the Analytical Instruments Division of Syntex Corp. The structure was solved by direct methods using the program MULTAN 74.[17] The probable phase set, as determined by statistics and based on three origin and three starting reflections, produced an $E$ map containing all 24 of the 24 heavy atoms in the structure. All atoms were varified in difference Fourier maps by using the program set CRYM.[18]

Full-matrix least-squares refinement of the heavy-atom positions minimizing the quantity $\sum w(F_o^2 - F_c^2)^2$, where $w = (1/\sigma^2)F_o^2$, was followed by the calculation of all hydrogen atoms except the methyl hydrogens, which were located in difference Fourier maps. At this point, seven cycles of isotropic full-matrix least-squares refinement resulted in a $R$ value $[=\sum(||F_o| - |F_c||)/\sum|F_o|]$ of 18.8. Further full-matrix least-squares analysis of 309 variables (coordinates and anisotropic temperature factors for 24 heavy atoms, coordinates and isotropic temperature factors for the 23 hydrogen atoms, and a scale factor) led to a final $R$ value of 5.0 and a goodness-of-fit $[=\sum w(F_o^2 - F_c^2)^2/(M - S)^{1/2}]$ for $M$ = 1744 observed reflections and $S$ = 309 parameters of 1.63. The $R_w$ value $[=[\sum w(F_o^2 - F_c^2)^2/\sum wF_o^4]^{1/2}$; 1645 reflections] was 7.2, and the $R$ factor for the $3\sigma$ data set was 3.5. The estimated standard deviations were computed from the inverse matrix of the last full-matrix least-squares cycle. All shifts in parameters were less than their estimated standard deviations in the final refinement cycle. The scattering factors and anomalous dispersion terms were taken from the literature.[22] The scattering factors for hydrogen were taken from the literature.[19]

**Acknowledgment.** We thank Dr. R. E. Marsh and Mrs. B. Jean Westphal of the California Institute of Technology for providing us with copies of CRYM.[18] Additional programs were taken from the CRYSP program package.[20] We also thank the Graduate Faculty Committee of The University of Akron for providing funds to start a program of X-ray crystallographic study. The Stauffer Chemical Co. is also thanked for generously supporting this research through gifts of diphenylphosphinous chloride.

**Registry No.** (*E*)-**1**, 17668-60-9; **2**, 80780-91-2; (*E*)-**3**, 80780-92-3; (*E*)-**4**, 80780-93-4; **6**, 80780-94-5; **8**, 80780-95-6; isoprene, 78-79-5; acetoxybutadiene, 1515-76-0.

**Supplementary Material Available:** Table II, positional parameters for the heavy atoms; Table III, anisotropic thermal parameters for the heavy atoms; Table IV, positional and thermal parameters for the hydrogen atoms; Table V, angles and torsion angles; Table VI, structure factor tables (16 pages). Ordering information is given on any current masthead page.

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# Unexpectedly Low Effective Molarity in the Dicarboxylate-Catalyzed Iodine Oxidation of a Sulfide

Paul R. Young* and Michele Till

*Department of Chemistry, University of Illinois at Chicago, Chicago, Illinois 60680*

*Received October 5, 1981*

The iodine oxidation of *N*-acetylmethionine methyl ester is strongly accelerated by dicarboxylate anions. For succinate, adipate, suberate, and sebacate dianions at pH 7.0, both first- and second-order catalytic terms are observed. The ratios of the first- to the second-order catalytic constants are 0.85, 0.69, 0.55, and 0.16 M, respectively. The iodide dependence is inverse squared (approaching inverse cubed) at both high and low buffer concentrations. Since the succinate-catalyzed oxidation of sulfides has been suggested to proceed by intramolecular deacylation of an intermediate *O*-acyl sulfoxide, the observed effective molarities and the dependence on chain length are surprisingly small. It is suggested that the intermediate *O*-acyl sulfoxides exist largely as sulfuranes, complexed with the intramolecular carboxylate anion, and that the breakdown of this sulfurane is rate limiting, giving rise to the low effective molarities.

The carboxylate-catalyzed iodine oxidation of sulfides is thought to proceed through the formation of an intermediate iodosulfonium ion,[1–4] or activated sulfur–iodine complex,[5] which is attacked by carboxylate anions to give an *O*-acyl sulfoxide. This intermediate can partition by reaction with the solvent or with another mole of carboxylate to give sulfoxide and carboxylate anhydride.[2,3] In dicarboxylate anions, the intramolecular carboxylate attacks the *O*-acyl sulfoxide to give cyclic anhydride.[2] We have recently described the mechanisms of buffer catalysis in the iodine oxidation of *N*-acetylmethionine and *N*-acetylmethionine methyl ester[3,4] (NAME). For *N*-acetylmethionine, the intramolecular carboxylate appeared to be a poor nucleophile toward the iodosulfonium ion, relative to intermolecular carboxylate catalysis.[3,4] In order to more clearly define the role of intramolecular carboxylates in these reactions, we have examined the catalysis of the oxidation of *N*-acetylmethionine methyl ester by carboxylate dianions interspaced by two, four, six, and eight methylene units.

## Experimental Section

**Materials.** Inorganic salts were reagent grade and were used as supplied. Organic acids were recrystalized prior to use. *N*-Acetylmethionine methyl ester was prepared by esterification of *N*-acetylmethionine, as previously described.[3] Stock solutions of the ester were prepared at about 0.1 M in methanol. Reactions

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0022-3263/82/1947-1416$01.25/0

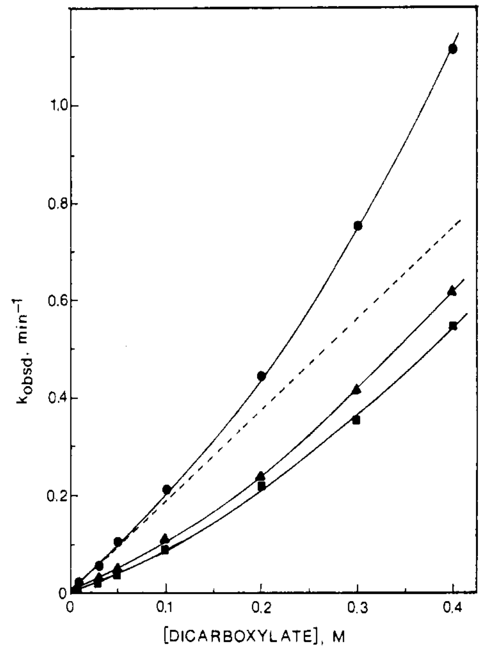


**Figure 1.** Plot of observed rate constants for the iodine oxidation of *N*-acetylmethionine methyl ester against the concentrations of succinate (●), adipate (■), and suberate (▲) dianions (pH 7.0, 0.05 M Hepes buffer, ionic strength 1.0 with KCl, 25 °C).

were initiated by the addition of iodine solution[3,4] to thermally equilibrated cuvettes containing dicarboxylate anion (previously adjusted to pH 7.0), *N*-acetylmethionine methyl ester, Hepes buffer (0.1 M, pH 7.0), KI solution, and the required amount of KCl to bring the ionic strength to unity. Glass-distilled water was used throughout. The pH of each cell was measured at the completion of the experiment by using a Corning 130 pH meter equipped with a combined glass electrode.

**Kinetic Measurements.** The rates of disappearance of $I_3^-$ were followed at 353 nm as previously described.[3] Constants for buffer catalysis were obtained from replots of (observed rate constants)/[dicarboxylate anion] vs. [dicarboxylate anion]. Rate constants were corrected for the background reaction between buffer solutions and iodine, whenever this rate was significant relative to the rate of the catalyzed oxidation reaction.

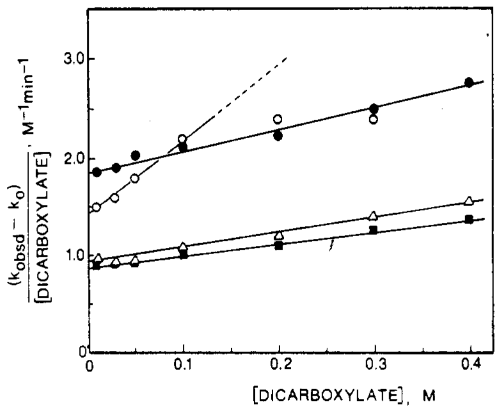


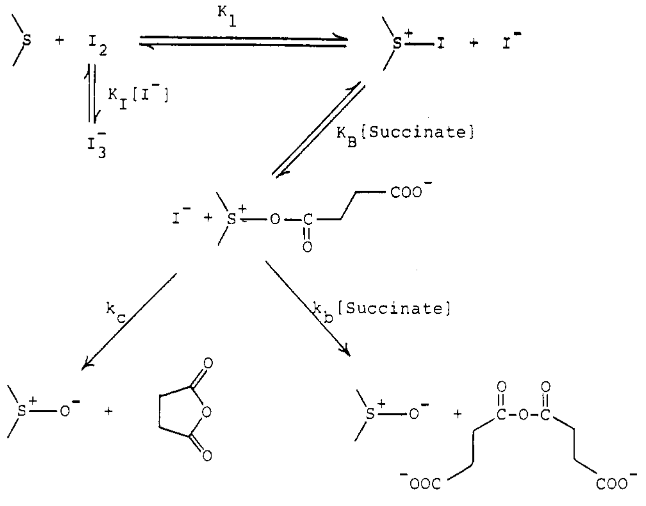
**Figure 2.** Second-order plot of observed rate constants for the dicarboxylate-catalyzed iodine oxidation of *N*-acetylmethionine methyl ester against dicarboxylate concentration for the following dicarboxylic acids: succinate (●), adipate (■), suberate (△), and sebacate (○) (pH 7.0, 0.05 M Hepes buffer, ionic strength 1.0 with KCl, 25 °C).

Table I. Dicarboxylate Catalysis of the Iodine Oxidation of *N*-Acetylmethionine Methyl Ester[a]

| catalyst | $K_1K_Bk_c$,[b] $M^{-1}$ $min^{-1}$ | $K_1K_Bk_b$,[c] $M^{-1}$ $min^{-1}$ | $k_c/k_b$, M |
|---|---|---|---|
| succinic acid | 1.85 | 2.18 | 0.85 |
| adipic acid | 0.85 | 1.24 | 0.69 |
| suberic acid | 0.90 | 1.63 | 0.55 |
| sebacic acid | 1.35 | 8.5 | 0.16 |

[a] Aqueous solution, pH 7.0, 25 °C; pH maintained with 0.05 M Hepes buffer. [b] Second-order rate constant for buffer catalysis. [c] Third-order rate constant for buffer catalysis.

Scheme I



## Results and Discussion

As the concentration of succinate, adipate, suberate, or sebacate dianion is increased, rate constants for the iodine oxidation of *N*-acetylmethionine methyl ester increase nonlinearly (Figure 1). In figure 1 the linear dependence observed at very low succinate concentrations is shown as the dashed line. The distinct upward curvature observed in these plots strongly suggests that the reaction is greater than first order with respect to the carboxylate catalysts. Catalytic constants for the first- and second-order processes can be obtained from standard replots of these data in which (observed rate constant)/[carboxylate] is plotted against [carboxylate] (Figure 2). In these plots, the slope of the line gives the observed third-order rate constant, and the *y* intercept gives the observed second-order catalytic constant. Values for these rate constants for the four dicarboxylates examined are collected in Table I. Since the experiments are performed well above the $pK_a$ of the dicarboxylates used,[6] these observed values are essentially the true values for the carboxylates as the free bases. The third-order catalytic constant for sebacic acid was taken from the data at low concentration, since, above about 0.1 M, downward curvature was observed. The buffer solutions, however, were turbid at these concentrations, suggesting micelle or aggregate formation. The nonlinearity observed at higher concentrations most likely results from reactions occurring at these micelle interfaces, which are known[7] to catalyze the iodine oxidation reactions of simple sulfides.

The iodide dependence at both high and low buffer concentration is nonlinear, being described by a curve breaking from inverse squared to inverse cubed[3] as the iodide concentration is increased. This observation is consistent with Higuchi's report[2] of an inverse-cubed iodide dependence in the dicarboxylate-catalyzed iodine oxidation

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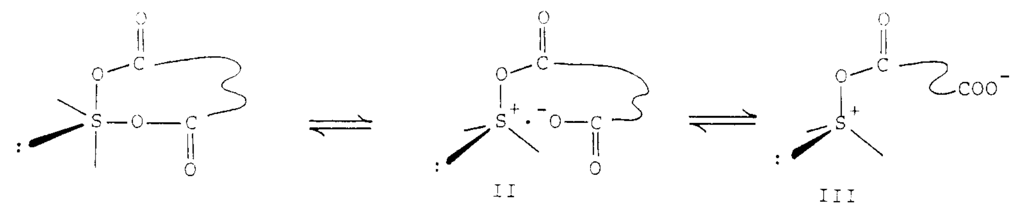
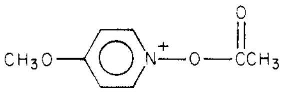
Scheme II



of tetramethylene sulfide. The data can be rationalized by the general mechanism of Scheme I and are described by eq 1, which is simplified to the condition of inverse-cubed iodide dependence.[3]

$$\frac{k_{\text{obsd}}}{[\text{NAME}]} = \frac{K_1 K_B [\text{B}](k_c + k_b[\text{B}])}{K_I[\text{I}^-]^3} \qquad (1)$$

Second-order terms for carboxylate catalysis in these reactions are not at all uncommon[1-3,7] and are usually rationalized in terms of a mechanism involving carboxylate attack at the oxidized sulfur, followed by a deacylation by a second mole of carboxylate. This deacylation step is suggested to be a nucleophilic reaction involving anhydride formation, the evidence being the formation of anilide when the oxidation is carried out in the presence of carboxylate buffers and at low concentrations of aniline.[1-3] Although the formation of anilide could result from the attack of the amine on the *O*-acyl sulfoxide, the second-order rate constant for the attack of aniline would have to be about $10^4$ times larger than the rate constant for attack by a carboxylate anion of roughly comparable p$K_a$. For acyl transfer from 1-acetoxy-4-methyoxypyridinium ion (I), the second-order rate constants for acetate and aniline differ by only about 50-fold.[8]



I

If the anhydride mechanism is taken to be essentially correct, Higuchi's observation[2] of the enhanced catalytic efficiency of succinate and other dicarboxylate anions, relative to acetate or other monocarboxylates, can be rationalized in terms of a rapid intramolecular deacylation reaction. The intramolecular carboxylate of the *O*-acyl sulfoxide shown in Scheme I would be expected to remain an efficient deacylation catalyst since the p$K_a$ of the free carboxylate would be lowered by only ~0.6 units from the electrostatic effect of the sulfonium group (based on the p$K_a$ differences between butanoic and $\gamma$-aminobutanoic acids[6]). The second step in the catalyzed oxidation reaction is essentially identical with the deacylation reactions of succinate half-esters[9] in which Bruice and co-workers observed intramolecular advantages of approximately $10^5$ over the deacylation reaction of the corresponding acetate ester with 1 M acetate as the nucleophile.

In the light of the ~$10^5$ advantage that would be expected for the intramolecular deacylation reaction over *inter*molecular deacylation, the observation of a second-order term for the four dicarboxylates which we have examined is very surprising. The ratios of the second- to the third-order rate constants for each dianion examined are given in Table I. These ratios have units of molar and they decrease from 0.85 to 0.16 M as the interspacing methylenes are increased from two to eight. Ratios of these types have been called "effective molarities", and they represent an entropic advantage associated with making an intermolecular reaction intramolecular.[10] On the basis of these data, we would have to conclude that there is *no* advantage associated with intramolecular deacylation. Further, there appears to be only a very small chain-length dependency to these effective molarities, contrary to the accepted notion that a factor of about 10 in rate or equilibrium (about 4.56 eu at 25 °C) would be associated with each additional methylene unit.[11]

In light of the large volume of literature on the subject, it seems likely that our expectation of a large effective molarity in the present case is justified. The simplest explanation is that the rate-limiting step in the reaction is not the one which we would expect to enjoy this large intramolecular advantage. Since there is a growing body of evidence that substitution reactions occurring at tricoordinate sulfur proceed through tetracoordinate sulfurane intermediates,[5,11] it is reasonable to suggest that *O*-acyl sulfoxides derived from dicarboxylate anions would be in rapid equilibrium with intramolecular sulfuranes.

Assuming that only the *O*-acyl sulfoxide undergoes the acyl-transfer reaction, the low effective molarity could result from a relatively slow breakdown of the *O*-acyl sulfoxide–carboxylate ion contact pair, II (Scheme II), to give the intermediate III, which could undergo the intramolecular deacylation reaction. Intermolecular deacylation, on the other hand, could proceed with either II or III, making the second-order reaction significant with respect to the intramolecular deacylation. Since sulfuranes involving the dicarboxylates must have the two electronegative oxygens located axial–equatorial, the involvement of these types of sulfuranes in this reaction would mean that addition–elimination reactions at tricoordinate sulfur need not proceed through sulfuranes with electronegative entering and leaving groups located diaxially. This means that the inversion that is observed in these types of reactions[12] could be proceeding through pseudorotation mechanisms.

**Registry No.** *N*-Acetylmethionine methyl ester, 35671-83-1; succinic acid, 110-15-6; adipic acid, 124-04-9; suberic acid, 505-48-6; sebacid acid, 111-20-6; $I_2$, 7553-56-2.

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