(1963); (c) K. K. Cheung, K. H. Overton, and G. A. Sim, *Chem. Commun.*, 634 (1965); (d) G. A. Jeffrey and S. H. Kim, *ibid.*, 211 (1966).

(3) (a) W. D. Closson and P. Haug, *J. Amer. Chem. Soc.*, **86,** 2384 (1964); (b) W. D. Closson, P. J. Orenski, and B. M. Goldschmidt, *J. Org. Chem.*, **32,** 3160 (1967).

(4) (a) W. Klyne in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Sadtler Research Laboratories, Inc., Philadelphia, Penn., 1967, Chapter 12; (b) P. Crabbé, "ORD and CD in Chemistry and Biochemistry," Academic Press, New York, N.Y., 1972, pp 50–54.

(5) (a) G. DiMaio, P. A. Tardella, and C. Iavarone, *Tetrahedron Lett.*, 2825 (1966); (b) R. N. Johnson and N. V. Riggs, *ibid.*, 5119 (1967); (c) R. C. Sheppard and S. Turner, *Chem. Commun.*, 77 (1968); (d) K. Sisido, K. Inomata, T. Kageyema, and K. Utimoto, *J. Org. Chem.*, **33,** 3149 (1968); (d) R. W. Rickard and R. M. Smith, *Tetrahedron Lett.*, 1025 (1970); (f) W. Herz, K. Aota, M. Holub, and Z. Samek, *J. Org. Chem.*, **35,** 2611 (1970); (f) R. N. Johnson and N. V. Riggs, *Aust. J. Chem.*, **24,** 1659 (1971).

(6) Preliminary accounts of parts of this work appeared in (a) F. I. Carroll and J. T. Blackwell, *Tetrahedron Lett.*, 4173 (1970); (b) F. I. Carroll, A. Sobti, and R. Meck, *Tetrahedron Lett.*, 405 (1971); (c) F. I. Carroll and J. T. Blackwell, *Chem. Commun.*, 1616 (1970); (d) F. I. Carroll and R. Meck, *Syn. Commun.*, **1,** 169 (1971).

(7) The Cahn, Ingold, and Prelog *R* and *S* designation of configuration is used in this paper: R. S. Cahn, C. Ingold, and V. Prelog, *Angew. Chem., Int. Ed. Engl.*, **5,** 385 (1966).

(8) B. Belleau and G. Malek, *J. Amer. Chem. Soc.*, **90,** 1651 (1968).

(9) N. Polgar and coworkers [(a) G. S. Mark and N. Polgar, *J. Chem. Soc.*, 3851 (1955); (b) I. A. Holliday and N. Polgar, *ibid.*, 2934 (1957)] reported that (−)-methyl 3-methyl-5-oxohexanoate, $[\alpha]^{16}\mathrm{D}$ −1.1° (Et_2O), could be obtained by the addition of methylzinc iodide to (+)-methyl hydrogen 3-methylglutarate. In attempts to repeat this work we obtained (−)-methyl 3-methyl-5-oxohexonate with $[\alpha]^{26}\mathrm{D}$ −0.42° (Et_2O).

(10) E. J. Eisenbraun, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **80,** 1261 (1958).

(11) Only one of the optical isomers is shown.

(12) F. Johnson, N. A. Starkovsky, and W. D. Gurowitz, *J. Amer. Chem. Soc.*, **87,** 3492 (1965).

(13) H. Booth, *Tetrahedron*, **22,** 615 (1966).

(14) Similar results were obtained when $Eu(dpm)_3$ was added to a $CDCl_3$ solution of **7** or **8** (Table II).

(15) The sign of J_{gem} in these lactones is opposite J_{vic} and is assumed to be negative.

(16) M. Barfield and D. M. Grant, *J. Amer. Chem. Soc.*, **85,** 1899 (1963).

(17) L. M. Jackman and S. Sternhell, "Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Elmsford, N.Y., 1969, p 334.

(18) Sheppard and Turner[5c] have proposed a similar conformation to explain the spectral properties of some steroidal δ-lactones.

(19) J. B. Lambert, *Accounts Chem. Res.*, **4,** 87 (1971).

(20) (a) J. B. Stothers, "Carbon-13 NMR Spectroscopy," Academic Press, New York, N.Y., 1972, Chapter 5; (b) N. K. Wilson and J. B. Stothers, *Top. Stereochem.*, **8,** 1 (1974); (c) J. B. Stothers, C. T. Tan, and K. C. Teo, *Can. J. Chem.*, **51,** 2893 (1973).

(21) D. K. Dallings and D. M. Grant, *J. Amer. Chem. Soc.*, **89,** 6612 (1967).

(22) F. J. Weigert and J. D. Roberts, *J. Amer. Chem. Soc.*, **92,** 1347 (1970).

(23) G. C. Levy and G. L. Nelson, "Carbon-13 Nuclear Magnetic Resonance for Organic Chemists," Wiley-Interscience, New York, N.Y., 1972, Chapter 3.

(24) See ref 20c for a discussion of the relation of dihedral angle to the γ effect.

(25) W. Klyne in "Optical Rotatory Dispersion and Circular Dichroism in Organic Chemistry," G. Snatzke, Ed., Sadtler Research Laboratories, Inc., Philadelphia, Penn., 1967, Chapter 12.

(26) G. Snatzke, H. Ripperger, C. Hortmann, and K. Schreiber, *Tetrahedron*, **22,** 3103 (1966).

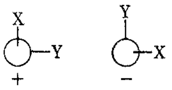
(27) J. Hrbek, Jr., L. Hruban, A. Klásek, N. K. Kochetkov, A. M. Likhosherstov, F. Santavý, and G. Snatzke, *Collect. Czech. Chem. Commun.*, **37,** 3918 (1972).

(28) (a) H. Wolf, *Tetrahedron Lett.*, 5151 (1966); (b) *ibid.*, 1075 (1965).

(29) (a) A. F. Beecham, *Tetrahedron Lett.*, 2355 (1968); (b) *ibid.*, 3591 (1968).

(30) M. Legrand and R. Bucourt, *Bull. Soc. Chim. Fr.*, 2241 (1967).

(31) The torsion angle is considered positive or negative according as the bond to the front atom X requires to be rotated clockwise or counterclockwise, respectively, in order that it becomes parallel with that of the rear atom Y



See IUPAC Tentative Rules for the Nomenclature of Organic Chemistry, *J. Org. Chem.*, **35,** 2849 (1970).

(32) Wolf has shown that the CD minimum of a half-chair conformation usually lies at longer wavelength than that of the corresponding half-boat (ref 25). The CD minimum of the conformation such as **8A** relative to a half-boat conformation has not been reported.

(33) (−)- and (+)-3-methylhexanoic acid have been related to (−)- and (+)-methylsuccinic acid which has been related with (*S*)- and (*R*)-glyceraldehyde.[33,34]

(34) E. J. Eisenbraun and S. M. McElvain, *J. Amer. Chem. Soc.*, **77,** 3383 (1955).

(35) J. A. Mill and W. Klyne, *Progr. Stereochem.*, **1,** 203 (1954).

(36) E. J. Eisenbraun, J. Osiecki, and C. Djerassi, *J. Amer. Chem. Soc.*, **80,** 1261 (1958).

(37) F. Johnson, N. A. Starkovsky, and A. A. Carlson, *J. Amer. Chem. Soc.*, **87,** 4612 (1965).

(38) We thank Dr. C. N. Moreland for carrying out these studies for us.

(39) Von Fr. R. Preuss and D. Müller, *Arzneim.-Forsch.*, **18,** 606 (1968).

(40) The progress of the resolution was followed by converting small samples of salt to the free acid and obtaining its optical rotation at 365 nm. The progrss of the resolution could also be followed by a procedure similar to that used to determine its optical purity which is described in the next experiment.

(41) The acid (+)-**5** was also prepared by ozonolysis of **12** using a formic acid 30% hydrogen peroxide work-up. However, the yield of acid (+)-**5** obtained by this method was low (14%), and the sample was not as pure as the sample obtained by ruthenium tetroxide oxidation.

The pH Independent Equilibrium Constants and Rate Constants for Formation of the Bisulfite Addition Compound of Isobutyraldehyde in Water[1]

Lawrence R. Green* and Jack Hine

Department of Chemistry, The Ohio State University, Columbus, Ohio 43210

Received July 18, 1974

The magnitudes of the apparent equilibrium constants for the formation of adduct in aqueous solutions of isobutyraldehyde and sodium bisulfite were determined spectrophotometrically and titrimetrically from pH 2.3 to 12.8 at 25°. The equilibrium constant for the addition of sulfite ion to isobutyraldehyde is 3.70 M^{-1} (at zero ionic strength) and the pK_a of the sodium bisulfite addition compound of isobutyraldehyde is 11.32 (at zero ionic strength). Rate constants were determined spectrophotometrically using potassium triiodide as a scavenger. General acids and general bases appear to have no effect on the rate of dissociation over the pH range of 4.4–7.8 and the rate-determining step is clearly a unimolecular decomposition of the doubly charged anion. The pH independent rate constants k_d and k_f, for decomposition and formation of this dianion, respectively, are 3800 sec^{-1} and 14,000 M^{-1} sec^{-1}, respectively.

Among the types of reactions used to characterize certain reactive ketones and aldehydes is the formation of sodium bisulfite addition compounds, which may at a later time be decomposed to yield the aldehyde or ketone. The fact that the carbonyl compound is recoverable is responsible for the role this reaction has as a means of separating aldehydes and reactive ketones from mixtures that contain other organic substrates. It is surprising that so little information is available with regard to the equilibria, kinetics, and mechanism of adduct formation and decomposition.

It is known that bisulfite addition compounds have at least largely the α-hydroxy sulfonate rather than the α-hydroxy sulfite structure.[2–5] Shriner and Land showed that the true structure in the case of acetaldehyde is of the former type by using an unambiguous method of synthesis.[6] Physical methods were used by Stelling and later by Caughlan and Tarter to determine the structure of the adduct in solution.[7,8] From the Raman spectra of saturated solutions (at 60°) it was concluded that there were no polymeric forms of the adduct, and that the sodium bisulfite adducts of formaldehyde, acetaldehyde, propionaldehyde, and acetone are all derivatives of α-hydroxy sulfonates. We know of no evidence that these adducts exist in solution in more than one form. However, the possibility that a small fraction of the adduct is present in the form of the α-hydroxy sulfite was not always considered in previous studies. We therefore investigated this possibility.

We are aware of only two other reports on the equilibration of an aldehyde or ketone and sulfite ion in alkaline solution,[9,10] and of no other studies where a significant portion of the curve relating the apparent equilibrium constant and pH has been determined for aliphatic aldehydes. For these reasons and in order to learn more about the possible relationships between rate constants and equilibrium constants for one-step Lewis acid–base reactions, we have studied the addition of sodium bisulfite to isobutyraldehyde over the pH range 2.3–12.8.

Experimental Section

Isobutyraldehyde (bp 63.5–64.0°) was freshly distilled before preparing solutions. Borax, boric acid, cacodylic acid (Fisher Scientific), sodium dihydrogen phosphate, sodium bicarbonate, and sodium barbitol were commercially available and used without further purification. Acetic acid was purified by several recrystallizations at 16.6°. Trifluoroethanol was shown to be pure by glpc analysis. The concentration of formic acid (Mallinckrodt 88% analytical reagent) was determined titrimetrically.

Stopped-flow experiments were conducted on a Durrum–Gibbson stopped-flow spectrometer equipped with a D-150 modular control unit. The photomultiplier signal was recorded as millivolt output on a Nicolet 1090 digital oscilloscope. Nmr spectral results were obtained on a Varian Model A-60A spectrometer using TMS as the reference. Ultraviolet and visible spectra were recorded on a Cary Model 1605 spectrometer. The pH measurements were made on a Radiometer Type 26 pH meter with a Type K401 reference electrode and Type G202C glass electrode. Sodium ion corrections to the pH were made where necessary.

Stopped-flow experiments were begun by placing a solution of isobutyraldehyde and sodium sulfite (approximately 0.001 M in each) in one of two storage reservoirs and a solution of potassium triiodide (approximately 0.003 M) in the other. Equal volumes of the two solutions, which were buffered and thermostated at 25°, were mixed by actuating the stopped-flow apparatus. The two solutions contained enough potassium iodide to give an ionic strength of 0.1 for the final mixture. The pH of the reaction mixture was determined after it exited from the apparatus. Slower reactions were followed using the Cary 1605. A solution of isobutyraldehyde and sodium sulfite was first prepared and to this solution was added an equal volume of potassium triiodide solution. A fraction of the solution was then placed in the thermostated cuvette, and the other portion was used for determining the pH.

Aqueous solutions of sulfite are easily oxidized, the extent of oxidation depending greatly on the method of preparation and handling. It was necessary to titrate the standard solution of sulfite ion before a series of experiments could be conducted even though we had taken elaborate precautions to prevent oxidation of sulfite. Blank experiments were conducted to show that there was no appreciable oxidation of sulfite solutions to which isobutyraldehyde had been added over the same period of time that was required to experimentally determine the apparent equilibrium constant in a solution to which isobutyraldehyde had been added. To obtain a standard solution of sulfite ion, solid sodium bisulfite was weighed, dissolved in double distilled degassed (boiled) water, and placed in a large reservoir under nitrogen. The reservoir was attached to a buret that could be filled or emptied without introducing oxygen from the atmosphere. This entire assembly was kept under a positive pressure of nitrogen. A measured volume of standard potassium iodate solution was used to generate a predetermined quantity of iodine in a 125-ml erlenmeyer flask to which had been added 0.5 N hydrochloric acid and potassium iodide. The volume of sulfite solution that was necessary to reach a starch–iodine end point and the number of milliequivalents of iodine originally present permitted the determination of the sulfite solution's normality. The difference between this and the value based on the weight of sodium bisulfite used was attributed to oxidation to sulfate.

The apparent equilibrium constant was determined titrimetrically as follows. A weighed amount of isobutyraldehyde was dissolved in doubly distilled water and diluted to 100 ml; 75 ml of this solution was placed in a 250-ml volumetric flask, which was then filled to the mark with standard sulfite solution, sealed with paraffin, and allowed to equilibrate thermally in a 25° water bath in a 25° laboratory. A known volume of this isobutyraldehyde–sulfite solution was added to the buffer solution in one of the seven or eight 25-ml volumetric flasks that were also in the 25° bath. This first solution was allowed to equilibrate and samples were removed for analysis and determining the pH before a second solution was prepared. An aliquot of the equilibrated mixture of sulfite and isobutyraldehyde was quenched by adding it with rapid stirring to a chilled solution of 0.5 N hydrochloric acid and iodine. The amount of excess iodine was determined by back-titrating to a starch–iodine end point with sodium thiosulfate.

The apparent equilibrium constants were also determined spectrometrically at 25°. A solution of isobutyraldehyde and sulfite ion was placed in one reservoir and a solution of the appropriate buffer or sodium hydroxide in the second reservoir of the stopped-flow apparatus, which was then actuated to mix equal volumes of the two solutions. A blank run was made following the same procedure except that distilled water was used in place of isobutyraldehyde solution. The concentration of free isobutyraldehyde at equilibrium was determined by subtracting the absorbance of the blank solution from the absorbance of the first solution and then dividing by the cuvette path length and the extinction coefficient. The apparent equilibrium constants were determined before aldol condensation reactions could interfere. The pH was determined in the same manner as in the kinetic experiments.

Sodium 1-Hydroxy-2-methylpropanesulfonate. In order to study the rate of dissociation of the complex and to study the approach to equilibrium from the other side, we prepared the sodium bisulfite addition compound of isobutyraldehyde in 95% ethanol. The product was recrystallized several times from ethanol, and dried in various ways. Samples were analyzed for free sodium bisulfite by adding them to 0.5 M hydrochloric acid and titrating iodometrically. They were analyzed for $Me_2CHCH(OH)SO_3Na$ by iodometric titration in a Borax buffer at pH 7, where the bisulfite addition compound decomposes rapidly, and correcting for the free bisulfite that had been found. These analyses showed that the material contained 86–91% bisulfite addition compound. Material dried in a current of air for 15–90 min contained only 0.1–0.2% free sodium bisulfite. Material that had been subjected to heat and high vacuum contained considerably more free sodium bisulfite, presumably as a result of loss of isobutyraldehyde from the addition compound. The pmr spectrum in 100.0% D_2O to which CD_3CO_2D had been added, τ 5.31 (s, 2.73, HOD), 5.81 (d, 0.95, J = 5 Hz, $CHSO_3$), 8.97 (d, 3.06, J = 6.5 H Hz, CH_3), 9.01 (d, 3.06, J = 6.5 Hz, CH_3), and 7.90 ppm (m, 1.05, Me_2CH), of a sample dried at 0.05 mm at room temperature for 24 hr showed no ethanol peaks nor evidence for any substances other than the bisulfite addition compound and water, of which there is seen to be about 0.86 mol of water/mol of addition compound in this sample. Sousa and Margerum described good evidence that the crystalline sodium bisulfite addition compound of benzaldehyde is a hemihydrate.[11] Elemental analysis of a sample dried at 0.05 mm at room temperature for 24 hr gave fairly good agreement with a hemihydrate structure. Therefore samples of this material were assumed to contain only the amounts of sodium bisulfite addition compound and free sodium bisulfite determined by analysis and water.

Anal. Calcd for $C_8H_{20}Na_2O_9S_2$: C, 25.95; H, 5.44; S, 17.32. Found: C, 26.02; H, 5.50; S, 17.97.

Results

The apparent equlibrium constant is defined by eq 1, in which adduct refers to all states of protonation of the bisul-

$$K_{app} = [\text{adduct}]/([i\text{-PrCHO}][\text{free sulfite}]) \quad (1)$$

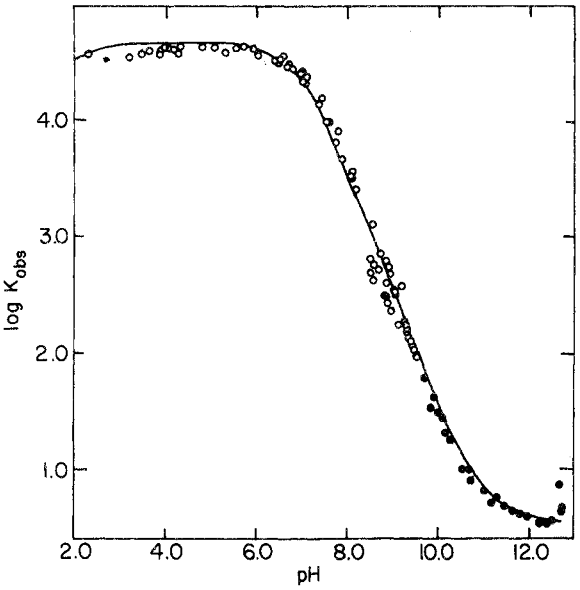


Figure 1. Log K_{app} *vs.* pH for isobutyraldehyde and sodium bisulfite in water at 25° (○, titrimetric; ●, spectrometric).

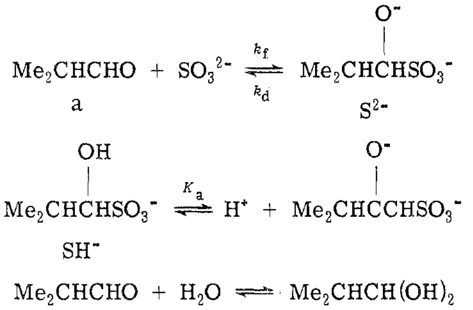
fite addition compound and free sulfite refers to sulfite and bisulfite ions and sulfur dioxide (essentially the only form in which "sulfurous acid" exists at equilibrium). In the titrimetric experiments the adduct concentration was set equal to the total concentration of sulfite known to be in the solution minus the concentration of free sulfite. The concentration of uncomplexed unhydrated aldehyde was then set equal to the total concentration of aldehyde in the solution minus the concentration of adduct and the concentration of aldehyde hydrate and its conjugate base calculated from the equilibrium constants for hydration of the aldehyde and for the acidity of the hydrate.[12] For example, an equilibrated solution 0.01412 *M* in total aldehyde and 0.006892 *M* in total sulfite at pH 9.258 and ionic strength 0.138 was found to be 0.003112 *M* in free sulfite. These data give a value of 188 M^{-1} for K_{app}. In the spectrophotometric experiments the adduct concentration was calculated from the difference between the total concentration of aldehyde and that seen spectrally to be present at equilibrium (allowing for hydration and hydrate acidity). The 92 values of K_{app} obtained over the pH range 2.3–12.8 are plotted logarithmically against pH in Figure 1 and are listed in Table III (in the miniprinted section of this paper).

Preliminary spectrophotometric kinetic studies carried out around pH 11 showed that the decomposition of adduct produced an increase in absorbance at the 285-nm aldehyde maximum followed by a decrease as the aldehyde was hydrated. It therefore seemed simpler to follow the reaction by a method similar to that of Stewart and Donnally[10] in which triiodide ions react with the sulfite ions as rapidly as they are formed and thus prevent reversal of the decomposition of the adduct. First-order rate constants were calculated from eq 2 in which $[I_3^-]_0$ is the initial and $[I_3^-]_\infty$ the final triiodide concentration (measured spectrophotometrically) and $[I_3^-]$ is the concentration at time *t*.

$$k_{\text{obsd}}t = \ln[([I_3^-]_0 - [I_3^-]_\infty)/([I_3^-] - [I_3^-]_\infty)] \qquad (2)$$

Discussion

Scheme I



$$\underset{\text{a}}{\text{Me}_2\text{CHCHO}} + \text{SO}_3^{2-} \underset{k_d}{\overset{k_f}{\rightleftharpoons}} \underset{\text{S}^{2-}}{\text{Me}_2\text{CH}\overset{\text{O}^-}{\overset{|}{\text{C}}}\text{HSO}_3^-}$$

$$\underset{\text{SH}^-}{\text{Me}_2\text{CH}\overset{\text{OH}}{\overset{|}{\text{C}}}\text{HSO}_3^-} \overset{K_a}{\rightleftharpoons} \text{H}^+ + \text{Me}_2\text{CH}\overset{\text{O}^-}{\overset{|}{\text{C}}}\text{CHSO}_3^-$$

$$\text{Me}_2\text{CHCHO} + \text{H}_2\text{O} \rightleftharpoons \text{Me}_2\text{CHCH(OH)}_2$$

$$K_{\text{S}^{2-}} = [\text{S}^{2-}]/([\text{a}][\text{SO}_3^{2-}]) \qquad (3)$$

$$K_{\text{SH}^-} = [\text{SH}^-]/([\text{a}][\text{HSO}_3^-]) \qquad (4)$$

$$K_a = [\text{H}^+][\text{S}^{2-}]\gamma_\pm^4/[\text{SH}^-] \qquad (5)$$

$$\text{p}K_a = \text{p}K_{\text{HSO}_3^-} + \log K_{\text{SH}^-} - \log K_{\text{S}^{2-}} \qquad (6)$$

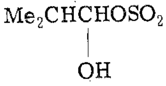
The reaction mechanism shown in Scheme I was assumed to be operating. Equilibrium constants for the formation of S^{2-} and SH^- and for the acidity of SH^- are defined in eq 3–5. At zero ionic strength these equilibrium constants are related to each other by eq 6, in which $K_{\text{HSO}_3^-}$ is the acidity constant for bisulfite ions. The apparent equilibrium constant may be expressed as shown in eq 7, in which $\gamma_\pm$ is the activity coefficient of a single-charged ion and K_{SO_2} is the acidity constant ($[\text{H}^+][\text{HSO}_3^-]/[\text{SO}_2]$) for sulfurous acid. Scheme I does not allow for the

$$K_{\text{app}} = \frac{K_{\text{S}^{2-}} + K_{\text{SH}^-}[\text{H}^+]\gamma_\pm^4/K_{\text{HSO}_3^-}}{1 + ([\text{H}^+]\gamma_\pm^4/K_{\text{HSO}_3^-})(1 + [\text{H}^+]\gamma_\pm^2/K_{\text{SO}_2})} \qquad (7)$$

formation of any electrically neutral α-hydroxysulfonic acid. Stewart and Donnally reported a pK_a value of −3 for the sulfonic acid derived from bisulfite and benzaldehyde. If the one derived from isobutyraldehyde is at all similar its concentration will be negligible at pH 2.3, the most acidic solution in which we made measurements.

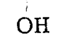
Figure 1 shows that K_{app} approaches $K_{\text{S}^{2-}}$ at high pH. On dropping to intermediate pH's, it increases and becomes essentially equal to K_{SH^-} around pH 4.5 before starting to drop below pH 3 (because of the transformation of significant fractions of the sulfite to "sulfurous acid," p*K* 1.764[13]). A least-squares treatment[14] of the observed values of K_{app} carried out using a p$K_{\text{HSO}_3^-}$ value of 7.205 at zero ionic strength[13] and the Davies equation[15] to calculate $\gamma_\pm$ gave the values of $K_{\text{S}^{2-}}$, K_{SH^-}, and K_a listed in Table I. The line in Figure 1 was calculated from these values for an ionic strength of 0.10 (although the experimental ionic strength ranged from 0.023 to 0.286).

In the α-hydroxy sulfite alternative **1** to the usually accepted α-hydroxy sulfonate structure **2** for the anion of bisulfite addition compounds, the sulfur is tetravalent. In view of the oxidizability of many tetravalent sulfur compounds, the ease of hydrolysis of sulfite esters,[16] and the fact that alkyl hydrogen sulfites (like sulfurous acid) are unknown, **1** would be expected to yield free sulfite or to behave like free sulfite when our equilibration solutions were quenched with acid before iodometric titration. Hence, when isobutyraldehyde is present in greater and greater excess over sulfite, the fraction of sulfite that is titratable should approach [**1**]/([**1**] + [**2**]). The results shown in Table II show that **1** comprises less than 0.3% of the total bisulfite addition compound. The bulky nature of the isopropyl groups should destabilize **2** relative to **1**, in which there is less branching at sulfur and the sulfur atom is farther from the isopropyl group. Hence if an α-hydroxy sulfite structure is ever important, it will probably have to be with a



$$\underset{\text{OH}}{\underset{|}{\text{Me}_2\text{CHCHOSO}_2^-}}$$

1



$$\underset{\text{OH}}{\underset{|}{\text{Me}_2\text{CHCHSO}_3^-}}$$

2

Table I
Summary of pH Independent Equilibrium Constants and Rate Constants for Aldehyde–Bisulfite Equilibrations in Water

Structure	$K_{S^{2-}}$, M^{-1}	$10^{-5}K_{SH^-}$, M^{-1}	pK_a[a]	k_d, sec^{-1}	$10^{-5}k_f$, M^{-1} sec^{-1}	Ref
Isobutyraldehyde[b]	3.70	0.48	11.3	3800	0.14	This work
Formaldehyde[b]	220,000	$\sim 10^5$	11.7	43	~95	9
Benzaldehyde[c]	65	0.10	9.6	180	0.12	10

[a] At zero ionic strength. [b] Temperature 25°. [c] Temperature 21°.

Table II
Per Cent Titrable Sulfite in the Presence of Excess Isobutyraldehyde at 25° in Water

Total aldehyde	$[NaHSO_3]_{total}$	$10^5[\text{Sulfite}]_{titrated}$	% titrable sulfite	pH	Buffer
0.08756	0.01222	0.0	0.00	5.669	Phosphate
0.07505	0.01222	2.2	0.18	5.662	Phosphate
0.05003	0.01222	2.2	0.18	5.666	Phosphate
0.03752	0.01222	3.1	0.25	5.663	Phosphate
0.02502	0.01222	6.2	0.52	5.670	Phosphate
0.01318	0.01217	147	12.10	6.097	Acetate
0.3592	0.01753	5.2	0.30	3.452	None
0.3353	0.01753	3.1	0.18	3.417	None
0.2395	0.01753	3.1	0.18	3.575	None
0.1916	0.01753	4.1	0.24	3.650	None
0.1197	0.10753	2.7	0.15	3.687	None
0.07184	0.01753	5.2	0.30	3.778	None
0.03592	0.01753	69.7	3.98	3.468	None
0.01895	0.01749	202	11.52	3.967	Acetate

much more crowded carbonyl compound than isobutyraldehyde.

The spectrophotometric method for determining K_{app} is most reliable for fairly small values of K_{app} but the values obtained above pH 11 are so small as to reduce the reliability somewhat. The proportion of isobutyraldehyde that forms a product can be regulated to some extent by adjusting the concentration of sulfite. If the concentration of sulfite ion greatly exceeds the concentration of isobutyraldehyde, a greater percentage of the aldehyde can be forced to react. Since we wanted to keep the ionic strength below 0.14 when possible, the amount of sulfite ion that could be used to force more of the aldehyde to react was limited. The fact that the apparent equilibrium constant becomes quite large as the solution is made more acidic also placed a limitation on the accuracy with which we could determine the concentration of isobutyraldehyde spectrophotometrically. It is for this reason that we chose to study the equilibrium below pH 9.5 by quenching an equilibrated mixture and then titrating to determine how much of the sulfite had not formed an adduct.

The titrimetric method for obtaining the equilibrium constant appears to be far more sensitive than the spectrometric method of analysis, particularly where a very large fraction of the isobutyraldehyde has reacted to form adduct. Unlike the spectrophotometric method of analysis, where the concentrations at equilibrium are directly obtained, the titrimetric method of analysis gives the concentration of sulfite ion in the much more acidic quenched solution. There are two criteria that must be met to assure that the calculated equilibrium constants are the correct constants. The first is that there be no change in the concentration of complexed sulfite ion as the reaction is quenched, and the second is that the rate of dissociation of the complex be negligible at the pH at which the solution is titrated. To learn whether the rate of dissociation is negligible at the pH at which the solutions were titrated, an equilibrated solution of isobutyraldehyde and sulfite ion was quenched in the manner described and the amount of excess iodine determined by back-titrating with sodium thiosulfate. However, in this experiment the amount of sodium thiosulfate necessary to remove the last trace of purple starch–iodine indicator was not added immediately. Instead, the solution was allowed to stand several minutes during which time the very faint purple color of the indicator persisted. The last drop of sodium thiosulfate was added after 30 min and the last trace of purple color was destroyed. If there had been a reaction during the 30-min experiment before adding thiosulfate, the color of the indicator would have faded. We estimate the rate constant for dissociation of the adduct to be less than 5.7×10^{-7} sec^{-1} under the conditions of the titration. The resulting error in the titration is negligible.

To learn whether the concentration of adduct shifts as equilibrated mixture of sulfite and isobutyraldehyde is quenched, let us compare the values of K_{app} determined titrimetrically with those determined spectrophotometrically. There is a portion of the curve in Figure 1 where points for the two types of K_{app} overlap (and agree satisfactorily). The pH range over which the two methods were compared could not be extended to more acidic solution because the spectrophotometric method became unreliable. Above pH 10 the equilibrium constant determined titrimetrically became larger than the value determined spectrophotometrically by amounts that increased with increasing pH. Apparently it was no longer possible to quench the reaction. The fact that the titrimetric equilibrium constants were too large suggests that significant amounts of free sulfite ion added to aldehyde during the addition of equilibrated solution to the hydrochloric acid and triiodide ion. The increase in acidity that occurs upon quenching is accompanied by an increase in K_{app}, which favors formation of more adduct. The dilution of the equilibrated mixture favors dissociation of adduct. The experimental results suggest that the presence of enough base in the equilibration solution will so slow the change in pH that the pH and the equilibration rate will remain high for a long enough time to permit an appreciable shift in equilibrium during quenching. We were unable to circumvent this difficulty even by using quenching solutions as acidic as 5 N hydrochloric acid. Since the rate of equilibrations is much slower in acidic solution, and since the spectrophotometric method and the titrimetric method are in good agreement where the initial solution's pH is less than or equal to 9.6, there is reason to believe that the K_{app} values determined titrimetrically at a pH less than 9.6 are reliable.

According to the mechanism in Scheme I, k_{obsd} should vary with the acidity as shown in eq 8. However, since the

$$k_{obsd} = k_d/(1 + [H^+]\gamma_\pm^4/K_a) \qquad (8)$$

pK_a is 11.32 and the kinetics were not followed at any pH above 7.6, k_{obsd} may be expressed simply as $k_dK_a/([H^+]\gamma_\pm^4)$. Although some of the deviations from the straight line shown are larger than the variations in log $\gamma_\pm^4$ the plot is linear within the experimental uncertainty. This supports the adequacy of Scheme I. Nevertheless, the possibility of general catalysis by the constituents of the acetate and cacodylate buffers was examined by a least-squares treatment of the k_{obsd} values. All the catalysis constants for general catalysis were within the estimated standard deviations of zero. The least-squares[14] best values of k_d and k_f are listed in Table I. Also listed are values calculated from literature data on formaldehyde[9] and benzaldehyde.[10] Some of the additional literature data on bisulfite addition to carbonyl compounds are difficult to compare with those in Table I. Sousa and Margerum[11] described evidence that Gubareva[17] was not justified in assuming that dissociation of bisulfite addition compounds during iodometric titration of unacidified solutions may be neglected. Sousa and Margerum's experimental method should give their reaction solutions a pH around 5. A K value at 21° interpolated from their data at 13 and 23° is about 60% as large as the value reported by Stewart and Donnally at pH 5 (in a pH region where K changes only slowly with changing pH).[10] Uncertainty in the pH makes it impossible to obtain values of k_d and k_f from Sousa and Margerum's rate data, however. Blackadder and Hinshelwood studied the rates of dissociation of the bisulfite addition compounds of acetone, propionaldehyde, acetaldehyde, formaldehyde, chloral, and a number of benzaldehyde derivatives.[18] They determined rate constants at two pH's but gave no equilibrium data. Geneste, Lamaty, and Roque[19,20] studied the rates of dissociation of the bisulfite addition compounds of several aliphatic aldehydes and ketones and several benzal-

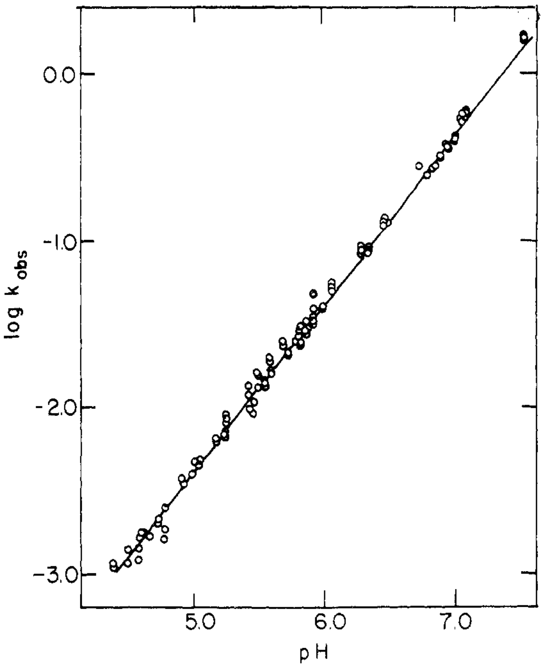


Figure 2. Log k_{obsd} *vs.* pH for sodium isobutyraldehyde bisulfite in water at 25° and 0.1 ionic strength.

Table III. Sodium Isobutyraldehyde Bisulfite Equilibrations in Water at 25°.

pH	Total [aldehyde] M	Total [sulfite] M	Uncomplexed [sulfite] M	μ	Log K_{app}	Buffer
2.312	0.007900	0.007900	0.0005631	0.127	4.569	Formic Acid
3.200	0.007110	0.007110	0.0005316	0.118	4.536	''
3.461	0.005530	0.005530	0.0004624	0.118	4.579	''
3.651	0.004741	0.004741	0.0004189	0.118	4.596	''
3.890	0.003951	0.003951	0.0003868	0.118	4.581	''
3.900	0.007531	0.007531	0.0005356	0.118	4.618	Acetic Acid
3.990	0.006778	0.006776	0.0004830	0.118	4.635	'
4.095	0.006025	0.006025	0.0004634	0.121	4.619	'
4.180	0.005272	0.005272	0.0004257	0.118	4.628	''
4.293	0.01824	0.01824	0.0008518	0.023	4.584	Cacodylic Acid
4.325	0.004535	0.004535	0.0003545	0.118	4.652	Acetic Acid
4.812	0.01672	0.01672	0.0007622	0.037	4.643	Cacodylic Acid
5.099	0.01520	0.01520	0.0007268	0.050	4.642	'
5.305	0.01368	0.01368	0.0007033	0.062	4.594	''
5.510	0.01216	0.01216	0.0006514	0.076	4.637	''
5.700	0.01064	0.01064	0.0005972	0.089	4.654	''
5.899	0.009122	0.009122	0.0005736	0.102	4.619	''
6.030	0.007601	0.007601	0.0005406	0.114	4.587	'
6.442	0.003617	0.003617	0.0003911	0.117	4.528	''
6.470	0.006303	0.006303	0.0005319	0.087	4.514	''
6.530	0.006093	0.006093	0.0005019	0.089	4.550	''
6.591	0.006081	0.006081	0.0004840	0.128	4.562	''
6.655	0.003215	0.003215	0.0003931	0.117	4.466	''
6.700	0.005673	0.005673	0.0005088	0.091	4.504	''
6.778	0.01941	0.01941	0.001013	0.034	4.458	Boric Acid
6.960	0.005253	0.005253	0.0005423	0.093	4.409	Cacodylic Acid
6.981	0.005321	0.005321	0.0005352	0.134	4.422	''
7.010	0.002813	0.002513	0.0004168	0.117	4.344	''
7.041	0.01857	0.01857	0.001148	0.040	4.325	Boric Acid
7.129	0.005042	0.005042	0.0005435	0.094	4.386	Cacodylic Acid
7.335	0.01772	0.01772	0.001359	0.047	4.151	Boric Acid
7.445	0.004832	0.004832	0.0006476	0.095	4.203	Cacodylic Acid
7.529	0.01688	0.01688	0.001579	0.053	3.992	Boric Acid
7.560	0.004940	0.004940	0.0008235	0.138	3.987	Cacodylic Acid
7.721	0.01604	0.01604	0.001838	0.060	3.826	Boric Acid
7.760	0.004727	0.004727	0.0008742	0.095	3.907	Cacodylic Acid
7.885	0.01519	0.01519	0.002080	0.066	3.686	Boric Acid
8.050	0.002511	0.002511	0.0008690	0.117	3.516	Cacodylic Acid
8.072	0.01435	0.01435	0.002392	0.073	3.524	Boric Acid
8.110	0.004622	0.004622	0.001226	0.096	3.558	Cacodylic Acid
8.211	0.01350	0.01350	0.002646	0.080	3.395	Boric Acid
8.497	0.008857	0.01160	0.005484	0.037	2.814	Sodium Barbitol
8.503	0.01311	0.01435	0.005918	0.131	2.688	Borax
8.547	0.01181	0.1181	0.003281	0.093	3.103	Boric Acid
8.571	0.006683	0.01138	0.005577	0.037	2.762	Sodium Barbitol
8.584	0.01388	0.01519	0.006405	0.131	2.634	Borax
8.645	0.008515	0.01116	0.005623	0.038	2.724	Sodium Barbitol
8.729	0.01505	0.01350	0.003911	0.053	2.856	''
8.772	0.01542	0.01688	0.007588	0.103	2.505	Borax
8.851	0.01099	0.01099	0.004909	0.023	2.606	Trifluoroethanol
8.859	0.01373	0.01232	0.004005	0.054	2.788	Sodium Barbitol
8.874	0.01620	0.01772	0.008317	0.132	2.425	Borax
8.912	0.01344	0.01205	0.004117	0.054	2.748	Sodium Barbitol
8.931	0.01316	0.01180	0.004199	0.054	2.683	''
8.955	0.01697	0.01857	0.008997	0.133	2.362	Borax
9.040	0.01238	0.01111	0.004862	0.054	2.525	Sodium Barbitol
9.040	0.01214	0.01089	0.004846	0.054	2.515	''
9.115	0.01774	0.01914	0.01003	0.133	2.253	Borax
9.182	0.008440	0.008440	0.004199	0.097	2.585	Boric Acid
9.258	0.01412	0.006892	0.003112	0.138	2.274	Borax
9.274	0.01412	0.008042	0.003791	0.138	2.250	''
9.300	0.01412	0.009190	0.004685	0.138	2.204	''
9.306	0.01412	0.01034	0.005530	0.137	2.175	Borax
9.330	0.01412	0.01149	0.006470	0.137	2.135	''
9.366	0.01412	0.01379	0.008180	0.137	2.110	''
9.388	0.01412	0.01608	0.009795	0.137	2.117	''
9.431	0.01412	0.02068	0.01367	0.136	2.062	''
9.456	0.01412	0.02298	0.01570	0.136	2.035	''
9.528	0.01928	0.02110	0.01284	0.136	1.970	''
9.690	0.01099	0.01099	0.008349	0.032	1.783	Trifluoroethanol
9.910	0.01340	0.01535	0.01209	0.125	1.629	Sodium Bicarbonate
9.817	0.01340	0.01535	0.01251	0.125	1.537	''
10.011	0.01340	0.01535	0.01266	0.126	1.502	'
10.094	0.01340	0.01535	0.01289	0.126	1.446	''
10.167	0.01340	0.01535	0.01334	0.126	1.326	''
10.248	0.01340	0.01535	0.01359	0.126	1.250	''
10.535	0.01340	0.01535	0.01407	0.126	1.060	''
10.696	0.01340	0.01535	0.01407	0.125	1.080	''
10.73	0.02441	0.02441	0.02199	0.068	0.9035	Bisulfite-Sulfite ion
11.04	0.01099	0.01099	0.01053	0.041	0.8220	Trifluoroethanol
11.20	0.01099	0.01099	0.01063	0.042	0.7074	''
11.34	0.01099	0.01099	0.01059	0.044	0.7572	''
11.48	0.01099	0.01099	0.01066	0.046	0.6662	''
11.66	0.01099	0.01099	0.01068	0.052	0.6397	''
11.80	0.02441	0.02441	0.02303	0.067	0.6208	Sodium Hydroxide
11.95	0.02441	0.02441	0.02307	0.067	0.6068	''
12.25	0.02441	0.02441	0.02331	0.087	0.5145	''
12.40	0.02356	0.02356	0.02250	0.138	0.5363	''
12.50	0.02356	0.02356	0.02246	0.128	0.5540	'
12.67	0.02356	0.02356	0.02155	0.266	0.8532	''
12.69	0.02356	0.02356	0.02232	0.196	0.6229	''
12.75	0.02356	0.02356	0.02221	0.236	0.6702	''

Table IV. Tri-iodide and Sodium Isobutyraldehyde Bisulfite Kinetics in Water at 25° and 0.1 Ionic Strength.

k_{obs} x 10^3 sec^{-1}	$[AcH]_T$ M	$[CacH]_T$ M	pH	$[I_3^-]_T$ M	$[Substrate]_T$ M
1.12, 1.17	0.2235		4.369	0.003137	0.00084
1.41	0.1932		4.490	0.003137	0.000766
1.19	0.1101		4.490	0.004182	0.000766
1.46, 1.23	0.1982		4.575	0.002091	0.000766
1.74	0.09700		4.591	0.004182	0.000766
1.80	0.1695		4.618	0.003137	0.000766
1.84	0.09259		4.621	0.004182	0.000766
1.75, 1.75	0.1745		4.661	0.002091	0.000766
1.84, 1.61	0.1422		4.770	0.003137	0.000766
2.51	0.08077		4.785	0.004182	0.000766
3.69	0.07049		4.918	0.004182	0.000766
3.51	0.1245		4.921	0.003137	0.000766
4.80, 4.50	0.08549		5.058	0.002925	0.000766
6.56, 6.11	0.1059		5.200	0.003137	0.000766
7.17, 6.95	0.1109		5.245	0.002091	0.000766
6.68, 7.15	0.07904		5.253	0.002928	0.000766
8.85, 8.44	0.09993		5.264	0.003137	0.00085
13.3, 12.0	0.09439		5.431	0.003137	0.00085
9.04, 10.8	0.05124		5.470	0.004182	0.000766
15.5, 16.0	0.09279		5.501	0.003137	0.00085
13.0, 13.7	0.09939		5.545	0.002091	0.00043
14.0, 14.7	0.07124		5.549	0.002928	0.000766
19.0, 19.4	0.09064		5.590	0.003137	0.00085
14.6, 16.1	0.09776		5.605	0.002091	0.00085
25.1, 24.7	0.08940		5.694	0.003137	0.00085
21.4, 20.8	0.09385		5.736	0.002091	0.00043
27.4, 25.9	0.09440		5.815	0.002091	0.00043
29.8, 31.0	0.08768		5.820	0.003137	0.00085
32.4, 46.9	0.08542		5.925	0.002091	0.00043
2.13		0.5525	4.727	0.004182	0.0014
5.97		0.3508	5.178	0.004182	0.00045
9.77		0.2504	5.440	0.004182	0.00045
24.4, 25.3, 25.0		0.1399	5.832	0.004182	0.0014
28.4, 27.7, 27.7		0.1261	5.860	0.004182	0.0019
34.2, 31.6, 32.1		0.1196	5.921	0.004182	0.0019
39.4, 38.9, 39.7		0.1098	6.020	0.004182	0.0014
51.3, 49.2, 52.5		0.09970	6.067	0.004182	0.0014
85.9, 90.2, 85.0		0.07960	6.305	0.004182	0.0014
86.8, 83.0, 83.9		0.1383	6.329	0.0039	0.001
125, 131, 121		0.06955	6.471	0.004182	0.0014
124, 123, 122		0.1203	6.491	0.0039	0.001
223, 223, 225		0.1031	6.743	0.0039	0.001
246, 249, 254		0.1003	6.815	0.0039	0.001
274, 272, 276		0.09854	6.858	0.0039	0.001
304, 300, 297		0.06909	6.872	0.0045	0.001
313, 316		0.09679	6.899	0.0039	0.001
355, 362, 385		0.08773	6.902	0.0039	0.001
400, 399, 412		0.09314	7.021	0.0039	0.001
498, 572, 540		0.06694	7.075	0.0045	0.0014
560, 557, 592		0.05270	7.111	0.0039	0.001
1710, 1520, 1636		0.08449	7.550	0.0039	0.001

dehyde derivatives at pH 4. In none of these studies were enough data obtained to permit the calculation of k_d or k_f values.

Sørensen and Andersen report a pK_a of 11.7 for the bisulfite adduct of formaldehyde at 25°. We have calculated their data, allowing for the acidity of formaldehyde hydrate,[21] which had been neglected, and get a pK_a of 11.8 ± 0.5, $K_{S^{2-}}$ of $(2.8 \pm 2) \times 10^5\ M^{-1}$, and K_{SH^-} of $10^{10}\ M^{-1}$. The uncertainty in the pK_a and in both constants, $K_{S^{2-}}$ and K_{SH^-}, is attributable to the uncertainty in the intercept (which is related to the pK_a and very near to zero) in the plot correlating $1/K_{obsd}$ with $1/[OH^-]$. However, the magnitude of K_{SH^-} agrees well with the value of $1.6 \times 10^{10}\ M^{-1}$ that can be obtained by combining the results of Skrabal and Skrabal[22] with the equilibrium constant for hydration of formaldehyde. Stewart and Donnally report a pK_a of 9.16 for the bisulfite adduct of benzaldehyde at 21° and ionic strength 0.10. This corresponds to a value of about 9.6 at zero ionic strength. Thus the thermodynamic pK_a values of compounds of the type $RCH(OH)SO_3^-$ are about 11.8, 11.3, and 9.6 when R is hydrogen, isopropyl, and phenyl, respectively. Acids of the type $RCH_2NH_3^+$ in which R is separated from the acidic proton by the same number of atoms, have pK_a values of 10.7, 10.4, and 9.3, at 26°, when R is hydrogen, isopropyl, and phenyl, resepctively.[23] Thus the effect of changing R from hydrogen to isopropyl in one series is the same, within the experimental uncertainty, as in the other. Phenyl, however, is an anomalously effective acid strengthening substituent in the α-hydroxy sulfonate series, not only by comparison to the ammonium ions but also by comparison to simple alcohols. Benzyl alcohol is about eight times as strong an acid as isobutyl alcohol and is only slightly stronger than methanol in isopropyl alcohol solution.[24] It may be relevant that if the titrimetric K_{app} values obtained above pH 10 by Stewart and Donnally were too large because of imperfect quenching, as ours were, too small a pK_a value for the bisulfite addition compound would result. We feel that their quenching method, in which acid but no cooling was employed, is probably not as effective as ours. However, if k_d is as much smaller for the benzaldehyde adduct as they report, perhaps a less effective quenching method would still be effective enough.

Acknowledgment. We thank the National Science Foundation for a grant that aided in the purchase of the nmr equipment used.

Registry No.—Sodium 1-hydroxy-2-methylpropanesulfonate, 13023-74-0; sodium bisulfite, 7631-90-5; isobutyraldehyde, 78-84-2.

Miniprint Material Available. Full-sized photocopies of the miniprinted material from this paper only or microfiche (105 × 148 mm, 24× reduction, negatives) containing all of the miniprinted and supplementary material for the papers in this issue may be obtained from the Journals Department, American Chemical Society, 1155 16th St., N.W., Washington, D.C. 20036. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-74-3896.

References and Notes

(1) This investigation was supported in part by Grant GP-32461X from the National Science Foundation.
(2) F. Raschig, *Ber.*, **59**, 859 (1926).
(3) F. Raschig and W. Prahl, *Justus Liebigs Ann. Chem.*, **448**, 265 (1926).
(4) H. J. Backer and H. Mulder, *Recl. Trav. Chim. Pays-Bas*, **51**, 769 (1932).
(5) W. M. Lauer and C. M. Langkammerer, *J. Amer. Chem. Soc.*, **57**, 2360 (1935).
(6) R. L. Shriner and A. H. Land, *J. Org. Chem.*, **6**, 888 (1941).
(7) C. N. Caughlan and H. V. Tarter, *J. Amer. Chem. Soc.*, **63**, 1265 (1941).
(8) O. Stelling, *Cellul-Chem.*, **9**, 100 (1928); *Chem. Abstr.*, **23**, 5465 (1929).
(9) P. E. Sørensen and V. S. Andersen, *Acta Chem. Scand.*, **24**, 1301 (1970).
(10) T. D. Stewart and L. H. Donnally, *J. Amer. Chem. Soc.*, **54**, 2333, 3555, 3559 (1932).
(11) J. A. Sousa and J. D. Margerum, *J. Amer. Chem. Soc.*, **82**, 3013 (1960).
(12) L. R. Green and J. Hine, *J. Org. Chem.*, **38**, 2801 (1973).
(13) H. V. Tarter and H. H. Garretson, *J. Amer. Chem. Soc.*, **63**, 808 (1941).
(14) $\Sigma(1 - K_{calc}/K_{obsd})^2$ or $\Sigma(1 - k_{calcd}/k_{obsd})^2$ was minimized.
(15) C. W. Davies, *J. Chem. Soc.*, 2093 (1938).
(16) C. W. Vass and E. Blanke, *Justus Liebigs Ann. Chem.*, **485**, 258 (1931). (1931).
(17) M. A. Gubareva, *Zh. Obschch. Khim.*, **17**, 2259 (1947).
(18) D. A. Blackadder and C. Hinshelwood, *J. Chem. Soc.*, 2720, 2728 (1958).
(19) G. Lamaty and P. Geneste, *Tetrahedron*, **27**, 5539 (1971).
(20) P. Geneste, G. Lamaty, and J. Roque, *Recl. Trav. Chim. Pays-Bas*, **91**, 188 (1972).
(21) R. P. Bell and D. D. Onwood, *Trans. Faraday Soc.*, **58**, 1557 (1962).
(22) A. Skrabal and R. Skrabal, *Monatsh. Chem.*, **69**, 11 (1936).
(23) D. D. Perrin, "Dissociation Constants of Organic Bases in Aqueous Solutions," Butterworths, London, 1965.
(24) J. Hine and M. Hine, *J. Amer. Chem. Soc.*, **74**, 5266 (1952).

An Automated Preparative Liquid Chromatography System

W. H. Pirkle* and R. W. Anderson

School of Chemical Sciences, University of Illinois, Urbana, Illinois 61801

Received July 15, 1974

The design, construction, and operation of an automated preparative liquid chromatography system capable of separating multigram quantities of materials is presented. The system repetitively injects the sample, monitors the effluent, detects and separately collects, as programmed, entire chromatographic bands, then distills and reuses the eluting solvent.

The general utility of liquid chromatography systems is now widely appreciated, several commercial units being available. Because these commercial systems are basically analytical units which operate at high pressures and employ small columns packed with expensive adsorbents, they are not particularly well suited for the routine separation of multigram quantities of materials. Recognizing a need among organic chemists for instrumentation capable of such separations, we herein describe an automated low-pressure preparative liquid chromatography system which repetitively injects the sample, monitors the effluent, detects and separately collects, as programmed, entire chromatographic bands, then distills and reuses the solvent. Apart from its ability to separate multigram quantities through unattended repetitive operation, the system obviates the use of large quantities of solvent, substantially