Protiodeacylation of 4-Substituted 1-Acetyl-2,6-dimethylbenzenes in Sulphuric Acid: Kinetics and Mechanism

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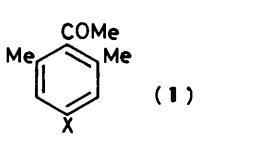
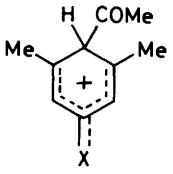
In 89.8% (w/w) sulphuric acid rate coefficients ($10^4k_1/s^{-1}$) for the protiodeacetylation of 4-substituted (X) 1-acetyl-2,6-dimethylbenzenes (**1**) were, at 25 °C; X = Br, 0.468; I, 0.509; Cl, 0.635; H, 1.345; F, 2.52; Ph, 31.5; Bu^t, 38.6; and Me, 47.2. At 25 °C the reaction of the ketone (**1**; X = OMe) was too fast, and at 80 °C reactions of the ketones (**1**; X = $CONH_2$ or CO_2H) were too slow, for convenient measurement. The carboxy nitrile (X = CN) underwent hydration to the amide (X = $CONH_2$) rather than protiodeacylation. The rate coefficients at 25 °C of eight ketones (**1**) gave an accurate Hammett correlation, with σ^+ constants, giving $\rho = -4.64 \pm 0.05$. The reaction of 1-acetyl-2,4,6-trimethylbenzene (**1**; X = Me) was studied of a range of acidity (73.6–99.9% sulphuric acid), and a maximum was found near 86.0% acid. Rates were also measured in D_2SO_4–D_2O. The mechanism is discussed.

Protiodeacylation, in which an acyl group is displaced by hydrogen in concentrated acid solutions, has been known for more than a century,[1] but, although many such aromatic substitution reactions are now known,[2] mechanistic studies have been scant. Substantially more work has been published on the kinetics of formally related reactions, *viz.* the decarbonylation of 2,4,6-trialkylbenzaldehydes,[3] and the decarboxylation of 2,4,6-trisubstituted benzoic acids.[4] Kinetics for the reactions of 1-acetyl-2,4,6-trimethylbenzene (acetylmesitylene) (**1a**),[5,6] 1-acetyl-2,6-dimethylbenzene (**1b**),[5] 1-acetyl-2,4-dimethylbenzene,[6] and 1-acetyl-2-methylbenzene[6] have been determined, for a range of sulphuric acid/water media. In each case the plot of rate coefficient ($k_{obs.}$) *vs.* acidity proceeds through a maximum.

Further studies have now been carried out, with a view to contributing to our understanding of the protiodeacylation reaction.



(**1**)



(**2**)

	X		X
a;	Me	**h**;	Br
b;	H	**j**;	OMe
c;	Bu^t	**k**;	OH
d;	Ph	**l**;	CN
e;	F	**m**;	$CONH_2$
f;	Cl	**n**;	CO_2H
g;	I	**o**;	NH_2

Effect of Substituents.—A series of 4-substituted 1-acetyl-2,6-dimethylbenzenes (**1**) was synthesised and the protiodeacylation kinetics were determined, with 89.8% (w/w) sulphuric acid as the medium.[2b] Such ketones were expected to have equivalent steric characteristics at the reaction site, so that rates should vary only according to the electronic properties of the *para*-substituents. The rates of protiodeacylation varied widely: extreme cases were observed of ketones which reacted too rapidly for measurement at 2 °C, or too slowly even at 150 °C. The data obtained are summarised in Table 1.

The magnitudes of enthalpies of activation ($\Delta H^‡$), calculated for 25 °C, cover only a narrow range (±8%); thus differences in rates are due mainly to changes in entropies of activation ($\Delta S^‡$). For those ketones which react fastest $\Delta S^‡$ values were found to be high, even slightly positive; this has been noted before.[2b,c,6] The rate coefficients, extrapolated to 25 °C, for the parent (**1b**) and seven substituted ketones (**1a** and **c**—**h**) cover a satisfactory ten-fold range.

The rate coefficients, computed for 25 °C, were examined for their linear free-energy correlation in the Hammett equation (1),[7] but the plot of log k *vs.* standard σ constants was poorly correlated ($r = 0.909$), with selectivity constant $\rho = -4.80$ (s.d. 0.90). When plotted against Brown and Stock's σ^+ constants,[8] however, an excellent correlation ($r = 0.9974$) was obtained, with $\rho = -4.68$ (s.d. 0.139). An even better correlation was achieved [$r = 0.9997$; $\rho = -4.64$ (s.d. 0.051)] when the parent ketone (**1b**) was omitted; this seems justified in the present case (see later).

Table 1 also includes a rate coefficient for the methoxy ketone (**1j**), determined at 2.5 °C, which represents the limit of precise measurement ($t_{\frac{1}{2}}$ at 2.5 °C is *ca.* 120 s). This provides a further, and important point (since MeO is a powerful $+M$ substituent) for a linear free-energy correlation; despite the necessary extrapolation of rate data beyond the experimental temperature ranges for most of the ketones, an excellent correlation ($r = 0.9990$) results, with $\rho = -4.58$ (s.d. 0.084) (parent ketone omitted).

The large negative value of the selectivity constant ρ provides evidence for the involvement of a 'late' transition state,[8,9] *i.e.* one which resembles the structure of the σ-complex (**2**) more closely than it does that of the initial state (**1**). The excellent correlation with σ^+ constants shows that a positive charge is introduced by the electrophile, and stabilised by resonance in the transition state, with participation of the substituents X.

$$\log k_X/k_H = \rho\sigma_X \quad (1)$$

A further refinement would involve the use of the dual-parameter Yukawa–Tsuno equation (2),[10] which sets out to

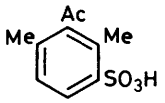
$$\log k_X/k_H = \rho[\sigma_p + r^+(\sigma_p^+ - \sigma_p)] \quad (2)$$

establish the extent of through-conjugation between a $+M$-type *para*-substituent and the reaction centre. Johnson[11] has, however, argued that this treatment is not required. The

Table 1. Rate and activation data for the protiodeacylation of 4-substituted (X) 1-acetyl-2,6-dimethylbenzenes (**1**) in 89.8% (w/w) sulphuric acid

	X	σ_p	σ_p^+	Computed rate coefficient $10^5k/s^{-1}$ (275.6 K)	Computed rate coefficient $10^4k/s^{-1}$ (298.2 K)	$\Delta H^{\ddagger a}$ kJ mol^{-1} (298.2 K)	$\Delta S^{\ddagger a}$ J K^{-1} mol^{-1} (298.2 K)	$\Delta G^{\ddagger a}$ kJ mol^{-1} (298.2 K)
(**1h**)	Br	0.232	0.14	0.293	0.468	81.6	−54	97.7
(**1g**)	I	0.180	0.13	0.266	0.509	87.1	−35	97.5
(**1f**)	Cl	0.227	0.10	0.408	0.635	80.7	−55	97.0
(**1b**)	H	0	0	0.712	1.345	86.7	−28	95.1
(**1e**)	F	0.062	−0.02	1.922	2.52	75.5	−61	93.6
(**1d**)	Ph	−0.01	−0.26	16.27	31.5	87.4	+0.5	87.3
(**1c**)	Bu^t	−0.197	−0.27	19.62	38.6	87.9	+3.6	86.8
(**1a**)	Me	−0.170	−0.30	27.6	47.2	82.9	−12	86.3
(**1j**)	MeO	−0.268	−0.60	565[b]				

[a] Mean 95% confidence limits: in $\Delta H^{\ddagger}$ ±1.8 kJ mol^{-1}, in $\Delta S^{\ddagger}$ ±5.8 J K^{-1} mol^{-1}, and in $\Delta G^{\ddagger}$ ±3.6 kJ mol^{-1}. [b] Experimental value.



(**3**)

selectivity constant for the reactivity series at 2.5 °C thus derived (−4.55) is very close to that obtained (−4.58) by use of the single-parameter equation; moreover, the value of r^+ (0.943) confirms that it is dependence on the σ^+ constants which dominates here.

The deliberate omission of the parent ketone (**1b**) from these correlations may be justified in the following way. In earlier studies the protiodeacylation of 1-acetyl-2,6-dimethylbenzene (**1b**) was followed by estimating the amount of acetic acid produced in the reaction.[5] Whereas in 85% (w/w) sulphuric acid the yield of acetic acid was quantitative, in 90% acid it was only 91.1%, and rapidly decreased at higher concentrations of acid. The reduction in yield was attributed to accompanying formation of 1-acetyl-2,6-dimethylbenzene-3-sulphonic acid (**3**), and rate coefficients for protiodeacylation were obtained for the ketone (**1b**) on the reasonable assumption that the competing sulphonation was a first-order reaction in excess of sulphuric acid. For the present study, if allowance is made for the accompanying (9%) sulphonation of the substrate (**1b**), the corrected rate coefficient fits near-perfectly in the plot (see before) of log k_X *vs.* σ^+, the new correlation (r = 0.9983) giving ρ = −4.69.

It will be shown that the rate of protiodeacylation is proportional to the concentration of unprotonated ketone (which varies with the acidity of the medium) and this is controlled by an acid–base pre-equilibrium. It is not surprising that the present system is nevertheless well correlated, since the effect of *para*-substituents in the pre-equilibria is governed also by the same (or a very similar) set of σ constants.

Several other ketones of the series (**1**) were investigated, but none of the data obtained could be included in the foregoing correlations. The phenol (**1k**) was examined in 89.8% sulphuric acid in the temperature range 2.0—49 °C, by following changes in light absorption at 312 or 350 nm. At best only moderate rate coefficients were obtained, and there was poor correlation on the Arrhenius plot (r = 0.55; whereas for the other ketones r > 0.999). The apparent rate coefficient at 2 °C (4.4 × 10^{-3} s^{-1}) was identical with the apparent k_1 value at 35.5 °C. Detailed study of light absorption showed that the reactions monitored were not simple, but were complex throughout the temperature range, in that there were no isosbestic points. A parallel study, over the temperature range 20—46 °C, of 3,5-dimethylphenol gave apparent rate coefficients almost identical with those obtained with the ketone (**1k**). It has been shown by Brückner[12] that no simple sulphonation product resulted from the action of concentrated sulphuric acid on 3,5-dimethylphenol at temperatures below 100 °C. Our kinetic and analytical studies suggest that formation of two disulphonic acids is already quite rapid at room temperature, and is followed by further sulphonation at higher temperatures. Even at 2 °C, the initial very rapid protiodeacylation reaction is followed by complex subsequent sulphonation processes. An estimate of the rate coefficient for the protiodeacylation of the ketone (**1k**), based on the σ^+ value (−0.92) for the *p*-OH substituent,[13] and using the ρ value already given, gave a predicted k_1 value at 2.5 °C of 1.59 × 10^{-1} s^{-1} (corresponding to $t_{\frac{1}{2}}$ = 4.4 s); this is *ca.* 40 times as fast as the reaction observed at 2 °C. Our experiment thus did not relate to the system being studied.

Ketones (**1**) with X = CN, $CONH_2$, or CO_2H, were also examined. The nitrile (**1l**) underwent a smooth reaction in 89.8% sulphuric acid (see Experimental section). The rate coefficient extrapolated for 25 °C does not fit the Hammett plot established for other *para*-substituents; moreover the calculated $\Delta S^{\ddagger}$ value is significantly lower than that for any other ketone of the series. The reaction observed was simple, since scans showed four good isosbestic points. The actual reaction observed under these conditions, and confirmed by a preparative reaction carried out at 60 °C for 1.5 h, is the quantitative hydration of the nitrile (**1l**) to the carboxamide (**1m**). The rate coefficient calculated for 25 °C (9.4 × 10^{-5} s^{-1}) for this hydration is very close to that observed, under the same conditions, for the hydration of benzonitrile.[14] The substituents present in the nitrile (**1l**) do not appear to exert an appreciable overall effect on rate.

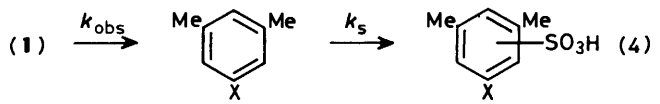
Both the carboxamide (**1m**) and the carboxylic acid (**1n**) showed no change in light absorption, even after 1.5 h at 80 °C. The acid (**1n**) remained unchanged in the acid medium up to *ca.* 150 °C. From known σ^+ values of *p*-$CONH_2$ and *p*-CO_2H protiodeacylation should have been readily observable in the range 60—80 °C. Since this was not so, an explanation was sought in terms of possible deactivation of these substrates in the acid medium. From the known[15] basicity of benzoic acid (pK_{BH^+} = −7.60), and the expression (3) (where n = 1 for

$$pK_{BH^+} = H_0 + n \log [BH^+]/[B] \qquad (3)$$

carboxylic acids),[15] one can estimate that the extent of conjugate acid formation will be *ca.* 97% in 89.8% sulphuric acid. For benzenecarboxamide (pK_{BH^+} = −2.15; n = 1.59[15]) the

proportion of conjugate acid at equilibrium will be >99.99%. The influence of the 4-acetyl-3,5-dimethyl substitution in each case should not be great. Thus, in 89.8% acid the species predominantly present will be the conjugate acids, $ArC(OH)=\overset{+}{O}H$[16] or $ArC(NH_2)=\overset{+}{O}H$,[15,17] and such cationic substituents will effectively deactivate the species (**1m**) or (**1n**). In effect, the rate coefficient for protiodeacylation will be reduced as a function of the proportion of free base present, *viz.* for the amide (**1m**) by a factor of *ca.* 30. These two cases represent examples, which must be rare, of reactions being slowed considerably by substituents remote from the reaction site.

As already indicated, there is indirect evidence that the reactions of the ketones (**1**) being observed in sulphuric acid are protiodeacylations; in most of these cases subsequent sulphonation, k_S, is very rapid [equation (4)], so that the actual reaction observed spectrophotometrically is the conversion of the ketone (**1**) into sulphonic acid(s) (**4**). Kinetic analyses appear to confirm



(**4**)

this.[2a] The intermediate deacylated compound has actually been isolated in a few cases: *m*-xylene was formed from the ketone (**1b**) in sulphuric acid of <85% strength, and mesitylene was formed from the ketone (**1a**) in <83% acid.[5] A claim of the conversion of the ketone (**1a**) into mesitylene[6] in 100% sulphuric acid is obviously an error.

An alternative path is, however, possible for the formation of the sulphonic acid (**4**), *via* the intermediate acyl sulphonic acid (**5**). The formation of an analogous intermediate (**6**) was considered, then discarded, as a possibility in the decarbonylation of mesitaldehyde.[18] The potassium salt of the conjectural intermediate (**5**; X = Me) was prepared by the action of oleum (25% SO_3) at room temperature. This substance proved very unreactive. It was converted into mesitylenesulphonic acid (**4**; X = Me) in 89.8% sulphuric acid at 76 °C, with a rate coefficient ($k_1 = 5.4 \times 10^{-4}$ s^{-1}) which was 2 300 times smaller than that for the protiodeacetylation of acetylmesitylene (**1a**). Compound (**5**; X = Me) is therefore not an intermediate.

Effect of Solvent Acidity.—Rate coefficients were obtained for the protiodeacylation of acetylmesitylene (**1a**) in various concentrations of sulphuric acid. In previous studies a narrower range of acidities was investigated, the upper limit being 87%,[5] or 93%,[6] whilst individual rate coefficients were determined with poor precision, *viz.* ±5%,[5] or ±10% (as seen from rate coefficients recalculated from the published Arrhenius data[6]). The data here obtained are summarised in Table 2. It may be seen that a maximum rate occurs in 86.0% (w/w) sulphuric acid. Maxima in plots of rate *vs.* acidity have also been recorded for the ketone (**1a**) at H_0 −8.5 to −8.0,[6] and for the ketone (**1b**) at H_0 −7.0 to −6.5;[6] also for the decarbonylation of 2,4,6-trialkylbenzaldehydes.[18] Since the maxima were observed at different H_0 values for different substrates, it must follow that an intrinsic property (*viz.* pK_B) of the various bases must be involved.

According to Hammett and Deyrup,[19] if the rate-determining step of an acid-catalysed reaction is a first-order decomposition

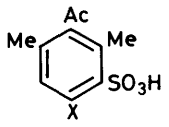
$$\log k + H_0 = \text{constant } (c, c') \qquad (5)$$

of a conjugate acid (BH^+), then equation (5) should hold, provided that $[BH^+]/([B] + [BH^+])$ is small, *i.e.* provided the substrate is present largely as the free base (**B**). The left-hand side of equation (5) applied to our data decreases with increasing acidity, the free base (**B**) not being present as the predominant species at acid strengths above 80%. Yet it has been claimed[6] that a linear relationship exists between log *k* and H_0 between the limits $[B] > [BH^+]$ and $[BH^+] \simeq 10[B]$, *viz.* for the ketone (**1a**) up to 85% acid. This claim must be incorrect.

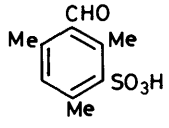
Table 2. Rate coefficients and derived parameters for the protiodeacylation of 1-acetyl-2,4,6-trimethylbenzene (B) in sulphuric acid at 25 °C

Sulphuric acid				
% (w/w)	M	$-H_0$[a]	$10^3 k_{obs.}$[b]/s^{-1}	% Free base B[c]
73.6	12.40	6.40	0.555	90.9
75.1	12.81	6.65	0.937	84.9
77.4	13.40	7.03	2.03	70.1
78.2	13.60	7.16	1.98	63.5
80.5	14.21	7.54	3.14	42.0
82.4	14.70	7.87	4.25	25.3
84.8	15.35	8.22	4.67	13.1
86.0	15.67	8.42	5.09	8.72
88.2	16.22	8.74	4.90	4.37
89.8	16.61	9.06	4.73	2.14
91.5	17.01	9.26	4.07	1.36
93.4	17.42	9.56	3.20	0.69
95.5	17.86	9.90	2.54	0.32
97.3	18.20	10.28	1.84	0.14
98.1	18.36	10.48	1.52	0.083
99.0	18.51	10.94	1.08	0.029
99.9	18.65	11.60	0.256	0.0063

[a] Values from ref. 29. [b] Measured in duplicate; replicability ±1—2%. [c] Obtained from equation (3), using $n = 1$, and $pK_{BH^+} = -7.4$ (ref. 15).



(**5**)



(**6**)

Departures from the Hammett–Deyrup equation (5) at higher concentrations of acid, with the ketone (**1b**) as substrate, led Schubert and Latourette[5] to derive equation (6), which

$$\log k + H_0 - \log \{[B]/([B] + [BH^+])\} = \text{constant} \qquad (6)$$

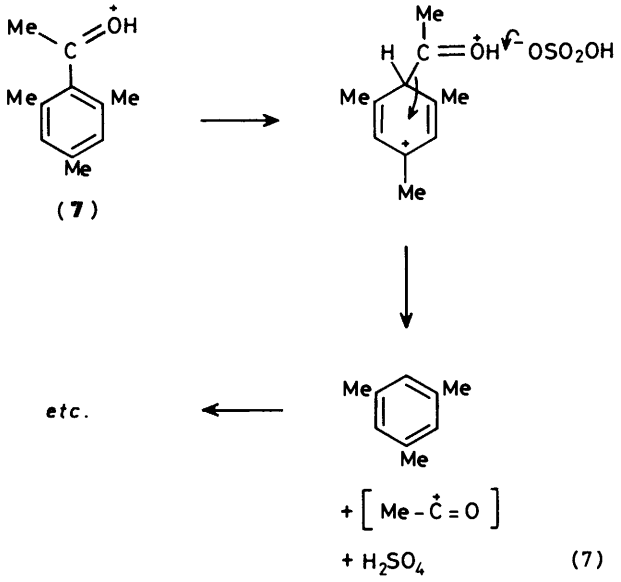
allowed for conjugate acid formation at high acidities. For the ketone (**1b**) they claimed a satisfactory agreement for equation (6), in up to 96% (w/w) sulphuric acid, even though there was a distinct downward drift. It was also emphasised that equation (6) was not to be taken as a sufficient criterion for the assignment of mechanism.[20]

Analysis of rate data by using equation (6) is beset with difficulties. It has been argued that H_0 is not appropriate as an acidity function for carbonyl bases,[21,22] and that the most reliable pK_{BH^+} values are given by application of the Bunnett–Olsen equation.[23] Further, the magnitude of the p*K* values must remain suspect, because of the notorious difficulty of measuring these accurately by acidity function techniques.[24] It is nevertheless encouraging that equation (6) holds for acidities up to $H_0 = -8.4$, and that the observed drift to lower values is only gradual.

Zalewski[6] sought to account for the observed deviations from equation (6) at high acidities in terms of the acetic acid released in the reaction of the ketone (**1a**); he postulated that the acetic acid released in the reaction decreased the catalytic acitivity of hydrogen ions in the medium. This suggestion is

untenable, since only a minute concentration ($< 10^{-4}$M) of acetic acid is released into solution.

To explain the deviation from linearity of the Schubert plot applied to the present data, the notion was explored that at high acidity a concurrent protiodeacylation reaction could take place, in which the conjugate acid (**7**) of the ketone is the substrate [equation (7)]. The overall rate ($R_{obs.}$) of protiodeacylation can then be written (8), with k and k' being the first-order rate coefficients for the free base [(**1a**) = B] and conjugate acid [(**7**) = BH^+], respectively. This becomes (9), where



(7)

$$R_{obs.} = k[B] + k'[BH^+] \quad (8)$$

$$k_{obs.} = k\left(\frac{[B]}{[B] + [BH^+]}\right) + k'\left(\frac{[BH^+]}{[B] + [BH^+]}\right) \quad (9)$$

$$k_{obs.} = \frac{10^{(c - H_0)}}{1 + 10^{(pK_a - H_0)/n}} + \frac{10^{(c' - H_0)} \cdot 10^{(pK_a - H_0)/n}}{1 + 10^{(pK_a - H_0)/n}} \quad (10)$$

$k_{obs.}$ is the experimentally measured rate coefficient. Equation (9) may be written as (10), using the Hammett definition of H_0 in its general form[15] [equation (3)]. By rearrangement one obtains (11); this can then be used to examine the rate data.

$$k_{obs.}[1 + 10^{(pK_a - H_0)/n}] = \underset{\text{(term B)}}{10^{(c - H_0)}} + \underset{\text{(term BH}^+\text{)}}{10^{[c' + pK_a/n - H_0(1 + n^{-1})]}} \quad (11)$$

We will consider first the two extreme cases.

(*a*) Reaction only of the ketone (**1a**) is significant. Then $k' = 0$ at all values of H_0 (*i.e.* $c' = -\infty$), and term BH^+ of equation (11) vanishes. From equation (11) one then obtains (12). A plot

$$\log k_{obs.} + \log [1 + 10^{(pK_a - H_0)/n}] = c - H_0 \quad (12)$$

of the left-hand side of equation (12) *vs.* $-H_0$ should then give a straight line of slope 1 and intercept c.

(*b*) Reaction only of the conjugate acid (**7**) is significant. Then $k = 0$ at all H_0 (*i.e.* $c = -\infty$), and term B of equation (11) vanishes. Then one obtains (13). The plot of the left-hand side of

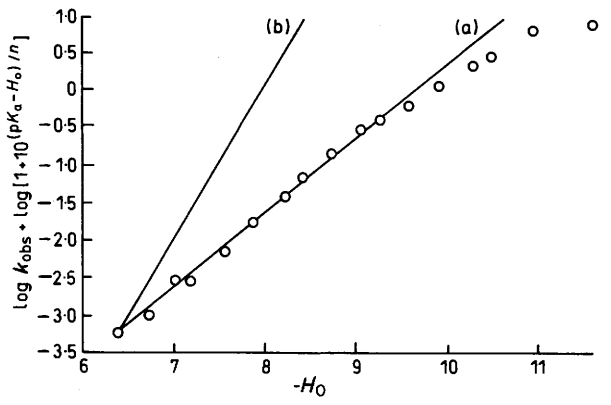


Figure 1. The reaction of 1-acetyl-2,4,6-trimethylbenzene in sulphuric acid: plot of $\log k_{obs.} + \log [1 + 10^{(pK_a - H_0)/n}]$ *vs.* H_0, for reactions at 25 °C. The circles are points calculated for $pK_a - 7.4$, with $n = 0.93$; (a) is the hypothetical line of slope = 1, (b) is that of slope = 2.07 (see text)

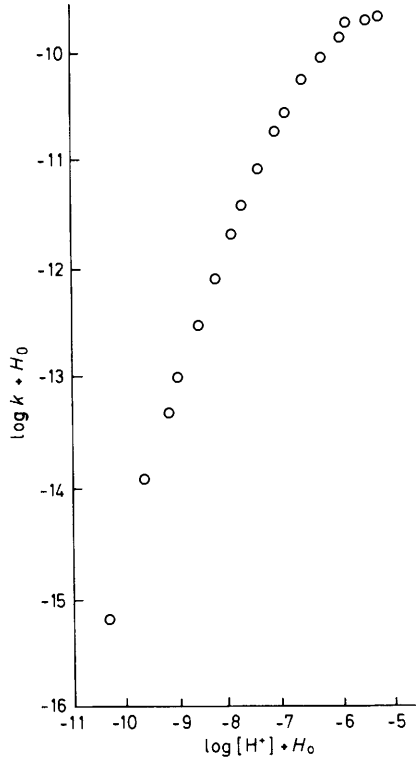


Figure 2. The reaction of 1-acetyl-2,4,6-trimethylbenzene in sulphuric acid: plot of $(\log k_{obs.} + H_0)$ *vs.* $(H_0 + \log [H^+])$, for reactions at 25 °C

$$\log k_{obs.} + \log [1 + 10^{(pK_a - H_0)/n}] = c' + pK_a/n - H_0(1 + n^{-1}) \quad (13)$$

equation (12) or (13) *vs.* $-H_0$ is given in Figure 1, together with straight lines of slope 1 and 2.07, respectively, passing through the lowest point plotted. The value of $n = 0.93$ is the most probable for the ketone (**1a**),[15] even though it was not determined with great precision; then $1 + n^{-1} = 2.074$. It is clear that the observed curve corresponds well with that described under (*a*), especially for values of H_0 up to *ca.* -10. There is no evidence of a contribution from the route given under (*b*), since departures of the observed curve from the theoretical line of slope 1, at higher acidities, are in the direction

opposite to that which would be evident if the second mechanism (*b*) became significant. This analysis is believed to provide strong evidence that the substrate in the protiodeacylation reaction is exclusively the free base (**1a**).

Bunnett and Olsen[25] found that a linear relationship exists between ($\log k + H_0$) and ($H_0 + \log[H^+]$) for reactions of weakly basic substrates in moderately concentrated mineral acids, and that such plots offer better correlation than relationships used previously. The straight lines, of slope φ, which resulted were thought to reflect both equilibrium protonation of the substrate and the transformation of protonated substrate to transition state. Figure 2 shows the Bunnett–Olsen plot for our data, which relate to a range of acidities much wider than looked at before,[25] and which go far beyond 'moderately concentrated acid.' The slope φ here varies from *ca.* 0.3 at low acid concentrations to *ca.* 1.9 in concentrated acid; this compares with a 'theoretical' slope (following an analysis analogous to that used for Figure 1) of unity. Clearly the application of the Bunnett–Olsen relationship does not offer any advantages, perhaps because the substrate is here the free base and not protonated base.

Effect of Added Potassium Sulphate.—In Table 3 are given the effects on observed rates of addition of potassium sulphate to the medium, 89.8% (w/w) sulphuric acid, for the protiodeacylation of the ketones (**1a** and **e**). The latter was used to allow a higher concentration of salt to be attained for a ketone which did not react inconveniently fast at the higher temperature. The addition of salt gave an enhancement of rate, which differed for the two substrates. The effect for the ketone (**1a**) was satisfactorily linear ($r = 0.991$) with concentration, as for a 'normal' salt effect [equation (14)].[26] Parameter *b* was 1.64 and 1.11 dm^3 mol^{-1}, for ketones (**1a**) and (**1e**), respectively. For the related reaction, the decarbonylation of mesitaldehyde in 100.1% sulphuric acid, the effect of added ammonium sulphate was similarly rate-enhancing, with parameter $b \simeq 1.45$ dm^3 mol^{-1}. However, the same substrate gave a rate *reduction* ($b = -1.1$ dm^3 mol^{-1}) with the same salt, in 86.4% sulphuric acid.

$$k = k_0(1 + b[MY]) \quad (14)$$

Table 3. Effect of added $KHSO_4$ on the rate of protiodeacylation of 1-acetyl-2,4,6-trimethylbenzene (**1a**) and the 4-fluoro analogue (**1e**) in 89.8% (w/w) sulphuric acid

Substrate (**1a**) $10^3k/s^{-1}$ [a] at 25 °C	$[KHSO_4]$	Substrate (**1e**) $10^3k/s^{-1}$ [a] at 45 °C
4.72[b]	0	1.87 ± 0.03
4.93 ± 0.15	0.050	
5.37 ± 0.22	0.100	
6.36 ± 0.07	0.200[c]	
	1.08[c]	2.08 ± 0.04

[a] ± refers to the standard deviation of replicate kinetic runs. [b] Table 1. [c] Saturation point.

The species H_2O is said to be a better nucleophile than HSO_4^- by a factor of *ca.* 100.[27] However, with increasing sulphuric acid concentration, as $[H_2O]$ decreases, the activity of HSO_4^- sharply increases, and in >80% H_2SO_4 the predominantly active nucleophile is believed to be HSO_4^-.[28] The addition of the common ion HSO_4^- to sulphuric acid solutions might affect the rate of protiodeacylation, if this species is involved in a rate-determining step, such as, possibly, in the second stage of the substitution process, *viz.* (7). However, since the species HSO_4^- is believed to be present at a concentration of 9.40 mol dm^{-3} for stoicheiometric concentrations of sulphuric acid of 16.6 mol dm^{-3},[29] the additional 0.20 mol dm^{-3} of the anion would represent an increase of no more than *ca.* 2% in concentration. It is evident that the role of HSO_4^- cannot be tested in this way.

Solvent Kinetic Isotope Effects.—The deacylation of the ketone (**1a**) was studied using various mixtures of deuteriosulphuric acid and deuterium oxide as solvent, in order to measure the solvent kinetic isotope effect.[30] The data obtained for the deuteriodeacylations are compared in Table 4 with those for protiodeacylation at the same molarity of acids. For the deuterio-solvents, as for the protonic solvents, maximal rates were observed for *ca.* 16.0 mol dm^{-3} acid, but the rate coefficients obtained in the latter solvents were appreciably higher. The observed kinetic isotope effect, k_H/k_D, increases gradually with acidity, rising sharply for the most concentrated acid. When rate data are compared for acid solutions having the same acidity functions, the effect is seen to be even more pronounced. At the highest acidity k_H/k_D exceeds 17, regarded as the maximum value which can be explained by loss of vibrational degrees of freedom in the transition state,[31] and suggests that quantum mechanical tunnelling is becoming important, *viz.* the C–H bond formation may take place to a significant extent without passing over the transition state maximum.[32] The most important conclusion which follows from these data is that C–H bond formation is involved in the rate-determining step, and this means that σ-complex formation in this reaction is irreversible. Such behaviour is generally observed in cases of very reactive electrophiles.[33]

Experimental

I.r. spectra were measured with a Pye Unicam SP 2000 spectrophotometer, and mass spectra with an MS 902 spectrometer. ^1H N.m.r. spectra were recorded at 60 MHz for solutions in $CDCl_3$, unless otherwise stated, with Me_4Si as standard.

Table 4. Protiodeacylation of 1-acetyl-2,4,6-trimethylbenzene in various concentrations of D_2SO_4 and H_2SO_4 at 25 °C

Acid concn.[a] (mol dm^{-3})	H_0[b]	$10^4k_H/s^{-1}$ in H_2SO_4–H_2O[c]	D_0[d]	$10^4k_D/s^{-1}$ in D_2SO_4–D_2O[e]	Interp. $10^4k_H/s^{-1}$ for $H_0 = D_0$[f]	k_H/k_D[g] (exp.)	k_H/k_D[h] (corr.)
18.2	−10.28	17.7	−10.06	0.92 ± 0.05	21.3	19.2 ± 1.0	23.2
17.8	−9.82	25.3	−9.74	4.92 ± 0.15	27.7	5.1 ± 0.2	5.6
16.0	−8.62	50.3	−8.69	10.97 ± 0.03	49.7	4.6 ± 0.03	4.5
14.3	−7.59	31.5	−7.79	9.23 ± 0.06	40.3	3.4 ± 0.05	4.4
12.8	−6.65	10.3	−6.91	3.40	13.5	3.0	4.0

[a] Either H_2SO_4 or D_2SO_4. [b] Data from ref. 29 (see also Table 2). [c] Interpolated values. [d] Data from: J. Sierra, M. Ojeda, and P. A. H. Wyatt, *J. Chem. Soc. B*, 1970, 1570. [e] ± refers to departures from the mean for 2—3 determinations. [f] k_H Values at $H_0 = D_0$ given in column 4. [g] Ratio of *k* values at the same concentration of acids. [h] Ratio of *k* values in solutions of same acidity.

Materials.—1-Acetyl-2,6-dimethylbenzene (**1b**)[34] was a colourless oil, b.p. 55 °C at 0.3 mmHg (lit.,[34] 96—99 °C at 13 mmHg); n_D^{25} 1.516 (lit.,[5] n_D^{28} 1.512); $\nu_{max.}$(film) 1 700 cm^{-1} (C=O); δ_H 2.26 (6 H, s, 2- and 6-Me), 2.44 (3 H, s, COMe), and 7.06 (3 H, complex, 3-, 4-, and 5-H).

1-Acetyl-2,6-dimethyl-4-t-butylbenzene (**1c**)[35] formed colourless crystals, m.p. 46.5—47 °C; b.p. 69—72 °C at 0.01 mmHg (lit.,[35] liquid, b.p. 127—134 °C at 7.0 mmHg); $\nu_{max.}$(KBr) 1 694 cm^{-1} (C=O); δ_H 1.32 (9 H, s, Bu^t), 2.25 (6 H, s, 2- and 6-Me), 2.43 (3 H, s, COMe), and 6.98 (2 H, s, 3- and 5-H).

1-Acetyl-4-amino-2,6-dimethylbenzene (**1o**) formed[34] white plates (yield 87%), m.p. 115 °C (from ethanol–water) (lit.,[34] 114—115 °C); $\nu_{max.}$(KBr) 3 460 and 3 358 (NH), 1 690 (C=O), and 1 610 cm^{-1} (NH); δ_H 2.14 (6 H, s, 2- and 6-Me), 2.40 (3 H, s, COMe), 3.62 (H, br s, NH; exchangeable with D_2O), and 6.22 (2 H, s, 3- and 5-H).

1-Acetyl-4-hydroxy-2,6-dimethylbenzene (**1k**) formed[36] crystals, m.p. 119—120 °C (lit.,[36] 119—120 °C).

1-Acetyl-4-methoxy-2,6-dimethylbenzene (**1j**) was obtained[36] as crystals, m.p. 47 °C (lit.,[37] 47 °C).

1-*Acetyl*-4-*chloro*-2,6-*dimethylbenzene* (**1f**).—This ketone was obtained (yield 36%) from the amine (**1o**) by the Sandmeyer reaction, in the usual way, giving a pale yellow *oil*, b.p. 98—100 °C at 0.2 mmHg (Found: C, 66.0; H, 6.2; Cl, 19.4. $C_{10}H_{11}ClO$ requires C, 65.8; H, 6.1; Cl, 19.4%); $\nu_{max.}$(film) 1 712 cm^{-1} (C=O); δ_H 2.18 (6 H, s, 2- and 6-Me), 2.42 (3 H, s, COMe), and 6.94 (2 H, s, 3- and 5-H); *m/z* 184 (M^+, 8.6%), 182 (M^+, 25.9), 169 (33, $M - CH_3$), 167 (100, $M - CH_3$), 141 (15.5, $M - COCH_3$), 139 (46.5, $M - COCH_3$), 103 (32.8, $M - COCH_3 - HCl$), *m** 155.2 (184 ⟶ 169), 153.2 (182 ⟶ 167), 117.6 (169 ⟶ 141), 115.7 (167 ⟶ 139), 76.3 (139 ⟶ 103), and 75.2 (141 ⟶ 103).

1-*Acetyl*-4-*bromo*-2,6-*dimethylbenzene* (**1h**).—*Method A.* After diazotisation of the amine (**1o**) in hydrochloric acid, sodium tetrafluoroborate was added. The solid diazonium tetrafluoroborate which settled out was dried *in vacuo* over P_2O_5, giving the salt (64%), m.p. 93—94 °C (decomp.). This salt was treated with copper(II) bromide in dimethyl sulphoxide, by a published general procedure,[38] to give 1-acetyl-4-bromo-2,6-dimethylbenzene (67%) as a colourless oil, b.p. 80—81 °C at 0.04 mmHg (lit.,[39] 60—61 °C at 0.5 mmHg) (Found: C, 52.9; H, 4.9; Br, 35.2. Calc. for $C_{10}H_{11}BrO$: C, 53.0; H, 4.9; Br, 34.9%); $\nu_{max.}$(film) 1 705 cm^{-1} (C=O); δ_H 2.20 (6 H, s, 2- and 6-Me), 2.44 (3 H, s, COMe), and 7.17 (2 H, s, 3- and 5-H) (lit.,[40] δ_H 2.22, 2.37, and 7.15).

Method B. (*cf.* method of Doyle *et al.*[39]). The amine (**1o**) (6.5 g) was added with stirring to a mixture of copper(II) bromide (10.7 g), t-butyl nitrite (6.1 g), and anhydrous acetonitrile (160 ml); nitrogen was evolved. The mixture was heated at 65 °C for 30 min, then cooled and poured into 20% hydrochloric acid (200 ml); the product was isolated by extraction into ether and distillation. Fractions boiling at 93—112 °C at 0.3 mmHg were refractionated three times, to give the ketone (**1h**) (1.3 g, 14%), b.p. 92—93 °C at 0.25 mmHg, identical with the foregoing compound.

1-*Acetyl*-4-*fluoro*-2,6-*dimethylbenzene* (**1e**).—This ketone was prepared by heating a mixture of 1-acetyl-2,6-dimethylbenzene-4-diazonium tetrafluoroborate (see before) and toluene under reflux for 0.5 h. The solvent was removed *in vacuo*, and the residue distilled to give a colourless *oil* (41%), b.p. 60 °C at 0.2 mmHg (Found: C, 72.45; H, 6.8; F, 11.3. $C_{10}H_{11}FO$ requires C, 72.3; H, 6.7; F, 11.4%); $\nu_{max.}$(film) 1 700 cm^{-1} (C=O); δ_H 2.19 (6 H, s, 2- and 6-Me), 2.40 (3 H, s, COMe), and 6.66 (2 H, d, 3- and 5-H; *J* 9 Hz).

1-*Acetyl*-4-*iodo*-2,6-*dimethylbenzene* (**1g**).—A solution of potassium iodide was added to a solution of 1-acetyl-2,6-dimethylbenzene-4-diazonium chloride, prepared from the amine (**1o**) (8.2 g), and the product was isolated in the usual way to give an oil (8.5 g, 62%), b.p. 100 °C at 0.2 mmHg, which on cooling gave *crystals*, m.p. 45 °C (Found: C, 43.9; H, 4.15. $C_{10}H_{11}IO$ requires C, 43.8; H, 4.05%); $\nu_{max.}$(KBr) 1 696 cm^{-1} (C=O); δ_H 2.17 (6 H, s, 2- and 6-Me), 2.46 (3 H, s, COMe), and 7.52 (2 H, s, 3- and 5-H).

4-*Acetyl*-3,5-*dimethylbiphenyl* (**1d**).—This ketone was obtained from the amine (**1o**), using the general procedure of Cadogan,[41] as colourless *needles* (22%), b.p. 126 °C at 0.3 mmHg, m.p. 117—118 °C (from ethanol–water) (Found: C, 85.5; H, 7.1. $C_{16}H_{16}O$ requires C, 85.7; H, 7.2%); $\nu_{max.}$(KBr) 1 693 cm^{-1} (C=O); δ_H 2.52 (6 H, s, 3- and 5-Me), 2.70 (3 H, s, COMe), 7.80 (2 H, s, 2- and 6-H), and 7.83—8.3 (5 H, complex, Ph); *m/z* 224 (M^+, 37%), 209 (100, $M - CH_3$), 181 (33, $M - COCH_3$), 166 (23, $M - COCH_3 - CH_3$), and 165 (37, $M - COCH_3 - CH_3 - H$), *m** 195.0 (224 ⟶ 209), 156.8 (209 ⟶ 181), 152.2 (181 ⟶ 166), and 164.0 (166 ⟶ 165).

1-*Acetyl*-2,6-*dimethylbenzene*-4-*carbonitrile* (**1l**).—This ketone was prepared, from 1-acetyl-2,6-dimethylbenzene-4-diazonium tetrafluoroborate (see before) by the general method of Kobayashi,[38] as an oil (47%), b.p. 102 °C at 0.05 mmHg, which gave *crystals*, m.p. 48—49 °C [from light petroleum (b.p. 40—60 °C)] (Found: C, 76.3; H, 6.5; N, 7.85. $C_{11}H_{11}NO$ requires C, 76.3; H, 6.4; N, 8.1%); $\nu_{max.}$(KBr) 2 230 (C≡N) and 1 702 cm^{-1} (C=O); δ_H 2.30 (6 H, s, 2- and 6-Me), 2.48 (3 H, s, COMe), and 7.37 (2 H, s, 3- and 5-H); *m/z* 173 (M^+, 30%), 158 (100, $M - CH_3$), 1.30 (44, $M - COCH_3$), and 103 (18, $M - COCH_3 - HCN$), *m** 144.3 (173 ⟶ 158), 107.0 (158 ⟶ 130), 81.6 (130 ⟶ 103), and 57.7 (103 ⟶ 77).

1-*Acetyl*-2,6-*dimethylbenzene*-4-*carboxamide* (**1m**).—*Method A.* Prepared from the acid (**1n**), *via* the acid chloride, in the usual way, the *amide* formed crystals (97%), m.p. 180—181 °C (from water) (Found: C, 69.0; H, 6.9; N, 7.1. $C_{11}H_{13}NO_2$ requires C, 69.1; H, 6.85; N, 7.3%); $\nu_{max.}$(KBr) 3 430 (NH_2), 1 708 (ketone C=O), 1 680 (amide C=O), and 1 625 cm^{-1} (NH_2); δ_H 2.33 (6 H, s, 2- and 6-Me), 2.53 (3 H, s, COMe), 6.1—6.5 (2 H, br s, NH_2; exchangeable with D_2O), and 7.63 (2 H, s, 3- and 5-H); *m/z* 191 (M^+, 22%), 176 (100, $M - CH_3$), 148 (19, $M - COCH_3$), 131 (13, $M - COCH_3 - NH_3$), 1.30 (4.7, $M - COCH_3 - H_2O$), 120 (17, $M - COCH_3 - CO$), 103 (14), and 93 (12), *m** 162.2 (191 ⟶ 176), 124.5 (176 ⟶ 148), 97.3 (148 ⟶ 120), and 72.1 (120 ⟶ 93).

Method B. The amide (**1m**) was also obtained by heating a solution of the nitrile (**1l**) in 90% (w/w) sulphuric acid at 60—65 °C for 1.5 h, the product (87%) being identical (i.r. and mixed m.p.) with that obtained by Method A.

1-*Acetyl*-2,6-*dimethylbenzene*-4-*carboxylic Acid* (**1n**).—Hydrolysis of the nitrile (**1l**) with 10% sodium hydroxide solution, in the usual way, gave the acid (81%), m.p. 160—161 °C [from benzene–light petroleum (b.p. 60—80 °C)] (lit.,[42] 160—161 °C) (Found: C, 68.8; H, 6.6. Calc. for $C_{11}H_{11}O_3$: C, 68.7; H, 6.3%); $\nu_{max.}$(KBr) 1 720 (ketone C=O) and 1 700 cm^{-1} (acid C=O); δ_H 2.37 (6 H, s, 2- and 6-Me), 2.55 (3 H, s, COMe), 7.92 (2 H, s, 3- and 5-H), and 11.1 (H, br s, OH; exchangeable with D_2O).

1-*Acetyl*-2,4,6-*trimethylbenzene*-3-*sulphonic Acid.*—To oleum (25% SO_3; 1.2 g) was added 1-acetyl-2,4,6-trimethylbenzene (1.0 g), and the mixture was left for 2 days. Ice was then added, followed by an excess of concentrated barium hydroxide solution, until no further precipitate formed. The precipitate

was filtered off, and the hot water washings were combined with the filtrate. Careful addition of dilute sulphuric acid gave a small amount of precipitate, which was filtered off. The filtrate was evaporated to dryness to give hygroscopic crystals of the *sulphonic acid* (Found: C, 52.1; H, 5.9; S, 12.4. $C_{11}H_{14}O_4S\cdot 0.5H_2O$ requires C, 52.5; H, 6.0; S, 12.7%); $\nu_{max.}$(KBr) 1 705 (C=O), 1 250 (S–O), and 1 050 cm^{-1} (S=O); $\delta_H(D_2O)$ 2.30 (3 H, s, 6-Me), 2.33 (3 H, s, 4-Me), 2.39 (3 H, s, 2-Me), 2.48 (3 H, s, COMe), and 6.58 (H, s, 5-H). The potassium salt formed pink hygroscopic crystals.

Kinetic Measurements.—The methods used for the kinetic measurements, and subsequent calculations, are those used before.[2a,c] Rate coefficients were generally obtained for duplicate runs, with replicability ±1—2%.

Protiodeacylations.—Rate coefficients were as follows ($10^4k/s^{-1}$ with T/K in parentheses): ketone (**1b**), followed at 312 nm: 2.57 (303.7), 4.48 (308.6), 4.74 (308.9), 7.45 (313.1), 7.92 (313.7), 13.13 (318.4), 21.4 (323.0), and 36.4 (328.3); ketone (**1c**), followed at 335 nm: 6.11 (283.9), 10.68 (288.0), 21.7 (293.7), 34.9 (297.4), and 72.1 (303.4); ketone (**1d**), followed at 370 nm: 4.79 (283.6), 9.97 (288.9), 17.32 (293.3), 32.1 (298.2), 32.1 (298.4), 34.4 (298.8), and 54.7 (303.0); ketone (**1e**), followed at 310 nm: 4.39 (303.9), 7.27* (308.6), 11.70* (313.3), 17.91* (318.0), 27.0 (322.7), and 43.9 (328.0); ketone (**1f**), followed at 324 nm: 5.17 (318.2), 8.29* (322.9), 13.70 (328.1), 13.96 (328.2), 21.5 (333.1), and 31.1 (337.5); ketone (**1g**), followed at 370 nm: 1.66 (308.5), 3.11 (313.7), 4.57 (317.4), 9.34 (324.5), 13.85 (328.3), 15.61 (329.4), and 23.3 (333.5); ketone (**1h**), followed at 330 nm: 3.48 (317.1), 6.43 (323.0), 9.87 (327.6), 10.12 (327.9), 15.42 (332.6), 15.73 (332.8), and 25.0 (337.7).

Hydration of the Ketone (**1l**).—The hydration of the ketone (**1l**) in 89.8% (w/w) suphuric acid was observed at 260 nm. Rate coefficients ($10^4k/s^{-1}$) were as follows (T/K in parentheses): 2.56 (308.6), 4.44 (313.6), 6.81 (318.4), 10.12 (322.7), 16.73 (328.2), and 24.0 (333.0). Derived parameters, calculated for 298.15 K, were: $k = 9.40 \times 10^{-3}$ s^{-1}, $\Delta H^{\ddagger}$ 75.0 kJ mol^{-1}, $\Delta S^{\ddagger}$ −70.5 J K^{-1} mol^{-1}, $\Delta G^{\ddagger}$ 96.0 kJ mol^{-1}.

Reaction of the Ketone (**1k**).—The reaction of the ketone (**1k**) in 89.8% (w/w) sulphuric acid was followed at 312 nm. Apparent rate coefficients ($10^3k/s^{-1}$) were as follows (T/K in parentheses): 4.04 (275.1), 0.955 (293.5), 1.04 (298.0), 2.39 (303.8), 4.42 (308.6), 6.26 (313.3), 8.61 (318.4), and 10.2 (322.2); replicability was ±9% (mean). The same rate coefficients (within ±10%) were obtained by using 1-hydroxy-3,5-dimethylbenzene as substrate.

* Refers to the mean of several kinetic runs.

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