Intramolecular Catalysis of the Hydrolysis of an Acetal by an Internally Hydrogen-bonded Hydroxy Group

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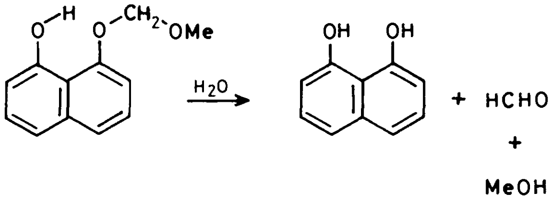
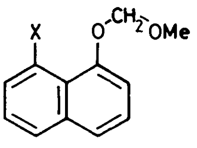
The hydrolysis of 1-methoxymethoxy-8-hydroxynaphthalene in aqueous solution at pH 2–4 is catalysed by the hydronium ion and the value of the catalytic coefficient is similar to that for 1-methoxymethoxynaphthalene. In the range pH 5–10 a pH-independent reaction with solvent is dominant and the rate coefficient for the neutral hydrolysis is estimated to be *ca.* 40-fold higher for 1-methoxymethoxy-8-hydroxynaphthalene than for 1-methoxymethoxynaphthalene. This is attributed to intramolecular catalysis by the hydrogen-bonded hydroxy group. As bond breakage and charge development occur in the transition state the internal hydrogen bond in the leaving group is strengthened.

Intramolecular acid catalysis is usually[1] associated with modest effective molarities of less than *ca.* 80 mol dm^{-3}. Exceptions are found when the acidic group is able to participate in internal hydrogen bonding[1] and then values of the effective molarity have been observed which approach those normally expected for neighbouring group participation involving nucleophilic attack. The interest in these mechanisms arises from the possibility that similar routes may be responsible for the efficiency of enzyme-catalysed reactions.[1,2] The examples of abnormally efficient intramolecular acid catalysis have usually involved salicylate ion as the leaving group. As the reaction proceeds the strong hydrogen bond which is present in salicylate ion is developed and the transition state for departure of the leaving group is thereby stabilised. Examples are found in the hydrolysis of acetals,[3] phosphate,[4] and sulphonate[5] esters, and ethers[6] containing salicylate ion as the leaving group.

Similar effects should be found with other hydrogen-bonded leaving groups and recently it has been shown that the dimethylammonium group is an efficient intramolecular catalyst in the hydrolysis of an acetal.[7] The leaving group is the strongly intramolecularly hydrogen-bonded 1-hydroxy-8-dimethylaminonaphthalene.[8] We have recently investigated[9] the hydrolysis of 1-hydroxy-8-acetoxynaphthalene in which the leaving group is the hydrogen-bonded 1,8-dihydroxynaphthalene monoanion. However, it was found that hydrolysis occurred predominantly by reaction of the ionised ester with solvent through a mechanism in which the ionised hydroxy group functioned as an intramolecular base catalyst. We now report studies of the hydrolysis of 1-methoxymethoxy-8-hydroxynaphthalene [equation (1)] which again involves the monoanion of 1,8-dihydroxynaphthalene as the leaving group. In this case, evidence has been found for enhanced reactivity of 1-methoxymethoxy-8-hydroxynaphthalene. The efficiency of catalysis in 1-methoxymethoxy-8-hydroxynaphthalene (1) is compared with that in 1-methoxymethoxy-8-naphthoic acid (2) and in 1-methoxymethoxy-8-*N*,*N*-dimethylnaphthylammonium ion (3). Intramolecular acid catalysis in the hydrolysis of acetals is of particular interest because of its possible involvement in the mechanism of action of lysozyme.[10]



(1)



(1) X = OH
(2) X = CO_2H
(3) X = Me_2NH^+

Experimental

Materials.—The preparations of 1-methoxymethoxynaphthalene[11] and 1-methoxymethoxy-8-hydroxynaphthalene were achieved by reaction of chloromethyl methyl ether with 1-naphthol and 1,8-dihydroxynaphthalene, respectively. Chloromethyl methyl ether was prepared[12] by allowing sieve-dried dimethoxymethane (3.8 cm^3) to react with freshly distilled acetyl chloride (3 cm^3) in the presence of dry methanol (0.1 cm^3) for 1 h. A solution of 1-naphthol (4 g) in dry dimethylformamide (5 cm^3) was added to a suspension of sodium hydride (0.83 g) in dimethylformamide (50 cm^3). After stirring for 30 min chloromethyl methyl ether (2.8 cm^3) was added and the mixture was stirred for a further 1 h. Aqueous sodium carbonate was added (100 cm^3, 0.1 mol dm^{-3}) and the product was extracted with diethyl ether. After drying and removal of solvent, 1-methoxymethoxynaphthalene was obtained as a red-brown liquid (30% yield) with δ_H[60 MHz; $(CD_3)_2CO$] 7.9–6.9 (m, 7 H, ArH), 5.2 (s, 2 H, CH_2), and 3.3 (s, 3 H, CH_3).

A similar procedure was used for the preparation of 1-methoxymethoxy-8-hydroxynaphthalene except that after reaction of the sodium salt of 1,8-dihydroxynaphthalene (0.5 g) with an equimolar amount of chloromethyl methyl ether (0.3 cm^3) in dimethylformamide, water was added (50 cm^3) and the mixture was adjusted to pH 7 by addition of conc. HCl before extraction into ether. The product was purified by flash chromatography on silica using 50:50 ethyl acetate–light petroleum (b.p. 40–60 °C) as the eluant. 1-Methoxymethoxy-8-hydroxynaphthalene was obtained (25% yield) as a red-brown liquid with δ_H(250 MHz; $CDCl_3$) 9.33 (s, 1 H, OH), 7.4–6.9 (m, 6 H, ArH), 5.27 (s, 2 H, CH_2), and 3.45 (s, 3 H, CH_3).

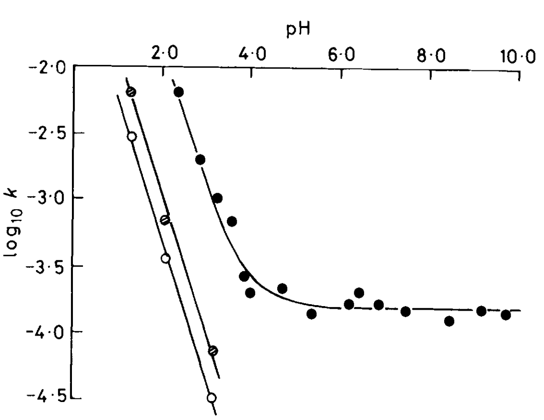
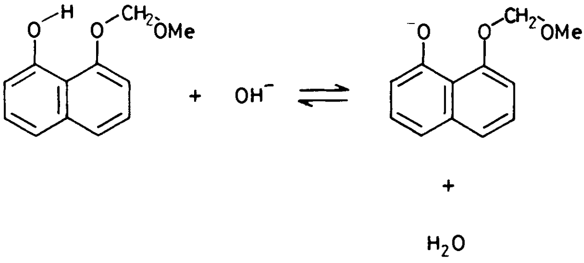


Figure. Rate coefficients (k/s^{-1}) for hydrolysis of 1-methoxymethoxynaphthalene at 65 °C (○) and for 1-methoxymethoxy-8-hydroxynaphthalene at 65 °C (○) and 96 °C (●)

Dissociation of 1-*Methoxymethoxy*-8-*hydroxynaphthalene*.—Equilibrium measurements of the acid dissociation of 1-methoxymethoxy-8-hydroxynaphthalene [equation (2)] were made at 25 and 65 °C in aqueous sodium hydroxide (0.001–0.02 mol dm^{-3}) at an ionic strength of 0.10 mol dm^{-3} maintained constant by addition of sodium perchlorate. The position of equilibrium was observed spectrophotometrically at 340 nm where the dissociated species absorbs strongly. The spectrum of undissociated 1-methoxymethoxy-8-hydroxynaphthalene was obtained in the absence of hydroxide ion and the spectrum corresponding to almost complete dissociation was obtained in the presence of 0.1 mol dm^{-3} hydroxide ion. Values of the equilibrium constants, K = [monoanion]/[acetal][OH$^-$], at 25 and 65 °C were 259 ± 14 and 75 ± 5 dm^3 mol^{-1} respectively. These were converted into pK values at ionic strength 0.1 mol dm^{-3} for 1-methoxymethoxy-8-hydroxynaphthalene of 11.39 ± 0.1 and 10.79 ± 0.1 at 25 and 65 °C, respectively and extrapolated to give pK 10.41 ± 0.1 at 96 °C.



(2)

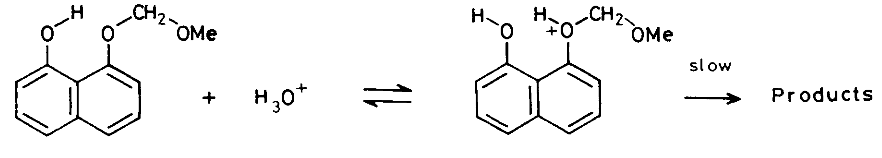
Kinetics of Hydrolysis.—The hydrolysis of 1-methoxymethoxynaphthalene at 65 °C and ionic strength 0.1 mol dm^{-3} was studied at hydrochloric acid concentrations of 0.001, 0.01, and 0.100 mol dm^{-3}. The reaction to 1-naphthol was followed by observing the increase in absorbance at 620 nm. The initial reaction solution contained 2 × 10^{-4} mol dm^{-3} of the acetal in the presence of disodium ethylenediaminetetra-acetic acid (1 × 10^{-4} mol dm^{-3}) to reduce decomposition[11] and sodium perchlorate to maintain constant ionic strength. The product of reaction was identified as 1-naphthol by comparison of the spectrum of the final reaction solution with that of an authentic sample of 1-naphthol. The values of the first-order rate coefficients for hydrolysis (k/s^{-1}) are given in the Figure. The value of the catalytic coefficient was calculated by dividing the first-order rate coefficients by the concentration of acid and the average result k_{H^+} 3.3 ± 0.2 × 10^{-2} dm^3 mol^{-1} s^{-1} was obtained, to be compared with a previous measurement[11] k_{H^+} *ca.* 2 × 10^{-2} dm^3 mol^{-1} s^{-1}.

The kinetics of the hydrolysis of 1-methoxymethoxy-8-hydroxynaphthalene was studied at 65 and 96 °C. At 65 °C the conditions and procedures were similar to those used for 1-methoxymethoxynaphthalene. The spectrum of the final reaction solution was found to be identical with that of a solution of 1,8-dihydroxynaphthalene under the same conditions. The reaction was studied at hydrochloric acid concentrations of 0.001, 0.01, and 0.100 mol dm^{-3} by observing the change in absorbance at 633 nm and the values of the first-order rate coefficients are given in the Figure. At 96 °C the kinetics of hydrolysis was studied in hydrochloric acid solutions and in buffer solutions over the range pH 3.5–9.7. Formate, acetate, phosphate, tris(hydroxymethyl)methylamine, and carbonate buffers were used and the pH values were measured after calibration of the meter with tris(hydroxymethyl)methylamine buffers at 96 °C. In buffer solutions, the hydrolysis occurs slowly and over the longer reaction times decomposition of the product of reaction (1,8-dihydroxynaphthalene) could not be completely eliminated. Decomposition was reduced by the presence of 1.0 × 10^{-3} mol dm^{-3} EDTA and by a continuous stream of nitrogen passed through the solution. Despite these precautions the reaction could not be followed to completion and infinity values were calculated from the value of the molar absorptivity of 1,8-dihydroxynaphthalene measured under the reaction conditions. The most suitable wavelength for following the reaction in buffer solutions was 333 nm and measurements were taken for at least one half life. The first-order rate coefficients were reproducible to within ± 10% for the slower reactions and to within ± 2% for the reactions in hydrochloric acid solutions. The values were found to be independent of buffer concentration and the dependence on pH is shown in the Figure.

The effect of added nucleophiles on the rate of hydrolysis of 1-methoxymethoxy-8-hydroxynaphthalene at 96 °C in the plateau region of the Figure was investigated by following the reaction in a phosphate buffer (pH 6.89) at a constant total ionic strength of 1.0 mol dm^{-3} maintained by addition of sodium perchlorate and with different concentrations of sodium iodide and bromide. The values of the first-order rate coefficients (10^4 k/s^{-1}) for the disappearance of the acetal were 0.9 ± 0.2, 3.5 ± 0.5, and 3.9 ± 0.3 at concentrations of sodium iodide of 0.0, 0.50, and 0.96 mol dm^{-3}, respectively. With sodium bromide at concentrations of 0.0, 0.50, and 0.96 mol dm^{-3} the values of the first-order rate coefficient (10^4 k/s^{-1}) were 0.9 ± 0.2, 2.5 ± 0.4, and 3.6 ± 0.3 respectively. Since the effects of added nucleophiles are quite small and the experimental uncertainties are large, studies with other nucleophiles were not undertaken.

Results and Discussion

The $\log_{10}k$–pH profiles for the hydrolysis of 1-methoxymethoxynaphthalene and 1-methoxymethoxy-8-hydroxynaphthalene at 65 °C show that both reactions are subject to specific acid catalysis which probably occurs by the mechanism given in

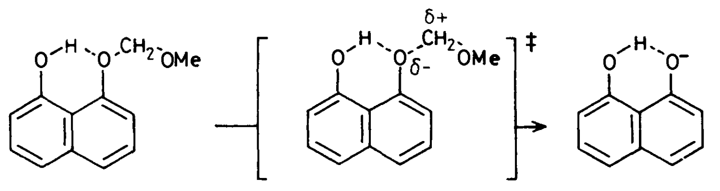


(3)

equation (3). The values calculated for the acid catalytic coefficients ($k_{\mathrm{H}'}$) for 1-methoxymethoxynaphthalene and the 8-hydroxy derivative are $k_{\mathrm{H}'}$ $3.30 \pm 0.2 \times 10^{-2}$ and $7.0 \pm 0.3 \times 10^{-2}$ dm^3 mol^{-1} s^{-1}, respectively. The data at 96 °C for the hydroxy derivative show that a pH-independent reaction becomes dominant above pH *ca.* 5 and the observed rate coefficient (k) for hydrolysis at this temperature is given by equation (4). The solid line through the data for 1-methoxymethoxy-8-hydroxynaphthalene at 96 °C is drawn using the

$$k = k_0 + k_{\mathrm{H}'}[\mathrm{H_3O^+}] \qquad (4)$$

values k_0 $1.51 \pm 0.2 \times 10^{-4}$ s^{-1} and $k_{\mathrm{H}'}$ 1.49 ± 0.1 dm^3 mol^{-1} s^{-1}. The pH independent reaction represents intramolecular catalysis of the spontaneous hydrolysis by the hydroxy group as shown in equation (5). The hydroxy group is considered to assist the hydrolysis by providing stabilisation of the developing negative charge on the oxygen of the leaving group. In the transition state the interaction between the hydroxy group and the oxygen of the acetal is likely to be strengthened compared with that in the ground state because of the increased negative charge that has developed in the transition state.



$$+ \ ^+\mathrm{CH_2OMe} \xrightarrow[\text{fast}]{\mathrm{H_2O}} \mathrm{HCHO} + \mathrm{MeOH} \qquad (5)$$

In the presence of sodium iodide and bromide, the kinetic data are consistent with an increase in the value of k_0 as a result of catalysis by iodide and bromide which are stronger nucleophiles than the solvent. Presumably the nucleophile (solvent, iodide, or bromide) is associated with the developing positive charge in the departing carbocation.

The data for the hydrolysis of 1-methoxymethoxy-8-hydroxynaphthalene (**1**) are very similar to the results that have been obtained for 1-methoxymethoxy-8-naphthoic acid (**2**)[11] and for 1-methoxymethoxy-8-*N*,*N*-dimethylnaphthylammonium ion (**3**).[7] For the acid-catalysed hydrolysis, values of $k_{\mathrm{H}'}$ 7.0×10^{-2}, 2.9×10^{-2}, and 3.0×10^{-3} dm^3 mol^{-1} s^{-1}, respectively were found for (**1**)–(**3**) at 65 °C. The neutral hydrolysis reactions of (**2**) and (**3**) at 65 °C were found to occur with rate coefficients k_0 1.05×10^{-4} and 2.0×10^{-4} s^{-1}, respectively. Because of the lower reactivity of 1-methoxymethoxy-8-hydroxynaphthalene the reaction was studied at 96 °C. The result k_0 1.5×10^{-4} s^{-1} was measured at this temperature to be compared with the value k_0 6.7×10^{-3} s^{-1} for (**3**) at 96 °C calculated by extrapolation of experimental data[7] obtained in the range 55–85 °C. Thus, the relative effects of the intramolecular catalytic groups on the rate of the spontaneous hydrolysis of 1-methoxymethoxynaphthalenes are $\mathrm{Me_2NH^+}$ (1.0):$\mathrm{CO_2H}$ (0.53):OH (0.022). The 1-methoxymethoxynaphthalenes are much less reactive towards spontaneous hydrolysis than 2-methoxymethoxybenzoic acid[11] which is *ca.* 100-fold more reactive than 1-methoxymethoxy-8-*N*,*N*-dimethylnaphthylammonium ion.

The factor that is most likely to determine the effectiveness of intramolecular catalysis in systems of this type is the increase in strength of the intramolecular hydrogen bond in going from the ground state to the transition state. The maximum effect that could be observed depends on the difference in strength of the hydrogen bonds in the ground state and in the leaving group. One measure of hydrogen bond strength is provided by the value of the equilibrium constant (K_{HB} = [open]/[closed]) for the equilibrium between the closed and open forms of the hydrogen-bonded species. For 4-(3′-nitrophenylazo)salicylate ion the value K_{HB} *ca.* 1×10^{-3} has been deduced[13] from the rate of proton transfer to an external base but the value could be *ca.* 10-fold lower for a salicylate ion which does not possess a strongly electron-withdrawing group. Hence the maximum enhancement in rate that can arise from intramolecular hydrogen-bond catalysis is likely to be *ca.* 1×10^4 for a salicylate leaving group. For 1-hydroxy-8-*N*,*N*-dimethylnaphthylammonium ion the value K_{HB} *ca.* 3×10^{-4} has been found.[8] A value for the strength of the internal hydrogen bond in the monoanion of 1,8-dihydroxynaphthalene is not known. However a rough estimate (K_{HB} 1×10^{-4} to 1×10^{-3}) can be obtained from the pK difference between 1,8-dihydroxynaphthalene (pK 6.7)[14] and 1-methoxymethoxy-8-hydroxynaphthalene (pK 11.6 at 25 °C and infinite dilution). The hydrogen bond is also responsible for the low acidity (pK > 13) of the monoanion of 1,8-dihydroxynaphthalene.[14]

To assess the efficiency of intramolecular catalysis by OH, COOH, and $\mathrm{Me_2NH^+}$ in the hydrolysis of 1-methoxymethoxynaphthalenes it is necessary to compare the k_0 values for the neutral hydrolysis of (**1**)–(**3**) with that for the hydrolysis of an acetal with a leaving group which does not form an internal hydrogen bond on departure. Comparison with k_0 for 1-methoxymethoxynaphthalene provides a rough estimate which can then be corrected to allow for the different inductive effects of OH, COOH, and $\mathrm{Me_2NH^+}$ on departure of the leaving group. The neutral hydrolysis of 1-methoxymethoxynaphthalene occurs at a negligible rate and k_0 values can only be measured for acetals with better (more acidic) leaving groups, for example 3,4-dinitromethoxymethoxybenzene (k_0 6.1×10^{-6} s^{-1} at 39 °C).[15] The values of k_0 for a series of acetals of the type $\mathrm{CH_3OCH_2OCOR}$ have been correlated with the pK value of the leaving group (RCOOH).[16] Similar results have been found for the hydrolysis of 2-aryloxytetrahydropyrans[17] though the sensitivity to the pK of the leaving group is higher. If it is assumed that the correlation found for acetals $\mathrm{CH_3OCH_2OCOR}$ holds for methoxymethoxybenzenes and methoxymethoxynaphthalenes, it is calculated from the value[15] of k_0 for 3,4-dinitromethoxymethoxybenzene (leaving group pK 5.42[14]) that the neutral hydrolysis of 1-methoxymethoxynaphthalene (leaving group pK 9.40[14]) would occur with k_0 *ca.* 4×10^{-9} s^{-1} at 39 °C. If the calculation is based on the results for 2-aryloxytetrahydropyrans, the value of k_0 estimated for 1-methoxymethoxynaphthalene is *ca.* 10-fold lower. The value k_0 7.5×10^{-6} s^{-1} at 39 °C can be calculated for 1-methoxymethoxy-8-*N*,*N*-dimethylnaphthylammonium ion from experimental data at 55–85 °C and using the estimate k_0 4×10^{-9} s^{-1} for 1-methoxymethoxynaphthalene it follows that the dimethylammonium group leads to an increase in k_0 of 1 900-fold. Assuming that the relative k_0 values for (**1**)–(**3**), are independent of temperature, the increase in rate resulting from the presence of COOH and OH groups is 1 000- and 40-fold respectively. Most of the calculated enhancement in rate for (**1**)–(**3**) compared with 1-methoxymethoxynaphthalene arises from the ability of the substituent to participate in an intramolecular hydrogen bond. However, some assistance to leaving-group departure is also provided by the inductive effects of the substituents,[18] OH (σ_m 0.13), COOH (σ_m 0.35), and $\mathrm{Me_2NH^+}$ (σ_m 0.84) and the efficiencies that have been calculated may overestimate the effect of the hydrogen bond, particularly in the case of (**3**). The value of k_0 for (**3**) should be compared with the k_0 value of an acetal with a rather more acidic leaving group than that present in 1-methoxymethoxynaphthalene. The correction cannot be calculated with certainty but it may be necessary to reduce the calculated efficiency of **(3)** by a factor of up to ten to estimate the effect of the hydrogen bond alone. Although an accurate value for the efficiency of catalysis by the hydroxy group in 1-methoxymethoxy-8-hydroxynaphthalene cannot be deduced, it is clear that the results do provide evidence that catalysis does occur. The magnitude of the effect is much lower than observed for the carboxy group in 2-methoxymethoxybenzoic acid.[11] The salicylate leaving group represents the most efficient catalysis of this type yet found.[1]

Acknowledgements

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