226. *Anhydrous Hydrolysis in Dimethyl Sulphoxide.*

By W. Roberts and M. C. Whiting.

The hydrolysis of methyl and ethyl esters of benzoic acid and of some sterically hindered (mesitoic, 9-anthranoic and *O*-methylpodocarpic) acids, and of benzonitrile, by suspensions of sodium hydroxide in dimethyl sulphoxide have been studied. As compared with reactions in hydroxylic solvents rates are enhanced by about 10^4—10^5. The observed rates and those of analogous reactions with suspensions of sodium methoxide indicate that the normal mechanism, rather than S_N2 attack on the alkyl group, is involved in the ester hydrolyses.

Solutions of " dimsylsodium," obtained from sodium hydride and dimethyl sulphoxide,[1] can be used to titrate very weak acids, with triphenylmethane as indicator; [2] water in this way gives a fine suspension of sodium hydroxide which rapidly hydrolyses ethyl benzoate at room temperature.[2] We now describe experiments which demonstrate the utility of this method in the hydrolysis of hindered esters, but indicate that no unusual mechanism is involved.

Sodium hydroxide and sodium methoxide suspensions were prepared [2] and centrifuged, and maximal values of their solubility were found to be $7{\cdot}6 \pm 0{\cdot}2 \times 10^{-4}$M and $1{\cdot}6 \pm 0{\cdot}3 \times 10^{-3}$M, respectively. The hydrolysis of ethyl benzoate was examined at 25°, using two different ester concentrations and two nominal sodium hydroxide " concentrations." First-order plots were linear with considerable scatter and rate constants were in the range $2{\cdot}5$—$3{\cdot}2 \times 10^{-2}$ sec.$^{-1}$, not significantly different. These results and *a priori* arguments suggest that the reaction involves the small proportion of sodium hydroxide present in solution, which would of course remain essentially constant through the reaction (a minor contribution from a reaction at the solid surface is not excluded.) Translated into a second-order constant *via* the maximal solubility value this gives 40 l. mole^{-1} sec.$^{-1}$, as compared with published [3] values in the range $6{\cdot}2$—34×10^{-4} l. mole^{-1} sec.$^{-1}$ in various aqueous organic solvents. Similarly, methyl benzoate gave rough first-order and derived second-order rate constants of 8×10^{-2} sec.$^{-1}$ and 100 l. mole^{-1} sec.$^{-1}$, as compared with 9×10^{-3} l. mole^{-1} sec.$^{-1}$ in 56% acetone–water.[3b] These figures imply a rate enhancement, as compared with aqueous solvents, of the order of 10^4—10^5, a result in good accord with enhancements of *ca.* 10^6 and *ca.* 10^4 for typical aliphatic and aromatic substitution reactions in aprotic solvents.[4,5]

The hydrolysis of methyl and ethyl mesitoates was examined at 25° with shaken suspensions, and led to k_2 values of 10^{-2} and 4×10^{-3} l. mole^{-1} sec.$^{-1}$, respectively. For the methyl ester, published values [6] in 60% dioxan in the range 111—140° extrapolate to $3{\cdot}8 \times 10^{-7}$ l. mole^{-1} sec.$^{-1}$ and thus an enhancement of 3×10^4. The anhydrous hydrolysis of ethyl and β-phenylethyl esters of 9-anthranoic acid were similarly examined, giving rate constants of 3×10^{-2} and 6×10^{-1} l. mole^{-1} sec.$^{-1}$, respectively. The difference suggests that the β-phenylethyl ester may in fact have undergone β-elimination to styrene instead of hydrolysis. Adam-Briers, Fierens, and Martin have reported [7] values for the ethyl ester in 85% alcohol at 70—100° which extrapolate to $8{\cdot}7 \times 10^{-6}$ l. mole^{-1} sec.$^{-1}$ at 25°; this gives an enhancement factor of 3×10^3 (however, Norman and Ralph [8] were

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[1] E. J. Corey and M. Chaykowski, *J. Amer. Chem. Soc.*, 1962, **5**, 866.

[2] G. Price and M. C. Whiting, *Chem. and Ind.*, 1963, 775.

[3] *Inter al.* (*a*) D. P. Evans, J. J. Gordon, and H. B. Watson, *J.*, 1937, 1430; (*b*) E. Tommila, *Ann. Acad. Sci. Fennicae*, Ser. 1942, *A*, **59**, 3, 3 (*Chem. Abs.*, 1944, **38**, 6172^7); (*c*) C. C. Price and R. H. Michel, *J. Amer. Chem. Soc.*, 1952, **74**, 3652.

[4] A. J. Parker, *Quart. Rev.*, 1962, **16**, 163, and references there cited.

[5] Musto, *Suomen. Kem.*, 1961, *B*, **34**, 92.

[6] H. L. Goering, T. Rubin, and M. S. Newman, *J. Amer. Chem. Soc.*, 1954, **76**, 787.

[7] M. Adam-Briers, P. J. C. Fierens, and R. H. Martin, *Helv. Chim. Acta*, 1955, **38**, 2021.

[8] R. O. C. Norman and P. D. Ralph, *J.*, 1961, 2221.

unable to hydrolyse the methyl ester of 9-anthranoic acid under the conditions of Adam-Briers *et al.* and concluded that these authors had overestimated the rate for the ethyl ester; thus the enhancement factor may be larger).

In view of the great enhancement of rates of aliphatic substitutions in dimethyl sulphoxide [4,5] it seemed possible that these ester hydrolyses, or at least those of methyl and ethyl mesitoates and of ethyl 9-anthranoate, were in fact bimolecular displacements on the alkyl group. To test this, analogous reactions were attempted with sodium methoxide suspensions, which should then yield dimethyl ether and the acid anion. Difficulty was encountered from adventitiously present water, which gave an initially rapid reaction, but rates of $<10^{-4}$ and 4×10^{-4} l. mole^{-1} sec.$^{-1}$ for the formation of acidic material from methyl benzoate and methyl mesitoate, respectively, were assured, *i.e.*, rates lower than those for sodium hydroxide by factors of 10^6 and 25, respectively. By an extrapolation procedure, Musto deduced [5] rates for the attack of HO^- and MeO^- on methyl iodide in dimethyl sulphoxide which gave a corresponding ratio of 4; thus for the benzoate certainly, and for the mesitoate probably, the hydrolysis must proceed mainly by some mechanism other than S_N2 attack at methyl, *i.e.*, in all probability by the normal mechanism. This conclusion was reinforced by an unsuccessful attempt to hydrolyse methyl *O*-methylpodocarpate, which is very hindered indeed; though complicated by the presence of a less unreactive impurity, our results indicated a rate of $<5 \times 10^{-5}$ l. mole^{-1} sec.$^{-1}$, *i.e.*, more than 200 times slower than methyl mesitoate. No doubt a lower limit corresponding to the S_N2 reaction does exist for very hindered methyl esters.

The hydrolysis of benzonitrile was briefly examined, products being analysed by infrared spectroscopy. Benzamide was obtained exclusively, at a rate of 5×10^{-3} l. mole^{-1} sec.$^{-1}$, *i.e.*, about the same as that for the hydrolysis of ethyl mesitoate. A published value [9] for the rate of hydrolysis in aqueous sodium hydroxide of $1{\cdot}24 \times 10^{-2}$ l. mole^{-1} min.$^{-1}$ at 70°, combined with plausible extremes [10] of 10^7 and 10^{12} for the temperature-independent factor, gives extreme energies of activation of 17 and 25 kcal./mole and a rate at 25° of between 7 and 25×10^{-7} l. mole^{-1} sec.$^{-1}$, *i.e.*, a value $1{\cdot}2$ to 5×10^{-4} times slower than that in dimethylsulphoxide.

These experiments suggest preparative applications. On a small scale the use of exactly these conditions should allow the direct alkaline hydrolysis of moderately hindered (*e.g.*, mesitoic, 9-anthranoic) esters, or of aromatic nitrile groups to amide functions, while massive sodium, or potassium,[11] hydroxides might be usable. In general, the reactivity of the conjugate anion of water, as of those derived from other hydroxylic compounds,[12] may be greatly reduced by the presence of water itself, and fully revealed only under anhydrous, indeed non-hydroxylic, solutions.

Added, August 18*th*, 1964.—Roberts [13] has shown that the hydrolysis of ethyl benzoate in aqueous dimethyl sulphoxide (15 : 85) is about 300 times faster than that in aqueous ethanol (15 : 85), and has discussed entropies and enthalpies of activation in these and similar systems.

EXPERIMENTAL

The preparation of " dimsylsodium " solution has been described; [1] even at molar concentration it has m. p. *ca.* 16°, little lower than that of dimethyl sulphoxide itself, and must be used at a temperature higher than that. It is best stored below 0°. All the work described was carried out in a room maintained at 25° ± 1°.

Solubilities of sodium hydroxide and sodium methoxide were determined by titration of very dilute solutions of water and methanol (70 c.c.) in the presence of triphenylmethane,[2]

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[9] Y. Ogata and M. Okano, *J. Chem. Soc.* (*Japan*), 1949, **70**, 32 (*Chem. Abs.*, 1951, **45**, 425*a*).

[10] A. A. Frost and R. G. Pearson, " Kinetics and Mechanism," Wiley, 1962, p. 148.

[11] Cf. E. C. Steiner and J. M. Gilbert, *J. Amer. Chem. Soc.*, 1963, **85**, 3054.

[12] D. J. Cram, B. Rickborn, C. A. Kingsbury, and P. Haberfield, *J. Amer. Chem. Soc.*, 1961, **82**, 3678; D. J. Cram, C. A. Kingsbury, and B. Rickborn, *ibid.*, 1961, **83**, 3688.

[13] D. D. Roberts, *J. Org. Chem.*, 1964, **29**, 2039.

followed by addition of more of the water or methanol solution until the colour was just discharged. The suspensions were stoppered and centrifuged, aliquot portions being removed, diluted with water, and titrated with 10^{-2}M and 10^{-3}M hydrochloric acid, respectively, to constant titre. About 3 hr. was necessary, and the solubilities estimated, quite possibly including colloidally suspended material, were $7{\cdot}6 \pm 0{\cdot}2 \times 10^{-4}$ and $1{\cdot}6 \pm 0{\cdot}3 \times 10^{-3}$M, respectively.

Hydrolysis of Ethyl Benzoate, etc.—Solutions of water (4·2 or 0·8M according to the amount of ester available) in dry dimethyl sulphoxide (1 c.c.) were placed in dried 10 c.c. flasks with a trace of triphenylmethane and sealed with a serum cap. Air was replaced by nitrogen using two hyperdermic needles and the solutions were titrated to a permanent red colour with approximately M-" dimsylsodium " solution, standardised with β-naphthol.[2] A fine suspension which did not settle noticeably for several minutes resulted. A solution of the ester in dimethyl sulphoxide (redistilled from " dimsylsodium " solution) was injected, volumes being calculated to bring the total to that intended. After the proper time, 2M-aqueous sulphuric acid was injected and the mixture was extracted with ether (3 × 10 c.c.), the final extract being washed with water (2 × 10 c.c.). The ether was evaporated and the acid was titrated with 0·08M-sodium hydroxide solution. A blank experiment showed that the recovery of benzoic acid was 97·5 ± 1%; similar blank experiments, giving equally high recoveries, were carried out with mesitoic and 9-anthranoic acids. A typical set of data is given below; each point defines an hydrolysis experiment. Zero time was set at 12 sec. after addition was begun, and runs *A*, *B*, and *C* refer to molar ester and sodium hydroxide " concentrations " of 0·236 and 0·944; 0·236 and 0·472; and 0·118 and 0·472, respectively. Graphically determined rate constants making allowance for zero-errors in the initial time are almost certainly more accurate than those determined arithmetically.

TABLE 1.

	A		*B*		*C*	
Time (sec.)	% react.	$k_1 \times 10^2$	% react.	$k_1 \times 10^2$	% react.	$k_1 \times 10^2$
3	12·1	4·3	13·8	5·0	15·4	5·6
18	40·0	2·8	34·5	2·4	29·5	1·9
33	60·4	2·8	62·9	3·0	55·0	2·4
48	81·1	3·5	80·9	3·5	64·2	2·1
63					80·0	2·6
78	95·6	4·0	94·3	3·7	82·4	2·2
108	98·6	4·0	94·0	2·6	96·4	3·1
138	99·1	3·4	94·2	2·1	96·2	2·4

Graphical values for k_1 from *A*, *B*, and *C* were 3·2, 3·2, and $2{\cdot}5 \times 10^{-2}$ sec.$^{-1}$, respectively.

	D			*E*	
Time $\times 10^{-3}$ (sec.)	% react.	$k_1 \times 10^6$	Time $\times 10^{-3}$ (sec.)	% react.	$k_1 \times 10^5$
45·0	14·6	3·3	9·0	22·8	2·8
86·6	19·5	2·7	18·0	39·8	2·8
97·5	28·8	3·3	44·3	68·3	2·6
166	31·9	2·9	81·0	85·1	2·5
340	57·6	2·8	145	94·5	2·5
563	83·3	3·2	221	99·0	—
889	91·1	3·1			

Graphical values for k_1 were $2{\cdot}9 \times 10^{-6}$ and $2{\cdot}3 \times 10^{-5}$ sec.$^{-1}$, respectively.

Hydrolysis of hindered esters was carried out in the same way, except that the mixture was shaken mechanically; here *D* and *E* refer to ethyl mesitoate and 9-anthranoate, respectively.

Hydrolysis of benzonitrile involved addition of known weights of the nitrile to suspensions of sodium hydroxide, which were shaken mechanically. After the proper time the nitrile and benzamide were isolated with ether and dissolved in carbon disulphide, the intensity (*I*) of the band at 2220 cm.$^{-1}$ (just outside the range of strong absorption by the solvent) being used to estimate unchanged nitrile. The amide (which was readily isolated from the longer hydrolysis mixtures) did not interfere; a blank experiment gave a recovery of 96%. The acidic fraction was negligible.

In reactions between sodium methoxide and esters, and in the hydrolysis of methyl *O*-methylpodocarpate, experiments with short reaction-times indicated much faster initial

TABLE 2.

Time × 10^3 (sec.)	Benzonitrile used (mg.)	I	% react.	10^6k_1 (sec.$^{-1}$)
16·2	101·5	26·2	13·0	9·0
63·4	106·7	28·4	22·2	4·5
88·6	106·7	28·0	21·3	3·0
153·4	106·7	37·7	39·8	3·5
237	108·0	47·4	54·4	3·5
317	57·3	79·3	73·3	4·5
402	152·3	60·7	78·2	4·0
517	119·7	80·6	88·5	4·5

The graphical rate was 4·2 × 10^{-6} sec.$^{-1}$.

reactions than were maintained, presumably because of adventitious water and of a more easily hydrolysed ester impurity, respectively. An estimate of the maximal slope was obtained from the later points.

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DYSON PERRINS LABORATORY, OXFORD UNIVERSITY. [*Received, June 24th,* 1964.]