Base-Catalyzed Addition of Ethanol to Acrylanilides[1]

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The kinetics of the hydroxide-catalyzed addition of ethanol to five *para*-substituted acrylanilides has been studied in ethanol at 55°. The observed second-order rate constants could be correlated with Hine's polar substituent constant using a ρ value of 1.77 ± 0.04. The amide link is an efficient transmitter of activation effects in this reaction.

This report is one of a series designed to explore the transmission of electronic effects through amide links. Quite a large body of work exists to correlate reactivity at the carbonyl group with effects of substituents at either the nitrogen or the carbonyl carbon. Much less work has been published to correlate reactivity at the methylene carbon of an N-substituted anilide with structural changes. Structure–reactivity studies in this system have relevance to protein chemistry as well as intrinsic interest in the ability of chains more complex than methylene groups to transmit activation effects in chemical reactions. The work had its inception with the observation that the rate of elimination of hydrogen bromide from N-(β-bromopropionyl)-N′-alkyl- (or aryl-) ureas was increased by a factor of three when the N′ substituent was changed from benzyl to phenyl.[3] The observation indicated that the acylurea system was functioning as an efficient transmitter of electronic effects. The elimination in the acylurea system reaction was very rapid, and it was decided to study the somewhat simpler β-bromopropionylanilides and related compounds.

The present report concerns the hydroxide-catalyzed addition of ethanol to five *para*-substituted acrylanilides chosen to cover a reasonable variation in σ constants,[4] methoxy, methyl, hydrogen, bromo, and carbethoxy. The *p*-nitro derivative was prepared, but its rate of addition could not be studied; large spectral changes occurred when hydroxide was added to an ethanol solution indicating an acid–base reaction at the N–H. Kinetic data on Michael-type reactions[5] are not common, and this also influenced the choice of reaction to be studied.

The anilides were prepared by either of two routes, reaction of acrylyl chloride with the appropriate aniline, or reaction of β-bromopropionyl chloride with the aniline followed by elimination of hydrogen bromide with triethylamine in chloroform.[3] The latter route was found to be more convenient, and the β-bromopropionanilides could be stored easily.

Hydroxide ion was found to catalyze the addition of ethanol to the acrylanilides efficiently; weaker bases such as triethyl amine were less effective. The reaction products were β-ethoxypropionanilides; they were isolated from reactions at the approximate concentrations of the kinetic runs and characterized. No evidence for the presence of β-hydroxypropionanilides was found; 5–10% hydroxy compound might have escaped detection. The kinetics were measured in absolute ethanol, and the reaction was followed by ultraviolet spectroscopy. Since products and starting materials had overlapping ultraviolet maxima, it was necessary to use a two-wavelength Beer's law equation[7] to determine concentrations. Concentrations were reproducible to ±1%, rate constants to ±3%.

The kinetics were found to be pseudo first order in acrylanilide in the presence of excess hydroxide ion. The kinetics of *p*-methylacrylanilide were examined at several base concentrations, and the reaction appeared to be second-order overall—first order in anilide and first order in base. The data is presented in Table I.

TABLE I

ADDITION OF ETHANOL TO *p*-METHYLACRYLANILIDE[a] AT 55°

Concn of OH^-, M	$10^5 k_1$,[b] sec^{-1}	$10^3 k_2$, $M^{-1} sec^{-1}$
9.78×10^{-3}	5.72	5.85
9.80×10^{-3}	5.72	5.84
1.71×10^{-2}	9.52	5.57
1.71×10^{-2}	9.88	5.78
2.11×10^{-2}	1.20	5.68
2.11×10^{-2}	1.18	5.59
Average		5.72

[a] Initial acrylanilide concentration 10^{-4} *M*; [b] Pseudo-first-order rate constant.

A normal Arrhenius plot over the temperature range 45–65° (Table II) gave these activation parameters for *p*-methylacrylanilide: $\Delta G^{\ddagger} = 23.2$ kcal/mol; $\Delta H^{\ddagger} = 20.2$ kcal/mol; $\Delta S^{\ddagger} = 7.3$ cal/deg. The reaction appears to be a normal Michael-type addition. See eq 1–3. The most likely rate-controlling step is the

TABLE II

EFFECT OF TEMPERATURE ON RATE OF ADDITION OF ETHANOL TO *p*-METHYLACRYLANILIDE[a]

Temp, °C	Concn of OH^-, $M \times 10^3$	$10^4 k_1$,[b] sec^{-1}	$10^2 k_2$, $sec^{-1} M^{-1}$
65.0 ± 0.05	9.48	1.45	15.3
55.0 ± 0.05	See Table I		5.72
50.0 ± 0.05	8.96	3.53	3.94
45.0 ± 0.05	9.73	2.14	2.20

[a] Initial anilide concentration 10^{-4} *M*; [b] Pseudo-first-order rate constant.

$$OH^- + C_2H_5OH \rightleftharpoons C_2H_5O^- + H_2O \qquad (1)$$

$$C_2H_5O^- + CH_2{:}CHCONHAr \longrightarrow C_2H_5OCH_2CH^-CONHAr \qquad (2)$$

$$C_2H_5OCH_2CH^-CONHAr + C_2H_5OH \rightleftharpoons C_2H_5COH_2CH_2CONHAr + C_2H_5O^- \qquad (3)$$

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(2) (a) NSF Undergraduate Research Participant, 1966–1967. (b) From senior research problem of V. A. Pena.

(3) H. W. Johnson, Jr., and M. Schweizer, *J. Org. Chem.*, **26**, 3666 (1961).

(4) L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Company, Inc., New York, N. Y., 1940, p 186. H. H. Jaffe, *Chem. Rev.*, **53**, 191 (1953).

(5) For general reference, see E. D. Bergmann, D. Ginsburg, and R. Pappo, *Org. Reactions*, **10** (1959). The first kinetic study is apparently that of Kamlet and Glover.[6]

(6) M. J. Kamlet and D. J. Glover, *J. Amer. Chem. Soc.*, **78**, 4556 (1956).

(7) H. H. Willard, L. L. Merritt, Jr., and J. A. Dean, "Instrumental Methods of Analysis," 4th ed, D. Van Nostrand Co., Inc., Princeton, N. J., 1965, p 94.

addition of ethoxide; though not determined specifically in this work, it would be very surprising if either the first or third steps were rate-determining. The high positive ρ described below also supports the addition as the rate step. No indications of equilibrium attainment[5] were observed; the infinity absorbances were the same as the absorption of the pure product at the same concentration. At each kinetic point the entire ultraviolet spectrum of the mixture was scanned; a single pair of maxima with an isosbestic point was obtained. The position of the maximum was essentially that of the product or starting material in ethanol in the absence of base. Occasional nmr scans of reaction mixtures at higher concentrations adduced no evidence for the presence of extraneous materials. Thus within the limits of detection of ultraviolet spectroscopy and nmr spectra, no material was present other than starting materials or final products.

The results of the addition of ethanol to the substituted acrylanilides in ethanol at 55° are shown in Table III with the Hine polar substituent constants[8–10] for the appropriate group. The best least-squares line has a slope corresponding to a ρ value of a 1.77 ± 0.04. A plot of log rate constant *vs.* the Hammett σ constant shows distinct curvature.[4,10]

TABLE III

RATE OF ADDITION OF ETHANOL TO *para*-SUBSTITUTED ACRYLANILIDES AT 55°

p-X	σ^a	$10^5\,k_1$,^{b} sec^{-1}	Concn of OH$^-$, $M \times 10^3$	$10^3\,k_2$, M^{-1} sec^{-1}
$-OCH_3$	−0.17	4.09	9.16	4.47
$-CH_3$	−0.13	5.72	9.78	5.72
H	0	8.43	8.60	9.80
Br	+0.25	27.1	10.9	24.9
$-CO_2C_2H_5$	+0.46	56.0	8.96	62.5

[a] Hine's polar substituent constants. Reference 8. [b] Pseudo-first-order rate constant. Acrylanilide concentration 10^{-4} M in all cases.

No really good model systems seem to be available for comparison with the present results. The addition of *t*-butyl amine to *para*-substituted aryl vinyl sulfones in ethanol at 25° gave a ρ value of +1.59.[11] A ρ of +1.0 was obtained for the β acyl group in the addition of methoxide to *trans*-dibenzoylethylenes.[12] The reaction of 1,1-diaryl-2-chloroethylenes with ethoxide shows a ρ value of 3.55 at 120° (using "normal" substituent constants).[13] Two reactions in which the substituted aromatic ring is on the carbon atom to which the attacking anion becomes attached have been reported, the reaction of barbituric acid with β-nitrostyrenes in dioxane–water at 30° (ρ +0.74)[6] and the addition of cyanoacetic ester to cinnamoylferrocenes with a ρ of 0.65 at 30°.[14] The ρ value found for the addition of ethoxide to acrylanilides in ethanol at 55° compares in magnitude with those reported above. The amide function is apparently serving as an efficient transmission medium for activation effects in this reaction where substantial negative charge is developed in the transition state.

Differences in the ability of the carbonyl group to support the negative charge in the transition state are presumably responsible for the results obtained. The carbonyl group is cross conjugated with the aromatic ring through the nitrogen atom. However, the presence of the nitrogen atom seems to make little difference in the ability of the aromatic ring to affect the carbonyl group as ring substituents change. The amide link is planar with about 40% contributions from the form with C:N as estimated by Pauling[15] and from[13] C–H coupling constants.[16] A very mobile, polarizable system of unshared electrons and p orbitals is available from the ring to the negative charge, and is probably responsible for the efficient transmission activation effects.

Other reactions are being studied to determine the efficiency of the amide and other similar groups in transmission of electronic activation effects.

Experimental Section

Melting points are uncorrected, and were measured with a Thomas Unitemp bath.

Kinetic Determinations.—The solutions of potassium hydroxide in absolute ethanol were prepared fresh for each kinetic run and were standardized by titration with 0.01 M sulfamic acid. The determinations were conducted in a 300-ml three-necked flask equipped with a Teflon-coated magnetic stirring bar, a condenser, a rubber septum, and a stopper. The flask was flushed with prepurified, carbon dioxide free nitrogen and a static pressure of nitrogen was maintained throughout the run. In a run 200 ml of the hydroxide solution were placed in the flask and allowed to equilibrate thermally for about 0.5 hr; the acrylanilide (weighed on a microbalance) was then added to give a 10^{-4} M solution. Samples were withdrawn with a hypodermic syringe and placed in 5-ml glass stoppered volumetric flasks precooled with Dry Ice. Samples were kept at −77° until the run was completed, whereupon they were allowed to come to room temperature and the ultraviolet absorption spectrum was measured with a Perkin-Elmer Model 450 spectrophotometer. Repetition of the freeze–thaw measurement cycle gave constant absorbance values indicating no appreciable reaction during the measurement cycle. Approximately 12–20 points were taken throughout three half-lives; the infinity value was taken approximately 8 hr after completion of the points; and three samples taken 1 hr apart showed no change in absorption. The ϵ's were identical with those from known products and starting materials at the same concentrations. The absorption curves were the same in the hydroxide solutions as in pure absolute ethanol. The data were analyzed using a two-parameter Beer's Law equation.[7] Good pseudo-first-order rate constants were noted to beyond 90% reaction. The average error in rate constant for a single run was 1.5%. In replicate determinations 3% agreement between runs was noted. The largest error in duplication of results appeared to be the result of carbon dioxide contamination of the alcoholic hydroxide solutions.

Attempts were made to quench the reaction by adding a sample to excess hydrochloric or acetic acid; the absorbance of the samples so treated varied with time. An acid-catalyzed reaction apparently occurred with an appreciable rate at room tempera-

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(8) J. Hine, *J. Amer. Chem. Soc.*, **82**, 4877 (1960).

(9) (a) For general discussions of σ scales see C. D. Ritchie and W. F. Sager in "Progress in Physical Organic Chemistry," S. G. Cohen, A. Streitweiser, and R. W. Taft, Ed., Vol. 2, Interscience Publishers, New York, N. Y., 1964, p 323; (b) S. Ehrenson, ref 9a, Vol. 2, p., 195; (c) P. R. Wells, S. Ehrenson, and R. W. Taft, ref 9a., Vol. 6, 1968, p 147.

(10) Insufficient data is at hand to discuss extensively choice of σ-scales in the present work. The emphasis here is simply to determine whether the amide link is an efficient transmitter of electronic effects. The comment of Ritchie and Sager, ref 9a, p 324, concerning σ values and library facilities is apt. In other reactions of functional groups at the methylene carbon of substituted acetanilides, where more data is being accumulated, it is clear that the Hammett σ scale is not appropriate.

(11) S. T. McDowell and C. J. M. Stirling, *J. Chem. Soc., B*, 348 (1967).

(12) T. I. Crowell, G. C. Helsley, R. E. Lutz, and W. L. Scott, *J. Amer. Chem. Soc.*, **85**, 443 (1963).

(13) P. Beltrame, P. L. Beltrame, O. Sighinolfi, and M. Simonetta, *J. Chem. Soc., B*, 1103 (1967).

(14) M. Furdik and S. Toma, *Chem. Zvesti*, 326 (1966); *Chem. Abstr.*, **65**, 7015 (1966).

(15) L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960, p 281.

(16) P. Haake, W. B. Miller, and T. A. Tyssee, *J. Amer. Chem. Soc.*, **86**, 3577 (1964).

ture. The freeze–quench method made quantitative transfer of samples unnecessary, since the sample withdrawn could be measured directly in the 1-cm cell. Table IV gives the wavelengths and extinction coefficients used in analyzing the data.

Activation parameters were calculated from $\Delta H^{\ddagger} = \Delta E_a - RT$; $\Delta S^{\ddagger}/4.576 - \log k - 10.753 - \log T + E_a/4.576T$; $\Delta G^{\ddagger} = \Delta H^{\ddagger} - T\Delta S^{\ddagger}$.

TABLE IV

ABSORPTION MAXIMA OF ACRYLANILIDES AND β-ETHOXYPROPIONANILIDES IN ETHANOL

p-X	Acrylanilide, λ_{max} ($10^4\ \epsilon$)	β-Ethoxypropionanilide, λ_{max} ($10^4\ \epsilon$)
$-OCH_3$	285 (1.32)	252.5 (1.64)
$-CH_3$	277.5 (1.20)	247.5 (1.60)
H	270 (1.08)	245.0 (1.49)
Br	275 (1.45)	252.5 (1.95)
$-CO_2C_2H_5$	290 (2.42)	272 (2.40)

Syntheses of β-Bromopropionanilides.—In a typical example 1 g of ethyl p-aminobenzoate was dissolved in 20 ml of anhydrous ether and mixed with 1 g of β-bromopropionyl chloride diluted with 10 ml of anhydrous ether. After filtering off the fluffy white precipitate of amine hydrochloride, the filtrate was washed with 5% hydrochloric acid and with water, and then evaporated on a rotary evaporator to yield yellow crystals. The yellow crystals were recrystallized from chloroform: p-H, mp 119–120° (lit. mp 119–120°); p-Br,[17] mp 135–136°; p-CH_3,[18] mp 137–138; p-OCH_3,[17] mp 111–112°; p-$CO_2C_2H_5$,[17] mp 119–120°.

Synthesis of Acrylanilides.—In a 50-ml pear-shaped flask equipped with a reflux condenser were placed 1 g of the bromopropionanilide, 20 ml of chloroform, and 1.5 ml of triethylamine. The solution was refluxed 1 hr and then cooled to room temperature. After washing three times each with 20 ml of water, 20 ml of 3 *M* hydrochloric acid, and water, the chloroform was dried with calcium chloride. After filtering the calcium chloride the chloroform was removed on a rotary evaporator, and the residue crystallized from chloroform–carbon tetrachloride. Most samples were then sublimed at reduced pressure: p-H, mp 93–95° (lit. mp 93–94°); p-Br,[17] mp 178–179°; p-CH_3,[17,19] mp 138–139°; p-OCH_3,[17,19] mp 91–92°; p-$CO_2C_2H_5$, mp 113–114° (lit. mp 110–112°).[18]

Synthesis of β-Ethoxypropionanilides.—These were prepared from the bromo compounds by the action of sodium hydroxide and ethanol. In a typical example 52 mg. of β-bromopropionanilide (2.3×10^{-4} mol) was dissolved in 200 ml of 0.030 *M* ethanolic potassium hydroxide and the solution was heated at 55° for 24 hr. After cooling, 0.5 *M* hydrochloric acid was added to an apparent pH of 6 (indicator paper). The solution was evaporated to 20 ml, and filtered with a Büchner funnel. The potassium chloride was washed with chloroform, and the combined filtrate and washings were evaporated on a rotary evaporator. The crude product was sublimed to yield 31 mg (80%) of product. Each preparation was repeated using 50 mg of the acrylanilide and 200 ml of approximately 0.015 *M* ethanolic potassium hydroxide; the work-up and yields were the same as for the bromo compounds. Two triplets were found for the methylene protons and the triplet–quartet pattern of the ethoxy group was easily identified in nmr spectra of the products: p-H,[17] mp 42–44°; p-Br,[17] mp 93–94°; p-CH_3, mp 63–64° (lit. mp 59–60°);[20] p-OCH_3,[17] mp 59–60°; p-$CO_2C_2H_5$,[17] mp 102–103°.

Registry No.—Ethanol, 64-17-5; 3,4′-dibromopropionanilide, 7661-10-1; 3-bromo-4′-methoxypropionanilide, 7661-14-5; 3-bromo-4′-ethoxycarbonylpropionanilide, 21690-53-9; acrylanilide, 2210-24-4; p-bromoacrylanilide, 13997-69-8; p-methylacrylanilide, 7766-36-1; p-methoxyacrylanide, 7766-37-2; p-ethoxycarbonylacrylanilide, 14745-58-5; β-ethoxypropionanilide, 21690-58-4; 4′-bromo-3-ethoxypropionanilide, 21690-59-5; 3-ethoxy-4′-methylpropionanilide, 21690-60-8; 3-ethoxy-4′-methoxypropionanilide, 21690-61-9; 3-ethoxy-4′-ethoxycarbonylpropionanilide, 21690-62-0.

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(17) Satisfactory C, H, and N analyses (±0.3%) were obtained for this compound.

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The Synthesis and Stereochemical Characterization of Derivatives of *cis*- and *trans*-3-Ethyl-4-piperidineacetic Acid[1a]

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Ethyl 1-benzoyl-3-ethyl-$\Delta^{4,\alpha}$-piperidineacetate (**4**) and ethyl 1-benzoyl-3-ethyl-1,2,3,6-tetrahydropyridine-4-acetate (**5**) have been prepared from 1-benzoyl-3-ethyl-4-piperidone by the phosphonate modification of the Wittig reaction. Compound **4** is partially isomerized into **5** in the presence of base. Catalytic reduction of **4** has been shown to give primarily ethyl *cis*-1-benzoyl-3-ethyl-4-piperidineacetate while **5** gives mainly ethyl *trans*-1-benzoyl-3-ethyl-4-piperidineacetate. The stereochemistry of these products has been established by interrelation with *cis*-1-benzoyl-3-ethyl-4-piperidineacetonitrile from cinchonine *via* trimethylsilyl derivatives of 3-ethyl-1-methyl-4-piperidineethanol. The literature assignments of stereochemistry to the *cis* and *trans* isomers of ethyl 5-ethyl-2-oxo-4-piperidineacetate are shown to be in error.

The 3-ethyl-4-piperidineacetic acid skeleton constitutes an important portion of the nonaromatic framework of a number of isoquinoline and indole alkaloids. In connection with synthetic work in the latter area we required a convenient source of 3-ethyl-4-piperidineacetic acid derivatives capable of functionalization at C-5 and having a known stereochemical relationship between the ethyl and acetic acid groups. Two compounds are of particular interest. Stork and McElvain[2] prepared ethyl 3-ethyl-4-piperidineacetate (**1**) but were able only to make a tentative (*cis*) stereochemical assignment. Evstigneeva and Preobrazhenskaya[3] have reported the preparation of crystalline (**2a**, mp 84–85°) and oily stereoisomers (**2b**) of ethyl 5-ethyl-2-oxo-4-piperidineacetate (**2**) and assigned *cis* stereochemistry to the crystalline isomer and *trans* configuration to

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