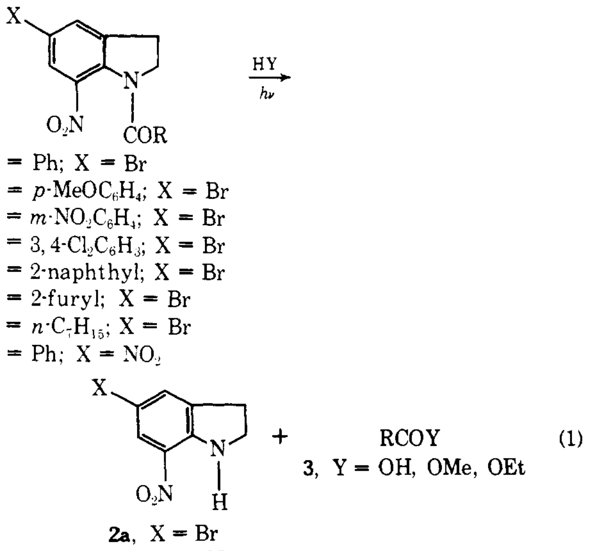
Light-Sensitive Amides. The Photosolvolysis of Substituted 1-Acyl-7-nitroindolines

Sir:

Carboxyl functions are generally protected by conversion to esters. Their protection via their amides is rarely encountered since the amide group is generally more resistant to basic and acidic solvolysis than the ester group, and therefore rather vigorous conditions are needed to cleave it. On the other hand, the stability of the amide bond towards solvolytic conditions could be turned to an advantage, if a specific and mild method for its cleavage were available. The photolysis of amides to furnish free carboxylic acids in significant yields has not been reported[1] until a few years ago. We have recently described amides derived from N-substituted *o*-nitroanilines[2] and 8-nitro-1,2,3,4-tetrahydroquinolines,[3] which on photolysis in benzene or alcohol afford the free carboxylic acids in high yields.

We now wish to report new light sensitive amides which undergo smooth photosolvolysis. Irradiation of amides **1**, derived from 5-bromo-7-nitroindoline (**2a**) and 5,7-dinitroindoline (**2b**), in the presence of water, furnished the free carboxylic acids (Table I) and the starting indolines **2a** and **2b** in nearly quantitative yields (eq 1). Similarly, irradiation of amides **1** in the presence of alcohols afforded in high yields the corresponding esters (Table I) and indolines (eq 1). These photosolvolytic reactions can easily be followed by uv since the products **2a** and **2b** display maxima at much longer wavelengths than the parent amides.[4] In a preparative scale experiment, amide **1e** in CH_2Cl_2-dioxane-H_2O (2:3:0.05) (505 ml of a 10^{-3} M solution) was irradiated for 9 h under the conditions given in Table I; 2-naphthoic acid was isolated in 95% yield by evaporating the solvent, taking up the residue in $CHCl_3$, extracting with base, and precipitating with acid. The remaining indoline **2a** was then obtained in 90% yield from the $CHCl_3$ solution by preparative TLC (silica gel, benzene).



1a, R = Ph; X = Br
b, R = *p*-$MeOC_6H_4$; X = Br
c, R = *m*-$NO_2C_6H_4$; X = Br
d, R = 3,4-$Cl_2C_6H_3$; X = Br
e, R = 2-naphthyl; X = Br
f, R = 2-furyl; X = Br
g, R = *n*-C_7H_{15}; X = Br
h, R = Ph; X = NO_2

2a, X = Br
b, X = NO_2

+ RCOY (1)
3, Y = OH, OMe, OEt

The above results indicate that indoline **2a** is a potential light-sensitive protecting group for the carboxyl function.[5] Furthermore, we find that the photosolvolysis reaction also takes place when the amides are irradiated with light of λ >400 nm, as their absorption extends into that region. Consequently indoline **2a** may find use in the protection of the carboxyl group in compounds which are light-sensitive to shorter wavelengths.

In addition to the solvolysis with water and alcohols, the 1-acylindolines **1** may also undergo photoaminolysis. For example, on irradiating **1a** or **1h** in CH_2Cl_2-dioxane-concentrated ammonia (10:20:1), benzamide was isolated in 70% yield. This phototransamidation reaction points to its possible use in the synthesis of peptides.

Table I. Uv Irradiation of 1-Acyl-7-nitroindolines **1**[a]

Compound[b]	Yield, % Acid formed[c,d]	Yield, % Ester formed[e]
1a	100	100
1b	100	100
1c	87	0[f]
1d	87	61
1e	100	100
1f	90	90
1g	100	100
1h	100	95

[a] Solutions of **1** (6 × 10^{-3} M, 7 ml) were irradiated for 6 h in an RPR-100 photochemical reactor (Rayonet, the Southern Co., Middletown, Conn.) with 3500-Å lamps (λ >305) in Pyrex tubes. [b] Correct elemental analyses were obtained for all new compounds. [c] Acids were obtained on irradiation in CH_2Cl_2–dioxane–H_2O (5:10:0.5). Yields were determined by conversion of the acids with CH_2N_2 to the methyl esters and GLC comparison with ester samples of known concentration on a Packard Model 7421 gas chromatograph using a 5% SE-30 column (6 ft × 0.25 in.). [d] Yields on irradiation in $MeCN–H_2O$ (25:1) were lower by 15–20%. [e] Esters were obtained on irradiation both in CH_2Cl_2–MeOH (6:1) and in CH_2Cl_2–EtOH (6:1). Yields were determined by GLC as above. [f] Amide **1c** disappeared completely on irradiation in CH_2Cl_2–MeOH or CH_2Cl_2–EtOH but no esters were formed because the nitro group is photoreduced by the alcohols: H. A. Morrison in "The Chemistry of the Nitro and Nitroso Groups", H. Feuer, Ed., Part 1, Interscience, New York, N.Y., 1969, p 165.

It should be stressed that the described photoreactions take place only when the 1-acylindolines are substituted with a nitro group in the 7-position. Thus we find that 1-benzoyl-5-nitroindoline and 1-benzoyl-6-nitroindoline on irradiation in CH_2Cl_2-MeOH (6:1) or CH_2Cl_2-dioxane-H_2O (5:10:0.5) are completely consumed but do not yield solvolysis products. Undoubtedly, the excited 7-nitro group activates the amide bond to nucleophilic attack.

It is interesting to note that photolysis of the 6-membered ring analogues of **1** (1-acyl-8-nitrotetrahydroquinolines) affords carboxylic acids not via solvolysis[6] but by a mechanism involving intramolecular oxygen transfer from the excited nitro group to the *N*-acyl residue.[3] The mechanism of the photosolvolysis of the 1-acyl-7-nitroindolines **1**, their photoreactions with other nucleophiles, and their use in the synthesis of natural products are at present under investigation.

Acknowledgment is made to the United States-Israel Binational Science Foundation for Grant No. 797 (1975).

References and Notes

(1) On photolysis aliphatic amides are generally cleaved to component-rich mixtures: I. Rosenthal in "The Chemistry of Amides", J. Zabicky, Ed., Interscience, London, 1970, p 289; *N*-aryl amides, on the other hand, undergo a photo-Fries type of rearrangement: D. Bellus, *Adv. Photochem.*, **8**, 1971; V. I. Stenberg in "Organic Photochemistry", O. L. Chapman, Ed., Vol. 1, Edward Arnold, London, 1967, p 127.
(2) B. Amit and A. Patchornik, *Tetrahedron Lett.*, 2205 (1973).
(3) B. Amit, D. A. Ben-Efraim, and A. Patchornik, *J. Chem. Soc., Perkin Trans. 1*, in press.
(4) In CH_2Cl_2-MeOH (8:2) *N*-acylindolines **1** have a long wavelength maximum around 350 nm, whereas the long wavelength maximum of nitroindolines **2** is at wavelengths longer than 440 nm.
(5) Amides **1a–g** are stable towards acidic conditions, e.g., 1 M HCl in dioxane or 45% HBr in acetic acid at room temperature for 48 h. They are also stable towards mildly basic conditions, such as 1.5 M ammonia in dioxane-ethanol (1:1) or 1 M hydrazine in dioxane-ethanol (1:1) at room temperature for 20 h. In 0.1 N NaOH in dioxane-ethanol (1:1) at room temperature these amides are unstable and decompose rapidly.
(6) It should be noted that in our work on the photocleavage of 1-acyl-8-nitrotetrahydroquinolines[3] we have not studied compounds of these series which bear a bromo or a nitro group in the para position to the amide

function. The different photochemistry of the 1-acyl-7-nitroindolines 1 cannot, however, be attributed to the additional substituent X (X = Br or NO_2). This is corroborated by our finding that 1-benzoyl-6-bromo-8-nitrotetrahydroquinoline and 1-benzoyl-6,8-dinitrotetrahydroquinoline did not undergo photosolvolysis upon irradiation in methanol or ethanol, but afforded free benzoic acid in 85% yields (unpublished results), thus behaving as 1-acyl-8-nitrotetrahydroquinolines[3] which bear no substituents.

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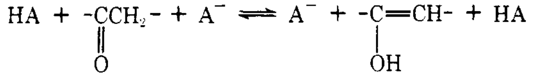
The Lack of Concertedness in the General Acid-Base Catalysis of the Enolization of Oxalacetic Acid. A Case for Stepwise Nucleophilic-General Base Catalysis

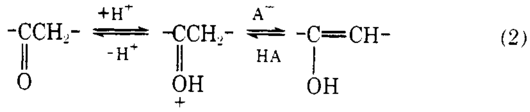
Sir:

Since the early studies of Dawson and Spivey[1] on the enolization of acetone, chemists have been concerned with the question of concerted general acid-general base (eq 1)

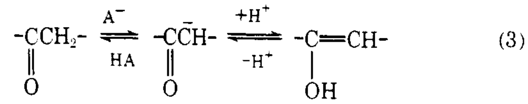


$$\mathrm{HA} + \underset{\underset{\mathrm{O}}{\|}}{\mathrm{-C}}\mathrm{CH_2-} + \mathrm{A^-} \rightleftharpoons \mathrm{A^-} + \underset{\underset{\mathrm{OH}}{|}}{\mathrm{-C}}\mathrm{{=}CH-} + \mathrm{HA} \qquad (1)$$

as compared to stepwise general acid and general base catalysis (eq 2 and 3) in enolization reactions.[2] These con-



$$\underset{\underset{\mathrm{O}}{\|}}{\mathrm{-C}}\mathrm{CH_2-} \underset{\mathrm{-H^+}}{\overset{\mathrm{+H^+}}{\rightleftharpoons}} \underset{\underset{\overset{\mathrm{OH}}{+}}{\|}}{\mathrm{-C}}\mathrm{CH_2-} \underset{\mathrm{HA}}{\overset{\mathrm{A^-}}{\rightleftharpoons}} \underset{\underset{\mathrm{OH}}{|}}{\mathrm{-C}}\mathrm{{=}CH-} \qquad (2)$$



$$\underset{\underset{\mathrm{O}}{\|}}{\mathrm{-C}}\mathrm{CH_2-} \underset{\mathrm{HA}}{\overset{\mathrm{A^-}}{\rightleftharpoons}} \underset{\underset{\mathrm{O}}{\|}}{\mathrm{-C}}\overset{-}{\mathrm{C}}\mathrm{H-} \underset{\mathrm{-H^+}}{\overset{\mathrm{+H^+}}{\rightleftharpoons}} \underset{\underset{\mathrm{OH}}{|}}{\mathrm{-C}}\mathrm{{=}CH-} \qquad (3)$$

cerns have revolved around the feasibility of concerted motion of heavy and light atoms in a single transition state[3,4] and the actual experimental detection of kinetic terms containing the concentration of ketone, general acid, and general base (i.e., $k_{ab}[\mathrm{K}][\mathrm{AH}][\mathrm{A}^-]$). The most convincing experimental evidence for a $k_{ab}[\mathrm{K}][\mathrm{AH}][\mathrm{A}^-]$ term has appeared to be that of Banks[5,6] for the enolization of oxalacetic acid (OA).[7] The present communication describes the most pertinent aspects of our reinvestigation of the enolization of OA. We find no evidence for concertedness in the reaction in the presence of buffers such as phosphate and imidazole as claimed by Banks.[6] In the presence of tertiary amines, the enolization of OA occurs via a mechanism ascribable to stepwise carbinolamine formation followed by general base catalyzed elimination of amine. To the knowledge of the investigators, nucleophilic catalysis has not been previously reported as a mechanism for enolization.

The rates of enolization of OA in water at 30 °C and μ = 0.5 (KCl) were determined using a stopped-flow spectrophotometer. Increase in absorption at 270 nm due to formation of the enol was monitored with 11 different buffer systems, with each buffer being investigated at two–four different pH values. The buffer dilution plots obtained with imidazole are given in Figure 1. If a concerted reaction were involved a plot of k_{obs} vs. [Imidazole] would exhibit upward curvature. There is no evidence of any upward curvature in this or in any of the other buffer dilutions obtained for this study. In the insert to Figure 1 is plotted Banks' data at pH 7.12 for imidazole (T = 1.5 °C, μ = 0.1). The positive deviation of the rate at 0.20 M total buffer and less marked positive deviations in other buffer dilution plots were responsible for the report of the operation of a concerted mechanism.[6] The evidence for the concerted mechanism, therefore, is less than convincing.[7] Since the experiments of Banks were carried out at low temperature, we investigated the reaction of imidazole at 3.8 °C (pH 7.12, μ = 0.5) at concentrations up to 1.0 M. The plots of k_{obsd} vs. [imidazole] obtained evidence linearity up to 0.2 M (slope = 0.16) followed by downward curvature leading to a slope of 0.04. This break in the buffer dilution plot is suggestive of intermediate carbinolamine formation as is seen with OA and tertiary amines at 30 °C (see below). As with imidazole at 30 °C, k_{obsd} is a linear function of [buffer] when phosphate and carbonate buffers are employed [0.02–0.20 M] at this temperature. The second-order rate constants for the general base catalysis of the mechanism of

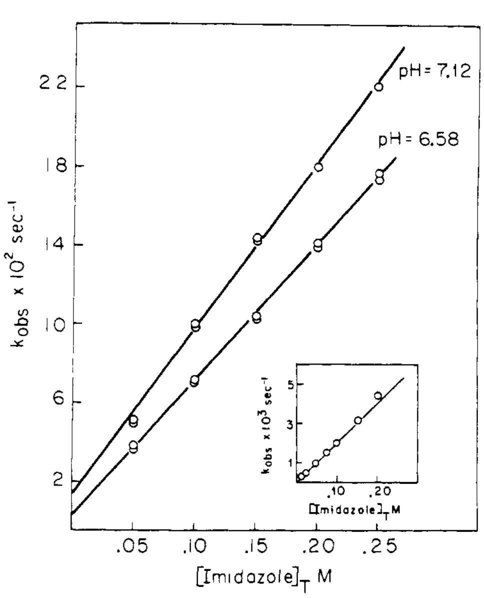


Figure 1. Plots of the observed first-order rate constants for the reaction of oxalacetic acid with imidazole (H_2O, μ = 0.5, 30 °C) vs. the total concentration of imidazole at two hydrogen ion concentrations. Insert to figure: data reported by Banks for the reaction of oxalacetic acid with imidazole (H_2O, μ = 0.1, 1.5 °C, pH 7.12).[6]

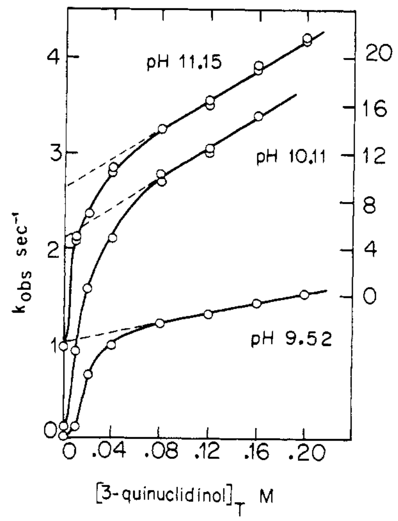


Figure 2. Plots of the observed first-order rate constants for the reaction of oxalacetic acid with 3-quinuclidinol (H_2O, μ = 0.5, 30 °C) vs. the total concentration of 3-quinuclidinol at three pH values. The pK_a of 3-quinuclidinol is 10.11. Left-hand axis pertains to experiments at 9.52 and 10.11 while the right-hand axis pertains to experiments at pH 11.15. Intercepts of dashed lines at [amine] = 0 provides k_{obsd} values for lyate species catalysis of the enolization of carbinolamine species. These values are seen to greatly exceed the k_{obsd} values for lyate species catalysis of enolization of OA.