Mechanisms of Nucleophilic Reactions of 4-Benzoyl-4-methylcyclohexa-2,5-dienone and its Benzoyl Substituted Derivatives

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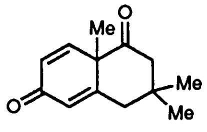
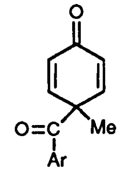
Studies have been made of the reactions with nucleophiles of 4-benzoyl-4-methylcyclohexa-2,5-dienone and its 4-chlorobenzoyl- and 4-methoxybenzoyl- analogues. Water effects hydrolysis to 4-methylphenol and the appropriate substituted benzoic acid. Kinetic measurements give a $\log k_{obs}$ *vs.* pH profile with slopes close to −1.0, 0, and 1.0, indicating proton, water, and hydroxide ion catalysis, respectively. The results suggest a mechanistic pattern similar to that found for the cleavage of benzaldehyde hemiacetals. Alcohols and alkoxides effect analogous cleavage to 4-methylphenol and the alkyl benzoates. Reaction of the 4-benzoyl-4-methylcyclohexa-2,5-dienone with dialkyl amines gives varying proportions of 4-methylphenyl benzoate and 4-methylphenol with *N,N*-dialkylbenzamide. An initial amine-induced rearrangement of the dienone to 4-methylphenyl benzoate is followed by cleavage by the amine to give the phenol and amide.

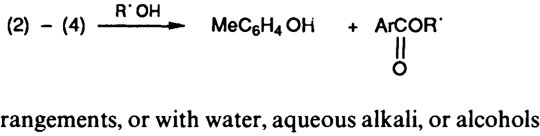
We recently reported the preparation of some 4-acylcyclohexa-2,5-dienones, a previously unknown class of compounds. The first prepared was 3,4-dihydro-3,3,8*a*-trimethylnaphthalene-1,6(2*H*,8*aH*)-dione (1):[1] the more reactive 4-benzoyl-4-methylcyclohexa-2,5-dienone (2) and its 4-chlorobenzoyl- (3), and 4-methoxybenzoyl- (4) analogues followed.[2] One reason for our interest in these compounds was our hope that we might be able to measure migratory aptitudes (migration tendencies) of acyl groups in carbocation rearrangements, as we did before for alkyl groups.[3,4] The rates of the fraction of rearrangement proceeding by path (*a*) for an acyl dienone [(5; R = COAr) in Scheme 1] would be compared with that known for methyl migration in the 4,4-dimethyl dienone (5; R = Me), both rearrangements being comparable stereochemically and in leaving a methyl group behind. Unfortunately, as we briefly reported earlier,[2,5] treatment of the 4-benzoylcyclohexa-2,5-dienones (2)–(4) with the aqueous acids often used to achieve such rearrangements, or with water, aqueous alkali, or alcohols, merely effects rapid solvolysis. Apparent attack by solvent at the benzoyl carbonyl group produces 4-methylphenol and the appropriate benzoic acid or its ester. Clearly, there must be a considerable driving force due to the conversion of the cyclohexadienone ring into a phenol.[1] One might expect, therefore, that the compounds (2)–(4) should also act as powerful benzoylating groups towards amines. When (2) was treated with secondary amines such as diethylamine in alcoholic solution the amides, *e.g.* *N,N*-diethylbenzamide, were formed, together with variable amounts of 4-methylphenyl benzoate. However, we have been able to show that the dienone and amine react rapidly to form 4-methylphenyl benzoate, followed by slower aminolysis of the latter to form the final amide and phenol. Some of these products are probably formed by direct attack on the benzoyl group of the dienone, but the contribution of this process has not yet been determined. We now report our kinetic and mechanistic studies of these reactions.



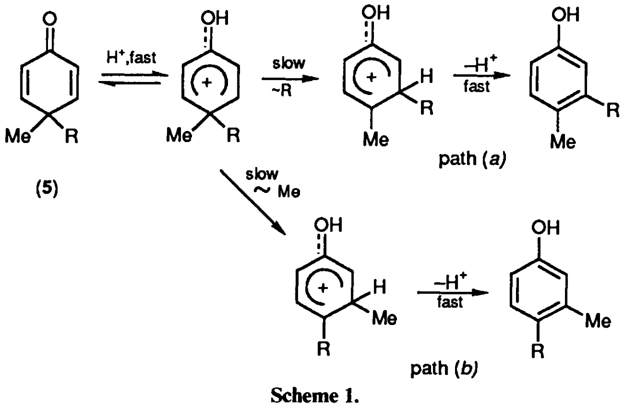
(1)



(2) Ar = Ph
(3) Ar = $4\text{-}ClC_6H_4$
(4) Ar = $4\text{-}MeOC_6H_4$



$$(2)-(4) \xrightarrow{R'OH} MeC_6H_4OH + ArCOR'$$



Scheme 1.

Results

Product Studies.—The parent dienone (2), in water, was found to be completely cleaved to 4-methylphenol and benzoic acid within 3 h at 20 °C. Similarly, cleavage was complete within 15 min in 1.0 mol dm^{-3} sodium hydroxide solution, and within 30 s in 10^{-2} mol dm^{-3} hydrochloric acid. The reaction with methanol was slower than in water, giving 20% conversion into methyl benzoate and 4-methylphenol in 17.5 h at 25 °C. Sodium methoxide in methanol (10^{-2} mol dm^{-3}) gave complete cleavage to the same products within 10 min at 25 °C. In later attempts to detect intermediates in the basic cleavage, the dienone (2) in [$^2H_4$]methanol was treated in the NMR spectrometer with sodium deuteriomethoxide (0.1 mol dm^{-3}) at −10 °C, but conversion into 4-methylphenol and [$^2H_3$]methyl benzoate was complete by the time the first spectrum was recorded (a few minutes).[2]

Table 1. Kinetics for hydrolysis of 4-benzoyl-4-methylcyclohexa-2,5-dienone (**2**) in aqueous solution at 25.0 °C.[a]

Solution	pH	I/mol dm^{-3} [b]	$-\log_{10}(k_{obs}/s^{-1})$
10^{-2} mol dm^{-3} HCl	2.0	0.01	0.61
Buffer	3.45	—[c]	2.43
Buffer	3.45	0.01	2.32
Buffer	3.45	0.10	1.85
10^{-4} mol dm^{-3} H_2SO_4	3.8	3×10^{-4}	2.65
Buffer	5.8	—[c]	3.41
Buffer	5.8	0.01	3.38
Buffer	5.8	0.10	3.14
H_2O			3.34
H_2O			3.35
Buffer	7.0	—[c]	3.38
Buffer	7.0	0.01	3.31
Buffer	7.0	0.10	2.94
Buffer	7.4	—[c]	3.25
Buffer	7.4	0.01	3.19
Buffer	7.4	0.10	2.88
Buffer	8.4	0.10	2.67
Buffer	8.9	0.01	2.44
NaOH	7.4	0.00	3.40
10^{-3} mol dm^{-3} NaOH	10.3	0.01	0.88
10^{-3} mol dm^{-3} NaOH	10.3	0.01	3.54[d]
10^{-3} mol dm^{-3} NaOH	10.5	0.10	0.41
10^{-3} mol dm^{-3} NaOH	10.5	0.10	3.73[d]
10^{-2} mol dm^{-3} NaOH	12.0	0.01	2.44[d]
10^{-1} mol dm^{-3} NaOH	12.9	0.10	1.24[d]

[a] All buffers are phosphate (see ref. 6). Values of pH were determined experimentally; for the NaOH solutions they differ from those expected by simple calculation. [b] Ionic strength, made up with NaCl. [c] Results extrapolated to [Buffer] = 0. [d] Rate for the second, slow phase of the reaction.

Table 2. Kinetics for hydrolysis of 4-(4-chlorobenzoyl)-4-methylcyclohexa-2,5-dienone (**3**) in aqueous solution at 25.0 °C.[a]

Solution	pH	I/mol dm^{-3} [b]	$-\log_{10}(k_{obs}/s^{-1})$
10^{-2} mol dm^{-3} HCl	2.0	0.01	1.09
10^{-2} mol dm^{-3} HCl	2.1	0.10	1.10
5×10^{-3} mol dm^{-3} HCl	2.3	0.01	1.37
5×10^{-3} mol dm^{-3} HCl	2.4	0.10	1.40
10^{-3} mol dm^{-3} HCl	3.0	0.01	2.13
10^{-3} mol dm^{-3} HCl	3.1	0.10	2.13
3.6×10^{-4} mol dm^{-3} HCl	3.5	0.01	2.80
3.6×10^{-4} mol dm^{-3} HCl	3.6	0.10	2.87
10^{-4} mol dm^{-3} HCl	4.0	0.01	3.15
10^{-4} mol dm^{-3} HCl	4.1	0.10	2.96
Buffer	5.8	0.01	3.17
Buffer	5.8	0.10	2.91
H_2O			3.21
Buffer	7.0	0.10	2.61
Buffer	7.4	0.01	2.90
Buffer	7.4	0.10	2.54
10^{-4} mol dm^{-3} NaOH	9.0	0.01	2.15
10^{-4} mol dm^{-3} NaOH	9.1	0.10	2.28
3.6×10^{-4} mol dm^{-3} HCl	9.7	0.01	1.04
3.6×10^{-4} mol dm^{-3} HCl	9.7	0.01	2.38[c]
3.6×10^{-4} mol dm^{-3} HCl	9.8	0.10	0.97
3.6×10^{-4} mol dm^{-3} HCl	9.8	0.10	2.38[c]
10^{-3} mol dm^{-3} NaOH	10.3	0.01	0.76
10^{-3} mol dm^{-3} NaOH	10.4	0.10	0.42

[a] All buffers are phosphate (see ref. 6). Values of pH were determined experimentally; for the NaOH solutions they differ from those expected by simple calculation. [b] Ionic strength, made up with NaCl. [c] Rate for the second, slow phase of the reaction.

Table 3. Kinetics for hydrolysis of 4-(4-methoxybenzoyl)-4-methylcyclohexa-2,5-dienone (**4**) in aqueous solution at 25.0 °C.[a]

Solution	pH	I/mol dm^{-3} [b]	$-\log_{10}(k_{obs}/s^{-1})$
10^{-3} mol dm^{-3} HCl	3.0	0.01	1.27
10^{-3} mol dm^{-3} HCl	3.1	0.10	1.29
3.6×10^{-4} mol dm^{-3} HCl	3.5	0.01	1.89
3.6×10^{-4} mol dm^{-3} HCl	3.6	0.10	1.92
10^{-4} mol dm^{-3} HCl	4.0	0.01	2.31
10^{-4} mol dm^{-3} HCl	4.1	0.10	2.40
Buffer	5.8	0.01	3.03
H_2O			2.92
Buffer	7.4	0.01	3.03
Buffer	7.4	0.10	2.93
10^{-4} mol dm^{-3} NaOH	9.0	0.01	2.36
10^{-4} mol dm^{-3} NaOH	9.1	0.10	2.22
3.6×10^{-4} mol dm^{-3} NaOH	9.7	0.01	1.39
3.6×10^{-4} mol dm^{-3} NaOH	9.8	0.10	1.50
10^{-3} mol dm^{-3} NaOH	10.3	0.01	0.79
10^{-3} mol dm^{-3} NaOH	10.5	0.10	0.84

[a] All buffers are phosphate (see ref. 6). Values of pH were determined experimentally; for the NaOH solutions they differ from those expected by simple calculation. [b] Ionic strength, made up with NaCl.

Kinetic Studies.—Kinetic measurements were made on the dienones in dilute hydrochloric or sulphuric acids, in sodium hydroxide, and in buffer solutions covering a pH range of *ca.* 3–11. The results are given in Tables 1–3. Our early measurements used phosphate buffers[6] of pH 3–9, at ionic strengths 0.01 and 0.1 mol dm^{-3}. The rates for the parent dienone (**2**) at any pH increased with increasing buffer concentration, but not by a constant factor. The same was found, but less markedly, for the substituted-benzoyl compounds (**3**) and (**4**). In order to discover whether the effect was due to the ionic strength, or to the operation of general acid or general base catalysis, we later used monobasic or monoacid buffers. The addition of sodium chloride to increase the ionic strength of reactions of (**3**) and (**4**) in dilute hydrochloric acid solutions from 0.01 to 0.20 mol dm^{-3} had no effect on the rates, so it was used subsequently to adjust ionic strengths when necessary.

Reaction of all three dienones showed the same kinetic form. Plots of the logarithm of the pseudo first-order rate constants against pH were bell shaped, with a flat region around pH 7, and rising linear portions at lower and higher pH. The flat portions of the plots are ascribed to the 'spontaneous', or water-induced hydrolysis reaction. For this, the rate constants, k_0, are in the order 4-methoxybenzoyl > 4-chlorobenzoyl > parent compound, with relative rates *ca.* 2.2:1.5:1.0. The observed rates were then dissected into the water-induced component and separate proton- and base-catalysed processes [see equation (1), and the subsequent discussion].

Hydrolysis in Acidic Solutions.—In dilute aqueous solutions of hydrochloric or sulphuric acid, or in buffer solutions, the cleavage rate for the parent dienone followed equation (2). That is, the logarithm of the rate constant due to acid hydrolysis, $\log_{10}k_H = \log_{10}(k_{obs} - k_0)$, varied linearly with pH. Over the pH range 2.0 to 4.0 the graphs of $\log(k_{obs} - k_0)$ for the three dienones, the 4-methoxybenzoyl, the parent, and the 4-chlorobenzoyl compound, were essentially parallel straight lines, having gradients close to minus unity. The relative rates were 3.2:1.0:0.3, respectively. The line for the bicyclic dienone (**1**)[1] was also approximately parallel, but that reaction was slower than the parent (**2**) by a factor of *ca.* 25. Limited Hammett plots, based on the three compounds, gave much better correlations with Hammett's σ than σ^+, with a ρ value of *ca.* -1.8 (at pH 2.5) and *ca.* -2.4 (at pH 3.5). This finding differs from our previous claim of a σ^+ correlation in the preliminary communication, which we interpreted in terms of

Table 4. Kinetics for hydrolysis of 4-benzoyl-4-methylcyclohexa-2,5-dienone (**2**) in buffer solutions at 25.0 °C.[a]

Buffer[b]	pH	[Buffer]/mol dm^{-3}	$k_{obs}/10^{-2}$ s^{-1}
Formate[c]	3.5	—	1.0[d]
Formate	3.5	0.01	1.1
Formate	3.5	0.03	1.2
Formate	3.5	0.05	1.2
Formate	3.5	0.075	1.2
Formate	3.5	0.09	1.2
Carbonate[e]	10.0	—	9.0[d]
Carbonate	10.0	0.01	9.1
Carbonate	10.0	0.01	9.3
Carbonate	10.0	0.02	10.9
Carbonate	10.0	0.02	11.7
Carbonate	10.0	0.03	11.9
Carbonate	10.0	0.03	11.9
Carbonate	10.0	0.03	12.4
Carbonate	10.0	0.04	8.5
Carbonate	10.0	0.04	11.1
Carbonate	10.0	0.05	12.9
Carbonate	10.0	0.05	14.5
Carbonate	10.5	—	19.0[d]
Carbonate	10.5	0.01	22.2
Carbonate	10.5	0.025	22.4
Carbonate	10.5	0.035	28.6

[a] Rates are for the first, faster reaction step. [b] Ionic strengths all 0.1 mol dm^{-3}, made up with NaCl. [c] Made from 1.0 mol dm^{-3} solutions of HCO_2H, NaOH, and NaCl, as described in ref. 21, using a variant of the program in Table 5.3 rewritten in BASIC. [d] Extrapolated to [Buffer] = 0. [e] Made from 1.0 mol dm^{-3} solutions of $NaHCO_3$, NaOH, and NaCl, as described in footnote *c*.

Table 5. Kinetics for hydrolysis of 4-benzoyl-4-methylcyclohexa-2,5-dienone (**2**) in ethanolamine/HCl buffer solutions at 25.0 °C.[a,b]

pH	[Buffer]/ mol dm^{-3}	[Amine]/ 10^{-3} mol dm^{-3}	[Amine•HCl]/ 10^{-3} mol dm^{-3}	$k_{obs}/10^{-2}$ s^{-1}
8.5	0.01	0.72	9.28	0.7
8.5	0.03	2.15	27.9	1.9
8.5	0.05	3.57	46.4	2.6
8.5	0.07	5.01	65.0	4.2
8.5	0.09	6.44	83.6	5.4
9.5	0.01	4.35	5.65	6.5
9.5	0.03	13.1	17.0	12.4
9.5	0.05	21.8	28.2	19.0
9.5	0.07	30.5	39.5	25.7
9.5	0.09	39.2	50.9	31.2
10.0	0.01	7.1	2.9	12.7
10.0	0.03	21.3	8.7	23.2
10.0	0.05	35.5	14.5	33.8
10.0	0.07	49.7	20.3	54.6

[a] Rates are for the first, faster reaction step. Buffers were made from 1.0 mol dm^{-3} solutions of ethanolamine, HCl, and NaCl, as described in ref. 21, using a variant of the program in Table 5.3 rewritten in BASIC. The ionic strengths were all 0.1 mol dm^{-3}. [b] Plots of k_{obs} *vs.* [Amine] gave the following gradients: pH 8.5, gradient (8.24 ± 0.05); pH 9.5, (9.1 ± 1.0); pH 10.0, (9.6 ± 1.3). Plots of k_{obs} *vs.* [Amine•HCl] gave the following: pH 8.5, gradient (0.63 ± 0.04); pH 9.5, (5.55 ± 0.1); pH 10.0, (23.5 ± 3.0). All intercepts are very close to zero.

Table 6. Values of the parameters in equations (1)–(4) for the dienones (**1**)–(**4**).[a]

Compound	*a*	*b*	*n*	$\log_{10} c$	$\log_{10} k_0$
(**1**)	−0.83	−0.45	1.22	3.26	*b*
(**2**)	−1.13	1.70	1.00	2.50	−3.40
(**3**)	−1.17	1.34	1.19	3.71	−3.20
(**4**)	−1.19	2.28	1.16	3.46	−3.04

[a] The parameters are not optimised, but give a good fit to the experimental points. [b] Not determined. Data from ref. 1.

an acylium ion loss in the rate-determining step of the cleavage reaction.[5] We will return later to the implications for the mechanism. Measurements were also made using a number of formate buffers, all at pH 3.5 and the same ionic strength, but having buffer concentrations varying over a ninefold range. These gave only a small variation of rate, which is normally taken as evidence that the reaction in acid is specific-acid catalysed. However, very weak buffer catalysis has been reported in the acid-catalysed hydrolysis of benzaldehyde diethyl acetal, where the use of 0.8 mol dm^{-3} cacodylic acid* increased the rate by only 12%.[7] In our own experiments the buffer concentrations only reached 0.09 mol dm^{-3}, so weak catalysis would not be noticed. However, the rate in phosphate buffer was 30% greater than in formate, and we take this as evidence of buffer catalysis. The discussion later makes use of a process which does require general-acid (*i.e.* buffer) catalysis.

Hydrolysis in Basic Solutions.—Two processes could be identified in basic solutions (pH > 8), one fast and a subsequent slower one. The products isolated from the preparative reactions in basic solutions (see earlier) represent the result of the combined processes. The following description of the kinetics relates to the initial fast reaction found for the parent dienone (**2**). Measurements using sodium hydrogencarbonate/sodium hydroxide buffers at pH 10.0 and 10.5, at constant ionic strength, gave linear plots of rate *vs.* buffer concentration. The gradient of the plot for pH 10.5 was much greater than that for pH 10.0 (Table 4). This is evidence of (weak) buffer catalysis by the hydrogencarbonate ion and of general-base catalysis in this pH region. To confirm these results we also used ethanolamine/hydrochloric acid buffers. Kinetics were measured at pH 8.5, 9.5, and 10.0, with varying buffer concentrations but constant ionic strength. They show (Table 5) that the rate ($k_{obs} - k_0$) varies directly both with the free amine and hydroxide ion concentration. Plots of the rate constants against the concentration of amine or amine hydrochloride were linear at each pH, but the latter plot had a much higher gradient at higher pH. Again, this confirms general-base catalysis in the pH region.[8]

The rate of the acid-induced reaction follows equation (2), and we assumed the hydroxide-induced reaction would follow equation (3). These rate equations were combined to give equation (4), where K_w is the dissociation constant of water. The constants therein were derived so that the curves calculated from them fitted the experimental data. Their values are given in Table 6. The constants are not optimised, because there are insufficient experimental points to justify further refinement. Similar rate-profiles have been reported for other reactions.[7,9]

$$k_{obs} = k_0 + k_H + k_{base} \tag{1}$$

$$\log_{10} k_H = a\text{pH} + b \tag{2}$$

$$k_{base} = c[OH^-]^n$$

$$\log_{10} k_{base} = \log c + n \log[OH^-] \tag{3}$$

$$\log k_{base} = \log c + n(\log K_w + \text{pH})$$

$$k_{obs} = k_0 + 10^{(a\text{pH}+b)} + c10^{n(\text{pH}+\log K_w)} \tag{4}$$

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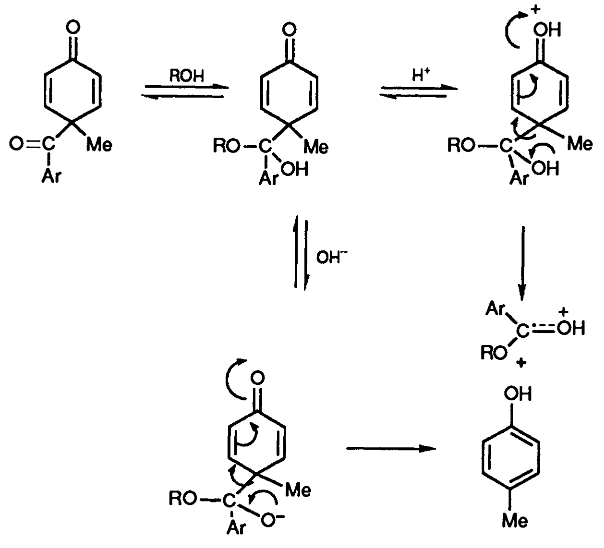
* Hydroxy(dimethyl)arsine oxide.

Reactions with Alcohols and Amines.—All three dienones (**2**)–(**4**) reacted with methanol. Compound (**2**) was 20% reacted within 17.5 h at 25 °C, with the formation of 4-methylphenol and methyl benzoate. The 4-methoxybenzoyl dienone (**4**) reacted similarly, to the extent of 60% in the same time. Kinetic measurements for (**4**) in methanol and in spectroscopic ethanol gave pseudo first-order rate constants (see Experimental section) 8.5×10^{-5} and 2.5×10^{-6} s^{-1}, respectively. Comparable values for the 4-chlorobenzoyl analogue (**3**) were 2.3×10^{-3} and 4.6×10^{-5} s^{-1}, respectively. The greater rate of reaction with methanol than ethanol is understandable on steric grounds. However, the order of reactivity, 4-chlorobenzoyl > 4-methoxybenzoyl > benzoyl is strange, and suggests a process which is not simple. Our expectation was that the alkaline hydrolysis and alcoholysis reactions would occur by a process very similar to that shown in Scheme 2.



Scheme 2.

Since all the cleavages show that the phenol or phenoxide ion acts as an excellent leaving group we believed that useful mechanistic and preparative information would be gained by using amines as nucleophiles. The parent dienone (**2**) reacted with a 50 molar excess of dimethylamine solution in ethanol (concentrations of dienone and amine 6.25×10^{-2}, and 3.12 mol dm^{-3}, respectively) within 10 min at 20 °C, to give 4-methylphenol, *N*,*N*-dimethylbenzamide, and 4-methylphenyl benzoate. The yields were consistent with 75% of the dienone having reacted to give the first two products, and 25% having rearranged to 4-methylphenyl benzoate.

Treatment of (**2**) with an equimolar amount of diethylamine (both 4.75×10^{-2} mol dm^{-3}) in ethanol gave no detectable reaction within 15 min, and reaction of (**2**) (7.8×10^{-5} mol dm^{-3}) with excess of the amine (3.1×10^{-2} mol dm^{-3}) in acetonitrile had not reached completion within 7 days at 20 °C. However, sufficiently rapid reaction did occur for kinetic measurements to be made in spectroscopic ethanol solution, with the initial concentrations of dienone at 7.86×10^{-5} mol dm^{-3} and diethylamine at 3.91×10^{-3} to 3.1×10^{-2} mol dm^{-3}. The pseudo first-order rate constant increased linearly with the amine concentration, showing the process to be second-order, *i.e.* first-order in the dienone and in the amine. The UV spectra recorded at the end of the kinetic runs were essentially identical to those of a freshly prepared solution of 4-methylphenyl benzoate at the same concentration in the same solvent. A preparative reaction of the dienone, initially at 6.4×10^{-2} mol dm^{-3}, at 20 °C for 60 min with a 100-fold molar excess of diethylamine in ethanol gave 4-methylphenol, *N*,*N*-diethylbenzamide, and 4-methylphenyl benzoate, ostensibly by (41 ± 3)% of cleavage and (59 ± 3)% of rearrangement to the 4-methylphenyl benzoate. We interpret the process (see later) in terms of an initial rearrangement of the dienone to 4-methylphenyl benzoate, with second-order rate constant 0.15 dm^{3} mol^{-1} s^{-1}, followed by a much slower aminolysis of the ester by diethylamine, with a second-order rate constant $(2.2 \pm 0.2) \times 10^{-5}$ dm^{3} mol^{-1} s^{-1}. Similar kinetic measurements were made using pyrrolidine as nucleophile. The dienone (**2**), at initial concentration 8.5×10^{-5} mol dm^{-3} in spectroscopic ethanol, reacted with pyrrolidine in 40, 80, 160, 240, 320, and 400-fold molar excess. The plot of rate *vs.* amine concentration allowed a second-order rate constant of 0.58 dm^{3} mol^{-1} s^{-1} to be derived, and suggested the residual rate due to solvent ethanol to be negligible. The UV spectrum, after *ca.* 3 half-lives, matched that of a freshly made solution of 4-methylphenyl benzoate in a similar ethanol/pyrrolidine solution. Reaction of the dienone (**2**) (7.43×10^{-2} mol dm^{-3}) for 30 min at 20 °C with pyrrolidine (2.52 mol dm^{-3}) in ethanol, followed by work-up and GLC analysis showed 5% of 4-methylphenyl benzoate to be present, with equal amounts of 4-methylphenol and *N*-benzoylpyrrolidine. An identical reaction, using 4-methylphenyl benzoate instead of the dienone showed 93% to have reacted to the same products in the same time. Crude calculations give a second-order rate constant of 5.9×10^{-4} dm^{3} mol^{-1} s^{-1}. We again interpret these results in terms of a fast rearrangement of the dienone to 4-methylphenyl benzoate, followed by a 10^{3} times slower reaction of this to the *N*-benzoyl amine and 4-methylphenol. The first step is four times faster, and the second 25–30 times faster for pyrrolidine than diethylamine.

Discussion

The fact that the same form is shown in the plots of log k_{obs} *vs.* pH for the monocyclic dienones (**2**)–(**4**), and the bicyclic analogue (**1**) suggests that all react by the same mechanisms. That is, all follow the same mechanism for acidic hydrolysis, and all follow the same mechanism for alkaline hydrolysis. The close similarity of their rates in alkaline solution and, for (**2**)–(**4**), in acidic and neutral media, supports this view. The rate profile is a continuous line which represents the only reaction detected in acidic and neutral solutions, and the relatively fast, initial reaction in the alkaline media.

Cleavage in Aqueous Acids.—The evidence from buffer studies seems to be that the acidic hydrolysis of the dienones (**2**)–(**4**) is specific-acid catalysed or, more likely, shows weak general-acid catalysis. The linear plot of log k_{H} *vs.* pH has a gradient close to minus unity, as is commonly found for acid-catalysed reactions and is expressed in the (non-general) Zucker–Hammett hypothesis.[10] However, since pH and the Hammett acidity function, H_0, are indistinguishable at our acidities, no detailed mechanistic deductions may be made from this fact. We suggest that the hydrolysis has mechanistic analogy with the acidic cleavage of acetals and hemiacetals of substituted benzaldehydes,[7] as shown in Scheme 2.* The hemiacetal cleavage has the same kinetic form as found for the dienones, with gradients for the plots of log k_{obs} *vs.* pH having the values −1 in acid, zero in the neutral pH region, and +1 in alkaline solution. For the acid cleavage of the hemiacetals and

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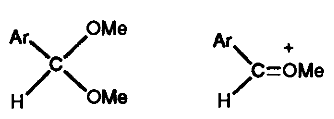
* We exclude a mechanism in which the protonated dienone ring departs, leaving behind a benzoyl cation. This would be analogous to the A-1 cleavage of some substituted benzoate esters, with acyl–oxygen fission. Such reactions are correlated by σ^{+}, with a ρ value close to −3.2 (M. L. Bender and M. C. Chen, *J. Am. Chem. Soc.*, 1963, **85**, 37).

acetals the Hammett σ correlations gave ρ values of -1.90 and -3.25, respectively. It is believed that the acetal reacts by rate-determining cleavage of the O-protonated species, and forms an oxocarbenium ion (**6**). Later work has also shown Hammett σ rather than σ^+ correlations for reactions in which the ion (**6**) is formed, suggesting that it shows little carbenium ion character at the benzylic carbon.[11] The hemiacetal hydrolysis is analogous, but is thought to have less extensive bond cleavage in the transition state. The same arguments would apply to breakdown of our hydrated benzoyl cyclohexadienones, in which the leaving group is regarded as the protonated dienone ring which will convert exothermically into a phenol molecule. This should result in an early transition state for the reaction, the Hammett σ rather than σ^+ correlation, and the numerically small ρ value.

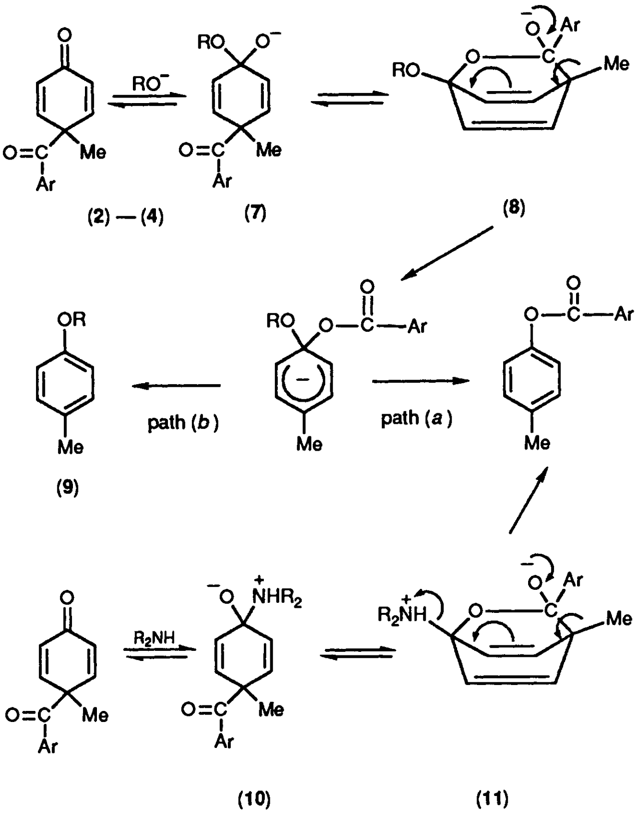


(**6**)

Cleavage in Aqueous Alkalis.—It is tempting to suggest that the cleavage of our (acyl-hydrated) cyclohexadienones in alkaline solution can also occur by the same mechanism as for benzaldehyde hemiacetals. That is, the benzoyl group of the dienone is rapidly hydrated. Then, in the simplest formulation, the hydrate would be deprotonated and the oxyanion would expel the 4-methylphenoxide ion in the rate-determining step. However, when hemiacetals contain a good leaving group it is believed that the anion may be too short-lived to have real existence.[12] Because the dienones contain an excellent leaving group, an incipient 4-methylphenoxide which can be formed with simultaneous aromatisation, we believe the same effect should occur here and give a very early transition state. Unfortunately, at the moment we do not have the necessary experimental data to provide further evidence on the nature of this process. The rate constants for hydroxide ion catalysed breakdown of benzaldehyde ethyl hemiacetal give a small ρ value (-0.3).[7] The rates for the dienones also vary little with the substituent, but not in a regular way.

We find that the hydrolysis in weakly basic solutions occurs by a relatively fast step followed by a much slower one. We now ask whether the fast reaction actually represents the hydrolysis, which is followed by some other, slow and irrelevant reaction which affects the UV spectrum of the solution, or whether it is a fast preliminary to the actual cleavage step. We believe the first explanation to be true, supported by the following facts. The slow reaction step is *ca.* 1/1 000 as fast as the fast step, and even in 10^{-3} mol dm^{-3} NaOH proceeds *ca.* 3 times more slowly than the minimum of the rate profile. This minimum is well defined by kinetic measurements in buffers covering a range of pH values, and in 'neutral water', and by preparative experiments in which the cleavage mixture was examined by ^{1}H NMR spectroscopy. Thus the preparative cleavage of (**2**) in water has a half-life less than 45 min at a little below 20 °C (hydrolysis is >95% complete within 3 h).[3] This matches adequately the rate measured by UV spectroscopy, and used on the rate profile ($t_{\frac{1}{2}}$ 28 min at 25 °C). If the rates measured for the slow, second step are extrapolated to pH 7 they give a value for the half-life greater than 61 h. Furthermore, the preparative reactions with methanol of the dienones (**2**) and (**4**) which give 4-methylphenol and methyl benzoate or methyl 4-methoxybenzoate, respectively, proceed with second-order rate constants 1.4×10^{-7} and 5.9×10^{-7} dm^3 mol^{-1} s^{-1}, respectively, which are 1.3% and 3.6% of their respective rate constants for hydrolysis in neutral aqueous solution. These values may also be compared with the rate ratios for methanolysis/ethanolysis which are 34 for the methoxybenzoyl dienone (**4**) and 50 for the chlorobenzoyl analogue (**3**). The reasonable relationship of these rates suggests that the hydrolysis, methanolysis and ethanolysis go by the same process which is that shown in Scheme 2.

In view of our later discussion of the reaction of the dienone (**2**) with amines we should consider the possible hydrolysis mechanism shown in Scheme 3. In this, the dienone carbonyl group may be hydrated and then deprotonated to give the anion (**7**; R = H) which undergoes intramolecular attack onto the benzoyl group. The bridged intermediate (**8**; R = H) might break down with loss of RO$^-$ (R = H) [path (*a*)], or of benzoate ion [path (*b*)]. The partitioning of (**8**; R = H) would depend on the leaving abilities of its substituents. Because the benzoate ion should be a much better leaving group than RO$^-$, path (*b*) should be followed, with the formation of 4-methylphenol and benzoate ion. In the hope of testing this hypothesis we allowed the dienone (**2**) to react with sodium isopropoxide in isopropyl alcohol (as being comparable in size to the secondary amines we have used), in the hope that some 4-isopropoxy methylbenzene (**9**; R = Pr^i) would be formed. However, the major product formed was isopropyl benzoate, presumably from direct nucleophilic attack onto the benzoyl group, similar to that found with methanol and ethanol. Only a trace of (**9**; R = Pr^i) was detected. Such attack at a site which resembles to some extent a neopentyl system may seem surprising, but molecular models suggest that the steric hindrance is not acute.



Scheme 3.

Reactions with Amines.—The rearrangement of the dienone to 4-methylphenyl benzoate which occurs upon treatment with secondary amines was unexpected. It represents an intramolecular transacylation reaction with nucleophilic involve-

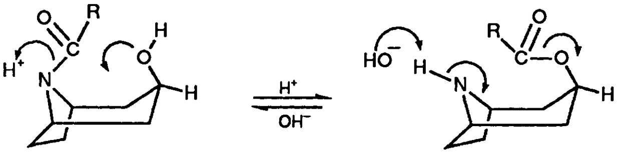
Table 7. Kinetics for reactions of 4-benzoyl-4-methylcyclohexa-2,5-dienone (**2**) with amines in solution at 25.0 °C.[a]

Amine	Solvent	[Amine]/10^{-3} mol dm^{-3}	$k_{obs}/10^{-3}$ s^{-1}
Diethylamine[a]	98% EtOH	4.24	1.11
Diethylamine	98% EtOH	8.18	1.73
Diethylamine	98% EtOH	20.0	2.47
Diethylamine	98% EtOH	33.0	4.19
Pyrrolidine[b]	98% EtOH	3.4	2.41
Pyrrolidine	98% EtOH	6.8	3.58
Pyrrolidine	98% EtOH	14.0	8.14
Pyrrolidine	98% EtOH	20.0	13.0
Pyrrolidine	98% EtOH	27.0	16.0
Pyrrolidine	98% EtOH	34.0	18.0

[a] Initial dienone conc. 8.25 × 10^{-5} mol dm^{-3}. Derived second-order rate constant = 0.15 dm^3 mol^{-1} s^{-1}. [b] Initial dienone conc. 8.49 × 10^{-5} mol dm^{-3}. Derived second-order rate constant = 0.58 dm^3 mol^{-1} s^{-1}.

ment of the amine in a second-order reaction. We suggested previously that the rearrangement starts with a relatively unhindered attack by the amine on the dienone carbonyl group to form an intermediate (**10**). This may be followed by intramolecular attack by the oxyanion portion of one epimer of (**10**) on the acyl group, to form a hemiacetal anion (**11**), which should then break down with expulsion of the amine molecule and aromatisation of the ring system to give 4-methylphenyl benzoate. The faster reaction with pyrrolidine than diethylamine is in accordance with its greater expected nucleophilicity.* The fact that the neutral amine molecule leaves from intermediate (**11**) is expected on the basis of its better leaving ability compared to the alternative benzoate ion. As an analogy, one may take many studies of the aminolysis of esters, and particularly of phenyl esters.[16]

A close analogy of the mechanism we suggest for the amine-catalysed acyl-transfer reaction is available in the interconversions of *N*-acetylnor-ψ-tropine (**12**; R = Me) with *O*-acetylnor-ψ-tropine (**13**; R = Me). This proceeds in the direction (**13**)→(**12**) under alkaline conditions, and the direction (**12**)→(**13**) under acidic conditions, reflecting the stabilities of the products. The *N*-benzoyl analogue (**12**; R = Ph) also is transformed into (**13**; R = Ph).[17]



(12) **(13)**

Experimental

GLC analyses employed a Pye 104 instrument with flame-ionisation detector and glass columns (7 ft × ¼ inch), packed with silicone gum (E30, 2%), cyanoethyl silicone fluid (XF1150, 25%), neopentyl glycol succinate (NGS, 20%), or fluorosilicone gum (QF1, 10%), on silanized Supasorb (60–80 mesh, BDH). Silica for column chromatography was Merck Kieselgel 60, mesh 70–230, or for medium-pressure use, mesh 230–400. ^{1}H NMR spectra were recorded on Varian XL 100 or Perkin-Elmer R14 instruments at 100 MHz, and ^{13}C NMR spectra on a JEOL FX60 instrument at 15.03 MHz (Me_4Si internal standard). IR spectra were recorded on Pye–Unicam SP1050 or SP3-100 instruments, calibrated using polystyrene film. UV spectra were measured with a Pye–Unicam SP8-100 spectrophotometer: UV kinetics were determined by the methods described in ref. 18.

The reaction rates for the dienones (**2**)–(**4**) depend on the ionic strength of the medium. For the 4-chloro- and 4-methoxybenzoyl compounds (**3**) and (**4**) the difference between rates at I = 0.01 mol dm^{-3} and I = 0.10 mol dm^{-3} are small. For the correlation of rates with equation (4) it does not matter much whether we use all the experimental points or only those at low ionic strength (I = 0.01 mol dm^{-3}). For the parent dienone (**2**) the rates vary rather more, and many of the most valuable kinetic points were determined at I = 0.1 mol dm^{-3}. However, for this compound the rates at I = 0.01 mol dm^{-3} only were correlated with equation (4) to give the values in Table 6.

Reaction of 4-*Benzoyl*-4-*methylcyclohexa*-2,5-*dienone with Sodium Isopropoxide.*—To the dienone (**2**) (9.8 mg) was added sodium isopropoxide (0.3 cm^3, 0.47 mol dm^{-3}) from sodium (21.6 mg) in isopropyl alcohol (2.0 cm^3). After being stirred for 10 min at 25 °C the solution was neutralised with aq. HCl (0.1 mol dm^{-3}), extracted with chloroform, and the washed and dried extracts evaporated to give an oily residue (8.8 mg). This was shown by ^{1}H NMR spectroscopy to contain isopropyl benzoate and 4-methylphenol (from direct attack on the benzoyl group), a trace of 4-isopropoxymethylbenzene from path (*b*) in Scheme 3, but no 4-methylphenyl benzoate [from path (*a*) of Scheme 3]. Analysis by GLC (QF1 column at 180 °C, NGS at 160 °C, and cyclohexyldimethanol succinnate at 170 °C) confirmed these results, but suggested that only a very small amount of the isopropyl ether was present. An authentic sample of isopropyl benzoate was made from benzoyl chloride and isopropyl alcohol,[19] and had b.p. 212–213 °C (lit.,[19] 218–219 °C); $\delta_H(CDCl_3$, 90 MHz) 1.38 (6 H, d, J 6–7 Hz, Me_2CH), 5.25 (septet, 1 H, J 6.5 Hz, Me_2CH), 8.07 (d, 2 H, J 8 Hz of d, J 2 Hz, *ortho* H), and 7.46 (m, 3 H, *meta* and *para* H). A sample of 4-isopropoxymethylbenzene, contaminated with some 4-methylphenol, was made by treating 4-methylphenol with 2-bromopropane and anhydrous potassium carbonate in acetone at reflux, as described for the preparation of allyl phenyl ether.[20] Work-up with distillation gave the ether; $\delta_H(CDCl_3$, 60 MHz) 1.26 (6 H, d, J 6 Hz, Me_2CH), 2.22 (>3 H, s, 4-Me of the ether and 4-methylphenol), 4.43 (septet, 1 H, J 6 Hz, Me_2CH), 5.35 (br s, OH of 4-methylphenol), and 6.58–7.11 (complex, two overlapping AB patterns, aryl H).

Acknowledgements

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* C. D. Ritchie[13] correlated the nucleophilicity of amines towards the carbonyl group of carboxylate esters with their pK_a values. Pyrrolidine has pK 11.31 compared with diethylamine's value of 10.84 (in water at 25 °C),[14] and pyrrolidine is found to be a stronger nucleophile than diethylamine.[15]

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