mechanism for anilides is analogous to that of esters,[3] the close adherence of anilide hydrolysis rates to a first-order law implies that acylation of chymotrypsin was the reaction studied.

In addition to the amide link, our substrates differ from O-acylphenols in their β-phenyl and α-acylamino groups. That this difference between esters and amides is not due to the α-acylamino group is shown by the facilitating effect of the p-methoxy substituent on the chymotrypsin-catalyzed hydrolysis of hydrocinnamanilides (Table I).

Although the observed negative ρ-value for the anilides reflects an increase in electron demand at the reaction site as the transition state is assembled, the rate constants for the chymotrypsin-catalyzed hydrolysis of anilides are much lower than those of O-acylphenols. This difference in rates between O-acylphenols and anilides corresponds to an increase in electron demand when the relative inductive effects of $-NHC_6H_5$ and $-OC_6H_5$ are compared.

The most straightforward way to resolve this dilemma is to assume that the amide nitrogen, but not the phenolic oxygen, is protonated in the transition state. The high rate of chymotrypsin-catalyzed hydrolysis of hydrocinnamamide relative to hydrocinnamanilide (Table I) is in accord with this hypothesis inasmuch as amines are more readily protonated than anilines. Thus the differences in response to polar changes between esters and amides may be reconciled with previous kinetic results.

The amide nitrogen must become much more basic in the transition state. Otherwise amides would be expected to show a much lower pH optimum than esters. The pH profiles for these reactions are now being studied. These experiments and complete experimental details for the work reported here will be submitted in the near future.

The reactions reported here were followed with an automatic, recording pH-Stat. The solvent for these reactions was prepared by mixing one volume of dimethyl sulfoxide with three volumes of an aqueous solution of 0.015 M KCl solution which was 0.0015 M in $CaCl_2$. α-Chymotrypsin, Worthington Biochemicals Corp., lot No. 6032 was used.

In the experiments with the N-benzoyl-L-tyrosine anilides, pseudo first-order rate constants were obtained by plotting log $(P_\infty - P_i)$ *vs.* time, t_i, where P_∞ is the titer. Linear plots were obtained to at least 95% completion of the reaction. Most reactions were followed to more than 99% completion to check for side reactions. The rate constants for hydrocinnamoyl derivatives, however, were determined from initial slopes, since the slow hydrolysis rates made it impractical to follow these reactions to completion. The numerical values of the rate constants for the hydrocinnamoyl compounds accordingly should be accepted with some reservation.

The H_- value[4] reported for these experiments was determined by spectrophotometric determination of the ratio of dissociated to undissociated 2-nitrophenol as a function of the e.m.f. between the glass and the reference electrodes of a Leeds and Northrup No. 124138 miniature electrode assembly. The electrodes and conditions were the same as those used for the kinetic experiments. The concentration ratios were determined in the unbuffered solvent described above. The measured value of $d(\text{e.mf.})/d[\log(C_I/C_{HI})]$ was 0.0589 volt; the calculated value of $2.303\ RT/F$ at this temperature is 0.0591 volt. The H_- scale was set using the reported pK_a value of 7.08 for 2-nitrophenol in aqueous solution.[5]

The N-benzoyl-L-tyrosine anilides were formed by treating the corresponding N-benzoyl-L-tyrosine azides with the appropriate aniline in ether solution. The azides were prepared by the action of nitrous acid in the corresponding hydrazides. The hydrocinnamate derivatives were formed by conventional procedures from hydrocinnamoyl chloride and the amine.[6] (Table II).

TABLE II

Compound	M.p.	Lit. m.p.	Ref.
N-Benzoyl-L-tyrosine anilide	208.6–209.6°	208.0–208.5°	(7)
N-Benzoyl-L-tyrosine-p-methoxyanilide	205.6–206.6°	...	
N-Benzoyl-L-tyrosine-m-methoxyanilide	158.0–159.0°	...	
N-(m-Nitrobenzoyl)-L-tyrosine anilide	199.6–200.2°	...	
Hydrocinnamamide	97.2–98.0°	99–100°	(8)
Hydrocinnamanilide	97.5–98.1°	97–98°	(9)
Hydrocinnam-p-methoxyanilide	130.2–130.8°	...	

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[3] M. L. Bender and B. Zerner, *J. Am. Chem. Soc.*, **84**, 2550 (1962).

[4] L. P. Hammett, "Physical Organic Chemistry," 1st Ed., McGraw-Hill Book Co., New York, N. Y., 1940, p. 269.

[5] M. Rapoport, C. K. Hancock, and E. A. Meyers, *J. Am. Chem. Soc.*; **83**, 3489 (1961).

[6] We are pleased to acknowledge the assistance of Sidney F. Bosen in preparing these compounds.

[7] S. W. Fox and C. W. Pettinga, *Arch. Biochem. Biophys.*, **25**, 13 (1950).

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DEPARTMENT OF CHEMISTRY
THE GEORGE WASHINGTON UNIVERSITY
WASHINGTON, D. C.

WILLIAM F. SAGER
PAUL C. PARKS

RECEIVED MAY 31, 1963

Photochemical Cleavage of Aromatic Aldazines

Sir:

In the course of our exhaustive research on reactions of phenyldiazomethane, we observed, when certain photosensitizers[1] were included in photolysis experiments, that whereas the yields of most products remained fairly constant, the yields of benzonitrile increased and the yields of benzalazine decreased correspondingly. Since we could not visualize this as being a direct reaction of phenyldiazomethane, the possibility of forming the nitrile directly from benzalazine[2] was investigated. When benzalazine (1,4-diphenyl-2,3-diazabutadiene-1,3) was photolyzed in quartz[3] with a low pressure mercury arc at room temperature, only about 1% of benzonitrile could be isolated, along with some 17% of *trans*-stilbene. If two equivalent weights of benzophenone were added, however, an 85% yield of benzonitrile was obtained in the same time (3 days, under these conditions). Similar results were obtained with substituted azines; these are summarized in Table I.

Our present thinking leads us to believe that the mechanism of the reaction is not a case of photosensi-

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[1] G. S. Hammond, N. F. Turro, and A. Fischer, *J. Am. Chem. Soc.*, **83**, 4674 (1961); K. R. Kopecky, G. S. Hammond, and P. A. Leermakers, *ibid.*, **84**, 1015 (1962).

[2] J. Meisenheimer and F. Heim, *Ann.*, **355**, 269 (1907), reported the formation of benzonitrile from benzalazine on pyrolysis. This reaction was studied briefly (J. E. Hodgkins and D. H. Gibson, unpublished work). The yield of nitrile amounts to *ca.* 30% and is formed from 130 to 250°. The yield is not increased by adding dehydrogenation agents such as selenium or sulfur to the pyrolysis. Some benzonitrile is formed from benzalazine on treatment with strong sulfuric acid.

[3] The reactions proceed in Pyrex equipment but the radiation time must be tripled.

TABLE I[a]

YIELD OF SUBSTITUTED NITRILES FROM THE CORRESPONDING AZINES

Solvent	Azine	Nitrile yield, %	Benzpinacol yield, %
Cyclohexane	Benzal	85	82
Cyclohexane	*o*-Chlorobenzal	88	84
Benzene	*p*-Chlorobenzal	82	80
Benzene	*p*-Methoxybenzal	82	79
Dioxane	*p*-Nitrobenzal	95	93
Benzene	*p*-Dimethylaminobenzal	80	78

[a] The yields are based on 1–5-g. experiments, repeated thrice, and averaged. The products were isolated in pure state by distillation or crystallization and the yields were checked with extraction procedures and gas chromatography. The last three entries of Table I required longer irradiation times to obtain the stated yields. The best procedure is to irradiate the solutions until the yellow golden color of the azines disappears or becomes very faint.

tization[4] but an example of triplet or diradical hydrogen transfer.[5] The mechanism can be outlined as

$$(C_6H_5)_2C{=}O \overset{h\nu}{\rightleftarrows} (C_6H_5)_2C{=}O^* \qquad (1)$$

$$(C_6H_5)_2C{=}O^* + C_6H_5{-}CH{=}N{-}N{=}CH{-}C_6H_5 \rightleftarrows C_6H_5{-}\dot{C}{=}N{-}N{=}CH{-}C_6H_5 + (C_6H_5)_2\dot{C}{-}OH \qquad (2)$$

$$C_6H_5{-}\dot{C}{=}N{-}N{=}CH{-}C_6H_5 + (C_6H_5)_2C{=}O \longrightarrow 2C_6H_5{-}CN + (C_6H_5)_2\dot{C}{-}OH \qquad (3)$$

$$2(C_6H_5)_2\dot{C}{-}OH \longrightarrow \text{benzpinacol} \qquad (4)$$

The synthetic usefulness of the reaction is somewhat clouded because aldehydes are normally employed to synthesize the azine derivatives. Synthesis of the azines[6] is, however, exceedingly simple and the yields are quantitative. Possible extension of this reaction to the aliphatic series is being investigated.

Acknowledgment.—This work was supported by a grant (P-058) from the Robert A. Welch Foundation.

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[4] G. S. Hammond, N. F. Turro, and P. A. Leermakers, *J. Phys. Chem.* **66**, 1144 (1962).

[5] See W. M. Moore, G. S. Hammond, and R. P. Foss, *J. Am. Chem. Soc.*, **83**, 2789 (1961), and ref. cited; S. G. Cohen, S. Orman, and D. A. Laufer, *ibid.*, **84**, 3905 (1962); S. G. Cohen and W. V. Sherman, *ibid.*, **85**, 1642 (1963).

[6] H. H. Hatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y. 1943, p. 395.

DEPARTMENT OF CHEMISTRY
TEXAS CHRISTIAN UNIVERSITY
FORT WORTH, TEXAS

JOE E. HODGKINS
JAMES A. KING

RECEIVED JUNE 27, 1963

Elimination Mechanisms. Position of Proton in E2 Transition States[1]

Sir:

We have found that the isotope effects for DO^- in D_2O *vs.* HO^- in H_2O as attacking bases in the E2 elimination reactions of two β-phenylethyl derivatives at 80° are $k_D/k_H = 1.79$ for $C_6H_5CH_2CH_2N^+(CH_3)_3Br^-$ and 1.57 for $C_6H_5CH_2CH_2S^+(CH_3)_2\ Br^-$ salts.[2]

The effect for the sulfonium salt is complicated by exchange of D for H on the carbon atoms adjacent to the sulfur atom. Any isotope effect from this source should be small, however, because the sulfur isotope effect for the reaction is exceedingly small, indicating very little C–S bond-breaking at the transition state.[4] These effects are so strong that we must conclude that the proton positions in the transition states for these reactions are product-like, *i.e.*, have a larger H–O than C–H stretching force constant. DO^- in D_2O is a stronger base than HO^- in H_2O by a factor of *ca.* 1.6 at 80°.[5] Thus, even allowing for a substantial solvent isotope effect (say 20%) superimposed upon the secondary isotope effect due to the attacking base, we still conclude that the proton must be considerably detached from the carbon atom in the transition state.

It is very probable that the *secondary* isotope effect k_D/k_H for attack of DO^- *vs.* HO^- must be considerably larger for the ammonium compound than for the sulfonium compound even after correction for possible *solvent* isotope effects caused by the fact that the DO^- reaction is carried out in D_2O while the HO^- reaction is carried out in H_2O. The *solvent* isotope effects should be weak and also should be similar for both compounds because in both cases a positively charged organic ion reacts with base.

Coupled with the primary isotope effects for eliminations under similar conditions, our results provide even stronger evidence. For $C_6H_5CD_2CH_2S^+(CH_3)_2Br^-$ *vs.* the corresponding completely nondeuterated compound $k_H/k_D = 4.14$ in H_2O with HO^- at 80°,[3] 5.05 in H_2O at 50°, 5.93 in H_2O at 30°, and 5.07 in ethanol with ethoxide at 30°. The effect for the compound with trimethylamine as leaving group in place of dimethyl sulfide is 2.98 in ethanol with ethoxide ion at 50° and 3.02 in 50% ethanol–water at 50°. These relatively small isotope effects indicate that the respective transition states have either a considerably larger H–O than C–H stretching force constant or a considerably larger C–H than H–O stretching force constant. For equal C–H and H–O stretching force constants, a maximal isotope effect is expected[6] (assuming that effects due to bending vibrations are small relative to those due to stretching vibrations and/or are nearly constant for transition states with different degrees of proton transfer). For example, a large isotope effect, $k_H/k_D = 7.11$ in ethanol with ethoxide at 30°, is observed for $C_6H_5CD_2CH_2Br$,[3] indicating the proton is approximately equally tightly bound by C and O in the transition state.

The relative values of the secondary isotope effects show that the proton is more tightly attached to the oxygen atom in the ammonium transition state than in the sulfonium transition state. Then the only way the ammonium compound can have a smaller primary isotope effect than the sulfonium compound is if the proton is more strongly bonded to oxygen than to carbon in the ammonium transition state. This evidence is based only on the relative magnitudes of the secondary and

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[1] Supported in part by the United States Atomic Energy Commission, to which royalty-free right of reproduction is hereby granted. Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

[2] Our rate constant for HO^- with the sulfonium salt agrees well with that in the literature.[3] Rate constants were measured by titration; for the ammonium compound, the amine was removed under reduced pressure before titration of each aliquot.

[3] W. H. Saunders, Jr., and D. H. Edison, *J. Am. Chem. Soc.*, **82**, 138 (1960).

[4] W. H. Saunders, Jr., and S. Ašperger, *ibid.*, **79**, 1612 (1957).

[5] Calculated from data given by C. G. Swain and R. F. W. Bader, *Tetrahedron*, **10**, 197 (1960). It is the square root of their equilibrium constant for eq. 9, *i.e.*, 1.79 at 25°, and, from the temperature dependence of equilibria 7 and 8, 1.6 at 80°. A recent estimate of *ca.* 1.25, probably too low, is given by A. J. Kresge and A. L. Allred, *J. Am. Chem. Soc.*, **85**, 1541 (1963). This low value does not seem consistent with their value for the relative acidities of D_3O^+ and the self-ionization constants of D_2O and H_2O. Using the two values of the isotope effect on the self-ionization of water, the DO^-–HO^- effect is either 1.79 or 2.27 at 25° (W. F. K. Wynne-Jones, *Trans. Faraday Soc.*, **32**, 1397 (1936); R. W. Kingerly and V. K. La Mer, *J. Am. Chem. Soc.*, **63**, 3256 (1941); it is not clear why the discrepancy exists). However, for reactions which appear to proceed *via* a prior equilibrium which converts hydroxide to water, the kinetic isotope effects seem too small to be consistent with a value as high as 2.27. For example, the cyclization of ethylene chlorohydrin is faster with DO^- in D_2O by a factor of 1.54 (C. G. Swain, A. D. Ketley, and R. F. W. Bader, *ibid.*, **81**, 2353 (1959); P. Ballinger and F. A. Long, *ibid.*, **81**, 2347 (1959)).

[6] F. H. Westheimer, *Chem. Rev.*, **61**, 265 (1961) .