The Hydrolysis of Amides of Dibasic Acids. Part III. The Acid Hydrolysis of Methyl-, Nitro-, and Amino-malonamides and of Methylmalonamic Acid.*

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Rates of hydrolysis in excess of hydrochloric acid of methyl-, nitro-, and amino-malonamides at 80° and 98° and of methylmalonamic acid at 80° have been measured. The results are compared with those for malonamide and malonamic acid (Part I *) and for oxamide and oxamic acid (Part II *). No simple relationship has been found between the electron-repelling or electron-attracting properties of the substituent groups and the observed rates of hydrolysis.

In Part I * the results of an investigation of the kinetics of hydrolysis of both malonamide and malonamic acid, in large molar excess of hydrochloric acid at 80° and 98°, were given. In the present work the kinetic study has been extended, under the same conditions of acid hydrolysis, to the *C*-substituted derivatives, methyl-, nitro-, and amino-malonamides and methylmalonamic acid.

Experimental and Results

Methylmalonamide was prepared by the action of saturated alcoholic ammonia at 130° (in sealed tubes) on ethyl methylmalonate. After several recrystallisations from alcohol it had m. p. 208°.

Nitromalonamide was made by the nitration of malonamide, following Ruhemann and Orton's method as modified by Johnson and Nicolet (*J. Amer. Chem. Soc.*, 1914, **36**, 361). After two recrystallisations from water it melted at *ca.* 174° (decomp., varying considerably with rate of heating).

Aminomalonamide was prepared by the reduction of nitromalonamide by aluminium amalgam (Johnson and Nicolet, *loc. cit.*) and after several recrystallisations from alcohol melted at 187° (decomp.).

Methylmalonamic acid was obtained from ethyl methylmalonate as follows: (*a*) the diethyl ester was converted into ethyl hydrogen methylmalonate by controlled hydrolysis with alcoholic potassium hydroxide at room temperature; (*b*) the acid ester was converted into ammonium methylmalonamate by keeping it with excess of anhydrous liquid ammonia for two days in a sealed tube at room temperature; (*c*) after the excess of ammonia had evaporated, the salt was dissolved in alcohol and dry hydrogen chloride bubbled through until the pH was reduced to approximately 2. Precipitation of ammonium chloride was completed by addition of ether and, after filtration, the solution was evaporated to an oil which crystallised on the addition of a little ether. The methylmalonamic acid so obtained was recrystallised several times from diethyl ketone (yield, 8%, on acid ester) and had m. p. 104—106° (decomp.) (Found: N, 12·3%; acid equiv., 120. $C_4H_7O_3N$ requires N, 12·0%; acid equiv., 117·1).

The experimental and analytical methods for the kinetic runs were essentially the same as described in Part I. Methylmalonamide, methylmalonamic acid, and nitromalonamide did not react appreciably with sodium hypobromite under the experimental conditions, so that the

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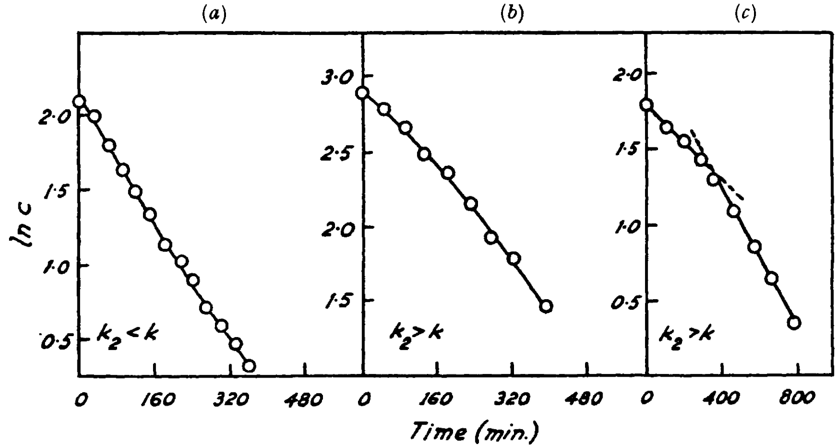
* Parts I and II, *J.*, 1952, **4516**, 3264.

direct method for the estimation of ammonia in the presence of unhydrolysed amide was used. However, aminomalonamide reacted with hypobromite, and the ammonia formed by hydrolysis was separated by distillation before being estimated.

Hydrolyses were followed for each compound at 80° and, except for methylmalonamic acid, at 98°, within the range [HCl] = 0·125—0·75M. In all cases runs were repeated, sometimes six times. First-order kinetics were assured, as before, by the use of a molar concentration ratio of acid : amide $\gg$ 100 : 1. For each run $\ln(a - x)$ was plotted against time. For each of the three diamides at any particular acid concentration the plot was linear up to about 50% hydrolysis. With methylmalonamide there was a very slight bending upwards beyond this point, corresponding to a very small falling off in the rate of hydrolysis of the second amide group (Fig., *a*) whereas with nitromalonamide there was a similarly small but opposite deviation from linearity, indicating that the second amide group in this case was hydrolysed very slightly more rapidly than the first (Fig., *b*). With aminomalonamide the second amino-group was hydrolysed sufficiently more rapidly than the first for it to be possible to draw two straight lines, one through the points corresponding to hydrolysis of less than 50% and the other through the points representing hydrolysis of greater than 50% (Fig., *c*).

Typical hydrolysis runs.



For meaning of k and k_2, see Part I (*loc. cit.*).
(*a*) Methylmalonamide in 0·25M-HCl at 80°. (*b*) Nitromalonamide in 0·625M-HCl at 80°.
(*c*) Aminomalonamide in 0·375M-HCl at 80°.

From the linear parts of these graphs corresponding to the first half of the hydrolysis, the values of the pseudo-unimolecular rate constants, k, measuring the rate of hydrolysis of the first amide group, were determined. The values so obtained were independent of the initial concentration of the amide, confirming the pseudo-unimolecularity of the hydrolysis under the conditions used. The rates of hydrolysis of the second amide group in aminomalonamide (*i.e.*, of the amide group in aminomalonamic acid) have been calculated from the slopes of the linear plots of the second half of the hydrolysis. The values of k_2 so obtained are probably less accurate than those of k (first amide group). The results for all three diamides are summarised in Table 1, the mean values

TABLE 1. *Pseudo-unimolecular rate constants* × 10^3(*min.*$^{-1}$).

		[HCl], M						
	Temp.	0·125	0·25	0·375	0·50	0·625	0·75	k/[HCl]
Methylmalonamide (k)	80°	2·9	5·1	—	10·6	—	16·0	21·3
,, ...	98	11·5	21·3	33·0	45·0	—	—	90·0
Methylmalonamic acid (k_2)	80	2·7	5·1	6·8	8·6	—	13·7	17·5 ± 1
Nitromalonamide (k)	80	—	1·4	2·3	2·9	3·8	4·6	6·4
,, ...	98	—	6·5	10·0	13·6	16·7	20·1	27·0
Aminomalonamide :								
1st amide group (k)	80	—	—	1·2	2·0	2·1	2·6	3·7
,, ...	98	1·4	2·7	4·9	6·7	—	10·3	13·0
2nd amide group (k_2)......	80	—	—	2·4	2·8	3·3	4·2	5·2
,, ...	98	2·1	4·0	7·0	9·0	—	15·0	17·6

only of k (or k_2) being given for each substance at each particular acid concentration. The agreement between the values obtained from repeated runs was in general of the same order as in the earlier work (Part I) and, for brevity and clarity, individual values have therefore been omitted.

To test the conclusions drawn from the slight curvatures of the $\ln(a - x)$–time plots (Fig., *a* and *b*), methylmalonamic acid was prepared and used in hydrolyses at 80° (but not at 98°). The $\ln(a - x)$–time plots were now linear throughout each run, and the values of k_2 calculated therefrom (Table 1) afford direct confirmation that the second amide group in methylmalonamide is, in fact, hydrolysed at a slightly, but measurably, smaller rate than the first amide group ($k_2 < k$, Fig., *a*).

DISCUSSION

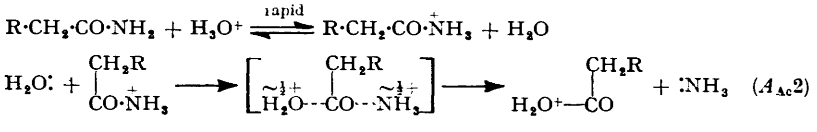
Table 2 brings together the results given in this and in Parts I and II for acid-catalysed hydrolysis of diamides.

TABLE 2. *Catalytic coefficients*, $k_{\mathrm{H}^+} \times 10^3$, *and Arrhenius parameters.*

	First amide group				Second amide group			
	80°	98°	E[a]	$\log_{10} B$[b]	80°	98°	E[a]	$\log_{10} B$[b]
Malonamide (from Part I)	23·6 *	93	20 *	10·8	32	100	16	8·7
Methylmalonamide	21·3	90	21	11·4	17·5	—	—	—
Nitromalonamide	6·4	27	21	10·7	—	—	—	—
Aminomalonamide	3·7	13	18	8·9	(5·2)	(17·6)	(18)	(8·8)
Oxamide (from Part II) ...	25(79·5°)	97(97·5°)	20	10·8	48(79·5°)	184(97·5°)	20	11·0

[a] In kcal. mole^{-1}; probable error ±1 [b] Probable error ±0·5.
* In Part I these quantities were inadvertently reported as 26 and 18·4 respectively.

A comparison of the figures for malonamide and its *C*-substituted derivatives shows that the electron-repelling methyl and the electron-attracting nitro- and amino-groups (the latter presumably as $-\mathrm{NH_3}^+$ in excess of acid) all bring about a reduction in the rate of acid hydrolysis when introduced into the methylene group of malonamide. It is clearly not yet possible to forecast, *a priori*, the effect of electron-repelling or electron-attracting substituent groups (on a neighbouring carbon atom) on the rate of acid hydrolysis, or even to conclude that the two types of groups will have opposite effects. One reason for this uncertainty, which is not found with alkaline hydrolysis, becomes apparent from a consideration of the probable mechanism of acid hydrolysis. If we accept the view, now supported by much indirect evidence (Ingold, " Structure and Mechanism in Organic Chemistry," Cornell Univ. Press, 1953; Bunton, Lewis, and Llewellyn, *Chem. and Ind.*, 1954, 1154), that in acid hydrolysis the protonated form of the amide is the entity which is attacked by the nucleophilic water and that the equilibrium between the protonated and the unprotonated form is rapidly established, two opposing polar effects of a substituent group are recognisable. The first concerns the equilibrium concentration of the protonated form, which should be favoured by electron-repelling groups and *vice versa*; the second effect concerns the ease of attack at the carbonyl-carbon atom of the protonated amide by the nucleophilic water molecule and here electron-attracting groups should facilitate the process and electron-repelling groups hinder it. Until it is possible to deduce which of these two polar effects predominates for any particular group and situation, the electronic effect of the substituent group on the rate of acid hydrolysis cannot be predicted.



$$\mathrm{R{\cdot}CH_2{\cdot}CO{\cdot}NH_2 + H_3O^+ \overset{rapid}{\rightleftharpoons} R{\cdot}CH_2{\cdot}CO{\cdot}\overset{+}{N}H_3 + H_2O}$$

$$\mathrm{H_2O\!: + \begin{array}{l} CH_2R \\ | \quad + \\ CO{\cdot}NH_3 \end{array} \longrightarrow \left[\begin{array}{c} CH_2R \\ \sim\!\tfrac{1}{2}+ \quad | \quad \sim\!\tfrac{1}{2}+ \\ H_2O\text{- -}CO\text{- -}NH_3 \end{array}\right] \longrightarrow \begin{array}{l} CH_2R \\ | \\ H_2O^+{-}CO \end{array} + :NH_3 \quad (\mathit{A}_{Ac}2)}$$

$$\mathrm{R{\cdot}CH_2{\cdot}CO_2H_2^+ + NH_3 \xrightarrow{rapid} R{\cdot}CH_2{\cdot}CO_2H + NH_4^+}$$

Arguments have been given for the view that, where the $A_{\mathrm{Ac}}2$ mechanism is operative, polar effects are weak and are liable to be masked by stronger steric effects (Ingold, *op. cit.*). Our results can be regarded as consistent with such a general conclusion. However it is only in aminomalonamide that the substituent group produces a significant change in either the Arrhenius energy of activation or the entropy ($\log_{10} B$) term. It is difficult to understand why such an effect should show up in this way for the amino- but not for the nitro- and methyl groups, unless it be assumed that there is an indirect entropy effect resulting from the positive ionic charge on the $-NH_3^+$ group (which is presumed to be present, to the virtual exclusion of the NH_2 group, in the large molar excess of acid used). Such an effect might result if the positive ammonium-ion group could, by coulombic interaction with the strongly polar protonated amide group, effectively control the conformation of the latter group with respect to the rest of the molecule.

The three substituent groups, methyl-, nitro-, and amino-, all bring about a reduction in the rate of acid hydrolysis of the amide group of malonamic acid when introduced at the methylene carbon atom. The amic acids (including oxamic acid) all fall into the same order for the relative rates of acid hydrolysis as do the diamides. A comparison of the corresponding amic acid and diamide shows that the replacement of an amide group by a carboxyl group increases the rate at which the remaining amide group undergoes acid hydrolysis, except for methylmalonamide where the opposite effect is observed. As would be expected, the accelerating effect of a carboxyl as compared with an amide group is considerably greater when the two groups are directly linked to one another (in oxamic acid) than when they are separated by a methylene group (in malonamic acid). The replacement of an amide by a carboxyl group in malonamide produces much bigger changes (partly compensating) in the energy of activation and in the entropy factor than it does in oxamide. The explanation of this difference is not obvious.

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