

Kinetics and Mechanism of the Salicyl Alcohol-Bisulfite Reaction

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Reaction between bisulfite or sulfite ion and salicyl alcohol appears to follow second-order kinetics over a wide (4.0–9.5) pH range. Results suggest two parallel S_N2 mechanisms involving uncharged salicyl alcohol with bisulfite or sulfite ion. The empirical heat of activation for the reaction was found to be 24 Kcal. mole⁻¹. The reaction shows a "normal" frequency factor of 4×10^{11} L. mole⁻¹ sec.⁻¹ characteristic of many ion-neutral molecule reactions. Entropy of activation was calculated as -7.1 e.u. with a standard state of moles per L.

SALICYL ALCOHOL reacts with bisulfite to yield *o*-hydroxyphenylmethane sulfonate (1); however, the scope of the reaction is not limited to salicyl alcohol as the substrate. The reaction has proved useful for the synthesis of various *ortho*- or *para*-hydroxybenzylsulfonates and, with modifications, for the preparation of similar alkoxybenzylsulfonates (2). Kinetics and mechanism of the salicyl-bisulfite reaction are of interest not only as a model for this unique reaction but also for comparison with results obtained in a study of the reaction of epinephrine with bisulfite (3). The kinetics and mechanism of epinephrine reaction with bisulfite have been studied in some detail. Two distinct mechanisms have been uncovered: an S_N1 reaction which predominates at pH values below 4 and an S_N2 reaction which predominates at pH values over 5. The catecholamine, epinephrine, differs from salicyl alcohol in that it contains an asymmetric secondary alcohol function and exists as a charged ion over the pH range 3–7.

EXPERIMENTAL

Materials and Apparatus.—Salicyl alcohol, Eastman WL, was recrystallized twice from water, m.p. 87°. All other chemicals were of reagent grade. A Beckman GS pH meter, a Cary model 11 recording spectrophotometer, and a Perkin-Elmer model 221 spectrophotometer were used.

Kinetic Studies.—Reactant solutions were prepared to contain equimolar (0.03) concentrations of salicyl alcohol and bisulfite or sulfite in 0.30 *M* buffers. Ionic strength of the solutions was adjusted to predetermined values by addition of appropriate amounts of sodium chloride. Solutions were flushed with nitrogen and filled into hard glass ampuls. Ampuls were sealed under nitrogen, then stored in a thermostat in which the temperature variation was less than 0.1°. Sampling was performed by removing ampuls from the thermostat and quickly chilling in an ice-water mixture. Prior to analysis, ampuls were equilibrated briefly at 25°. Available bisulfite was determined by iodometric titration.

Product Isolation.—Reaction between equimolar (0.25) concentrations of salicyl alcohol and bisulfite or sulfite ion was carried out at pH 5 and 8 using previously described procedure (2).

Product Isolated from pH 5 (Bisulfite Ion) Reaction in 67% Yield.

Anal.—Calcd. for C₇H₇NaO₄S: C, 40.00; H, 3.36; S, 15.26. Found: C, 40.10; H, 3.48; S, 15.41. Infrared spectrum showed the following bands: —OH, 3,180 cm.⁻¹; salt, 2,760, 2,620 cm.⁻¹; C=C, 1,615, 1,600, 1,515 cm.⁻¹; —SO₃⁻, 1,380, 1,180, 1,155 cm.⁻¹; C—O, 1,225, 1,100, 1,040 cm.⁻¹; aromatic substitution, 870, 795, 750 cm.⁻¹. Ultraviolet spectrum in ethanol: ϵ 213 = 7,250; ϵ 274 = 2,100.

Product Isolated from pH 8 (Sulfite Ion) Reaction in 48% Yield.

Anal.—Calcd. for C₇H₇NaO₄S: C, 40.00; H, 3.36; S, 15.26. Found: C, 39.67; H, 3.36; S, 15.19. Infrared and ultraviolet spectra identical with pH 5 product.

RESULTS AND DISCUSSION

Second-order characteristics of the reaction between equimolar amounts of reactants are shown in Fig. 1 in which reciprocal bisulfite or sulfite concentration is plotted against time. The reaction appears to follow second-order kinetics over a wide range of hydrogen ion concentration. This would seem to indicate that both singly and doubly charged ions of sulfurous acid can participate in the reaction with the uncharged salicyl alcohol. Below pH 9, salicyl alcohol, pK_a 9.9 (4), exists mainly as a neutral molecule. The apparent second ionization constant of sulfurous acid, K_a'₂ 4.5×10^{-7} (determined in a nitrogen atmosphere at 65° in solution of ionic strength equal to unity), fixes the ratio of bisulfite to sulfite ion for any hydrogen ion concentration: bisulfite ion predominates at pH 4 with very little sulfite ion present while the converse is true at pH 8.5. This treatment does not consider further possible species such as pyrosulfite which can exist in equilibrium with bisulfite (5).

The pH profile of the reaction is shown in Fig. 2 in which the logarithm of the observed second-order rate constant, *k*, is plotted as a function of pH. The rate constant shows little variation with respect to hydrogen ion concentration between pH 4 and 5.5. The specific rate constant, *k*₁, at pH 4.5 and 65° under experimental conditions where bisulfite ion is the main species, was found to be 8.9×10^{-6} L. mole⁻¹ sec.⁻¹. The relative concentration of

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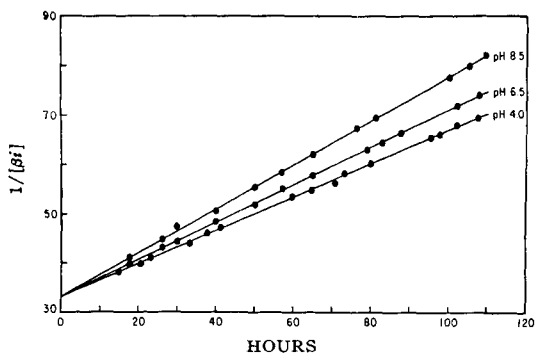


Fig. 1.—Typical second-order plots in which reciprocal bisulfite-sulfite concentration $[\beta i]$ is plotted as a function of time. Equimolar (0.03) solution of reactants in 0.30 M buffer with total ionic strength of 1.0 reacted under nitrogen at 65°. The specific rate constant at pH 4 is 0.32 L. mole⁻¹ hr.⁻¹ while at pH 8.5 it is 0.45 L. mole⁻¹ hr.⁻¹.

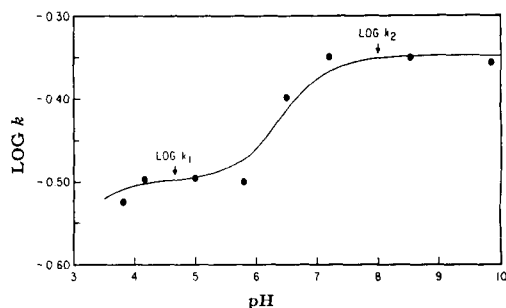
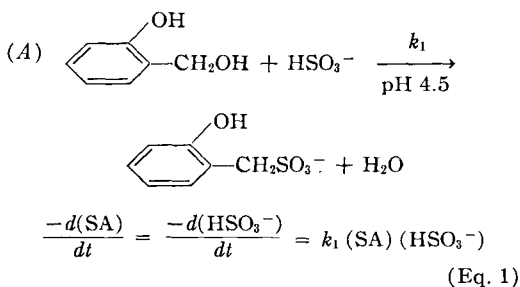
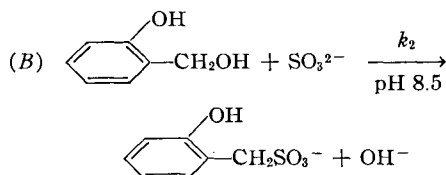


Fig. 2.—Logarithm of second-order rate constants (L. mole⁻¹ hr.⁻¹) obtained by reacting equimolar (0.03) reactants in various 0.30 M buffers under nitrogen at 65°. Ionic strength of solutions adjusted to 1.0. Theoretical values indicated by solid line calculated from Eq. 5. Experimentally determined values indicated by solid circles. $\log k_1 = -0.50$; $\log k_2 = -0.35$.

sulfite species and the observed rate constant increases with pH at pH values above 6 (sulfurous acid $pK_a' 6.35$, 65°, $\mu 1.0$). When the added this compound is totally present as sulfite species (pH > 8), the observed rate constant shows no further pH dependence. The specific rate constant, k_2 , at pH 8.5 and 65° under experimental conditions where sulfite ion is the main species, was found to be 1.25×10^{-4} L. mole⁻¹ sec.⁻¹. The results suggest parallel Sn2 reactions which lead to identical hydroxybenzyl-sulfonates



where (SA) = salicyl alcohol concentration.



$$\frac{-d(\text{SA})}{dt} = \frac{-d(\text{SO}_3^{2-})}{dt} = k_2 (\text{SA}) (\text{SO}_3^{2-}) \quad (\text{Eq. 2})$$

The overall rate expression is the sum of Eqs. 1 and 2

$$\frac{-d(\text{SA})}{dt} = k_1 (\text{SA}) (\text{HSO}_3^-) + k_2 (\text{SA}) (\text{SO}_3^{2-}) \quad (\text{Eq. 3})$$

Equation 3 may be formulated in terms of added this compound, St, by introduction of the relationship

$$\text{St} = (\text{HSO}_3^-) + (\text{SO}_3^{2-}) \quad (\text{Eq. 4})$$

along with the apparent second ionization constant of sulfurous acid, $K_a' 4.5 \times 10^{-7}$, determined under experimental conditions (65°, $\mu 1.0$):

$$\frac{-d(\text{SA})}{dt} = \frac{-d(\text{St})}{dt} = k_1 (\text{SA}) (\text{St}) + (\text{SA}) (\text{St}) \frac{(k_2 - k_1)}{\left[\frac{(\text{H}^+)}{K_a'} + 1 \right]} \quad (\text{Eq. 5})$$

The theoretical pH profile obtained with Eq. 5 is shown in Fig. 2 as a solid line. The approximate validity of the expression is apparent from the fit of experimentally determined points to the theoretical line.

Mechanism (A) indicates that the bisulfite reaction would proceed with no change in hydrogen ion concentration while mechanism (B) shows the formation of one mole of hydroxide ion for each mole of product. Both reactions were found to give the identical product in good yield and, under conditions corresponding to A, the pH was found to remain nearly constant (pH 5 ± 0.5) while under conditions corresponding to B, stoichiometric production of hydroxide ion was observed, as shown in Table I.

TABLE I.—HYDROXIDE ION PRODUCTION IN THE SALICYL ALCOHOL-SULFITE ION REACTION AT pH 8 UNDER REFLUX CONDITIONS^a

Minutes	[Sulfite], meq.	[Salicyl Alcohol], mmole	Total OH ⁻ Production, ^b meq.
0	50	50	0
35	33.4	32	16.5
90	22.2	21	27.6
120	19.4	20	30.5
150	16.7	17	43.2
210	13.1	12	37.0
390	8.1	8	42.0

^a Initial solution composition: 0.05 moles salicyl alcohol, 0.05 moles sodium sulfite in 200 ml. of distilled water. This was reacted in a nitrogen atmosphere under reflux conditions with pH maintained at 8. ^b Determined by continuous titration with hydrochloric acid to maintain pH of reaction mixture at 8.

The effect of ionic strength on the rate constant of the reaction is shown in Fig. 3. Increasing the ionic strength results in a slight decrease in the specific rate constant. In dilute solutions ($\sim 10^{-3}$ M) Debye-Hückel theory (6) leads to an equation of the following form

$$\ln k \approx \ln k_0 + K\sqrt{\mu} (Z \text{ salicyl}) (Z \text{ HSO}_3^-) \quad (\text{Eq. 6})$$

which predicts no effect due to ionic strength, μ , inasmuch as the product of the charges, Z , of the reactants equals zero (salicyl alcohol is an uncharged molecule). It should be noted that the experimental ionic strengths are greater than this by several orders of magnitude and as such are not amenable to Debye-Hückel treatment. The changes in the activity coefficient of salicyl alcohol and in the apparent ionization constants of sulfurous acid at higher ionic strengths undoubtedly contribute to the observed slight decrease in the specific rate constant. Equations have been developed to extend Eq. 6 to higher ionic strengths by including a first power ionic strength term (7), but the coefficients cannot be predicted with certainty.

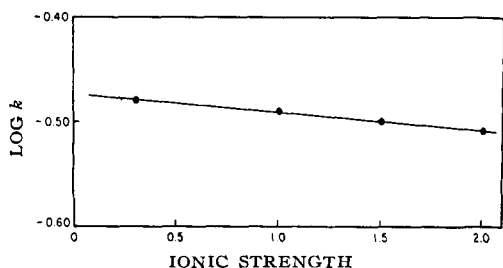


Fig. 3.—Logarithm of second-order rate constant, k_1 , (L. mole $^{-1}$ hr. $^{-1}$) as a function of ionic strength. Equimolar (0.03) solution of reactants in 0.30 M acetate, pH 4.9 buffer maintained at 65° under nitrogen atmosphere.

The empirical activation energy, E_a , obtained from Fig. 4 is 24 Kcal. mole $^{-1}$. This corresponds to conditions of mechanism (A) where bisulfite ion and neutral salicyl alcohol are reactants. Reaction between epinephrine and bisulfite or sulfite ion exhibits a similar (24 Kcal. mole $^{-1}$) experimental heat of activation (3) and the analogous Sn2 alkyl halide hydrolytic reactions show similar (23 Kcal. mole $^{-1}$) activation energies (8). The Arrhenius frequency factor was calculated for the salicyl alcohol-bisulfite reaction using 24 Kcal. mole $^{-1}$ as the empirical activation energy with rate constants obtained at various temperatures. The average value for the frequency factor was found to be 4×10^{11} L. mole $^{-1}$ sec. $^{-1}$; frequency factors for many ion-neutral molecule reactions appear to be of the order 10^{11} L.

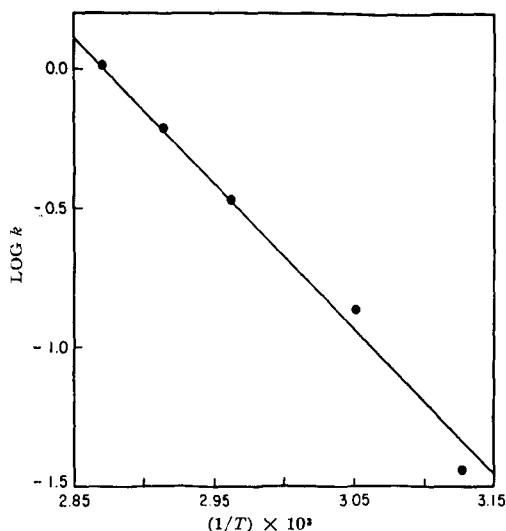


Fig. 4.—Logarithm of second-order rate constant, k_1 , (L. mole $^{-1}$ hr. $^{-1}$) as a function of reciprocal absolute temperature. Equimolar (0.03) solution of reactants in 0.30 M acetate, pH 4.9 buffers with total ionic strength of 1.0 reacted under nitrogen atmosphere.

mole $^{-1}$ sec. $^{-1}$ (9) as predicted by collision theory (10). Entropy value for the reaction calculated with the Eyring equation (8)

$$k = \frac{RT}{Nh} e^{-\Delta H_a/RT} e^{\Delta S_a/R} \quad (\text{Eq. 7})$$

gave an average value of -7.1 e.u. with a standard state of moles per L. Evaluation of the exponential term, $e^{\Delta S_a/R}$, using the experimental $\Delta S_a = -7.1$ e.u. gave the value of 2.8×10^{-2} ; this value appears to be in proper order of magnitude (10^{-2}) for reactions which obey simple collision theory (8).

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