unchanged into scopolamine methyl bromide, that the anticholinergic action of acetylscopolamine methyl bromide is unique unto itself and not due to change prior to arrival at this site.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Kinetics of the Alcoholysis of *o*- and *p*-Nitroacetanilides[1]

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The kinetics of the base-catalyzed alcoholysis of *p*-nitroacetanilide in methanol and ethanol and of *o*-nitroacetanilide in methanol have been studied with the aid of ultraviolet spectrometry. The results are in accord with the normal acyl-oxygen ester hydrolysis mechanism.

Of the common carbonyl reactions of esters and amides susceptible to basic catalysis only the alcoholysis of amides has failed to receive careful kinetic investigation. This is, of course, not particularly surprising in view of the unfavorable equilibrium constant for that reaction in most cases.[2] The interesting discovery of Verkade,[3] that *o*- and *p*-nitroanilides react readily with methanol under catalysis by methoxide ion to give high yields of the corresponding free amine and a methyl ester provided the opening for kinetic examination of this reaction. Since acetylation of the nitroanilines has been shown to cause a marked hypsochromic shift in the ultraviolet spectral band nearest the visible,[4] a suitable method of analysis was thus available. The work reported here was initiated in early 1948 and completed in 1951, but publication was held up in the hope that further work might be accomplished on this interesting reaction. Despite the fact that Verkade[5] reported some semi-quantitative kinetic measurements shortly after this work was commenced, a report of our somewhat more accurate study seems in order.

Experimental

Spectra.—All spectral measurements were carried out using a Beckman model DU spectrometer with matched quartz cells.

Materials.—Methanol was distilled through a bubble-cap column rated at twelve plates and a cut boiling from 64.7–64.9° was treated with furfural and potassium hydroxide.[6] Product boiling at 64.8–64.9° was dried according to Lund and Bjerrum,[7] and the product distilled directly into a storage vessel, fitted with an all-glass automatic syphon and protected from both moisture and carbon dioxide by Drierite and soda lime. Ethanol was prepared in similar manner (excepting the furfural treatment) and a cut boiling over 0.1° was used.

Solutions of the sodium alkoxides were prepared under a dry oxygen-free nitrogen atmosphere by adding sodium freshly cut under dry ether to the cold alcohol in an apparatus carefully protected from atmospheric moisture and carbon dioxide. These solutions were stored in an inert atmosphere and in the dark. Though the solutions were reasonably stable when dilute, freshly prepared solutions were used in all cases. Their concentration was determined by titration with aqueous hydrochloric acid using phenolphthalein. Solutions of hydrogen chloride in methanol and ethanol were prepared by passing the dried gas into cold alcohol. Their concentration was determined by titration against aqueous sodium hydroxide using phenolphthalein.

p-Nitroaniline was Eastman Kodak Co. white label grade crystallized from ethanol to a constant melting point of 150.5–151.0°. *p*-Nitroacetanilide was prepared by acylation of the above product using acetic anhydride and was crystallized from glacial acetic acid. The nearly white crystals melted at 212–213.5°. *o*-Nitroaniline, of similar grade, was recrystallized from 50% aqueous ethanol, m.p. 72.5–73.0°. The corresponding anilide was prepared by direct acylation and crystallized from glacial acetic acid and finally acetone, m.p. 93.0–94.0°.

Kinetic Procedure.—Stock solutions of the anilide in the various alcohols were prepared by adding accurately weighed amounts of the anilide to the proper solvent in a volumetric flask. Initial concentrations were determined from the known concentration of the stock solution. Solutions of both anilide and alkoxide were thermostated prior to each run. Ten-milliliter samples of anilide solution were placed in test-tubes fitted with ground glass stoppers. To initiate a run, tubes were removed from the thermostat at one-minute intervals and appropriate amounts of alkoxide solution added. The bath was maintained at 30.00 ± 0.01° checked against a thermometer calibrated by the National Bureau of Standards. At appropriate intervals tubes were withdrawn from the bath, the base neutralized with alcoholic hydrogen chloride and the optical density determined.

Analytical Method.—Solutions of the amines in the various alcohols were found to obey Beer's law, and though neither anilide nor acid at low concentration caused interference, the presence of anilide and base caused a notable interference. Thus the rate could not be followed directly, and analysis was carried out after neutralization with alcoholic hydrogen chloride. Analysis for *p*-nitroaniline was made at 450 mμ and for *o*-nitroaniline at 500 mμ. Solutions of the amines in the alcohols were stable, being unchanged within experimental error in 148 hr.

Results

The ultraviolet absorption spectra for *o*- and *p*-nitroaniline and the corresponding anilides were determined under a variety of conditions. For

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[3] P. E. Verkade and P. H. Witjens, *Rev. trav. chim.*, **62**, 201 (1943).

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[5] P. E. Verkade and B. M. Wepster, *Rec. trav. chim.*, **67**, 425 (1948); **68**, 77 (1949).

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[7] H. Lund and J. Bjerrum, *Ber.*, **64**, 210 (1931).

TABLE I

ULTRAVIOLET SPECTRA IN ABSOLUTE ETHANOL

Compound	Conditions[a]	λ	ε max	λ	ε max	λ	ε max
p-Nitroaniline	....	228	6,900	..	..	372	16,000
p-Nitroaniline	34 moles HCl	224	9,300	..	..	370	16,000
p-Nitroaniline	16 moles NaOEt	229	6,300	..	..	372	16,000
p-Nitroacetanilide	....	225	3,700	..	..	314	11,500
p-Nitroacetanilide	140 moles NaOEt	<225	>11,000	..	..	315	15,500
o-Nitroaniline	....	231	17,000	276	5000	405	5,400
o-Nitroaniline	150 moles HCl	232	14,000	277	4500	405	5,400
o-Nitroacetanilide	....	232	17,300	275	4500	342	2,750
o-Nitroacetanilide	100 moles NaOEt	232	16,000	..	..	398	2,700

[a] Since the amounts added were small in absolute magnitude they are expressed in moles substance added per mole of material whose spectrum was being determined.

comparison purposes and because some are not recorded elsewhere, the data in absolute ethanol are given in Table I. Those values for which comparable data are available are in good accord with the literature.[8]

The alkoxide ion catalyzed alcoholysis of *p*-nitroacetanilide was studied in methanol and in ethanol, in which solvents the rate was nicely first order in anilide and, in any single run, independent of the base concentration. The data were handled conveniently by obtaining pseudo first-order rate constants (k_1) from the integrated equation ln $a_0/a_t = kt$, where a_0 = the initial anilide concentration and a_t = the anilide concentration at time t (*cf.* Fig. 1). As first-order kinetics demand, the rate was independent of the initial concentration of the anilide which was varied in the several runs by a factor of about three. The rate varied with the catalyst concentration and, as is indicated by Fig. 2, the rate depends on the first power of the catalyst concentration. A similar situation pertains with *o*-nitroacetanilide in methanol. In Table II are listed the second-order rate constants (k_2) obtained from the equation $k_2 = k_1/[\text{RO}^-]$.

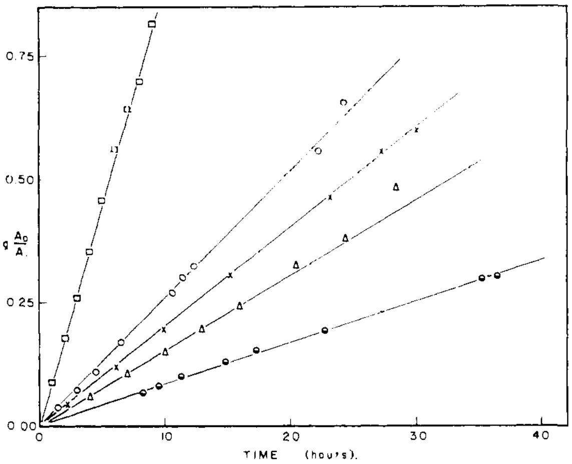

Fig. 1.—Typical first-order plots: ⊖, *p*-nitroacetanilide 0.01414 *M*, MeO⁻ 0.03755 *M*; Δ, *p*-nitroacetanilide 0.03807 *M*, MeO⁻ 0.07840 *M*; ×, *p*-nitroacetanilide 0.03637 *M*, EtO⁻ 0.00818 *M*; O, *p*-nitroacetanilide 0.01970 *M*, EtO⁻ 0.01140 *M*; □, *o*-nitroacetanilide 0.0150 *M*, MeO⁻ 0.00517 *M*.

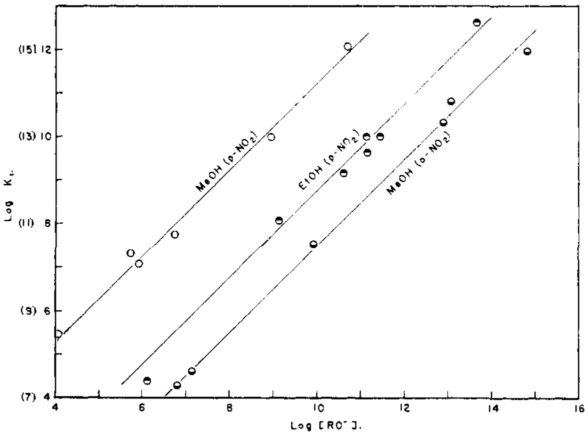

Fig. 2.—Relation between first-order rate constants and catalyst concentration. The figures on the axes are related to the curves as follows: MeOH (*p*-NO₂), *x*-axis = 2 + log [MeO⁻], *y*-axis = 6 + log K_1; EtOH (*p*-NO₂), *x*-axis = 3 + log [EtO⁻], *y*-axis = 6 + log K_1 (use the numbers in parentheses); MeOH (*o*-NO₂), *x*-axis = 3 + log [MeO⁻], *y*-axis = 5 + log K_1 (use the numbers in parentheses).

TABLE II

RATE CONSTANTS IN METHANOL AND ETHANOL

Compound	Solvent	$k_2 \times 10^5$, l./mole sec.
p-Nitroacetanilide	Methanol	0.134 ± 0.006
p-Nitroacetanilide	Ethanol	1.47 ± .07
o-Nitroacetanilide	Methanol	11.0 ± .7

Discussion

Sources of Error.—It is immediately obvious that with the very low concentrations of reactants employed the greatest problem lies in preventing interference by water. However, there is good reason for believing that no such interference occurs in this work. Thus most of the runs were made with both reactant and base of comparable concentration and should water be present in appreciable concentration under such conditions the reaction rate would have been second rather than first order. Furthermore in six runs with *o*-nitroacetanilide in methanol and in five runs with *p*-nitroacetanilide in ethanol the initial catalyst to substrate ratio was considerably less than one. In all these cases the reaction was carried well beyond the point at which the catalyst would have been exhausted had water been present mole for mole with the base. In only one of these cases was the

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(8) *Cf.* (a) W. D. Kumler, THIS JOURNAL, **68**, 1184 (1946); (b) W. R. Remington, *ibid.*, **67**, 1838 (1945); (c) R. A. Morton and A. McGookin, *J. Chem. Soc.*, 901 (1934).

rate constant at the last point significantly lower than at the first point.

Mechanism.—Previous studies of base-catalyzed hydrolysis of esters and amides,[9] ammonolysis of esters[2,10] and ester exchange[11] have indicated that in the case of acyl–oxygen fission all can probably be included in one mechanistic scheme. The O^{18} studies of Bender (see ref. 10a) show that this must involve, for ester hydrolysis at least, an addition of base to the carbonyl group giving an ionic intermediate. For the hydrolysis of amides the O^{18} exchange evidence is permissive and the lack of salt effect[10d] is in accord with that interpretation. The data recorded here permit the inclusion of amide alcoholysis in the same group.

In support of this conclusion the following evidence may be cited. The rate is first order in anilide and first order in base and more rapid when the more basic[12] catalyst ethoxide ion replaces methoxide. Jaffé[13] using the data accumulated by Verkade and his co-workers[14] has shown that a Hammett plot of the rate *versus* σ-constants for various substituents is linear with $\rho = +1.723$. This ρ-value is in good agreement with that for hydroxyl ion catalyzed hydrolysis of ethyl benzoates (+2.37)[15] and that for methoxide ion catalyzed ester exchange of menthyl benzoates (+2.530).[11] Also using the data of Verkade[14] and assuming a temperature of 65° for his work, it is possible to approximate (Table III) energies and entropies of activation for this reaction. The results agree reasonably with values for other reactions in the series as is illustrated by Table IV.

TABLE III

ESTIMATED ENERGIES AND ENTROPIES OF ACTIVATION FOR METHANOLYSIS OF *o*- AND *p*-NITROACETANILIDES

	o-NO_2	*p*-NO_2
$k_2(30°)$	1.10×10^{-2}	1.34×10^{-4}
$k_2(65°)^a$	19×10^{-2}	80×10^{-4}
k_a, kcal./mole	16.7	23.8
$\Delta S^{\pm}(303°)$, cal./deg.-mole	−12.4	2.3

[a] Data from Verkade, *et al.*[14]

TABLE IV

ACTIVATION ENERGIES AND ENTROPIES

Reaction	E_A, kcal./mole	$\Delta S^{\pm}$, cal./deg.	Refer.
p-Nitrobenzamide and OH^-	16.1	−30.0	9c
Menthyl *o*-nitrobenzoate and MeO^-	16.9	−20.4	11
Menthyl *p*-nitrobenzoate and MeO^-	14.8	−19.9	11
Ethyl *o*-nitrobenzoate and OH^-	14.5	−20.4	15
Ethyl *p*-nitrobenzoate and OH^-	14.8	−14.1	15
p-Nitrophenyl acetate and OH^-	11.0	−17.4	15

The spectral results make it seem probable that the alcoholysis reaction is preceded by a rapidly established equilibrium between the catalyst and the substrate. The anilide ion produced thus

$$\text{ArNHCOCH}_3 + \text{OR}^- \rightleftharpoons \text{ArNCOCH}_3^- + \text{ROH}$$

would be expected to show a more intense absorption than the anilide itself. That the reaction is reversible was illustrated by reappearance of the original spectra after neutralization of the base. If the equilibrium constant for the reaction is small, it can be shown easily that the equilibrium will not influence the nature of the kinetic results, which seems to be the case under the conditions of our study.

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[9] For discussion and references see (a) J. Hine, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1956, pp. 266–268, 295–298; also (b) A. Bruylants, *et al.*, *Bull. soc. chim. Belges*, **60**, 191 (1951); **63**, 140 (1954); (c) K. Laidler and I. Meloche, THIS JOURNAL, **73**, 1712 (1951); (d) J. Packer, A. Thompson and J. Vaughn, *J. Chem. Soc.*, 2601 (1955); (e) C. Bunton and O. Spatcher, *ibid.*, 1079 (1956).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY]

Chemistry and Spin Resonance Spectroscopy of Radicals from Thioaromatic Compounds[1]

BY ANTONINO FAVA,[2] P. B. SOGO AND MELVIN CALVIN

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The deeply colored solutions which result when a wide variety of aromatic sulfides are dissolved in concentrated H_2SO_4 are shown to contain free radicals having the thianthrene nucleus. These result from the condensing and oxidizing properties of concentrated H_2SO_4. A simplified system in trifluoroacetic acid has been studied in detail and the radical shown to have an oxidation level lying between the monoxide and dioxide of thianthrene. An interpretation of the spin resonance spectrum permits a choice of specific radical structure.

Recently it has been reported by Hirshon, Gardner and Fraenkel[3] that the sulfuric acid solutions of certain sulfur-containing aromatic compounds show electron spin resonance and contain free radicals in substantial amounts. The substances studied include phenyl and *p*-tolyl disulfides, the corresponding thiols and diphenylene sulfide (Thianthrene). No definite hypothesis was made concerning the nature of the free radicals, although the authors seemed to suggest the formation of a biradical.

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[2] On leave from the University of Padova, Italy. International Cooperation Administration Fellow, 1954–1956.

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