Equilibria and Kinetics of the Hydration and Cyclisation of Semiphorone in Acidic Media

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In acidic media 6-hydroxy-2,6-dimethylhept-2-en-4-one (semiphorone) undergoes three parallel transformations: (*a*) hydration to form 2,6-dihydroxy-2,6-dimethylheptan-4-one (triacetone dialcohol); (*b*) cyclisation to 2,2,6,6-tetramethyltetrahydro-γ-pyrone and, to a lesser extent, (*c*) dehydration to form 2,6-dimethylhepta-2,5-dien-4-one (phorone). At higher temperatures appreciable amounts of acetone, diacetone alcohol, and mesityl oxide are also formed, even with relatively short reaction times.

The equilibria and the kinetics of the cyclisation and hydration have been examined at different temperatures and catalyst concentrations, using polarographic, infrared, and nuclear magnetic resonance techniques. Indicative values of the thermodynamic data are given and reaction mechanisms are proposed.

In a preceding Note [1] one of us reported the results of a kinetic study of the hydration of phorone (I) in acidic media and observed that the product, semiphorone (II), undergoes further acid-catalysed reactions. As a result of a study carried out by polarographic, infrared (i.r.), and nuclear magnetic resonance (n.m.r.) techniques we observed that in these reactions (II) cyclises to tetramethyltetrahydro-γ-pyrone (III) and simultaneously (*a*) hydrates to triacetone dialcohol (IV) and (*b*) loses a water molecule, being converted into (I). These reactions are reversible but other irreversible reactions

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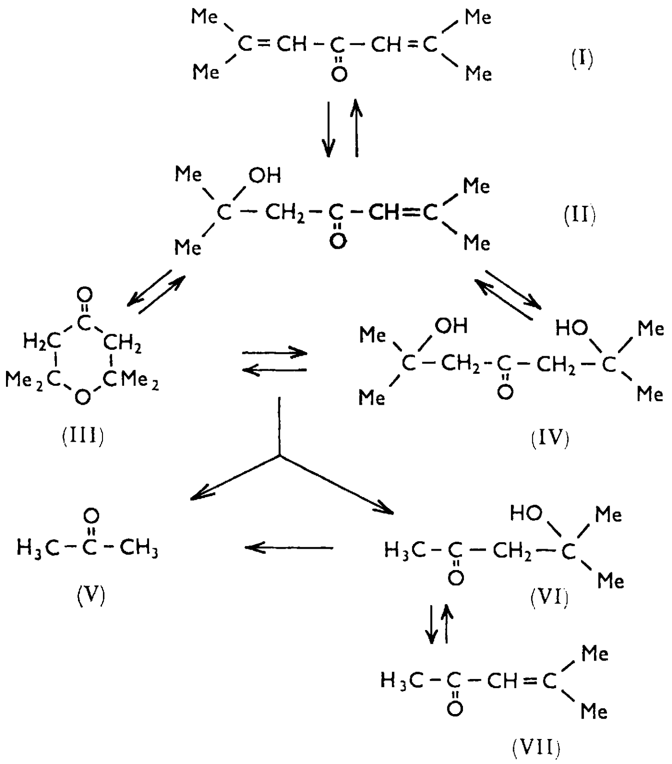
[1] S. Cabani, *Boll. sci. Fac. Chim. ind. Bologna*, 1962, **20**, 85.

also take place, with formation of acetone (V) and diacetone alcohol (VI); this latter reversibly changes into mesityl oxide (VII) and decomposes with formation of acetone (Scheme 1).



Scheme 1

As will be shown later, the concentration of (I) is always very low, the reaction (III) $\rightleftharpoons$ (IV) is virtually negligible, and at low temperatures the irreversible processes can be neglected. Scheme (1) can thus be simplified to the form:

$$\text{(III)} \underset{k_{23}}{\overset{k_{32}}{\rightleftharpoons}} \text{(II)} \underset{k_{42}}{\overset{k_{24}}{\rightleftharpoons}} \text{(IV)} \qquad (1)$$

Nazarov and Nagibina[2] noticed that, in acidic media, phorone cyclises to tetramethyltetrahydro-γ-pyrone. Leopold and Schacke,[3] and later Connolly,[4] obtained phorone, semiphorone, and tetramethyltetrahydro-γ-pyrone by treating triacetone dialcohol with acids. To the best of our knowledge nobody has ever studied the thermodynamic and the kinetic aspects of these reactions. The object of the present work was to study the equilibria and rates of these processes (reaction 1) over a wide range of conditions in order to obtain information on the reaction mechanism.

The n.m.r. spectra of the compounds of Scheme 1, show lines in the range 1·9—2·6 p.p.m. (reference tetramethylsilane) given by the methyl and methylenic groups. These lines overlap in the region of 1·95 (II + VII), 2·15 (II + VII + V + VI) and 2·5 p.p.m. (II + IV + VI). Only the methylenic groups of (III) give a specific line, at 2·30 p.p.m. The ratios h_i-h_γ (i = α, β, or δ), where α, β, γ, and δ are the lines at ~1·95, ~2·15, 2·30, and ~2·50 p.p.m., respectively, and h_α, h_β, h_γ, and h_δ their heights, are useful for studying the progress of the reactions.

An examination of the n.m.r. spectra of samples prepared by keeping a solution of (III) in 1M-hydrochloric acid at 30° (Figure 1a), shows that the ratios h_α/h_γ and h_β/h_γ are equal and rapidly reach a value which remains constant, even after a long reaction time; the ratio h_δ/h_γ also reaches a constant value, though more slowly. At higher temperatures (Figure 1b), h_α/h_γ is lower than h_β/h_γ and the curves for h_β/h_γ and h_δ/h_γ have positive slopes whose values grow higher with time. This is in accordance with the presence, at 30°, of compounds (II), (III), and (IV) only, while at higher temperatures (V), (VI), and (VII) are also formed. In the first case, the α and β lines are given by the *cis*- and *trans*-methyl groups of semiphorone and the δ line by triacetone dialcohol * methylenic groups, and the ratios h_i/h_γ can then be used for the analytical determination of the concentration ratios (II)/(III) and (IV)/(III). In the second case this is impossible because of overlapping.

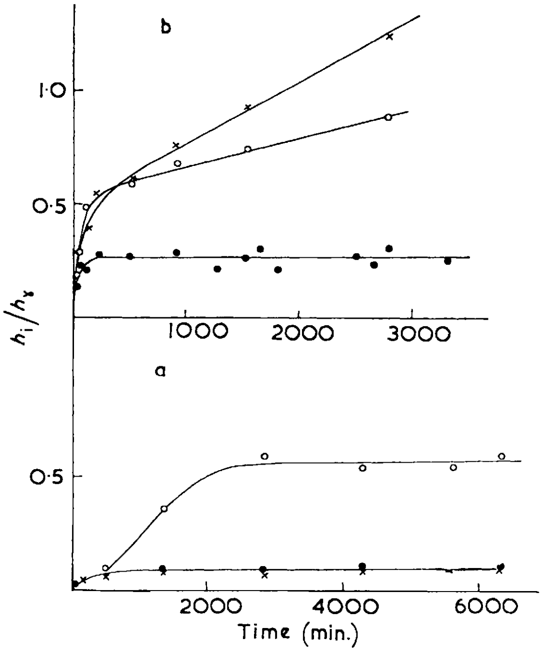


FIGURE 1 Plot of the ratios h_i/h_γ for different suitable n.m.r. peaks of samples prepared from solutions of tetramethyltetrahydro-γ-pyrone in 1M-hydrochloric acid at (a) 30° and (b) 56·7°. The meaning of the symbols is explained in the text

At 30°, the shorter time necessary to reach a constant value of h_α/h_γ (or h_β/h_γ) with respect to h_δ/h_γ suggests that the reaction (III) $\rightleftharpoons$ (IV) does not occur and that (IV) must be obtained from (II). This is confirmed by

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* If (VI) is absent the methylenic group of (II) has an n.m.r. line sufficiently separated from that of the methylenic groups of (IV) to allow one to relate the ratio h_δ/h_γ to the concentration ratio (IV)/(III).

[2] I. N. Nazarov and T. D. Nagibina, *Bull. Acad. Sci. U.S.S.R.*, **1943**, 206.

[3] Leopold and Schacke, D.R.P. 483,823/1929.

[4] E. F. Connolly, *J. Chem. Soc.*, **1944**, 338.

the i.r. spectra (Figure 2) and by the polarographic data.

The polarograms show two waves: the first is attributed to phorone and the second to semiphorone alone or to a semiphorone–mesityl oxide mixture. The symbols j_{I} and j_{II} indicate the ratios between the diffusion currents of these waves and the initial concentration (mmoles/l.) of the components of the solution [(II), (III), (IV), or their mixtures]. At low temperatures (see, *e.g.*, Figure 3) j_{I} and j_{II} reach a finite limit whose value can be used to calculate the concentrations of (I) and (II) in the equilibrium mixture.

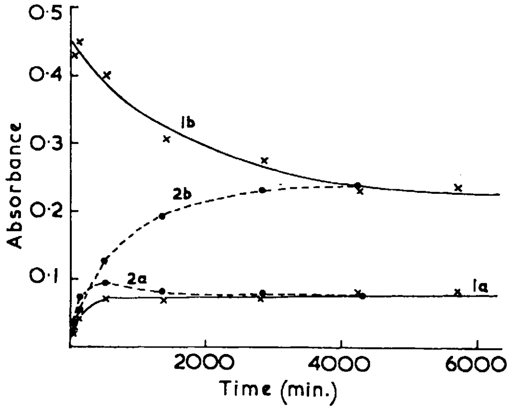

FIGURE 2 Evolution with time of the i.r. absorption band at 6·18 μ (curves 1a and 2a) and of OH band at 2·88 μ (curves 1b and 2b) observed with tetramethyltetrahydro-γ-pyrone (dotted lines) or triacetone dialcohol (solid lines) as starting materials. Times are those at which the reaction was frozen. Reaction medium, 1M-hydrochloride acid at 30°. Each point corresponds to one single experiment; in different experiments the starting concentrations of triacetone dialcohol (×) or tetramethyltetrahydro-γ-pyrone (●) were changed each time. The absorptions reported on the ordinates are referred to a constant weight ratio of extracted products (10 g.) and dioxan (100 g.)

TABLE 1

Progress of reactions (III) $\rightleftharpoons$ (II) $\rightleftharpoons$ (IV) starting from pure (III) and (IV) (catalyst: 1M-hydrochloric acid, 30°)*

Starting compound	Time (min.)	A (II) (%)	A (III) (%)	A (IV) (%)	B (II) (%)	B (III) (%)	B (IV) (%)
(III)	55	5·6	94·4	0	4·0	96·0	0
,,	135	9·4	90·6	0	9·3	90·7	0
,,	510	11·8	80·2	8·0	12·3	76·0	11·7
,,	1355	11·2	62·5	26·3	10·7	62·2	27·1
,,	2835	10·7	52·8	36·5	10·8	53·6	35·6
,,	4275	10·9	54·6	34·5	10·6	52·9	36·5
(IV)	30	2·5	—	—	1·4	2·0	96·6
,,	62	3·6	—	—	2·9	5·1	92·0
,,	105	5·2	—	—	4·5	1·5	94·0
,,	520	9·1	—	—	9·0	13·8	77·2
,,	1420	9·8	—	—	9·7	37·4	52·9
,,	2860	10·5	—	—	9·9	50·6	39·5
,,	4275	10·2	—	—	10·4	53·1	36·6
,,	5710	10·6	—	—	10·5	52·8	36·7

* Compositions are given in weight per cent. In the column under the heading A, (II) % is the semiphorone percentage, polarographically determined; (III) % and (IV) % are the percentages of tetramethyltetrahydro-γ-pyrone and triacetone dialcohol, respectively, calculated by combining the n.m.r. results with the polarographic (II) % value. Under the heading B the data obtained from i.r. measurements only are reported.

In Table 2 equilibrium values of j_{I} and j_{II} are reported for the range 20—52°. Since $j_{\text{I}} \ll j_{\text{II}}$ the dehydration of semiphorone to phorone will be neglected, as said before. At higher temperatures a steady value of j_{II} is no longer reached owing to the occurrence of irreversible processes.

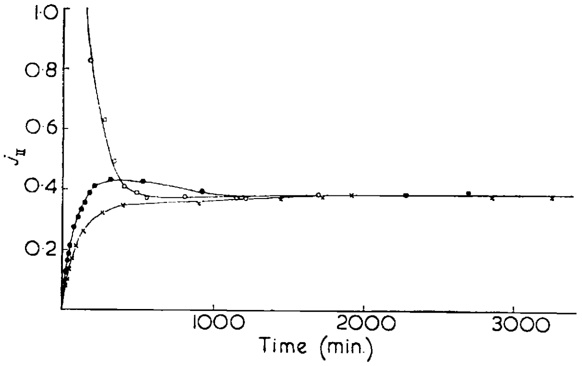

FIGURE 3 Plot of the diffusion currents, j_{II}, referred to 1 mmole of product per litre of solution examined polarographically, against time. Reaction medium, 1M-hydrochloric acid at 30°. Starting materials and initial concentrations: (●) tetramethyltetrahydro-γ-pyrone 29·13 × 10^{-3}M; (×) triacetone dialcohol 9·761 × 10^{-3}M; (○) semiphorone 2·692 × 10^{-3}M. On the abscissæ are reported the times at which the reaction was frozen

TABLE 2

Values of j_{I} and j_{II} for the equilibrium state at various temperatures

Temp.	20·1°	30·0°	44·0°	52·0°
j_{I}	0·007	0·014	0·033	0·051
j_{II}	0·305	0·370	0·525	0·640

Distillation of a solution of (III) in 1M-hydrochloric acid, kept for 4 days at 70°, gave a large amount of acetone, a small amount of diacetone alcohol, and negligible quantities of mesityl oxide and unidentified high-boiling products. In Figure 4 the function j_{II} is compared with that, j_{VII}, obtained in experiments in which the starting material was diacetone alcohol and the product was mesityl oxide. For short reaction times (of the order of few minutes) j_{VII} is smaller than j_{II}. For long reaction times the derivatives $\mathrm{d}j_{\text{II}}/\mathrm{d}t$ and $\mathrm{d}j_{\text{VII}}/\mathrm{d}t$ are negative and $|\mathrm{d}j_{\text{VII}}/\mathrm{d}t| > |\mathrm{d}j_{\text{II}}/\mathrm{d}t|$. These

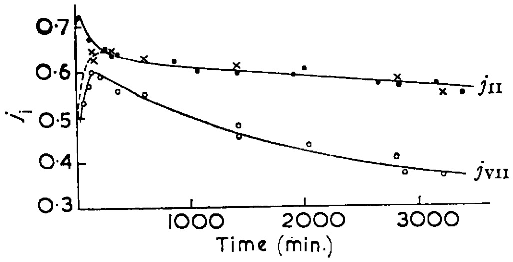

FIGURE 4 Plot of polarographic function j_i at 56·7° against time. Reaction medium, 1M-hydrochloric acid. Starting materials and initial concentrations: (●) tetramethyltetrahydro-γ-pyrone 19·49 × 10^{-3}M; (×) triacetone dialcohol 17·04 × 10^{-3}M; (○) diacetone alcohol 25·85 × 10^{-3}M. On the abscissæ are reported the time at which the reaction was frozen

facts suggest that the irreversible process (II) $\longrightarrow$ (V) + (VI) is slower than the reversible processes (III) $\rightleftharpoons$ (II) $\rightleftharpoons$ (IV). Therefore, since for short reaction times the diffusion current is due to semiphorone alone, polarographic data at high temperatures maintain their validity for the kinetic study of the cyclisation and hydration reactions of this compound.

The interpretation of the polarographic curves also justifies the curve h_α/h_γ, calculated from n.m.r. data, referring to the reactions at 56·7° (Figure 1b). When $h_\beta > h_\alpha$, a constant value of h_α/h_γ indicates that the concentration ratio [(II + (VII)]/(III) is constant.

Equilibria. Values for the concentrations of the single components, determined by i.r., n.m.r., and polarographic techniques, were used to determine the equilibrium constants at 30° for 1M-hydrochloric acid solutions. By transforming the data of Table 1 for the equilibrium state from weight percent to moles percent, values of $K_1 = \text{(III)}/\text{(II)} \simeq 5$ and $K_2 = \text{(IV)}/\text{(II)} \simeq 3$ were obtained. The value of $(K_1 + K_2)$ is in fair agreement with the ratio of the equilibrium concentrations $R = [\text{(III)} + \text{(IV)}]/\text{(II)}$ determined polarographically (Table 3).

Different experimental conditions were used to study the effect of electrolytes and temperature on the equilibria and reaction rates. Since i.r. and n.m.r. determination of the concentrations of (II), (III), and (IV) turned out to be rather laborious and led to inaccurate results (Table 1), at all conditions other than 30° and 1M-acid, the reactions were followed only by polarographic determination of the concentration of (II).

The effect of electrolytes on the ratio of the equilibrium concentrations was examined only with respect to the pseudoconstant R at 30°. The effect of temperature on the equilibrium states was limited to the investigation of the variation of R and R' in the range 20—45° (Table 3).

In Figure 5 the effect of acids (HCl or $HClO_4$) or salts (NaCl or $NaClO_4$) on R is shown: Cl^- ions favour formation of (II), whilst ClO_4^- and Na^+ ions show the opposite effect. These effects were justified by the values of the activity coefficients of (II), (III), and (IV) obtained by means of partition measurements of these compounds between carbon tetrachloride or cyclohexane and an aqueous solution containing known quantities of sodium chloride or perchlorate.

The logarithms of the ratios R and R' vary linearly with the reciprocal of the absolute temperature according the equations:

$$\log R = (1{\cdot}16 \times 10^3/T) - 2{\cdot}95 \qquad (2)$$

$$\log R' = (1{\cdot}66 \times 10^3/T) - 4{\cdot}05 \qquad (3)$$

which were obtained by applying the least-squares method to the data of Table 3. R' values were calculated from the equation

$$R' = \chi_{II} i_{II}(\text{eq})/\chi_I i_I(\text{eq}),$$

and R values from the equation

$$R = \frac{C^* - \chi_{II} i_{II}(\text{eq})}{\chi_{II} i_{II}(\text{eq})} - \frac{\chi_I i_I(\text{eq})}{\chi_{II} i_{II}(\text{eq})},$$

where C^* is the total molar concentration of the compounds present in the solution being examined by polarography, χ_I and χ_{II} are suitable coefficients to transform the diffusion currents of (I) and (II) into their respective molar concentrations, and i_I(eq) and i_{II}(eq) are the diffusion currents of (I) and (II) in the solution at equilibrium. The concentrations of (III) and (IV) ranged from 30 × 10^{-3}M to 9 × 10^{-3}M, and the concentration of (II) from 3 × 10^{-3} to 10^{-3}M. At least six determinations were made at each temperature, in which one of the three compounds, or a mixture of them, was the starting material. 1M-Hydrochloric acid was used as catalyst

TABLE 3

Ratios of the molar equilibrium concentrations,
$R = [\text{(III)} + \text{(IV)}]/\text{(II)}$ and $R' = \text{(II)}/\text{(I)}$,
at various temperatures

Temp. ...	20·1°	30·0°	40·0°	44·0°	45·3°
R	9·47	7·61	5·35	5·03	4·62
R′	43	26	—	16	—

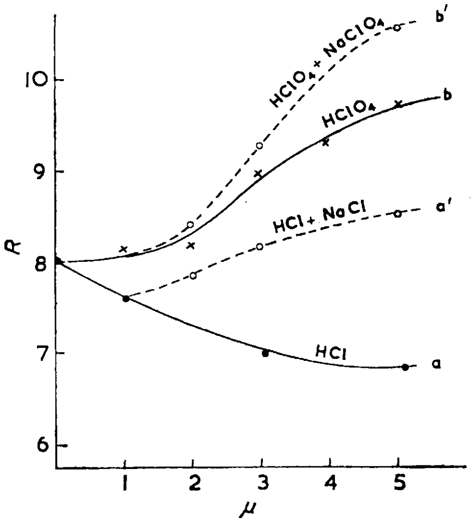

FIGURE 5 Dependence of the pseudoconstant R (at 30°) on the ionic strength of the medium. Curves (a) and (b) refer to acid solutions containing HCl (●) or $HClO_4$ (×); in the case of curves (a′) and (b′), instead, increasing amounts of NaCl or $NaClO_4$ were added to 1M-HCl or 1M-$HClO_4$ solutions, respectively

Values of $\Delta H° = -7{\cdot}6 \pm 0{\cdot}7$ kcal./mole and $\Delta S° = -18{\cdot}5 \pm 2{\cdot}5$ e.u. were obtained from the temperature coefficient of the logarithm of the equilibrium constant R'. Values of $\Delta H_{\text{app}} = -5{\cdot}3 \pm 0{\cdot}4$ kcal./mole and $\Delta S°_{\text{app}} = -13{\cdot}5 \pm 1{\cdot}5$ e.u. were similarly obtained from the change with temperature of the pseudoconstant R.*

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[5] G. Barbensi, " Introduzione Alla Biometria," ed. Vallecchi, Firenze, 1952, p. 220.

* Errors in ΔH were evaluated from the mean-square deviation of the slope, assuming a fiducial limit of 0·95; [5] errors in ΔS from the ratio $\Delta(\Delta H)/298$. The errors in ΔF were negligible compared to those calculated for the enthalpy changes.

The entropy change found for the hydration reaction of phorone to semiphorone ($\Delta S^\circ = -18{\cdot}5$ e.u.) is of the same order of magnitude as that obtained by Bell and McDougall[6] for the hydration of some aldehydes and ketones and by Bakule and Long[7] for the acquisition of one water molecule by cyclohexane-1,2-dione. This change may be logically attributed to a loss of translational entropy by one water molecule. On the other hand, the magnitude of the enthalpy change ($\Delta H^\circ = -7{\cdot}6$ kcal./mole) seems reasonable and comparable to that obtained by Pressman, Brewer, and Lucas[8] for the hydration of mesityl oxide to diacetone alcohol ($\Delta H = -7{\cdot}5$ kcal./mole).

The value of ΔH_{app} relative to reactions (III) $\rightleftharpoons$ (II) $\rightleftharpoons$ (IV) depends on the enthalpy changes in the hydration (ΔH_{hydr}) and in the cyclisation (ΔH_{cycl}) of semiphorone, according to the equation:

$$\Delta H_{\text{app}} = (K_1\,\Delta H_{\text{cycl}} + K_2\,\Delta H_{\text{hydr}})/(K_1 + K_2) \quad (4)$$

K_1 and K_2 being the equilibrium constants of the cyclisation and of the hydration, respectively.

Because of the reasons mentioned above we have only measured K_1 and K_2 at 30°. For calculating acceptable values of ΔH_{cycl} and ΔH_{hydr} the values of K_1 and K_2 should be known at least at four temperatures. However, if the heat of hydration in the reaction (II) + $H_2O \rightleftharpoons$ (IV) is assumed to be equal to the heat of hydration of phorone (which is the same as that of mesityl oxide) a value of ΔH_{cycl} of about $-3{\cdot}9$ kcal./mole and a corresponding ΔS_{cycl} value of about -10 e.u. can be calculated. These values, though of limited meaning because of the way they were calculated, still seem reasonable, with respect to both the sign and the magnitude. The difference between the entropy values of gaseous (II) (131 e.u.) and (III) (116 e.u.), obtained using the tables of group contributions,[9] partly explains the value which we calculated for the entropy change in the isomerisation in solution.

Kinetics and mechanism. In order to calculate the values of the rate constants which characterise the processes represented in reaction (1), the reactions starting from a pure component alone were considered irreversible, as a zero-order approximation, at the limit $t = 0$. Approximate values of the constants were thus obtained from the tangents, at $t = 0$, to the curves $i_{\text{II}} = \text{f}(t)$.

Let I_{II} be the coefficient which connects the diffusion current of component (II) with its concentration ($i_{\text{II}} = I_{\text{II}} \,.\, C_{\text{II}}$) and C^* be the concentration of (III) or (IV) at zero time (concentrations in mmoles/l.), the constants k_{32}° ($C^* = C_{\text{III}}$) and k_{42}° ($C^* = C_{\text{IV}}$) can be evaluated from the ratios:

$$\frac{1}{I_{\text{II}}C^*}\left(\frac{\mathrm{d}i_{\text{II}}}{\mathrm{d}t}\right)_{t\to 0}$$

If the initial component is (II), instead, the values of the sum ($k_{23}^\circ + k_{24}^\circ$) can be evaluated from the ratios:

$$\frac{1}{i_{\text{II}}^\circ}\left(\frac{\mathrm{d}i_{\text{II}}}{\mathrm{d}t}\right)_{t\to 0}$$

where i_{II}° is the diffusion current of (II) at zero time. At some specific acid concentrations (see C_{HX} in Table 4) different experiments were run in which the concentration of the starting material was varied up to ten times.

By applying the differential method to the data obtained in these experiments, the order of reaction was found to be roughly 1 in all cases. Also fairly concordant zero-order approximation values of the rate constants were found.

In order to verify the self-consistency of the values of the group of rate constants corresponding to each C_{HX}, the sums ($k_{23}^\circ + k_{24}^\circ$), listed in Table 4, were first split into their composing terms by means of the following relationships:

$$k_{24}^\circ = (k_{23}^\circ + k_{24}^\circ)\Big/\left[1 + \frac{C_{\text{eq}}}{D_{\text{eq}}}\cdot\frac{k_{32}^\circ}{k_{42}^\circ}\right] \quad (5)$$

which were derived from:

$$\frac{k_{23}}{k_{24}} = \frac{(C_{\text{eq}})}{(D_{\text{eq}})}\cdot\frac{k_{32}}{k_{42}} \quad (6)$$

The rate constants k_{23}°, k_{24}°, k_{32}°, k_{42}° were then introduced into equations:[10]

$$\beta = \frac{k_{42}k_{32}}{\lambda_2\lambda_3} + \frac{(\lambda_2 - k_{42})(\lambda_2 - k_{32})}{\lambda_2(\lambda_2 - \lambda_3)}\mathrm{e}^{-\lambda_2 t} + \frac{(\lambda_3 - k_{32})(k_{42} - \lambda_3)}{\lambda_3(\lambda_2 - \lambda_3)}\mathrm{e}^{-\lambda_3 t}$$

$$\gamma = \frac{k_{42}k_{32}}{\lambda_2\lambda_3} + \frac{k_{32}(k_{42} - \lambda_2)}{\lambda_2(\lambda_2 - \lambda_3)}\mathrm{e}^{-\lambda_2 t} + \frac{k_{32}(\lambda_3 - k_{42})}{\lambda_3(\lambda_2 - \lambda_3)}\mathrm{e}^{-\lambda_3 t} \quad (7)$$

$$\delta = \frac{k_{42}k_{32}}{\lambda_2\lambda_3} + \frac{k_{42}(k_{32} - \lambda_2)}{\lambda_2(\lambda_2 - \lambda_3)}\mathrm{e}^{-\lambda_2 t} + \frac{k_{42}(\lambda_3 - k_{32})}{\lambda_3(\lambda_2 - \lambda_3)}\mathrm{e}^{-\lambda_3 t}$$

where $\lambda_2 = 1/2\,(p + q)$, $\lambda_3 = 1/2\,(p - q)$ and $p = (k_{23} + k_{24} + k_{32} + k_{42})$; $q = [p^2 - 4\,(k_{42}k_{23} + k_{24}k_{32} + k_{42}k_{32})]^{\frac{1}{2}}$ The values of β, γ, and δ were then utilised to evaluate the ratio:

$$C_{\text{II}}/C^* = x_{\text{II}}^\circ\beta + x_{\text{III}}^\circ\gamma + x_{\text{IV}}^\circ\delta \quad (8)$$

where C_{II} is the concentration of (II) at the time t, C^* is the overall concentration of the components, and x_{II}°, x_{III}°, and x_{IV}° are the mole fractions of (II), (III), and (IV) in the original solution.

When compound (I) is initially present, the process (I) $\longrightarrow$ (II) can be regarded as irreversible with fairly

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[6] R. P. Bell and A. O. McDougall, *Trans. Faraday Soc.*, 1960, **56**, 1280.

[7] R. Bakule and F. A. Long, *J. Amer. Chem. Soc.*, 1963, **85**, 2309.

[8] D. Pressman, L. Brewer, and N. J. Lucas, *J. Amer. Chem. Soc.*, 1942, **64**, 1122.

[9] O. A. Hougen, K. M. Watson, and R. A. Ragatz, "Chemical Process Principles," Wiley, New York, 1959, p. 1004.

[10] A. A. Frost and R. G. Pearson, "Kinetics and Mechanism," Wiley, New York, 1961, p. 176.

TABLE 4

Approximate rate constants obtained by the tangent method

C_{HX}	X	k_{32}° (min.$^{-1}$)	k_{42}° (min.$^{-1}$)	$k_{23}^\circ + k_{24}^\circ$ (min.$^{-1}$)
0·01	Cl	$8·44 \times 10^{-6}$	$8·89 \times 10^{-6}$	$6·00 \times 10^{-5}$
0·05	Cl	$3·99 \times 10^{-5}$	$4·18 \times 10^{-5}$	$3·20 \times 10^{-4}$
0·10	ClO_4	$1·11 \times 10^{-4}$	$8·97 \times 10^{-5}$	—
0·16	Cl	$1·58 \times 10^{-4}$	—	$1·11 \times 10^{-3}$
0·20	Cl	—	$1·73 \times 10^{-4}$	—
0·25	ClO_4	$2·59 \times 10^{-4}$	—	—
0·40	Cl	$4·30 \times 10^{-4}$	—	—
0·50	Cl	—	$4·43 \times 10^{-4}$	—
0·63	ClO_4	$7·12 \times 10^{-4}$	—	$4·32 \times 10^{-3}$
1·00	Cl	$1·25 \times 10^{-3}$	$9·14 \times 10^{-4}$	$7·37 \times 10^{-3}$
1·60	ClO_4	$2·26 \times 10^{-3}$	—	$2·47 \times 10^{-2}$
2·00	Cl	—	$2·37 \times 10^{-3}$	—
2·50	Cl	$5·29 \times 10^{-3}$	—	$3·22 \times 10^{-2}$
2·98	ClO_4	$1·00 \times 10^{-2}$	$4·45 \times 10^{-3}$	$8·70 \times 10^{-2}$
2·98	Cl	$8·99 \times 10^{-3}$	$5·36 \times 10^{-3}$	$5·80 \times 10^{-2}$
3·95	Cl	—	$8·51 \times 10^{-3}$	$1·21 \times 10^{-1}$
3·96	ClO_4	$1·56 \times 10^{-2}$	$6·57 \times 10^{-3}$	$1·93 \times 10^{-1}$
5·60	Cl	$4·26 \times 10^{-2}$	—	—
5·96	Cl	—	$2·65 \times 10^{-2}$	—

good approximation, and one more term $x_I^\circ\alpha\beta$ must be added to expression (8). x_I° is the mole fraction of phorone initially present, β has the fore-mentioned meaning and α is the difference $(1 - e^{-k_{12}t})$ in which k_{12} is the rate constant of the reaction (I) $\longrightarrow$ (II). Values of this constant, at different acid concentrations, have been listed.[1]

The formation and the decomposition curves of (II) thus calculated only roughly fit the corresponding experimental curves. Better agreement is obtained by utilising the rate constants evaluated by applying a "trial and error" procedure to triplets of experiments in which, at a fixed acid concentration, (II), (III), and (IV) were used respectively as starting material.

For the various groups of experiments carried out at each C_{HX}, sets of constants (see Table 5) could be established which describe correctly the course of the reactions whatever the starting composition of the solution.

TABLE 5

Cologarithms of the rate constants (in min.$^{-1}$) of the direct and reverse hydration and cyclisation processes of semiphorone at different acid concentrations at 30°

C_{HX}	X	pC_{HX}	H_0	pk_{32}	pk_{42}	pk_{23}	pk_{24}
0·01	Cl	2·00	2·00	4·96	5·00	4·26	4·52
0·05	Cl	1·30	1·30	4·24	4·30	3·54	3·83
0·10	ClO_4	1·00	1·00	3·85	3·91	3·16	3·44
0·16	Cl	0·80	0·77	3·70	3·78	3·01	3·30
0·20	Cl	0·70	0·66	3·64	3·68	2·94	3·23
0·25	ClO_4	0·60	0·55	3·50	3·64	2·80	3·16
0·40	Cl	0·40	0·32	3·30	3·44	2·61	2·98
0·50	Cl	0·30	0·19	3·11	3·22	2·42	2·76
0·63	ClO_4	0·20	0·08	3·05	3·21	2·33	2·73
1·00	Cl	0·00	−0·20	2·84	2·99	2·16	2·52
1·60	ClO_4	−0·20	−0·57	2·55	2·75	1·84	2·27
2·00	Cl	−0·30	−0·69	2·25	2·52	1·59	2·09
2·50	Cl	−0·40	−0·87	2·19	2·41	1·54	1·98
2·98	Cl	−0·47	−1·04	2·00	2·20	1·36	1·78
2·98	ClO_4	−0·47	−1·22	1·94	2·24	1·20	1·72
3·95	Cl	−0·60	−1·38	1·72	2·03	1·09	1·61
3·95	ClO_4	−0·60	−1·68	1·70	2·09	0·93	1·54
5·60	Cl	−0·75	−1·97	1·21	1·64	0·58	1·23
5·96	Cl	−0·775	−2·10	1·11	1·52	0·48	1·12

H_0 values are those given by Paul and Long.[11]

In Figure 6 a typical case is reported where the experimental data are compared with the curves calculated using both the former constants and the final ones.

Since at every acid concentration considered, all three types of calculated curves fit well with the corresponding experimental ones, the values of the rate constants given in Table 5 are proved to be, in our opinion, the correct ones. The reasonable agreement observed between experimental curves obtained in 1M-hydrochloric acid [representing the concentrations of (III) and (IV)] and those calculated with the constants of Table 5 confirms our conclusion (Figure 7).

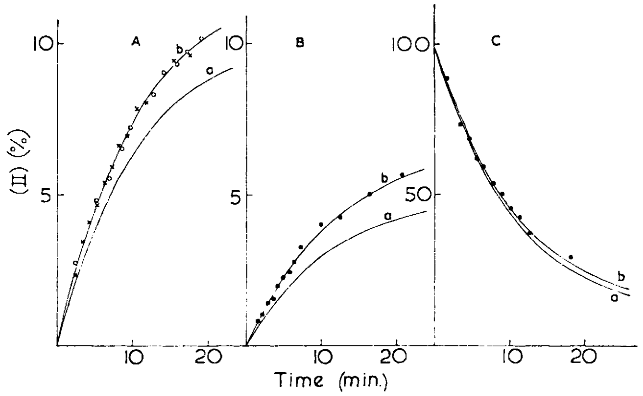

FIGURE 6 Comparison between experimental values (×, ○, and ●) and calculated formation (A and B) and decomposition (C) curves of (II). Temp. 30°; catalyst concentration: $C_{HClO_4} = 2·98$M. Initial concentrations [III] = $2·95 \times 10^{-2}$M (×) and $2·60 \times 10^{-2}$M (○) (A); [IV] = $4·175 \times 10^{-2}$M (●) (B); [II] = $3·25 \times 10^{-3}$M (●) (C). Curves (a) were calculated by utilising the zero-order approximation constants: $k_{32}^\circ = 1·00 \times 10^{-2}$, $k_{42}^\circ = 4·45 \times 10^{-3}$, $k_{23}^\circ = 6·86 \times 10^{-2}$, $k_{24}^\circ = 1·84 \times 10^{-2}$ min.$^{-1}$. Curves (b) were calculated by utilising the final constants: $k_{32} = 1·15 \times 10^{-2}$, $k_{42} = 5·75 \times 10^{-3}$, $k_{23} = 6·38 \times 10^{-2}$, $k_{24} = 1·92 \times 10^{-2}$ min.$^{-1}$.

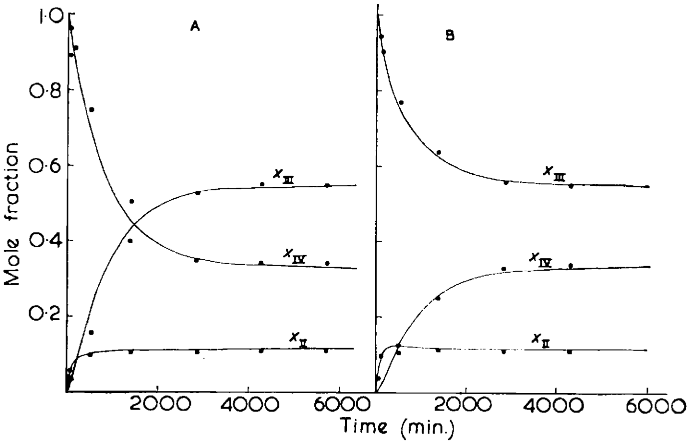

FIGURE 7 Change with time of the concentrations of (II), (III), and (IV) in 1M-hydrochloric acid solution at 30°. The curves were calculated by using the following rate constants: $k_{23} = 6·92 \times 10^{-3}$, $k_{32} = 1·44 \times 10^{-3}$, $k_{24} = 3·02 \times 10^{-3}$, $k_{42} = 1·02 \times 10^{-3}$ min.$^{-1}$. Experimental points refer to i.r. data. Starting materials were triacetone dialcohol (A) and tetramethyltetrahydro-γ-pyrone (B)

Plots of the cologarithms of the values of final rate constants as a function of acid concentration (expressed

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[11] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

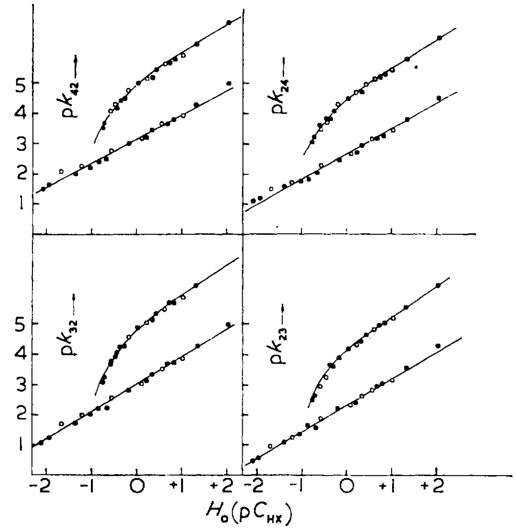


FIGURE 8 Variation of the cologarithms of the rate constants of the direct and reverse hydration (pk_{24} and pk_{42}) and cyclisation (pk_{23} and pk_{32}) processes of semiphorone as a function of the cologarithms of the acid concentration of the medium expressed as H_0 (lower curves) or as pC_{HX} (upper curves). For clarity the upper curves are shifted two logarithmic units upwards. The experiments were carried out in HCl (●) or $HClO_4$ (○) at 30°

as cologarithm of the molar acid concentration or of the Hammet function H_0) are shown in Figure 8.

The pk_{ij} of the single processes are clearly seen to depend linearly upon the acid concentration, when this is expressed in terms of H_0. However, the rate of isomerisation (II) $\rightleftharpoons$ (III) is more sensitive to strong acid catalysis than is the reaction (II) + H_2O $\rightleftharpoons$ (IV). On the contrary, catalysts other than hydronium ion show exactly the opposite influence, as proved by experiments carried out at 30° in H_3PO_4–KH_2PO_4-buffered solutions (Table 6). While the cyclisation is unaffected by the phosphate species, the hydration is strongly catalysed (Figure 9). The dependence of the rate constant k_{42} upon the molar concentration of H_3PO_4 and $H_2PO_4^-$ can be expressed by:

$$k_{42} = 1{\cdot}03 \times 10^{-3}[H^+] + 2{\cdot}9 \times 10^{-4}[H_3PO_4] - 4{\cdot}97 \times 10^{-5}[H_2PO_4^-] \quad (9)$$

The species H_3PO_4 appears to be a catalyst of the hydration (and conversely of the dehydration) slightly less effective than the hydronium ion; the $H_2PO_4^-$ ion, instead, shows a slight negative action. There is a positive salt effect for all processes, but larger for the cyclisation than for the dehydration (Table 7).

In Table 8 values of the rate constants at various temperatures are reported. The parameters of the Arrhenius equation (Table 9) were calculated by applying the least-squares method to the linear relationship:

TABLE 6

Rate constants in H_3PO_4 and KH_2PO_4 solutions * at 30°; $\mu = 0{\cdot}1$

pH†	$[H_3PO_4] \times 10^3$ (moles/l.)	$[H_2PO_4^-] \times 10^3$ (moles/l.)	$[KCl] \times 10^3$ (moles/l.)	$k_{32} \times 10^5$ (min.$^{-1}$)	$k_{23} \times 10^5$ (min.$^{-1}$)	$k_{42} \times 10^5$ (min.$^{-1}$)	$k_{24} \times 10^5$ (min.$^{-1}$)
1·98	9·3	10·2	90	1·00	5·10	1·22	3·73
1·98	51·8	55·5	45	1·08	5·51	2·25	6·88
1·98	94·5	100·7	—	1·10	5·61	3·20	9·79
2·24	8·5	16·6	84	0·59	3·01	0·76	2·33
2·24	26·8	52·2	50	0·60	3·06	1·05	3·21
2·24	52·1	100·3	—	0·58	2·98	1·58	4·85

* H_3PO_4 and $H_2PO_4^-$ concentrations are the molar concentrations in solution calculated as previously described.[1]
† Measured with a pH-meter standardised with HCl–KCl solutions (μ = 0·1) on assuming pH = pC_{HCl}.

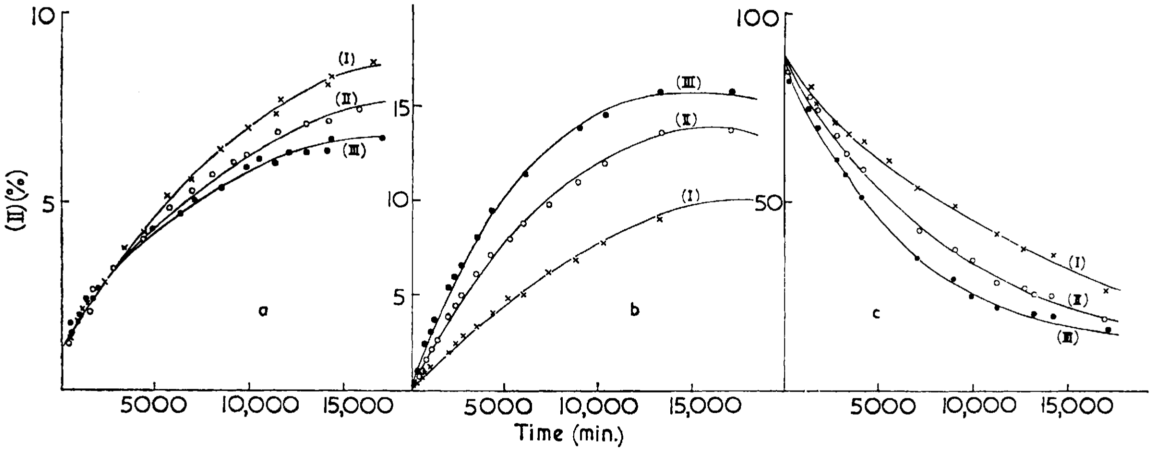


FIGURE 9 Formation (a, b) and decomposition (c) curves of semiphorone in H_3PO_4–KH_2PO_4 solutions at pH = 1·98 and 30°. In the various groups of experiments the starting materials were (a) tetramethyltetrahydro-γ-pyrone (containing 1·1% semiphorone), (b) triacetone dialcohol, and (c) semiphorone (containing 11% phorone). The data refer to solutions of the following composition: (×) H_3PO_4 = 1·95 × 10^{-2}M; KCl = 9 × 10^{-2}M (i). (○) H_3PO_4 = 6·25 × 10^{-2}M; KH_2PO_4 = 4·68 × 10^{-2}M; KCl = 4·5 × 10^{-2}M (ii). (●) H_3PO_4 = 1·052 × 10^{-1}M; KH_2PO_4 = 9·2 × 10^{-2}M (iii)

TABLE 7

Variation of the rate constants (in min.$^{-1}$) with the salt content of the medium (30°; HCl or $HClO_4$ 1M)

C_{NaX} (moles/l.)	X	$k_{42} \times 10^3$	$k_{32} \times 10^3$	$k_{24} \times 10^3$	$k_{23} \times 10^3$
0	Cl	1·0	1·4	3·0	6·9
1	,,	1·7	2·5	5·0	12·2
2	,,	2·2	3·3	6·7	16·8
4	,,	4·0	8·6	12·8	45·7
1	ClO_4	1·5	2·4	4·7	12·6
2	,,	2·1	3·7	7·1	21·6
4	,,	2·9	8·2	11·6	53·4

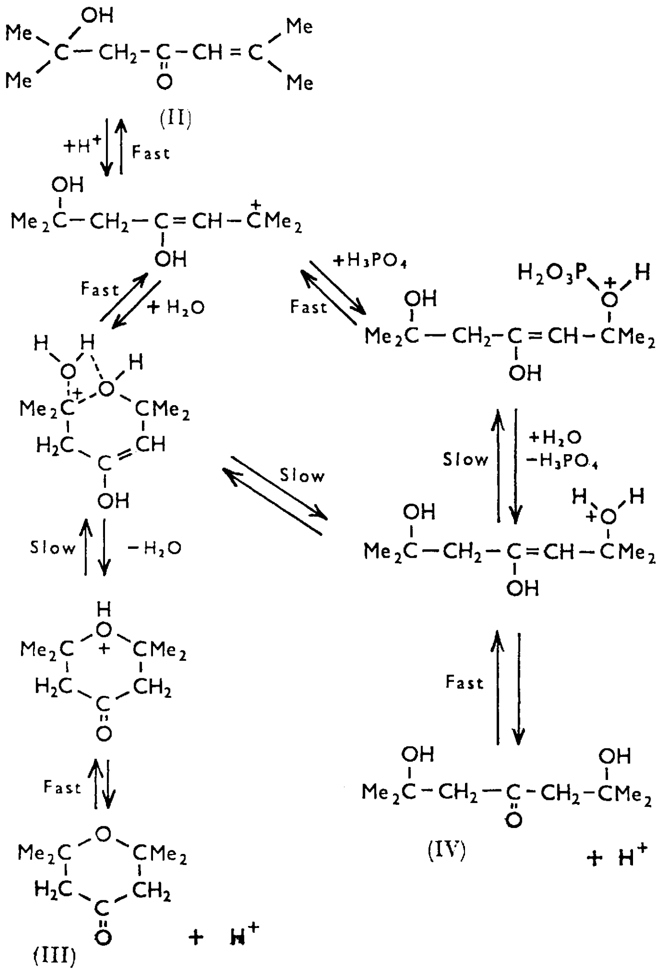
TABLE 8

Rate constants (min.$^{-1}$) (in 1M-HCl) at various temperatures

	Zero-order approximation values			Improved values			
Temp.	$(k_{23}^{\circ} + k_{24}^{\circ}) \times 10^3$ (min.$^{-1}$)	$k_{32}^{\circ} \times 10^4$ (min.$^{-1}$)	$k_{42}^{\circ} \times 10^4$ (min.$^{-1}$)	$k_{23} \times 10^4$ (min.$^{-1}$)	$k_{32} \times 10^4$ (min.$^{-1}$)	$k_{24} \times 10^4$ (min.$^{-1}$)	$k_{42} \times 10^4$ (min.$^{-1}$)
15·6°	1·82	1·33	1·54	10·9	1·68	9·84	1·86
22·9	4·72	3·79	3·97	28·1	5·10	18·8	4·90
30·0	7·37	12·5	9·14	69·2	14·4	30·2	10·2
40·5	28·5	43·9	27·7	204	54·0	65·7	35·5

$\log k_{ij} = f(1/T)$. The activation entropies were calculated by equalising the frequency factor A_{ij} to the expression $\frac{kT}{\boldsymbol{h}} \cdot e^{\Delta S^*/\boldsymbol{R}}$.

The activation energies of the direct processes are quite different from each other; however, the compensation of the entropy effects is such as to make hydration unfavourable (in 1M-HCl), from a kinetic point of view, with respect to cyclisation. An analogous situation is met for the reverse processes, although in this case the differences between the corresponding activation energies are smaller.



Scheme 2

For the kinetics of the system under examination the mechanism shown in Scheme 2 is proposed. The rapid proton attack on the semiphorone carbonyl group is followed by the rapid formation of an intermediate characterised by strong interaction among the carbonium ion, the alcoholic oxygen, and the oxygen of a solvent molecule. This intermediate possibly undergoes a slow rearrangement into the oxonium complex corresponding to tetramethyltetrahydro-γ-pyrone or to triacetone dialcohol. These two oxonium complexes, by rapid elimination of a proton, could give tetramethyltetrahydro-γ-pyrone or triacetone dialcohol, respectively. When phosphoric acid is present, the conjugate acid of semiphorone possibly interacts with both the oxygen of a hydroxyl function of the phosphoric acid molecule and that of a solvent molecule.

TABLE 9

Activation energies and entropies for the hydration and cyclisation reactions of semiphorone (30°; 1M-HCl *)

Process	k_{ij} (min.$^{-1}$)	ΔE_{ij} * (kcal./mole)	A_{ij} (sec.$^{-1}$)	ΔS_{ij} * (e.u.)
(II) $\longrightarrow$ (III)	$6{\cdot}92 \times 10^{-3}$	21·2 ± 2·2	$2{\cdot}1 \times 10^{11}$	−6·7 ± 0·1
(III) $\longrightarrow$ (II)	$1{\cdot}44 \times 10^{-3}$	25·1 ± 2·1	$3{\cdot}1 \times 10^{13}$	+3·2 ± 0·1
(II) + H_2O $\longrightarrow$ (IV)	$3{\cdot}02 \times 10^{-3}$	13·7 ± 1·4	$3{\cdot}7 \times 10^{5}$	−33·1 ± 0·1
(IV) $\longrightarrow$ (II) + H_2O	$1{\cdot}02 \times 10^{-3}$	21·0 ± 2·2	$2{\cdot}4 \times 10^{10}$	−11·1 ± 0·1

* From the values, at different temperatures, of the kinetic constants k_{32}° and k_{42}° obtained by the tangent method, one can calculate: (*a*) for the process (III) $\longrightarrow$ (II): $\Delta E_{32}^* = 25{\cdot}5 \pm 4{\cdot}4$ kcal./mole; $\Delta S_{32}^* = +3{\cdot}9 \pm 0{\cdot}2$ e.u.; (*b*) for the process (IV) $\longrightarrow$ (II) + H_2O: $\Delta E_{42}^* = 20{\cdot}8 \pm 1{\cdot}5$ kcal./mole; $\Delta S_{42}^* = -12{\cdot}1 \pm 0{\cdot}1$ e.u. Errors in the activation energies were calculated from the standard deviation of the slope assuming a 95% probability limit;[5] errors on activation entropies were obtained by multiplying the standard deviation by the factor 2·3 $\boldsymbol{R}$.

The cyclisation requires the formation of a carbonium-ion intermediate, in agreement with Nazarov's proposal.[12] Kinetic data suggest ring formation to be the rate-determining step. This hypothesis is supported by the following considerations: (*a*) a negative entropy change, as observed in the direct reaction, is normal when

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[12] I. N. Nazarov, *Bull. Acad. Sci. U.S.S.R.*, 1948, 107.

a cyclic activated intermediate is formed from a non-cyclic compound;[13] (*b*) the catalytic constants depend linearly on h_0, as found by many authors[14] for monomolecular processes involving a carbonium ion as the intermediate; (*c*) a positive salt effect is in agreement with ionic intermediates; (*d*) there is specific acid catalysis.

As far as the hydration is concerned, the above Scheme justifies the general acid catalysis and the dependence of the rate constants on h_0. General acid catalysis could arise from the possible attack of a phosphoric acid molecule on the carbonium ion. The formation of the cyclic intermediate *via* an intramolecular bond becomes less probable and the reaction leading to the saturated dihydroxy-ketone is favoured. The bimolecular reaction between the ionic substrate and the phosphoric acid molecule is followed by hydrolysis of the compound thus formed. This hydrolysis can proceed by fission of the carbon–oxygen bond, the phosphorus–oxygen bond, or both, as observed by Bunton and co-workers[15] in the acid hydrolysis of monomethylphosphate.

The slight negative catalytic action of $H_2PO_4^-$ ion on the formation of triacetone dialcohol can be explained by its competitive action against both water and phosphoric acid through the formation of a phosphate monoester. The hydrolysis of this ester requires a preliminary protonation leading to that oxonium compound which is instead readily formed when the ionic substrate is directly bonded to a phosphoric acid molecule.

The rate constants of mesityl oxide[16] and phorone[1] hydrations, unlike those of the hydration of semiphorone, show a linear dependence on the mineral acid stoicheiometric concentration rather than on h_0. However, the hydration processes of these three ketones undergo general acid catalysis. Since semiphorone, unlike phorone and mesityl oxide, contains an alcohol group, the difference observed in the dependence of the rate constants on mineral acid concentration is possibly due to this group.

EXPERIMENTAL

Semiphorone and tetramethyltetrahydro-γ-pyrone were prepared by adding phorone to a medium-concentration hydrochloric acid solution: the mixture was then maintained at about 40° for some days with continuous stirring. The organic compounds were extracted with ether, the ether was left to evaporate, and the residue was distilled under reduced pressure. The fraction boiling at 80°/20 mm., which was almost pure tetramethyltetrahydro-γ-pyrone, was collected and further purified by crystallisation. The final product was a colourless liquid with camphor-like odour, m. p. 12·8°, n_D^{20} 1·4432; these data and the i.r. spectrum agree with those given by Connolly[4] and by Craven and Ward.[17] The residue was distilled at 0·5 mm. and the fraction boiling at 56·57° was retained. This was a slightly yellow liquid whose refractive index (n_D^{20} 1·4667) and i.r. spectrum are the same as those reported by Connolly[4] for semiphorone.

Triacetone dialcohol, a crystalline solid, m. p. 56°, was very kindly supplied by Dr. E. C. Craven (Distillers Co. Ltd.) whom we heartily thank. The other compounds used in this research were commercial products of controlled purity.

For polarographic measurements sodium acetate or sodium acetate–sodium hydroxide was added to acidic solutions in order to quench the reactions, giving a pH of about 4. Polarograms were obtained using a Sargent model XXI polarograph. The polarographic cell was kept in a thermostat at 20° and a KCl or NH_4Cl bridge was used to connect the cell to the reference electrode. 0·01% Gelatine was used as a maximum suppressor. The solutions were freed from oxygen by letting high-purity nitrogen pass through them: before arriving at the polarographic cell, the nitrogen passed through a sample of the same solution contained in the cell, kept at 20°. The possibility of the polarographic determination of semiphorone was tested in solutions having the same composition as those obtained after quenching the reactions. Empirical relationships were found for the dependence of the diffusion current on the salt type and concentration.

For i.r. and n.m.r. measurements the samples were prepared by quenching the reactions with Na_2HPO_4. The products were recovered by extraction with ether. After drying, the ether was evaporated and two solutions were made with known quantities of dioxan (i.r.) or of carbon tetrachloride (i.r. and n.m.r.). The i.r. spectra were recorded on a Perkin-Elmer model 137 Infracord spectrometer. Calibration curves for semiphorone and triacetone dialcohol were determined in dioxan or carbon tetrachloride as solvents. The base-line technique, as suggested by Wright,[18] was used to measure the intensities. Sodium chloride window cells were used, 0·05 mm. thick for dioxan solutions and 0·5 mm. for carbon tetrachloride solutions. The absorption of (II)—(IV) mixtures was found to differ from the sum of the absorptions of (II) and (IV) solutions having the same concentrations as the mixed solution. Calling Δ the difference:

$$\Delta = [(A_{\mathrm{OH}}{}^{\circ}{}_{\mathrm{II}}) + (A_{\mathrm{OH}}{}^{\circ})_{\mathrm{IV}}] - (A_{\mathrm{OH}})_{\mathrm{II+IV}} \qquad (10)$$

where $(A_{\mathrm{OH}}{}^{\circ})_{\mathrm{i}}$ are the absorption intensities of pure (II) and (IV) at the same concentration as in the mixture and $(A_{\mathrm{OH}})_{\mathrm{II+IV}}$ the intensities of the mixture, it is possible to draw a family of curves: Δ *vs.* the ratio (II)/(IV), each corresponding to a certain concentration of (IV). In the actual i.r. determination of (II) and (IV) formed in the reaction, an iteration procedure was used: once the percentage of (II) in the mixture has been evaluated (by polarography or the absorption band at 6·18 μ), as a zero-order approximation one may assume:

$$(A_{\mathrm{OH}}{}^{\circ})^{\circ}{}_{\mathrm{IV}} = (A_{\mathrm{OH}})_{\mathrm{II+IV}} - (A_{\mathrm{OH}})_{\mathrm{II}} \qquad (11)$$

where $(A_{\mathrm{OH}})_{\mathrm{II}}$ is the value corresponding, on the calibration curve, to the known (II) concentration and $(A_{\mathrm{OH}})_{\mathrm{II+IV}}$ is the experimental absorption intensity of the mixture. From the i.r. intensity *vs.* concentration curve of (IV) and the value of $(A_{\mathrm{OH}}{}^{\circ})^{\circ}{}_{\mathrm{IV}}$ obtained from equation (11), a zero approximation value of the percentage (IV) in the

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[13] Ref. 10, p. 111.

[14] M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 935.

[15] C. A. Bunton, D. R. Llewellyn, K. C. Oldham, and C. A. Vernon, *J. Chem. Soc.*, 1958, 3574.

[16] R. P. Bell, J. Preston, and R. B. Whitney, *J. Chem. Soc.*, 1962, 1166.

[17] E. C. Craven and W. R. Ward, *J. Appl. Chem.*, 1960, **10**, 18.

[18] N. Wright, *Ind. Eng. Chem. Analyt.*, 1941, **13**, 1.

mixture was evaluated. Then, by the following equation:

$$(A_{\mathrm{OH}}{}^{\circ})_{\mathrm{IV}}' = [(A_{\mathrm{OH}})_{\mathrm{II+IV}} - (A_{\mathrm{OH}})_{\mathrm{II}}] + \Delta^{\circ} \qquad (12)$$

a better value of the concentration of (IV) and a first-approximation Δ′ were obtained. This procedure was repeated to convergence. By independent checks it was found that with this procedure the concentrations of (II) and (IV) in the mixture could be determined to within ±5% of their values, even when (III) was present.

The n.m.r. spectra were recorded by means of a Varian D.P. 60 instrument, with tetramethylsilane as internal standard. As a result of several tests on various mixtures of (II), (III) and (IV) in carbon tetrachloride, where the ratios (II)/(III) and (IV)/(III) were varied from 0·1 to 1 and 0·2 to 4, respectively, the following relations were obtained between the weight ratios of the relevant compounds and the relative height of the peak of our interest: (IV)/(III) = (1·20 ± 0·02) h_{δ}/h_{γ} and (II)/(III) = (2·47 ± 0·16) h_{α}/h_{γ}.

In the measurements of the partition coefficients between carbon tetrachloride or cyclohexane and water solutions, known quantities of (II), (III), or (IV) were put into sealed tubes with known volumes of the two phases and shaken in a Kahn shaker at a speed of 280 oscillations per minute, for 3 hr. The organic phase was then used to determine the concentration of (III) and (IV) and the aqueous phase to determine the concentration of (II), in the former case by i.r. spectroscopy and in the latter by polarography. Salts always produce a " salting-out " effect, however this effect was rather small with sodium perchlorate but much more marked with sodium chloride.

The technique employed for the kinetic study has been described.[1]

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