Organic Reactions in Melts and Solids. Part IX.[1] Thermogravimetric Studies of Reactions between Acetanilide and Aromatic Monocarboxylic Acids

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Isothermal thermogravimetric analysis was used to follow the transacylation reactions in melts of acetanilide with 3,5-dinitrobenzoic acid, 1-naphthoic acid, and 4-methoxybenzoic acid. Reactions were carried out at 106 and 110° with anhydrous aluminium chloride as catalyst. They were found to be of the second order (first order in acetanilide and in the acid). The correlations of rate coefficients with acid strengths and with the concentrations of reactants and catalyst were studied.

STUDIES of reactions in melts and solids have shown [2-4] that reversible transacylation reactions occur between carboxylic acids and amides when they are melted together. Often the presence of Lewis acid catalysts is necessary. The reactions occur in melts with neat materials but not in solution [2] and they are therefore controlled by the special conditions prevailing in melts, such as the lack of solvation of reactants, changes in polarity of the medium during the reaction,[3] changes in sample volume and hence in the concentrations of reactants,[3,5] and perhaps other factors which are related to reactions of solventless or frozen systems.[6,7] However, a number of kinetic studies of reactions in melts have been reported in spite of these difficulties.[3,6-9] In a previous Part [3] the reactions of acylanilines with phthalic acid have been investigated. Rate measurements were possible since the reactions proceeded irreversibly. The reactions of carboxylic acids with diacylanilines have also been studied.[1] In these cases the reactions were followed by analysing samples at predetermined reaction times. In the present work we have followed the transacylations continuously, by use of isothermal thermogravimetric analysis (t.g.a.). The reversible reactions of aromatic monocarboxylic acids such as 3,5-dinitrobenzoic acid, 4-methoxybenzoic acid, and 1-naphthoic acid with acetanilide, can be studied by t.g.a., as one product, acetic acid, volatilises under the reaction conditions. Although the technique of t.g.a. has been available for some time,[10] its applications to problems in organic chemistry have been few and it was one of our objectives to test its potential usefulness as a tool for following organic reactions in melts and solids.

EXPERIMENTAL

Materials.—Acetanilide and the aromatic acids were purified commercial products. The aluminium chloride (Hopkin and Williams) contained sulphate (0·01% max.) and iron (0·05% max.).

3,5-Dinitrobenzanilide [11] (IIIa), 1-naphthanilide [12] (IIIb) and 4-methoxybenzanilide [13] (IIIc) were prepared by Schotten–Baumann reactions between the corresponding amine and the acid chloride. They were characterized as follows: (IIIa), m.p. 232°, τ 0·3br (1H, s, NH), 1·3 (1H, d, *J* 3 Hz, *p*-ArH), 1·4 (2H, d, *J* 3 Hz, *o*-ArH), and 2·5—3·6 (5H, m, Ph); (IIIb), m.p. 161°, τ 1·9—3·2 (m, ArH) and 7·5br (1H, s, NH), $\nu_{max.}$ 3300m, 1650vs, 1600m, 1530m, 1500m, 1470vs, 1380s, 1320m, 1260m, 1160w,

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1080w, 780s, 770m, 745s, and 690s cm^{-1}; and (IIIc), m.p. 171°, τ 2·4 (d) and 3·4 (d, J 4 Hz) (*o*- and *m*-ArH), 2·5—3·2 (5H, m, Ph), and 6·47 (3H, s, OMe), $\nu_{\text{max.}}$ 3350m, 1660vs, 1600s, 1535m, 1470vs, 1380s, 1330w, 1245m, 1185m, 1105w, 1030w, 850s, 762w, 750s, and 695s cm^{-1}.

T.l.c.—T.l.c. was carried out on Kieselgel G (*ca.* 250 µm thick). The R_F values were as follows: reaction of (I) with (IIa) [n-hexane–acetone–chloroform, 16 : 3 : 1 (v/v)], R_F (IIa) 0·05, (I) 0·25, and (IIIa) 0·49 [(IIIa) from an independent synthesis 0·49]; reaction of (I) with (IIb) (hexane–acetone–chloroform, 7 : 2 : 2), R_F (IIb) 0·35, (I) 0·28, and (IIIb) 0·54 (0·54); and reaction of (I) with (IIc) (hexane–acetone–chloroform, 7 : 2 : 5), R_F (IIc) 0·14, (I) 0·22, and (IIIc) 0·28 (0·28).

Instrumentation.—N.m.r. spectra were determined for solutions in hexadeuterioacetone at 25° with a Varian T-60 spectrometer (tetramethylsilane as standard). I.r. spectra were determined with a Perkin-Elmer 337 spectrophotometer. Titrations of acetic acid were carried out potentiometrically with a titrator type TTTlc (Radiometer Copenhagen), using 0·1N-sodium hydroxide solutions.

Kinetic Measurements.—T.g.a. measurements (Figure 1) were carried out with a Cahn RG electrobalance of the 'null-point-balance' type, enclosed in a sealed glass tube. The sample holder consisted of a cylindrical (15 × 5 mm diam.) crucible made of gold, suspended on a long wire inside a 1·5 in diam. glass tube which could be immersed in a cylindrical furnace which at 100° had the accuracy of ±0·5°. Weight changes were continuously recorded with a 'Speedomax H' Leeds and Northrup recorder. A thermometer was suspended beside the sample to measure its temperature.

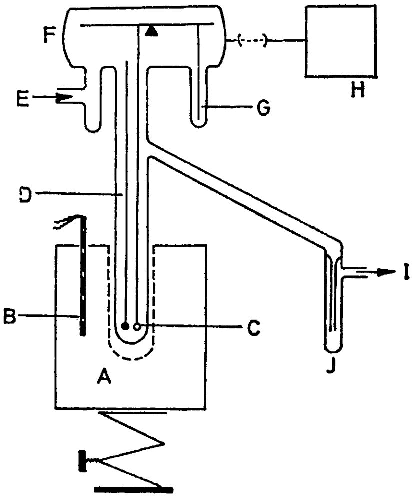

FIGURE 1 A, furnace; B, thermocouple; C, sample; D, thermometer; E, inlet for inert gas; F, Cahn RG electrobalance; G, static weight; H, recorder calibration, recorder control, and recorder; I, outlet for inert gas; J, cold trap

A standard sample contained 70—250 mg of material. A stream of dry nitrogen was passed over the sample for 40 min until the weight became constant and the sample was then immersed in the hot zone of the oven. All reactions were carried out under a stream of dry nitrogen which removed any vapour of acetic acid formed, and which was passed through an acetone–dry ice trap where the acetic acid was quantitatively collected. In all measurements, 10 min were allowed for samples to reach the appropriate reaction temperature.

In order to verify that any acetic acid formed was immediately vaporised, and that the weight loss conformed with acetic acid formation, a typical mixture, consisting of acetanilide, 4-methoxybenzoic acid, and aluminium chloride (molar ratio 4 : 1 : 0·5) (92 mg), was mixed with acetic acid (20 mg) and treated as above. During the first 40 min at room temperature acetic acid (5 mg) was collected from the gas stream. During the first 10 min of heating to 107°, an additional 7·5 mg was collected and within another 10 min at 107° a further 8 mg was obtained. The excess may be a reaction product.

The quantity of acetic acid obtained from reactions of acetanilide with all three acids as determined by titration, was in agreement with the weight loss (Table 1).

Reaction Mixtures.—Mixtures of acetanilide with an aromatic acid contained at least a two-fold (Table 2, run 8) molar excess of amide. With excess of acid, effervescence occurred upon heating which caused unmeasurable changes in the densities of the mixtures. Mixtures having a four-fold excess of amide usually had the lowest m.p.s and hence were used for preference. Most of the reaction mixtures melted at 107° or 109° within 10 min, but in some cases melting was incomplete.

Reproducibility of Results.—Table 3 shows results obtained independently from two separately prepared mixtures [(MI) and (MII)] of acetanilide, 4-methoxybenzoic acid (IIc) or 1-naphthoic acid (IIb), and aluminium chloride in the molar ratio of 4 : 1 : 0·5. The densities of the mixtures were 1·126 and 1·107 ± 0·025 g cm^{-3}, respectively. Concentrations of the reactants were 5·92, 1·48, and 0·735 mol l^{-1} for the reaction with the acid (IIc), and 5·68, 1·42, and 0·71 for the reaction with the acid (IIb). In some cases a mixture was melted by heating for 30—60 s at 130°, cooled until solid, and only then caused to react, to check whether rates differed from those obtained from heterogeneous powdered samples.

Calculation.—Rate constants were determined from the second-order rate equation $kt = 1/(b - a) \ln [a(b - x)/b(a - x)]$, where b and a are initial molar concentrations of the amide and acid, respectively and $b - x$ and $a - x$ are the concentrations at time t. These concentrations were calculated from the measured densities of the molten mixtures, which were determined as previously.[3] The value of x was determined from the yield of acetic acid, *i.e.* (weight loss)/(sample volume × 60). Calculations were carried out with the aid of a computer program and straight lines were computed for $\ln[a(b - x)/b(a - x)]$ against t. The best fit for a straight line was checked by a standard mean squares calculation. The correlation coefficient was in all cases $>0·9990$. The intercept with the y axis always had a small positive value (Table 4). This was due to excessive weight loss during the first 10 min (dotted lines in Figure 2) of the measurements and was probably caused by the presence of traces of humidity or other volatile residues in the sample. The first 10 min were therefore neglected and the value of intercept with the y axis was subtracted from the values of $\ln[a(b - x)/b(a - x)]$ before the rate coefficients were calculated. The reactions were followed continuously, but for the sake of calculation, six (or more) points were chosen arbitrarily at 30 min intervals. Reactions were measured as far as 40—70% completion. In the case of the acid (IIa), measurements up to 600 min had to be taken. In runs 9 and 10 with the acid (IIb), 75% completion of the reaction was reached within 120 min, after which there was a considerable increase in reaction rates which was not taken into account.

Control Experiments to Test the Applicability of the T.g.a. Method.—The following weight losses were recorded. Data are given in the order: material tested, m.p. of pure substance or composition of mixtures in molar ratios, temperature of test, and weight loss (% h^{-1}).

Pure substances: acetanilide (I), 114°, 160°, 0·277; (I), 114°, 177°, 0·455; 3,5-dinitrobenzoic acid (IIa), 206°, 178°, 0·178; 1-naphthoic acid (IIb), 162°, 106°, 0·060; (IIb), 162°, 110°, 0·090; (IIb) 162°, 116°, 0·120; 4-methoxybenzoic acid (IIc), 185°, 105°, 0·063; (IIc), 185°, 116°, 0·116; (IIc), 185°, 125°, 0·207; (IIc), 185°, 136°, 0·525; benzoic acid, 122·4°, 100°, large; 2-chlorobenzoic acid, 142°, 167°, 6·94; 4-iodobenzoic acid, 250°, 140°, large; and 4-bromobenzoic acid, 240°, 140°, large.

TABLE 1

		Acetic acid (mg)		Reaction (%)	
Acid	Time (min)	Determined by titration	Determined by weight loss	Calc. by titr.	Calc. by w.l.
3,5-Dinitrobenzoic	360	4·80	5·00	17·6	18·35
	330	3·90	4·10	21·9	23·0
	300	2·64	2·80	18·4	19·3
1-Naphthoic	180	2·88	3·00	44·2	46·0
	180	3·60	3·65	44·0	44·7
4-Methoxybenzoic	180	3·72	3·85	54·7	56·0
	180	4·50	4·85	56·0	60·3
	180	4·80	4·90	60·3	61·3

TABLE 2

Composition of mixtures, densities,[a] and second-order rate coefficients in reactions of acetanilide (I) with 3,5-dinitrobenzoic acid (IIa), 1-naphthoic acid (IIb), and 4-methoxybenzoic acid (IIc) in the presence of aluminium chloride as a catalyst [b]

Composition of mixtures (molar ratios)				Densities (g cm^{-3}) [a] in reaction with			10^6k_2/l mol^{-1} s^{-1} at 106·5° ± 0·5			10^6k_2/l mol^{-1} s^{-1} at 109·5° ± 0·5		
Run	(I)	(II)	($AlCl_3$)	(IIa)	(IIb)	(IIc)	(IIa)	(IIb)	(IIc)	(IIa)	(IIb)	(IIc)
1	4	1	$\frac{3}{4}$			1·159			20·92			
2	4	1	$\frac{1}{2}$	1·148	1·107	1·126	2·17	10·02	17·18	2·22	16·68	29·3
3	4	1	$\frac{1}{4}$	1·133	1·080	1·074	1·84	7·81	11·81			
4	4	1	$\frac{1}{8}$	1·121	1·061	1·049	1·20	5·02	7·26			
5	4	1	$\frac{1}{16}$	1·116	1·052	1·038	0·95	3·89	4·77			
6	4	1	$\frac{1}{32}$		1·058	1·033		2·48	3·52			
7	4	1		1·152	1·067	1·075			No reaction			
8	2	1	$\frac{1}{2}$	1·218	1·138		1·98 [d]	10·17		2·44 [c]		
9	8	1	$\frac{1}{2}$	1·131	1·057		1·71 [d]	24·62		2·95 [c]		
10	16	1	$\frac{1}{2}$	1·078	1·022		2·79 [d]	26·21		3·45 [d]		

[a] ±0·025; average of three determinations. [b] Typical composition (mol l^{-1}) run 1: [I] 5·850, [II] 1·460, [$AlCl_3$] 1·110. [c] Completely molten during the run. [d] Partially molten during the run.

TABLE 3

		10^6k_2/l mol^{-1} s^{-1}						
	Mixture:	(MI)	(MI)	(MI)	(MII)	(MII)	(MII)	Average k_2 × 10^5
Temp. (°C) †	Acid							
106·5	(IIb)	10·0	10·2		9·7			9·9 ± 0·3
	(IIc)	15·6	16·0	17·0	14·5	15·4	17·2 *	15·9 ± 1·4
109·5	(IIb)	14·6	17·6		16·7			16·3 ± 1·7
	(IIc)	31·6 *			25·3		29·3 *	28·8 ± 3·4

† ±0·5 °C. * Molten before reaction.

TABLE 4

Sample run at 106·5° ± 0·5 [*cf.* Table 2 run 2 for acid (IIb)]

Density = 1·107 g ml^{-1} (sample weight 85 mg)

	Concentration of acid (mol l^{-1}) 1·420 (=a)		Concentration of amide (mol l^{-1}) 5·680 (=b)		
Time (min)	Weight loss (mg)	Reaction (%)	Concentration of acid formed (mol l^{-1}) (=x)	$\ln[a(b-x)/b(a-x)]$	$k_2 \times 10^6$/l mol^{-1} s^{-1}
30	0·850	13	0·185	0·106	13·4
60	1·400	21·4	0·305	0·186	11·9
90	1·900	29	0·413	0·268	11·5
120	2·300	35	0·500	0·342	11·0
150	2·650	40·6	0·576	0·414	10·7
180	3·000	46	0·653	0·493	10·7

Slope of best straight line computed for $\ln[a(b-x)/b(a-x)]$ *vs.* t 4·27 × 10^{-5} s^{-1}, correlation coefficient 0·9998, intercept with y-axis 0·0326. Rate constant calculated from this slope, $k_2 = 10·0 \times 10^{-6}$ l mol^{-1} s^{-1}. k_2 (average) = 11·58 ± 1·8 × 10^{-6} l mol^{-1} s^{-1}.

Mixtures: (I) + (IIa), 1 : 1, 150°, 0·16; (I) + (IIa), 4 : 1, 120°, 0·08; (I) + (IIa), 4 : 1, 130°, 0·10; (I) + (IIb), 1 : 1, 106°, 0·07; (I) + (IIb), 1 : 1, 110°, 0·09; (I) + (IIb), 1 : 1, 169°, 1·80; (I) + (IIb), 1 : 4, 106°, 0·065; (I) + (IIb), 4 : 1, 110°, 0·090; (I) + (IIc), 1 : 1, 101°, 0·087; (I) + (IIc), 1 : 1, 107°, 0·151; (I) + (IIc), 1 : 1, 116°, 0·220; and (I) + (IIc), 4 : 1, 107°, 0·131.

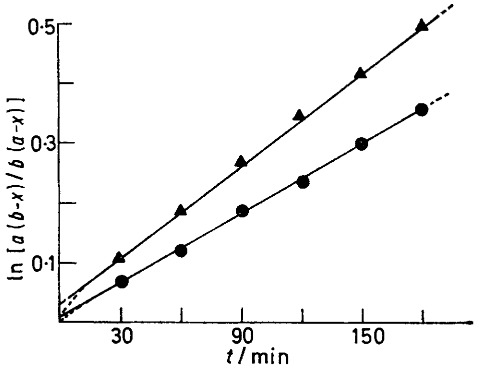

FIGURE 2 Typical plots of $\ln[a(b - x)/b(a - x)]$ against time (min): ▲, reaction of (I), (IIb), and $AlCl_3$ in molar ratio 4 : 1 : 1/2 (run 2); ●, reaction of (I), (IIc), and $AlCl_3$ in molar ratio 4 : 1 : 1/8 (run 4)

RESULTS AND DISCUSSION

The reaction studied is shown in equation (1). The choice of materials was limited to compounds which did not sublime at the reaction temperature.

$$\underset{(I)}{PhNHAc} + \underset{(II)}{ArCO_2H} \xrightarrow[107-110^\circ]{AlCl_3} \underset{(III)}{PhNH{\cdot}COAr} + AcOH \quad (1)$$

a; Ar = $3,5\text{-}(NO_2)_2C_6H_3$:
b; Ar = $1\text{-}C_{10}H_7$:
c; Ar = $4\text{-}MeO{\cdot}C_6H_4$.

No reactions took place between acetanilide and the acids in the absence of a catalyst at 110° or at somewhat higher temperatures. Weight loss (% h^{-1}) of mixtures of acids and acetanilide did not exceed the values expected for evaporation of the pure materials. In addition, no products were detected by t.l.c. and no acetic acid was evolved. Aluminium chloride was therefore used in all cases.

The rate coefficients were independent of the physical condition of the sample. A number of samples melted completely during the reaction, others were only partially molten and others remained solid throughout [run 6 with the acid (IIc)]. Several samples were heated before the reaction to 130° for 30—60 s until they were completely melted, then cooled and afterwards caused to react. Others were caused to react in the form of heterogeneous powders. In all these cases the deviation of the rate coefficients was about ±10%. This seems to indicate that reactions actually take place in the molten phase [6] even in these samples that outwardly appear to be solid.

The rate coefficients were dependent on the concentration of aluminium chloride. The dependence was of the order of a little more than $[AlCl_3]^{\frac{1}{2}}$ (Table 2, runs 1—6). Acetanilide reacted with the acids according to second-order kinetics (first order in both the acid and acetanilide). The fact that this relationship holds as far as 50—70% completion of the reaction is probably due to the presence of acetanilide (I) in excess in all experiments, which decreases the effect of any changes in sample volume or polarity that might take place towards the end of the reaction. Previously [3] it was shown that such changes influence the rates beyond 40% reaction and that these changes are most evident when acid and amide are present in equivalent molar ratios.

In runs 8, 2, 9, and 10 the molar ratio of acetanilide to the acid (IIa) or (IIb) was gradually increased from 2 : 1 to 16 : 1. In the case of the acid (IIa) the rate coefficients both at 106·5 and at 109·5° are basically the same in the first three runs but are greater in the fourth (run 10). An increase in rate coefficient is also observed with the acid (IIb) (runs 9 and 10) but the change is much greater. The difference between the two cases suggests that the reason for this increase is a change in the dielectric constant of the medium. The dipole moment of acetanilide is reported [14] as 3·5—4·05 D, and that of the acid (IIb) as 1·85 D.[14] The value for the acid (IIa) has, to the best of our knowledge, not been reported but may be expected to be near the value [14] for 4-nitrobenzoic acid (3·5—4·18 D). Admittedly these values have a clear physical meaning only in very dilute solutions, and the mutual effect of two dipoles on each other in condensed phase cannot be anticipated. However, if excess of acetanilide increases the dielectric constant, the effect in the case of the acid (IIb) should be more profound, as indeed it is, and the increase in rate coefficients indicates increase, if anything, of polarity of the medium. This influence of reactant ratios on rates is characteristic for reactions in melts, as well as in solids.[5,6]

Reactions were studied at 106·5 ± 0·5 and 109 ± 0·5°. The temperature range was limited since at higher temperatures sublimation of material interfered with the thermogravimetric measurements and at lower temperatures reactions were too slow to be followed. The ratios of the rate coefficients at the two temperatures were, for the reaction of the acid (IIa), 1·23, 1·02, 1·72, and 1·37 (runs 8, 2, 9, and 10, respectively), for the acid (IIb), 1·47, 1·73, and 1·73 (repetition of run 2), and for the acid (IIc), 2·1, 1·75, and 1·71 (repetition of run 2). Hence the effect of temperature is considerable at least for the reactions of the acids (IIb) and (IIc), and an estimated value for the energy of activation would be 50—60 kcal mol^{-1}. In other cases [8] reactions in melts were shown to have high energies of activation but since only a very narrow temperature range is available to us at present, any definite conclusions would be premature.

The reactions were faster when weaker acids were used (Table 2). Of the three acids (IIa) (pK_a 2·80), (IIb) (pK_a 3·69), (IIc) (pK_a 4·45), the highest values of

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[14] A. L. McClellan, 'Tables of Experimental Dipole Moments,' W. H. Freeman, San Francisco, 1963

the rate coefficients were obtained with (IIc). This supports the view [1-3] that these transacylations involve attack on the amide by an acylium ion or an acylium ion–aluminium chloride complex, the formation of which is facilitated by the same substituent effects (such as the $+R$ effect), which decrease the acidity of aromatic acids. It has been observed recently [1] that transacylation with *NN*-diacylanilines was faster for 4-methoxybenzoic acid (IIc) than for 4-nitrobenzoic acid.

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