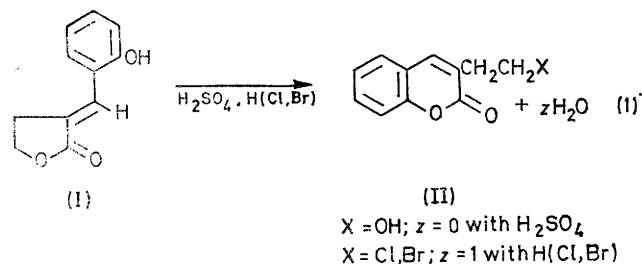


Kinetics of Intramolecular Acylation of 3-(2-Hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one in Concentrated Acids

By Ignazio R. Bellobono,* Bruno Marcandalli, and Luciano Zanderighi, Laboratorio di Dinamica Chimica, Istituto di Chimica Fisica, Università di Milano, 20133 Milan, Italy
Cornelia Parini, Laboratorio Chimica degli Ormoni-C.N.R., 20131 Milan, Italy

Acid-catalysed intramolecular acylation of *trans*-3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one was studied kinetically in 5–11.5M-HCl, 2–8.8M-HBr, and 5–18M-H₂SO₄ solutions at 70–105, 70–120, and 80° respectively. The rate dependence on acidity is discussed on the basis of hydration parameter treatments. A kinetic scheme is proposed, visualizing the transition state as leading from the protonated substrate through its *cis*-form to the products. This scheme is consistent with the hydration parameters and acyl- or alkyl-oxygen fission concerted with acylation, the second being the operative mechanism in halogen acid solutions.

CONDENSATION of aromatic aldehydes in the presence of organic bases with the α -methylene group of γ -lactones has been studied from a preparative point of view.¹⁻³ The base-catalysed reaction between 2-hydroxy-substituted aromatic aldehydes and furan-2(3H)-ones proceeds readily to give coumarin derivatives,⁴ while in the corresponding reaction with 4,5-dihydrofuran-2(3H)-ones, 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-ones are the main products and these can subsequently be converted photochemically⁵ or by acid catalysis⁶ into coumarin derivatives, thus undergoing intramolecular acylation. The reactions of 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one (I) and similar



substrates have recently attracted much attention, and a mechanistic scheme for the photoinduced reaction involving the conversion of *trans*- (I) into *cis*- (I), followed by nucleophilic attack of the phenolic hydroxy-group on the carbon atom of the electrophilic carbonyl group, has been suggested.⁶

We deemed it useful to study the acid-catalysed intramolecular acylation of (I), in order to obtain information on the mechanism.

EXPERIMENTAL

Materials.—Analytically pure reagents and freshly prepared NaOMe were employed to synthesize (I) by the literature method.² Compound (I) was crystallized several times from MeOH, m.p. 184.5–185° (lit.,² 184°), λ_{max} (MeOH) 329.5 and 279 nm (ϵ 10 600 and 15 800 l mol⁻¹ cm⁻¹), ν_{max} 3 230br, 1 715, 1 650, and 1 610 cm⁻¹, δ (CF₃-COCF₃, 0.5D₂O) 2.90 (2 H, OCH₂CH₂C=), 4.28 (2 H, OCH₂CH₂C=), 6.7–7.2 (4 H, aromatic), and 7.75 (1 H, C=CH).

¹ J. Thiele, R. Tischbein, and E. Lossow, *Annalen*, 1901, **319**, 180.

² (a) W. F. Von Ottingen, *J. Amer. Chem. Soc.*, 1930, **52**, 2024; (b) H. Zimmer and J. Rothe, *J. Org. Chem.*, 1959, **24**, 28.

³ H. Kröper, in Houben-Weyl, 'Methoden der Organischen Chemie,' G. Thieme Verlag, Stuttgart, 1963, vol. VI/2, p. 561.

3-(2-Chloroethyl)coumarin (II; X = Cl).—Compound (I) (100 mg) in 37% w/w HCl (30 ml) was maintained during 24 h under oxygen-free nitrogen in a reaction tube at 120°. Excess of acid was removed by evaporation under vacuum and (II; X = Cl) was precipitated quantitatively by addition of H₂O, m.p. 88–89° (from MeOH) (Found: C, 63.35; H, 4.45; Cl, 17.05. Calc. for C₁₁H₉ClO₂: C, 63.3; H, 4.35; Cl, 17.0%), λ_{max} (MeOH) 309 and 277 nm (ϵ 8 900 and 13 800 l mol⁻¹ cm⁻¹), ν_{max} 1 705, 1 635, 1 615, and 1 575 cm⁻¹.

3-(2-Bromoethyl)coumarin (II; X = Br). This was prepared as for (II; X = Cl), with 48% w/w HBr, m.p. (from MeOH-EtOH) 97–98° (lit.,⁶ 99°) (Found: C, 52.1; H, 3.6; Br, 31.5. Calc. for C₁₁H₉BrO₂: C, 52.2; H, 3.6; Br, 31.55%), λ_{max} (MeOH) 313 and 278 nm (ϵ 8 500 and 14 500 l mol⁻¹ cm⁻¹), ν_{max} 1 705, 1 635, 1 615, and 1 580 cm⁻¹.

3-(2-Hydroxyethyl)coumarin (II; X = OH). This was prepared analogously by reaction with 55–65% w/w H₂SO₄ at 80°. The reaction mixture was poured into ice, neutralized in the cold, and extracted with CHCl₃. The extracts were dried and (II; X = OH) was separated by t.l.c. on elution with 100:100:60 (v/v) ethyl acetate-benzene-n-hexane, m.p. 88–89° (from cyclohexane) (Found: C, 69.25; H, 5.25. Calc. for C₁₁H₁₀O₃: C, 69.45; H, 5.3%), λ_{max} (MeOH) 310 and 277 nm (ϵ 8 000 and 12 600 l mol⁻¹ cm⁻¹), ν_{max} 3 520sh, 1 690, 1 635, 1 610, and 1 580 cm⁻¹, δ (CDCl₃) 2.62 (1 H, s, OH), 2.81 (2 H, t, CH₂CH₂OH, J 6 Hz), 3.91 (2 H, t, CH₂CH₂OH, J 6 Hz), 7.2–7.5 (4 H m, aromatic), and 7.6 (1 H, s, C=CH).

N.m.r. spectra were obtained at 60 MHz with tetramethylsilane as internal standard.

Dipole Moment of *trans*-Furanone (I).—The dipole moment μ of (I) was determined in anhydrous dioxan solution at 25.0 ± 0.05°. Dioxan was first refluxed and fractionated (101–103°) over KOH, then carefully dried by a prolonged refluxing over Na, and rectified before use. The dielectric constants *D* of the solvent and solutions were measured with a WTW dipolmeter model DM 01. The variation of refractive indices of solutions relative to that of the solvent was found to be negligible. The solute molar polarization, extrapolated to infinite dilution, was obtained from experimental data by the simplified Guggenheim method.⁷ Parameters for its evaluation are reported in Table I where ΔD is the difference between the dielectric

⁴ (a) D. H. Marrian and P. B. Russell, *J. Chem. Soc.*, 1940, 753; (b) D. H. Marrian, P. B. Russell, and A. R. Todd, *Biochem. J.*, 1949, **45**, 533.

⁵ H. Zimmer, F. Haupter, J. Rothe, W. E. J. Schrof, and R. Walter, *Z. Naturforsch.*, 1963, **18b**, 165.

⁶ H. Zimmer, F. Haupter, S. P. Kharidia, H. Pauling, R. G. Gailey, T. Pampalone, T. C. Purcell, and R. Walter, *Tetrahedron Letters*, 1968, 5435.

⁷ E. A. Guggenheim, *Trans. Faraday Soc.*, 1949, **45**, 714.

constants of solutions and that of the solvent, and w_2 the weight fractions of (I). The experimental dipole moment

$10^5 w_2$	124.6	342.7	458.7	577
$10^5 \Delta D$	2 236	6 258	8 211	11 000

$d\Delta D/dw_2$ 18.841; μ 5.42 \pm 0.03 D.

may be favourably compared with that calculated (μ 5.63 D) for *trans*- (I) in benzene solution by means of vector composition analysis, using the values of dipole moments of γ -butyrolactone (4.12 D⁸), styrene (0.12 D⁹), and hydroxy-group (1.45 D⁹). The stereochemical identification of (I) was thus ascertained.

Kinetic Procedure.—5–7 $\times 10^{-4}$ M Solutions of (I) in analytically pure acid were deoxygenated by oxygen-free nitrogen. Aliquot portions of the reaction solution were placed in nitrogen-filled tubes equipped with pressure plugs. The reaction was initiated by immersing the tubes in a constant temperature bath and was stopped, when desired, by quenching. Spectrophotometric analysis was carried out, after appropriate dilution with H₂O. Pseudo-first-order equations were employed to obtain kinetic coefficients from absorption data at four wavelengths in the range 325–340 nm. Mean values of pseudo-first-order kinetic coefficients of the runs are reported in Tables 2–4. The errors are reported as standard deviations.

Acidity Functions.—The effect of temperature on the Hammett acidity function H_0 for aqueous sulphuric acid was evaluated from literature data.¹⁰ A mean $\Delta H_0/\Delta T$ value¹¹ (0.0032 K⁻¹) was employed and extrapolated beyond the highest values of concentrations (6.5M) and temperature (80°) reported,¹¹ to account for the temperature variation of H_0 at 25°,¹² for 5–12M-HCl solutions. H_0 Values of 2–8.8M-HBr solutions as a function of temperature were obtained from H_0 at 25°¹³ and the same value of $\Delta H_0/\Delta T$ as that used for HCl solutions. Concentrations reported in Tables 2–4 are at 25°; they were corrected, when needed, for linear free energy relationships by taking into appropriate account thermal expansion of solutions.

RESULTS AND DISCUSSION

Intramolecular acylation of *trans*- (I), which closely followed the stoichiometry of reaction (1), was studied in H₂SO₄, HCl, or HBr solutions. The resulting product was found to be 3-(2-hydroxyethyl)coumarin (II; X = OH) for the reaction in aqueous and concentrated H₂SO₄, or 3-(2-halogenoethyl)coumarin (II; X = Cl or Br) for the corresponding reaction in the halogen acid solutions. The kinetics of reaction (I) were examined by spectrophotometric analysis of (I). Pseudo-first-order kinetic coefficients k are reported in Tables 2–4 for the reaction in H₂SO₄, HCl, and HBr solutions respectively.

The rate dependence on the Hammett acidity function H_0 , for the temperatures at which kinetic coefficients k were evaluated, is shown graphically in Figure 1 for the reaction catalysed by H₂SO₄ and in Figure 2 for the reaction with HCl and HBr. It is apparent that for the reaction with the halogen acids rate profiles are linear

⁸ R. J. Marsen and L. E. Sutton, *J. Chem. Soc.*, 1936, 1383.

⁹ J. W. Smith, 'Electric Dipole Moments,' Butterworths, London, 1955, pp. 96, 222.

¹⁰ C. D. Johnson, A. R. Katritzky, and S. A. Shapiro, *J. Amer. Chem. Soc.*, 1969, **91**, 6654.

TABLE 2

Pseudo-first-order rate constants k and standard deviations for the intramolecular acylation of 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one, catalysed by H₂SO₄ at 80°

[H ₂ SO ₄]/M	$10^5 k/s^{-1}$	[H ₂ SO ₄]/M	$10^5 k/s^{-1}$
5.00	0.335 \pm 0.005	11.60	38.5 \pm 0.9
6.25	1.18 \pm 0.03	11.73	20.6 \pm 0.9
7.65	2.80 \pm 0.06	12.55	5.19 \pm 0.25
8.60	6.85 \pm 0.05	12.77	5.62 \pm 0.12
8.83	12.0 \pm 0.35	13.97	3.75 \pm 0.14
8.97	15.2 \pm 0.31	14.25	3.41 \pm 0.10
9.95	28.5 \pm 0.8	14.75	3.66 \pm 0.02
10.15	26.2 \pm 0.4	15.80	2.17 \pm 0.10
11.42	34.9 \pm 3.3	16.90	0.971 \pm 0.011
11.45	27.5 \pm 2.8	17.65	0.708 \pm 0.028

TABLE 3

Pseudo-first-order rate constants k and standard deviations for the intramolecular acylation of 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one, by reaction with aqueous HCl, at various temperatures

70°				
[HCl]/M	$10^5 k/s^{-1}$	8.88	10.25	11.75
		2.22	6.36	26.2
		\pm 0.03	\pm 0.16	\pm 0.02
80°				
[HCl]/M	$10^5 k/s^{-1}$	4.99	7.48	9.41
		0.275	2.08	10.4
		\pm 0.019	\pm 0.98	\pm 1.3
97°				
[HCl]/M	$10^4 k/s^{-1}$	4.95	6.10	8.05
		0.121	1.09	2.11
		\pm 0.059	\pm 0.08	\pm 0.14
105°				
[HCl]/M	$10^4 k/s^{-1}$	4.96	6.28	8.90
		0.144	0.819	6.10
		\pm 0.005	\pm 0.049	\pm 0.70

TABLE 4

Pseudo-first-order rate constants k and standard deviations for the intramolecular acylation of 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one by reaction with aqueous HBr at various temperatures

70°					
[HBr]/M	$10^4 k/s^{-1}$	8.76			
		1.04 \pm 0.02			
80°					
[HBr]/M	$10^4 k/s^{-1}$	8.61			
		3.15 \pm 0.09			
120°					
[HBr]/M	$10^4 k/s^{-1}$	2.05	2.46	4.06	6.75
		0.258	0.385	1.01	12.4
		\pm 0.048	\pm 0.016	\pm 0.04	\pm 1.6
					14.1
					\pm 0.6

with slopes ($\log k/ - H_0$) near unity up to the highest concentration of the aqueous acids. Similar behaviour is exhibited by sulphuric acid solutions up to H_0 ca. -4.5, but after an initial steady rate increase of $\log k$ with increase of acidity, Figure 1 is characterized by a local maximum (at ca. 10.5–11.5M-H₂SO₄), followed by a rapid and then smoother rate decrease in the more

¹¹ A. I. Gel'bshtein, G. G. Shcheglova, and M. I. Temkin (a) *Doklady Akad. Nauk S.S.S.R.*, 1956, **107**, 108; (b) *Zhur. neorg. Khim.*, 1956, **1**, 282.

¹² M. A. Paul and F. A. Long, *Chem. Rev.*, 1957, **57**, 1.

¹³ C. H. Rochester, 'Acidity Functions,' Academic Press, London-New York, 1970, p. 40.

concentrated acid solutions. The Bunnett¹⁴ and Yates¹⁵⁻¹⁷ hydration parameter treatments of kinetic data are illustrated in Figure 3 for the reaction in H₂SO₄-H₂O solutions at 80°. For the plots of Figure 3 the water activity ($a_{\text{H}_2\text{O}}$) values at 80° were evaluated by assuming that the correlation $H_0/a_{\text{H}_2\text{O}}$ ^{18,19} was temperature independent. For the Yates treatment of kinetic data, the function $0.62H_0$, considered to be a good approximation of the ionization behaviour of esters,¹⁷

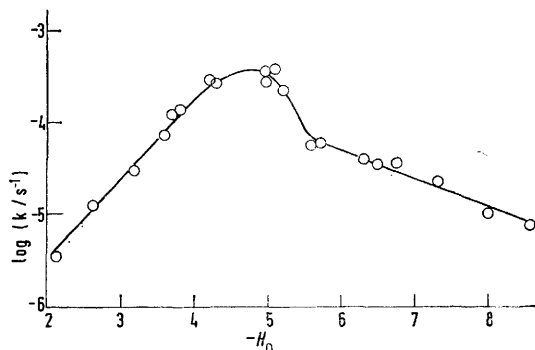


FIGURE 1 Rate constants (k) versus acidity dependence for the intramolecular acylation of 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one in H₂SO₄-H₂O solutions at 80°

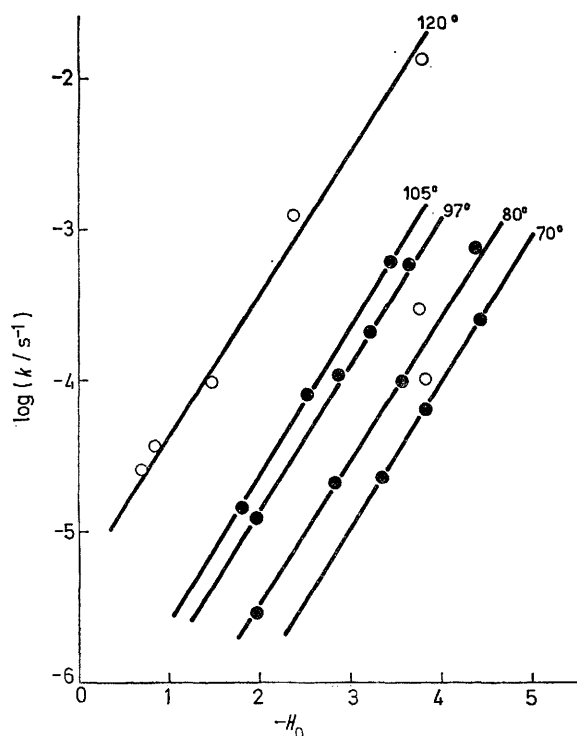


FIGURE 2 Rate constants (k) versus acidity dependence for the intramolecular acylation of 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one in HCl-H₂O (●) and in HBr-H₂O (○) solutions at various temperatures

was used as the acidity function appropriate to the substrate under examination. Both types of treatment

¹⁴ J. F. Bunnett, *J. Amer. Chem. Soc.*, 1961, **83**, 4956, 4968, 4977, 4978.

¹⁵ K. Yates and J. B. Stevens, *Canad. J. Chem.*, 1965, **43**, 529.

¹⁶ K. Yates and J. C. Riordan, *Canad. J. Chem.*, 1965, **43**, 2328.

¹⁷ K. Yates, *Accounts Chem. Res.*, 1971, **4**, 136.

show two linear regions and a sharp break for reaction (1) in H₂SO₄-H₂O solutions. The values of Bunnett (w),

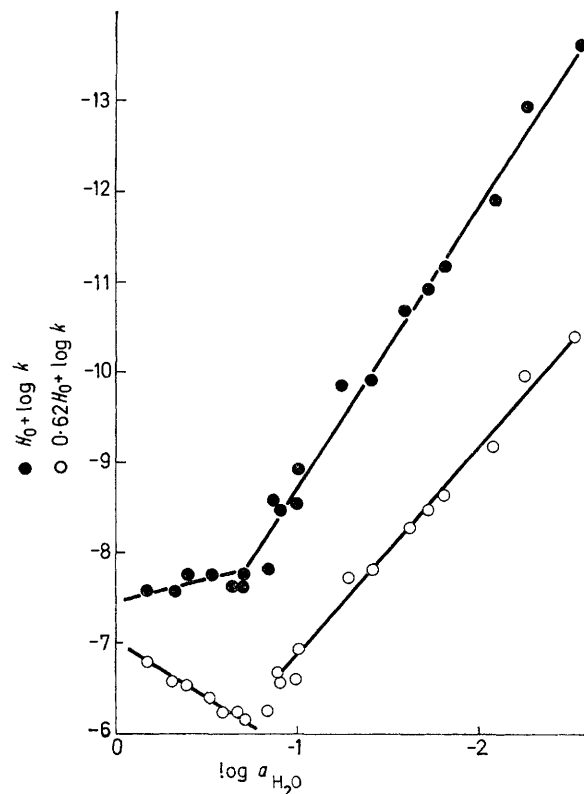


FIGURE 3 Plots to obtain w (●) and r (○) hydration parameters for the intramolecular acylation of 3-(2-hydroxybenzylidene)-4,5-dihydrofuran-2(3H)-one in H₂SO₄-H₂O solutions at 80°

Yates (r), as well as those of ϕ ²⁰ hydration parameters for reaction (1) catalysed by H₂SO₄ are reported in Table 5, together with the values for reaction (1) with the halogen acids.

TABLE 5

w , ϕ , and r Parameters for reaction (1) in concentrated acids				
Acid	Temp. (°C)	w	ϕ	r
5-11.5M-HCl	80	~0	~0	-2.0
5-9M-HCl	97	~0	~0	-2.0
5-9M-HCl	105	~0	~0	-2.0
5-10M-H ₂ SO ₄	80	0.5 ± 0.1	~ 0.08	-1.2 ± 0.1
12-18M-H ₂ SO ₄	80	3.3 ± 0.2	1.5 ± 0.1	2.3 ± 0.1

The theoretical interpretation of the slopes of linear free energy relationships for acid catalysis presents many difficulties inherent in the approximations involved. Nonetheless, if for negative r slopes the general interpretation can be given¹⁷ that transition states are on the average less hydrated than the starting protonated substrate, then all values of Table 5 relative to reaction (1) both with H(Cl,Br) and H₂SO₄ (but for this latter at concentrations less than that of the maximum on the

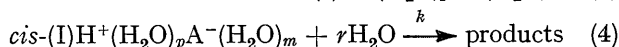
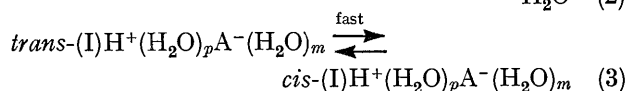
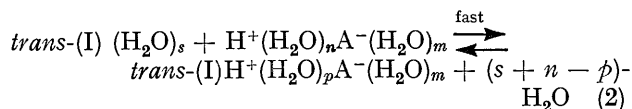
¹⁸ W. F. Giaque, E. W. Hornung, J. E. Kunzler, and T. R. Rubin, *J. Amer. Chem. Soc.*, 1960, **82**, 62.

¹⁹ K. Yates and H. Wai, *J. Amer. Chem. Soc.*, 1964, **86**, 5408.

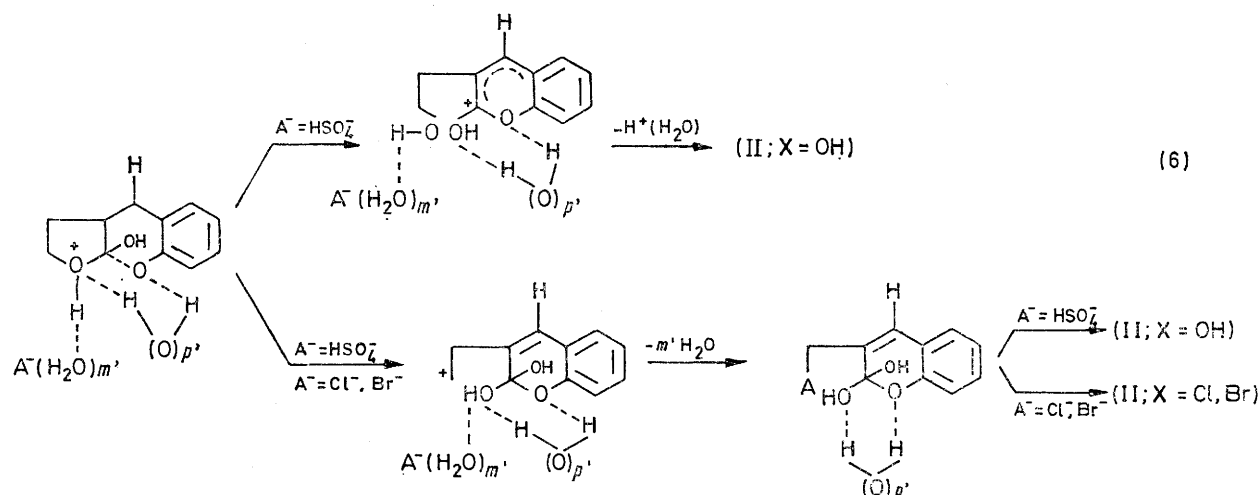
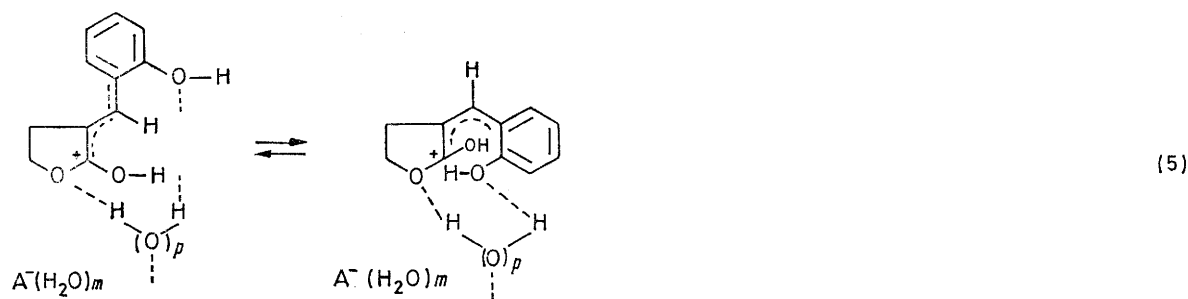
²⁰ J. F. Bunnett and F. P. Olsen, *Canad. J. Chem.*, 1966, **44**, 1917.

rate profile of Figure 1) point to the same conclusion. Water is not 'consumed' in the rate-determining step: on the contrary, a desolvation is observed, particularly with the halogen acids. This is not unreasonable, both because counterions Cl^- and Br^- are certainly more solvated than HSO_4^- or SO_4^{2-} , and because the presence of nucleophilic ions is necessary in going from the transition state to the coumarin.

Reactions (2)—(4) should be taken into account.



The transition state may be visualized as being formed by the protonated substrate in the *cis*-form {derived



from the *trans* [equation (5)] and leading by equation (6) to the products, with $m' + p' = m + p + r$.

Some kind of pre-equilibrium may be considered between the protonated *trans*- and *cis*-forms, both equilibria (2) and (3) being displaced to the left under the experimental conditions, and established more rapidly than reaction (4), the rate of which was measured. That

this must be the case, and in any case that the transformation of the *trans*- into the *cis*-form, which is equally acid-catalysed, cannot represent the slow step for the present investigation, was demonstrated experimentally by the fact that *cis*-(I), isolated photochemically,²¹ was thermally unstable towards isomerization but not towards cyclization, and that it could be converted into (II; X = OH, Cl, or Br) by acid catalysis, at the same rate at which *trans*-(I) was found to react. Thus the identity of the slow step [reaction (4)] is shown when starting with either geometrical isomer.

The effect of nucleophilic anion participation in the reaction with $\text{H}(\text{Cl}, \text{Br})$ stems experimentally from the fact that pseudo-first-order rate coefficients measured with 48% w/w HBr at 70 and 80° are slightly but appreciably higher than those at the same temperature and corresponding acidity function for the reaction with HCl (cf. Figure 2). The difference seems to be significant beyond the uncertainty of H_0 variation with temperature for HBr solutions, which was assumed to be the same as

that for HCl solutions. A conclusion along the same lines may be drawn from the activation parameters of reaction (1), which can be calculated for some reference acidity functions by interpolating the lines of Figure 2. Results of this evaluation are reported in Table 6.

²¹ I. R. Bellobono, L. Zanderighi, S. Omarini, B. Marcandalli, and C. Parini, following paper.

Although the ΔS^* values in Table 6 are based on pseudo-first-order coefficients, dependent on acidity, comparison between the two sets shows the influence of halide ion on rate.

In the H(Cl,Br) solutions nucleophilic anion desolvation, which is a prerequisite to obtain (II; X = Cl,Br), and probably cation desolvation too, represent the main hydration effects. In H₂SO₄ solutions there is only cation desolvation in the transition state at concentrations $< ca. 11M$ (the r parameter indicates $p' \sim p - 1$, if $m' \sim m$), and the proton transfer role of water in equation (6) is played by solvating and/or hydrogen

sulphate anion as nucleophiles) and acyl-oxygen fission should be considered on principle. However, the only slightly lower rate coefficients for H₂SO₄ solutions, as compared with those for halogen acid solutions at the same acidity function values, should rule out a nucleophilic role for water. Competition between nucleophilic attack by the anion of the acid and water in the halogen acid solutions, given the measured values of rate constants, should yield a mixture of (II; X = OH) and (II; X = Cl,Br): this was not observed experimentally. Furthermore, on the basis of the nucleophilicities²² of H₂O, Cl⁻, and Br⁻, a greater effect on rate

TABLE 6
Rate coefficients and activation parameters of reaction (1) at some reference acidity function values

$-H_0$	log (k/s^{-1}) at			105°	120°	$\Delta E^*/kcal\ mol^{-1}$	log(A/s^{-1})	$\Delta S^*/cal\ mol^{-1}\ K^{-1}$ at 360.7 K
	70°	80°	97°					
				HCl solutions				
1.80	-6.14	-5.66	-5.04	-4.82		22.4 ± 0.2	8.17 ± 0.15	-23.5
2.80	-5.17	-4.72	-4.08	-3.85		22.7 ± 0.2	9.29 ± 0.16	-18.4
3.80	-4.22	-3.76	-3.11	-2.88		22.4 ± 0.3	10.11 ± 0.22	-14.6
				HBr solutions				
3.80	-3.97	-3.48			-1.74	28.2 ± 0.5	14.0 ± 0.4	+2.97

bonding water molecules already present in the protonated substrate. When water activity is decreased below 10^{-1} and the protonated substrate becomes increasingly less solvated, the solvation requirements of the transition state are clearly shown by hydration parameters, and proton transfer by water molecules becomes kinetically evident as a controlling factor. The break in the rate profile of Figure 3 would thus be suggestive of the change in hydration parameters, as indicated particularly by r values, when increasing the H₂SO₄ concentration, the decrease in rate beyond the maximum of Figure 1 being due to the decreasing availability of water.

In the presence of halide ions, alkyl-oxygen fission concerted with intramolecular acylation seems to be the most reasonable reaction path. In H₂SO₄ solutions, both the possibilities of alkyl-oxygen (water or hydrogen

would be expected for H₂O than that observed. The nucleophilic attack by hydrogen sulphate (or possibly sulphate) anion, followed by rapid hydrolysis, under the reaction conditions is, on the contrary, compatible both with observed rate constants and with the orders of nucleophilic strength. The difference of 1 between the numbers of hydrogen-bonded water molecules of the protonated *cis*-substrate (5) and the transition state (6) is compatible with the suggested geometrical configuration. Moreover, if $m = m' = 1$ and $p' = 1$ is assumed, for instance, in equations (3)–(6), then all values of hydration parameters of Table 5 are perfectly consistent with the proposed mechanism.

[4/2280 Received, 4th November, 1974]

²² C. G. Swain and C. B. Scott, *J. Amer. Chem. Soc.*, 1953, **75**, 141.