Enol–keto tautomerism of 9-anthrol and hydrolysis of its methyl ether

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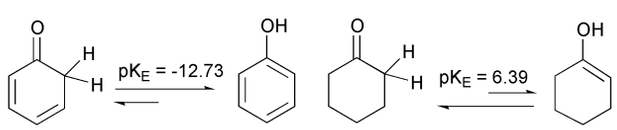
The equilibrium constant for keto–phenol tautomerisation of anthrone to 9-anthrol (K_E = [phenol]/[ketone]) has been determined as pK_E ($-\log K_E$) = 2.10 from ratios of rate constants for ketonisation of anthrol and phenolisation of anthrone in aqueous acetic acid buffers at 25 °C. Combining this value with pK_a = 10.0 for the ionization of anthrone, measured spectrophotometrically in piperazine and borate buffers, gives pK_a = 7.9 for the phenolic hydroxy group of anthrol. Measurements of rate constants for tautomerisation showed acid catalysis by H_3O^+ in aqueous HCl but by the base component only in buffer solutions of weaker acids. The H_3O^+-catalysed reaction is subject to a solvent isotope effect k_{H_3O}/k_{D_3O} = 4.8, consistent with protonation of 9-anthrol at the 10-carbon atom of the anthracene ring in the rate-determining step. Comparison with hydrolysis of the methyl ether of anthrol showed that ketonisation is faster by a factor of 3000. This large rate difference is consistent with NMR measurements which show that deuterium isotope exchange at the 10-position of the anthryl methyl ether occurs in competition with hydrolysis. This accounts for a 60–70 fold of the rate difference. The residue is attributed to (a) a normal difference of 16-fold in protonation rates of phenols and the corresponding methyl ethers and (b) a minor contribution from steric hindrance to resonance stabilisation of the anthracen-9-onium ion intermediate in the hydrolysis reaction from interaction of the conjugating methoxy group with the 1,8-hydrogen atoms of the adjacent phenyl rings.

Introduction

The exceptional stability of phenol relative to its keto tautomers presents a marked contrast to enols of simple aldehydes and ketones.[1] Equilibrium constants (K_E = [enol]/[ketone]) for enolisation of the superficially similar keto form of phenol (**1**) and cyclohexanone differ by nearly 10^{20} as indicated by values of pK_E ($-\log K_E$) in aqueous solution at 25 °C for the equilibria shown below.[2,3]



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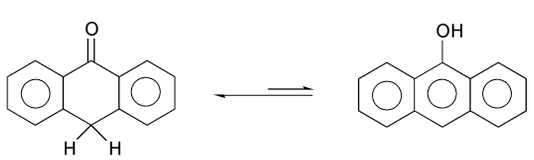
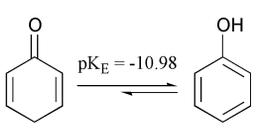
The large negative pK_E for phenol is a consequence of aromatic stabilisation of the 'enol' tautomer. For phenols with lower stabilisation energies the tautomeric equilibrium should lie more in favour of the ketone, and this is particularly true of anthrol (9-hydroxyanthracene, **3**) for which resonance stabilisation comes from the weakly aromatic central ring of anthracene. Indeed in most solvents, the keto form, anthrone (**2**), is known to be the more stable.[4–8]



2 **3**

To provide a quantitative comparison of the tautomerism of anthrone and anthrol with that of other ketones and phenols we have undertaken measurements of the tautomeric constant for the equilibrium (**2** ⇌ **3**) in aqueous solution. Strictly speaking anthrone is more appropriately compared with the more stable cyclohexa-2,5-dienone (**4**) than cyclohexa-2,4-dienone (**1**) tautomer of phenol. However the difference in stabilities of the two molecules is still very large.



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In earlier studies Mills and Beak[4] and others[5] showed that anthrol is stabilised relative to anthrone in media which accept hydrogen bonds, and that in DMF the two tautomers are present in nearly equal amounts.[4] This suggested that rates of ketonisation might be measured by quenching a DMF solution into water and observing relaxation of the anthrol to the now more stable anthrone. The rate of ketonisation so determined could then be combined with a rate for enolisation of anthrone, measured by trapping anthrol with iodine, to yield the tautomeric constant.†

After completion of these measurements a comparison of rate constants showed that the H_3O^+-catalysed ketonisation of 9-anthrol occurs 3000 times more rapidly than hydrolysis of its methyl ether. Such a large rate difference seemed at first surprising because, by analogy with the corresponding reaction of vinyl ethers, the hydrolysis, like the tautomerisation, had been supposed to occur with rate-determining protonation at the 10-position of the anthracene ring.[6] Further investigation established, however, that protonation of the anthryl methyl ether occurs at a considerably *greater* rate than hydrolysis. This

† After this paper was completed we became aware of a preliminary report of an independent study of the tautomerisation of anthrone by J. Wirz (*Chem. Unserer Zeit*, 1998, **32**, 311). A full account of this work has appeared: B. Freiermuth, B. Hellrung, S. Perterli, M. F. Schultz, D. Wintgens and J. Wirz, *Helv. Chim. Acta*, 2001, **84**, 3796.

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behaviour reflects a dependence of the rate-determining step for the hydrolysis of vinyl and weakly aromatic aryl ethers upon the degree of stabilisation (including aromatic stabilisation) of the reacting carbon–carbon double bond.[7]

Results

Ionization measurements

Anthrone shows a normal UV spectrum for an aromatic ketone with $\varepsilon = 1.56 \times 10^4$ at $\lambda = 268$ nm in ethanol as the most intense peak above 220 nm.[4] In aqueous sodium hydroxide this peak is replaced by an intense absorption with λ_{max} = 269 nm ($\varepsilon = 8.9 \times 10^4$) more consistent with an anthracene chromophore and this may be attributed to the anthrolate anion.[8–10] In a short time the anthrolate spectrum is transformed into that of anthraquinone ($\varepsilon = 3.6 \times 10^4$ and 1.1×10^4 at $\lambda_{max} = 255$ nm and λ = 276 nm [shoulder] respectively). However, provided solutions are prepared in boiled out distilled water and degassed by bubbling nitrogen before use, the absorbance of the anthrolate anion at the time of mixing can be extrapolated by monitoring the decrease in absorbance with time. From the dependence of the initial absorbances upon [OH^-] in piperazine buffers the pK_a of anthrone was found to be 10.0 (in aqueous solution at 25 °C and ionic strength 0.1). This value is preferred to an earlier determination of 10.8 from potentiometric titration.[10]

A pK_a for anthrol was measured approximately by injecting a few microlitres of an equilibrated mixture of anthrone and anthrol in DMF (in which solvent a substantial proportion of anthrol is present) into a spectrophotometric cell containing 2 cm^3 of aqueous buffer in the pH range 7–9. The anthrol reacted to anthrone, but measurement of initial absorbances of anthrol (λ_{max} = 256 nm) or its anion (269 nm) as a function of pH allowed evaluation of a p$K_a \cong 8.0$.

Kinetic measurements

Rate constants for ketonisation of anthrol were measured by injection of the DMF solution of anthrone and anthrol into an aqueous buffer or solution of strong acid as described, and monitoring the decrease in absorbance at λ_{max} = 256 nm accompanying conversion of the anthrol to anthrone. The change in spectrum was similar to that for the corresponding reaction of the anthrol methyl ether shown in Fig. 1. The reaction showed catalysis by HO^-, H^+ and the basic components of buffers as well as an uncatalysed reaction.

For ketonisation in buffer solutions a plot of measured first order rate constants (k_{obs}) against buffer base concentration ([B^-]) at constant buffer ratio gave a straight line described by eqn. (1), in which k and k_o are the slope and intercept.

$$k_{obs} = k_o + k\,[B^-] \qquad (1)$$

Values of k and k_o for piperazine, borate, acetate, glycolate and cyanoacetate buffers are shown in Table 1, which also includes measurements for acetate buffers in D_2O. In principle k includes contributions from catalysis by both buffer acid and buffer base. In practice only base catalysis was observed and k corresponds to a rate constant for general base catalysed ketonisation k_{GB}^{K}.

Rate constants for ketonisation were also measured in aqueous HCl solutions and in DCl in D_2O. These measurements are shown in Table 2 and are plotted against acid concentration in Fig. 2. The slopes and intercepts of the plots yield rate constants $k_{H_3O} = 3.27 \times 10^{-2}$ and $k_{D_3O} = 6.84 \times 10^{-3}$ $M^{-1}\,s^{-1}$ for catalysis by H_3O^+ and D_3O^+ respectively and $k_o^H = 2.3 \times 10^{-3}$ and $k_o^D = 5.0 \times 10^{-4}$ s^{-1} for pH-independent reactions.

Rate constants for enolisation of anthrone were measured

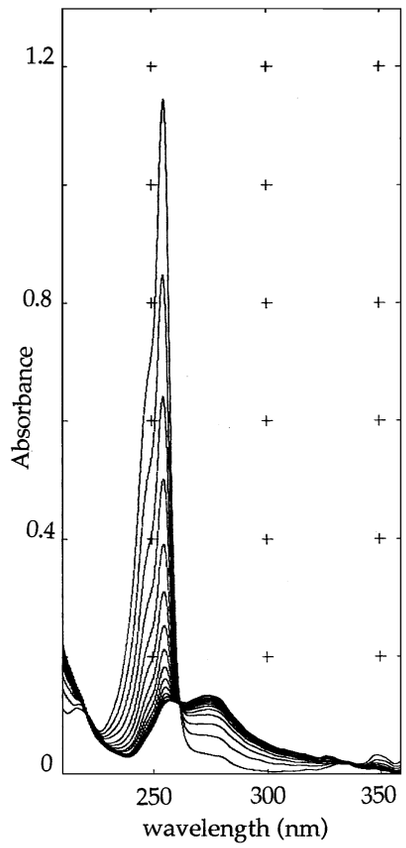


Fig. 1 Repetitive scans of UV spectra for hydrolysis of 9-methoxyanthracene to anthrone (1.2×10^{-5} M substrate in 4.9 M $HClO_4$).

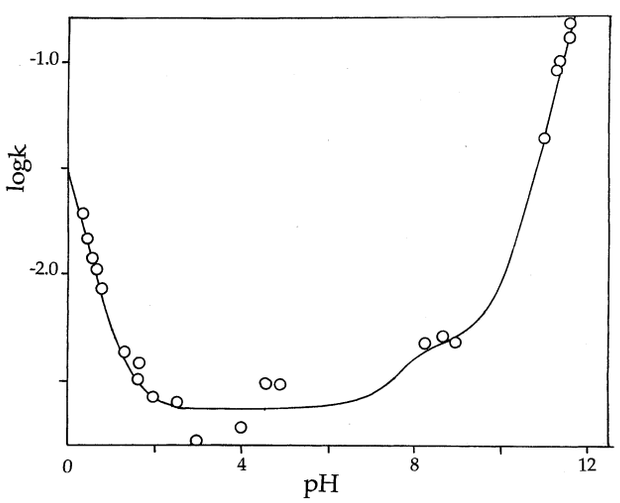


Fig. 2 Log k–pH profile for the tautomerisation of 9-anthrol (**3**) to anthrone (**2**).

by halogenation with iodine as described elsewhere[1,11] using acetate, lutidine and borate buffers. The dependence of k_{obs} on buffer concentration is also described by eqn. (1) and values of k and k_o at different buffer ratios are recorded in Table 1. The values of k correspond to rate constants for general base catalysed enolisation k_{GB}^{E}.

Rate constants for ionisation of anthrone to its anthrolate anion in aqueous NaOH were measured directly from the rate of appearance of the anion monitored spectrophotometrically and are recorded in the Experimental section. The reaction was faster than the subsequent oxidation to anthrone and most of the measurements were made using a stopped flow spectrometer. The slope of the plot of k_{obs} against [OH^-] gave a rate constant $k_{OH} = 54$ $M^{-1}\,s^{-1}$.

Table 1 Slopes (k) and intercepts (k_o) of plots of first order rate constants for ketonisation of anthrol and iodination of anthrone against buffer base concentration at constant buffer ratio in aqueous solution of ionic strength 0.1 M at 25 °C

	Ketonisation				Iodination			
Buffer	pH	R [a]	k/1 mol^{-1} s^{-1}	10^3k_o/s^{-1}	pH	R [a]	10^5k/1 mol^{-1} s^{-1}	10^5k_o/s^{-1}
	4.82	0.67	0.26	3.0	5.17	0.31	1.69	4.0
Acetate	4.59	1.0	0.285	3.0	4.59	1.0	1.90	4.4
					4.33	1.8	1.69	4.1
Acetate (D_2O)		1.0	0.0292 [b]	0.10 [b]				
Glycolate	2.97	4.9	0.110	4.2				
	3.40	1.9	0.101	4.1				
	3.78	0.83	0.107	5.5				
Cyanoacetate	2.16	1.3	.0150	4.0				
	2.65	0.45	0.137	5.5				
Lutidine					6.48	1.5	16.7	3.2
					7.37	0.66	12.6	3.5
Borate	8.17	9.0	0.93	4.7	8.51	0.40	0.67	6.8
	8.62	3.0	0.73	4.9				
	8.93	1.5	0.78	4.8				

[a] Buffer ratio R = [buffer acid]/[buffer base]. [b] In D_2O.

Table 2 Observed rate constants for protonation of anthrol and its methyl ether in HCl–H_2O and DCl–D_2O

Anthrol				9-Methoxyanthracene			
[HCl]/M	$10^3k^H_{obs}$/s^{-1}	[DCl]/M	$10^3k^D_{obs}$/s^{-1}	[HCl]/M	$10^5k^H_{obs}$/s^{-1}	[DCl]/M	$10^5k^D_{obs}$/s^{-1}
0.5	19.4	0.80	6.51	2.06	6.74	2.29	4.02
	19.0	0.56	3.94	2.25	7.57	2.61	5.44
0.4	14.5	0.40	2.99	2.65	11.70	2.88	7.72
0.3	12.4	0.28	2.04	2.91	16.50	4.27	35.08
	11.2	0.112	0.90	4.30	74.12	5.60	144.7
0.25	10.9	0.056	1.50	5.64	354.9		
	10.6	0.03	0.82				
0.2	8.64	0.0095	0.50				
	8.2	0.001	0.68				
0.05	4.6	0.0005	0.52				
	4.31						
0.03	3.80						
0.025	4.30						
0.01	3.20						
	2.62						
0.001	1.64						
0.0001	1.91						

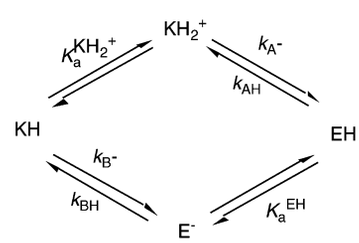
Tautomeric constant

A tautomeric constant K_E = [anthrol]/[anthrone] may be derived from ratios of halogenation to ketonisation rate constants measured under the same conditions and corrected for the small degree of reversibility of ketonisation. From the rate constants for general base catalysis by acetate ion $K_E = 1.93 \times 10^{-5}/2.67 \times 10^{-3} = 7.2 \times 10^{-3}$ and $pK_E = 2.10$. From the rate constants k_o obtained as intercepts of the acetate buffer plots $K_E = 1.4 \times 10^{-2}$. Because these intercepts are small and, as discussed below, subject to significant errors, the former value is preferred. Attempts to measure rates of iodination in HCl solutions were unsuccessful probably because the iodination is reversible at these acid concentrations.

Combining the value of K_E with the ionisation constant of anthrone K_a^{KH} yields the ionisation constant (K_a^{EH}) of its anthrol tautomer from the usual relationship[2,11] $K_a^{EH} = K_a^{KH}/K_E$. The value of pK_a^{EH} so obtained is 7.90, which is in satisfactory agreement with the more approximate value of 8.0 obtained directly from spectrophotometric measurements.

Microscopic rate constants

From the measured rate and equilibrium constants for ketonisation and enolisation microscopic or 'molecular' rate constants for the individual steps of these reactions can be derived based on the usual acid- and base-catalysed pathways for the tautomerisation shown in Scheme 1.[11] In this scheme



Scheme 1

KH, EH, KH_2^+ and E^- represent respectively anthrone, anthrol and their common conjugate acid and base; K_a^{EH} and $K_a^{KH_2^+}$ are ionisation constants of the enol and protonated ketone respectively and K_a is the ionisation constant of the acid–base catalyst (AH/A^-). The rate constants k_{AH} and k_{A^-} refer to the forward and reverse proton transfers between anthrol and its conjugate acid and k_{BH} and k_{B^-} to the corresponding proton transfers for the anthrolate anion and anthrone.

Table 3 Rate constants[a] k_{AH} and k_{BH} for protonation of anthrol and the anthrolate anion and k_{A^-} and k_{B^-} for the reverse reactions of protonated and unprotonated anthrone in aqueous solution at 25 °C

Acid (AH and BH)	pK_a	k_{B^-}	k_{BH}	k_{A^-}	k_{AH}
H_3O^+	−1.76	$1.6 \times 10^{-5}/55.5$	1.6×10^{5}	28.2/55.5	3.24×10^{-2}
$CNCH_2COOH$	2.43	9.3×10^{-5}	3.45×10^{3}		
$HOCH_2COOH$	3.83	7.5×10^{-5}	1.11×10^{3}		
CH_3COOH	4.75	1.93×10^{-3}	3.4×10^{2}		
Lutidinium	6.79[b]	1.47×10^{-4}	24		
H_2BO_3	9.24[b]	6.5×10^{-4}	3.7×10^{-3}		
H_2O	15.76	45.5	$4.55 \times 10^{-3}/55.5$		

[a] Units l mol^{-1} s^{-1}. [b] From measurements of rates of iodination.

For a full dissection of measured rate constants into microscopic values it is necessary to know the ionisation constant of the *O*-protonated anthrone. This has been determined spectrophotometrically as $pK_a^{KH_2^+} = -5.09$.[12] However, this is only required for catalysis by H_2O in so far as for weaker (buffer) acids catalysis was restricted to the conjugate base, *i.e.* reaction *via* the lower (forward and reverse) pathways of Scheme 1.

Rate constants k_{GB}^{K} and k_{GB}^{E} for catalysis of ketonisation and enolisation reactions by buffer bases correspond as we have seen to an average of values of k at different buffer ratios in Table 1. They are related to k_{B^-} for enolisation and to k_{BH} for ketonisation by eqns. (2) and (3). In eqn. (2), k_{GB}^{E} is identified

$$k_{B^-} = k_{GB}^{E} \quad (2)$$

$$k_{BH} = k_{GB}^{K} K_a/K_a^{EH} \quad (3)$$

with k_{B^-} on the lower (left to right) pathway of Scheme 1, and eqn. (3) comes from the relationship $pK_{GB}^{K} = k_{BH}K_a^{EH}/K_a$ for the right to left reaction, where k_{BH} refers to the rate-determining protonation of the enolate anion, as we have seen, and K_a/K_a^{EH} to the 'pre-equilibrium' ionisation of the enol. Where ketonisation rates had not been determined k_{BH} could be evaluated from the rate constant for enolisation k_{GB}^{E} using eqn. (4).

$$= k_{GB}^{E} K_a/K_a^{KH} \quad (4)$$

Values of these rate constants for the buffers studied are shown in Table 3. Values for boric acid are not included because the predominant reactant species in borate buffers is the anthrolate anion which is expected to react with the acid component of the buffer whereas the small amount of catalysis observed was basic. This was presumed to be an artifact.

The only rate constants for acid catalysis, k_{AH} and k_{A^-}, relate to proton transfer from H_3O^+ (or to H_2O). These were obtained from the experimental second order rate constants for H^+ catalysis of the ketonisation reaction $k_{H_3O}^{K}$ using eqns. (5) and (6).

$$k_{AH} = k_{H_3O} \quad (5)$$

$$k_{A^-} = k_{H_3O}K_a^{KH_2}K_E \quad (6)$$

Thus $k_{H_3O}^{K} = 3.24 \times 10^{-2}$ s^{-1} may be identified with k_{AH} (eqn. (5)) and yields $k_{A^-} = 28.2$ s^{-1} for reaction of protonated anthrone with water as a base from eqn. (6), in which $K_a^{KH_2^+}K_E$ represents the ionisation constant for *C*-protonation of anthrol. The rate constant for hydroxide-catalysed enolisation $k_{OH}^{E} = 54$ M^{-1} s^{-1} corresponds to k_{B^-} for the hydroxide ion and yields $k_{BH} = k_{B^-}K_w/K_a^{KH} = 4.55 \times 10^{-3}$ for *C*-protonation of the anthrolate ion by water.

Values of k_{A^-} and k_{B^-} can be combined to yield a proton activating factor (paf),[13] *i.e.* the activating effect of *O*-protonation of anthrone upon C–H bond-breaking at the 9-carbon atom. From the ratio k_{A^-}/k_{B^-} for H_2O paf = 1.8×10^{6}.

pH-Profile

The rate constants for H^+ catalysis of ketonisation in Table 2 and values of k_o in Table 1 may be used to construct a pH-profile as shown in Fig. 2. Also included in the profile are rate constants for hydroxide-catalysed ionisation of anthrone (k_{obs}/s^{-1} listed in the Experimental section). This implies that the ordinate of the Figure corresponds to the (log of) the sum of forward and reverse rate constants for tautomerisation or (above the pK_a of anthrol) ionisation of anthrone. The curve drawn through the points is based on eqn. (7), which is derived

$$k_{obs} = k_{H_3O}[H^+] + \frac{(k_{H_3O}'[H^+] + k_{H_2O}')}{(1 + [H^+]/K_a^{EH})} + k_{OH}[OH^-] \quad (7)$$

from Scheme 1 with rate constants k_{H_3O}, k'_{H_3O}, k_{OH} and k'_{H_2O} corresponding respectively to k_{AH} and k_{BH} for H_3O^+, k_{B^-} for OH^- and k_{BH} for H_2O; as before, K_a^{EH} is the ionisation constant of anthrol; it may be noted that $K_a^{KH_2^+}$, the ionisation constant of the protonated anthrone, does not appear in the equation because under conditions of acid catalysis the reaction is observable only in the ketonisation direction. Rate constants were chosen to give a best fit to the experimental points, with K_a^{EH} taken as its independently measured value ($pK_a^{EH} = 7.9$).

At low pH the reaction of anthrol to anthrone shows catalysis by H^+ corresponding to the first term of eqn. (7). Above pH 2 this gives way to an uncatalysed reaction with $k_o = k'_{H_3O}K_a^{EH}$. Above pH 7 a hydroxide catalysed reaction probably appears representing reaction of the anthrolate intermediate with H_2O rather than H_3O^+. However this is quickly saturated as the reactant changes from anthrol to anthrolate anion (at pH 7.9), leading to a second pH independent reaction. At higher pH the anthrolate anion becomes more stable than anthrone and the observed reaction is the ionisation of anthrone promoted by hydroxide ion. The pH at which this occurs (10.1) provides an independent measure of the spectrophotometrically determined pK_a for anthrone (10.0).

In practice the pK_a for ionisation of anthrone based on Fig. 3

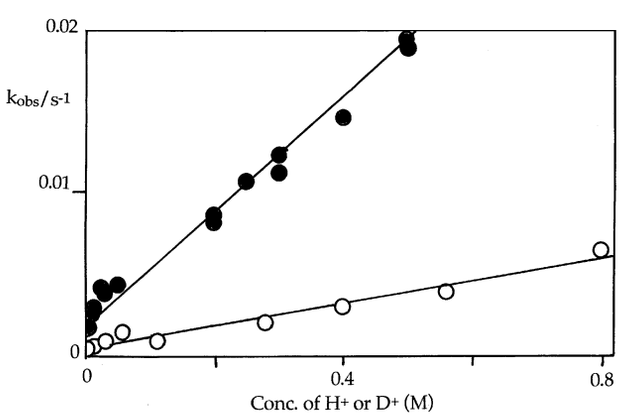


Fig. 3 The dependence of first order rate constants upon acid concentration for tautomerisation of 9-anthrol (**3**) to anthrone (**2**) in $HClO_4$ (●) and $DClO_4$ (O).

is probably not very reliable because neither of the two pH-independent reactions, above pH 2 or above pH 8, is adequately determined by the experimental measurements. That between pH 2 and pH 7 is best defined by the intercept of the plot of first order rate constants against H^+ concentration for reactions in aqueous HCl (Fig. 3). Intercepts from carboxylic acid buffer plots (k_o in Table 1) give larger values, as shown by the points close to pH 5 for acetic acid buffers. However the ratio of intercept to slope for acetic acid buffers is ten times smaller than for the reaction with HCl, and the intercept is correspondingly subject to greater uncertainty: at the higher pH too the error may be increased by competing oxidation. Values of k_o from the more acidic buffers in Table 1 are similar to those for acetic acid but are not included in Fig. 2 because precautions were not taken against oxidation. On the other hand, the values for borate buffers, which help define the pH-independent protonation of anthranolate anion by water above pH 8 and lead to kinetic evaluation of the pK_a for anthrone, show a high ratio of intercept to slope for their buffer plots and values of k_o are judged to be more accurate. In practice, the rate constant for this reaction is based on the rate constant for the reverse ionisation of anthrone by hydroxide ion with the independently measured equilibrium constant for the reaction (pK_a = 10).

Isotope effects

Rate constants were measured for ketonisation of anthrol in D_2O catalysed by DCl and acetate ions (in 1 : 1 AcOD : NaOAc buffers) and in the absence of catalysts. First order rate constants for ketonisation of anthrol in solutions of HCl in H_2O and DCl in D_2O are shown plotted against acid concentration in Fig. 3. From the ratio of slopes of the plots k_{H_3O}/k_{D_3O} for *C*-protonation of anthrol by H_3O^+ and D_3O^+ is 4.8.

The uncatalysed and acetate catalysed ketonisations also showed significant isotope effects with k_{H_2O}/k_{D_2O} = 4.6 and $k_{ACO}^{H_2O}/k_{ACO}^{D_2O}$ = 9.2 respectively. These values arise from a combination of primary and secondary (solvent) isotope effects.[14] For the uncatalysed reaction the process in D_2O may be written as in eqn. (8) with ArOD representing deuterated

$$D_2O + ArOD \underset{}{\overset{K_D}{\rightleftharpoons}} ArO^- + D_3O^+ \xrightarrow{k_{D_3O}} Anthrone \quad (8)$$

anthrol. The overall isotope effect is the product of an equilibrium contribution K_H/K_D for the ionisation of anthrol and a kinetic isotope effect k'_{H_3O}/k'_{D_3O} for *C*-protonation of the anthrolate anion. Isotope effects upon the ionisation of phenols [eqn. (8)] depend on the pK_a of the phenol[15] ($pK_a^H - pK_a^D$ = 0.380 − 0.026 pK_a), and for anthrol (pK_a = 7.9) K_a^H/K_a^D is predicted to be 3.8. Combining this value with the observed isotope effect (k_{H_2O}/k_{D_2O} = 4.6) we obtain the rather small value k_{H_3O}/k_{D_3O} = 1.2. However, as k_{H_2O} and k_{D_2O} are obtained as (small) intercepts of the plots of first order rate constants against concentration of HCl and DCl in Fig. 1, and are sensitive to competing oxidation to anthraquinone, k'_{H_2O}/k'_{D_2O} may be subject to significant errors, most probably making it too low.

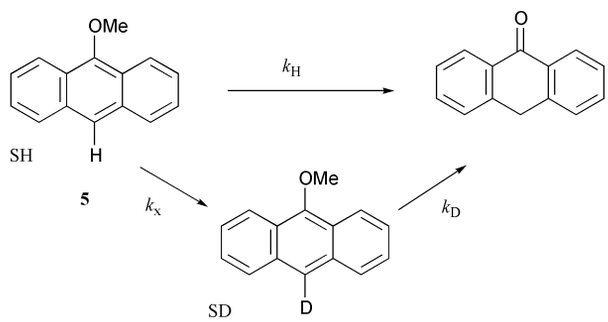
For ketonisation catalysed by acetate ion a preequilibrium proton transfer between anthrol and acetate ion is followed by *C*-protonation of the anthrolate anion by acetic acid. The large isotope effect upon the ionisation of anthrol is now compensated by that upon the corresponding ionisation of acetic acid (K_a^H/K_a^D = 3.27) so the net effect amounts only to K_H/K_D = 1.2. When combined with the experimental measurement of 9.2 this gives a primary isotope effect k_{AcOH}/k_{AcOD} = 7.8. This is a reasonable value for proton transfer to a carbon base but much larger than the value for H_3O^+ and D_3O^+. Presumably this reflects a less reactant-like transition state and lack of compensation between the primary isotope effect and a secondary effect from the non-reacting hydrogens of H_3O^+, as well as greater precision of the measurements.

Methoxyanthracene

Rates of acid-catalysed hydrolysis of 9-methoxyanthracene (**5**) to form anthrone were measured by monitoring the disappearance of the intense UV absorption of the reactant (λ_{max} = 255 nm) shown in Fig. 1. In dilute acid solutions the reaction was slow, but rate constants could be measured in more concentrated solutions in H_2O and D_2O, and these are listed in Table 2. A limiting rate constant k_{H_3O} = 1.00 × 10^{-5} M^{-1} s^{-1} in dilute solution was extrapolated from a plot of log ($k_{obs}/[H_3O^+]$) *versus* the 'excess acidity function' $X_o = -(H_o + \log C_{H^+})$ to $X_o = 0$.[16]

A limiting rate constant in D_2O, k_{D_3O} = 5.38 × 10^{-6} M^{-1} s^{-1} was similarly extrapolated using X_o values for HCl in H_2O.[17] This is consistent with the near identity of H_o and D_o functions in $HClO_4$ and $DClO_4$ (and presumably HCl and DCl) when expressed as functions of molarity.[18] Combining the limiting rate constants yields an isotope effect k_{H_3O}/k_{D_3O} = 1.86.

The possibility of hydrogen exchange at the 10-position of the anthracene ring competing with hydrolysis of the anthrol methyl ether (Scheme 2) was examined by NMR measurements



Scheme 2

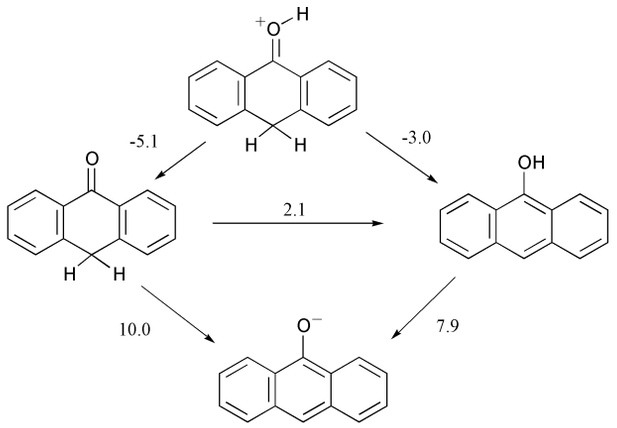
for a solution of DCl in D_2O and CD_3CN.[7] In the NMR spectrum the 10-hydrogen atom of the reactant could be observed as a singlet slightly downfield from the other aromatic hydrogens. Monitoring this hydrogen showed that it disappeared more rapidly than the product anthrone appeared. The analysis required to convert the exchange measurements into relative rates of exchange and hydrolysis is described in the Experimental section. It is based on Scheme 2 where k_H and k_D are rate constants for hydrolysis of protio and deutero substrates in D_2O and k_x is the rate constant for deuterium exchange. Ratios of rates of exchange to hydrolysis in D_2O (k_x/k_D) were measured as 4 in ~6 M DCl and 6 in ~3 M DCl. If these are not affected by the presence of CD_3CN then the ratio for dilute acid in D_2O should be ~7.

To convert the exchange measurements to a ratio of protonation to hydrolysis rate constants for reaction in H_2O it is necessary to assign an isotope effect for the protonation step. For isotope effects of 7.0 and 9.0, which are typical of aromatic hydrogen isotope exchange of reactive substrates[19] (and consistent with the large solvent isotope effect k_{H_3O}/k_{D_3O} = 4.8 for the protonation of anthrol) the exchange reaction can be estimated to be respectively 70 and 80 times faster than hydrolysis. Smaller isotope effects yield smaller rate ratios.

Discussion

Tautomeric and ionisation constants

Equilibrium constants (*K*) for the interconversion and ionisation of anthrone and its phenolic tautomer 9-anthrol are summarised in the form of p*K*s (−log *K*) in Scheme 3. In the scheme the normal double arrows representing equilibria are replaced by single arrows to indicate the direction of reaction to which the p*K*s refer. The value of pK_E = 2.1 for the tautomerisation of anthrone to anthrol implies that in aqueous solution at 25 °C a little under 1% of anthrol is present at equilibrium. Also



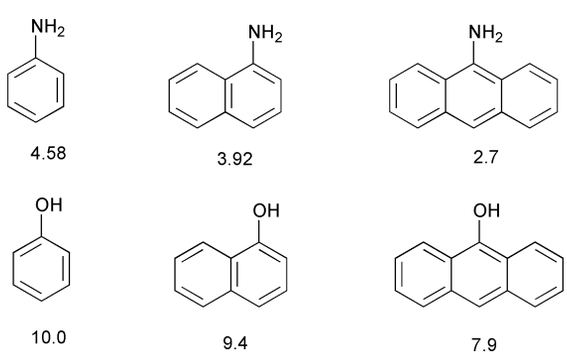
Scheme 3

included in the scheme is pK_a = −5.1 for *O*-protonation of anthrone, determined by Stewart, Granger, Moodie and Muenster from measurements in concentrated $HClO_4$.[12] When combined with pK_E = 2.1 this yields pK_a = −3.0 for *C*-protonation of anthrol at the 10-carbon atom of the anthracene ring.

The relative stability of 9-anthrol compared with enols lacking aromatic stabilisation is apparent from the low values of the p*K*s for *C*-protonation and for the anthrone–anthrol tautomerisation. The corresponding pK_E and pK_a for acetophenone, for example, are 7.9 and 3.7 respectively.[20,21] On the other hand, 9-anthrol lacks the overwhelming stability of phenol for which the pK_a for *C*-protonation is estimated[22] as −14 and pK_E has been measured[3] as −11.

The value of pK_a = 7.9 for the ionisation of 9-anthrol to its anthrolate anion is obtained by combining pK_E = 2.1 with the measured pK_a = 10.0 for the more stable anthrone. These values are in good agreement with pK_E = 2.17 and pK_as = 7.84 and 10.1 reported by Wirz using different experimental methods. †

When its pK_a is compared with pK_as for other unsubstituted phenols, such as phenol itself (10.0) and α-naphthol (9.4), 9-anthrol appears to be unusually acidic. However, the differences in acidity closely match those of the corresponding anilinium ions[23] (including protonated 9-ammonioanthracene[24]), the conjugate bases of which are shown below. They suggest that the resonance interaction between the anthryl ring and a substituent at the 9-position bearing a lone pair of electrons is stronger than for phenyl or naphthyl rings, which is consistent with the weak aromatic stabilisation of the central ring of anthracene.



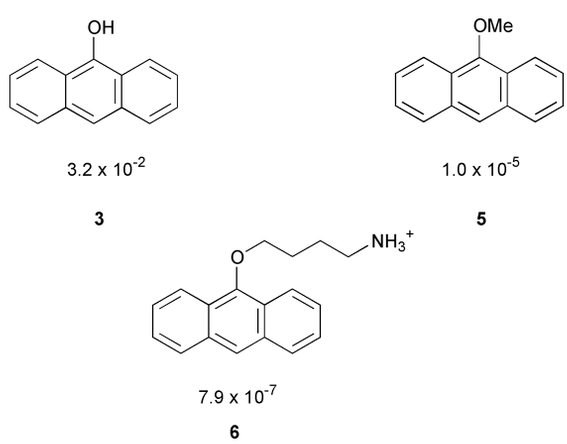
Acid–base catalysis

As expected from their relatively high acidities, the predominant kinetic pathway for tautomerisation of anthrone and anthrol involves base catalysis. Thus, ketonisation occurs readily in carboxylic acid buffers but catalysis only by the basic component of the buffer is observed. This catalysis and the measurement of a large isotope effect, k_{H_3O}/k_{D_2O} = 9.2 for reaction of 9-anthrol with acetate ion, are consistent with rate-determining protonation of the conjugate base of the anthrol reactant and reaction along the lower pathways shown in Schemes 1 and 3 (although the arrows in Scheme 3 represent directions of equilibria not reactions). This mechanism is similar to that for ketonisation of an enol, with the anthrolate anion replacing the enolate anion as intermediate. Based on measurements in acetic, glycolic and chloroacetic acid buffers the Brønsted exponent α for protonation of the anthrolate anion is 0.35, which is consistent with the "downhill" protonation of this strong carbon base.

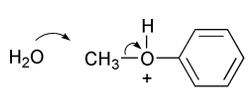
Only for H_3O^+ is an acid-catalysed reaction observed. In the ketonisation direction, by analogy with keto–enol tautomerisations,[1] this reaction should involve rate-determining protonation of 9-anthrol at the 10-carbon atom, as shown in the upper pathway of Scheme 2. This mechanism is confirmed by the large value of the solvent isotope effect k_{H_3O}/k_{D_3O} = 4.8, which must include a primary contribution and is the same as the value measured for the related H_3O^+-catalysed reaction of vinyl alcohol to form acetaldehyde.[25]

Mechanism of hydrolysis of 9-methoxyanthracene

Comparison of the ketonisation of 9-anthrol with the hydrolysis of its methyl ether (**5**) reveals that there are large differences in rate constants and isotope effects for the H_3O^+-catalysed reactions. The rate constant for ketonisation exceeds that for hydrolysis by a factor of 3000 while k_{H_3O}/k_{D_3O} for the hydrolysis is 1.95 compared with 4.8 for ketonisation. These differences are corroborated by measurements by Powell which show a similar difference in isotope effect and even larger differences in rates for the hydrolysis of (*N*-protonated) aminoalkyl anthryl ethers.[6] Reaction of the 4-ammoniobutyl ether (**6**), for example, occurs 40,000 times less rapidly than the ketonisation of anthrol. Rate constants ($M^{-1}s^{-1}$) for these substrates are shown below under their structures.



In 1987 Powell demonstrated that the mechanism of hydrolysis of 9-anthryl ethers differs from that of monocyclic aryl ethers such as anisole. The latter undergo protonation on oxygen followed by S_N2 nucleophilic displacement of the phenol by water as shown below (**7**).



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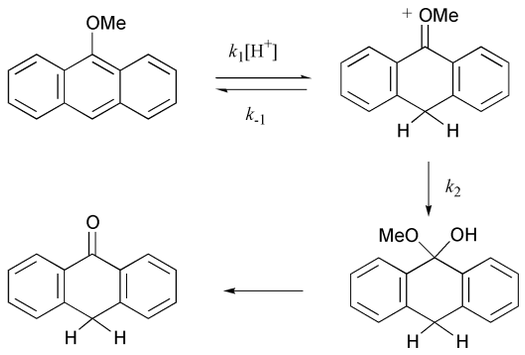
Powell proposed that the hydrolysis of anthryl ethers is analogous to that of enol ethers. As shown in Scheme 4, in the initial step of the reaction protonation takes place at the 10-carbon atom of the central aromatic ring. This is followed by attack of water on the carbocation centre generated at the 9-carbon atom to yield a hemiacetal, which further reacts to form anthrone. As evidence for the difference in mechanisms, Powell demonstrated that hydrolysis of the anthryl ether in



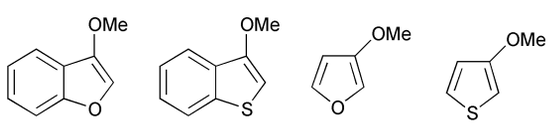
Scheme 4

$H_2{}^{18}O$ enriched water gives the oxygen isotope exclusively in the anthrone and not the alcohol product as is found *e.g.* for anisole.

In the hydrolysis of enol ethers the rate-determining step is the initial protonation. Powell concluded that the same was true of anthryl ethers and that protonation of the 10-anthryl carbon atom was rate-determining. His conclusion was based on the observation of catalysis by the acid component of the acetic acid buffers and measurement of a solvent isotope effect k_{H_3O}/k_{D_3O} = 1.85, consistent with the contribution of a primary isotope effect.

However, there are difficulties with this conclusion. Rate constants for protonation of enol ethers are smaller than for protonation of the corresponding enols but the differences are usually small, typically a factor of twenty-fold. This contrasts sharply with the differences of 3000–40,000-fold between anthrol and the anthryl ethers **5** and **6**. Moreover, while the solvent isotope effect k_{H_3O}/k_{D_3O} = 1.85 for **6** is similar to that for the hydrolysis of 9-methoxyanthracene it is considerably less than that for the protonation of anthrol (k_{H_3O}/k_{D_3O} = 4.8).

In 1987 also Capon and Kwok described the acid-catalysed hydrolysis of a series of heteroaromatic phenol ethers, including 3-methoxyfuran, 3-methoxythiophene and their benzo derivatives (**8**–**11**, Scheme 5).[7] They adopted the same



	8	**9**	**10**	**11**
k_x/k_{hyd}	<0.05	31	83	2.6×10^4
k_{H_3O}/k_{D_3O}	3.08	1.36	0.51	0.52

Scheme 5

mechanism as Powell, with protonation of the heterocyclic ring occurring *o*- to the heteroatom. However, they also showed that as the aromatic character and hence stability of the double bond subject to protonation increases the protonation step becomes reversible and ceases to be rate-determining.

Capon and Kwok established the reversibility of protonation by measuring rates of hydrogen isotope exchange in D_2O–CD_3CN mixtures using NMR. It was shown that the ratio of exchange to hydrolysis (k_x/k_{hyd}) increases as the aromaticity of the heterocyclic ring increases. This is illustrated by the rate constant ratios shown under the structures in Scheme 5. For the weakly aromatic 3-methoxybenzofuran, for example, no exchange was detectable, but for 3-methoxybenzothiophene exchange is 31 times faster than hydrolysis, and for the more strongly aromatic 3-methoxyfuran and 3-methoxythiophene this ratio is even larger.

These results suggested that proton transfer might also be reversible in the hydrolysis of anthryl ethers. NMR measurements similar to those made by Capon and Kwok were undertaken for 9-methoxyanthracene therefore. The measurements showed that in D_2O–CD_3CN mixtures the rate of exchange is indeed faster than hydrolysis, by a factor of approximately four-fold in concentrated DCl and by six-fold at ~3 M DCl. Taking the value in dilute acid as seven-fold, and making allowance for an isotope effect upon the exchange reaction, a greater rate of protonation than hydrolysis of about 70-fold is estimated for the reaction of H_3O^+ in H_2O. There is some uncertainty in this ratio arising from an incomplete knowledge of isotope effects for the exchange reaction and the difference in solvents between the exchange and hydrolysis measurements, but the faster rate of protonation than hydrolysis cannot be doubted.

This result goes a long way towards explaining the difference in rates and isotope effects between protonation of anthrol and hydrolysis of its methyl ether. However, some inconsistencies remain. Thus a kinetic analysis of the hydrolysis reaction in D_2O based on Scheme 2 indicates that competition between hydrolysis and isotope exchange leads to a series first order dependence of the concentration of the anthryl ether upon reaction time, *t*. This dependence is shown in terms of absorbance in eqn. (9) in which A_0 and A_∞ are initial and final

$$(A - A_\infty)/(A_0 - A_\infty) = (1 - q)e^{-(k_H + k_x)t} + qe^{-k_D t} \quad (9)$$

absorbances in the reaction, and the notation for rate constants is that of Scheme 2. The term $q = k_x/(k_x + k_H - k_D)$ reflects the relative magnitudes of rate constants for exchange and hydrolysis. When $q = 0$ there is no exchange (k_H, $k_D \gg k_x$) and when $q = 1$ there is rapid exchange ($k_x \gg k_H - k_D$).

In practice, kinetic measurements in D_2O showed no obvious deviation from first order kinetic behaviour. This reflects partly the high ratio of exchange to hydrolysis rate constants. However, analysis of simulated data showed that even when rates of exchange and hydrolysis are comparable departures from first order behaviour are not pronounced. For slow reactions, in which a first order rate constant is determined by iteration, departures from first order behaviour are also compensated by adjustment of the values of A_0 and A upon which the iteration is based.

A second apparent inconsistency is that a higher rate of exchange than hydrolysis might have been expected to lead to faster hydrolysis in D_2O than H_2O, as observed by Capon for 3-methoxyfuran and 3-methoxythiophene (Scheme 5). In principle, the observed isotope effect in the opposite direction (k_{H_3O}/k_{D_3O} = 1.95) could be consistent with the combination of (a) a small ratio of exchange to hydrolysis rate constants and (b) underestimation of the rate constant for hydrolysis (of the deuterium-exchanged substrate) in D_2O stemming from a forced first order fit to series first order behaviour.

In practice, the rate of exchange relative to hydrolysis is too high to allow such an explanation of the faster rate in H_2O. An apparently necessary explanation is that the isotope effect arises from a proton transfer in the subsequent rate-determining step, which should be either attack of water on the carbocation intermediate or hydrolysis of the hemiacetal formed following this attack. Fife has shown that general acid-catalysis and solvent isotope effects with $k_{H_2O}/k_{D_2O} > 1.0$ can occur for the hydrolysis of acetals leading to sufficiently stable carbocations;[26] the 9-methoxyanthracenium ion certainly has sufficient stability to qualify as such an ion.

Inspection of Capon and Kwok's results in Scheme 5 suggests that a similar situation obtains for the hydrolysis of 2-methoxybenzofuran. Again the ratio of exchange to hydrolysis rates is too high to be consistent with slow exchange being responsible for $k_{H_2O}/k_{D_2O} > 1.0$. Arguably, in this case the carbocation is again stable enough for general acid-catalysis to prevail in the formation or reaction of the hemiacetal. However, surprisingly, there is a reversion to $k_{H_2O}/k_{D_2O} < 1.0$ for the

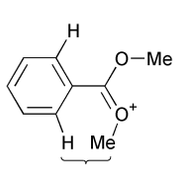
structurally related 3-methoxyfuran and 3-methoxythiophene. Selective general acid catalysis of these steps remains the most likely explanation of these variable isotope effects, but further investigation would be required to resolve this question.

The possibility of general acid catalysis of a step following protonation of the anthracene ring is pertinent to the remaining evidence suggesting slower protonation than hydrolysis in Powell's study of anthryl ethers, namely his report of buffer catalysis of the reaction in acetic acid buffers. Inspection of Powell's data suggests that the extent of buffer catalysis (relative to the buffer independent reaction) is untypically small for a rate-determining proton transfer to carbon. However, such weak catalysis is typical of proton transfer between oxygen atoms and would be consistent with general acid catalysis of hemiacetal formation or reaction in the rate determining step.[14] Whether or not this explanation is correct, there can be no doubt that for the hydrolysis of anthryl methyl ether at 25 °C, the initial protonation of the aromatic ring is not rate-determining.

Methoxy substituent effect

If the rate constant for hydrolysis of 9-methoxyanthracene is now corrected by 70-fold to obtain a more realistic value of the rate constant for protonation at the 10-carbon atom we find that the reaction is still 40-fold slower than the ketonisation of anthrol. This remains somewhat larger than the difference between ketonisation and hydrolysis for the heteroaromatic phenols and their methyl ethers studied by Capon and Kwok, which appear to provide the most appropriate mechanistic comparison for the anthryl methyl ether. Rate constants for H_3O^+-catalysed ketonisation of the heteroaromatic phenols corresponding to the methyl ethers of Scheme 5 have been reported by Capon and Kwok.[27] For the methoxybenzofuran (**8**) the rate ratio k_{OH}/k_{OMe} is 16, and similar values are obtained for the other substrates if their exchange rates in D_2O[7] are corrected to values in H_2O by assigning reasonable isotope effects[22] for the exchange reaction.

A clue to the origin of a larger effect of methylation on the rate of protonation of anthrol than of the apparently comparable heteroaromatic phenols is suggested by the destabilisation observed for a dimethoxymethyl cation following substitution by an α-phenyl group.[28,29] This has been interpreted as arising from steric interference of the *o*-hydrogen atoms of the benzene ring with the planarity of one of the methoxy groups (**12**).[30] It is easy to imagine that in the protonated anthrol the 1,8-hydrogen atoms of the anthracene ring similarly interfere with achievement of an in plane conformation of the alkoxy substituent, thus inhibiting stabilisation of the anthryl cation (**13**). If the steric requirement of a hydroxy group in this situation is less than that of methoxy, as would seem likely, then the remaining difference in rate constants for protonation of anthrol and its methyl ether is explained.



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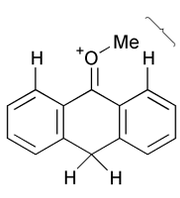

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Experimental

The instrumentation used in this work was similar to that described in an earlier paper.[11] Anthrone was purchased from Aldrich and recrystallised from ethanol. 9-Methoxyanthracene was prepared by the method of Pickle and Finn,[31] recrystallised from ethanol and stored under nitrogen.

Stock solutions of anthrone or anthrol for equilibrium or kinetic measurements were degassed by bubbling nitrogen or argon. The anthrone stock solution (in MeOH) was acidified to pH 3 to inhibit oxidation to anthraquinone. Equilibrated solutions of anthrone and anthrol in DMF were prepared daily. The DMF was 'anhydrous' grade supplied by Aldrich and stored under N_2 in 'sure seal' bottles.

Equilibrium measurements

The basic ionisation constant of anthrone was measured spectrophotometrically in solutions of piperazine buffers which were degassed before the measurements. The anthrone was introduced from a stock solution by microlitre syringe, typically 25 μl in 2 ml of buffer, and the injections were shown to be reproducible. The absorbance of the anthrolate anion was monitored as a function of time at λ_{max} = 269 nm and extrapolated to the time of injection to correct for changes in absorbance arising from oxidation to anthraquinone. The loss of absorbance from oxidation occurred more readily in basic solutions but the rate of oxidation became roughly constant at pH > 11, consistent with reaction of the anthrolate anion with O_2 and the complete formation of this anion at high pH.

The pK_a for ionisation of anthrone was found to be 10.0 based on the following absorbance measurements at the pHs indicated: 0.270, 9.07; 0.410, 9.33; 0.511, 9.52; 0.520, 9.70; 0.636, 9.97; 0.76, 10.10; 0.77, 10.30; 0.970, 10.55. The concentration of substrate was ~1.30×10^{-5} M and the ionic strength of the piperazine buffers was 0.1. Limiting absorbances at 0.01 M NaOH and in unbuffered water were 1.16 and 0.19 respectively.

The pK_a of anthrol was found to be 8.0, based on measurements of initial absorbances in aqueous borate and phosphate buffers of ionic strength 0.1 M after injecting a few microlitres of anthrol and anthrone in DMF. The measured absorbances of anthrol at λ_{max} = 256 nm at the indicated pHs were as follows: 0.276, 8.02; 0.362, 8.62; 0.458, 8.16; 0.520, 8.05; 0.567, 7.78; 0.599, 7.68; 0.63, 7.40. Measurements in water and 0.1 M NaOH gave absorbances 0.835 and 0.135. The concentration of anthrol + anthrone was 7.3×10^{-6} M.

Unchecked measurements of extinction coefficients at absorption maxima recorded for ionised and unionised anthrol were as follows: anthrolate anion (in H_2O) 76,000 (269 nm), 4000 (358 nm), and 9000 (375 nm); anthrol (H_2O) 77,000 (256 nm), 3000 (365 nm). The values for anthrol were estimated from initial absorbances after quenching a DMF solution in H_2O using Beak's (approximate) estimate of the anthrol–anthrone tautomeric constant in DMF.[4] They were similar to the following values measured for 9-methoxyanthracene (in water): 111,000 (255 nm), 4000 (350 nm), 6700 (368 nm), 5500 (387 nm). Spectra for 9-methoxyanthracene and anthrone are shown in Fig. 3. Anthrone has ε = 17,000 at λ_{max} 272 nm.

Kinetic measurements

Rate constants for ketonisation of anthrol were measured by quenching an anthrol rich tautomeric mixture in DMF into an aqueous solution using a microlitre syringe and monitoring disappearance of the intense peak at 256 nm or the much weaker peak at 365 nm. Solutions of DCl were prepared from a concentrated solution in D_2O (Aldrich).

Rate constants for the reaction of anthrone to form the anthrolate anion in aqueous sodium hydroxide were measured by stopped flow spectrophotometry. The following first order rate constants (k_{obs}/s^{-1}) were measured at 25 °C at the indicated concentrations of hydroxide ion: 0.044, 0.01 M; 0.102, 0.002 M; 0.171, 0.003 M; 0.234, 0.004 M; 0.308, 0.006 M; 0.428, 0.008 M; 0.520, 0.010 M. No salt was added to maintain ionic strength.

Rate constants for enolisation of anthrone in acetic acid buffers were measured by iodination in the usual manner.[1,11]

Because of the low solubility of anthrone very low concentrations of iodine had to be used, typically [anthrone] = 2×10^{-5} M and [I_3] = 1.8×10^{-6} (absorbance = 0.07). Nevertheless satisfactory and reproducible zero order kinetics were observed and agreement between tautomeric constants based on uncatalysed and acetate-catalysed reactions in H_2O was good. Measurements in D_2O had to accommodate a distinctly lower solubility of the substrate (~20%).

Isotope exchange measurements

Measurements of isotope exchange at the 10-position of the anthracene ring of 9-methoxyanthracene and the accompanying hydrolysis to anthrone were carried out using a Varian Unity 500 MHz NMR spectrometer. Exchange and hydrolysis reactions were initiated by injection of 37% DCl in D_2O into a saturated solution of 9-methoxyanthracene in CD_3CN and D_2O (*e.g.*, 0.25 ml DCl, 0.65 ml of CD_3CN and 0.1 ml of D_2O).

Measurements were possible at relatively high acid concentrations (~6.7 M DCl) or low acid concentrations (~3 M DCl) in which case the peak for HD_2O^+ fell respectively below or above the aromatic region of the 9-methoxyanthracene analysed in the measurements. At the higher acid concentrations the exchange reaction was a little too fast to be monitored easily by NMR, and at the lower acid concentrations the hydrolysis reaction was slow; moreover some oxidation of the hydrolysis product to anthraquinone occurred.

Structures of reactants and products from exchange and hydrolysis, with the hydrogen atoms labelled to correspond to peaks assigned in the NMR spectra, are shown in Fig. 4. Peaks (*a*)–(*c*) refer to the reactant, 9-methoxyanthracenene: (*a*) refers to the 10-hydrogen atom, (*b*) the 1,8-hydrogen atoms and (*c*) the 4,5-hydrogen atoms. Peak (*d*) refers to the 1,5 hydrogen atoms of the anthrone product. The spectra were recorded between 8.0 and 8.35 ppm; other hydrogens of the reactant and product absorb at higher field. Spectra measured at 6.7 M DCl were based on 32 FIDs and were taken at intervals over a period of one hour for varying extents of hydrolysis and exchange. A selection of these spectra are also shown in Fig. 4 and labelled (i)–(iv), corresponding to approximate reaction times 0, 3.5, 20 and 60 min.

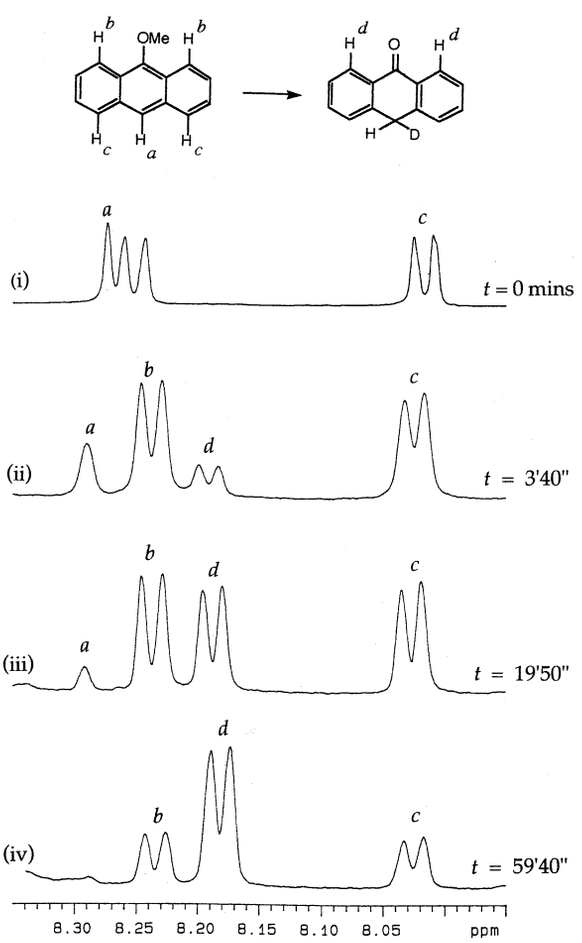


Fig. 4 Proton NMR spectra (500 MHz) of 9-methoxyanthracene in DCl–D_2O–CD_3CN (~6.7 M) showing extents of exchange and hydrolysis at different time intervals.

The first spectrum in Fig. 4 shows the 9-methoxyanthracene reactant with the 10-hydrogen (*a*) appearing at lowest field as a singlet and the 1,8 and 4,5-hydrogens as doublets (i). As exchange and hydrolysis proceed the intensity of the 10-hydrogen atom decreases (ii), and after 20 min it is extensively exchanged (iii). At the same time two new peaks appear corresponding to the 1,8-hydrogens of the anthrone product (*d*), as can be seen in spectrum (ii). The reactant hydrogens (*b*) and (*c*) decrease more slowly than (*a*), consistent with hydrolysis occurring less rapidly than exchange. Their decrease occurs at the same rate as appearance of the doublet (*d*) assigned to the 1,8-hydrogens of the anthrone product, as can be seen in spectra (iii) and (iv). The final spectrum in Fig. 4 indicates that hydrolysis has occurrred to the extent of 75% in one hour.

The principal kinetic measurements were carried out at ~3 M DCl in 35% aqueous D_2O–CD_3CN. For each measurement, up to ten spectra based on 16 FIDs were recorded over a period of one hour. Relative concentrations of exchanged and unexchanged reactant and of reactant and product were determined by integration of the peaks referred to above (and shown in Fig. 4). Analysis of the exchange data would have been eased if isotope exchange in the reactant could have been monitored from the amount of deuterium remaining in the 9-position of the anthrone product. However, the product is subject to independent isotope exchange at the 9-position. This was established by integration of the product peaks and is also expected on the basis of rates of exchange calculated from rate constants for tautomerisation of anthrone and anthrol. (In a difficult experiment, Powell[6] failed to detect exchange in the product of hydrolysis of the anthracenyl ether [**6**]).

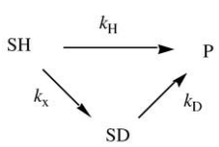
In analysing the NMR data it can be recognised that the total concentration of methoxyanthracene reactant may be expressed in terms of the sum of the intensities of hydrogens *b* and *d*. The fractional concentrations of protio (SH) and deutero (SD) reactants are then given by eqns. (10) and (11) in

$$[SH] = 2a/(b + d) \quad (10)$$

$$[SD] = (b - 2a)/(b + d) \quad (11)$$

which the letters refer to the intensities of the corresponding peaks (the intensities of *b* and *c* are the same).

A kinetic analysis of competing exchange and hydrolysis reactions may then be based on Scheme 6 (an abbreviated form



Scheme 6

of Scheme 2), in which SH and SD represent protio- and deutero-substrates, k_H and k_D are rate constants for their hydrolysis and k_x is the rate constant for deuterium exchange of the 10-hydrogen atom. From a series first order analysis we obtain the relationships shown in eqns. (12) and (13), in which A_0 is the initial concentration of SH and $q = k_x/\{(k_x + k_H) - k_D\}$.

$$[SH] = A_0 e^{-(k_x + k_H)t} \quad (12)$$

$$[SD] + q[SH] = A_0 e^{-k_D t} \quad (13)$$

As shown in eqn. (12) we may obtain a value of $k_x + k_H$ from a plot of log[SH] against t. In principle a value of k_D may also be obtained from a plot of log[SD] *versus* t after all of the SH has been exchanged. In practice, it is more convenient to assign an approximate value of the parameter q and plot log{[SD] + q[SH]} *versus* t. For reasonable ratios of rates of exchange and hydrolysis q is sufficiently close to 1.0 (*i.e.* in the range 1.0–1.3) to be easily determined by iteration. An initial choice of q allows evaluation of k_D which leads to a refined value of q after k_H has been determined as described below. Plots of log{[SD] + q[SH]} and log[SH] *versus* t are shown in Fig. 5.

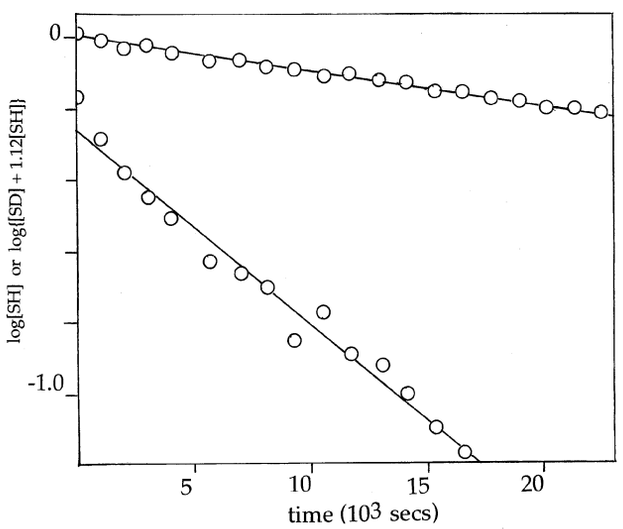
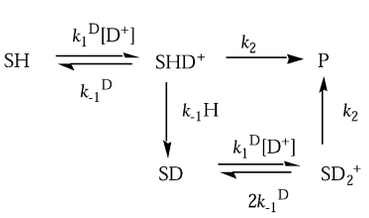


Fig. 5 Plots of log[SH] (lower line) and log{[SD] + 1.12[SH]} (upper line) *versus* time for exchange and hydrolysis respectively of 9-methoxyanthracene in ~3 M DCl in D_2O–CD_3CN at 25 °C, based on NMR measurements: SH refers to 10-protio and SD to 10-deuterio substrates respectively.

To obtain the rate constant for exchange, k_x, the sum of the rate constants $k_x + k_H$ must be corrected for the contribution of k_H. As this correction represents an adjustment of no more than 10–15%, values of $k_x + k_H$ and k_D offer a close approximation to relative exchange and hydrolysis rate constants. At ~3 M DCl, we found $q = 1.12$, $k_x + k_H = 6.3 \times 10^{-5}$ s^{-1} and $k_D = 1.0 \times 10^{-5}$ s^{-1}, which imply a six-fold greater rate of exchange than hydrolysis. At the higher acid concentration (~6.7 M DCl), we found $q = 1.25$, $k_x + k_H = 1.6 \times 10^{-3}$ s^{-1} and $k_D = 3.8 \times 10^{-4}$ s^{-1}, consistent with a four-fold ratio of exchange to hydrolysis. These measurements are not of high precision, but suggest that in dilute aqueous acid solution exchange is approximately seven times faster than hydrolysis, if the presence of acetonitrile does not significantly affect their relative rates.

The empirical rate constants of Schemes 2 and 6 may be replaced by microscopic rate constants based on Scheme 7,



Scheme 7

in which SHD^+ represents protonated and SD_2^+ deuterated 9-methoxyanthracene-9-*d*. The rate constants k_1 and k_{-1} in Scheme 7 refer to protonation of the methoxyanthracene and deprotonation of its protonated form respectively; k_2 is a rate constant for attack of water on the protonated intermediate. The scheme refers to reaction of protio-substrate in D_2O and the reacting isotopes are indicated as superscripts.

The relationships between experimental rate constants and microscopic rate constants are shown in eqns. (14)–(16).

$$k_H = \frac{k_2 k_1^D}{(k_2 + k_{-1}^H + k_{-1}^D)} \quad (14)$$

$$k_x = \frac{k_{-1}^H k_1^D}{(k_2 + k_{-1}^H + k_{-1}^D)} \quad (15)$$

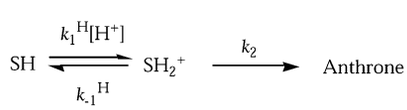
$$k_D = \frac{k_2 k_1^D}{(2k_{-1}^D + k_2)} \quad (16)$$

The ratio of rate constants for exchange and hydrolysis in D_2O, k_x/k_D, may be expressed in terms of the ratio k_2/k_{-1}^D (denoted x) and an isotope effect upon deprotonation of the intermediate k_{-1}^H/k_{-1}^D (denoted y) as in eqn. (17).

$$\frac{k_x}{k_D} = \frac{y(2+x)}{(1+y+x)x} \quad (17)$$

To obtain k_H, and also to deduce a ratio of rate constants for protonation and hydrolysis of methoxyanthracene in H_2O, it is necessary to assign an isotope effect k_{-1}^H/k_{-1}^D (= y) for deprotonation of the protonated methoxyanthracene intermediate. By analogy with other measurements of hydrogen isotope exchange in aromatic substrates[19,32] a value of 5–10 is judged to be reasonable. Alternatively, a more specific estimate can be based on the solvent isotope effect of $k_{H_2O}/k_{D_2O} = 4.7$ for protonation of anthrol. If relative values of k_{H_2O}/k_{D_2O} for protonation of enols and hydrolysis of their enol ethers are taken as a guide, k_{H_2O}/k_{D_2O} for the protonation of the anthryl ether should be smaller than that for protonation of anthrol, *e.g.* $k_{H_2O}/k_{D_2O} = 3.5$. Combining $k_{H_2O}/k_{D_2O} = 3.5$ with (a) a solvent isotope effect contribution estimated from analogy with other proton transfer reactions as 0.7 for the protonation (k_1) of the anthryl methyl ether and (b) a ratio of fractionation factors for the reacting hydrogen in H_3O^+ and the protonated substrate (SH_2^+) (also ~0.7) allows us to convert an isotope effect for the forward reaction (k_1^H/k_1^D) to that of the back reaction as $k_{-1}^H/k_{-1}^D = k_1^H/k_1^D/0.7 = 3.5/0.7^2 = 7$. Finally, k_{-1}^H/k_{-1}^D may be corrected for a (secondary) isotope effect from the second hydrogen in the protonated substrate to give k_{-1}^H/k_{-1}^D ~8.

We may now solve eqn. (17) with $y = k_{-1}^H/k_{-1}^D = 8$ to obtain k_2/k_{-1}^D (= x) = 0.28. This in turn allows us to obtain the ratio of hydrolysis rate constants of protio and deutero substrates in D_2O, $k_H/k_D = (2 + x)/(1 + x + y) = 0.25$, by combining eqns. (14) and (16). We thence obtain a value of k_H which may be used in the iterative evaluation of k_D and q described above. From comparison of Schemes 7 and 8 it can be seen that k_H is



Scheme 8

smaller than k_D because the intermediate SHD^+ reverts to reactants more readily than does SD_2^+, as a result of the large isotope effect (k_{-1}^H/k_{-1}^D) on the reversion step.

We can also evaluate the main objective of this exercise, the ratio of rate constants for protonation and hydrolysis of the anthryl methyl ether in H_2O (rather than D_2O). Based on Scheme 8 the rate constant for hydrolysis in H_2O can be written

as $k_1^H k_2/(2k_{-1}^H + k_2)$ and the ratio of rate constants for protonation (k_1^H) and hydrolysis in H_2O as $1 + 2k_{-1}^H/k_2$. The factor 2 multiplying k_{-1}^H arises because of the possibility of losing one of two equivalent hydrogens from the methoxyanthracenonium ion (SH_2^+). By combining $y = k_{-1}^H/k_{-1}^D = 8$ and $x = k_2/k_{-1}^D = 0.28$ we obtain $= y/x = 28.5$ and the ratio of protonation to hydrolysis rates $(1 + 2y/x)$ as 58.

In these calculations it is assumed that the ratio k_{-1}/k_2 is independent of the nature of the isotopic solvent since k_{-1} and k_2 involve attack of H_2O as base and nucleophile respectively on the same substrate and thus should be subject to similar solvent isotope effects. However, k_1 and k_{-1} will be sensitive to secondary isotope effects and if secondary isotope effects of 0.9 and 1.1 respectively are applied to the two rate constants the ratio of protonation to hydrolysis rate constants is increased from 58 to 67.

These calculations are also sensitive to the assumed value for k_{-1}^H/k_{-1}^D. If this is increased from 8 to 10 the ratios of rates of protonation to hydrolysis in H_2O are increased to 80 and 70 depending on whether or not the secondary isotope effects implicit in k_{-1}^H/k are taken into account. Importantly, a change in k_{-1}^H/k_{-1}^D has practically no effect upon q, so that $k_x + k_H$ and k_D can be evaluated from the exchange data independently of the choice of isotope effects. This is because k_H makes only a small contribution to q.

Solvent isotope effect

Finally, it is necessary to establish whether or not the isotope exchange measurements are consistent with the measured solvent isotope effect for the hydrolysis of 9-methoxyanthracene, $k_{H_2O}/k_{D_2O} = 1.8$. In the first place it should be noted that the value of k_{D_2O} is based on a measurement for the reaction of the protio substrate in D_2O. To obtain this rate constant k_{D_2O} it was assumed that the reaction obeyed first order kinetics. Strictly speaking, the reaction is series first order, and is described by eqn. (18), as may be seen from combining eqns. (12) and (13).

$$[SH] + [SD] = A_0 e^{-k_D t} + (1 - q)A_0 e^{-(k_x + k_H)t} \qquad (18)$$

It is easy to show that k_{D_2O} for a deuterated substrate, which corresponds to k_D in eqn. (18), is represented by the limiting rate constant at long reaction times when exchange is complete. Likewise the initial rate constant for a reaction of protio substrate in D_2O is k_H. In principle, therefore, limiting values of the measured solvent isotope effect k_{H_2O}/k_{D_2O} must be given by k_{H_2O}/k_D and k_{H_2O}/k_H.

Values of k_H and k_D can be expressed in terms of microscopic rate constants by making use of eqns. (14) and (16) based on Scheme 7; k_{H_2O} has been evaluated as $k_1^H k_2/(2k_{-1}^H + k_2)$. Dividing k_{H_2O} through by k_2 and combining with eqns. (13) and (14) leads to the relationships of eqns. (19) and (20) for limiting

$$\frac{k_{H_2O}}{k_D} = \frac{k_1^H(1 + 2k_{-1}^D/k_2)}{k_1^D(1 + 2k_{-1}^H/k_2)} = 0.4(0.5) \qquad (19)$$

$$\frac{k_{H_2O}}{k_H} = \frac{k_1^H(1 + k_{-1}^D/k_2 + k_{-1}^H/k_2)}{k_1^D(1 + 2k_{-1}^H/k_2)} = 1.8(2.0) \qquad (20)$$

values of k_{H_2O}/k_{D_2O} at small and large reaction times. These yield the numerical values shown based on $k_H/k_D = 7$, $k_{-1}^H/k_{-1}^D = 8$ and $k_1^H/k_1^D = 3.5$, with corrections made, as before, for secondary isotope effects (the values shown in brackets are uncorrected). Again it is assumed that there is no solvent isotope effect upon the ratio k_{-1}/k_2.

It can be seen that limiting solvent isotope effects at complete exchange of H for D in the substrate (eqn. (19)) gives a faster reaction in D_2O with $k_{H_2O}/k_{D_2O} = 1.8$. Thus the measured isotope effect apparently corresponds closely to that for the initial rate of reaction (k_{H_2O}/k_H, eqn. (20)).

In practice, however, it is clear that the experimental isotope effect cannot correspond to the initial rate of reaction in D_2O. Assignment of a relatively large ratio of exchange to hydrolysis rate constants ($k_x/k_D = 7$) and a large isotope effect for proton transfer from the anthracenium ion intermediate ($k_{-1}^H/k_{-1}^D = 8$) are quite incompatible with $k_{H_2O}/k_{D_2O} > 1$. Although eqn. (18) indeed represents series first order kinetics, the exchange reaction implicit in the second exponential is apparent only as a relatively minor perturbation of the initial part of the reaction, even when exchange is relatively slow (*e.g.* $k_x/k_D = 2$). Moreover, for a slow reaction, which is monitored spectrophotometrically and where the limiting absorbance at long reaction times is iterated with the assumption that the kinetics are first order, departures from first order kinetics are concealed by compensating adjustments in the intial and limiting absorbances, as becomes clear from analysis of model data. The derived rate constant is therefore somewhat smaller than the limiting (true) value of k_{D_2O} at long reaction times, tending to increase k_{H_2O}/k_{D_2O}, but the discrepancy, even if exchange is quite slow relative to hydrolysis, does not exceed 20–30%. In other words k_{H_2O}/k_{D_2O} could not be greater than ~0.5.

Careful inspection of our experimental data revealed a barely detectable induction period at the beginning of the reactions of protio substrate in D_2O. The difficulty we experienced of detecting departure from first order behavior is consistent with the exchange being relatively fast, and confirms that the derived first order rate constants provide a good approximation to k_{D_2O}. It seems clear therefore that it is not possible to explain the measured value of $k_{H_2O}/k_{D_2O} = 1.8$ in terms of partially rate determining proton transfer to the 9-methoxyanthracene.

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