0.55 g. of colorless liquid to distill into the receiver. The residue in the reaction flask (unchanged diphenylacetamidine) solidified on cooling. The infrared spectrum of the distillate (determined with a Beckman IR-7 spectrophotometer) exhibited only peaks appearing in the spectra of authentic samples of aniline and ethyl *N*-phenylacetimidate. Twenty of these peaks (at 663, 870, 905, 930, 950, 1005, 1095, 1165, 1375, 1393, 1447, 1537, 1660, 1735, 1985, 2030, 2480, 2560, 2870, and 2980 wave numbers) appear in the spectrum of ethyl *N*-phenylacetimidate, but not in that of aniline. A rough quantitative calculation of the composition of the liquid reaction product from spectral transmittancy data showed that it consisted of approximately equimolar amounts of aniline and ethyl *N*-phenylacetimidate.

Preparation of N,N'-diphenylacetamidine from aniline and ethyl orthoacetate. A mixture of 0.4 mole (37.2 g.) of aniline, 0.2 mole (32.4 g.) of ethyl orthoacetate, and a few milligrams of *p*-toluenesulfonic acid monohydrate was heated in a 100-ml. round bottomed flask having a thermometer well and fitted with a Claisen head, adapter, and receiver. Ethanol distilled over rapidly at first, then much more slowly, and the temperature of the reaction flask rose from 90° to 196°. After 2.5 hr., evolution of ethanol had practically ceased. The reaction mixture was heated overnight at 170°. Upon cooling, it partially crystallized. Flash distillation of the reaction mixture at 0.001 mm., using a Dry Ice-cooled receiver, yielded 13.6 g. of liquid distillate whose infrared spectrum exhibited only peaks attributable to aniline and ethyl *N*-phenylacetimidate. The crude, crystalline N,N'-diphenylacetamidine remaining in the reaction flask weighed 30.4 g. (72%). Recrystallization from aqueous ethanol yielded 26.4 g. of colorless crystals, m.p. 134.5–136°. This corresponds to an over all yield of purified product of 63%.

Attempted preparation of ethyl N-phenylacetimidate from N,N'-diphenylacetamidine and ethyl orthoacetate. Ethyl orthoacetate (0.14 mole, 25 ml.), N,N'-diphenylacetamidine (0.10 mole, 21.0 g.), and a few milligrams of *p*-toluenesulfonic acid monohydrate were heated in a 50-ml. round bottomed flask fitted with a 15-cm. glass helix-packed column, total reflex-partial take-off still head, and receiver. A total of 8.22 g. of ethanol, b.p. 75–80°, was collected at the still head during a 22-hr. period (theoretical yield of ethanol for formation of ethyl *N*-phenylacetimidate, 4.6 g.). At this point the reaction mixture was cooled, whereupon it partially solidified. Reduced pressure distillation of the reaction mixture, using a 10-cm. semi-micro Vigreux column, yielded 8.25 g. of unchanged ethyl orthoacetate (b.p. 60–68° at 41.5 mm.), a small intermediate fraction, and 3.2 g. of a colorless liquid, b.p. 112–112.5° at 40.6 mm. At this point, distillation ceased and the temperature at the bottom of the Vigreux column rose to 180°. The residue in the reaction flask, assumed to be N,N'-diphenylacetamidine, solidified completely on cooling. The higher boiling distillate fraction had an odor similar to that of ethyl orthoacetate. Since its infrared spectrum was completely different from that of ethyl *N*-phenylacetimidate and showed no peaks assignable to C_6H_5—, this material is assumed to have been formed by decomposition of ethyl orthoacetate. Its identity was not established.

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GOLETA, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT SANTA BARBARA]

Mechanism of Acid-Catalyzed Hydrolysis of N,N'-Diarylacetamidines

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The effects of aryl substituents, temperature, and solvent acidity on the rate of hydrolysis of symmetrically substituted N,N'-diarylacetamidines in acidic 20% dioxane solutions have been studied. The acetamidines hydrolyze by essentially the same mechanism as that previously proposed for N,N'-diarylformamidine hydrolysis, but are less than one one-thousandth as reactive. The reason for this unusually large reactivity difference between acetic acid and formic acid derivatives is discussed.

A recent study of the effect of aryl substituents, temperature, solvent polarity, solvent acidity, and nucleophilic catalysts on the rate of hydrolysis of N,N'-diarylformamidines [Equation (1), R = H]

$$\mathrm{Ar{-}NH{-}CR{=}N{-}Ar} + \mathrm{H_2O} \longrightarrow \mathrm{Ar{-}NH{-}CRO} + \mathrm{Ar{-}NH_2} \quad (1)$$

led to the conclusion that the reaction involves nucleophilic attack by water on hydrated amidinium ions.[1] In order to determine whether diarylacetamidines undergo acid hydrolysis [Equation (1), R = CH_3] by the same mechanism, and to assess the effect of the acetamidine C-methyl group on reactivity, a similar study of the hydrolysis of several symmetrical N,N'-diarylacetamidines was undertaken.

(1) R. H. DeWolfe, *J. Am. Chem. Soc.*, **82**, 1585 (1960).

EXPERIMENTAL

The dioxane used in the reaction solutions was purified by the procedure of Fieser.[2] Reagent grade inorganic chemicals were used in preparing all of the kinetic solutions. The symmetrically substituted N,N'-diarylacetamidines used in this study were prepared from the appropriate arylamines and acetanilides by the procedure of Bradley and Wright[3] or that of Oxley, Peak, and Short.[4] All are known compounds except N,N-di-*m*-chlorophenylacetamidine and N,N'-di-*p*-chlorophenylacetamidine.

N,N'-Di-m-chlorophenylacetamidine, m.p. 86.5–87.5°. *Anal.* Calcd. for $C_{14}H_{12}N_2Cl_2$: C, 60.22; H, 4.33. Found: C, 60.32; H, 4.37.

N,N'-Di-*p*-chlorophenylacetamidine, m.p. 115–116°.

(2) L. F. Fieser, *Experiments in Organic Chemistry*, Third ed., D. C. Heath and Co., New York, N. Y., 1955, p. 284.

(3) W. Bradley and I. Wright, *J. Chem. Soc.*, 646 (1956).

(4) P. Oxley, D. A. Peak, and W. F. Short, *J. Chem. Soc.*, 1618 (1948).

Anal. Calcd. for $C_{14}H_{12}N_2Cl_2$: C, 60.22; H, 4.33. Found: C, 60.05; H, 4.28.

Because of the very slight solubility of diarylacetamidines in water, aqueous dioxane was used as the solvent for kinetic experiments. Reaction solutions were prepared as described in reference (1).

Except at 86.0° and 100°, hydrolysis rates were determined spectrophotometrically using the apparatus and procedure described previously.[1] The rates measured at 86.0° and 100° were determined by spectrophotometric analysis of aliquots of the reaction mixture which had been sealed in evacuated glass vials and heated for measured time intervals in a thermostatted bath before being quenched for analysis.

First order rate constants, energies of activation, and entropies of activation were calculated by the usual procedures.[1] The rate constants given in Table I are averages of at least three runs.

RESULTS AND DISCUSSION

A number of symmetrical *N,N'*-diarylacetamidines were hydrolyzed at two or three temperatures in aqueous 20% dioxane which was 0.415*N* in hydrochloric acid. The kinetic data are summarized in Table I.

TABLE I

HYDROLYSIS OF *N,N'*-DIARYLACETAMIDINES (XC_6H_4—NH—$C(CH_3)$=N—C_6H_4X) IN 20% DIOXANE–AQUEOUS 0.415*N* HCl

X	T (°C.)	10^6k_1 (sec.$^{-1}$)
p-CH_3O	86.0	0.51
p-CH_3O	100	1.9
p-CH_3	86.0	1.75
p-CH_3	100	3.7
m-CH_3	86.0	2.6
m-CH_3	100	8.5
H	86.0	4.2
H	100	14.6
p-Cl	52.2	0.98
p-Cl	67.8	4.6
p-Cl	84.1	19.3
m-Cl	52.2	2.86
m-Cl	67.8	13.6
m-Cl	84.1	53
p-NO_2	25.0	76.5
p-NO_2	35.0	194
p-NO_2	50.0	550

Acid hydrolysis of diarylacetamidines, like that of the diarylformamidines,[1] is strongly accelerated by electron-withdrawing aryl substituents. The least squares slopes of Hammett $\rho\sigma$ plots[5] of the rate data for all of the acetamidines studied except *N,N'*-di-*p*-nitrophenylacetamidine yielded $\rho = 3.11$ at 86.0° and $\rho = 3.10$ at 100°. (In these calculations, rates for the *m*- and *p*-chlorophenylacetamidines were estimated by extrapolation from rates at lower temperatures.)

Arrhenius activation energies and entropies of activation were calculated for the *p*-nitro-, *p*-chlolo-, and *m*-chlorophenylacetamidines, for which kinetic data at three temperatures were available. The effect of substituents on rates is due to their influence on activation energies, electron-withdrawing substituents lowering the energy of activation. As is true for diarylformamidines,[1] the entropy of activation has a large negative value which does not vary appreciably with structure of the aryl group (Table II). The temperature-independence of the Hammett ρ value for diarylacetamidine hydrolysis is further evidence for the lack of influence of *m*- and *p*-aryl substituents on ΔS^*.[6] For comparison, Table II also lists energies and entropies of activation for *N,N'*-di-*m*-chlorophenylformamidine and *N,N'*-di-*p*-chlorophenylformamidine.[1] The strong rate-decreasing effect of the diarylacetamidine C-methyl group is due mainly to a 5 kcal./mole increase in activation energy when H on the amidine carbon atom is replaced by CH_3.

TABLE II

QUANTITIES OF ACTIVATION FOR HYDROLYSIS OF XC_6H_4—NH—CR=N—C_6H_4X IN 20% DIOXANE–AQUEOUS 0.415*N* HCl

X	E_a, kcal./mole		ΔS^*, e.u. (52°)	
	R = H	R = CH_3	R = H	R = CH_3
p-NO_2	—	16.9	—	−23
m-Cl	16.4	21.1	−20	−22
p-Cl	17.2	21.4	−22	−22

It was found that the rate of diarylformamidine hydrolysis diminishes rapidly as the acidity of the reaction solution increases. The rate of hydrolysis of the formamidines in strongly acidic solutions is described by the equation:

$$k = C\cdot[H_3O^+]a_{H_2O}/h_0 \qquad (1)$$

Diarylacetamidine hydrolysis has a similar dependence on reaction medium acidity, although this dependence was not thoroughly studied because of the very slow rates of reaction in strongly acidic solutions. The rate of hydrolysis of *N,N'*-di-*m*-chlorophenylacetamidine in 20% dioxane at 84.1° was 5.5×10^{-5} sec.$^{-1}$ when [HCl] = 0.08*N*, and 6.5×10^{-6} sec.$^{-1}$ when [HCl] = 5.0*N*.

The kinetic data, and quantities derived from them, indicate that diarylacetamidine hydrolysis and diarylformamidine hydrolysis have the same mechanism.[1] The strong rate-accelerating effect of electron-withdrawing aryl substituents, the effect of medium acidity on rate of hydrolysis, and the large negative entropy of activation, are all adequately accounted for by a rate-determining nucleophilic attack by water on the amidinium or hydrated amidinium ion.

The very large difference in reactivity between the diarylformamidines and the diarylacetamidines is also in agreement with the proposed mechanism of hydrolysis. The formamidines hydrolyze from 1000 to 2500 times more rapidly in acidic 20%

(5) L. P. Hammett, *Physical Organic Chemistry*, McGraw-Hill Book Company, Inc., New York, N. Y., 1940, p. 184.

(6) J. E. Leffler, *J. Phys. Chem.*, **23**, 2199 (1955).

TABLE III

RELATIVE REACTIVITIES OF DIARYLFORMAMIDINES AND DIARYLACETAMIDINES (X—C_6H_4—N=CR—NH—C_6H_4—X, R = H, CH_3) TOWARD HYDROLYSIS IN 20% DIOXANE–AQUEOUS 0.415N HCl

X	T, °C	10^4k_H[a]	$10^7k_{CH_3}$	k_H/k_{CH_3}
p-CH_3O	86.0	5.0	5.1	980
p-CH_3	86.0	17	17.5	971
m-CH_3	86.0	44	26	1692
H	86.0	65	42	1548
p-Cl	52.2	24	9.8	2449
m-Cl	52.2	66	28.6	2308

[a] Rate constants calculated from data at other temperatures (Ref. 1).

dioxane than do the corresponding acetamidines (Table III). Acid hydrolysis of formate esters, on the other hand, is only 20–30 times faster than acid hydrolysis of acetate esters.[7]

The very great sensitivity of amidine acid hydrolysis to structural changes in the amidine molecule is due to the fact that amidines are much stronger bases than carboxylate esters. With the esters, equilibrium is reached in dilute aqueous acid solutions when only a minute fraction of the ester is protonated. That is, for equilibrium II, $K<<1$. Replacing H of HCO_2R' with the electron-

$$\underset{\text{II}}{RCO_2R' + H_3O^+ \overset{K}{\rightleftharpoons} RCO_2HR'^+ + H_2O}$$

releasing methyl group of CH_3CO_2R' should increase the equilibrium concentration of the reactive conjugate acid of the ester, while simultaneously decreasing its susceptibility to nucleophilic attack by water. For acid-catalyzed ester hydrolysis, these opposing substituent effects tend to cancel each other. This is in agreement with the fact that Hammett's ρ for ethyl benzoate hydrolysis is approximately zero in acid solutions,[8] and is supported by Taft's conclusion that the rate of acid-catalyzed carboxylate ester hydrolysis is practically independent of the electronic (but not the steric) properties of R in RCO_2R'.[9]

The amidines, which are much stronger bases than are esters, are present almost exclusively as amidinium ions in dilute solutions of mineral acids; *i.e.*, for equilibrium III, $K>>1$. The most

$$\underset{\text{III}}{Ar{-}NH{-}CR{=}N{-}Ar + H_3O^+ \overset{K}{\rightleftharpoons} Ar{-}NH{-}\overset{+}{C}R{=}NH{-}Ar + H_2O}$$

important effect of the acetamidine C-methyl group, according to the proposed mechanism of amidine acid hydrolysis, is its influence on the susceptibility of the amidinium ion or hydrated amidinium ion to nucleophilic attack by water molecules. An electron-releasing methyl group bonded to the site of nucleophilic attack should repel approaching nucleophiles by both its polar and steric properties, and should also render more difficult the bond-breaking process. These three factors, all acting to decrease reactivity, probably account for the very small reactivity of diarylacetamidines, compared to the analogous formamidines.

The foregoing considerations may be generalized to apply to all A-2 solvolysis reactions: Polar substituent effects on acid-catalyzed bimolecular solvolyses are greatest when the solvent is so acidic that the reactant is present predominantly in the form of its conjugate acid. This rule applies only to the effect of substituents on *relative* reaction rates, since the absolute rate for a particular compound will decrease with increasing acidity once the compound is nearly completely protonated, due to diminishing activity of the solvent.

With weakly basic substrates at low acidities, changing the polar properties of substituents causes opposing shifts in the equilibrium concentration of the reactive conjugate acid and its rate of reaction with solvent, so that polar effects on observed reaction rate are small.[9] When the substrate is almost completely protonated, however, reactivity will be determined only by the susceptibility of the conjugate acid to nucleophilic attack, and polar substituent effects will be much more pronounced.

Available kinetic data permit only a limited test of the validity of this hypothesis as applied to reactions of substances having alkyl substituents on the carbon atom which undergoes nucleophilic attack. The most reliable test case is acid hydrolysis of carboxamides, which are intermediate in basicity between carboxylate esters and amidines. It can be shown from the data of Rabinovitch and Winkler[10] that formamide hydrolyzes 107 times faster than acetamide in 8.5M hydrochloric acid, but only 16 times faster in 1.0M hydrochloric acid. The case of carboxylate ester hydrolysis is less clear cut, owing to the much lower basicity of esters. However, the data of Bell and co-workers[7] show that ethyl formate hydrolyzes 27 times faster than ethyl acetate in 3M hydrochloric acid, and 37 times faster in 7M hydrochloric acid.

Alkyl substituents at the reaction site exert both steric and polar effects on reactivity. A reaction for which only electronic substituent effects are important is the acid hydrolysis of benzamides. Leisten found that this reaction is strongly ac-

(7) R. P. Bell, A. L. Dowding, and J. A. Noble, *J. Chem. Soc.*, 3106 (1955).

(8) See Ref. (5), p. 191.

(9) R. W. Taft in M. S. Newman, *Steric Effects in Organic Chemistry*, John Wiley and Sons, Inc., New York, N. Y., 1956, p. 587.

(10) B. S. Rabinovitch and C. A. Winkler, *Can. J. Research*, **20B**, 73 (1942).

celerated by electron-withdrawing substituents in aqueous solutions above $6M$ in perchloric acid ($\rho = +1.2$),[11] while in weakly acidic solutions the reaction is relatively insensitive to substituent effects ($\rho = +0.118$).[5]

(11) J. A. Leisten, *J. Chem. Soc.*, 765 (1959).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

Applicability of the Hammett Equation to the Indole System: Acidity of Indole-3-carboxylic Acids[1]

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The acidities of six 5- and 6-substituted indole-3-carboxylic acids were determined in aqueous ethanol and their pK's were plotted against the Hammett substituent constants of the respective substituents. A good correlation was obtained using the one term Hammett equation ($\log K/K^\circ = \rho\sigma$) using σ_m for groups in the 5- position and σ_p for groups in the 6- position. These results are taken to indicate that electronic effects are transmitted to the acid center through the carbon para to the 6- position and that virtually no transmission occurs through the indole nitrogen atom. It was also found that the 5-bromoindole-3-carboxylic acid is somewhat less acidic than expected, an effect attributed to steric and electronic factors. Infrared data indicate that whereas the 6-aminoindole-3-carboxylic acid exists as the free acid, the 5-amino isomer exists in its zwitterionic form.

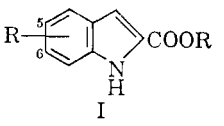
A vast amount of literature has been as accumulated relating to the applicability of the Hammett equation to monocyclic compounds. Much less is known regarding the transmission of electrical effects from one ring to a site on an adjacent ring of a fused ring system. Pioneer work in this problem area has been done by Jaffé.[3]

An additional feature that has not been extensively studied is the transmission of electrical effects through such a fused ring system wherein one of the rings contains a hetero-atom. One such study involved the application of the Hammett equation to the quinoline system.[4] In order to study the transmission of electrical effects from sites within a benzene ring to a site on a fused heterocyclic ring, the author chose for study the indole-3-carboxylic acid system. Previous work in these laboratories concerned the indole-2-carboxylic acid system and the coumarilic acid system.[5] The previous work showed that in the indole-2-carboxylic system I (acid pK's and ester hydrolysis rate constants being used in the log k/k° term of the equation) there is a good qualitative agreement with the following equation for groups in the 5- position

$$\log k/k^\circ = \rho_{CH}\sigma_m + \rho_{NH}\sigma_p \quad (1)$$

and for groups in the 6- position

$$\log k/k^\circ = \rho_{CH}\sigma_p + \rho_{NH}\sigma_m \quad (2)$$



I

The ratio of ρ_{CH}/ρ_{NH} was found to be close to unity.[5] Thus transmission to the 2- position occurs both through the nitrogen and through the carbon joined to the benzene ring. This is in accord with the previous study.[3]

Another interesting study relating to the transmission of electrical effects in the indole system was made by Hall and co-workers.[6] These authors studied the rates of reaction of the enzyme tryptophanase using 5- and 6-substituted tryptophans. They found that groups (chloro and methyl) in these positions gave a very good agreement with the equation:

$$\log k/k^\circ = \rho\sigma \quad (3)$$

when σ_p values were used for groups in the 5- position σ_m values were used for groups in the 6- position. From these results they conclude that the reaction with the enzyme occurs at the 1- position (the indole nitrogen atom).

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(3) H. H. Jaffé, *J. Am. Chem. Soc.*, **76**, 4261 (1954).

(4) E. Baciocchi and G. Illuminati, *Gazz. Chim. Ital.*, **87**, 981 (1957).

(5) Y. Otsuji and H. H. Jaffe, *Abstracts*, 137th Meeting, American Chemical Society, April 1960, p. 76-80.

(6) A. N. Hall, J. A. Leeson, H. N. Rydon, and J. C. Tweedle, *Biochem. J.*, **74**, 209 (1960).