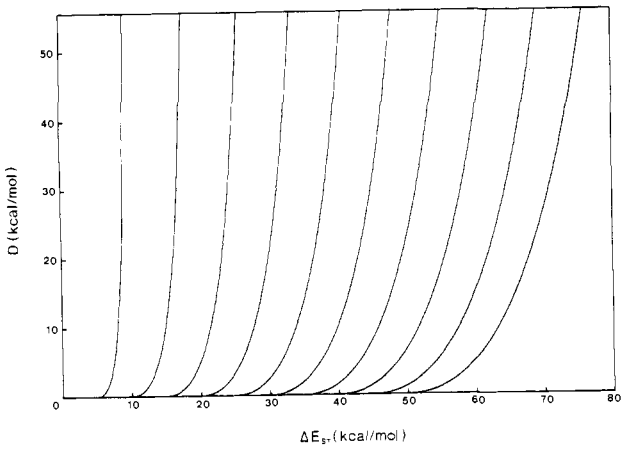

Figure 5. Barriers to planarity versus ΔE_{ST} as calculated from eq 20 for the set of $\sigma + \pi$ bond energies from 20 kcal/mol (left) to 200 kcal/mol (right).

hypothesis, but it proved to have some success in explaining and predicting nonclassical distortions.[1]

The present MO treatment provides further information which was not given by the previous VB model. It first defines the entire domain of existence of a double bond scheme, beyond which a direct X=X link no longer occurs. In addition, for trans-bent structures, the model provides simple analytical expressions to evaluate the trans-bending angle, the barrier to planarity, and the wagging force constant (this last index is also given for planar structures). The previous model was unable to predict these measurements of the *extent* of trans bending. A forthcoming paper will describe detailed orthogonal valence bond analyses and determine whether the avoided crossing hypothesis is valid or not.[6]

One might question the formulation in terms of ΔE_{ST} and $E_{\sigma+\pi}$ rather than moving back to fundamental atomic properties. This reductive operation is neither necessary nor straightforward since there exist contradictory trends between, for instance, the $(\epsilon_s - \epsilon_p)$ energy difference and the spatial properties of the atomic s and p orbitals.[25]

The semiquantitative success of such treatment may even be astonishing. It is likely that some error compensation fortuitously occurred among the three crudest approximations which are as follows: (1) neglecting overlap (which simplifies the MO spacing in Figure 1), (2) neglecting $\sigma-\pi^*$ mixing, and (3) assimilating $(\epsilon_p - \epsilon_n)$ to ΔE_{ST}. In its present form, however, this modelization brings forward certain of the conditions required for good ab initio calculations (such as a correct ΔE_{ST} separation). It also provides simple rationalizations of unusual and sensitive phenomena affecting the structure of a whole family of double bonds and an elementary evaluation of their amplitude. More generally, it generates prospective ideas about overall conditions for bond building.

(20) Gordon, M. S. *Chem. Phys. Lett.* **1985**, *114*, 348.
(21) Selmani, A.; Salahub, D. R. *J. Chem. Phys.* **1988**, *89*, 1529.
(22) Philips, R. A.; Buenker, R. J.; Beardsworth, R.; Bunker, P. R.; Jensen, P.; Kraemer, W. P. *Chem. Phys. Lett.* **1985**, *118*, 60.
(23) Balasubramanian, K. *Chem. Phys. Lett.* **1986**, *127*, 585.
(24) Gleghorn, J. T.; Hammond, N. D. A. *Chem. Phys. Lett.* **1984**, *105*, 621.
(25) Kutzelnigg, W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 272.

Carboxylic Acid Participation in Amide Hydrolysis. Competition between Acid-Catalyzed Dehydration and Anhydride Formation

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Abstract: The hydrolysis of 4′-methoxysuccinanilic acid in acidic solution proceeds via intramolecular catalysis, initially producing succinic anhydride and anisidine. The disappearance of the reactant is acid-catalyzed, but this is initially due to dehydration to produce an unstable equilibrium with 4′-methoxy-*N*-phenylsuccinimide. In contrast, the acid-catalyzed reaction of 4′-methoxymaleanilic acid does not produce an imide. In the case of the maleanilic acids, the low kinetic barrier to the formation of the hydrolysis products prevents the intermediate formation of an imide.

The rapid hydrolysis of amides through a reaction involving participation by a neighboring carboxylic acid is a reaction that has received attention as a model for enzymic catalysis.[1-5] Formation of addition intermediates of amides by a bimolecular reaction is subject to a high activation barrier[6,7] and reaction with the intramolecular carboxylic acid minimizes the entropic component of that process. After a carboxylic acid group adds to an amide to form a tetrahedral intermediate, elimination of the amine moiety produces an anhydride. Since the kinetic barrier to the hydrolysis of anhydrides is considerably lower than that for the hydrolysis of an amide, the intramolecular addition of a carboxyl group to the amide produces a catalytic route for hydrolysis.

In acidic solutions, the undissociated carboxylic acid form of an amic acid (an amic acid is a compound with neighboring amide and carboxyl groups) is the kinetically significant reaction species in the formation of the anhydride.[1-5] In less acidic solutions, the conjugate base of the amic acid predominates and the rate of reaction decreases. The slow hydrolysis may occur in competition with an initial dehydration to the corresponding imide,[8] especially where deprotonation on nitrogen can occur. Imide formation is also observed for reactions in nonaqueous solutions where dehydration is promoted.[8,9]

(1) Bender, M. L. *J. Am. Chem. Soc.* **1951**, *73*, 1626.
(2) Kirby, A. J.; Lancaster, P. W. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1206.
(3) Kluger, R.; Chin, J.; Choy, W.-W. *J. Am. Chem. Soc.* **1979**, *101*, 6976.
(4) Suh, J.; Chun, K. H. *J. Am. Chem. Soc.* **1986**, *108*, 3057.
(5) Menger, F. M.; Ladika, M. *J. Am. Chem. Soc.* **1988**, *110*, 6794.
(6) Fastrez, J. *J. Am. Chem. Soc.* **1977**, *99*, 7004.
(7) Guthrie, J. P. *Acc. Chem. Res.* **1983**, *16*, 1222.
(8) Sauers, C. K.; Gould, C. L.; Ioannou, E. S. *J. Am. Chem. Soc.* **1972**, *94*, 8156.
(9) Chin, J.; Breslow, R. *Tetrahedron Lett.* **1982**, *23*, 4221.

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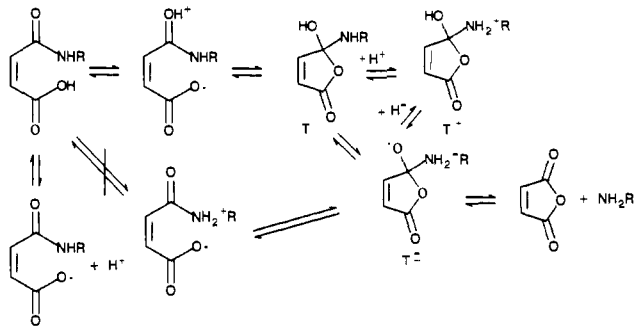
Scheme I



The observation of formation of an imide from an amic acid has not been reported for reactions in acidic solutions, consistent with the rapid formation of anhydrides under these conditions. However, if imides form from amic acids under other conditions, their formation may be favored by thermodynamic factors and the absence of their formation in acidic solutions would be the result of kinetic factors. Therefore, one might expect to see imide formation where anhydride formation is not particularly rapid.

Related background comes from the pattern of specific acid-catalyzed formation of anhydrides from amic acids.[10] This occurs in dilute acid solutions by accelerating a path through a zwitterionic form of the initially formed tetrahedral intermediate (T to $T^{\pm}$, Scheme I).[11]

We have reported in detail the factors controlling the competition between mechanisms involving the various forms of the tetrahedral intermediate.[11] On the basis of this analysis, it could be concluded that reaction of succinamic acids in dilute acid solutions would proceed directly via $T^{\pm}$ without initial reaction to form T. This removes the role for acid catalysis and therefore, unlike the reactions of maleamic acids,[10] specific acid catalysis should not be observed for the reactions of succinamic acids. Yet, Higuchi and co-workers had reported a significant acid-catalyzed rate constant for the hydrolysis of succinanilic acid in dilute acid solution.[12]

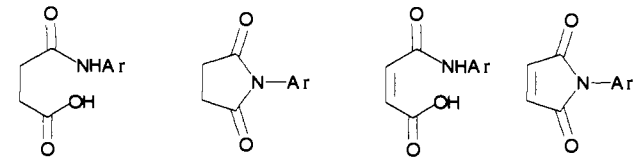
We have now investigated the hydrolysis of a succinanilic acid and find that the acid-catalyzed reaction in dilute acid solution is not hydrolysis but rather attainment of an equilibrium between the succinanilic acid and its dehydration product, the *N*-phenylsuccinimide. The equilibrium mixture hydrolyzes via the succinanilic acid without acid catalysis in dilute acid solution. The recognition of initial formation of an imide from an amic acid in acidic aqueous solution confirms the validity of relating the observed catalytic pattern to the stepwise mechanism.

Experimental Section

Equipment. UV–visible measurements were taken with a Varian Cary 210 spectrophotometer. Kinetic data were collected through a microprocessor-controlled interface built at Comspec Ltd., Downsview, ON. The spectrophotometer was connected to a Commodore 2001 microcomputer equipped with an internal clock. The temperature of the spectrophotometer cell compartment was maintained by a circulating water bath controlled within a 0.1 °C range by a Neslab Ex-1000 circulator. The temperature inside the cell compartment was monitored with a thermistor connected to a Fisher 119 combination meter. Measurements of pH were taken with a Radiometer pH Meter 26 equipped with a Canlab combination pH electrode. ^{1}H NMR spectra were obtained on a Varian T-60 spectrometer. Melting points are uncorrected.

Syntheses. 4′-Methoxysuccinanilic Acid [4-[(4-Methoxyphenyl)-amino]-4-oxobutanoic Acid], MSA. Succinic anhydride (1.32 g, 0.0132 mol) was dissolved in a minimum volume of tetrahydrofuran. The volume was brought to 50 mL with ether. To this solution was added dropwise *p*-anisidine (1.63 g, 0.0132 mol; recrystallized from water) in 100 mL of ether. The mixture was stirred overnight. Solvent was removed on a rotary evaporator and a pale yellow powder was obtained. Recrystallization to colorless translucent needles (60% yield) was effected over several days using a 50:50 mixture of THF and hexanes left open to the air: mp 170–171 °C (lit.[13] mp 163 °C).

Chart I



MSA MS I MMA MMI

Table I. Uncorrected Observed First-Order Rate Constants for Conversion of MSA to Succinic Anhydride and Anisidine at 50.0 °C

pH	$10^6 k_{obsd}$, s^{-1}	pH	$10^6 k_{obsd}$, s^{-1}
2.0	17.00	3.5	14.60
2.5	16.40	3.8	13.30
3.0	15.20	4.0	11.80
3.0	14.70	4.2	10.20
3.2	14.50	4.4	8.29
3.5	14.80	4.4	8.31

***N*-(*p*-Methoxyphenyl)succinimide [1-(4-Methoxyphenyl)-2,5-pyrrolidinedione], MSI.** This compound was synthesized by a modification of the procedure of Berlinguet.[14] 4′-Methoxysuccinanilic acid (MSA) was heated to 200 °C for 3 h. The resulting brown material was taken up in a 50:50 mixture of THF and water and decolorized. The solvent was removed on a rotary evaporator. The crude material readily crystallized from ethanol to form pale yellow needles (40% yield): mp 160–161 °C (lit.[15] mp 163 °C).

(*p*-Methoxyphenyl)maleimide [1-(4-Methoxyphenyl)-pyrrole-2,5-dione], MMI. The procedure of Berlinguet[14] yielded an intractable tar. An alternative procedure was therefore used. To sodium acetate (0.37 g, 0.0045 mol), which had been gently fused in the bottom of a round-bottomed flask, was added freshly distilled acetic anhydride (3.6 g, 0.035 mol). The 4′-methoxymaleanilic acid (2.15 g, 0.0097 mol) was added with stirring. The mixture was heated and then stirred for 20 min at 100 °C. The hot solution was poured onto 10 g of ice contained in a separatory funnel. After the ice had melted, the solution was extracted five times with 100 mL of diethyl ether. The solution was dried with anhydrous $MgSO_4$ and the ether was removed by a rotary evaporator. Recrystallization from ethanol readily yielded bright yellow crystals: mp 151–152 °C; (lit.[16] mp 146–148 °C).

Kinetic Methods. Data of absorbance as a function of time were collected and stored on disks. Up to 650 points were collected for each run at a rate of ~11 points/s. Within these constraints, the maximum number of data points were collected for a given kinetic experiment. The ionic strength of solutions with an acid concentration of less than 1 M was maintained at 1.0 with potassium chloride unless otherwise specified. Reactions were initiated by injection of 5–12 μL of the reactant dissolved in acetonitrile or methanol.

Solutions with acid concentrations greater than 1 M were prepared by weighing out H_2SO_4 followed by dilution with distilled water. Acidity function tables were used to determine H_0 values.[17] Solutions with acid concentrations of 1–0.0063 M (pH 2.2) were prepared by the dilution of a standard 1 M HCl solution (Fisher). Chloroacetate buffers were used in the pH range 2.5–3.7.

Results and Discussion

The compounds that form the basis of our study are shown in Chart I. The acronyms are related to the systematic names listed in the experimental section.

The rates and products of hydrolysis of MSA in solutions of pH 2–4.5 appear to be typical of other amides with adjacent carboxyl functional groups (Table I).

The rate is independent of solution acidity and decreases due to the extent of ionization of the carboxylic acid function at pH > 4. The reaction progress followed the integrated first-order rate equation with a correlation coefficient >0.999 for at least 5

(10) Kluger, R.; Lam, C.-H. *J. Am. Chem. Soc.* **1976**, *98*, 4154.
(11) Kluger, R.; Hunt, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 3325.
(12) Higuchi, T.; Eberson, L.; Herd, A. K. *J. Am. Chem. Soc.* **1966**, *88*, 3805.
(13) Roderick, W. R.; Bhatia, P. L. *J. Org. Chem.* **1963**, *28*, 2018.
(14) Paris, G.; Gaudry, R.; Berlinguet, L. *Can. J. Chem.* **1955**, *33*, 1725.
(15) Fahmy, A. F. M.; Aly, N F.; Elkomy, M. *Indian J. Chem.* **1979**, *17B*, 399.
(16) Matsuda, I.; Akiyama, K.; Toyoshima, T.; Kato, S.; Mizuta, M. *Bull. Chem. Soc. Jpn.* **1978**, *48*, 3675.
(17) Johnson, C. D.; Katritzky, A. R.; Shapiro, S. A. *J. Am. Chem. Soc.* **1969**, *91*, 6654.

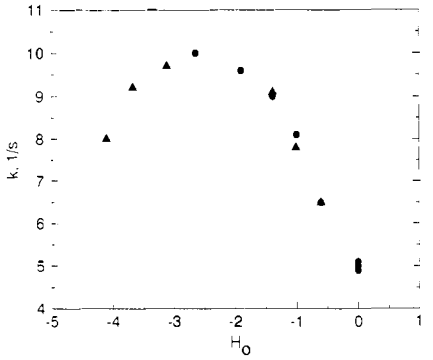
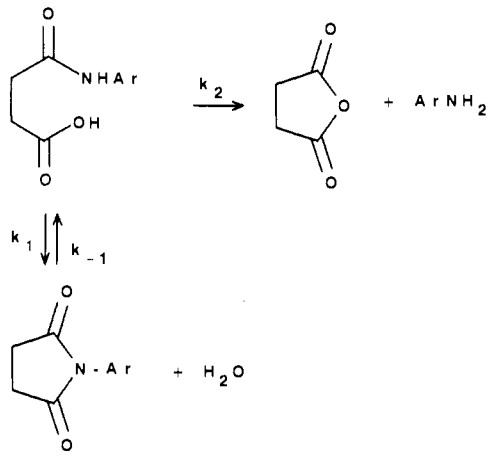


Figure 1. Observed first-order rate constant (multipled by 10^6) for second phase of reaction of MSA (●) and for hydrolysis of MSI (▲), 50.0 °C. Three points at $H_0 = 0$ are at different ionic strengths (1.0, 2.0, 3.0) with no difference in rate within experimental error.

Scheme II



half-lives. The pH-independent observed first-order rate constant is 1.50×10^{-5} s^{-1} at 50.0 °C, based on 24 measurements with a standard deviation for a set of six experiments at pH 3.5 of 1×10^{-7}. The final UV spectrum of the reaction solution was identical with that obtained from an equimolar mixture of succinic acid and *p*-anisidine.

In solutions of acidity equivalent to 1 M HCl or more, the rate of the reaction does not follow the first-order rate equation. Instead, biphasic kinetics are observed during the reaction. This indicates that the reaction occurs in two stages, with an intermediate forming during the course of the reaction. The second phase of the hydrolysis of MSA followed first-order kinetics and the observed rate constant for the H_0 range 0 to −5 is shown in Figure 1.

The possibility that the intermediate is the corresponding imide, *N*-(4′-methoxyphenyl)succinimide (MSI), was tested by comparing the rate and products of hydrolysis of MSI. The rate of hydrolysis of MSI is shown on the same plot as the second phase of the hydrolysis of MSA (Figure 1) and the plots are coincident. Therefore, the intermediate that forms in the hydrolysis of MSA in acidic solution and MSI have the same reactivity.

The UV spectrum of the product mixture of the hydrolysis of the imide after reaction in 1 M HCl is identical with that obtained for the hydrolysis of MSA, indicating that the final products of the reaction are succinic acid and *p*-anisidine. Scheme II summarizes the proposed relationship between the amic acid, imide, and hydrolysis products.

The apparent first-order rate constant for the formation of MSI is indicated as k_1 and that for formation of hydrolysis products is k_2, where these rate constants represent all terms in the rate expression.

Since the reaction of MSA is not simply first order because of the formation of the intermediate, rate constants for the initial phase of the reaction of MSA in solutions of high acidity were determined by the method of initial rates. Three products are formed: MSI, succinic acid, and anisidine; and all extinction coefficients at several wavelengths were determined separately, permitting concentrations of each to be determined by solving simple linear equations.

Table II. Excintion Coefficients of MSA at 248 nm As a Function of Acidity, 50.0 °C[a]

H_0	ϵ_{248}	log ϵ_{248}	H_0	ϵ_{248}	log ϵ_{248}
0.00	9610	3.98	−1.61	9285	3.97
−0.46	9660	3.98	−2.94	7730	3.89
−0.87	9700	3.99	−4.09	6100	3.79
−1.25	9370	3.97			

[a] Data are extrapolated to time of mixing.

The expression used to find the first-order rate constant for the initial stage of the reaction from changes in absorbance at a specific wavelength is given by eq 1, where ϵ_S is the extinction

$$k = m[\epsilon_S/(\epsilon_S - \epsilon_P)]A_0 \quad (1)$$

coefficient of MSA and ϵ_P is the sum of the extinction coefficients of the products, m is the initial slope of the change in absorbance as a function of time, and A_0 is the initial absorbance of the solution.

The change in absorbance at any time under initial conditions is

$$-d(A_T)/dt = k[(\epsilon_S - \epsilon_P)/\epsilon_S]A_0 \quad (2)$$

Under initial rate conditions

$$A_T = -k[(\epsilon_S - \epsilon_P)/\epsilon_S]A_0 t + A_0 \quad (3)$$

A plot of absorbance, A_T, vs time will have a slope, m, from which the rate constant can be obtained by using eq 1.

As we show later, the initial product distribution (imide vs succinic acid and anisidine) is a function of the acidity of the reaction solution. At acidities less than ~0.01 M, the reaction goes exclusively to the hydrolysis products. Formation of the imide from MSA is acid-catalyzed so that as the acid concentration is increased the relative initial yield of imide increases.

MSA is a weak base and becomes protonated in moderately acidic solution. The pK_A of its conjugate acid (protonated on the oxygen of the amide) should be approximately −1.1, based on the pK_A of the corresponding acetanilide.[18] (The kinetically determined pK_A of maleanilic acid is −0.9.[10]) This indicates that MSA will undergo changes in protonation state in the region $H_0 = 0$ to −2. The extinction coefficient at 248 nm for MSA (50 °C) was determined as a function of acidity in this region. Table II contains these data. We find also that the spectra of the imide and hydrolysis products are invariant in the $H_0 = -4.1$ to −0.46 range of acidity. Thus, all the extinction coefficients for the species in eq 1 are available.

In order to determine observed first-order rate constants with eq 1, the initial product composition under the conditions of the measurement must be known accurately. The only quantity not measured directly in eq 1 is the ratio $\epsilon_S/[\epsilon_S - \epsilon_P]$. Changes in the ratio of products do not cause a change in this expression since ϵ_S is much larger than ϵ_P, whatever products form. Values of ϵ_S vary from about 6000 to 10 000, while the extinction coefficient of the imide is 1300 and the extinction coefficient for the hydrolysis products is 626 at 248 nm. The exact product ratio therefore need not be precisely known. The concentrations can be determined accurately by using linear equations for extinction coefficients determined independently. The maximum possible error varies from 7% at "pH" 1.3 to 13% at $H_0 = -4$.

Errors of less than 10% in the product ratio determination give final ratio errors of 1.1–1.4% since these are subtracted from the large extinction coefficient of MSA. Therefore, reliable values for the first-order rate constant can be obtained by the initial rate method.

Table III summarizes first-order rate constants (pseudo-first-order conditions) for conversion of MSA to MSI and ex-

(18) Higuchi, T.; Miki, T.; Shah, A. C.; Herd, A. K. *J. Am. Chem. Soc.* **1963**, *85*, 3655.

Table III. Calculated First-Order Rate Constants for the Conversion of MSA to MSI at 50 °C[a]

H_0	10^6k_1, s^{-1}	$\epsilon_S/(\epsilon_S - \epsilon_P)$	H_0	10^6k_1, s^{-1}	$\epsilon_S/(\epsilon_S - \epsilon_P)$
−4.09	650	1.25	−1.25	330	1.16
−3.65	980	1.22	−1.00	270	1.15
−3.27	980	1.20	−0.46	150	1.15
−2.94	960	1.18	0.00	100	1.14
−2.47	840	1.17	0.30	66	1.13
−2.33	830	1.17	0.60	42	1.12
−1.90	600	1.17	1.00	29	1.10
−1.61	440	1.16			

[a] The extinction coefficient ratio term is used to derive rate constants as described in the text.

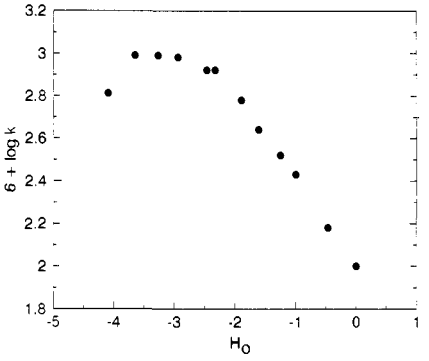


Figure 2. Calculated first-order rate constants for the conversion of MSA to MSI at 50 °C.

tinction coefficient ratios. The extinction coefficient of the reactant is taken from independent measurements. The extinction coefficient for the product mixture is taken from the product ratio as measured spectrophotometrically and solved from a linear equation based on the spectra of MSA and MSI under the same conditions. The rate constants are plotted as a function of H_0 in Figure 2.

After the initial steady-state spectrum is obtained, the solution is slowly converted to the two hydrolysis products following the rate for the uncatalyzed reaction determined in solutions of low acidity.

Hydrolysis of 4′-Methoxymaleanilic Acid (MMA). Since 4-methoxysuccinanilic acid is converted to the imide in acidic solution, the reaction of the corresponding maleamic acid, 4′-methoxymaleanilic acid, was monitored in 1 M HCl (50 °C). The half-life of this reaction is ~90 s under these conditions. The UV spectrum from this reaction and the spectrum of an equimolar mixture of maleic acid and *p*-anisidine are identical. After 4 h under these conditions, there was no additional change in the product spectrum.

Hydrolysis of (4′-Methoxyphenyl)maleimide (MMI). Since succinimide formation competes with succinanilic acid hydrolysis, we also checked some of the results of earlier studies of maleate derivatives.[10] The above results made obvious the possibility that workers studying maleanilic acid hydrolysis might have missed rapid formation of maleimide. To address this question, the reactivity of (4′-methoxyphenyl)maleimide (MMI) was studied under conditions similar to those used to study the corresponding maleanilic acid. The observed first-order rate constant at H_0 = −0.995 (50 °C) is 2.2×10^{-4} s^{-1}. At H_0 = −1.90 (50 °C) the rate constant is 3.4×10^{-4} s^{-1}. The rate constants for hydrolysis of MMA at the same acidities but at 30 °C are 3.3×10^{-3} and 4.8×10^{-3} s^{-1}, respectively.[10] Therefore, MMA is converted to the hydrolysis products much more rapidly than it is converted to the maleimide MMI, which hydrolyzes much more slowly than MMA. The absence of formation of an intermediate and the slow reactions associated with MMI show that imide formation is not a complicating feature of the maleanilic acid hydrolysis reaction nor is it likely to be a problem in other reactions where anhydride formation is rapid, so that previous interpretations are correct.

These results allow the calculation of the equilibrium constant for the interconversion of MMI and MMA. Since MMI hydrolyzes via MMA, the rate constant for imide hydrolysis is k_2/K_1 (as in Scheme II). This was determined in 1 M HCl solution at 50 °C to be 1.08×10^{-4} s^{-1}. The value of k_2, measured directly for the hydrolysis of MMA at 50 °C, is 1.20×10^{-2} s^{-1}.[17] The value of K_1, MMI/MMA, is then 110. Therefore, the anilic acid is converted to the hydrolysis products due to kinetic control of the initial reaction.

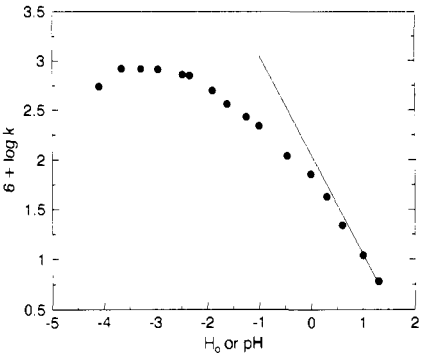


Figure 3. Logarithmic plot of k_{1H}, for the formation of MSI from MSA in acidic soludion, 50.0 °C. The line is drawn with unit slope, as indicated in the text.

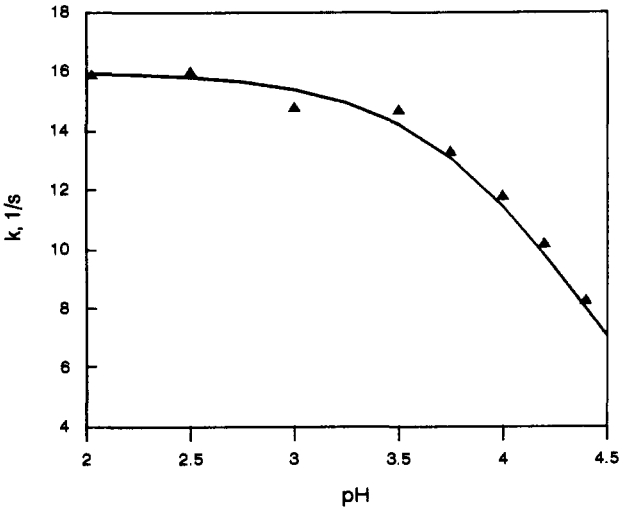


Figure 4. Corrected first-order rate constant, multiplied by 10^6, for conversion of MSA to succinic anhydride and anisidine. The data are plotted according to a titration equation for an acid of pK_A 4.4 (see text).

Kinetic Analysis. Our data permit the determination of k_1, k_{-1}, and k_2 of Scheme II. In solutions, of acidity from pH 1.3 to H_0 = 3, the observed rate constant for the reaction of MSA (using the data collected during the first part of the biphasic reaction) increases with acidity, indicating that the formation of the imide is acid-catalyzed. Product analysis at H_0 = −3.1 gives the relationship in eq 4.

$$k_{2H} = 0.15\ k_{1H} \tag{4}$$

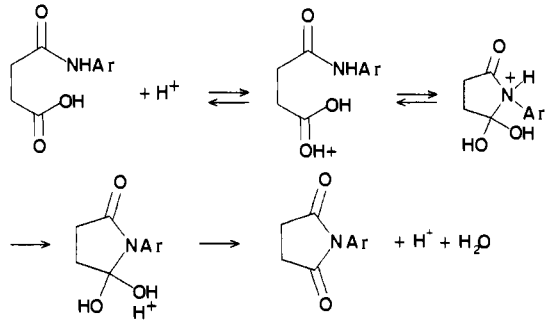
The quantities k_{2H} and k_{1H} are the observed first-order rate constants for the acid-catalyzed processes (in concentrated acid) corresponding to components of k_1 and k_2 in Scheme II at any given acid concentration.

$$k_{obsd} = k_{1H} + k_2 + k_{2H} \tag{5}$$

The value of k_2, the "water rate" for hydrolysis can be estimated from our data to be 1.6×10^{-5} s^{-1}. The value of k_2 and eq 4 and 5 were used to calculate the values of k_{1H}, which are plotted in Figure 3 as a function of acidity. A solid line of slope −1.0 is drawn, giving equal weights to the points at H_0 = 1.00 and 1.30. Based on this line, the second-order rate constant for acid-catalyzed formation of MSI from MSA is $k_{1H'}$. The equation of that line is

$$\log k_{1H'}[H^+] = -pH - 3.9 \tag{6}$$

Scheme III



This gives a value for the second-order rate constant for acid catalysis in formation of MSI, $k_{1H'} = 1.1 \times 10^{-4}$ M^{-1} s^{-1}.

In Table I, the value of log k_{obsd} for the apparent hydrolysis of MSA versus pH increases slightly at acidities greater than pH 3. This is due to the significance of $k_{1H'}$ for imide formation, which is not detected separately. The value of k_{2H} is insignificant at this acidity. The values of $k_{1H'}$ in this region can be calculated by extrapolation of the solid line in Figure 3 into the pH region. The values for k_2 (corrected for the rate of imide formation) are plotted in Figure 4.

Undissociated amic acids form anhydrides much more rapidly than do their conjugate bases.[1-5,10] The kinetic data plotted in Figure 4 follow the form of a titration curve with K_A equal to that of the carboxylic acid:

$$k_{obsd} = k_2/(1 + K_{A'}/[H^+]) \quad (7)$$

The data were fit to eq 7, which gives $k_2 = 1.6 \times 10^{-5}$ s^{-1} and a $pK_{A'}$ of 4.45 for MSA. The $pK_{A'}$ of the unsubstituted succinanilic acid has been determined by titration to be 4.4 (0.5 M NaCl, 25 °C).[18]

MSA partitions equally toward the imide MSI (Scheme II), and the hydrolysis products at the acidity in which the apparent rate constants are equal.

$$k_{1obsd} = k_{1H} \quad (8)$$

$$k_{2obsd} = k_2 + k_{2H} \quad (9)$$

Thus k_{1obsd} is equal to k_{2obsd} at "pH" 0.78.

Mechanism of Imide Formation. Acid-catalyzed formation of an imide from an amide can be formulated to occur by the mechanism in Scheme III. Protonation of the carboxyl group is followed by attack of the amide nitrogen at the carboxyl carbon, forming a protonated tetrahedral intermediate. Proton transfer and elimination of water produces the imide. Hydrolysis of the imide occurs by the reverse reaction, followed by hydrolysis of the amic acid.

The hydrolysis of MSA has a much weaker acid-catalysis component than does the formation of the imide from MSA. This small rate component is most likely due to the direct reaction of water with MSA and not the reaction in which carboxyl participation is involved. The rate constant is consistent with expectations for the reaction of a simple amide in strong acid solution.

Conclusions

The well-known rapid hydrolysis of amic acids in acidic solution involves a transacylation reaction, which potentially competes initially with a dehydration reaction leading to formation of an imide. The pseudoequilibrium between amic acid and imide is drained by the conversion of the amic acid to the amine and dicarboxylic acid via the anhydride. This complication in the behavior of amic acids indicates that changes in the initial spectrum of amic acids in acidic solution do not necessarily indicate the formation of hydrolysis products.

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Nucleic Acid Derived Allenols: Unusual Analogues of Nucleosides with Antiretroviral Activity[1]

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Abstract: Racemic 1,2-butadien-4-ols substituted with a nucleic acid base were prepared by a base-catalyzed isomerization of the corresponding 2-butynols. With basic heterocycles such as adenine, cytosine, 5-methylcytosine, or *N*-[(dimethylamino)methylene]guanine, the respective allenes were obtained without difficulty, but with guanine, side reactions were observed. Reaction of 2-butynols in stronger base (1 M NaOH) gave cyclized products—oxacyclopentenes **8a-c**. (±)-Adenallene (**3a**) and (±)-cytallene (**3c**) are strong inhibitors of replication of human immunodeficiency virus (HIV) in vitro. (±)-Adenallene (**3a**) and butyne **6a** are substrates for adenosine deaminase. Racemic **3a** was deaminated quantitatively to (±)-hypoxallene (**3h**), indicating a low stereoselectivity as contrasted with the natural substrate—adenosine. When the deamination was stopped at ca. 50% conversion, (−)-adenallene (**3a**) and (+)-hypoxallene (**3h**) were obtained. Antiretroviral and adenosine deaminase substrate activities are discussed in terms of the similarity of several steric and stereoelectronic features of allenic derivatives of nucleic bases with those of the corresponding nucleosides or 2′,3′-dideoxyribonucleosides.

Nucleoside analogues are the center of current interest as antiviral chemotherapeutic agents. Especially important are "acyclic" analogues, which can be formally derived by a cleavage of one or more bonds of the furanose ring. Thus, structure **1a** is an acyclic analogue of adenosine lacking the $C_{2'}$ and $C_{3'}$ atoms. Both adenine[2] and guanine derivatives **1a** and **1b** are biologically active; indeed, the latter is a clinically useful antiherpetic drug, acyclovir.[3] Similarly, analogue **2a** relates to the antibiotic aristeromycin,[5] and the corresponding guanine derivative **2b** is an

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(2) Schaeffer, H. J.; Gurwara, S.; Vince, R.; Bittner, S. *J. Med. Chem.* **1971**, *14*, 367.

(3) Elion, G. B.; Furman, P. A.; Fyfe, J. A.; de Miranda, P.; Beauchamp, L.; Schaeffer, H. J. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5716.

(4) Schaeffer, H. J.; Vogel, D. *J. Med. Chem.* **1965**, *8*, 507.

0002-7863/89/1511-5925$01.50/0