6 and one part of what we tentatively believe to be their isomers **7**. Separation of these unstable compounds was not possible, and the only evidence in favor of structure **7** is the presence of *C*-methyl signals in the nmr spectrum of the crude reaction mixture. Steam distillation in the presence of dilute sulfuric acid gave a single product in 15% yield whose infrared, ultraviolet, and mass and nuclear magnetic resonance spectra were indistinguishable from those of "natural" kahweofuran (**1**). The question as to whether the isomeric furan **8** derived from the minor Grignard adduct **7** was not formed or destroyed under the conditions used remains unanswered. In any event, the possibility that the synthesis described has actually given the furan **8** rather than **1** is excluded by the nmr evidence already discussed. Kahweofuran (**1**) in the pure state has a violent sulfury odor, but in high dilution it develops a pleasant roasted and smoky note.

Experimental Section

Microanalyses were performed in the laboratory of Dr. E. Palluy, Firmenich et Cie, Geneva. Boiling points are uncorrected. Vapor phase chromatographic (vpc) analyses were performed on a F & M 720 instrument, using a Carbowax 20M column. The following spectrometers were used: nuclear magnetic resonance (nmr), Varian A-60 (TMS as internal standard); infrared (ir), Perkin-Elmer Model 237; ultraviolet (uv), Cary Model 14. Silicic acid Mallinckrodt 100 mesh and silica gel Merck 70–325 mesh were used for column chromatography.

2-Acetyl-3-ketotetrahydrothiophene (3 and 4).—Sodium hydride (1.31 g, 33 mmol, washed free of mineral oil) and 20 ml of dry 1,2-dimethoxyethane were placed in a three-necked flask fitted with a stirrer and a gas inlet tube. A slow stream of nitrogen was passed through the apparatus. The flask was immersed in an ice bath and 3.06 g (30 mmol) of 3-ketotetrahydrothiophene[6] was added to the stirred mixture over a period of 15 min. After hydrogen evolution had ceased (5–10 min), dry ethyl acetate (10 ml) was added over 5 min. Stirring was continued for 60 min at 5° and 60 min at room temperature. The mixture was decomposed with ice and 20 ml of 2*N* H_2SO_4 and extracted with ether. The organic layers were washed with saturated salt solution, dried (Na_2SO_4), and evaporated. Distillation of the residue yielded 865 mg (20%) of the yellow diketone, bp 43–47° (0.2 mm), containing 15–16% 4-acetyl-3-ketotetrahydrothiophene (**5**). Further purification was achieved by vpc collection: uv max (EtOH) 219 mμ (ε 7000), 353 (5200); uv max (EtOH + NaOH) 219 mμ (ε 7530), 353 (6830); ir ($CHCl_3$) 1740 (w), 1640 (s), 1600 cm^{-1} (s); nmr (CCl_4) enol form, δ 1.95 (s, 3 H), 2.71 (m, 2 H), 3.06 (m, 2 H), 12.6 (s, broad, 1 H) (disappears on exchange with D_2O); nmr (CCl_4) diketone form, δ 2.27 (s, 3 H), 2.71 (m, 2 H), 3.06 (m, 2 H), 3.96 (s, 1 H); mass spectrum (70 eV) *m/e* (rel intensity) 144 (89.8), 126 (23.2), 102 (50.2), 88 (100), 43 (81.6).

Anal. Calcd for $C_6H_8O_2S$: C, 49.98; H, 5.60. Found: C, 49.93; H, 5.66.

4-Acetyl-3-ketotetrahydrothiophene (5).—This substance was also obtained by collection: uv max (EtOH) 286 mμ (ε 6500); uv max (EtOH + NaOH) 306 mμ (ε 17,000); ir ($CHCl_3$) 1710 (w), 1640 (s), 1600 cm^{-1} (s); nmr (CCl_4) δ 2.07 (s, 3 H), 3.58 (m, 2 H), 3.69 (s, 2 H), 14.2 (s, broad, 1 H) (disappears on exchange with D_2O); mass spectrum (70 eV) *m/e* (rel intensity) 144 (93.4), 102 (31.4), 70 (50.4), 55 (39.8), 43 (100).

Grignard Adducts 6 and 7.—Magnesium (2.58 g, 0.106 g-atom) was placed in a three-necked flask and activated by heating with a trace of iodine. A slow stream of nitrogen was passed through the apparatus, and 20 ml of freshly distilled methylal and some crystals of mercuric chloride were added. Several minutes after the addition of a few drops of 8.75 g (0.106 mol) of freshly distilled chloromethyl methyl ether, an exothermic reaction commenced, the flask was then immersed in a Dry Ice–acetone bath and the rest of the chloromethyl methyl ether was slowly added at −5° (60 min) with vigorous stirrring. The mixture was stirred for a further 60 min at −5°. A solution of 3.8 g (26.4 mmol) of diketone **3** and **4** in 35 ml of dry methylal was added dropwise at such a rate that the temperature remained between −40 and −50° (30 min). Stirring was continued for 2 hr while the temperature was allowed to rise to room temperature. The reaction product was then poured into cold saturated NH_4Cl solution and extracted with ether twice, washed with saturated salt solution, dried (Na_2SO_4), and evaporated. Distillation gave a yellow oil (3.6 g), bp 80–100° (0.05–0.07 mm), which was chromatographed on 100 g of silicic acid. Elution with chloroform–ethanol (98:2) followed by distillation gave a colorless oil (3.0 g, 60%), bp 64–66° (0.03 mm). Nmr spectroscopy indicated that this material was a 2:1 mixture of the epimers of 2-acetyl-3-hydroxy-3-methoxymethyltetrahydrothiophene (**6**) and 2-(1-hydroxy-1-methoxymethyl)ethyl-3-ketotetrahydrothiophene (**7**), respectively. The spectrum (CCl_4) had bands at δ 1.15 (s), 1.25 (s), 2.15 (s), 2.25 (s), 3.3–3.4 (four-overlapping singlets); ir ($CHCl_3$) 3530 (broad), 1710, 1110 cm^{-1}.

Anal. Calcd for $C_8H_{14}O_3S$: C, 50.52; H, 7.42. Found: C, 50.70; H, 7.24.

Kahweofuran (1) (2-Methyl-3-oxa-8-thiabicyclo[3.3.0]-1,4-octadiene).—The mixture of carbinols **6** and **7** (1.6 g) was added dropwise during 30 min to 50 ml of 1 *N* H_2SO_4 while steam distilling. After 1 hr, the distillate (150 ml) was extracted twice with ether, washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated. The remaining orange oil was chromatographed on 20 g of silica gel using hexane–ethyl acetate (9:1) as eluent. Distillation gave kahweofuran as a colorless oil (177 mg, 15%): bp 105–107° (20 mm); uv max (EtOH) 245 mμ (ε 3100); ir ($CHCl_3$) 1630, 1575, 1100, 1075, 920 cm^{-1}; nmr (CCl_4) δ 2.17 (s, 3 H), 2.81 (t, 2 H, J = 7 Hz with fine splitting of 1.5 Hz), 3.57 (t, 2 H, J = 7 Hz with small fine splitting), 6.91 (t, 1 H, J = 1.5 Hz); mass spectrum (70 eV) *m/e* (rel intensity) 140 (100), 139 (28.4), 111 (37.9), 97 (29.2). The mass spectrum, ir, nmr, and uv spectra of synthetic kahweofuran were indistinguishable from those of the natural product.

Anal. Calcd for C_7H_8OS: C, 60.00; H, 5.75. Found: C, 60.32; H, 5.96.

Registry No.—**1**, 26693-24-3; **3**, 26693-25-4; **4**, 26693-26-5; **5**, 26693-27-6; **6**, 26693-28-7; **7**, 26693-29-8.

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The Effect of Pressure on Acetal Equilibria[1]

DONALD G. KUBLER*[2] AND HAROLD W. YOUNG[3]

Department of Chemistry, Furman University,
Greenville, South Carolina 29613

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The influence of pressure upon the rates of chemical reactions in solution continue to be widely investigated.[4-6] Far less interest has been generated for studies concerned with the influence of pressure on chemical equilibria in the solution.[4,6] This general lack of research interest is surprising because (1) pressure remains as a physical variable which can be changed

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(2) Author to whom correspondence should be addressed.

(3) Undergraduate Research Participant, summer, 1969. We wish to acknowledge help given by Mr. Thomas S. Davis with the experimental work.

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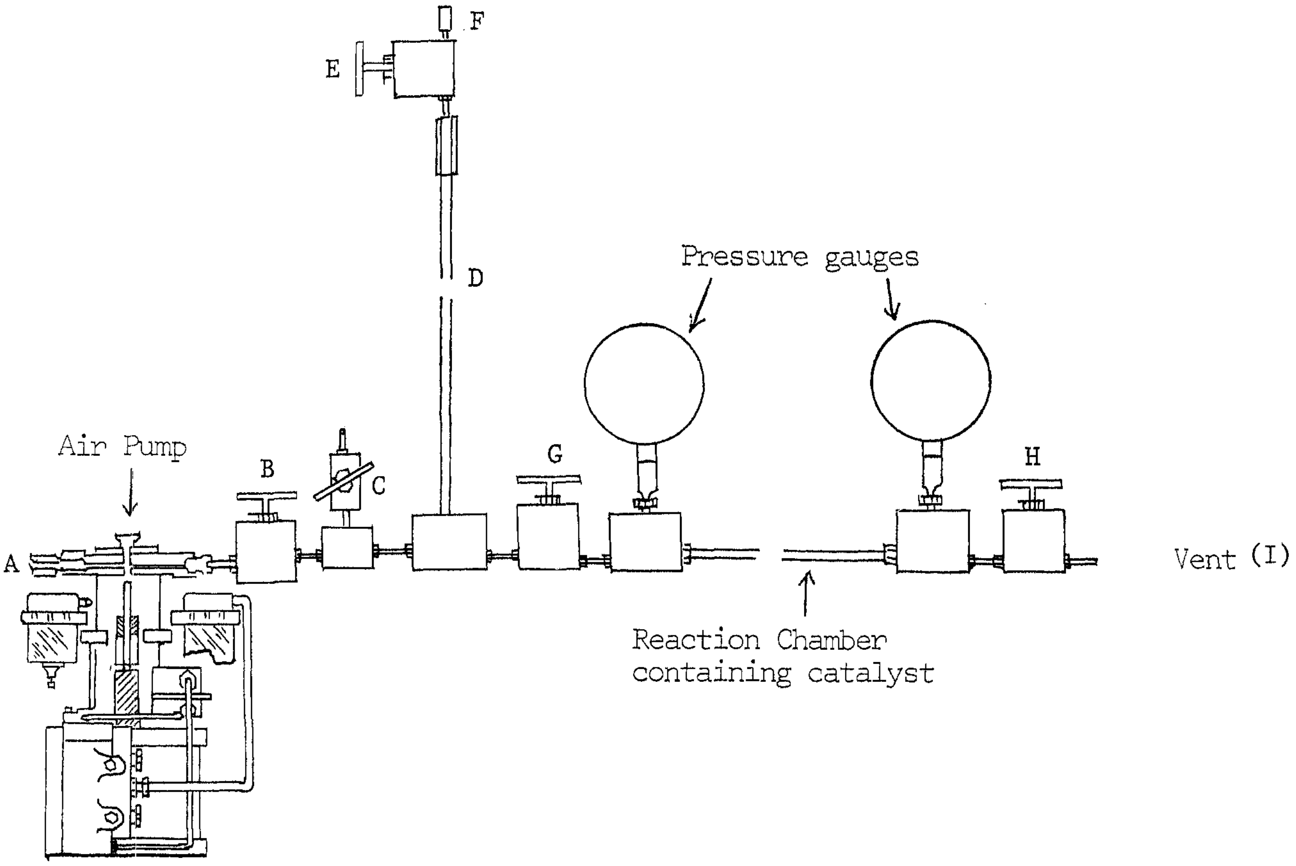

Figure 1.—High pressure reactor.

nearly without limit, (2) remarkable accomplishments have been made with high pressure on an industrial basis (*e.g.*, the polymerization of ethylene and the synthesis of diamonds), and (3) sophisticated components for high pressure studies are available commercially.[7]

For a general chemical system, $aA + bB \rightleftharpoons cC + dD$, beginning with the reactants A and B, one expects the most beneficial effect of pressure upon equilibria when $\Delta n < 0$. Even for cases for which $\Delta n \geqq 0$, the use of an appropriate solvent may alter molar volumes such as to provide negative volumes of reaction. Consideration of the equilibria for the conversion of an aldehyde to an acetal, for which $\Delta n = -1$, suggested that the acetal equilibria might be a good choice to evaluate pressure effects on chemical equilibria in solution. Calculation of volumes of reaction based upon densities of reactants and of products for a large number of combinations of aldehydes or ketones with various alcohols gave negative volumes of reaction (values varied from −5 to −20 ml/mol) in each case. Calculation of volumes of reaction based on densities for the esterification of various acids with alcohols ($\Delta n = 0$) gave values near zero in every case (for twenty calculations, Δv varied from +1.2 ml/mol to −3.3 ml/mol).

We report our preliminary pressure studies for the reactions of propionaldehyde, benzaldehyde, and cyclohexanone with methanol to form the corresponding dimethyl acetals. Mole ratios of 5:1 of alcohol to the carbonyl compound were used in each case. The reactions were conducted at 25° in a continuous flow reactor while varying the pressure from 1 to 2040 atm. Dowex-50 ion exchange resin was used as the catalyst. This choice of catalyst obviated problems of neutralization of homogeneous acid catalysts under pressure or of having to analyze the mixtures under pressure because once the reactants passed the catalyst zone, the equilibrium was "frozen" and could be vented to atmospheric pressure for analysis.

The results of our studies are summarized in Table I. The volumes of reaction were calculated by plotting log K_x (mole fraction equilibrium constant) against the pressure and determining the slopes.[8] Straight line plots were obtained in each case.

TABLE I

Propionaldehyde and methanol		Cyclohexanone and methanol		Benzaldehyde and methanol	
Pressure, atm	K_x[a]	Pressure, atm	K_x[a]	Pressure, atm	K_x[a]
2040	4.30	2040	0.51	2040	0.93
1700	4.04	1700	0.42	1360	0.64
1360	4.01	1360	0.36	680	0.40
1020	3.58	1020	0.32	272	0.28
680	3.43	680	0.26	1	0.24
1	3.10	1	0.17		
−4.60[b]		−12.5[b]		−17.5[b]	

[a] Mole fraction equilibrium constants. [b] Volume, ml/mol.

It is apparent from these data that the acetal equilibrium is shifted significantly by an increase in pressure. Because of the simplicity of the operation and the marked improvement in yields, such devices may become more useful in laboratory synthetic work. Further obvious improvements for the systems studied can be realized by (1) using higher mole ratios of alcohol

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[7] Reference 4, p 208.

[8] $\Delta V = -2.3RT\dfrac{\Delta \log K_x}{\Delta P}$.

to the carbonyl moiety and recycling unreacted alcohol, (2) using low temperatures since the heat of reactions is negative,[9] and (3) using significantly higher pressures.

The particular apparatus used in this work is limited to an upper pressure of about 2500 atm. As an example of the value of using much higher pressures we extrapolated the results for cyclohexanone and methanol to 10,000 atm. The extrapolated value of K_x was in excess of 10, which is over a 50-fold increase in K_x compared to the value at atmospheric pressure (0.17).

A brief evaluation also was made of the reaction of benzaldehyde and ethylene glycol and of acetic acid and methanol. The glycol solution "froze" above 270 atm which prevented further pumping. The reaction of acetic acid and methanol was found to be aided by pressure with a volume of reaction being about -5 ml/mol.

Experimental Section

High Pressure Apparatus.—The schematic of the high pressure apparatus is shown in Figure 1. All components of the apparatus were purchased from the American Instrument Co., Silver Spring, Md. The air pump is driven by 80 psi air pressure input to a 6-in. piston with a 0.25-in. output piston, with a maximum discharge pressure of 40,000 psi (2720 atm). The gauges are 6 in., 0–40,000 psi Bourdon-type gauges. The tubing is 304 stainless steel superpressure tubing of $^9/_{16}$, in. o.d., $^3/_{16}$ in i.d. The fittings (connectors, sleeves, couplings, etc.) are all rated at 0–100,000 psi with the bodies constructed of 316 stainless steel and the nuts and sleeves of 416 stainless steel. The valves are rated at 30,000 psi with the bodies constructed of 316 stainless steel and the nuts and sleeves of 416 stainless steel.

The catalyst (75–100 ml of Dowex-50) was contained in the superpressure tubing between the two valve blocks and was retained in the tube by means of a sintered stainless steel filter disk of medium porosity. To the bottom of the left gauge block there was connected a steel tube supporting a 32,000 psi rupture disk.

Operational Procedure.—With all valves open except E, the reaction mixture was fed from a separatory funnel to the system at A and pumped until a free flow was obtained at the vent I. Valve E was then opened and valve H closed to pump solution into the ballast tube D until liquid vented at F. Pumping was suspended and, with all valves closed except E and G, nitrogen was introduced at F under 100 psi. Valve C was opened until 50 ml of liquid (one-half the volume of tube D) vented while maintaining the nitrogen pressure. Valves E and C were closed; pumping was resumed until the desired reaction pressure was reached. Valve H was opened to give a slight flow through vent I at the desired reaction pressure by adjusting the inlet pump pressure and the opening of valve H. The reaction mixture was pumped sufficiently long to establish homogeniety (usually 1 l. or more of mixture). The flow rate had to be sufficiently low to ensure the establishment of equilibrium. With the volume of catalyst used, a flow rate of about 3 ml/min was sufficient for all three acetal systems studied. About 25–30 ml of mixture was collected for analysis, the pressure and flow rate were readjusted, and, after discharging about 250 ml of mixture, another sample was collected for analysis. Upon completion of a run, the system was flushed throughly with anhydrous methanol.

Purification of Reagents and Analyses.—Methanol was purified in 5-l. batches by the method of Lund and Bjerrum.[10] The distillation column (32 × 700 mm) was adiabatic with reflux control and packed with glass helices. Water content, determined for each batch by the Karl Fischer method, was always less than 0.01%.

The Dowex-50, X8 ion exchange resin (H form, strong acid, 20–50 mesh) was washed with water until the water tested neutral to acid test paper. The water was removed by repeated washing of the resin with small amounts of anhydrous methanol and the catalyst was air-dried.

Propionaldehyde was distilled (24 × 450 mm glass column) at atmospheric pressure. The material which boiled from 48–49° was collected. Solutions containing 5 mol of methanol to 1 mol of propionaldehyde were prepared, flushed with nitrogen, and permitted to cool (heat of hemiacetal formation) back to room temperature. The solutions were always used the same day they were prepared to diminish air oxidation of the aldehyde.

The propionaldehyde content of the reaction mixtures was determined by the hydroxylamine–pyridine method.[11] The equilibrium mole fractions were calculated by means of the final propionaldehyde content, the initial amount of reagents, and the stoichiometry. From these values, the mole fraction equilibrium constants were calculated.

Benzaldehyde and cyclohexanone were purified in a standard manner[12] and analyzed for carbonyl content on a Perkin-Elmer 202 spectrophotometer. Extinction coefficients (λ_{max} = 281 mμ for benzaldehyde and λ_{max} = 288 mμ for cyclohexanone) were determined with freshly prepared methanol solutions.

Registry No.—Methanol, 67-56-1; propionaldehyde, 123-38-6; cyclohexanone, 108-94-1; benzaldehyde. 100-52-7.

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[9] A useful technique used with ion exchange resins as acetal catalysts developed by N. B. Lorette, W. L. Howard, and J. H. Brown, *J. Org. Chem.*, **24**, 1731 (1959).

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The Relative Ease of 1,2-Proton Shifts. The Origin of the Formyl Proton of Salicylaldehyde Obtained by the Reimer–Tiemann Reaction

D. S. Kemp

Department of Chemistry, Massachusetts
Institute of Technology, Cambridge,
Massachusetts 02139

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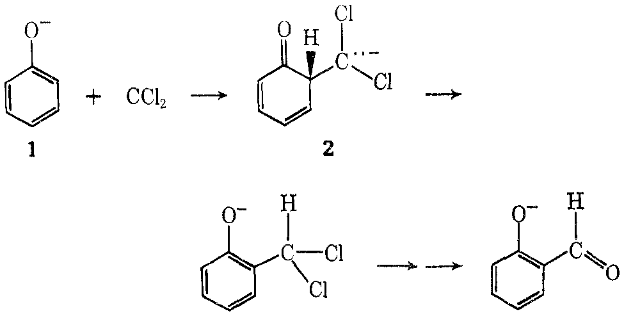
As a result of Hine's demonstration[1] in 1959 of the intermediacy of dichlorocarbene, the Reimer–Tiemann reaction has been widely accepted as proceeding by the following path, although evidence for the intermediates **2** and **3** has been entirely inferential. The transformation **2** → **3** is an interesting one in that it can be envisaged as occurring *via* a 1,2-proton transfer. Either on the basis of simple Hückel theory[2] or from orbital symmetry considerations,[3] such transfers are expected to occur with difficulty; yet one can regard **2** → **3**



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