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).

(10) H. Lund, and J. Bjerrum, *Ber.*, **64**, 210 (1931).

(11) S. Siggia, "Quantitative Organic Analysis via Functional Groups," 2nd ed, Wiley, New York, N. Y., 1957.

(12) J. M. Bell, D. G. Kubler, P. Sartwell, and R. G. Zepp, *J. Org. Chem.*, **30**, 4285 (1965).

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

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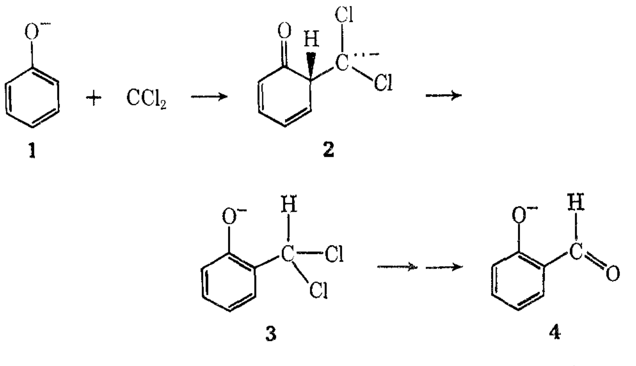
As a result of Hine's demonstration[1] in 1959 of the intermediacy of dichlorocarbene, the Reimer–Tiemann reaction has been widely accepted as proceeding by the following path, although evidence for the intermediates **2** and **3** has been entirely inferential. The transformation **2** → **3** is an 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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(1) J. Hine and J. M. van der Veen, *J. Amer. Chem. Soc.*, **81**, 6447 (1959).

(2) See, for example, J. D. Roberts and M. C. Caserio, "Basic Principles of Organic Chemistry," W. A. Benjamin, New York, N. Y., 1965, p 399.

(3) R. B. Woodward and R. Hoffmann, *Angew. Chem. Int. Ed. Engl.*, **8**, 781 (1969).

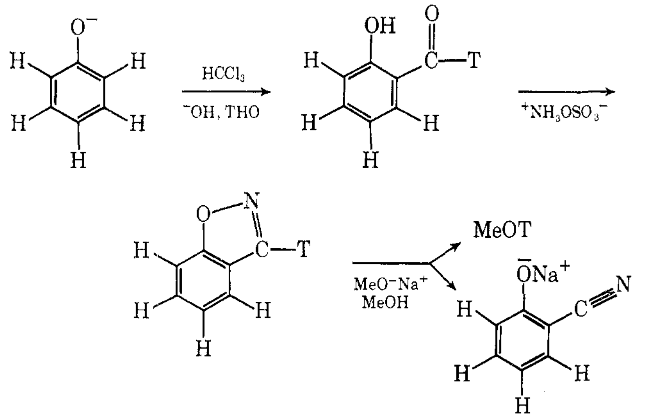
as posing a limiting extreme for either of these analyses in that **2** may be estimated as 40–60 kcal/mol less stable than **3**. Specifically, can the symmetry required of these analyses apply in a situation which is energetically so unsymmetrical?

Some years ago we made the relevant observation that when carried out in D_2O, the Reimer–Tiemann synthesis yields salicylaldehyde bearing >97% deuterium in its formyl grouping and insignificant deuterium in its ring positions.[4] In the present paper I wish to describe results which define this result mechanistically and which explore its scope by means of the more sensitive tool of tritium labeling.

When *O*-acetoxybenzal chloride (**5**) was hydrolyzed under conditions (40% NaOD in D_2O, 70°) exactly the same as those used in the Reimer–Tiemann reaction, a 54% yield of salicylaldehyde was obtained which contained less than 5% of deuterium in its formyl hydrogen position. Since **5** must linger longer as a neutral molecule in this medium it must be more susceptible to exchange than **3**, and this finding therefore requires that deuterium be introduced in the Reimer–Tiemann sequence prior to the appearance of **3**.

As a more compelling probe of the exchange results, the Reimer–Tiemann synthesis of salicylaldehyde was carried out in THO, and the isolated aldehyde was subjected to the indicated degradation scheme (Scheme I).

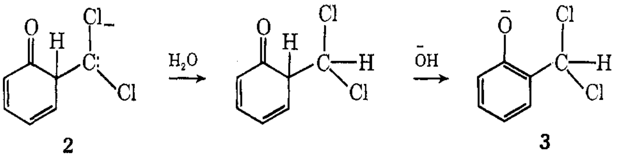
SCHEME I



Salicylaldehyde was obtained which contained 99.6% of its tritium in its formyl group and less than 0.4% in its ring positions. This result establishes the possibility of a very sensitive distinction between protons derived from the ring pool and those derived from the solvent.

Phenol bearing tritium in either the 2 or the 4 position was synthesized by acid-catalyzed exchange with THO and was shown by conversion to 2,4,6-tribromophenol to contain no more than 0.03% of its tritium in the 3 position. When a Reimer–Tiemann synthesis of salicylaldehyde was carried out using this phenol at 0.4% concentration, less than 0.06% of the total molecular tritium of the product was found in the formyl position, a quantity which is within experimental error of the expected value for tritium lost to and reincorporated from solvent during the synthesis. Unfortunately, technical difficulties prohibited carrying out the synthesis under conditions involving greater dilutions of starting material.

These results may be taken to imply that the conversion of **2** → **3** is the actual path for the reaction and that it cannot occur by a single 1,2-proton shift but most probably by a pair of intermolecular proton transfers. The selectivity favoring the latter process must be much greater than a 1000-fold.



2 **3**

The anion **2** might be expected to react at diffusion-controlled rates with water molecules, and one must be able to assess the concentration of free water in these reaction media in order to set numerical limits on a rate constant for the hydride shift. Yagil and Anbar[5] have observed that in such solutions one may anticipate less than an order of magnitude decrease in free water concentration over that of pure water. Thus, while the present findings demonstrate remarkable discrimination against a thermodynamically favorable intramolecular process, the disfavored hydride shift could still conceivably be occurring with a rate constant of *ca.* 10^8 sec^{-1} and not contribute significantly to formation of the observed product.

Experimental Section

7-^2H-Salicylaldehyde.[6]—Into a 1-l. three-necked flask equipped with stirrer, condenser, thermometer, and nitrogen inlet was placed 260 g (13 mol) of 99.5% deuterium oxide; the flask and contents were cooled to 5° during the cautious addition of 100 g (4.4 g-atoms) of clean Na metal. Toward the end of the addition (40 min) the ice bath was removed and the mixture vigorously stirred to promote reaction; 27 g of phenol (0.29 mol) was added; and the slurry was warmed to 80° and stirred until the phenoxide dissolved. The temperature was maintained at 70–80° during the hour required to add 67 g (0.56 mol) of chloroform. The mixture was warmed at 65° for 90 min and then allowed to stand overnight and acidified to pH 1 with cold 5 *N* sulfuric acid. Steam was introduced and distillation allowed to proceed until only clear distillate collected. The distillate was saturated with sodium chloride and extracted with six 10-ml portions of dichloromethane which were pooled, dried, and evaporated to yield 19 g of crude product. The aldehyde was purified through its copper chelate[7] and then was distilled through a spinning-band column, bp 78.5–79.0° (14 mm), 11.1 g, 31%. Mass spectral and nmr data indicated the sample to bear greater than 97% deuterium in its formyl grouping, ir (CCl_4) 2100 cm^{-1} (C–D stretch).

***O*-Acetoxybenzal Chloride.**—Distilled *O*-acetoxybenzaldehyde, 8.1 g (48 mmol), was dissolved in 20 ml of dichloromethane and treated at 20° with 10.1 g (50 mmol) of phosphorus pentachloride. When solid had disappeared, the solvent was stripped, and the residue was distilled, bp 91–96° (3 mm), 9.1 g, 86%. Crystallization from cyclohexane gave solid: mp 48.0–48.8°; nmr (CCl_4) δ 2.2 (s, 3), 7.0 (s, 1), 7.1–8.0 (m, 4); ir (CCl_4) 1770 cm^{-1} (ester C=O). *Anal.* Calcd for $C_9H_8Cl_2O_2$: C, 49.34; H, 3.68; Cl, 32.37. Found: C, 49.26; H, 3.76; Cl, 32.45.

2- and 4-^3H-Phenol.—Phenol, 20 g, was added to 10 ml of 10% sulfuric acid containing 0.245 mCi of tritium. After 4 days of heating to reflux, the mixture was cooled and extracted with ether. The pooled extracts were extracted with fifteen 20-ml portions

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[4] D. S. Kemp and R. B. Woodward, unpublished observations.

[5] G. Yagil and M. Anbar, *J. Amer. Chem. Soc.*, **85**, 2376 (1963).

[6] Nmr spectra were taken with a Varian A-60 spectrometer using tetramethylsilane as internal standard. Counting was performed with a Packard 3375 liquid scintillation spectrometer; samples were standardized externally and internally. Microanalysis was performed by Scandinavian Microanalytical Laboratory, Copenhagen, Denmark.

[7] "Organic Syntheses," Coll. Vol. III, Wiley, New York, N. Y., 1955, p 166.

of water, dried ($MgSO_4$), and concentrated. The residue was distilled to yield 8.7 g of phenol, specific activity 0.336 μCi/mmol (calcd: 0.37 μCi/mmol for completed exchange of 2, 4, and 6 protons). Bromination of a sample of this phenol in water containing hydrobromic acid yielded 2,4,6-tribromophenol, mp 188.5–191.0°, specific activity $\leq 1 \times 10^{-4}$ μCi/mmol.

Reimer–Tiemann Synthesis with ^{3}H-Phenol.—The Reimer–Tiemann procedure given above was repeated by adding 0.81 g of the above phenol and 0.10 g of unlabled salicylaldehyde to a solution of 100.5 g (2.63 mol) of sodium hydroxide in 115 ml of water and treating the solution with 40 g of chloroform. After acidification and steam distillation, the distillate was extracted with fifteen 3-ml portions of dichloromethane which were pooled, dried, and evaporated. The resulting 0.4 g of crude salicylaldehyde was converted directly to benzisoxazole by treatment with 1 g of hydroxylammonium *O*-sulfonate in 2 ml of water, followed by extraction with dichloromethane to remove neutral impurities. The aqueous layer was brought to pH 7 with sodium bicarbonate and extracted with three 5-ml portions of dichloromethane, which were pooled and evaporated. The residue was distilled in a bulb-to-bulb apparatus at 1 mm to yield 0.12 g of benzisoxazole, identified by its infrared spectrum, specific activity 0.134 μCi/mmol. When 97.85 mg of this sample was treated with excess sodium methoxide in methanol and the methanol was recovered quantitatively by lyophilization, it was found to show 71.1 dpm/0.822 mmol or 3.9×10^{-5} μCi/mmol; *o*-cyanophenol recovered by acidification of the lyophilization residue was found to possess 99% of the activity of the benzisoxazole.

Registry No.—Salicyladehyde, 90-02-8; *O*-acetoxybenzal choride, 26693-22-1.

Electronegativity, Acids, and Bases. IV. Concerning the Inductive Effect of Alkyl Groups

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Although the inductive effects of alkyl groups have long been appreciated, there has been some confusion concerning the electron donating or withdrawing ability of alkyl groups relative to each other and to the hydrogen atom. Thus, there has been some uncertainty concerning the basicity of alkylamines based upon pK_b's in aqueous solution, but Condon[1] has shown clearly that, if hydration effects are accounted for, the basicity order is $R_3N > R_2NH > RNH_2 > NH_3$, in accord with increasing electron density on the nitrogen with increasing substitution. Furthermore, $(CH_3)_3C > (CH_3)_2CH > CH_3CH_2 > CH_3 > H$ in *electron donating* ability toward N, O, C_6H_5, etc. These results have been confirmed in gas phase studies by Munson[2] and by Brauman and Blair.[3]

Recently, Brauman and Blair[3] have measured gas-phase acidities of various aliphatic alcohols and have shown that acidity increases in the order $H_2O < CH_3OH < CH_3CH_2OH < (CH_3)_2CHOH < (CH_3)_3COH < (CH_3)_3CCH_2OH$ and $CH_3CH_2OH < CH_3CH_2CH_2OH < CH_3CH_2CH_2CH_2OH < CH_3CH_2CH_2CH_2CH_2OH < (CH)_3COH$. This indicates that in the alkoxide ions, $R'O^-$, *electron withdrawing* ability also decreases $R_3C > R_2CH > RCH_2 > CH_3 > H$. In terms of any concept of fixed electronegativity[4] the apparent reversal of electronegativity seems paradoxical. Recent molecular orbital calculations by the MINDO[5] and CNDO/2[6] methods have rationalized the experimental results of Brauman and Blair. Some of these "predictions" would have been more useful had they not appeared *a posteriori*. It is the purpose of this note to call attention to earlier, though neglected, work in this area and to interpret these results in terms of simple model.

Though the inductive effects of alkyl groups have been discussed almost exclusively in terms of electron donation, Ingold[7] pointed out that this common behavior was a result of the fact that these groups are generally attached to *more electronegative substituents*. More recently, Schubert and coworkers[8] have cogently argued the same point, alkyl groups can donate *or* accept electron density depending upon the nature of the substrate. Furthermore, the latter workers made an extremely important observation; larger alkyl groups tend to be better electron donors because they are more polarizable. Therefore, they should also *be better electron acceptors when bonded to less electronegative substrates*. Two parameters are thus involved in charge transfer: inherent electronegativity and capacity (polarizability).

In a previous paper,[9] the group electronegativities of alkyl groups were calculated using the principle of electronegativity equalization,[10,11] and it was shown that the inherent or neutral electronegativities of alkyl groups are (1) slightly higher than hydrogen, (2) very similar to each other, ranging from 2.27 to 2.29,[12] and (3) not sufficient to differentiate among the groups. It was also shown that the principal differences among them lie in their varying *charge coefficient*, *b*, the rate at which the electronegativity changes with gain or loss of electron density. The increased electron donor ability of more highly substituted groups (toward electronegative substrates such as N, O, C_6H_5, etc.) results from their relatively low values of *b*, where the electronegativity is expressed as

$$\chi = a + b\,\delta \tag{1}$$

Simply stated, other things being equal, the more atoms in a group, the more readily the group can donate electron density since the resulting charge can be spread over more atoms.

In the previous paper[9] it was suggested that the same effect should be operative in allowing a group to *absorb* electron density. At that time, no good examples were known to the author for alkyl groups since the most obvious compounds to consider, the metal alkyls, $M^{\delta+}—R^{\delta-}$, are polymeric and not amenable to treatment. It was pointed out, however, that the electron withdrawing ability of perfluoroalkyls should increase with increasing size and that for transfers of charge density greater than *ca.* 0.1 they will be better acceptors

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[1] F. E. Condon, *J. Amer. Chem. Soc.*, **87**, 4481, 4485, 4491, 4494 (1965).

[2] M. S. B. Munson, *ibid.*, **87**, 2332 (1965).

[3] J. I. Brauman and L. K. Blair, *ibid.*, **90**, 6561 (1968); **92**, 5986 (1970).

[4] L. Pauling, "The Nature of the Chemical Bond," 3rd ed, Cornell University Press, Ithaca, N. Y., 1960.

[5] N. C. Baird, *Can. J. Chem.*, **47**, 2306 (1969).

[6] T. P. Lewis, *Tetrahedron*, **25**, 4117 (1969).

[7] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953 p 70.

[8] W. M. Schubert, R. B. Murphy, and J. Robins, *Tetrahedron*, **17**, 199 (1962).

[9] J. E. Huheey, *J. Phys. Chem.*, **69**, 3284 (1965).

[10] R. T. Sanderson, *J. Chem. Educ.*, **31**, 2 (1954); "Chemical Periodicity," Reinhold, New York, N. Y., 1969.

[11] J. Hinze and H. H. Jaffé, *J. Amer. Chem. Soc.*, **84**, 540 (1962); J. Hinze, M. A. Whitehead, and H. H. Jaffé, *ibid.*, **85**, 148 (1963).

[12] Based on electronegativities from ref 11: $C_{te} = 2.46$; $H_s = 2.21$; $F_p = 3.90$.