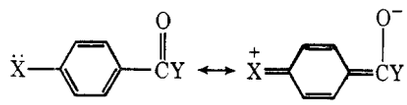
in Hammett substituent constants, eq 3. An "insulated" para substituent constant[3,12] has been defined which eliminates



(3)

the resonance contribution shown in eq 3. Comparison of the Hammett para substituent constants[3] with these "insulated" constants[12] shows essentially no difference between the two scales for the substituents in Table I except for methoxy. Thus the resonance contribution to E_s values analogous to eq 3 is negligible except for methoxy. The resonance contribution to the E_s value for methoxy may, in reality, be smaller than anticipated by the above comparison. Taft[4] has shown for the saponification of ethyl *p*-dimethylaminobenzoate that only part of the resonance interaction of the *p*-dimethylamino group with the carbonyl group is lost in going from the ester to the saponification transition state. It is only this fraction of the resonance interaction lost which contributes to the E_s value.

The ρ^* values for the catalyzed hydrolysis of ortho-substituted benzamides,[4] benzohydroxamic acids,[9] and *N*-methylbenzohydroxamic acids are 0, −0.868, and −0.688, respectively, for similar but not identical reaction conditions. A negative ρ^* value for the hydrolysis of the benzohydroxamic acids compared to the zero value for benzamides is consistent with the greater electronegativity of *N*-hydroxyl compared to NH in changing from amides to hydroxamic acids,[9] provided that the polar effect upon the protonation step in the mechanism is greater than the polar effect on nucleophilic attack by water on the protonated intermediate. Substitution of a methyl group for the *N*-hydrogen on the hydroxamic acids should offset somewhat the effect of the substitution of hydroxyl for the *N*-hydrogen of the amide and thus reverse the *trend* in the ρ^* values.

Experimental Section

The 2-substituted *N*-methylbenzohydroxamic acids were synthesized by adaptations of the method used previously for the preparation of the 2-chloro and 2-methyl derivatives.[10] ^{1}H NMR and IR spectra are consistent with the structures listed. Satisfactory analyses (C, H, N; maximum difference between calculated and observed analysis (%): C, 0.21; H, 0.20; N, 0.16) were obtained for all new compounds and were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. 2-Substituent and melting point: methoxy, 138.5–139.2 °C; bromo, 135.0–135.8 °C; iodo, 145.1–145.8 °C; nitro, 170.8–171.6 °C dec.

Kinetic measurements were accomplished using the methods and procedures described previously.[10]

References and Notes

(1) Abstracted from Ph.D. dissertation of I. E. Ward, Western Michigan University, 1977.
(2) J. Shorter in "Advances in Linear Free Energy Relationships", J. Shorter and N. B. Chapman, Ed., Plenum Press, New York, N.Y., 1972, Chapter 2.
(3) O. Exner in ref 2, Chapter 1.
(4) R. W. Taft, Jr., in "Steric Effects in Organic Chemistry", M. S. Newman, Ed., Wiley, New York, N.Y., 1956, Chapter 13.
(5) M. Charton, *J. Org. Chem.*, **40**, 407 (1975), and references cited therein.
(6) M. Charton, *Prog. Phys. Org. Chem.*, **8**, 235 (1971).
(7) Reference 3, pp 39, 46.
(8) L. L. McCoy and E. E. Riecke, *J. Am. Chem. Soc.*, **95**, 7407 (1973).
(9) D. C. Berndt and I. E. Ward, *J. Org. Chem.*, **39**, 841 (1974).
(10) D. C. Berndt and I. E. Ward, *J. Org. Chem.*, **41**, 3297 (1976).
(11) D. A. Leabo, "Basic Statistics", 4th ed, Richard D. Irwin, Inc., Homewood, Ill., 1972, Chapter 16.
(12) R. W. Taft, Jr., *J. Phys. Chem.*, **64**, 1805 (1960).

Kinetics of the Reactions of Hydrazine and Acethydrazide with Acetic Acid

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A kinetic study of the reactions of monoacetylhydrazine (MAH) and hydrazine (H) with acetic acid at 61 °C has been made using HPLC separation of salicylaldehyde derivatives. Both reactions involve pseudo-first-order reaction with acetic acid to produce an acetylated base and a rapid disproportionation of MAH to yield diacetylhydrazine (DAH) and hydrazine. The hydrazine acetylation is faster than the MAH acetylation. Mechanisms have been proposed for both series of reactions using approximations, and the predictions are in good agreement with experimental findings.

The reaction of hydrazine (H) with acetic acid was described by Harris and Stone.[2] This kind of reaction, a loss of basicity with time, was also reported by Medwick[3] in a study of various hydrazides. In related work, Posgay[4] found that the basicity of some amino compounds was lost owing to acetylation by acetic acid, and Kadin[5] reported that more than 10% of procainamide was acetylated in acetic acid in a few minutes at room temperature. Both authors attribute the acetylation to unavoidable small traces of acetic anhydride in glacial acetic acid. No careful kinetic study of the H or acethydrazide (MAH) reaction with acetic acid has been reported; Harris and Stone[2] used a spectrophotometric procedure that was inadequate due to the interference of MAH in the H assay.

In the present study, the reactions of H and MAH with acetic acid at 61 °C have been thoroughly investigated using specific analytical procedures. Salicylaldehyde derivatives of H and MAH [and of symmetrical diacetylhydrazine (DAH), after hydrolysis] are formed and can be separated using high-pressure liquid chromatography (HPLC). These compounds offer high molar absorptivities and make measurement of very small quantities possible. These analyses permit measurement of each hydrazine reaction participant and yield data that is used to propose a complex kinetic mechanism. Rate constants are calculated by approximation methods based on the experimental data. The findings of this study have been applied to some hydrazine derivatives that are useful analytically and medicinally.

Results and Discussion

The analytical procedure used in this study effectively separated the salicylaldehyde derivatives of MAH (retention time r_t 5.0 min) and H (r_t 16.3 min) and salicylaldehyde (r_t

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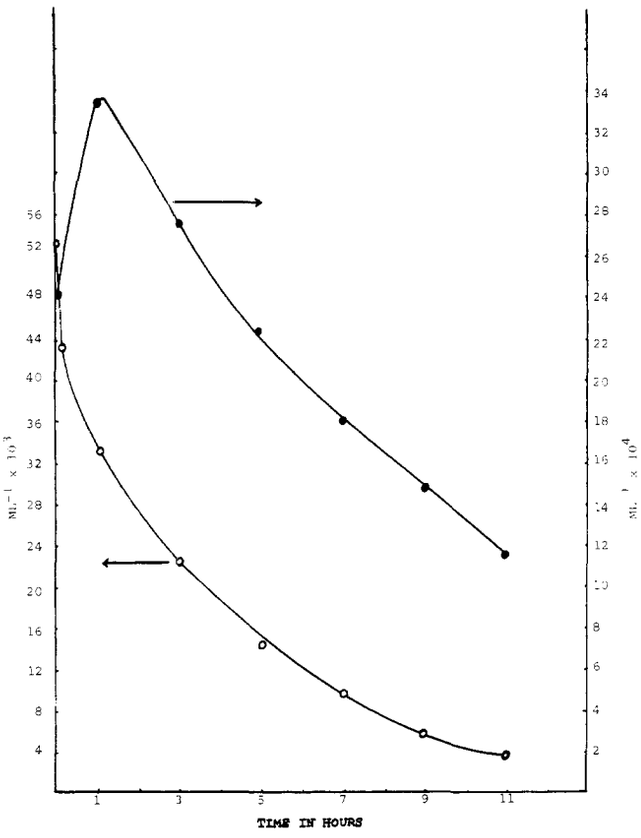

Figure 1. Kinetic behavior of MAH in acetic acid at 61 °C: (○) concentration of MAH at indicated time; (●) concentration of H at indicated time.

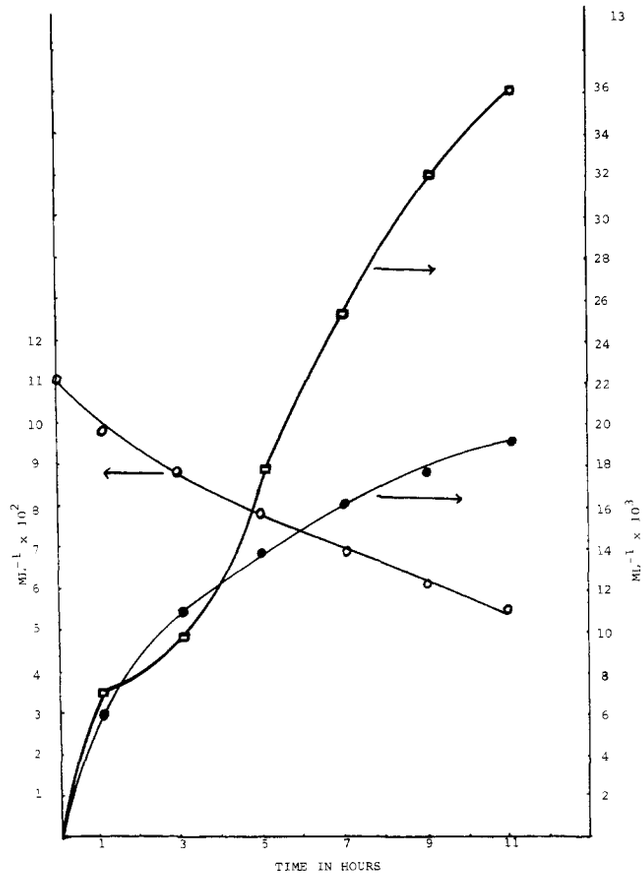

Figure 2. Kinetic behavior of H in acetic acid at 61 °C: (○) concentration of H at indicated time; (●) concentration of MAH at indicated time; (□) concentration of DAH at indicated time.

8.5 min) as may be noted from the different retention times.

The salicylaldehyde reactions with MAH (concentration range 0.20–0.80 mg/mL) and with H (concentration range 0.10–0.60 mg/mL) were complete and well behaved, since, in both cases, the chromatographic response was linear (correlation coefficients 0.99999 and intercepts essentially 0). The minimum detectable quantities of both MAH and H were 5×10^{-5} M.

The temperature chosen for this study, 61 °C, was a choice dictated by the nature of the MAH and H reactions with salicylaldehyde. In both cases, the reactions are practically instantaneous at 61 °C, thus introducing no temperature disturbances through analytical necessity. Due to the presence of both consecutive and parallel bimolecular reactions in the suggested mechanisms, difficulties were encountered in integrating the differential rate equations. Mathematical treatments reported by Chien[10] and later by Pearson et al.[11] for solving less-complicated mechanisms using transforms and the introduction of Bessel functions were investigated; however, the solution was complicated in this case due to the presence of the H loop (i.e., its regeneration from the MAH disproportionation). Although an exact solution for this complicated mechanism may still be possible, an approximation was used. Linear least-squares lines were obtained for the MAH and H concentration vs. time profiles seen in Figures 1 and 2. This permitted use of slopes for derivatives, i.e., $d[A]/dt \simeq \Delta[A]/\Delta t$ and $d[B]/dt \simeq \Delta[B]/\Delta t$. When concentrations of A and B were required, the values on the least-squares line at 5 h, approximately the midpoint representing a point where deviation of the least-squares point from experimental values would be at least, were chosen.

Reactions of MAH with Acetic Acid. The reaction profiles of H and MAH are presented in Figure 1. The concentration of MAH decreases regularly, whereas H is seen to decrease only after an initial increase. The mechanism that is proposed must account for the presence of H and explain its concentration profile.

The compounds present as well as their change with time suggested the following reactions:

$$\mathrm{MAH} + \mathrm{MAH} \xrightarrow{k_1} \mathrm{DAH} + \mathrm{H} \quad (1)$$

$$\mathrm{H} + \mathrm{HOAc} \xrightarrow{k_2} \mathrm{MAH} + \mathrm{H_2O} \quad (2)$$

$$\mathrm{MAH} + \mathrm{HOAc} \xrightarrow{k_3} \mathrm{DAH} + \mathrm{H_2O} \quad (3)$$

If A = H, B = MAH, and C = DAH and recognizing the invariant status of HOAc, then the reactions may be written explicitly in order to respect the implied stoichiometries.

$$2\mathrm{B} \xrightarrow{k_1} \mathrm{C'} + \mathrm{A} \quad (4)$$

$$\mathrm{A} \xrightarrow{k_2} \mathrm{B'} \quad (5)$$

$$\mathrm{B'} \xrightarrow{k_3} \mathrm{C''} \quad (6)$$

These equations are described by the following rate expressions.

$$\frac{d[B]}{dt} = -2k_1[B]^2 + k_2[A] - k_3[B] \quad (7)$$

$$\frac{d[A]}{dt} = k_1[B]^2 - k_2[A] \quad (8)$$

$$\frac{d[C]}{dt} = k_1[B]^2 + k_3[B] \quad (9)$$

A mass balance equation on total B-derived materials may be solved for 2B:

$$[2B] = M_B - ([C] + [A] + [B'] + [C'']) \quad (10)$$

where M_B is the total concentration of all B-related species. Equation 10 may be differentiated:

$$\frac{2d[B]}{dt} = -\left(\frac{d[C']}{dt} + \frac{d[A]}{dt} + \frac{d[B']}{dt} + \frac{d[C'']}{dt}\right)$$

$$qc = -(k_1[B]^2 + k_1[B]^2 - k_2[A] + k_2[A] + k_3[B] - k_3[B])$$

$$= -2k_1[B]^2 \quad (11)$$

Equation 11 leads to eq 12 and 13.

$$\frac{d[B]}{dt} \simeq \frac{\Delta[B]}{\Delta t} = -k_1[B]^2 \quad (12)$$

$$k_1 = \frac{-\Delta[B]/\Delta t}{[B]^2} \quad (13)$$

From eq 13, $k_1 = 1.96 \times 10^{-3}\ M^{-1}\ s^{-1}$. Equations 7 and 8 show $k_2 = 2.14 \times 10^{-5}\ s^{-1}$ and $k_3 = 4.60 \times 10^{-6}\ s^{-1}$.

The values calculated for k_1, k_2, and k_3 agree with the general statements made by Harris and Stone[2] in that the rate of disproportionation of MAH (eq 1) is significantly faster than the acetylations of both H and MAH.

An examination of some experimental plots made from concentrations of MAH and H shows them to be in keeping with the proposed mechanisms. The rate of disappearance of MAH is pseudo-first-order [correlation coefficient of 0.9997, k (from slope) = $5.68 \times 10^{-5}\ s^{-1}$, intercept of 4.10×10^{-2} M]. This intercept value is lower than the initial value, 5.4×10^{-2} M, seen in Figure 1. But it must be remembered that the rate of disappearance of MAH is a complex process (eq 7) and this deviation indicates the initial importance of the k_1 process. Equation 7 which described the disappearance of MAH can be seen to be a combination of three factors; however, since k_1 is large, B diminishes rapidly making the equation reduce to $k_2[A] - k_3[B]$, a combination of first-order processes producing an overall first-order change.

The disappearance of H is shown to be a first-order process; the log c vs. t plot has a correlation coefficient of 0.9996, a slope of 0.0455 h^{-1}, and an intercept of 3.8×10^{-3} M. This finding is in keeping with eq 8 which shows that $k_2[A]$ is the rate-controlling factor, since k_1 is large. In order to check the possibility that the appearance of H in the MAH acetous solution resulted from MAH hydrolysis (reverse of eq 2), another mechanism which involved a k_{-2} rate constant was tested. All the data obtained from such a mechanism did not correlate with any of the experimental data.

Reaction of Hydrazine with Acetic Acid. The concentration–time profiles for H and MAH are presented in Figure 2. The disappearance of H is characterized by a short induction period. Taking into account the nature of the products and their concentration–time profiles, the following mechanism is proposed using the symbols previously introduced.

$$A \xrightarrow{k_2} B \quad (14)$$

$$B \xrightarrow{k_3} C' \quad (15)$$

$$2B \xrightarrow{k_1} C'' + A' \quad (16)$$

(k_2 loop)

This scheme is complicated by the loop made necessary by the appearance of H in eq 16. As before, however, an approximate solution was accomplished using graphical values. Equations 14, 15, and 16 may be described by the differential equations seen as eq 17, 18, and 19.

$$\frac{d[A]}{dt} = -k_2[A] + 0.5k_1[B]^2 - 0.5k_2[A] \quad (17)$$

$$= -\tfrac{3}{2}k_2[A] + 0.5k_1[B]^2$$

$$\frac{d[B]}{dt} = k_2[A] - k_3[B] - k_1[B]^2 + 0.5k_2[A] \quad (18)$$

$$= \tfrac{3}{2}k_2[A] - k_3[B] - k_1[B]^2$$

$$\frac{d[C]}{dt} = k_3[B] + 0.5k_1[B]^2 \quad (19)$$

In order to specify compounds taking part in different portions of the rate process, a mass balance expression, using M_A to indicate the total concentration of H-related compounds, is written.

$$[A] = M_A - ([B] + [C'] + [C''] + [A'] + 0.5[B]) \quad (20)$$

Differentiating eq 20 and expressing the result as differentials yields the following.

$$\frac{d[A]}{dt} = -\tfrac{3}{2}\frac{d[B]}{dt} + \frac{d[C']}{dt} + \frac{d[C'']}{dt} + \frac{d[A']}{dt} \quad (21)$$

$$\frac{d[A]}{dt} + \tfrac{3}{2}\frac{d[B]}{dt} = -\frac{d[C']}{dt} - \frac{d[C'']}{dt} - \frac{d[A']}{dt} \quad (22)$$

Evaluating differentials from eq 15 and 16 and substituting in eq 22 results in eq 23.

$$\frac{d[A]}{dt} + \tfrac{3}{2}\frac{d[B]}{dt} = -k_3[B] - 0.5k_1[B]^2 - 0.5k_1[B]^2 + 0.5k_2[A]$$

$$= -k_3[B] - k_1[B]^2 + 0.5k_2[A] \quad (23)$$

Subtracting eq 18 from 23 results in eq 24 from which k_2 may be evaluated.

$$\frac{d[A]}{dt} + 0.5\frac{d[B]}{dt} = -k_2[A] = \frac{\Delta[A]}{\Delta t} + 0.5\frac{\Delta[B]}{\Delta t} \quad (24)$$

Using graphical values from Figure 2 for $d[A]/dt$ and $d[B]/dt$, $k_2 = 2.04 \times 10^{-5}\ s^{-1}$. This value used in eq 17 together with [A] and [B] shows that $k_1 = 2.11 \times 10^{-3}\ L\ mol^{-1}\ s^{-1}$. Similarly, eq 18 yields $k_3 = 1.26 \times 10^{-5}\ s^{-1}$.

Since it may be seen from eq 17, 18, and 19 that $\Delta[C]/\Delta t = \Delta[A]/\Delta t + \Delta[B]/\Delta t$, a corroboration of the validity of the calculated rate constants may be attempted. The experimental value for $\Delta[C]/\Delta t$, $3.19 \times 10^{-3}\ M\ h^{-1}$, compares very well with the calculated result $3.22 \times 10^{-3}\ M\ h^{-1}$. The agreement of k_1 and k_2 values from the MAH and H studies is good; only in the case of k_3 is a large variation experienced.

The experimental data shows that H disappearance is pseudo-first-order [correlation coefficient = 0.9985, k (from slope) = $1.70 \times 10^{-5}\ s^{-1}$ (predicted $2.04 \times 10^{-5}\ s^{-1}$), intercept = 10.6×10^{-2} M (predicted 10.0×10^{-2} M)]. These values are in good agreement and indicate that the proposed mechanism is valid, since eq 17 becomes a first-order process ($k_1 \gg k_2$).

Experimental Section

Materials and Solutions. All chemicals used were reagent grade unless otherwise specified. The following chemicals were used as obtained: hydrazine (97%, anhydrous) and hydrazine hydrate (64%), Matheson, Coleman and Bell; spectranalyzed grade methanol, ethanol, 2-propanol, chloroform, and acetonitrile (99 mol %), Fisher. Salicylaldehyde (from bisulfite compounds), Eastman White Label, was redistilled immediately before use. Glacial acetic acid was distilled three times before use and exhibited no impurities by HPLC when examined using the system used in the kinetic studies. The distilled acetic acid was stored in and delivered from an all-glass delivery system to offer protection from moisture. TLC silica plates (Eastman) were 100-μm thick silica layer coated on a plastic support, 12.5-in. square.

Mobile Phase for HPLC Analysis. The mobile phase consisted of acetonitrile (52 ± 2%, v/v) and 0.14 M aqueous potassium dihydrogen phosphate (48 ± 2%, v/v). The mobile phase was filtered and degassed under vacuum before use.

Standard MAH Solution and Standard H Solution. Separate solutions of MAH and H in 2-propanol were prepared (2 mg/mL each). For each solution the following dilutions were made: to three low-actinic glass 10-mL volumetric flasks, 4-, 2-, and 1-mL volumes were pipetted, followed by 0.4, 0.2, and 0.1 mL of acetic acid, respectively. These diluted standard MAH and H solutions were then processed together with the respective sample solutions and treated exactly in the same manner.

Salicylaldehyde Reagent Solution. Fifty milliliters of salicylaldehyde was diluted to 100 mL with 2-propanol.

Instrumentation. The 61 °C temperature used in the kinetic study was maintained by means of a Lauda/Brinkmann circulator Model K-2/RD.

The modular liquid chromatograph used consisted of a Laboratory Data Control (LDC) Model 2396 minipump, an LDC Model 709 pulse dampener, and an LDC Model 1285 UV monitor operated at 254 nm. A sample injection valve (Chromatronix HPSV-20) with a fixed volume of 20 μL (nominal) was used for sample introduction onto the chromatograph. The detector response was displayed on a 10-mV recorder. The analytical HPLC column used was a 30-cm long by 4-mm i.d. stainless-steel tube packed with spherical siliceous microbeads 5–10 μm to which is chemically bonded a monomolecular layer of octadecyltrichlorosilane (μ Bondapak C_{18}, Waters Assoc.). A flow rate of 1.2–1.4 mL/min (at 1000 psig) was maintained at room temperature.

Synthesis of MAH. To 19.5 g of hydrazine hydrate, 27.5 g of ethyl acetate was added, gradually and with continuous stirring, followed by 20 mL of absolute alcohol. The mixture was refluxed for 48 h and dried in vacuo until a paste was obtained. The paste was shaken twice with ether and the supernatant liquid was decanted and discarded. The residue was heated on a water bath at 60 °C until all the ether evaporated, and then cooled immediately in a freezing mixture of ice and salt where a deliquescent solid was obtained. The product was pressed between two filter papers and dried for 48 h in a vacuum desiccator. The melting point of the dried MAH crystals (yield 79.5%) was 63.9 °C [lit.[6,7] 62–64 °C].

The purity of the MAH crystals was checked by both TLC and HPLC. The TLC system consisted of a mobile phase composed of 7.5% 2-propanol in chloform and a silica thin-layer plate. The MAH crystals were dissolved in alcohol, spotted on the plate, and developed for about 2 h after which the plate was sprayed with Ehrlich's reagent and viewed under short-wavelength (254 nm) UV light. Only a single purple spot, R_f 0.40, was noticed when compared with other plates on which H and MAH had been run and treated similarly (H appeared as a yellow spot R_f 0.05). The MAH showed no trace of H when analyzed by the HPLC system used in the kinetic study. To detect the presence of any traces of DAH in the MAH, a second plate was spotted and developed in the TLC system described above for 2 h after which the plate was sprayed with aqueous alcoholic hydrochloric acid and heated at 80 °C for 10 min, and then the plate was sprayed again with the Ehrlich's reagent and viewed under short wavelength UV light. Again only a single yellow spot (DAH hydrolyzed to H, R_f 0.58) was noticed when compared with other plates on which MAH and DAH had been treated similarly.

Synthesis of DAH. To 100 mL of pyridine contained in a 250-mL flask, 8.3 g of anhydrous hydrazine was added slowly and with continuous shaking. The mixture was transferred gradually and with continuous mixing to another 250-mL flask containing 52.5 g of acetic anhydride; the DAH started to precipitate immediately. The suspension was left overnight at room temperature, filtered, and recrystallized twice, first from acetone and then alcohol (yield 75%). The melting point, 137.5 °C, agreed with the literature.[8,9]

The purity of the DAH so obtained was checked using the TLC system described for MAH. Only a single yellow spot was observed, R_f 0.58, and no trace of H or MAH was seen.

Kinetic Study. All kinetic runs were conducted in duplicate. **(a) MAH.** A quantity, 0.989 g, of MAH was transferred to a 250-mL low-actinic volumetric flask containing about 100 mL of acetic acid. After mixing, the solution was brought to volume with acetic acid (MAH concentration, 5.346×10^{-2} M). For a few minutes, nitrogen was bubbled through the solution and the top of the flask was flushed with nitrogen. The flask was stoppered, sealed with aluminum foil, and placed in a water bath at 61.00 ± 0.01 °C. At specified times, 2-mL aliquots were withdrawn and transferred to a 10-mL low-actinic volumetric flask which was immediately stoppered, sealed, and stored in a freezer where the acetous solution froze. After all the samples were collected, they were removed from the freezer and 0.04 mL of the salicylaldehyde reagent calculated to be approximately 50% in stoichiometric excess was added to each flask. All the flasks were transferred to a 55 °C water bath for 5 min to ensure complete derivatization. The flasks were removed from the water bath and 5 mL of chloroform was added to each. Finally, all the solutions were brought to volume with methanol and were subjected to chromatographic analysis.

(b) H. A quantity, 0.822 g, of anhydrous H was weighed and transferred using a syringe to a 250-mL low-actinic volumetric flask (H concentration, 1.09×10^{-1} M). The solution was treated as described for the MAH kinetic study except for the fact that 0.18 mL of the salicylaldehyde reagent was added to each flask.

Calculation of the quantity in grams of MAH or H in each sample solution was done using the formula

$$(H_u/H_s)W_sP$$

where H_u is the height of a specific component in the sample solution, H_s is the height of the corresponding peak in the standard chromatogram, W_s, is the weight in grams of that standard component initially taken, and P is the purity expressed as a decimal of the standard MAH or H.

(c) MAH and H. For DAH analysis, a separate 2-mL volume of the kinetics sample solution was pipetted into a 10-mL low-actinic volumetric flask to which was added 2 mL of aqueous alcoholic HCl acid solution. The flask was immersed in a 60 °C water bath for 5 min and then 0.16 mL of the salicylaldehyde reagent was added. The sample thereafter was treated in the same manner as the MAH and H samples. Calculations of the quantity of DAH in solution was obtained by the difference between the total amount of H after hydrolysis and the amount of H obtained from the nonhydrolyzed sample.

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Registry No.—Hydrazine, 302-01-2; ethyl acetate, 141-78-6; MAH, 1068-57-1; DAH, 3148-73-0; acetic anhydride, 108-24-7; acetic acid, 64-19-7.

References and Notes

(1) Taken, in part, from a thesis submitted by Hamed M. Abdou to the Graduate School, Rutgers University, May 1977, for the Ph.D. degree. Present address: E. R. Squibb & Sons, Inc., New Brunswick, N. J. 08903.
(2) W. C. Harris and K. G. Stone, *J. Org. Chem.*, **23**, 2032 (1958).
(3) T. Medwick, *Diss. Abstr.*, **19**, 1214 (1958).
(4) E. Posgay, *Acta Pharm. Hung.*, **39**, 88 (1969); *Chem. Abstr.*, **71**, 67213f (1969).
(5) H. Kadin, *J. Pharm. Sci.*, **63**, 919 (1970).
(6) T. H. Curtius and T. S. Hofmann, *J. Prakt. Chem.*, **2**, 53, 524 (1896).
(7) A. M. Kost and R. S. Sagitullin, Jr., *Zh. Obshch. Khim.*, **27**, 3338 (1957); *Chem. Abstr.*, **52**, 9071 (1958).
(8) L. B. Turnbull, A. S. Yard, and H. McKennis, Jr., *J. Med. Pharm. Chem.*, **5**, 1327–1334 (1962).
(9) H. McKennis, Jr., A. S. Yard, J. H. Weatherby, and J. A. Hagy, *J. Pharmacol. Exp. Ther.*, **126**, 109 (1959).
(10) J. Y. Chien, *J. Am. Chem. Soc.*, **70**, 2256 (1948).
(11) R. G. Pearson, L. C. King, and S. H. Langer, *J. Am. Chem. Soc.*, **73**, 4149 (1951).