with stirring and continued cooling. This was followed by the addition of a second 7.5-ml. portion of ethyl alcohol 25 min. later. The cooling bath was removed and the ammonia was allowed to evaporate in a stream of nitrogen.

The reaction mixture was diluted with 450 ml. of distilled water, brought to pH 5 by the addition of 600 ml. of 1 *N* oxalic acid, and extracted with 800 ml. of ether. The water phase was separated and extracted with two successive portions of 400 ml. of ether. The ether extracts were washed with water, combined, dried, and evaporated to leave a solid residue weighing 2.55 g. A mixture of this crude Birch reduction product, 24 ml. of 2 *N* hydrochloric acid, and 12 ml. of water in 120 ml. of methyl alcohol was warmed to a gentle reflux for 40 min. After the addition of 35 ml. of 2 *N* sodium hydroxide solution the reaction mixture was warmed for an additional 15 min. under nitrogen. This was followed by the addition of 250 ml. of water and concentration of the suspension to about 200 ml. under vacuum. The slurry was made acidic by the addition of 100 ml. of 10% hydrochloric acid, warmed on the steam bath for 15 min., and allowed to cool. The precipitate was collected on a filter, washed with several small amounts of water and dried overnight at 60° under reduced pressure to leave 2.25 g. of a mixture, m.p. 166–182°. The above product was pyrolyzed at 220° under high vacuum for 60 hr. and the reaction product was purified by chromatography[17] on 220 g. of silica gel. The benzene–ether (8:2) eluates gave, after evaporation of the solvent and recrystallization from acetone–petroleum ether, 0.364 g. (16%) of unreduced methoxylactone XIX, m.p. 223–225° (identified by mixed melting point determination and comparison of the infrared spectrum with that of a reference sample of XIX).

The residues from the ether and ether–acetone (9:1) eluates yielded 1.281 g. of impure 3-(17β-hydroxy-3-oxo-4-estren-16β-yl)-propionic acid lactone (XXI). The compound was recrystallized from acetone–petroleum ether to yield 0.669 g. of the lactone XXI, m.p. 218–220°. A second crop amounted to 0.133 g., m.p. 215–218°, bringing the yield to 37%.

A part of the first crop was sublimed under high vacuum and recrystallized from acetone–petroleum ether to a constant melting point of 223–224°. The sample had $[\alpha]^{26}\text{D}$ +144° (*c*, 1.117); $\lambda_{\max}^{\text{CH}_3\text{OH}}$ 240 mμ (ε 17,400) $\lambda_{\max}^{\text{CHCl}_3}$ 5.80 μ, 6.02 μ, 6.18 μ.

Anal. Calcd. for $C_{21}H_{28}O_3$: C, 76.79; H, 8.59. Found: C, 76.88; H, 8.88.

Potassium Carbonate Hydrolysis of 3-(3β,17β-Dihydroxy-5α-androstan-16β-yl)propionic Acid Lactone (VI).[17]—A mixture of 0.346 g. of the lactone VI, 0.26 g. of potassium carbonate, 2.6 ml. of water, and 21 ml. of methyl alcohol was swirled to obtain a solution and allowed to stand at room temperature for 60 hr. The addition of 25 ml. of water was followed by concentration of the suspension to about 25 ml. under reduced pressure at room temperature. The resulting slurry was made acidic with 30 ml. of 10% hydrochloric acid; the precipitate was collected on a filter, washed with several small amounts of water, and dried at 60° under reduced pressure overnight. The compound was recrystallized from acetone to give 0.273 g. (75%) of the dihydroxy acid V, m.p. 196–197°, resolidification at 200°, and second melting at 224–227°.

A sample was recrystallized to a constant melting point of 202–203°, resolidification at 208–210°, and second melting point at 235–238°. The compound dried at 65° had $[\alpha]\text{D}^{25}$ +8° (*c*, 0.588 dioxane); $\lambda_{\max}^{\text{KBr}}$ 3.00 μ, 3.75–4.5 μ, 5.86 μ.

Anal. Calcd. for $C_{22}H_{36}O_4$: C, 72.49; H, 9.96. Found: C, 72.33; H, 9.78.

The above compound was identical to a reference sample of 3-(3β,17β-dihydroxy-5α-androstan-16β-yl)propionic acid (V).

Acknowledgment.—We wish to thank Mr. Elmer Shelberg and his staff for microanalyses. We are indebted to Mr. William H. Washburn and his associates for the recording and interpretation of the infrared spectra. We also thank Mr. Victor E. Papendick for the measurement of the ultraviolet spectra.

The Kinetics of the Silver Metal-catalyzed Cannizzaro Reaction[1]

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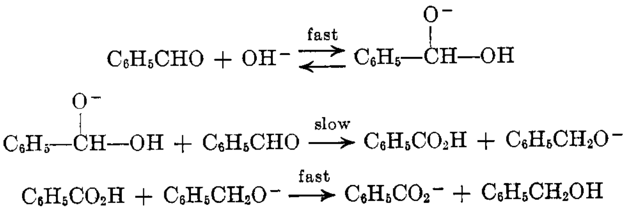
The kinetics of the silver metal-catalyzed Cannizzaro reaction of benzaldehyde and sodium hydroxide in 50% aqueous ethanol has been measured, and it has been found that the order of the reaction varies from initially first order in benzaldehyde to zero order in the latter stages of the reaction, that the reaction is linearly dependent on the amount of silver metal catalyst used, is zero order in sodium hydroxide, and apparently takes place on the catalyst surface. The rate constant for the first 7–12% of reaction at 30° was found to be 4.9 ± 0.3 × 10^{-3} min.$^{-1}$ on the basis of 20 mg. of silver per 100 ml. of solution, and a $k_H k_D$ rate factor of 6.8 ± 0.5 measured with benzaldehyde-α-d_1. Benzyl benzoate could not be detected among the reaction products, although it was shown that the ester is saponified at a slower rate than the rate of formation of products from the reaction. A mechanism has been proposed which is consistent with the results and all known facts.

The Cannizzaro reaction is the disproportionation of two aldehyde molecules to form the corresponding carboxylate anion and alcohol in the presence of alkali. It has been previously reported that the rate for this reaction with benzaldehyde, as well as with many of its derivatives, was second order in aldehyde and first order in base.[3] Strong evidence has been furnished that a hydride transfer occurs between two aldehyde groups and that a hydrogen transfer from solvent to aldehyde is not involved.[4,5] Thus, when a Cannizzaro reaction was carried out with benzaldehyde in deuterium oxide solution, it was found that the resulting benzyl alcohol contained no deuterium atom bonded to carbon.[4,5] Furthermore, when benzaldehyde-α-d_1 was caused to dismutate in the presence of base, benzyl alcohol-α,α-d_2 ($C_6H_5CD_2OH$) was formed. Evidence that the hydride transfer takes place in the rate-determining step is that a k_H/k_D value of 1.8 has been found for the disproportionation of benzaldehyde.[6] A reaction scheme frequently proposed is



$$C_6H_5CHO + OH^- \underset{}{\overset{\text{fast}}{\rightleftarrows}} C_6H_5{-}\overset{\displaystyle O^-}{\overset{|}{C}}H{-}OH$$

$$C_6H_5{-}\overset{\displaystyle O^-}{\overset{|}{C}}H{-}OH + C_6H_5CHO \xrightarrow{\text{slow}} C_6H_5CO_2H + C_6H_5CH_2O^-$$

$$C_6H_5CO_2H + C_6H_5CH_2O^- \xrightarrow{\text{fast}} C_6H_5CO_2^- + C_6H_5CH_2OH$$

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(1) From the Ph.D. thesis of D. R. L., University of Connecticut, 1962. The complete compilation of the experiments can be found in this thesis. Presented at the 142nd National Meeting of the American Chemical Society, Atlantic City, N. J., September, 1962, p. 20Q.

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(3) J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1956, p. 259.

(4) H. Fredenhagen and K. F. Bonhoeffer, *Z. physik Chem.*, **181A**, 379 (1938).

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Benzyl benzoate has been found to be an isolable product under certain reaction conditions.[7]

It has been reported that the presence of silver causes the dismutation of benzaldehyde to occur at an accelerated rate and that *o*- and *p*-hydroxybenzaldehydes which do not undergo the Cannizzaro reaction under normal conditions,[8] do so in the presence of an active silver catalyst to form the corresponding acid and alcohol products.[9,10] The silver by complexing apparently changes the electronic nature of the hydroxyaldehyde.

It has also been observed that the presence of an alcohol has no apparent effect on the mechanism of the Cannizzaro reaction.[11]

Results

To establish a set of conditions under which the silver metal-catalyzed Cannizzaro reaction would proceed at a reasonable and readily followed rate and to determine the contribution made to the reaction products, if any, by a noncatalyzed reaction, a number of exploratory experiments (1–21)[1] some of which are summarized in Table I, were carried out. In addition, it was necessary to find an effective silver catalyst, and for this purpose three different silver preparations (no. 1–3) were tested in those initial experiments carried out in the presence of a catalyst. Some of the exploratory experiments were conducted in an effort to determine the reaction order. All Cannizzaro reactions were carried out with benzaldehyde and sodium hydroxide in 50% (by weight) aqueous ethanol, and it was found that equimolar quantities of alcohol and acid were produced.

TABLE I

EXPLORATORY EXPERIMENTS

No.[a]	Solvent, ml.	C_6H_5CHO, mole	NaOH, mole	Silver,[b] g.	Temp., °C.	Time, min.	Per cent completion
6	69	0.197	0.0292	3.15[c]	82.5	1230	0
8	90	.0883	.0907	. .	75	300	75
9	90	.0885	.0910	5.18[d]	75	60	100
17	100[e]	.0203	.00872	0.244	27	120	80
18	100[e]	.0192	.00825	.2004	30	180	77
19	90[e]	.0995	.00710	.1998	30	120	87
20	100[e]	.0194	.00900	.1003	30	395	35

[a] Samples were removed at various times from all reaction mixtures. [b] Silver no. 3 unless noted otherwise. [c] Silver no. 1. [d] Silver no. 2. [e] All or in part as sodium hydroxide solution.

A limiting set of conditions of temperature and concentrations, below which no reaction of any kind takes place, was provided by experiment 6, for which no reaction occurred. Experiment 6, furthermore, was conducted in the presence of silver catalyst no. 1, which was thus proved to be ineffective. In experiment 9, carried out with catalyst no. 2, the reaction was brought to completion in less than one fifth the time required to bring about 75% reaction in experiment 8, which was carried out under similar conditions but in the absence of catalyst. Thus it was established that catalysis of the Cannizzaro reaction by metallic silver, under the conditions of experiment 9 at least, was possible. The effectiveness of silver catalyst no. 3 was tested in experiment 17 under conditions such that no noncatalyzed reaction was possible. This catalyst was effective in bringing about approximately 40 and 80% reaction after one and two hours, respectively. In addition, experiment 17 provided a set of conditions under which the reaction appeared to proceed at a reasonable and readily followed rate. Because it was desirable to carry out the reactions at a relatively low temperature, and yet, one which could be controlled conveniently, 30° was chosen as the reaction temperature for all subsequent experiments. Benzyl benzoate was occasionally looked for in the gas chromatographic analyses of these experiments and was always found to be absent.

Silver catalyst no. 3 was used in experiments 18–20 which were carried out in an effort to determine the order of the reaction. The results of experiment 18 indicated that, under the reaction conditions, the rate was initially rapid (72% reaction occurring during the first 90-min. period), and that it changed to a slow constant value in the latter stages (5% additional reaction occurring during the second 90-min. period). Similar results were observed for experiment 19 in which 70% of the reaction took place within the first 30 min. and 17% took place within the following 90 min. The slow constant reaction rate was made manifest in experiment 20 in which it was brought about at an earlier stage of the reaction by using less silver catalyst, for it was observed that the rate was virtually constant after 22% reaction (120 min.) and that only 13% additional reaction occurred within the 275-min. period which followed.

From the results of the last three experiments, it was apparent that the order of the reaction under study changed from a value, thus far undetermined, to zero order (the slow reaction rate). An attempt was made to determine the initial order of the reaction, with the data collected from experiments 19 and 20, by conventional methods which included the method of isolation, the differential method (both graphically and by calculation), the time required to complete a given fraction of the reaction, and the method of integration.[12] The results of these determinations indicated that the reaction order changed greatly with time, but were otherwise meaningless since no agreement could be found among values obtained from the various methods.

The necessity of investigating the initial stages of the reaction more closely became apparent. The principal problems involved in studying this area were the rapidity of the reaction and the consequent difficulty in making accurate measurements. For the purpose of determining the initial order of the reaction a modification of the differential method[13] was devised. The method is dependent on the fact that the rate of a reaction of a given order is linearly dependent on the concentration of reactant raised to a power of the given order, $dx/dt = kc^n$, where dx/dt is the rate of formation of products at a given time, c is the concentration of reactant at a given time, k is the proportionality con-

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[6] K. B. Wiberg, *J. Am. Chem. Soc.*, **76**, 5371 (1954).

[7] T. A. Geissman, *Org. Reactions*, **II**, 94 (1944).

[8] G. I. Kudryavtsev and E. A. Shilov, *Dokl. Akad. Nauk SSSR*, **64**, 73 (1949); *Chem. Abstr.*, **43**, 4651 (1951).

[9] I. A. Pearl, *J. Am. Chem. Soc.*, **67**, 1628 (1945).

[10] I. A. Pearl, *J. Org. Chem.*, **12**, 89 (1947).

[11] M. S. Kharasch, and R. H. Snyder, *ibid.*, **14**, 819 (1949).

[12] S. Glasstone, "Textbook of Physical Chemistry," 2nd ed., D. Van Nostrand Co., Inc., Princeton, N. J., 1946, p. 1066.

[13] Ref. 12, p. 1067.

stant, and n is the order of reaction with respect to the reactant. For two different concentrations, $(dx/dt)_1 = kc_1^n$ and $(dx/dt)_2 = kc_2^n$, and the proportionality constants are calculated from these equations with different values of n. The value of n which best correlates the data, as determined by calculation of the constant k, is selected as the correct order of the reaction with respect to the reactant varied.

Experiments 22–25[1] were carried out with the intention of determining the initial order of the reaction by the above-described method. The amount of one of the reagents was varied from one reaction to another (within a given set of experiments) in the following ratios: The amount of silver was varied in a ratio of 1:4.00 (five experiments). The amount of silver was varied in a ratio of 1:2.00 (two experiments). The amount of benzaldehyde was varied in a ratio of 1:1.85 (three experiments), and the amount of sodium hydroxide was varied in a ratio of 1:2.00 (three experiments). The value of dx/dt was approximately determined by measuring $\Delta x/\Delta t$ within the first few per cent of reaction, and a proportionality constant was calculated for each set of experiments. Thus, the proportionality constants were found for those sets of experiments in which the amount of silver was varied, when calculated from conversion rate/mg. Ag ($4.0 \pm 0.1 \times 10^{-6}$ mole $C_6H_5CO_2H$/min. × mg. Ag), and for the set of experiments in which the amount of benzaldehyde was varied, when calculated from conversion rate/mole C_6H_5CHO ($8.1 \pm 0.1 \times 10^{-3}$ mole $C_6H_5CO_2H$/min. × mole C_6H_5CHO). A constant conversion rate ($2.30 \pm 0.04 \times 10^{-4}$ mole $C_6H_5CO_2$/min.) was observed for the set of experiments in which the amount of sodium hydroxide was varied. The results indicated that the reaction rate is linearly dependent on the amounts of silver catalyst and benzaldehyde and that it is independent of sodium hydroxide concentration.

Because it had been found that an average of 0.3% benzoic acid was contained in the samples of benzaldehyde used, it was of interest to determine if a small additional amount of benzoic acid affected the results. Thus experiment 26A, Table II, was carried out for comparison with experiment 26B, which contained benzoic acid in a ratio to benzaldehyde of about 1:100, but which otherwise was run under the same conditions. A negligible difference between the results of the experiments was observed. Although precautionary measures were taken, exposure of benzaldehyde samples to the atmosphere could not be completely avoided. To determine if such exposure affected the results, experiment 27A was carried out for comparison with experiment 27B, which was run with a sample of benzaldehyde, aerated immediately before use, but which otherwise was run under the same conditions. Virtually no difference was observed in the results of these experiments.

TABLE II

EXPERIMENTS TO INVESTIGATE POSSIBLE COMPLICATING FACTORS[a]

No.	C_6H_5CHO, mole × 10^2	NaOH, mole × 10^2	Silver,[b] mg.	Time, min.	Yield $C_6H_5CO_2H$, mole × 10^2
26A	1.83	0.454	40.0	3	0.0630
26B[c]	1.83	.456	40.0	3	.0600
27A	1.83	.459	40.0	3	.0471
27B	1.83[d]	.459	40.0	3	.0468
28–29[e]	1.07	2.60	..	5	.00047
101	1.07	2.60	20.0	5	.049

[a] All reaction mixtures contained 100 ml. of solvent. [b] Silver no. 5. [c] Benzoic acid (4.1×10^{-5} mole) added. [d] Benzaldehyde taken from 5-ml. sample aerated (10 min. at 4.7 ml./min.) immediately before use. [e] Contained silver oxide (4.7×10^{-6} mole).

Since there existed the possibility that catalysis was due to silver oxide contained in the silver metal samples, it was of interest to test the catalytic property of the oxide. Thus experiments 28 and 29 contained no silver but instead contained silver oxide in an amount equivalent to that which would be contained in a 20.0-mg. sample of silver, 5% of which was in the form of the oxide. The amount of benzoic acid produced, as determined by titration, was stoichiometrically equivalent to that expected from the oxidation of benzaldehyde by the silver oxide and less than 1/100 of that which was produced under the same conditions (experiment 101) with 20.0 mg. of silver metal.

Experiments 37–100 are summarized in Table III where the amounts of reactants and catalyst were varied among these reactions by the following ratios: silver, 5.0; benzaldehyde, 3.4; and sodium hydroxide, 4.6. The ratios of the reactants and catalyst with each other were varied as follows: benzaldehyde–sodium hydroxide, 1.1:4.0; silver (g.)–sodium hydroxide (mole), 2.2:10; and silver (g.)–benzaldehyde (mole), 0.11:0.49. Conversion rates ($\Delta C_6H_5CO_2H/\Delta t$) were measured and were found to be essentially identical when placed on the same molar basis of benzaldehyde to the first power and when corrected to the same amount of silver catalyst. A proportionality constant was thus obtained, in the manner previously described, for the differential method of determining reaction

TABLE III

EXPERIMENTS TO ESTABLISH REACTION ORDER AND CORRESPONDING RATE CONSTANTS[a]

No.	C_6H_5CHO, mole × 10^2	NaOH, mole × 10^2	Silver, mg.	Time, min.	Rate constant,[b] min.$^{-1}$ × 10^3
37	1.95	0.975	50.0[c]	2	4.5
38	1.95	.488	50.0[c]	2	5.1
39	2.03	.970	100.0[d]	2	4.9
40	1.83	.920	40.0[d]	1.5	4.5
41	1.83	.920	20.0[d]	3	4.8
42–43	1.83	.458	40.0[d]	3	4.3 ± 0.0
44	1.83	.458	20.0[d]	6	4.7
45, 47	1.83	.454	40.0	3	4.5 ± 0.1
46	1.83	.454	20.0	3	5.6
48–49	1.83	.456	40.0	3	5.0
50[e]	1.83	.456	40.0	3	4.9
51, 53	1.83	.459	40.0	3	4.4 ± 0.1
52	0.99	.459	40.0	5.55	5.5
54	.99	.459	40.0	4.33	5.5
55–57	1.07	.105	20.0	5[f]	4.9 ± 0.3
58–67	1.07	.052	20.0	5	5.1 ± 0.3
68–78	0.592	.052	20.0	8	4.7 ± 0.2
79–81	.816	.0523	20.0	6	4.8 ± 0.2
82–89	1.35	.0523	20.0	4	4.6 ± 0.2
90–94	0.592	.104	20.0	5	5.2 ± 0.2
95–100	.592	.207	20.0	5	5.4 ± 0.3

[a] All reaction mixtures contained 100 ml. of solvent and silver no. 5 unless noted otherwise. [b] $\Delta C_6H_5CO_2H/\Delta t \times C_6H_5CHO$; based on 20.0 mg. silver. [c] Silver no. 3. [d] Silver no. 4. [e] Benzoic acid (4.1×10^{-5} mole) added. [f] Time for one run was 2.5 min.

order, which is the reaction rate constant for the reaction with a given amount of catalyst. It should be noted that although experiments 37 and 38 contained silver no. 3, experiments 39–44 silver no. 4 and experiments 45–100 silver no. 5, their rate constants are essentially the same.

The average reaction rate constant for experiments 37–100 (64 experiments as described in Table III) was found to be $4.9 \pm 0.3 \times 10^{-3}$ min.$^{-1}$, based on reactions run to 7–12% conversion.

Experiments 101–104[1] were carried out under identical conditions and contained sodium hydroxide in a concentration higher than that of any of the other experiments for which a reaction rate constant was calculated. The average rate constant for these four reactions was abnormally high (9.6×10^{-3} min.$^{-1}$), and it was apparent that a different reaction begins to take place at this concentration.

Because benzyl benzoate could not be detected among the reaction products, it was of interest to determine the fate of the ester under the conditions of the reaction. Thus, benzyl benzoate, in an amount equivalent to that which could be produced from benzaldehyde after 5% reaction, was allowed to undergo saponification under Cannizzaro reaction conditions for the period of time required for benzaldehyde to undergo 5% reaction. Complete saponification of the ester would be expected if it were an intermediate in this reaction. However, only 10% saponification was found to have occurred in two identical experiments.

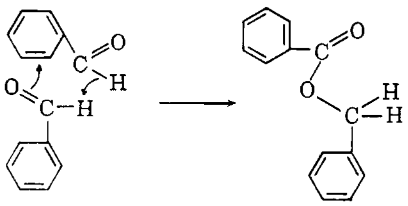
Cannizzaro reactions were carried out, on a scale one half that normally used, in deuterated solvent, to the extent of 13, 25, and 71% reaction of benzaldehyde. Infrared analysis showed that no exchange had taken place between the deuterium of the solvent and the carbonyl hydrogen of benzaldehyde. Cannizzaro reactions were also carried out with benzaldehyde-α-d_1 and their conversion rates were measured. The average reaction rate constant, k_D, from three identical experiments was $7.2 \pm 0.3 \times 10^{-4}$ min.$^{-1}$, and benzyl alcohol-α,α-d_2 was isolated and identified. Compared to the average reaction rate constant, k_D, obtained from experiments 37–100, the k_H/k_D value of this reaction was found to be 6.8 ± 0.5. A method for the determination of the k_H/k_D rate factor by a competitive reaction of benzaldehyde and benzaldehyde-α-d_1 was considered; however, due to the complexity of the reaction, it was found to be inapplicable.

Discussion

This investigation has provided information from which a reasonable mechanism may be proposed for the silver metal-catalyzed Cannizzaro reaction of benzaldehyde and sodium hydroxide. A comprehensive explanation of the following results must be incorporated in such a mechanism. The rate of the dismutation reaction is linearly dependent on the amount of catalyst used, is initially first order in benzaldehyde and zero order in base, and is zero order over-all in the latter stages. In addition, a k_H/k_D rate factor of 6.8 was found for benzaldehyde and benzaldehyde-α-d_1. Benzyl benzoate is not a detectable product in this Cannizzaro reaction, although the ester is saponified at a much slower rate than if it were formed under the reaction conditions. There is a direct hydride transfer.

From the large k_H/k_D value it can be stated with reasonable certainty that the rate-determining step of reaction must include the breaking of the carbonyl C—H bond. The results pertaining to benzyl benzoate eliminate any mechanism in which the ester is postulated as an intermediate and in which it is saponified on the catalyst surface at a rate slower than its rate of adsorption. These results also eliminate any mechanism in which benzyl benzoate is postulated as an intermediate and in which it is saponified at a rate slower than its rate of desorption from the catalyst surface.

Mechanisms which can be eliminated on kinetic grounds are as follows: 1. A four-center type disproportionation of two benzaldehyde molecules on the catalyst to form benzyl benzoate which involves: (a) a sparsely covered catalyst surface, for this would be expected to give second-order kinetics, and (b) an almost completely covered catalyst surface, for this would be expected to result in zero-order kinetics throughout.



2. The formation of benzyl benzoate in the slow step from the intermediate $(\mathrm{C_6H_5}\text{—}\overset{\mathrm{OH}}{\overset{|}{\mathrm{CH}}}\text{—O—}\overset{\mathrm{O}}{\overset{|}{\mathrm{CH}}}\text{—}\mathrm{C_6H_5})^-$ adsorbed on the catalyst surface, which is, (a) sparsely covered by the intermediate, for this situation would be expected to give third-order kinetics, and (b) almost completely covered by the intermediate, for this would be expected to give zero-order kinetics throughout.

Another possibility which must be considered is that the mechanism includes the slow formation of benzyl benzoate on the catalyst, and the subsequent saponification of the ester at a faster rate than that of its adsorption. Thus, it would appear that a conflict is avoided with the results pertaining to benzyl benzoate. Such mechanisms are as follows.

3. The formation of benzyl benzoate by a four-center type disproportionation (see above) between a free molecule of benzaldehyde and one which is adsorbed on the catalyst, the surface of which is almost completely covered with benzaldehyde.

4. An equilibrium in which the intermediate $(\mathrm{C_6H_5}\text{—}\overset{\mathrm{OH}}{\overset{|}{\mathrm{CH}}}\text{—O—}\overset{\mathrm{O}}{\overset{|}{\mathrm{CH}}}\text{—}\mathrm{C_6H_5})^-$ is formed on the catalyst from free benzaldehyde and hydroxylated benzaldehyde adsorbed on, and almost completely covering, the surface of the catalyst, and the subsequent formation of benzyl benzoate from this intermediate by an intramolecular hydride transfer and displacement of hydroxyl ion.

One objection to mechanism 3 is that if it were possible, it appears to be less probable than mechanism 1b, where both reacting molecules are on the catalyst surface. An objection to mechanism 4 is that there are no

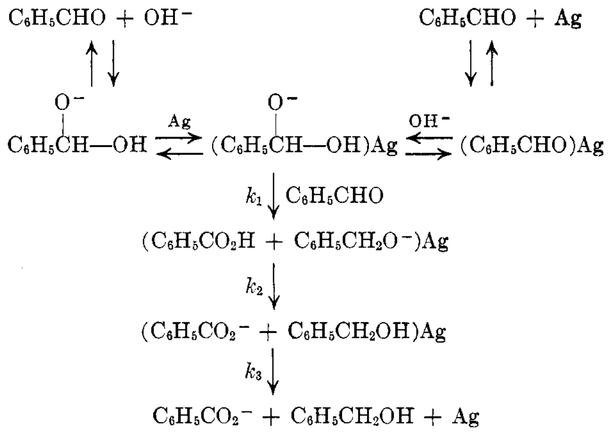


Fig. 1.—Proposed reaction mechanism for the silver metal-catalyzed Cannizzaro reaction of benzaldehyde.

known instances in which a hydride ion displaces a hydroxide ion from a saturated carbon atom.[14]

The extent to which a solute is adsorbed is principally dependent on the available amount of adsorbent. The adsorption is almost invariably reversible and an equilibrium is rapidly established depending on the concentration of solute and the amount of adsorbent.[15] The saponification experiments with benzyl benzoate were set up such that the concentration of the ester and the quantity of available catalyst were extremely high by comparison to the situation required in mechanisms 3 and 4. Both mechanisms depend on a very rapid adsorption of solutes in order for the catalyst surface to be almost completely covered with reactant. To postulate, at the same time, that benzyl benzoate is adsorbed at a very slow rate and that the results pertaining to benzyl benzoate do not apply, is unreasonable.

A mechanism can be proposed which is completely consistent with the results of the kinetic studies of the silver metal-catalyzed Cannizzaro reaction and the other available data and is outlined in Fig. 1.

The initial step is the rapid formation, and/or adsorption, of hydroxylated benzaldehyde on the catalyst, the surface of which rapidly becomes almost completely covered. The rate-determining step, k_1, involves a hydride transfer to free benzaldehyde from the hydroxylated species on the catalyst, which initially is in almost constant supply. Thus, the requirement that the reaction initially be first order in benzaldehyde is fulfilled. The final products, benzoate ion and benzyl alcohol, are formed rapidly in the next step, k_2, from benzoic acid and benzylate ion, followed by the slow desorption, k_3, of the products from the catalyst surface. The rate constant of desorption, k_3, being slightly smaller than that of the hydride transfer, k_1, eventually becomes the controlling factor of the reaction.

The k_H/k_D value of 6.8 found for the silver metal-catalyzed reaction is rather high compared to the value of 1.8[6] found for the noncatalyzed reaction and indicates that the mechanisms of the two reactions are different. The suggestion has been made that the reaction is free radical in nature, there are too few facts which support this contention. The relatively high k_H/k_D rate factor found for the catalyzed reaction suggests a large amount of bond breaking in the transition state of the reaction.

Experimental

Reagents.—The following were used without purification: ethanol (Commercial Solvents Corp.), sodium hydroxide (Baker and Adamson, reagent), benzyl benzoate (R. Gesell, Inc., n^{21}D 1.5682), silver nitrate, sodium bisulfite (J. T. Baker Chemical Co.), silver oxide (Merck & Co.), benzil (Fairmount Chemical Co., Inc., m.p. 96–96.5°), lithium aluminum deuteride (Metal Hydrides, 98.4%), and deuterium oxide (General Dynamics Corp., 99.5%).

The following was distilled through a 30-in. silvered column packed with glass helices: chloroform (Baker and Adamson, b.p. 60.5°, n^{18}D 1.4470).

Purification of Benzaldehyde.—Benzaldehyde (Fisher Scientific Co.) was converted to its sodium bisulfite addition compound which was washed with 95% ethanol. The addition compound was decomposed with 10% sodium hydroxide solution; the benzaldehyde was separated, washed with distilled water, and dried over sodium sulfate in a nitrogen atmosphere immediately before being distilled (at pressures ranging from 5–18 mm.) through a 12-in. silvered column equipped with a tantalum wire spiral. Nitrogen was the only gas present in the system. The benzaldehyde was distilled directly into 1-oz. brown bottles. The bottles were stored under nitrogen in the dark and usually were used within 2 months. Benzaldehyde was never used from a bottle which had been opened more than 5 hr. previously. The average amount of benzoic acid (analyzed by titration) in the benzaldehyde samples used was 0.3%.

Silver Metal Catalyst Preparations.—(1) A solution of silver nitrate (12.5 g., 0.0745 mole) in water (50 ml.) at 54° was slowly added to a solution containing water (100 ml.), sodium hydroxide (16.1 g., 0.403 mole), benzaldehyde (9.2 g., 0.087 mole), and absolute ethanol (60 ml.) at 41° and stirred by a magnetic stirring bar. The maximum temperature on mixing was 51°. The resulting dark, powder-like solid (7.5 g.) was separated by filtration while hot and washed with water and absolute ethanol.

(2) A solution of silver nitrate (18.1 g., 0.106 mole) in water (50 ml.) at 60° was slowly added to a solution containing water (150 ml.), sodium hydroxide (25.1 g., 0.628 mole), benzaldehyde (15.5 g., 0.146 mole), and absolute ethanol (85 ml.) at 60° and stirred by a magnetic stirring bar. The maximum temperature on mixing was 78°. The resulting fluffy, metallic-like solid (10.5 g.) was separated by filtration while hot and washed with water and absolute ethanol.

(3) The procedure followed, and the amounts of materials used in this preparation were the same as the previous one. Stirring was accomplished with a mechanical stirrer. The maximum temperature on mixing was 76°. The silver was separated while hot and washed with water and absolute ethanol. The fluffy, metallic-like solid (10.6 g.) that was isolated was clumped in small aggregates, and a slurry of the material in water was stirred by a mechanical stirrer to break up the aggregates.

(4) A solution of silver nitrate (36.2 g., 0.213 mole) in water (100 ml.) at 61° was slowly added to a solution containing water (300 ml.), sodium hydroxide (50.2 g., 1.26 moles), benzaldehyde (31.0 g., 0.292 mole), and absolute ethanol (170 ml.) at 61° and stirred by a mechanical stirrer. The maximum temperature on mixing was 73°. The resulting dark gray powder (23.0 g.) was separated and washed with water and absolute ethanol. A test for silver ion indicated the presence of an appreciable amount of silver oxide and thus the process was repeated.

The silver previously prepared (shifted through a no. 80 wire mesh) and benzaldehyde (22.6 g., 0.213 mole) were added to a solution of sodium hydroxide (8.52 g., 0.213 mole) in 50% (by weight) aqueous ethanol (250 ml.), at room temperature, and stirred by a mechanical stirrer. An exothermic reaction immediately resulted and stirring was allowed to continue for 3.5 hr. The resulting light gray powder (23.0 g.) was filtered and washed with water and absolute ethanol. A test for silver ion indicated that a slight amount of silver oxide was present. The silver was passed through a no. 80 wire mesh, washed with concentrated ammonium hydroxide, distilled water, and absolute ethanol, and dried in a vacuum desiccator.

(5) The bulk of the previously prepared silver was washed with concentrated ammonium hydroxide, distilled water, and absolute ethanol. The washed silver was then placed in a vacuum desic-

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[14] E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., New York, N. Y., 1959, p. 548.

[15] Ref. 12, p. 1216.

TABLE IV

PRECISION OF AMOUNT BENZALDEHYDE DELIVERED BY SYRINGE

C_6H_5CHO, mole × 10^2	Standard deviation, %	Number of determinations
1.83	0.6	6
0.99	3.7	9
1.07	0.7	15
0.592	1.6	5
1.95	0.7	6
0.816	.6	6
1.35	1.8	6
2.03 (pipet)	0.9	6

cator which was flushed with nitrogen and the silver was allowed to dry overnight under vacuum. This amount of silver was sufficient for all kinetic runs.

Methods of Analysis.—(1) Studies were made to determine the feasibility of following the reactions spectrophotometrically and potentiometrically. The results indicated, however, that these methods were impractical.

(2) The method of analyzing for products with gas chromatography was investigated and found to be useful. The method consisted in the occasional sampling of the reaction mixture, immediate extraction of each sample with an organic solvent, and analysis of the organic layer for benzyl alcohol with a gas chromatograph (Aerograph Master A-100, Wilkens Instrument and Research, Inc., equipped with a 10-mv. Varian recorder an a 10-ft. Ucon, polar column. Conditions: temp. 154–208°, pressure 7.5–14 p.s.i., filament current 200 ma.). The method was employed to follow experiments 6, 8, 9, and 17–19.

(3) Experiments 20, and 25A–25C were analyzed by isolation and titration of the benzoic acid formed after a given time. The method was found to be inconvenient because of the number of operations involved.

(4) The method employed in the analysis of experiments 18, 37, and 38 involved the isolation and subsequent weighing of the benzoic acid formed in the reaction when the reaction was quenched after a given time. Although this method was considered to be good, it was believed that a method more convenient and, possibly, more accurate could be found.

(5) The method of titration of benzoic acid was the method which was finally settled upon and was employed in the heretofore unmentioned analyses of Cannizzaro reactions. The method consisted in quenching the reaction after a given time with excess hydrochloric acid solution followed by immediate back-titration with standard sodium hydroxide to the phenolphthalein end point. Excess acid (hydrochloric acid and benzoic acid not formed in the reaction) was determined by titrating standards containing the requisite amounts of solvent, sodium hydroxide, hydrochloric acid, and benzaldehyde. In some cases the standard did not contain benzaldehyde, and the amount of benzoic acid in the benzaldehyde sample was determined separately as a check on the latter. The precision was determined, by titrating standards, before each reaction and was always found to be well within 1%.

Kinetic Procedures for Cannizzaro Reactions.—Experiments 6, 8, 9, and 17–20, were carried out in a 250-ml. two-neck flask equipped with a thermometer well and a reflux condenser. One neck of the flask was covered with a gum rubber cap. Fifty per cent (by weight) aqueous ethanol, sodium hydroxide, and silver were placed in the flask, brought to thermal equilibrium, and placed under an inert atmosphere maintained with nitrogen or argon and a mercury bubbler. Benzaldehyde, the amount of which was measured by weight difference, was transferred to the flask by means of a hypodermic syringe. The reaction mixtures were stirred by a magnetic stirring bar. In the case of experiments 6, 8, 9, and 17 the temperature was controlled, when not at reflux temperature, by a Thermocap relay, and, in the case of all remaining experiments by means of a large water bath, the temperature of which was controlled by an Electronic relay. Temperature control by the latter method was found to result in a temperature variation of ±0.05° as compared to ±1° with the former method. Samples (1.00 ml.) were removed from the reaction mixture at various times through the gum rubber cap with a hypodermic syringe, except in the case of experiment 20. Samples were removed from the latter reaction mixture by means of a 1.0-ml. pipet through a gum rubber cap specially prepared for its entrance. In the case of all reactions containing silver, stirring had been stopped 2 min. prior to each sampling.

Experiments 22–29 and 35–100, were carried out in 250-ml. flasks. Into the reaction flask was placed a solution of sodium hydroxide in 50% (by weight) aqueous ethanol (100 ml.) and the silver catalyst. The system was brought to thermal equilibrium and an inert atmosphere was obtained with nitrogen and a mercury bubbler. Constant temperature was maintained with the large water bath, the temperature of which was controlled by an Electronic relay, and the mixture was stirred by a magnetic stirring bar. In the case of experiments 25, 37, and 38, benzaldehyde was measured and transferred to the reaction flask with a pipet. In the case of all the remaining experiments this transfer was accomplished with a hypodermic syringe. After a given time the reactions were quenched with hydrochloric acid solution and analyzed. The data from all these kinetic experiments are reported in a previous section.

Saponification of Benzyl Benzoate.—(1) Into a 250-ml. flask was placed a solution of sodium hydroxide in 50% aqueous ethanol (0.0520 *M*, 100.0 ml.) and silver (20.0 mg., no. 5). The system was flushed with nitrogen and brought to thermal equilibrium. Benzyl benzoate (0.00571 mole) was injected into the reaction flask with a hypodermic syringe. The temperature was maintained at 30° with the water bath, and the mixture was stirred by a magnetic stirring bar. After 10 min. the reaction was quenched with a slight excess of hydrochloric acid solution and immediately back-titrated to determine the amount of benzoic acid produced. Thus it was found that 11.7% saponification had occurred.

(2) This reaction was a duplication of the preceding one with the exception that 2.6×10^{-4} mole of benzyl benzoate was brought into reaction for 5 min. Ten per cent saponification was found to have occurred.

(3) This reaction was a duplication of the preceding one. Ten per cent saponification was found to have occurred.

Exchange Tests in Deuterated Solvent.—The solvent, 96.7% deuterated, was prepared by mixing ethanol-O-*d* (prepared from sodium ethoxide and deuterium oxide) and deuterium oxide in the molar ratio, 1:2.55, calculated for 50% (by weight) aqueous ethanol. The requisite amount of sodium hydroxide was dissolved in the solvent to make the solution 0.052 *M*.

Into a 100-ml. flask was placed a solution of sodium hydroxide in the deuterated solvent (0.052 *M*, 50 ml.) and silver (10.0 mg., no. 5). The system was flushed with nitrogen, brought to thermal equilibrium, and benzaldehyde (0.0063 mole) added to the reaction mixture. The temperature was maintained at 30° with the water bath and the mixture was stirred by a magnetic stirring bar. The reaction was quenched with hydrochloric acid and the mixture immediately added to an ice-cold solution of 2,4-dinitrophenylhydrazine. Benzaldehyde 2,4-dinitrophenylhydrazone was isolated and weighed. Three identical runs were made having reaction times of 10 min., 2 hr., and 9.25 hr. in which benzaldehyde was found to have undergone 13, 25, and 71% conversion, respectively. Analysis of the recovered 2,4-dinitrophenylhydrazone by infrared (Perkin–Elmer Model 21) with the band at 12.54 μ indicated that virtually no exchange had occurred in any of the runs.

Cannizzaro Reaction of Benzaldehyde-α-d_1.—Into a 250-ml. flask was placed a solution of sodium hydroxide in 50% aqueous ethanol (0.051 *M*, 100.0 ml.) and silver (20.0 mg., no. 5). The system was deaerated with nitrogen, brought to thermal equilibrium, and benzaldehyde-α-d_1 (0.0059 mole, b.p. 50.5–51.0° at 5 mm.), previously prepared after the manner of Wiberg,[6] added to the reaction mixture. The temperature was maintained at 30° with the water bath and the mixture was stirred by a magnetic stirring bar. The reaction was quenched with excess hydrochloric acid after 56 min. and immediately back-titrated with standard base to determine the amount of benzoic acid formed in the reaction. The reaction was run in triplicate and the yields of benzoic acid were found to be, 2.56×10^{-4}, 2.30×10^{-4}, and 2.36×10^{-4} mole. The benzyl alcohol was isolated by gas chromatography and mass spectrographic analysis indicated the benzyl alcohol to be greater than 98% α,α-dideuterated.

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The Synthesis of Highly Fluorinated Compounds by Use of Potassium Fluoride in Polar Solvents

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Fluorination of highly chlorinated compounds of three or more carbon atoms by the action of potassium fluoride in polar solvents—*e.g.*, N-methyl-2-pyrrolidone—has been found to give fair to excellent yields of highly fluorinated products. Dechlorination and dehydrochlorination of the substrate appear to be first steps in the mechanism, often followed by addition of the elements of hydrogen fluoride, and finally replacement by fluorine of all but highly hindered chlorine atoms. For example, the three-carbon substrates octachloropropane, heptachloropropane, and hexachloropropane yield $CF_3CCl_2CF_3$, $CF_3CHClCF_3$, and $CF_3CH_2CF_3$, in mixtures of varying proportions that can be controlled to some degree by choice of conditions. Hexachlorobutadiene yields the new fluoroölefins *cis*- and *trans*-$CF_3CH{=}CFCF_3$. Cyclic compounds are particularly responsive to this technique—*e.g.*, perfluorocyclopentene is obtained in high yield from perchlorocyclopentene.

The synthesis of organic compounds containing isolated fluorine atoms by the action of anhydrous potassium fluoride on compounds having suitably reactive chlorine atoms has long been known.[1] Glycol solvents have often been used,[2] and more recently the polar amide solvents have been employed, often in more complex exchange reactions.[3] Henne and Sedlak[4] recently showed that vinylic chlorine atoms can be replaced with fluorine by the action of potassium fluoride in polar solvents if they are flanked by highly fluorinated structures. Miller[5] and co-workers have postulated nucleophilic substitution of vinylic chlorine atoms by potassium fluoride in formamide, although the existence of the direct substitution products was obscured by the fact that only saturated hydrogen fluoride addition products could be isolated under the conditions employed.

We have now found, in a study of new routes to highly fluorinated organic compounds, that wholesale replacement of chlorine in highly chlorinated compounds of more than two carbon atoms can be readily accomplished with reactive alkali fluorides in certain polar solvents. Among the most useful solvents are N-methyl-2-pyrrolidone and dimethyl sulfone. The reactions have been carried out at about 200° in ordinary open glass laboratory equipment and are so rapid that even starting materials boiling substantially lower than the reaction mixture can be successfully converted to highly fluorinated products.

Results and Discussion

One- and Two-carbon Compounds.—The reactions of one- and two-carbon compounds were not found to yield useful quantities of fluorinated products, although the observations made with these substrates are helpful in understanding the reaction mechanisms involved in systems of this sort. Table I summarizes the reactions observed.

TABLE I

REACTIONS OF CHLORINATED ONE- AND TWO-CARBON COMPOUNDS WITH KF IN N-METHYL-2-PYRROLIDONE[a]

Starting material	Products	Yield, %
	One-carbon compound	
CCl_4	$CHCl_3$	53
	CHF_3	Minor
	Two-carbon compounds	
CCl_3CCl_3	$CCl_2{=}CCl_2$	54-80
$CHCl_2CCl_3$	$CCl_2{=}CCl_2$	65
$CCl_2{=}CCl_2$	CF_3CHCl_2	5
$CHCl{=}CCl_2$	$CCl\equiv CCl$	?
	$CHF{=}CCl_2$	15
	$CHF{=}CClF$	?
$CH_2{=}CHCl$	$CH\equiv CH$	?

[a] Where yields are indicated as minor or in question, identification was qualitative, based on infrared absorption spectra.

The data of Table I show that solvent attack on chlorocarbon substrates is an important step in reactions in this system. The reduction of carbon tetrachloride to chloroform and the dechlorination of hexachloroethane to tetrachloroethylene suggest that abstraction of the elements of chlorine by the solvent is involved. N-Methylpyrrolidone alone converted hexachloroethane to tetrachloroethylene in 40% yield, although the yield was as high as 80% when potassium fluoride was also present. In the latter case the inorganic salts isolated from the reaction mixture contained substantial amounts of potassium bifluoride. Apparently abstracted chlorine can react with a solvent proton to yield hydrogen chloride, which then reacts with potassium fluoride to give hydrogen fluoride. This hydrogen fluoride can add to olefinic bonds as shown by Fried and Miller[3c] and as will be discussed later. The fate of the solvent involved in this reaction has not been determined.

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(1) A. L. Henne, *Org. Reactions*, **II**, 49 (1944).

(2) (a) F. W. Hoffman, *J. Org. Chem.*, **15**, 425 (1950); (b) F. L. M. Pattison and J. J. Norman, *J. Am. Chem. Soc.*, **79**, 2311 (1957), and other papers in this series.

(3) (a) I. Blank, Br. Patent 727,768 (April 6, 1955); (b) G. C. Finger and C. W. Kruse, *J. Am. Chem. Soc.*, **78**, 6034 (1956); (c) J. Fried and W. T. Miller, Jr., *ibid.*, **81**, 2078 (1959).

(4) (a) A. L. Henne and J. Sedlak, Abstracts of Papers, 138th National Meeting of the American Chemical Society, New York, N. Y., September 11–16, 1960; (b) A. L. Henne, U. S. Patent 3,024,290, (March 6, 1962).

(5) W. T. Miller, J. Fried, and H. Goldwhite, *J. Am. Chem. Soc.*, **82**, 3091 (1960).

(6) Made by sulfur tetrafluoride treatment of choranil.