Dienone–Phenol Rearrangement Mechanism of 8,8-Dimethyl- and 6,8,8-Trimethyl-naphthalene-1,4,5(8*H*)-triones in Acetic Anhydride Solution

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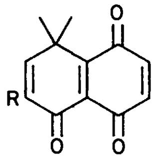
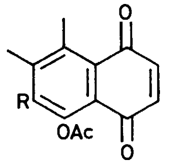
Dienone–phenol rearrangement of 8,8-dimethyl- and 6,8,8-trimethyl-naphthalene-1,4,5(8*H*)-triones (**1**) and (**2**) in acetic anhydride as solvent is the subject of a kinetic study. The effects of sulphuric and acetic acids are also investigated. Both substrates show limiting [H_2SO_4] dependence and an inhibiting effect with acetic acid. The effect of temperature in the reaction of (**1**) and that of the C-6 methyl group of (**2**) are discussed. The results are rationalized in terms of the formation of acylated intermediate cations and schematic representation is provided.

The acid-induced rearrangement of cyclohexadienones to phenols is a well known reaction used mainly in the field of steroid synthesis.[1] This transformation is usually performed in acetic anhydride containing sulphuric acid as catalyst, and the generated acetoxyarene is hydrolysed to the respective substituted phenol. Kinetic evidence of the rearrangement of some non-linear conjugated cyclohexadienones in aqueous sulphuric and perchloric acids has firmly established the existence of a cyclohexadienyl cation produced by protonation.[2,3]

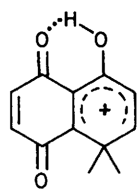
In a recent paper we have reported that naphthalenetriones (**1**) and (**2**) undergo an unusually rapid dienone–phenol rearrangement in acetic anhydride–sulphuric acid solution to give 5-acetoxy-7,8-dimethyl- and 5-acetoxy-6,7,8-trimethyl-1,4-naphthoquinones (**3**) and (**4**) in high yields.[4] Interestingly, quinones (**1**) and (**2**) were unreactive toward dienone–phenol rearrangement in non-acylating conditions (acetic acid–sulphuric acid, and methanol–hydrochloric acid). These results may be explained if it is considered that acetic anhydride participates during the rearrangement in a step previous to the isomerization. It is noteworthy that no kinetic studies so far have been reported on the dienone–phenol rearrangement in acetic anhydride solution. Nevertheless, the attack of a protonated acetic anhydride species to the carbonyl group of the substrate in a previous step to the isomerization has been suggested.[5,6]



(**1**) R = H
(**2**) R = Me



(**3**) R = H
(**4**) R = Me



(**5**)

Experimental

Visible spectra of different kinetic samples were recorded either on a Pye-Unicam SP-1800 or a Perkin-Elmer Lambda-3 spectrophotometer, using 10 mm cuvettes.

Materials.—8,8-Dimethylnaphthalene-1,4,5(8*H*)-trione (**1**), 6,8,8-trimethylnaphthalene-1,4,5(8*H*)-trione (**2**), 5-acetoxy-7,8-dimethyl-1,4-naphthoquinone (**3**), and 5-acetoxy-6,7,8-trimethyl-1,4-naphthoquinone (**4**) were obtained as previously reported.[4] Acetic anhydride, acetic acid, and concentrated sulphuric acid were Merck reagent grade and were used as purchased.

Kinetic Measurements.—Solutions (2.5—3.5 ml) of (**1**) (3.96×10^{-4} mol dm^{-3}) or (**2**) (3.7×10^{-4} mol dm^{-3}) in the appropriate acetic anhydride–acetic acid mixture were introduced into 1 cm cells and placed in the thermostatted cell holder of the above spectrophotometer. After thermal equilibration the reactions were started by addition of concentrated H_2SO_4 (5—25 μl) with a micropipette. The reactions were followed by monitoring the increase in absorbance at 360 nm. To ensure that acetic anhydride was not hydrolysed, tightly stoppered Teflon cells (Hellma 110 QS) were used throughout. All the reactions were followed for more than 10 half-lives and no changes in absorbance were observed thereafter.

Pseudo-first-order rate constants were observed ($k_{obs.}$) in all cases and these were determined as slopes of ln (absorbance) *vs.* time plots. All the kinetic runs were performed in duplicate, and plots giving correlation coefficients smaller than 0.999 were discarded.

Results and Discussion

Spectrophotometric study (300—500 nm) of the reaction of (**1**) and (**2**) in acetic anhydride solution in the presence of different concentrations of sulphuric acid as catalyst shows an increase in the absorption band at 360 nm. This band corresponds to the 5-acetoxy-7,8-dimethyl- and 5-acetoxy-6,7,8-trimethyl-1,4-naphthoquinones (**3**) and (**4**), respectively, assigned by comparison of the spectra of authentic samples in the same reaction media. For each substrate all the equilibrium spectra were identical under different sulphuric acid concentrations.

The kinetics of the reactions were studied in acetic anhydride as the solvent, sulphuric acid as the catalyst and in the presence of acetic acid (in the absence of acetic acid poor first-order kinetics were found). Table 1 shows the observed rate constants ($k_{obs.}$) for the reactions of (**1**) and (**2**) under different experimental conditions. The empirical equations obtained in this study are summarized in Table 2.

It is worth recalling that neither (**1**) nor (**2**) undergo rearrangement in AcOH–H_2SO_4 or in MeOH–HCl solutions at ambient or boiling temperatures.[4] These results indicate that cation formation (**5**), which is in accord with the accepted mechanism[2,3] for the rearrangement reaction, is not favoured. It is likely that the most important factor which hinders the formation of (**5**) is the destabilization due to the electron-withdrawing effect of the quinone nucleus which in turn is enhanced by hydrogen-bonding interaction.

Table 1. Pseudo-first-order rate constants ($k_{obs.}$) for the reactions of (**1**) and (**2**) in acetic anhydride solution under different experimental conditions

		$10^2\,k_{obs.}/s^{-1}$							
	Substrate:	(**1**)							(**2**)
	Temperature:	25 °C					30 °C	35 °C	25 °C
$[H_2SO_4]$/ mol dm^{-3}	[AcOH]/mol dm^{-3}	0.07	0.175	0.35	0.525	0.7	0.07	0.07	0.7
0.235		8.10	6.71	4.27	3.30	2.81	9.26	13.7	7.76
0.188		7.76	6.22	4.06	3.10	2.38	9.18	12.6	6.75
0.157		7.55	5.99	3.53	2.57	1.94	8.60	12.7	5.71
0.094		—	4.81	—	1.98	1.53	7.87	9.73	4.87
0.075		—	—	2.33	—	—	—	—	—
0.063		5.63	3.77	1.91	1.38	1.04	5.99	8.27	3.00
0.053		4.98	3.37	1.79	1.27	0.89	5.40	7.43	3.10
0.044		4.36	2.71	1.31	0.91	0.69	4.31	7.80	2.44
0.038		4.19	—	—	0.83	0.64	—	6.47	2.14
0.031		—	—	1.07	0.68	—	3.54	5.10	—
0.028		3.26	—	—	—	—	—	—	—

Table 2. Empirical equations[a] for the reactions of (**1**) and (**2**) in acetic anhydride solution

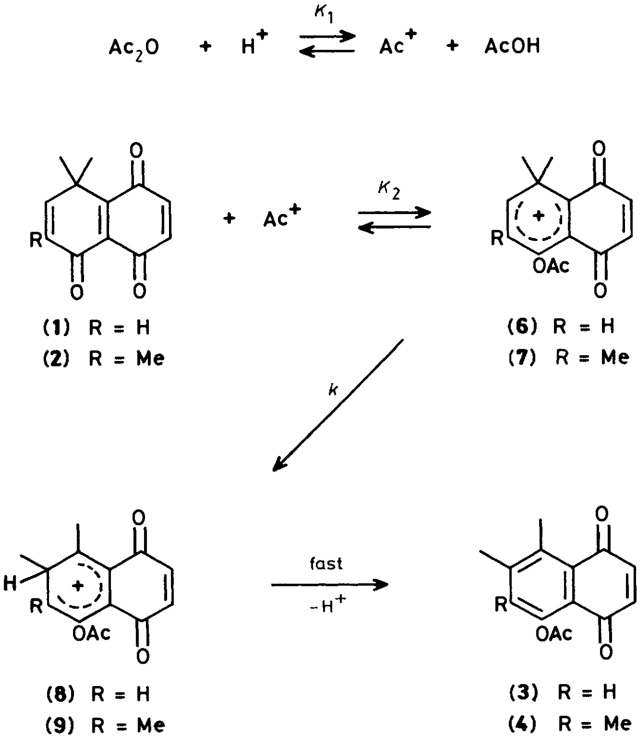
Substrate	Equation	Condition
(**1**)	$k_{obs.}^{-1} = C_1[H_2SO_4]^{-1} + C_2$ $C_1 = C_3[AcOH]$	[AcOH] = const.
(**1**)	$k_{obs.}^{-1} = C_4[AcOH] + C_5$ $C_4 = C_6[H_2SO_4]^{-1}$	$[H_2SO_4]$ = const.
(**2**)	$k_{obs.}^{-1} = C_7[H_2SO_4]^{-1} + C_8$	[AcOH] = const.

[a] The C_i (i = 1—8) are constants.

Table 3. Linear regressions[a] of $k_{obs.}^{-1}$ *vs.* $[H_2SO_4]^{-1}$ plots for the reaction of (**1**) at 25 °C

[AcOH]	m	I	r^2	No. of points	F^b
0.07	0.59 ± 0.03	9.4 ± 0.6	0.987	8	459
0.157	1.13 ± 0.07	9.5 ± 0.9	0.983	7	295
0.35	2.6 ± 0.1	11 ± 2	0.985	8	390
0.525	4.2 ± 0.2	9 ± 3	0.987	9	533
0.7	5.5 ± 0.2	12 ± 3	0.991	8	664

[a] Errors are standard errors. [b] E statistic (significance of fit allowing for degrees of freedom).



Scheme.

Consideration of these facts as well as the substrate and product structures suggests that two reactions are involved: rearrangement and acylation (see the Scheme). If we assume that the rearrangement reaction is the rate-determining step and that the two equilibria steps are rapid, equation (1) can be

$$k_{obs.} = kK_1K_2[AA][H^+](K_1K_2[AA][H^+] + [AcOH])^{-1} \quad (1)$$

obtained where [AA] and [AcOH] represent the concentrations of acetic anhydride and acetic acid, respectively. The last step is considered fast because it is an aromatization reaction.

As the concentration of sulphuric acid is increased a greater concentration of acyl cation in the medium is obtained and the second equilibrium can be displaced fully to the right. Under these conditions all the substrate can be acylated to give (**6**) or (**7**) and equation (1) is invalid since $k_{obs.} = k$ and the reaction is independent of both the sulphuric acid and acetic acid concentrations. Equation (1) is applicable to concentrations of acetic and sulphuric acids such that the equilibria of the Scheme are not fully displaced to the left or right.

Equation (1) can be rearranged as equation (2) which is in accord with the empirical equations shown in Table 2 if the equilibrium $H_2SO_4 \rightleftharpoons H^+ + HSO_4^-$ is fully displaced towards the bisulphate ion. This condition is necessary because the empirical equation involves the stoicheiometric H_2SO_4 concentration while equation (2) involves $[H^+]$.

$$k_{obs.}^{-1} = k^{-1} + [AcOH](kK_1K_2[H^+][AA])^{-1} \quad (2)$$

Tables 3 and 4 summarize, respectively, the statistics of the straight lines of the $k_{obs.}^{-1}$ *vs.* $[H_2SO_4]^{-1}$ and *vs* [AcOH] plots obtained for the reaction of (**1**). From the intercepts of the $k_{obs.}^{-1}$ *vs.* $[H_2SO_4]^{-1}$ plots (I in Table 3) $k = 0.098\ s^{-1}$ is obtained (a mean of those values obtained for five acetic acid concentrations); from the intercepts of $k_{obs.}^{-1}$ *vs.* [AcOH] plots (I in Table 4) $k = 0.134\ s^{-1}$ is obtained (a mean value of those values

Table 4. Linear regressions[a] of $k_{\mathrm{obs.}}^{-1}$ *vs.* [AcOH] plots for the reaction of (**1**) at 25 °C

$[H_2SO_4]$	m	I	r^2	No. of points	F^b
0.235	39 ± 2	9.3 ± 0.8	0.993	5	415
0.188	47 ± 2	8.6 ± 0.8	0.995	5	562
0.157	62 ± 3	7 ± 1	0.993	5	448
0.094	85.1 ± 0.1	5.87 ± 0.01	0.999	3	7.4×10^5
0.063	127 ± 4	7 ± 2	0.997	5	940
0.053	146 ± 8	6 ± 4	0.990	5	309
0.044	198 ± 6	6 ± 2	0.998	5	1 249
0.038	211 ± 3	9 ± 1	0.999	3	6 206

[a] Errors are standard errors. [b] E statistic (significance of fit allowing for degrees of freedom).

obtained for eight different sulphuric acid concentrations). It must be emphasized that the errors of the intercepts of the reciprocal plots are significant and lead to uncertainty in the k value, but a probable value is about 0.1 s^{-1}.

From the slopes of the $k_{\mathrm{obs.}}^{-1}$ *vs.* $[H_2SO_4]^{-1}$ plots (m in Table 3), a value of 0.124 s^{-1} M^{-1} is obtained for $kK_1K_2[AA]$; from the slopes of the $k_{\mathrm{obs.}}^{-1}$ *vs.* [AcOH] plots (M in Table 4) the value is 0.127 s^{-1} M^{-1} (see empirical equations in Table 2). Assuming $k = 0.1$ s^{-1} and $[AA] = 10.5M$ (the molarity of acetic anhydride itself), we obtain $K_1K_2 \approx 0.12$ for the reaction of (**1**).

For reaction with $[AcOH] = 0.07M$, $k = 0.1$ s^{-1} and $kK_1K_2[AA] = 0.125$ s^{-1} M^{-1}, $[H^+] \geqslant 0.6M$ is necessary in order for $k_{\mathrm{obs.}} = k$; under these conditions a first term is obtained which is ten-fold greater than the second in the denominator of equation (1). For the reaction with $[AcOH] = 0.7M$, the concentration of $[H^+]$ needed is greater than 6M. The maximum $[H^+]$ concentration used is 0.235M; therefore the maximum value is not observed but the $k_{\mathrm{obs.}}$ *vs.* $[H_2SO_4]$ plots are seen to level off.

In Table 1 it is observed that the reaction of (**2**) is about 3 times faster than that of (**1**) at the same $[H_2SO_4]$ and [AcOH]; this shows that the methyl group at C-6 accelerates the rearrangement. This result is in accord with that observed by Waring and his co-workers[7,8] in some dienone–phenol rearrangement reactions in concentrated sulphuric acid.

From the $k_{\mathrm{obs.}}^{-1}$ *vs.* $[H_2SO_4]^{-1}$ plots for the reaction of (**2**) (Table 1) the equation obtained is $k_{\mathrm{obs.}}^{-1} = (6.8 \pm 1.4) + (1.48 \pm 0.08)\ [H_2SO_4]^{-1}$. This result leads to $k = 0.147$ s^{-1} and $K_1K_2 = 0.307$ (assuming $[AA] = 10.5M$).

A comparison of the k values obtained for (**1**) and (**2**) indicates that the rearrangement step is about 50% faster in (**2**) due to the electronic effect of the C-6 methyl group stabilizing the corresponding transition state. If we consider that K_1 must be the same for the reaction of the two substrates, the quotient of the K_1K_2 values determined is also the ratio between the acylation equilibrium in both substrates. This result indicates that the acylation equilibrium is favoured 2.3 times to the right for (**2**) relative to (**1**). This result can be explained from the electrical properties of both acylated intermediates; the presence of the C-6 methyl group allows greater stabilization of (**7**) compared to (**6**). On the other hand, (**2**) must be more basic than (**1**). Consequently, the greater reactivity of (**2**) is principally due to the acylation step and, to a lesser extent, to the rearrangement one.

In order to obtain more information about the mechanism of the reaction of (**1**), the reaction was also studied at 30 and 35 °C (see Table 1). The $k_{\mathrm{obs.}}^{-1}$ *vs.* $[H_2SO_4]^{-1}$ plots lead to the equations $k_{\mathrm{obs.}}^{-1} = (7.1 \pm 0.7) + (0.65 \pm 0.04)\ [H_2SO_4]^{-1}$ for 30 °C and $k_{\mathrm{obs}}^{-1} = (5.6 \pm 0.6) + (0.40 \pm 0.03)\ [H_2SO_4]^{-1}$ for 35 °C. These results yield $k = 0.141$ s^{-1} at 30 °C and $k = 0.179$ s^{-1} at 35 °C, and $K_1K_2 = 0.073$ at 30 °C and $K_1K_2 = 0.093$ at 35 °C. These constants, together with the 25 °C values, show that it is not possible to determine the behaviour of both equilibria with temperature but from the Eyring plot we obtain for the rearrangement step $\Delta H^{\ddagger} = 38 \pm 2$ kJ mol^{-1} and $\Delta S^{\ddagger} = -133 \pm 6$ JK^{-1} mol^{-1}. Errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ have been introduced from the slope and intercept errors, respectively by the squared means procedure; however, taking into account that there are only three temperature values in a temperature range of only 10 °C and that the kinetic results are ±10%, the errors in $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ could be underestimated.[9]

Based on the contribution from the different degrees of freedom, for a unimolecular step (as the rearrangement), we would expect a smaller intrinsic activation entropy but as previously reported,[10–12] in solution it is difficult to interpret the entropy changes of a reaction since these are dominated by solvent effects.[11–13] The negative value indicates that solvation takes place in the formation of the transition state in the rearrangement step, suggesting a transition state more polar than (**6**).

In conclusion, the results of this study indicate that the acetic anhydride solvent is responsible for the dienone–phenol rearrangement in quinones (**1**) and (**2**), generating the acylated cations (see the Scheme). Although further studies are needed in order to generalize, the steps of the Scheme appear adequate for the rearrangements of other dienones in acetic anhydride solution.

Acknowledgements

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