Protonated secondary sulfides show extraordinary stability toward the strongly acidic medium. Protonated isopropyl sulfide shows no appreciable cleavage up to +70° in a solution of FSO_3H-SbF_5 (1:1). At this temperature it slowly decomposed. No nmr identifiable products were noted at this elevated temperature.

Experimental Section

Materials. Thiols, symmetrical dialkyl sulfides, isopropyl methyl sulfide, and *t*-butyl methyl sulfide were reagent grade materials and were used without further purification.

sec-Butyl isopropyl sulfide was prepared according to the method of Vecera[10] by the reaction of *sec*-butylthiol in ethoxide–ethanol solution with isopropyl bromide. The product was purified by distillation. The fraction between 139 and 140° was used.

t-Butyl isopropyl sulfide was prepared according to the method of McAllan[11] by the reaction of *t*-butyl alcohol in 25% aqueous sulfuric acid with isopropylthiol. The product was purified by distillation. The fraction between 130 and 132° was used.

Isopropyl sulfoxide was prepared by the method of Addison[12] by the reaction of isopropyl sulfide with dinitrogen tetroxide. The product was purified by vacuum distillation. The fraction between 91 and 92° (12 mm) was used. The nmr spectra of the sulfoxide dissolved in sulfur dioxide at −60° is shown in Figure 9.

Nmr Spectra. Varian Associates Model A-56-60A and HA 60-IL nmr spectrometers with variable temperature probes were used for all spectra. Samples of S-protonated thiols and sulfides were prepared by dissolving approximately 1.5 ml of HSO_3F-SbF_5 (1:1 *M* solution) in an equal volume of sulfur dioxide and cooling to −76°. The thiol or sulfide (approximately 0.2 ml) was dissolved in 1 ml of sulfur dioxide, cooled to −76°, and with vigorous agitation slowly added to the acid solution. Samples prepared in this manner gave nmr spectra which showed no appreciable chemical shift differences with temperature or small concentration variations. The acid was always in excess of the sulfide or thiol as indicated by the large acid peak at −10.2 ppm. Samples undiluted with sulfur dioxide were prepared by cooling the 1:1 *M* acid to 0° and adding, with vigorous agitation, the neat, cooled sulfide or thiol. The nmr spectra of such samples showed a downfield solvent shift of about 0.3 ppm for all peaks because of the absence of sulfur dioxide.

Protonated hydrogen sulfide was prepared by passing gaseous hydrogen sulfide for a short time through a stirred solution of 2 ml of 1:1 FSO_3H-SbF_5 diluted with 2 ml of sulfur dioxide and cooled to −76°.

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[11] D. T. McAllan, T. V. Cullum, R. A. Dean, and F. A. Fidler, *J. Am. Chem. Soc.*, **75**, 3627 (1951).

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Acid Anhydride–Free Acid Equilibria in Water in Some Substituted Succinic Acid Systems and Their Interaction with Aniline[1]

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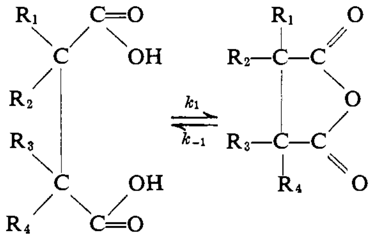
Abstract: The rates of formation of cyclic acid anhydrides in aqueous solutions of methyl-substituted succinic acids are shown to increase as expected with the degree of substitution. For the unsubstituted and mono- and disubstituted acids, at least, the estimated equilibrium concentration of the anhydride in the acid solution ranges from 1 to 50 ppm and appears to be largely determined by the rate of formation than by its hydrolysis. The aniline method was not found to be applicable to the tri- and tetrasubstituted acids because of the rapid formation of the corresponding imides.

Recent experimental evidence points to the existence of rather sluggish equilibria in water between certain sterically favored polycarboxylic acids and their corresponding cyclic internal anhydride.[3] Although such a process may be expected to be favored by, for example, alkyl substitution[4] in succinic acid, quantitative evaluation of such an effect had not been widely attempted, particularly on systems in which the relative concentration of the anhydride species would be expected to be low. The present report is concerned with results of an attempt to determine the rates of formation and the relative concentrations of these active species in aqueous solutions of methyl-substituted succinates at several temperatures.

Direct spectrophotometric determination of the forward rate of reaction 1 as carried out recently[5] was not possible in these systems since the relative concentrations of the anhydrides are always much too low to permit convenient determination. For the present purpose, the aniline method developed earlier for studies



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[1] Supported in part by a grant from the National Institutes of Health, Bethesda, Md., under GM-05830.

[2] Author to whom reprint requests should be directed.

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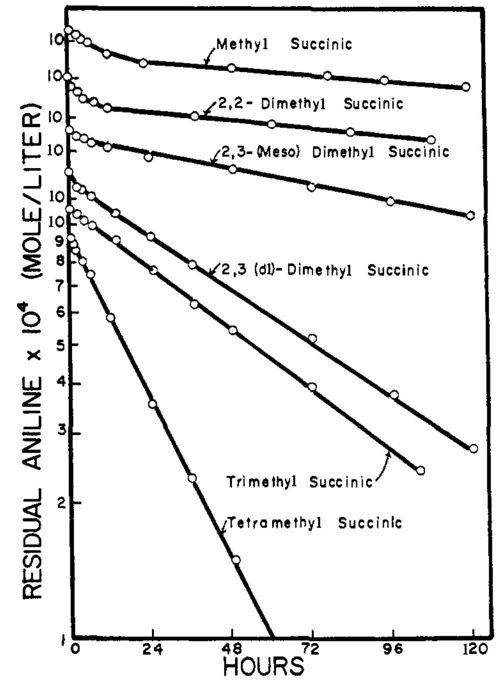

Figure 1. Semilogarithmic plot of aniline concentration as a function of time in several methyl-substituted succinic acid buffers at pH 4.0 and 60°. All buffers were 0.06 *M*.

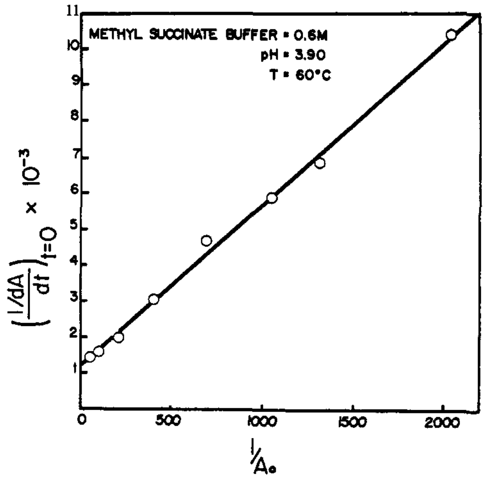

Figure 2. Reciprocal plot of the initial rate of disappearance of aniline in pH 3.90 methylsuccinate buffer (0.6 *M*) at 60° as a function of the reciprocal initial aniline concentration.

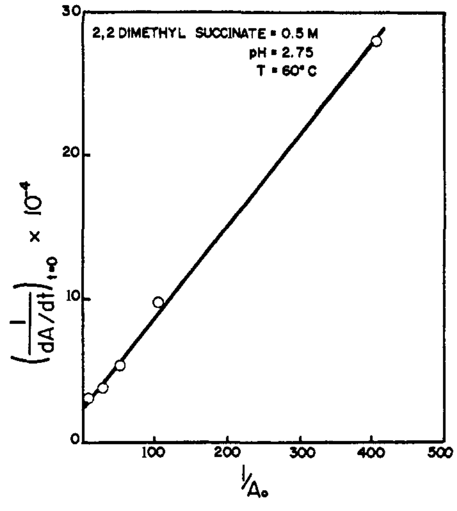

Figure 3. Reciprocal plot of the initial rate of disappearance of aniline in pH 2.75, 2,2-dimethylsuccinate buffer (0.5 *M*), at 60° as a function of the reciprocal initial aniline concentration.

on the unsubstituted succinate system[3] was applied. The method is based on the observation that the formation of anilic acid in aqueous solutions of these dicarboxylic acids and aniline is mediated entirely through intermediate production of the corresponding cyclic anhydride, measurement of the rate of formation of the amide thus affording estimation of both the rate of formation of the anhydride and the equilibrium constant for the cyclization reaction.

Results and Observations

General Behavior of Aniline–Succinate Systems. In Figure 1 the observed residual concentration of aniline in the presence of six methyl-substituted succinate buffers, 0.06 *M* at pH 4.0, is shown as a function of time at 60°. The initial concentration of the amine in each instance was 0.001 *M*. As is evident from the plots, the terminal phase of each reaction exhibited pseudo-first-order reaction kinetics. Since in the trimethyl and tetramethyl systems crystalline precipitates of the corresponding anils were observed, the over-all reaction appears to be

$$\text{dicarboxylic acid} \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} \text{acid anhydride} \underset{\underset{-\text{aniline}}{k_{-2}}}{\overset{\overset{\text{aniline}}{k_2}}{\rightleftharpoons}} \text{anilic acid} \xrightarrow{k_3} \text{anil}$$

on the basis of previously established chemistry of the succinate system. The initial nonlinearity observed with the mono- and dimethyl systems is presumably due to buildup of the corresponding anilic acid.

If the above rationalization is correct, the indicated equilibrium between the dicarboxylic acid and the anilic acid occurs with increasing facility as the degree of substitution is increased. It is evident in the case of tri- and tetramethyl systems that the initial equilibria are established too quickly to permit convenient measurement of the unidirectional rate, at least at 60°. It appeared possible, however, in the remaining four systems to determine the initial rates of loss of aniline in the manner previously described for estimating the k_1 values for these acids.

Estimation of k_1. The absolute rate of formation of the postulated acid anhydride species for monomethyl- and two dimethyl-substituted succinic acids was estimated by determining the limiting initial rate of reaction with excess aniline in these systems. The reciprocal of initial rates was plotted *vs.* the reciprocal of initial aniline concentrations to give plots such as those represented by Figures 2 and 3 for the methylsuccinate and 2,2-dimethylsuccinate buffer systems, respectively. The limiting initial rate represented by the intercept of such plots can be used to calculate k_1. The values of k_1 obtained in this manner are shown in Figure 4 plotted in the usual Arrhenius manner against $1/T$, the actual range of temperature being 40–70° for the monomethylsuccinic system and 50–80° for two dimethylsuccinic systems. Measurement was not attempted in the case of the *meso*-dimethylsuccinate system because of the low solubility of the acid and because of

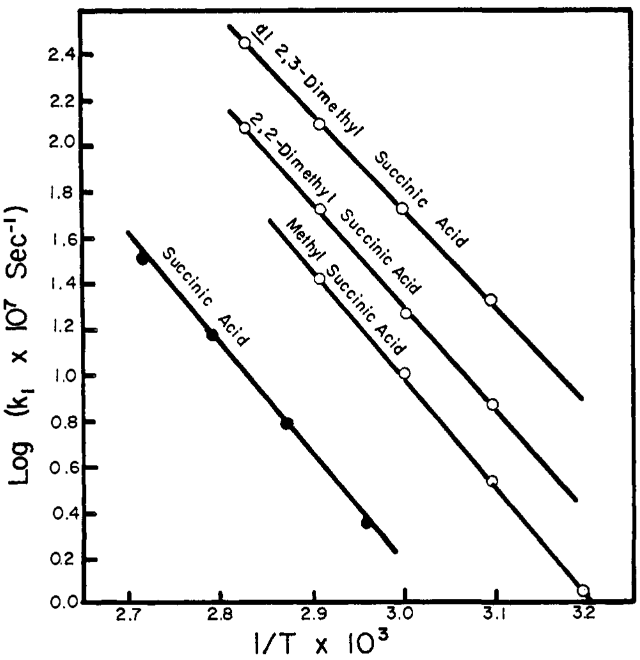

Figure 4. Arrhenius plots of k_1, the anhydride formation constant for four anhydrides.

its limited availability. Data for the unsubstituted succinic acid obtained earlier[3] are also included for comparison purposes. In Table I numerical values obtained at 60° are given, together with E_a, the energies of activation estimated from the Arrhenius plots. Eyring's $\Delta H^{\ddagger}$ would differ from these by 0.66 kcal/mole. Entropies of activation have been calculated for k_1 at 60° and are also included in Table I.

Table I. Rate of Cyclic Anhydride Formation in Water at 60°

Acid	$k_1 \times 10^7$ sec^{-1}	E_a, kcal/mole	$-\Delta S^{\ddagger}$, eu
Succinic	1.5	22.2	25.2
Methylsuccinic	9.9	21.7	22.9
2,2-Dimethylsuccinic	18.2	21.1	23.4
2,3-*dl*-Dimethylsuccinic	52.5	19.6	25.7

Estimation of K_1 ($=k_1/k_{-1}$). The equilibrium constants for the cyclization step can be readily estimated from the k_1 values since the reverse reactions have been studied by Eberson.[6] In Table II the constants, or equivalently the fraction of these acids present at these temperatures in their respective anhydride forms at equilibrium, are listed.

Table II. Equilibrium Constant for Anhydride Formation

Temp, °C	$K_{eq} \times 10^6$ (k_1/k_{-1}) Succinic	Methyl-succinic	2,2-Dimethyl-succinic	2,3-*dl*-Dimethyl-succinic
95	21	130	340	600
75	10	60	165	320
50	4[a]	19.5	56	130
25	1[a]	5.5[a]	16[a]	49[a]

[a] Extrapolated values.

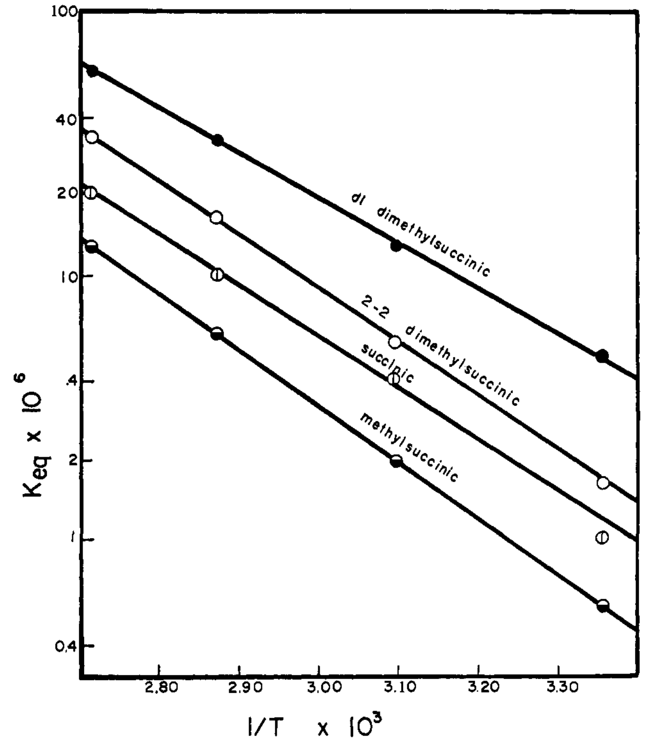

Figure 5. Equilibrium constant for formation of cyclic anhydride in water plotted against $1/T$.

The values shown in the table for succinic acid require some explanation since the extrapolated constant at 25° of 1×10^{-6} differs significantly with that of 0.2×10^{-6} reported earlier.[3] In making the earlier estimate, the rate constants (k_1) obtained experimentally at 95, 85, 75, and 65° for succinic acid were considered to form a curved rather than a linear Arrhenius plot, the nonlinear extrapolation yielding a rather rough estimate for K_{eq} of 2×10^{-7} at 25°. The slight departure from linearity is evident for the point shown in Figure 4. If, however, we assume that the line is more or less linear as are others of the series, the equilibrium constant at 25° for succinic comes out to be approximately 1×10^{-6}. The magnitude of the uncertainty introduced by extrapolation reflects the relatively high activation energy for the reaction. The higher equilibrium value for succinic anhydride would reduce the free energy of its hydrolysis from −9250 cal/mole recently calculated from our earlier data by Jencks, *et al.*,[7] to −8310 cal/mole.

The equilibrium constants given in Table II are shown plotted in Figure 5 against $1/T$. The enthalpic changes for cyclization of the four acids shown do not appear to differ significantly, the mean indicated heat of the reaction being of the order of 9 kcal/mole.[8] The plot for succinic acid appears to support the higher extrapolated value of the equilibrium value at 25° since it falls essentially on the line.

Evaluation of k_2. Determinations of k_2, the rate constant for reaction between free aniline and anhydride,

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[6] L. Eberson, *Acta. Chem. Scand.* **18**, 534 (1964).

[7] W. P. Jencks, F. Barley, R. Barnett, and M. Gilchrist, *J. Am. Chem. Soc.*, **88**, 4464 (1966).

[8] The observed lack of dependence on methyl substitution is at variance with the conclusion drawn from calorimetric measurements (J. B. Conn, G. B. Kistiakowsky, R. M. Roberts, and E. A. Smith, *ibid.*, **64**, 1747 (1942)). These were, however, carried out on solid anhydrides and involved guesses as to heats of fusion. The mean value of 9 kcal is in reasonable agreement with the mean of the calorimetric estimates.

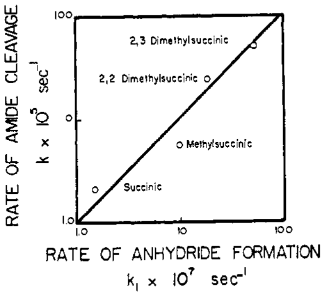

Figure 6. Plot of rates of hydrolysis of succinanilic acids against rates of anhydride formation from corresponding acids.

were performed for five methyl-substituted succinic anhydrides. These determinations were made at 20, 25, and 30° at pH 4.65 using a 0.05 M buffer composed of an acid–salt system corresponding to the anhydride studied. The values of k_2 obtained at 25°, based on free aniline concentration at the chosen pH, are shown in Table III. Check runs on methylsuccinic anhydride and aniline at pH 3.30 and 3.90 at 25° yielded results which agreed with that obtained at higher pH. The apparent heat of activation, E_a, for the formation of all the anilic acids was found to be essentially the same, about 4.6 ± 0.3 kcal/mole.

Table III. Comparison of Rate of Reaction with Aniline, k_2, with Rate of Hydrolysis, k_{-1}, at 25°

Acid anhydride	k_2, M^{-1} sec^{-1}	$k_1 \times 10^3$, sec^{-1}
Succinic	19.3	2.64
Methylsuccinic	15.3	3.65
2,2-Dimethylsuccinic	5.3	2.84
dl-2,3-Dimethylsuccinic	9.2	3.95
meso-2,3-Dimethylsuccinic	13.4	5.73

General Discussion

It is apparent from the data presented that substitution of methyl groupings for methylene hydrogens in succinic acid markedly increases the cyclization tendency as expected. The order and magnitude of the observed rate enhancement essentially parallel that recently reported for formation of the same anhydrides from the corresponding succinanilic acids,[9] as is evident from the log–log plot of the specific rate constants as shown in Figure 6. Since the reverse hydrolytic reaction rates represented by k_{-1} in Table III are relatively unaffected by methyl substitution, the equilibrium points appear to be largely determined by the formation rate.

Experimental Section

Equipment and Reagents. Mineral oil baths regulated to 0.05° were used for the kinetic runs to determine k_1. All final determinations of residual aniline were carried out spectrophotometrically on a Cary Model 11 MS spectrophotometer. The adjustment and determinations of pH were made with a Beckman pH meter with an expanded scale.

Aniline was freshly distilled and kept under nitrogen. The methyl-substituted succinic acids used have been previously described.[5] The anhydrides were prepared by treating the corresponding acids with excess acetyl chloride and recrystallizing from anhydrous diethyl ether or diethyl ether-petroleum ether (bp 30–60°) mixtures. All other chemicals used were reagent or analytical grade.

Procedure for Kinetic Runs to Determine k_1. The several 0.5 or 0.06 M buffers at the desired pH also contained aniline in various concentrations. The ionic strength was adjusted to 1.0 with sodium chloride. These solutions were filled into glass ampoules of appropriate capacity, sealed under nitrogen, and then immersed in a thermostated mineral oil bath at the desired temperature. Ampoules were periodically withdrawn as samples and chilled to quench the reaction, after which a measured volume was withdrawn, made strongly alkaline with concentrated sodium hydroxide solution, and extracted with three portions of chloforom to remove residual aniline. The aniline concentration in the chloroform extract was determined spectrophotometrically at 287 mμ. This procedure is essentially that reported earlier[3] except that sampling times were generally more frequent with the methyl-substituted succinic acids than with succinic acid since the former reacted more rapidly with aniline.

The dissociation constants employed in calculating k_1 values were obtained potentiometrically in systems at 70° and in acid concentration conditions identical with those used in the rate studies. The values obtained are given as compound (molarity), pK_1, pK_2; succinic acid (0.5), 4.4, 4.8; methylsuccinic acid (0.6), 3.75, 5.15; 2,2-dimethylsuccinic acid (0.5), 3.80, 6.0; *dl*-2,3-dimethylsuccinic acid (0.5), 3.75, 5.65.

Procedure for Determination of k_2. These rate constants were determined in a conventional manner in a thermostated Cary Model 11 spectrophotometer. The reactions carried out directly in the photometer cell were made pseudo first order with respect to anhydride by using anhydride in 40-fold excess over the aniline concentration, with the latter having a zero-time concentration of about 2.5 × 10^{-4} M. The anhydride was first introduced into the reaction cell in varying amounts of dioxane such that the final dioxane concentration ranged from 3.2 to 19.2% on a volume basis. The aniline was next introduced in a 0.05 M buffer composed of the acid–salt system corresponding to the anhydride being studied in the reaction. The composition of the solution in the reference cell was identical except for the omission of anhydride. The increase in absorbance at 235 mμ was used to follow the reaction rate. Semilogarithmic plots of the equilibrium value of the absorbance minus the value of the absorbance at time t, $A_\infty - A_t$, gave good first-order plots over several half-lifes, and the resulting rate constants were then extrapolated to zero dioxane concentration. The second-order constants were calculated from these rate values on the basis of the anhydride concentration employed and the estimated value of f_2, the fraction of unprotonated aniline in the solution at the pH and temperature of the reaction.

The dissociation constant of aniline was determined spectrophotometrically at 20, 25, and 30° in the presence of buffers of the same concentration as used in the studies to determine k_2. The pK_a' of aniline determined in this manner was 4.81, 4.74, and 4.69, respectively, at 20, 25, and 30°.

In these studies, a buffer effect was noted on both k_2 and, when determining the pK_a' of aniline, the fraction of total aniline present as the free amine. Increasing buffer concentration caused a decrease in both the value of k_2 and in the fraction of free amine present, the magnitude of the effect being comparable in both cases. Since it is the free amine form that is postulated as the reactive species with the acid anhydrides, the decrease of the concentration of this form would be expected to reflect itself in a corresponding decrease in k_2. However, at concentrations of 0.05 M buffer, the values of k_2 obtained differ by about only 2% or less from buffer-free values, and the values in Table III for k_2 are uncorrected for buffer effects.

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[9] T. Higuchi, L. Eberson, and A. K. Herd, *J. Am. Chem. Soc.*, **88**, 3805 (1966).