mechanism which best accounts for all the evidence are shown in Scheme 1.

In D_2O the initial proton transfer reaction of **4***E* gives the high-energy oxonium intermediate **7**-*d*, which is significantly stabilised in the conformation shown by a strong intramolecular hydrogen bond between the acidic[1] deuteron α to C=O$^+$Me and the dimethylamino-group nitrogen atom. Rotation about bond *a* in **7** coupled with the reversal of the proton-transfer step would lead to *E* ⇄ *Z* isomerisation of the starting materials, but this will be slower than rotation about a normal single bond because of the σ-delocalisation of the α-C–H(D) bond involved in the strong hydrogen bond, and is not observed to a significant extent. To revert to starting materials the deuteron simply jumps back along this hydrogen bond, losing H-bonding stabilisation but relocalising the positive charge on nitrogen.



Scheme 1

To go on to product **9** the intramolecular hydrogen bond must open, producing a yet more reactive system **10**, with a free dimethylamino group in close (high EM) proximity to C=O$^+$Me. This species would not be expected to exist for a significant time in aqueous solution even in the absence of the neighbouring dimethylamino group.[12] In the present case it is rapidly neutralised by the addition of nitrogen, which competes favourably with the addition of water, itself expected to be a diffusion-controlled process. There is thus no time for conformational equilibration, by rotation about bonds *a* or *b* before collapse to product **11**. This accounts for the observed preference for *syn* addition of the dimethylammonium group. The geometrical restrictions and the short lifetime of the intermediate **7**-*d* presumably direct the addition of water (indicated in parentheses in Scheme 1) to the opposite face of the C=O$^+$Me group: once the hydrogen bond has opened hydration is not expected to compete with cyclisation. The only reaction of **10** likely to compete with cyclisation is reformation of the hydrogen bond, to give back **7**. This will happen only if it is comparable in rate to cyclisation, and thus also faster than conformational equilibration, so will involve specifically the deuteron of **10**-*d*. No deuterium exchange into unchanged starting materials is therefore expected even if the initial proton-transfer step is a fast pre-equilibrium.

If a single step is cleanly rate determining for the overall reaction it is likely to be the one (**A** in Scheme 1) in which the intramolecular hydrogen bond opens. Equilibrium constants for the opening of strong intramolecular N–N···N and O–H···N hydrogen bonds in similar situations are of the order of 10^{-5}, (with correspondingly low rate constants).[13–15] The rate of the thermodynamically favourable proton jump by which **7** reverts to enol ether seems certain to be faster.* The small solvent deuterium isotope effect, and the closely similar rates observed for the reactions of **4***Z* and **4***E* can then be understood as reactions of the two diastereoisomers of **7**-*d*, differing only in the relative positions of the C–H and C=O$^+$Me groups. (The difference in ground-state geometry between the *E* and *Z* forms which normally makes the *Z* isomer of an enol ether more reactive is retained in the pre-equilibrium **4**⇄**7**, and step A involves breaking only a hydrogen bond.)

Efficiency of Proton Transfer.—If the initial proton transfer from the dimethylammonium group to the enol carbon atom of **4** is a fast pre-equilibrium the observed rate of the reaction sets only a minimum on the efficiency of this process. The efficiency is clearly very high, as shown by the extraordinarily high rates of hydrolysis of **4***Z* and **4***E*, and by the consequent absence of external acid catalysis of the hydrolysis of the enol ether group. This makes direct measurement of effective molarities impossible, in the absence of a relevant intermolecular comparison. (Not surprisingly, we could detect no general acid catalysis of the hydrolysis of **4***Z* by general acids, including the hydroxonium ion.)

* The product distribution shows that the hydration of **7** to give **9** is slower than the opening of the intramolecular hydrogen bond, so the addition of water to **7** is likely to be rate determining for the formation of the true hydrolysis product.

The simplest measure of efficiency is the rate enhancement ascribable to the presence of the Me_2NH^+ group. This is given by the vertical difference in rate between the lines of the pH–rate profiles at pH > pK_a (Fig. 1) for the compounds with and without this group, *i.e.*, by the ratio k_0/k_HK_a for a given compound. For **4***E*, where a full data set is available (k_H as an upper limit) the ratio is $>2 \times 10^5$ mol dm^{-3}. For a true EM, based on inter- and intra-molecular reactions proceeding by the same mechanism,[2] we need to estimate the second-order rate constant for catalysis by a general acid of pK_a = 4.01. We can do this only approximately, using the limiting value of k_H and an estimated Brønsted α: for the general acid catalysed hydrolysis of enol ethers, this is typically 0.6 ± 0.1.* The second-order rate constant for catalysis of the hydrolysis of **4***E* by a general acid of pK_a 4.01 will thus be smaller by a factor of at least $10^{0.6\times(4.01+1.74)}$, giving an estimate for k_{HA} of $<8.9 \times 10^{-7}$ dm^3 mol^{-1} s^{-1} (close to the figure of 3×10^{-6} dm^3 mol^{-1} s^{-1} estimated for a general acid of this pK_a from the two-point Brønsted plot for general acid catalysis of the hydrolysis of **1***E*).[1] Our best value is thus EM > 6×10^4 M for the dimethylammonium group of **4***E*.

This is a deliberately conservative estimate, and takes no account of the possibility that the proton-transfer step is not rate determining. Even so, intramolecular general acid catalysis of the reaction of **4***E* is the most efficient yet observed in a simple system. In particular it is substantially more efficient than in the reaction of acetal **3**, in part at least because some intramolecular hydrogen bonding to the *peri*-oxygen is already present in the ground state (as discussed above and as detected for the 8-methoxy compound by Awwal and Hibbert).[15]

Conclusions

The thesis that strong hydrogen bonding to the in-flight proton is the key to efficient general acid–base catalysis is further supported by the observation of the most efficient intramolecular general acid catalysis yet observed, in the reactions of the enol ethers **4***Z* and **4***E*. The evidence in this and the preceding paper[1] shows that the generalisation applies to proton transfer to and from carbon as well as from better known hydrogen bond donors. In fact proton transfer to and from carbon is particularly efficient because hydrogen bonding is absent in the ground and product states of enolisation and ketonisation reactions, so that the transition state for proton transfer is stabilised selectively. The geometrical requirements for such transition states in enzyme reactions, where general acid–base catalysis is expected to be an efficient process, can be predicted in detail on the basis of this work.

Experimental

Kinetic Methods.—Reactions were followed at 39 °C and an ionic strength of 1.0 mol dm^{-3} (KCl), in the thermostatted cell compartment of a Cary 3 spectrophotometer. Runs were initiated by injecting 10–20 mm^3 of a *ca.* 10^{-2} mol dm^{-3} stock solution (freshly prepared) of the appropriate substrate in CH_3CN into 2 cm^3 of the appropriate buffer. The reaction was followed for the first three half-lives with an end-point obtained after at least ten. HCl solutions prepared from Convol™ concentrates were used for the measurements at low pH while formate, acetate and phosphate buffers were used to maintain pH in the region 1–5. No buffer catalysis could be detected.

Deuterium Exchange Experiments.—5–10 mg of the appropriate enol ether was dissolved in sufficient quantity of 0.01 mol dm^{-3} DCl in D_2O to form a solution and an NMR spectrum obtained immediately. A spectrum of the protio-product **9** was obtained by first dissolving in 0.05 mol dm^{-3} HCl in H_2O, evaporating to dryness and redissolving in D_2O. Samples for ^{2}H NMR were prepared similarly, by initially dissolving in 0.01 mol dm^{-3} DCl in D_2O and replacing the solvent with H_2O.

(Z)- *and* (E)-1-*Dimethylamino*-8-(2-*methoxyethenyl*)*naphthalene* (**4***Z and* **4**E).—According to Levine:[18] dry ether (6 cm^3) was added to dry triphenyl(methoxymethyl)phosphonium chloride (0.344 g, 1.004 mmol) under an atmosphere of argon, forming a suspension. Phenyllithium (0.56 cm^3 of a 1.8 mol dm^{-3} solution, 1.008 mmol, in 70:30 cyclohexane–ether) was added slowly, resulting in the formation after several minutes of a deep red solution containing an orange precipitate. After being stirred for a further 15–20 min at room temperature to ensure complete formation of the Wittig reagent, the suspension was cooled to − 78 °C and a solution of 8-dimethylaminonaphthalene-1-carbaldehyde[19] (100 mg, 0.502 mmol) in dry ether (3 cm^3) added slowly. The mixture was then stirred at −78 °C for *ca.* 1 h during which time the precipitate appeared to decolorise and the supernatant solution became orange/yellow in colour. After being stirred for a further 2 h at room temperature, the reaction mixture was filtered to remove suspended solids and the ethereal filtrate concentrated to a yellowish oil. By TLC (10% ether–hexane), this oil consisted of a small quantity of unchanged starting material and two products, running close together, corresponding to triphenylphosphine oxide and the enol ether. The latter two spots were difficult to separate by column chromatography, even using gradient elution techniques, but preparative layer chromatography was successful (eluent 10% ether–hexane). This procedure gave a mixture of (*Z*)- and (*E*)-dimethylamino-8-(2-methoxyethenyl)naphthalene (**4***Z* and **4***E*, *ca.* 1:2 by ^{1}H NMR spectroscopy) as a single band. These isomers could not be separated by standard chromatographic techniques under the conditions investigated, nor by preparative HPLC using a Dynamax macro silica gel column.

(Z)- *and* (E)-1-(2-*Methoxyethenyl*)*naphthalene* (**5***Z and* **5**E).—Triphenyl(methoxymethyl)phosphonium chloride (0.822 g, 2.4 mmol) in dry ether (10 cm^3) was stirred as a suspension at room temperature while one equivalent of phenyllithium (1.33 cm^3 of 1.8 mol dm^{-3} in 70:30 cyclohexane–ether) was slowly added. A deep red solution containing an orange/yellow precipitate developed after *ca.* 5 min. After being stirred for a further 15–20 min the suspension was cooled to −78 °C and a solution of 1-naphthaldehyde (0.22 cm^3, 1.6 mmol) in dry ether (4 cm^3) was added slowly. The mixture was stirred for a further 2 h at this temperature and then allowed to warm to −60 °C over the next hour. The cooling bath was removed and stirring continued for a further 45 min. The mixture was then filtered to remove suspended solids, which were washed with ether. The combined washings and filtrate were evaporated yielding a yellowing oil. A preliminary purification was carried out using column chromatography (10% ether–hexane as the eluent) to remove baseline material and separate off any unchanged starting material and triphenylphosphine oxide. The mixture of *cis* and *trans* isomers so obtained was separated by preparative HPLC (eluent 5% ether–hexane) on a Dynamax macro silica gel column, yielding the *trans* isomer **5***E* as a colourless oil, t_R 19.5 min; δ_H(250 MHz; $CDCl_3$ [filtered through K_2CO_3]) 8.10–8.06 (1 H, m, Ar), 7.85–7.80 (1 H, m, Ar), 7.73–7.67 (1 H, m, Ar), 7.56–7.45 (2 H, m, Ar), 7.43–7.35 (2 H, m, Ar), 6.98 (1 H, d, *J* 12.6, enol C*H*Ar), 6.46 (1 H, d, *J* 12.6, enol C*H*OMe), 3.80 (3 H, s, OMe) and the *cis* isomer **5***Z*, also as a colourless oil, t_R 22 min;

* The point for the hydroxonium ion generally shows a negative deviation from Brønsted plots for general acid catalysis,[16] but this has been convincingly ascribed to an electrostatic effect,[17] so will apply equally to a reaction catalysed by the dimethylammonium group.

δ_H(250 MHz; $CDCl_3$ [filtered through K_2CO_3]) 8.10–8.06 (1 H, m, Ar), 8.01 (1 H, d, *J* 7.27, Ar), 7.83–7.78 (1 H, m, Ar), 7.69 (1 H, d, *J* 8.21, Ar), 7.52–7.42 (1 H, m, Ar), 6.38 (1 H, d, *J* 7.2, enol C*H*Ar), 5.90 (1 H, d, *J* 7.2, enol C*H*OMe) and 3.79 (3 H, s, OMe).

(Z)- and (E)-1-Dimethylamino-8-(2-methoxyethenyl)naphthalene (**4Z** *and* **4E**).—*(i) Adduct Formation.* LDA was prepared by adding *n*-butyllithium (2.4 cm^3 of 1.5 mol dm^{-3} solution in hexane) to a stirred solution of diisopropylamine in dry THF (4 cm^3) at 0 °C under argon. The resulting solution was stirred for an additional 20 min at 0 °C to allow complete formation of the base. The solution was maintained at 0 °C, while a solution of methoxymethyldiphenylphosphine oxide [5] in dry THF (20 cm^3) was added. A bright red colour developed in the solution, which was stirred for a further 10 min. The solution was cooled to −78 °C and 8-dimethylaminonaphthalene-1-carbaldehyde [19] (0.40 g, 2.01 mmol) in dry THF (5 cm^3) added dropwise with stirring. Once the addition was complete, the solution (which had become dark orange in colour) was allowed to come to room temperature. Saturated ammonium chloride solution (20 cm^3) and ether (20 cm^3) were added and the aqueous layer extracted a further three times with ether. The combined organic extracts were dried ($MgSO_4$) and concentrated giving a pale yellow solid. TLC (ethyl acetate) showed two closely spaced spots at R_f of 0.28 and 0.34. One recrystallisation from ethyl acetate gave fine white needles (one spot on TLC, lower R_f) of the *phosphine oxide* **6a**, m.p. 215–217 °C; ν_{max}(KBr)/cm^{-1} 3260 (OH), 1450 (PPh), 1185 (P=O), 1085 (C–O–C); δ_H(250 MHz; $CDCl_3$) 8.0–7.1 (17 H, m, Ar + C*H*OH), 6.70 (1 H, s, OH), 4.17 (1 H, dd, *J* 5.75 and 1.15, C*H*OMe), 2.56 (3 H, s, OMe), 2.45 (3 H, s, NMe) and 2.27 (3 H, NMe); δ_C($CDCl_3$) 151.07, 137.20, 136.62 (d, J_{CP} 95, aromatic C adjacent to P=O), 132.85 (d, J_{CP} 94, aromatic C adjacent to P=O), 132.11, 132.02, 131.73, 131.31, 131.22, 130.66, 128.80, 128.62, 128.51, 128.27, 128.15, 125.94, 126.68, 125.42, 125.20, 125.16, 117.09, 84.93 (d, J_{CP} 87, P=OCHOMe) 69.77 (OMe), 61.67 (d, J_{CP} 7, CHOH), 47.55 (NMe) and 42.73 (NMe); [Found (+ve FAB): $M^+ + 1$, 446.185 80. $C_{27}H_{29}NPO_3$ requires $M + 1$, 446.188 51] (Found: C, 72.5; H, 6.25; N, 3.05; P, 6.95. $C_{27}H_{28}NPO_3$ requires C, 72.79; H, 6.33; N, 3.14; P, 6.95%). The filtrate was evaporated and purified by column chromatography (ethyl acetate as the eluent) giving the other *diastereoisomer* **6b**, m.p. 208–216 °C; ν_{max}(KBr)/cm^{-1}; δ_H(250 MHz; $CDCl_3$) 8.09 (1 H, d, *J* 7.3, Ar), 7.93–7.85 (2 H, m, Ar), 7.56–7.19 (12 H, m, Ar + C*H*OH), 7.11 (1 H, d, *J* 7.3, Ar), 6.86 (1 H, dd, *J* 7 and 6.9, Ar), 5.92 (1 H, br s, OH), 3.92 (1 H, dd, *J* 3.0 and 7.6, C*H*OMe), 2.54 (3 H, s, OMe), 2.53 (3 H, s, NMe) and 2.46 (3 H, s, NMe); [Found (+ve FAB): $M^+ + 1$, 446.1889. $C_{27}H_{29}NPO_3$ requires $M + 1$, 446.1851].

(ii) Enol ether formation. A solution of the appropriate adduct (65 mg, 0.146 mmol) in dry THF (5 cm^3) was added to NaH (32 mg, 50% dispersion in oil, washed with dry hexane under argon) in dry THF (2 cm^3). The reaction was stirred at room temperature under argon for *ca.* 23 h, after which period no starting material could be detected by TLC (ethyl acetate) and a new higher-running spot was observed. The mixture was filtered to remove the suspended sodium diphenylphosphinate and the filtrate evaporated leaving an oily residue (0.027 g, 81%) which solidified on cooling. Attempted removal of any remaining baseline material using a plug column appeared to result in isomerisation, at least of the *cis* isomer, so this operation was omitted in subsequent attempts. However the reaction was virtually spot to spot and ^1H NMR spectroscopy showed no more than traces of extra signals, so the material thus obtained was used for the kinetic studies. Isomeric purities of >95% were generally obtained in these syntheses.

(Z)-1-Dimethylamino-8-(2-methoxyethenyl)naphthalene (**4Z**), m.p. 41–44 °C; R_f (10% ether–hexane) 0.30; ν_{max}(KBr)/cm^{-1} 1630 (C=C), 1215 (C–O–C asymm. str.) and 1100 (C–O–C symm. str.); δ_H[250 MHz; $CDCl_3$ (filtered through K_2CO_3 and run immediately)] 7.94 (1 H, d, *J* 7.2, ArH-7), 7.62 (1 H, d, *J* 8.1, Ar), 7.5–7.3 (3 H, m, Ar), 7.05 (1 H, d, *J* 7.4, Ar), 6.74 (1 H, d, *J* 7.3, enol C*H*Ar), 6.18 (1 H, d, *J* 7.3, enol C*H*OMe), 3.76 (3 H, s, OMe) and 2.70 (6 H, s, NMe_2); δ_H(250 MHz; CD_3CN) 7.87 (1 H, d, *J* 7.3, Ar), 7.60 (1 H, d, *J* 8.0, Ar), 7.42 (1 H, d, *J* 8.0, Ar), 7.06 (1 H, d, *J* 6.2, Ar), 6.66 (1 H, d, *J* 7.3, enol H), 6.20 (1 H, d, *J* 7.3, enol H), 3.68 (3 H, s, OMe) and 2.62 (6 H, s, NMe_2) *m/z* (Found: M^+, 227.1315. $C_{15}H_{17}NO$ requires *M*, 227.131).

(E)-1-Dimethylamino-8-(2-methoxyethenyl)naphthalene (**4E**), m.p. 59–63 °C; R_f (10% ether–hexane) 0.30; ν_{max}(KBr)/cm^{-1} 1630 (C=C), 1210 (C–O–C asymm. str.); δ_H[250 MHz; $CDCl_3$ (filtered through K_2CO_3 and run immediately)] 7.64 (1 H, dd, *J* 2.7 and 6.7, Ar), 7.48 (1 H, dd, *J* 1.1 and 8.1, Ar), 7.36–7.25 (4 H, m, 3 Ar and 1 enol C*H*Ar), 7.10 (1 H, dd, *J* 7.4 and 1.2, Ar), 6.88 (1 H, d, *J* 12.7, enol C*H*OMe), 3.72 (3 H, s, OMe) and 2.70 (6 H, s, NMe_2); (Found: M^+, 227.1315. $C_{15}H_{17}NO$ requires *M*, 227.131).

8-Dimethylaminonaphthalene-1-carbaldehyde (**5**).[5]—*n*-Butyllithium (4.54 cm^3 of 15.1% solution in hexane; 10.72 mmol) was added in a continuous stream to a stirred solution of 1-dimethylaminonaphthalene (0.38 cm^3, 2.34 mmol, $d = 1.042$) in dry ether (5 cm^3). Stirring was continued at room temperature for a further 48 h. The solution of the lithio compound was cooled to −78 °C and a solution of dry DMF (1.13 cm^3) in dry ether (6 cm^3) added dropwise with stirring. The temperature was gradually allowed to come to *ca.* 20 °C over 4 h (the solution was placed in a dry ice–acetone bath for *ca.* 1 h and in the freezer). At this point a solution of methanol (0.44 cm^3) in ether (2.4 cm^3) was added and the mixture allowed to warm to room temperature. The yellow/orange suspension was then diluted with a further 10 cm^3 of ether, extracted three times with water and three times with brine, dried ($MgSO_4$) and concentrated yielding an oily orange solid. TLC (25% ether–hexane) showed this to consist mainly of a compound of R_f 0.2 and some unchanged starting material (R_f 0.5). This residue was separated using column chromatography (gravity) on silica 7734 with 25% ether–hexane as the eluent. A pale yellow solid (0.32 g, 67%) was obtained in this manner. The solid thus obtained was recyrstallised from hexane yielding pale yellow crystals, m.p. 85–88 °C, lit.,[5] m.p. 86–87 °C; R_f (25% ether–hexane) 0.2; δ_H(MHz, $CDCl_3$) 10.65 (1 H, s, HC=O), 7.89 (1 H, dd, *J* 7.4 and 2.0, Ar), 7.64 (1 H, dd, *J* 8.1 and 0.9, Ar), 7.5–7.4 (3 H, m, Ar), 7.32 (1 H, dd, *J* 7.4 and 1, Ar) and 2.70 (6 H, s, NMe_2).

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