

Other Compounds.—In addition to the amino acids and the agents tabulated in Table II, catechol, aniline, and 2-hydroxy-1-naphthoic acid were evaluated. None of these compounds altered the rate of the reaction.

EXPERIMENTAL

Reagents.—All chemicals used in the preparation of the buffers and the kinetic solutions were analytical reagent grade with the exception of the catalytic agents tested. These compounds were all purified by recrystallization from suitable solvents prior to use.

Analytical Procedure.—Residual thiamine was determined by the U.S.P. XVI (7) thiochrome

method. All substances added to the system were checked for interference with the assay method.

Kinetic Procedure.—The procedure for the kinetic runs was identical with that previously described (1).

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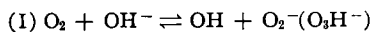
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Kinetics of Air Oxidation of Sulfurous Acid Salts

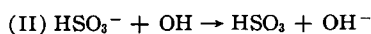
By LOUIS C. SCHROETER

Sulfurous acid salts in common with many pharmaceutical antioxidants and oxygen-sensitive drugs undergo oxidation by a radical process. This has important implications in the testing and evaluation of oxidative tendencies of formulations since radical processes are inordinately sensitive to slight amounts (10^{-6} M) of compounds acting as radical inhibitors or initiators. Measurable inhibition of the rate of sulfite oxidation occurred in the presence of 10^{-6} M DMA or DMF; the inhibition is described by an empirical equation. Effect of hydrogen ion concentration on the oxidation of sulfurous acid salts was studied in detail and the results described in terms of a theoretically derived equation. Experimental data are presented in corroboration of the Abel theoretical equations and radical mechanism for sulfite oxidation.

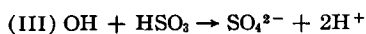
SULFUROUS ACID salts in aqueous solution undergo oxidation in the presence of molecular oxygen by a radical process (1). Radical initiation very likely occurs through interaction of oxygen with an anion to produce free radicals



which in turn react with hydrogen sulfite species to produce a highly reactive radical.



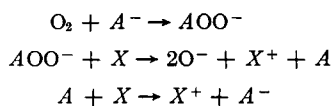
The product of the oxidation, sulfate ion (SO_4^{2-}), may be formed by the interaction of HSO_3 and OH radicals



Other mechanistic interpretations consistent with the concept of a radical process and conforming to the energetics of the system may adequately explain the experimental data. Consideration of plausible radical mechanism is aided by reviewing treatment accorded to other radical systems

(2) and especially to free radical reactions occurring in solution (3).

Abel (4, 5) has proposed the following scheme for generalized anionic auto-oxidation



in which the hydroxyl ion appears to be the preferred electron donor, A^- . In this scheme X would represent hydrogen sulfite species, HSO_3^- .

Radical processes are extraordinarily sensitive to small amounts of compounds which may act to inhibit or to catalyze the reaction. Addition of sulfurous acid salts to pharmaceutical formulations generally results in rather complex systems from the standpoint of free radical chemistry. Drug molecules or other additives in the formulation may act as initiators, inhibitors, or catalysts of the oxidative process. Systems which decrease the efficiency of the antioxidant ultimately result in poor stability of the drug since failure of the antioxidant is generally followed by oxidative attack on the drug.

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Antioxidants are added to pharmaceutical formulations as redox systems possessing higher oxidative potentials than the drug which they are designed to protect or as chain inhibitors of radical induced decomposition (6). Selection of the antioxidant is often based on sound theoretical grounds, such as the difference in redox potential between the drug and the compound; however, electrometric measurements only rarely serve to predict actual efficiency of antioxidants in complex pharmaceutical systems. Kinetics of the oxidation process and radical inhibitory or initiating action of the drug and/or the antioxidant cannot be deduced from redox potentials. Obviously, the most reliable information is obtained under field conditions (7). Laboratory evaluation of antioxidants in pharmaceutical formulations by exposing the system to oxygen under controlled conditions is a more realistic and dependable method. Manometric techniques have found considerable favor among investigators studying oxidations and auto-oxidations. Jorissen (8) describes typical manometric procedures in his interesting text on induced oxidation. Manometric techniques suffer from three main disadvantages: (a) in complex systems containing several oxidizable molecules or species it is not possible to assign oxygen uptake to a specific compound; (b) it is operationally difficult to assay the solution by an independent method while the experiment is underway; and (c) it is difficult to provide adequate stirring of the solution in contact with oxygen.

Many of the reported studies which have used manometric techniques are of questionable value inasmuch as critical evaluation of experimental techniques indicates that the diffusion rate of oxygen was the rate-determining step. If oxidation is sufficiently rapid, and if the stirring of the solution is slow, the rate at which oxygen is dis-

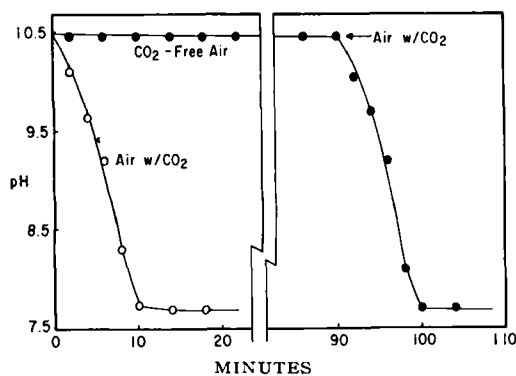


Fig. 1.—Effectiveness of gas scrubbers in removing CO_2 from air supply. Standard reactor containing 300 ml. water with 0.1 meq. NaOH stirred at 1000 r.p.m. at 25° with air flow rate of $50 \text{ cm}^3 \text{ sec}^{-1}$.

TABLE I.—EFFECT OF AIR FLOW RATE ON OXIDATION OF 0.02 M SODIUM SULFITE AT 25° IN STANDARD REACTOR

Air Flow Rate ^a	Initial pH	Reaction, %	Final pH	Specific First-Order Constant
$25 \text{ cm}^3 \text{ sec}^{-1}$	9.4	90	7.4	$2.2 \times 10^{-2} \text{ sec}^{-1}$
$38 \text{ cm}^3 \text{ sec}^{-1}$	9.4	88	7.3	$2.8 \times 10^{-2} \text{ sec}^{-1}$
$50 \text{ cm}^3 \text{ sec}^{-1}$	9.3	94	7.4	$2.9 \times 10^{-2} \text{ sec}^{-1}$
$62 \text{ cm}^3 \text{ sec}^{-1}$	9.4	93	7.3	$3.0 \times 10^{-2} \text{ sec}^{-1}$

^a CO_2 -free air.

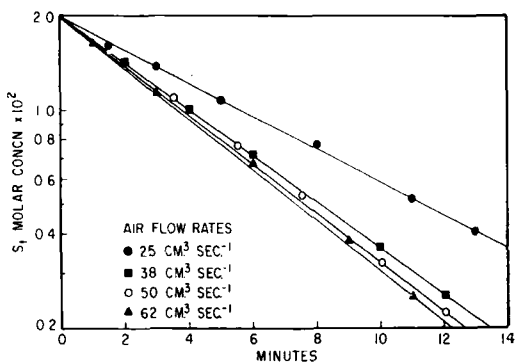


Fig. 2.—Effect of air flow rates on oxidation rate of 0.02 M sodium sulfite at 25° in standard reactor. Solutions stirred at 1000 r.p.m. CO_2 -free air saturated with water at 25° .

solved into the solvent determines how rapidly the system is oxidized.

The comparative value of various antioxidants in protecting drug formulations is best accomplished by subjecting the system to standard oxidative conditions and periodically assaying the formulation for both drug and antioxidant. This procedure requires a maximum of effort but yields the most useful information for rational formulating. Complexity of radical oxidative processes and their sensitivity to small amounts of material place stringent limitations on the validity of comparisons among different pharmaceutical systems.

This study was designed to evaluate the operation of a standard air oxidation reactor with aqueous sulfurous acid salts and to make critical comparisons with theoretically derived kinetic data (9).

EXPERIMENTAL

Apparatus and Material.—Air oxidation of sodium sulfite solutions was carried out in a Pyrex vessel with a volume of approximately 600 ml. The vessel was provided with a gas dispersion tube, sampling port, short condenser, and a glass stirrer in a ground-glass bearing. Stirring speeds could be varied up to 1000 r.p.m. The reaction vessel was immersed in a thermostat maintained at $25 \pm 0.01^\circ$.

Air supplied to the reactor was passed through a filter and molecular sieve to remove suspended solid and liquid particles. The air stream was then conducted through three gas scrubbing towers in series maintained in a thermostat at the same tem-

TABLE II.—SUMMARY OF FIRST-ORDER SPECIFIC RATE CONSTANTS^a

Sulfite Sample ^b	Initial Conc., <i>M</i>	No. Runs	Average % Completion	<i>k</i> (sec. ⁻¹)
A	0.02	3	80	2.4×10^{-3}
B	0.02	2	75	2.8×10^{-3}
C	0.02	2	80	3.7×10^{-3}
D	0.02	2	90	2.6×10^{-3}
E	0.02	2	70	2.8×10^{-3}
			Av.	2.86×10^{-3} sec. ⁻¹

^a Standard 500-ml. Pyrex reactor stirred at 1000 r.p.m. containing 300 ml. solution. Air (CO₂-free) saturated with water at 25° bubbled through solution at rate of 50 cm.³ sec.⁻¹. ^b Sample A—Fisher certified reagent sodium sulfite; B sample prepared by 2× recrystallization of A; C sample—sodium sulfite N.F., Matheson Coleman and Bell; D sample prepared by 1× recrystallization of C; E sample prepared by 1× recrystallization of D.

perature as the reactor. Air flow rate was measured with a calibrated wet gas flow meter¹ and maintained within 5 cm.³ sec.⁻¹ of the desired flow rate. Tubing was Pyrex glass with short pieces of Tygon used for connections.

Water was distilled twice from a Pyrex apparatus and stored not longer than 12 hours under nitrogen atmosphere. Prior to use, this water was once again distilled and used within 4 hours for making solutions, filling gas scrubbers, and rinsing equipment. Sodium sulfite was recrystallized from distilled water and dried at 100° under vacuum. N,N-dimethylformamide and N,N-dimethylacetamide were spectroquality reagents (Matheson Coleman, and Bell).

Carbon Dioxide Removal from Air Supply.—Air was passed through three thermostated scrubbing towers containing water; flow rate was maintained at 50 ± 5 cm.³ sec.⁻¹. This air was conducted through the standard reactor which contained 0.1 meq. sodium hydroxide in 300 ml. triple distilled water. The reactor was maintained at $25 \pm 0.01^\circ$ and stirred at 1000 r.p.m. Samples were periodically removed for pH measurement. The procedure was repeated with another 300-ml. volume of solution containing 0.1 meq. hydroxide ion through which air scrubbed free from carbon dioxide by passage through (a) sodium hydroxide solution, (b) sulfuric acid solution, and (c) triple distilled water was conducted. After 90 minutes with no significant change in pH of the basic solution, air supply to the reactor was conducted through water scrubbers.

Effect of Air Flow Rate.—Three-hundred ml. of 0.02 *M* sodium sulfite contained in the standard reactor was stirred at 1000 r.p.m. at $25 \pm 0.01^\circ$. Air (CO₂ free) was introduced through a medium glass frit beneath the surface of the stirred fluid at varying flow rates. Samples were removed periodically through the sample port with a syringe. Total sulfite concentration was determined iodometrically. The pH was determined using a Beckman GS pH meter.

Sulfite as a Function of Time.—The standard reactor was used for all studies. Three-hundred ml. of sulfite solution was stirred at 1000 r.p.m. at $25 \pm 0.01^\circ$ while water-saturated, carbon dioxide-free air was introduced at 50 ± 5 cm.³ sec.⁻¹ beneath the surface of the fluid. Total sulfite concentration of samples was determined iodometrically. The pH

¹ Flowrator, Fischer-Porter Co., Hatboro, Pa.

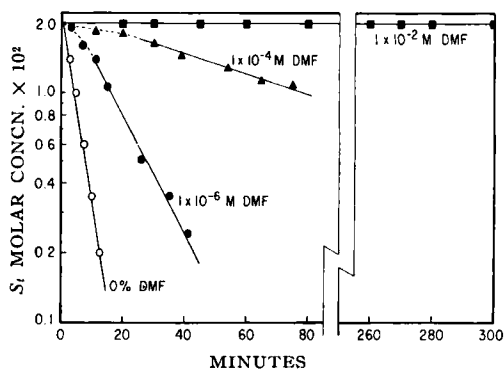


Fig. 3.—Inhibitory action of N,N-dimethylformamide (DMF) on sulfite oxidation (0.02 *M*) in standard reactor stirred at 1000 r.p.m. at 25°. Air (CO₂-free) flow rate: 50 cm.³ sec.⁻¹

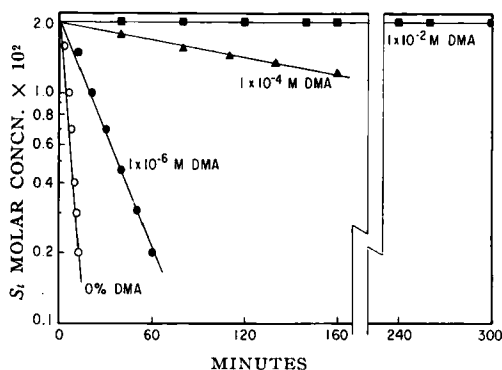


Fig. 4.—Inhibitory action of N,N-dimethylacetamide (DMA) on sulfite oxidation (0.02 *M*) in standard reactor stirred at 1000 r.p.m. at 25°. Air (CO₂-free) flow rate: 50 cm.³ sec.⁻¹

of samples removed from the reactor was determined with a Beckman GS pH meter.

RESULTS AND DISCUSSION

Removal of carbon dioxide as well as acidic or basic contaminants from air supplied to the reactor was especially important inasmuch as the aqueous sulfurous acid system is known to be sensitive to a wide variety of inhibitors and catalysts. Air contains about 0.03% by volume of carbon dioxide; thus, air flow rates around 3 L./min. result in the introduction of about 1 ml. of carbon dioxide per minute into the reactor. Effectiveness of the gas

TABLE III.—INHIBITORY EFFECT OF DMA AND DMF ON AIR OXIDATION OF SULFITE (0.02 *M*) IN STANDARD REACTOR^a AT 25°

Inhibitor, <i>M</i> concn.	Completion, %	<i>k</i> ₂ (sec. ⁻¹)	<i>k</i> ₂ / <i>k</i> ₁	$\left(\frac{A}{B+m}\right)^c$
0	90	2.88×10^{-3}	1.00	1.00
1×10^{-6} DMF	88	1.05×10^{-3}	0.365	0.45
1×10^{-4} DMF	72	1.78×10^{-4}	0.062	0.05
1×10^{-2} DMF	0 ^b
1×10^{-6} DMA	85	6.4×10^{-4}	0.222	0.182
1×10^{-4} DMA	75	5.3×10^{-5}	0.018	0.018
1×10^{-2} DMA	0 ^b

^a Solution stirred at 1000 r.p.m. Air (CO₂-free) flow rate: 50 cm.³ sec.⁻¹. ^b No reaction detectable after 380 minutes.

^c *m* = molar concentration of inhibitor; *A* and *B* constants for each inhibitor: (DMF): *A* = 0.5×10^{-3} , *B* = 1×10^{-6} ; (DMA): *A* = 0.25×10^{-3} , *B* = 1×10^{-4} .

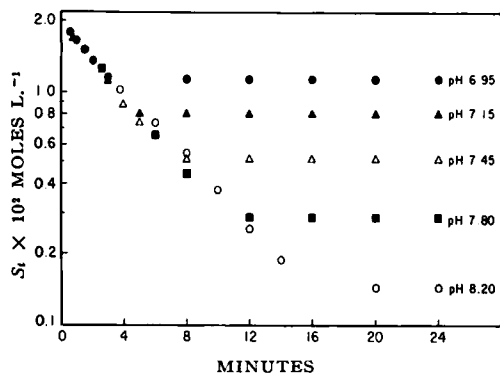


Fig. 5.—Effect of initial pH on oxidation rate of 0.02 *M* sodium sulfite at 25°. Standard reactor stirred at 1000 r.p.m. with CO₂-free air (50 cm.³ sec.⁻¹).

scrubbers in removing carbon dioxide from the air supply is shown in Fig. 1. Air introduced at a rate of 3 L./min. into a weakly basic solution contained in the reactor caused a rapid increase in hydrogen ion concentration of the solution; however, passing air through gas scrubbers effectively removed carbon dioxide: the pH of the solution changed little even after 270 L. of air had passed through it.

Preliminary tests showed that diffusion of oxygen was not a controlling factor with stirring rates greater than about 800 r.p.m. when the air flow rate was maintained at approximately 50 cm.³/sec. Effect of air flow rate when the rate of stirring was held constant at 1000 r.p.m. is shown in Table I and Fig. 2. Flow rates greater than 38 cm.³ sec.⁻¹ appear to cause no significant variation in the rate of oxidation. It was therefore concluded that diffusion of oxygen was not a controlling factor in experiments in which the air flow rate was maintained at 50 ± 5 cm.³ sec.⁻¹ and the solution stirred at 1000 r.p.m.

Specific first-order rate constants for the oxidation of five different sodium sulfite solutions in the presence of air are shown in Table II. Recrystallization of the sodium sulfite effected a significant change in the rate of oxidation of but one sample. Order of the reaction with respect to oxygen was not experimentally determined. Nevertheless, a very favorable comparison can be made between these data obtained from air oxidation studies and Fuller and Crist's data (10) obtained in a pure oxygen system. Concentration of dissolved oxygen in water in

equilibration with the pure gas at atmospheric pressure is approximately five times greater (11, 12) than the concentration of dissolved oxygen in equilibrium with air at atmospheric pressure. Assuming a first-order dependence with respect to dissolved molecular oxygen, the observed rate of reaction in the presence of air should be one-fifth that which is observed in the presence of oxygen. Thus, the specific reaction rate constant in pure oxygen is given by Fuller and Crist as 13 × 10⁻³ sec.⁻¹; one-fifth of this value is 2.6 × 10⁻³ sec.⁻¹, corresponding to the rate constant for the reaction in the presence of air. This latter theoretical value shows close agreement with the average experimental value 2.86 × 10⁻³ sec.⁻¹ reported in Table II.

Inhibitory effect of small amounts of *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMA) on sulfite oxidation is shown in Figs. 3 and 4. Oxidation of sulfite is so inhibited in the presence of either 0.01 *M* DMF (0.73 mg. ml.⁻¹) or 0.01 *M* DMA (0.87 mg. ml.⁻¹) that no detectable reaction takes place within 380 minutes (ten half-lives of the noninhibited reaction). Comparison of inhibitory effects is shown in Table III in which the ratio of the first-order rate for the inhibited reaction, *k*₂, to the uninhibited reaction, *k*₁ is presented. The inhibitory effect of these amides on sulfite oxidation may be described with the following equation

$$\frac{-d(S_t)}{dt} = \frac{k_1(S_t)A}{B + m} \quad (\text{Eq. 1})$$

where *S_t* is the total sulfurous acid species, *k*₁ is the specific rate constant for the uncatalyzed reaction, 2.88 × 10⁻³ sec.⁻¹, *m* is the molar concentration of additive, and *A* and *B* are constants. The form of this equation describing sulfite inhibitors was first employed by Bäckström (13) and later modified by Fuller and Crist (10) in which they found *B* = *A* for mannitol inhibition over a 10⁵-fold concentration range. Their modification of the empirical inhibitory equation (Eq. 1) has found considerable application in describing sulfite inhibitors (1, 14).

Effect of initial hydrogen ion concentration on the rate and course of sulfite oxidation is shown in Fig. 5. Absolute initial rate of loss of sulfurous acid species, -*d(S_t)/dt*, is very nearly the same over a rather wide range of initial hydrogen ion concentrations as shown in Table IV. The course of the reaction, however, appears to be determined by the initial pH: higher hydrogen ion concentrations decreasing the total amount of sulfurous acid species oxidized during the time period of the experiment.

TABLE IV.—ABSOLUTE INITIAL RATE OF SULFITE LOSS AND MAGNITUDE OF THE CATALYTIC CONSTANT AS A FUNCTION OF INITIAL PH

pH	$\sqrt{[H^+]} \times 10^4$	$[HSO_3^-] \times 10^{24}$	$k \text{ (sec.}^{-1}) \times 10^3$	$\frac{-d(S_t)/dt \times 10^6}{(M/L. \text{ sec.}^{-1})}$	$\frac{g \times 10^6}{(M/L.)^{1/2} \text{ sec.}^{-1b}}$
6.95	3.34	1.13	3.2	6.5	2.0
7.15	2.65	0.91	3.4	6.8	2.0
7.45	1.88	0.60	3.3	6.6	2.0
7.80	1.26	0.32	3.1	6.2	2.4
8.20	0.79	0.14	2.7	5.3	2.9

^a Calculated with the expression $[HSO_3^-] = S_t - SO_3^{2-} = S_t - \frac{S_t}{\left[\frac{[H^+]}{K a_2} + 1 \right]}$; apparent second ionization constant of sulfurous acid experimentally determined: $K_{HSO_3^-} = 8.4 \times 10^{-8}$. ^b $g = \frac{(-d(S_t)/dt) \sqrt{[H^+]}}{[HSO_3^-]}$.

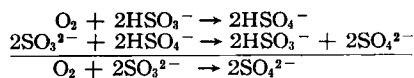
TABLE V.—EFFECT OF ACIDITY ON REACTION VELOCITY

Initial pH	t(sec.)	$S_t \times 10^{2a}$	$[\text{HSO}_3^-] \times 10^{2b}$	$[\text{SO}_3^{2-}] \times 10^2$	$[\text{H}^+] \times 10^8 c$
6.95	0	2.00	1.13	0.87	11.2
	30	1.80	1.13	0.67	(14)
	60	1.65	1.13	0.52	(18)
	90	1.50	1.13	0.37	(26)
	120	1.35	1.13	0.22	(42)
	300	1.13	1.13	0.00	3100.
	1200	1.13	1.13	0.00	3100.
7.15	0	2.00	0.91	1.09	7.1
	60	1.60	0.91	0.69	(11)
	120	1.30	0.91	0.39	(19)
	180	1.07	0.90	0.17	(53)
	300	0.80	0.80	0.00	2400.
	1200	0.80	0.80	0.00	2400.
7.45	0	2.00	0.60	1.40	3.6
	60	1.65	0.60	1.05	(4.8)
	180	1.08	0.60	0.48	(11)
	240	0.86	0.60	0.26	(19)
	300	0.74	0.60	0.14	(36)
	600	0.52	0.52	0.00	2100.
	1200	0.52	0.52	0.00	2100.
7.80	0	2.00	0.33	1.67	1.6
	120	1.35	0.33	1.02	(2.7)
	240	0.90	0.31	0.59	(4.4)
	360	0.68	0.30	0.38	(6.6)
	480	0.46	0.30	0.16	(15.7)
	960	0.28	0.28	0.00	1600.
	1200	0.28	0.28	0.00	1600.
8.20	0	2.00	0.14	1.86	0.63
	120	1.40	0.14	1.26	0.95
	240	1.05	0.14	0.91	(1.3)
	480	0.55	0.14	0.41	(2.9)
	720	0.26	0.14	0.12	(9.8)
	1200	0.14	0.14	0.00	1300.
1500	0.14	0.14	0.00	1300.	

^a $S_t = [\text{HSO}_3^-] + [\text{SO}_3^{2-}]$. ^b Calcd.: $[\text{HSO}_3^-] = S_t - \text{SO}_3^{2-} = S_t - \frac{[\text{H}^+]}{K_a' + 1}$. Apparent second ionization constant of sulfurous acid; $K_{\text{HSO}_3^-} = 8.2 \times 10^{-8}$. ^c Experimentally determined $[\text{H}^+]$ except for calculated values shown in brackets.

The region at which the rate of oxidation appears to be invariant corresponds to conditions where the sulfurous acid species is present almost wholly as hydrogen sulfite, HSO_3^- , as shown in Table V.

At first glance one may intuitively infer that sulfite species are selectively oxidized. This is patently incorrect since it leads to the improbable conclusion that bisulfite species are not air oxidizable. It was pointed out by Abel (9) that the apparent course of the oxidation of mixed sulfurous acid species



is a consequence of the different strengths (12) of the two acids, HSO_3^- and HSO_4^-

$$\frac{K_{\text{HSO}_3^-}}{K_{\text{HSO}_4^-}} = \frac{[\text{SO}_3^{2-}][\text{HSO}_4^-]}{[\text{SO}_4^{2-}][\text{HSO}_3^-]} = \frac{6.24 \times 10^{-8}}{2 \times 10^{-2}} = 3.12 \times 10^{-6}$$

Thus, the oxidation of a solution containing both bisulfite and sulfite ions will always appear to change in total amount of sulfurous acid species, S_t , at the expense of the sulfite species.

The mechanism of sulfurous acid salt oxidation in aqueous systems has been discussed in rigorous detail by Abel (9), and the general aspects of kinetics and mechanism have been the subject of a recent review (1). Abel derived theoretically an expression describing the effect of hydrogen ion concentration on sulfite oxidation

$$-\frac{d(S_t)}{dt} = \frac{g[\text{HSO}_3^-]}{\sqrt{[\text{H}^+]}} \quad (\text{Eq. 2})$$

Validity of this equation was proved by demonstrating that it would describe Fuller and Crist's highly reliable experimental data on sulfite oxidation in presence of pure oxygen (9). Evaluation of g , the catalytic constant, for a pure oxygen system gave the value $8.7 \times 10^{-6} (\text{mole/L.})^{1/2} \text{sec.}^{-1}$. Since this value is proportional to the rate of loss of sulfurous acid species, S_t , and since we may assume a first-order dependency of the rate on dissolved oxygen concentration, air systems in which dissolved oxygen is one-fifth that of pure oxygen systems should yield a value of about $1.8 \times 10^{-6} (\text{mole/L.})^{1/2} \text{sec.}^{-1}$. Experimentally determined values of the constant, g , shown in Table IV appear to stand in reasonable agreement with this value.

The standard oxidation reactor employed in this study appears to provide reproducible and reliable data which are consistent with other carefully done independent studies on sulfite oxidation. Kinetics of the sulfite oxidation process are adequately described by Abel's theoretically derived equations which have received but little attention in pharmaceutical literature. This study corroborates much of Abel's mechanistic interpretations and kinetic expressions.

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