

593. *Tracer Studies in Ester Hydrolysis. Part V.* The Kinetic Form and Stereochemical Course of the Hydrolysis of p-Methoxydiphenylmethyl Acetate.*

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Hydrolysis of *p*-methoxydiphenylmethyl acetate in aqueous dioxan is accelerated by both hydroxide and hydrogen ions. Hydroxide ions attack the acyl carbon atom, with a second-order rate law, by mechanism $B_{Ac}2$. Acid hydrolysis is by alkyl-oxygen bond fission, and the rate in aqueous 60% dioxan is proportional to the Hammett function, h_0 , rather than to hydrogen-ion concentration; the mechanism is therefore $A_{Al}1$. The rate of acid hydrolysis is greater in a deuterium oxide-dioxan solvent than in the corresponding aqueous solvent, confirming that the acid catalysis is specifically by the hydrogen ion. The alkyl-oxygen bond is broken in neutral hydrolysis, with complete loss of optical activity, by mechanism $B_{Al}1$, and the rate of hydrolysis, measured chemically, is close to that measured polarimetrically. Thus each molecular process of alkyl-oxygen fission results in complete loss of asymmetry of the alkyl carbon atom. Azide and acetate ions reduce the hydrolysis rate, measured chemically, by capturing the carbonium ions, but they do not affect the rate of loss of optical activity during hydrolysis. This shows that the asymmetry of the alkyl carbon atom is lost before any of these nucleophilic reagents attacks this atom, *i.e.*, the carbonium ion is completely flattened before attack of the reagent.

WHILE investigating the hydrolysis of hydrogen phthalates of optically active secondary alcohols, Kenyon and his co-workers observed considerable racemisation with *p*-methoxydiphenylmethyl hydrogen phthalate, and pointed out that this result indicated that the alkyl-oxygen bond of this ester was broken in hydrolysis.¹ Such a result is to be expected in the hydrolyses of esters having electron-releasing groups attached to the alkyl carbon atom. The hydrolysis of the sodium salt of *p*-methoxydiphenylmethyl hydrogen phthalate to the alcohol and acid in water and in aqueous alkali has been followed kinetically, with determination of the position of bond fission by use of oxygen-18, and the stereochemical course examined.² The results were in general those expected, but the system was complicated by the low solubility of the ester in concentrated aqueous sodium hydroxide and by the separation of insoluble alcohol and dialkyl phthalate during hydrolysis. Therefore a parallel study was made of the hydrolysis of *p*-methoxydiphenylmethyl acetate in aqueous dioxan, where these complications do not arise. The hydrolysis was followed kinetically in initially neutral solution, in solutions containing hydrogen or hydroxide ions, and in those containing neutral salts. The position of bond fission was determined in all conditions and the stereochemistry examined.

Position of Bond Fission.—The acetic acid or alcohol formed by hydrolysis in aqueous dioxan containing $H_2^{18}O$ was isolated, and its ^{18}O abundance determined. Within the limit of uncertainty due to oxygen exchange between water and the products, the neutral and acid hydrolyses give complete alkyl-oxygen, and alkaline hydrolysis gives complete acyl-oxygen, bond fission.

Kinetic Form of Hydrolysis.—Reaction with hydroxide ion (in aqueous 70% dioxan) follows a second-order rate law, as required for mechanism $B_{Ac}2$. The rate is very similar to that of the alkaline hydrolysis³ of diphenylmethyl acetate (at 25°, $10^2k_2 = 1.2 \text{ l. sec.}^{-1} \text{ mole}^{-1}$), the *p*-methoxyl group having virtually no effect on the rate of attack of hydroxide ion on the acyl carbon atom.

* Part IV, *J.*, 1957, 963.

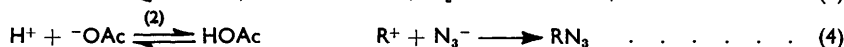
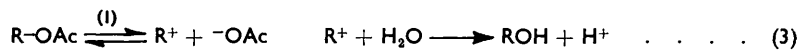
¹ Davies and Kenyon, *Quart. Rev.*, 1955, **9**, 203.

² Bourns, Bunton, and Llewellyn, *Proc.*, 1957, 120.

³ G. Israel, unpublished results.

In marked contrast to its small effect on the attack of hydroxide upon the acyl carbon atom, the *p*-methoxy-group has a large effect on the rate of alkyl-oxygen bond fission in the neutral hydrolysis (mechanism B_{A1}). The rate of neutral hydrolysis of diphenylmethyl formate (with mixed acyl and alkyl bond fission) (Part IV) is about 1/30th of that of *p*-methoxydiphenylmethyl acetate.

This assignment of mechanism is confirmed by examination of the kinetic salt effects. Added chloride ions have only a small effect on this neutral rate (*ca.* 0.2M-lithium chloride increases it by 20%), but acetate ions decrease it considerably (0.2M-lithium acetate fourfold). This is the well-known common-ion salt effect, first observed in hydrolyses of diphenylmethyl halides (see scheme, where $R = p$ -methoxydiphenylmethyl),⁴ and the



retarding effect of acetate ions measures the relative rates of steps 2 and 3. In the conditions of these neutral hydrolyses (Table), approximately three carbonium ions are captured by acetate ions for every one captured by water molecules, the same factor being found in the neutral hydrolysis of triphenylmethyl acetate in a slightly less aqueous solvent.⁵ Acetic acid, formed during hydrolysis, has no effect upon the rate, and is therefore ineffective in capturing carbonium ions.

TABLE. *Rates of hydrolysis in aqueous dioxan.*

Solvent : aqueous 70% dioxan (except where otherwise specified). $k_A = k_1/[H_2SO_4]$

(A) Base hydrolysis.

Temp.	0.0°	17.5°	25.0°	33.7°					
[LiOH] (M)	0.034	0.0381	0.067	0.033					
$10^3 k_2$ (sec. ⁻¹ mole ⁻¹ l.)	0.152	0.844	1.73	3.47					

(B) Initially neutral hydrolysis.

Temp.	44.8°	72.9°	72.9°	72.9°	72.9°	72.9°	100°	100°	100°
Reagent	—	—	—	0.194M- LiCl	0.162M- NaN ₃	0.214M- LiOAc	—	0.208M- LiCl	0.193M- LiOAc
$10^3 k_1$ (sec. ⁻¹)	0.0557	1.63	1.56 *	1.51 *	1.25 *	1.25 *	17.6	21.8	4.43

(C) Acid hydrolysis (at 44.8° unless otherwise specified). $10^3 k_A = 1.44$ sec.⁻¹ mole⁻¹ l.

[H ₂ SO ₄] (M)	0.0165	0.024	(with 0.208M-LiCl)		0.0415	0.0545	0.020	(at 72.9°)	
$10^3 k_1$ (sec. ⁻¹)	2.43	3.28			5.74	8.10	75.7		

In aqueous 60% dioxan; temp. 25°. In deuterium oxide-60%
dioxan ‡

[HClO ₄] (M) ...	0.199	0.263	0.319 †	0.470 †	0.553 †	0.911	1.34	0.285	0.339
$10^4 k_1$ (sec. ⁻¹)	1.14	1.66	2.89	5.90	8.34	28.6	134	4.23	5.63

All rates followed by titration except those marked * polarimetrically and † dilatometrically.
‡ $[D_2O]/([D_2O] + [H_2O]) = 96\%$.

Azide ions⁴ are still more effective as intervening agents, and when added as *ca.* 0.3M-sodium azide captures virtually all the carbonium ions formed.

The acid-catalysed hydrolysis was examined in aqueous 70% dioxan with added sulphuric acid (<0.2M), and in aqueous 60% dioxan with added perchloric acid in concentration up to 1.3M. The former conditions were chosen to allow comparison between the rates of hydrolysis of other esters (Part IV), and the latter because values of the Hammett acidity function, H_0 , are known from indicator measurements on this system.⁶ Reactions which show specific hydrogen-ion catalysis, and in which the slow step is the unimolecular breakdown of the conjugate acid (*e.g.*, mechanisms A_{Ac1} and

⁴ Hughes, *Trans. Faraday Soc.*, 1941, **37**, 603.

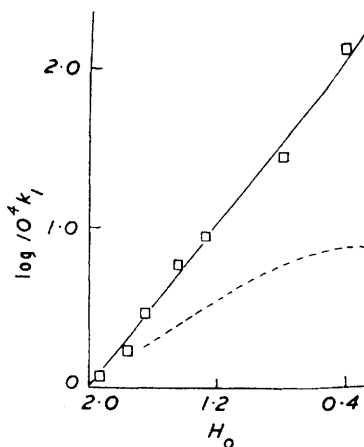
⁵ Bunton and Konasiewicz, *J.*, 1955, 1354.

⁶ Bunton, Ley, Rhind-Tutt, and Vernon, *J.*, 1957, 2327.

A_{A1}) will have rates proportional to the acidity function h_0 ($H_0 = -\log h_0$) rather than to the concentration of hydrogen ions, whereas the rates of bimolecular reactions in which water molecules attack the conjugate acid in the slow step of the reaction (*e.g.*, mechanism A_{Ac2}) will be proportional, at least approximately, to the hydrogen-ion concentration. This test has been applied with satisfactory results⁷ to mechanisms A_{Ac1} and A_{Ac2} . A plot of the logarithm of the first-order rate constant for acid hydrolysis against H_0 had a slope of -1.3 (see Figure) and the rate increases much more rapidly than does the perchloric acid concentration. The acidity function begins to diverge from acid concentration at fairly low acid concentrations in aqueous dioxan,⁶ and the range of acid concentration used is therefore sufficient to distinguish between the two limiting kinetic forms. Although the Zucker-Hammett hypothesis predicts unit slope for a plot of $\log k$ against $-H_0$, divergencies from this value may arise from the assumptions of the hypothesis. They are often found for reactions in water,⁸ and are more likely to occur in organic or aqueous organic solvents of low dielectric constant.

Relation between rate of hydrolysis and acidity.

The broken line shows the curve expected for a bimolecular hydrolysis.



It is usually assumed that catalysis of hydrolyses of esters by strong acids is a specific hydrogen-ion catalysis, and this has been proved for reactions involving acyl-oxygen bond fission.⁹ That the acid hydrolysis in deuterium oxide-dioxan is twice as fast as that in aqueous dioxan of the same molar composition (Table) confirms it here.

The values for the Arrhenius parameters are as follows: base hydrolysis, $k = 10^{9.5} \exp(-15,400/RT)$ ($\text{sec.}^{-1} \text{ mole}^{-1} \text{ l.}$); neutral, $k = 10^{10.6} \exp(-24,600/RT)$ (sec.^{-1}); acid, $k = 10^{12.8} \exp(-25,600/RT)$ ($\text{sec.}^{-1} \text{ mole}^{-1} \text{ l.}$).

Stereochemical Course of Hydrolysis.—Interest in the steric course of ester hydrolysis centres on mechanisms of alkyl-oxygen bond fission, because acyl-oxygen fission leaves the asymmetric carbon atom of the alkyl group untouched. It is not experimentally possible to study the stereochemistry of the acid hydrolysis of *p*-methoxydiphenylmethyl acetate because the acid-catalysed racemisation, and oxygen exchange, of *p*-methoxydiphenylmethyl alcohol is considerably faster than the acid hydrolysis of its acetate.¹⁰ As might be expected from the effect of structure on the stereochemistry of the S_N1 reaction (analogous to the B_{A1} mechanism here), the alcohol produced from neutral hydrolysis was racemised. The rate of loss of optical activity in neutral hydrolysis is very close to that of formation of acetic acid (Table), but this "polarimetric" hydrolysis rate is, unlike the "chemical" rate, only slightly affected by added azide or acetate ions.

⁷ Long *et al.*, *J. Phys. Chem.*, 1951, **55**, 813, 829; *J. Amer. Chem. Soc.*, 1950, **72**, 3267; 1956, **78**, 3326; Bell, Dowding, and Noble, *J.*, 1955, 3106.

⁸ Long and McIntyre, *J. Amer. Chem. Soc.*, 1954, **76**, 3240, 3243.

⁹ Bell "Acid-Base Catalysis," Oxford Univ. Press, 1941, p. 146.

¹⁰ Wilson, unpublished results.

That the "chemical" and the "polarimetric" hydrolysis rate are very similar shows that there is no internal return of a partially formed (and racemised) carbonium ion to the oxygen atom. The absence of any marked effect of azide and acetate ions on the "polarimetric" rate proves that the carbonium ion has lost its asymmetry, by becoming completely planar, before attack of the nucleophilic reagent [reactions (2), (3), and (4)]. This course of events is not usual for S_N1 reactions in aqueous solvents, most of which give optically inverted products with racemisation whose extent depends upon environment and the structure of the compound.¹¹ (Exceptions to this are that silver, or other heavy-metal, ions often increase the extent of racemisation, and that configuration-holding groups in the molecule may lead to retention of configuration in S_N1 reactions.) In *p*-methoxydiphenylmethyl acetate the phenyl groups attached to the alkyl carbon atom, and the electron-releasing methoxyl group force the carbonium ion to become planar. Although it is easy to make such acetates, it is in general not possible to make optically active alkyl halides which generate carbonium ions whose stability is sufficiently high for them to become completely planar before attack of the reagent. This is because such alkyl halides ionise so readily that they racemise during their formation and isolation. Carboxylic esters do not suffer from this disability; they can often be resolved directly, as in the hydrogen phthalates,¹ or prepared by reactions which do not affect the bonds of the alkyl carbon atom. They therefore provide useful systems for studies on the stereochemical course of S_N1 reactions.

EXPERIMENTAL

Materials.—*p*-Methoxydiphenylmethyl alcohol, prepared from *p*-methoxybenzaldehyde and phenylmagnesium bromide,¹² had m. p. 65.5°; it was acetylated by acetic anhydride in pyridine. The ester had b. p. 158°/0.9 mm., n_D^{25} 1.5593.

The hydrogen phthalate was resolved as its cinchonidine salt¹² and reduced to *p*-methoxydiphenylmethyl alcohol with lithium aluminium hydride in dry ether. The alcohol had $[\alpha]_D^{25}$ -10.6° in CS_2 . It was acetylated in pyridine, with an excess of acetic anhydride, and was kept under these acetylating conditions for 48 hr. to ensure that the ester contained no unchanged alcohol. Instead of removing pyridine, acetic acid, and unchanged acetic anhydride by extraction, as was done in the preparation of the racemic ester, they were pumped off at *ca.* 10⁻⁴ mm. into a receiver cooled in liquid nitrogen. The optically active ester had n_D^{25} 1.559, and on reduction with lithium aluminium hydride gave an alcohol with $[\alpha]_D^{25}$ -3.4° in CS_2 . Considerable racemisation had therefore occurred during acetylation, probably because the reaction time was too long. Fortunately the specific rotation of the ester was higher in aqueous 70% dioxan, $[\alpha]_D^{25} \approx -12^\circ$, than in CS_2 .

Kinetic Measurements.—The solvent was aqueous dioxan, containing 60% or 70% of purified dioxan (v/v).

The hydrolysis of the racemic ester was followed by acid-base titration, and for a few of the acid runs by dilatometry. In hydrolyses in initially neutral, and in dilute acidic solution, the acetic acid formed was estimated by titration with standard alkali (*ca.* $N/40$). With acid concentrations >0.9M the volume of alkali required for neutralisation was large, so a sufficient known amount of more concentrated standard alkali to neutralise most of the acid was added from an automatic pipette, and the residual acid titrated in the normal way.

Dilatometry was used for acid hydrolyses in aqueous 60% dioxan for perchloric acid concentrations between 0.3 and 0.6M at 25°, with conventional tap dilatometers; first-order rate coefficients were calculated graphically.

The alkaline hydrolysis was followed by acid-base titration. The alkali was lithium hydroxide, made by dissolving lithium metal in the solvent. Hydrolysis was stopped by addition of an excess of standard acid, which was then determined by titration. The concentrations of both ester and hydroxide ion were restricted by their low solubilities in aqueous dioxan. The rate coefficients were calculated graphically from the usual second-order rate equation, or from an alternative approximate form when the initial concentrations of ester (*a*)

¹¹ Hughes, *Trans. Faraday Soc.*, 1938, **34**, 202.

¹² Balfe, Dougherty, Kenyon, and Poplett, *J.*, 1942, 605.

and hydroxide ions (b) were similar: $k_2t = (3a - b - 2x)/[2(a - x)^2] - (3a - b)/2a^2$, where x is the extent of reaction. (This equation is derived by expansion of the usual second-order equation for the special case where the reactants are in similar concentrations.) As an example of alkaline hydrolysis at 0° , with initial molar concentrations of lithium hydroxide and ester of 0.034 and 0.029 respectively, the percentages of reaction after various times (hr., in parentheses) were as follows: 17.2 (1), 29.9 (2), 37.2 (3), 44.7 (4), 50.7 (5). From this, $10^3k_2 = 1.52 \text{ sec.}^{-1} \text{ mole}^{-1} \text{ l.}$

The extent of the capture of carbonium ions by azide ions was estimated by titration of acetic acid produced in complete hydrolysis of a known amount of ester in initially neutral aqueous 70% dioxan, at 100° , in the presence of azide ion. The results of these experiments are:

[NaN ₃] (M)	0	0.148	0.292
Concn. of HOAc in c.c. of 0.0263N-NaOH per 5 c.c. portion	19.76	1.66	0.63
Carbonium ions captured (%)	—	92	97

Hydrolyses of the optically active ester were followed polarimetrically in initially neutral aqueous 70% dioxan at 72.9° . Control experiments showed that the alcohol was optically stable under the conditions of neutral hydrolysis and in the presence of 0.1M-lithium hydroxide. The latter result suggests that carbanions are not formed in these conditions.

Added azide and acetate ions slightly decrease the polarimetrically measured rate of hydrolysis in initially neutral solution, but chloride ions have no effect. This may be, at least partially, because the anions of these weak acids generate small amounts of hydroxide ion which would react rapidly with the ester to give an optically active alcohol, hence reducing the rate of loss of optical activity. Such an effect must be small because both these ions reduce the rate of hydrolysis as measured chemically, whereas hydroxide ions increase it very considerably.

Position of Bond Fission.—This was determined by isolating either product and determining its isotopic composition. The water in the aqueous dioxan contained 0.715 atom % excess of oxygen-18. Hydrolysis in initially neutral aqueous 70% dioxan at 72.9° for 165 hr. gave an alcohol with isotopic abundance of 0.722 atom % excess; that from a control experiment with added acetic acid had an abundance of 0.053 atom % excess. Base hydrolysis in aqueous 70% dioxan ([LiOH] = 0.061M) at 25° for 18 hr. gave an alcohol with isotopic abundance of 0.005 atom % excess. The alcohol was not isolated from experiments on acid hydrolysis because it exchanges completely in the hydrolysis conditions. The exchange of acetic acid is slower than the acid hydrolysis, and to minimise the extent of exchange the reaction was stopped after one half-life and acetic acid isolated as its silver salt.

Silver acetate isolated from acid hydrolyses in aqueous 60% dioxan at 25° ([HClO₄] = 0.191M for 104 min. and [HClO₄] = 0.281M for 70 min.) had isotopic abundances of 0.206 and 0.208 atom % excess respectively. Control experiments with the above concentrations of perchloric acid for 89 and 45 min. respectively gave silver acetate of abundance 0.310 and 0.192 atom % excess respectively.

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