Mechanism and Catalysis for Phenylhydrazone Formation from Aromatic Heterocyclic Aldehydes[1]

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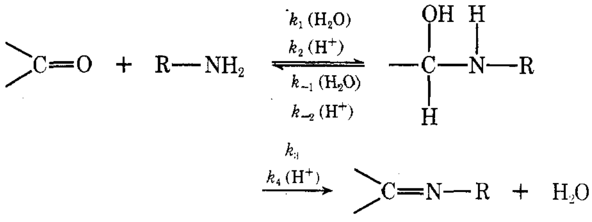
As is typical for the addition of amines to carbonyl compounds, the reaction of 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde with phenylhydrazine exhibits rate-determining formation of carbinolamine under acidic conditions and rate-determining dehydration of the carbinolamine intermediate under neutral and basic conditions. The addition of phenylhydrazine to form carbinolamines from these substrates is subject to general acid catalysis by carboxylic acids; the Bronsted exponent is 0.35 for addition to 2-thiophenecarboxaldehyde and *N*-methylpyrrole-2-carboxaldehyde, and 0.90 for addition to pyrrole-2-carboxaldehyde. Logarithms of rate constants for catalysis of the attack of phenylhydrazine on furfural, 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde by the hydrated proton, carboxylic acids, and water are linearly related to values of pK_a for the corresponding acids: $\log k = \gamma \log K_a + C$. Values of γ increase with increasing pK_a of catalyst. The dehydration of the carbinolamines derived from the addition of phenylhydrazine to the aromatic heterocyclic aldehydes exhibits both acid-catalyzed and pH-independent reactions.

The addition of amines to carbonyl compounds usually proceeds with one or more changes in rate-determining step which are reflected in breaks in pH–rate profiles.[2,3] Under slightly acidic conditions, formation of the carbinolamine intermediate is slow, reflecting either rate-determining attack of the nucleophile or rate-determining protonation of the zwitterionic addition product.[4,5] Under neutral or basic conditions, dehydration of the carbinolamine becomes the slow step:



$$\rangle C{=}O + R{-}NH_2 \underset{k_{-1}(H_2O),\ k_{-2}(H^+)}{\overset{k_1(H_2O),\ k_2(H^+)}{\rightleftharpoons}} -\overset{OH}{\underset{H}{C}}-\overset{H}{N}-R \xrightarrow{k_3,\ k_4(H^+)} \rangle C{=}N{-}R + H_2O \quad (1)$$

There exist a number of quantitative relationships between structure and reactivity. Most of these correlations are concerned with the effect of substituents on the reactivity of a functional group linked to an aromatic ring. One of the oldest is the Hammett equation,[6] which correlates the nature of polar substituents in meta/para-substituted benzene derivatives with both equilibrium and rate constants for their reactions. Subsequent to the formulation of the Hammett equation, a very large amount of experimental information concerning the effects of polar substituents on reaction rates and equilibria has been correlated with the appropriate substituent constants in the benzene series.[7-10] Corresponding treatment of substituent effects in heterocyclic aromatic systems is limited, although some progress has been made.[8,10-13]

In work reported herein a previous study of furfural phenylhydrazone formation[13] has been elaborated to include a series of aromatic five-membered heterocyclic aldehydes, viz., 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde, to attempt to understand the relationship between structure and reactivity in this series.

Experimental Section

Materials. All reagents employed were obtained commercially and, with the exception of reagent grade inorganic salts, were either redistilled or recrystallized before used. Solutions of phenylhydrazine were prepared just prior to use. Solutions of carboxylic acids in 20% aqueous ethanol were prepared just prior to use to avoid esterification.

Kinetic measurements were carried out spectrophotometrically at 25 °C with the aid of a Zeiss PMQ II spectrophotometer equipped with a thermostated cell holder. The reaction of 2-thiophenecarboxaldehyde and phenylhydrazine was followed by observing the appearance of the product at 354 nm (pyrrole-2-carboxaldehyde and *N*-methylpyrrole-2-carboxaldehyde at 340 nm) with an initial concentration of aldehydes of 5.0×10^{-5} M. In all cases a sufficient excess of nucleophilic reagent was employed so that pseudo-first-order rate behavior was observed. First-order rate constants were evaluated from plots of log $(OD_\infty - OD_t)$ against time in the usual manner.

It was difficult to determine spectrophotometrically the equilibrium constants for the formation of the carbinolamines from the aldehydes and phenylhydrazine owing to the strong interference absorption of the latter substance. Similar difficulties have been noted in attempts to determine equilibrium constants for the formation of other phenylhydrazones.[14,15] Sander and Jencks[16] have determined the values of the equilibrium constants for the addition of hydroxylamine (pK_a = 5.97) and semicarbazide (pK_a = 3.65) to furfural; these are respectively 5.2 and 1.1 M^{-1}. On the basis of these values, it is estimated that the equilibrium constants for the addition of phenylhydrazine (pK_a = 5.2) to furfural is close to 3 M^{-1}. Since 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde are less reactive than furfural toward phenylhydrazine it is possible to use relatively high concentrations of phenylhydrazine under neutral and basic conditions without accumulation of appreciable carbinolamine. In addition, with each of the aromatic heterocyclic aldehydes studied, the reaction is first order in phenylhydrazine over the concentration 5.0×10^{-3} to 5.0×10^{-2} M at pH 7. Consequently, all kinetic studies above pH 7 (in which dehydration is rate determining) have been made employing phenylhydrazine concentrations lower than 5.0×10^{-2} M. Second-order rate constants could therefore be determined directly by dividing first-order rate constants by the concentration of phenylhydrazine free base.

In the pH region in which phenylhydrazine attack is principally rate determining, rate constants have been corrected for the influence of the rate of carbinolamine dehydration as described by Sayer and Jencks.[17] Catalytic (third-order) rate constants were evaluated from the slopes of plots of second-order rate constants against the concentration of catalyst. All kinetic experiments were carried out at 25.0 ± 0.1 °C in 20% aqueous ethanol at an ionic strength of 0.50, maintained with KCl, with 2.0×10^{-4} M EDTA. Values of apparent pH were recorded with a Radiometer Model PHM 4d meter equipped with a glass electrode. Calculation of the concentration of phenylhydrazine free base and undissociated carboxylic acids were made employing the Henderson–Hasselbalch equation and values of pK_a determined in this work.

pK_a Determinations. The pK_a of *N*-methylpyrrole-2-carboxylic acid (pK_a = 4.64 ± 0.01) was measured at 25.0 ± 0.1 °C in water at an ionic strength of 0.01 by careful partial neutralization of nine samples of the acid with known amounts of standard potassium hydroxide solution, to obtain different buffer solutions. The pH values of these solutions were measured with a Methron Herisau Compensator E 388 equipped with a combined glass electrode. The pK_a was obtained from the Henderson–Hasselbalch equation (Table I, supplementary material), and the thermodynamic value was calculated.

The values of pK_a of acetic acid (4.741 ± 0.017), β-bromopropionic acid (4.103 ± 0.008), formic acid (3.625 ± 0.014), chloroacetic acid (2.881 ± 0.020), and cyanoacetic acid (2.462 ± 0.004) (Table II, sup-

Table IV. Catalytic Constants for Several Acids for Attack of Phenylhydrazine on Aromatic Heterocyclic Aldehydes in 20% Ethanol at 25 °C and Ionic Strength 0.50[a]

Catalyst	pK_a	Furfural[b]	2-Thiophene-carboxaldehyde	Pyrrole-2-carboxaldehyde	*N*-Methylpyrrole-2-carboxaldehyde
H_3O^+	−1.74	3.3×10^5	2.5×10^5	1.4×10^5	1.3×10^5
$CNCH_2CO_2H$	2.46	2.6×10^4	1.2×10^4	1.8×10^3	6.5×10^2
$ClCH_2CO_2H$	2.88	1.6×10^4	7.1×10^3	9.0×10^2	3.7×10^2
HCO_2H	3.63	8.3×10^3	3.2×10^3	1.7×10^2	2.1×10^2
$BrCH_2CH_2CO_2H$	4.10	9.2×10^3	3.3×10^3	7.3×10^1	2.2×10^2
CH_3CO_2H	4.74	4.8×10^3	1.7×10^3	1.3×10^1	1.0×10^2
H_2O	15.74	3.3	1.1	1.0×10^{-1}	6.0×10^{-2}

[a] Catalytic constants have the units M^{-2} min^{-1}. [b] Reference 13.

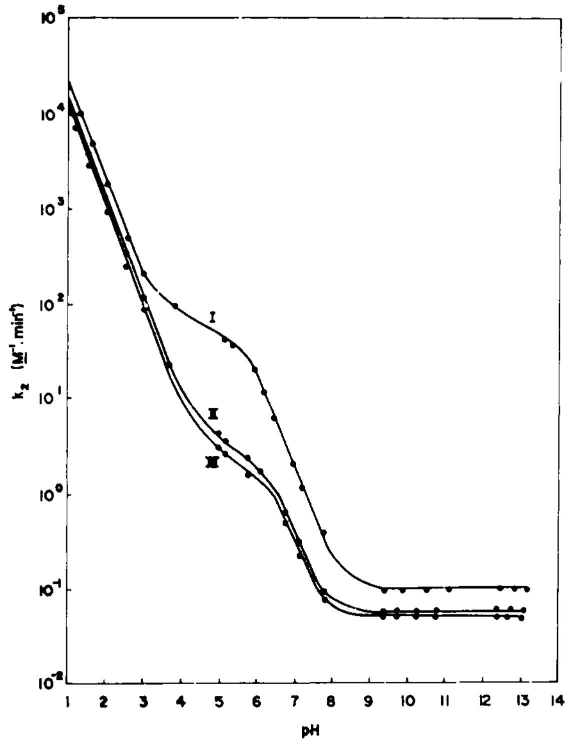


Figure 1. Logarithms of second-order rate constants for phenylhydrazone formation from 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and *N*-methylpyrrole-2-carboxaldehyde (III) in 20% aqueous ethanol at 25 °C and ionic strength 0.50 plotted as a function of pH. All points refer to zero buffer concentration. The lines are theoretical (see text).

plementary material), and phenylhydrazinium ion (5.302 ± 0.028) (Table III, supplementary material) were measured at 25.0 ± 0.1 °C in 20% aqueous ethanol and ionic strength 0.50, maintained with KCl, by careful partial neutralization of four samples of the acids with known amounts of standard potassium hydroxyde solution, to obtain different solutions. The pH values of these solutions were measured with a Methron Herisau Compensator E 148, equipped with a combined glass electrode. The glass electrode was initially calibrated with a blank solution of the same ionic strength containing 0.0100 M hydrochloric acid, whose pH was taken as 2.00. Under such conditions the measured values of pH refer to hydronium ion concentration, rather than hydronium ion activities. The pK_a's were obtained from the Henderson-Hasselbalch equation. The results were excellent, except for those for cyanoacetic acid, with acid concentration higher than 0.100 M.

Results

Table V. Rate Constants for the Acid-Catalyzed and pH-Independent Reactions for Aromatic Heterocyclic Aldehyde Phenylhydrazone Formation under Conditions of Rate-Determining Dehydration at 25 °C

Aldehyde	k_H, M^{-2} min^{-1}	k_0, M^{-1} min^{-1}
Furfural[a]	5.0×10^7	2.0×10^{-1}
2-Thiophenecarboxaldehyde	1.8×10^7	1.0×10^{-1}
Pyrrole-2-carboxaldehyde	3.5×10^6	6.0×10^{-2}
N-Methylpyrrole-2-carboxaldehyde	3.0×10^6	5.5×10^{-2}

[a] Reference 13.

In Figure 1 second-order rate constants for the reaction of phenylhydrazine with 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and *N*-methylpyrrole-2-carboxaldehyde (III) in 20% aqueous ethanol at 25 °C and ionic strength 0.50 are plotted as a function of pH. Where necessary, the second-order rate constants were extrapolated to zero buffer concentration. The lines in this figure are theoretical ones based on the following rate law derived from eq 1.

$$\text{Rate} = \frac{k_3[k_1(H_2O) + k_2a_{H^+}] + k_4a_H\,[k_1(H_2O) + k_2a_{H^+}]}{k_{-1}(H_2O) + k_{-2}a_{H^+} + k_3 + k_4a_{H^+}} \times (\text{>C=O})(RNH_2) \quad (2)$$

The values of the rate constants were taken from Tables IV and V and it was assumed that the equilibrium constant for the addition of phenylhydrazine to the aromatic heterocyclic aldehydes, K_{ad}, is 1.0 M^{-1}.

The general shape of the curves is familiar and reflects (going from basic to acid conditions) uncatalyzed and acid-catalyzed dehydration of the carbinolamine intermediate as rate-determining step, and water-catalyzed and acid-catalyzed attack of the nucleophile (or trapping of the zwitterionic intermediate[4,5]), as rate determining.[2,3,13,14]

In the region of rate-determining formation of carbinolamine, second-order rate constants are sensitive functions of the nature and concentration of the carboxylic acid–carboxylate buffers employed to maintain constant pH. Studies of the buffer catalysis demonstrated that, as usual, it is of the general acid type[2,3] (Table VI, supplementary material). Catalytic constants for various carboxylic acids were evaluated in the usual way. These constants are collected in Table IV.

Catalytic constants for the carboxylic acids are well correlated by the Bronsted catalysis law. Least-squares treatment of the data yield the following values for α: 2-thiophenecarboxaldehyde, 0.35; pyrrole-2-carboxaldehyde, 0.90; and *N*-methylpyrrole-2-carboxaldehyde, 0.35 (Figure 2).

In Figure 3, values of the logarithms of the catalytic constants for the hydrated proton and water for the attack of phenylhydrazine on furfural, 2-thiophenecarboxaldehyde, pyrrole-2-carboxaldehyde, and *N*-methylpyrrole-2-carboxaldehyde, and values of the logarithms of the catalytic constants for cyanoacetic acid catalysis and acetic acid catalysis for the attack of phenylhydrazine on furfural, 2-thiophene-

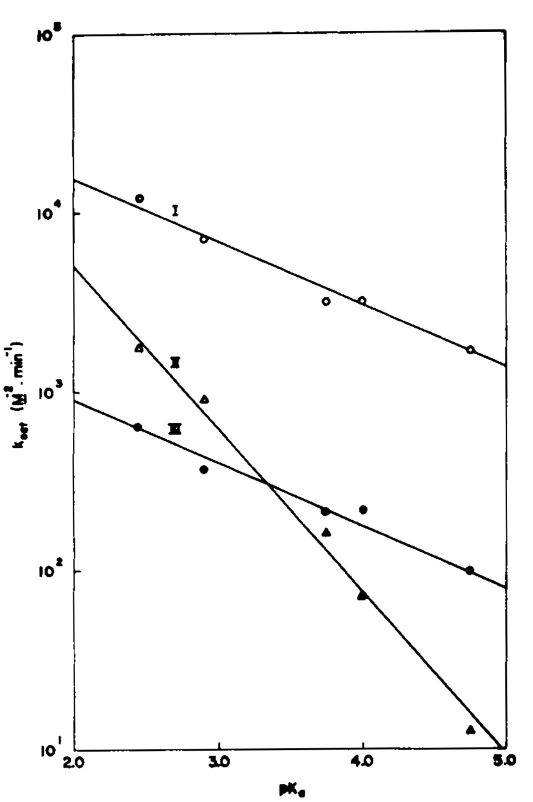


Figure 2. Logarithms of the catalytic constants for several acids for the attack of phenylhydrazine on 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and N-methylpyrrole-2-carboxaldehyde (III) in 20% aqueous ethanol at 25 °C and ionic strength 0.50 plotted against the pK_a values of the catalytic constants listed in Table IV.

carboxaldehyde, and N-methylpyrrole-2-carboxaldehyde are plotted against the pK_a values of the corresponding acids (2-furoic acid, 3.12;[18] 2-thiophenecarboxylic acid, 3.47;[19] pyrrole-2-carboxylic acid, 4.41;[20] and N-methylpyrrole-2-carboxylic acid, 4.64, this work). Data for all the compounds fall on good straight lines. The straight lines of Figure 3 can conveniently be expressed by the equation $\log k = \gamma \log K_a + C$, in which the two variables are $\log k$ and $\log K_a$, the slope of the line is γ, and the intercept is C. The significance of γ is that it measures the sensitivity of the reaction to the nature of the aromatic heterocyclic ring system.

Dehydration of the intermediate carbinolamine is the rate-determining step above pH 7. The dehydration reaction for all the aromatic heterocyclic aldehydes studied is susceptible to specific acid catalysis and to a pH-independent reaction (Figure 1). The appropriate rate constants are collected in Table V.

Discussion

A. The Bronsted Catalysis Law. Correlation of catalytic constants with pK_a values of carboxylic acids for meta/para-substituted benzaldehyde phenylhydrazone formation and for 5-substituted 2-furfural phenylhydrazone formation[13] in Bronsted plots by least-squares analysis yields values for α of 0.35 ± 0.01; significantly smaller values characterize a number of related reactions.[17] In this work, correlations of the catalytic constants of carboxylic acids for 2-thiophenecarboxaldehyde and N-methylpyrrole-2-carboxaldehyde phenylhydrazone formation in Bronsted plots by least-squares analysis yields values for α of 0.35. In contrast, general acid catalysis for pyrrole-2-carboxaldehyde phenylhydrazone formation yields a value for α of 0.90. As the N-methylpyrrole-2-carboxaldehyde exhibits the usual behavior, but the pyrrole-2-carboxaldehyde does not, it is reasonable to assume that the hydrogen linked to heterocyclic nitrogen plays a role in this unique behavior.

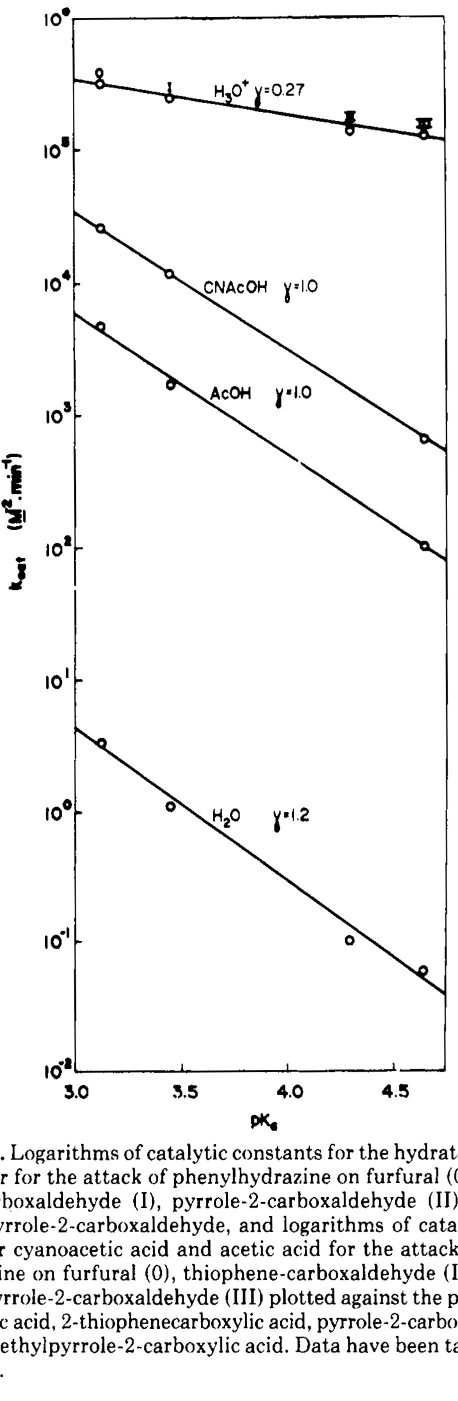
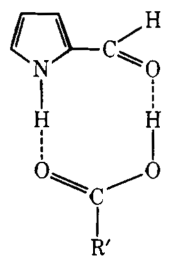


Figure 3. Logarithms of catalytic constants for the hydrated proton and water for the attack of phenylhydrazine on furfural (0), 2-thiophenecarboxaldehyde (I), pyrrole-2-carboxaldehyde (II), and N-methylpyrrole-2-carboxaldehyde, and logarithms of catalytic constants for cyanoacetic acid and acetic acid for the attack of phenylhydrazine on furfural (0), thiophene-carboxaldehyde (I), and N-methylpyrrole-2-carboxaldehyde (III) plotted against the pK_a values of 2-furoic acid, 2-thiophenecarboxylic acid, pyrrole-2-carboxylic acid, and N-methylpyrrole-2-carboxylic acid. Data have been taken from Table IV.

One possible explanation is that the carboxylic acid catalysts for this reaction function as bifunctional catalysts for the attack reaction in the way shown below:



In this formulation, the carbonyl oxygen acts as a general base catalyst by withdrawing a proton from the substrate in the transition state. At the same time, the hydroxyl component acts as a general acid catalyst by partially protonating the carbonyl oxygen atom of the substrate. Since polar substituents in the carboxylic acid will affect the proton-donating powers of the hydroxyl function and the proton-withdrawing powers of the carbonyl oxygen atom in opposite fashions, it would be anticipated that the catalytic constants would be independent of the nature of such substituents. In other words, α should be smaller than 0.35. This is in contrast with the observed value of α (0.90) and rules out this explanation.

The possibility of rate-determining proton transfer from the carboxylic acid to the zwitterionic addition compound[4,5] is also inconsistent with the data since such reactions are expected to be diffusion controlled or nearly so and, hence, have rate constants independent of the acidity of the catalyst. In addition, unusual mechanisms for phenylhydrazone formation from pyrrole-2-carboxaldehyde seem unlikely since the reactivity of this compound is consistent with that expected on the basis of its relatives (see below).

We are left without a satisfactory explanation for the unusually large value of α for this reaction. It evidently depends on having the proton on the heterocyclic nitrogen atom and may or may not depend on the bifunctional character of the carboxylic acid. Further studies will be required to settle this point.

B. Free Energy Relationships. In this work we have found a linear free energy relationship between the reactivity of derivatives of aromatic heterocyclic rings, viz., furan, thiophene, and pyrrole, and the acidity of the corresponding acids.

The sensitivity of the attack reaction of phenylhydrazine on the aromatic heterocyclic aldehydes is highest when the reaction is water catalyzed ($\gamma = 1.2$), intermediate when the reaction is catalyzed by carboxylic acids ($\gamma = 1.0$), and smallest when the reaction is catalyzed by the hydronium ion ($\gamma = 0.27$). The variation of the γ values with the acidity of the general acid catalyst together with the considerations concerning variation in transition state structures as function of reactivity is in accord with the considerations of Hammond,[21] Leffler,[22] and Swain and Thornton.[23]

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Registry No.—Phenylhydrazine, 100-63-0; furfural, 98-01-1; 2-thiophenecarboxaldehyde, 98-03-3; pyrrole-2-carboxaldehyde, 1003-29-8; *N*-methylpyrrole-2-carboxaldehyde, 1192-58-1; *N*-methylpyrrole-2-carboxylic acid, 6973-60-0; acetic acid, 64-19-7; β-bromopropionic acid, 590-92-1; formic acid, 64-18-6; chloroacetic acid, 79-11-8; cyanoacetic acid, 372-09-8; phenylhydrazinium ion, 55668-06-9.

Supplementary Material Available. Tables I, II, III, and VI that report full determination of the acidity constants data for *N*-methylpyrrole-2-carboxylic acid, acetic acid, bromopropionic acid, formic acid, chloroacetic acid, cyanoacetic acid, and phenylhydrazinium ion (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) Supported in part by the Fundação de Amparo à Pesquisa do Estado de São Paulo.
(2) W. P. Jencks, *Prog. Phys. Org. Chem.*, **2**, 63 (1964).
(3) W. P. Jencks, "Catalysis in Chemistry and Enzymology," McGraw-Hill, New York, N.Y., 1969.
(4) J. M. Sayer, G. Pinsky, A. Schonbrunn, and W. Washsturi, *J. Am. Chem. Soc.,*, **96**, 7998 (1974).
(5) S. Rosenberg, S. M. Silver, J. M. Sayer, and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7986 (1974).
(6) L. P. Hammett, *J. Am. Chem. Soc.*, **59**, 96 (1937).
(7) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).
(8) P. R. Wells, *Chem. Rev.*, **63**, 171 (1963).
(9) S. Ehrenson, *Prog. Phys. Org. Chem.*, **2**, 196 (1964).
(10) J. E. Leffler and E. Grunwald, "Rates and Equilibria of Organic Reactions", Wiley, New York, N.Y., 1963.
(11) M. J. S. Dewar and P. J. Grisdale, *J. Am. Chem. Soc.*, **84**, 3584 (1962).
(12) H. H. Jaffé and H. Lloyde Jones, *Adv. Heterocycl. Chem.*, **3**, 209 (1964).
(13) L. do Amaral, *J. Org. Chem.*, **37**, 1433 (1972).
(14) L. do Amaral and M. P. Bastos, *J. Org. Chem.*, **36**, 3412 (1971).
(15) W. P. Jencks, *J. Am. Chem. Soc.*, **81**, 475 (1959).
(16) E. G. Sander and W. P. Jencks, *J. Am. Chem. Soc.*, **90**, 6154 (1968).
(17) J. M. Sayer and W. P. Jencks, *J. Am. Chem. Soc.*, **91**, 6353 (1971).
(18) Y. Otsuji, M. Kubo, and E. Imoto, *Nippon Kagaku Zasshi,* **80**, 1300 (1959).
(19) E. Imoto and R. Motoyama, *Bull. Naviwa Univ.*, **A2**, 127 (1954).
(20) G. Magnani, *Gazz. Chim. Ital.*, **26**, 92 (1896).
(21) G. S. Hammond, *J. Am. Chem. Soc.*, **77**, 334 (1955).
(22) J. E. Leffler, *Science*, **117**, 340 (1953).
(23) C. G. Swain and E. R. Thornton, *J. Am. Chem. Soc.*, **84**, 817 (1962).

Stereochemistry of Photochemical Cycloadditions: Addition of Ethylene to a Δ^9-1-Octalone[1]

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Photochemical cycloaddition of ethylene and 1 gave only **2**, a result consistent with the Wiesner model for photoaddition of olefins to cyclohexenones.

The photochemical cycloaddition of olefins to enones is a synthetically useful reaction. Wiesner[2] has rationalized the stereochemistry of such additions to cyclohexenones in terms of an excited enone in which the β carbon becomes nearly tetrahedral with an electron-rich orbital in a pseudoaxial orientation. This model is consistent with a large number of cycloadditions to cyclohexenones of the cholestenone type. We report here the first test of the Wiesner model in a Δ^9-1-octalone.

The enone 1[3] underwent photochemical cycloaddition with ethylene in methylene chloride solution at −60 °C to give exclusively **2** in 82% yield. The structure of **2** was established by single-crystal x-ray diffraction analysis of the *p*-bromobenzoate **3b**.