linkage at C-9 in the real substrate (**3**).

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(17) R. Ratcliffe and R. Rodehorst, *J. Org. Chem.*, **35**, 4000 (1970).

(18) The trans-fused symmetrical ketone analogous to **32** has a C-2 axis. Therefore, the methyl groups are equivalent and the trans ketone would only exhibit seven signals. The cis-fused diketone **32**, on the other hand, has no C-2 axis and thus the methyl groups are diastereotopic.

(19) The methyl peaks of **32** also overlapped in the ^1H NMR. The $Eu(fod)_3$ spectrum shifted them from δ 1.0 to two singlets at δ 3.0 and 3.05.

(20) H. C. Brown and S. Krishnamurthy, *J. Am. Chem. Soc.*, **94**, 7159 (1972).

(21) G. Hofle and W. Steglich, *Synthesis*, 619 (1972), and references cited therein.

(22) N. S. Bhacca, J. E. Gurst, and D. H. Williams, *J. Am. Chem. Soc.*, **87**, 302 (1965).

(23) If one assumes that isomers **17** and **19** are "normal", then the characteristic shift for H_a in $CDCl_3$ should be $(4.30 + 4.15)/2 \simeq \delta$ 4.22. The deshielding caused by the carbonyl group is therefore $\delta \sim 0.53$ for isomer **16** and $\delta \sim 0.58$ for isomer **18**. In C_6D_6 the "normal" position for H_a is at $(4.45 + 4.85)/2 \simeq \delta$ 4.65. The deshielding for isomer **16** is therefore $\delta \sim 0.4$ and 0.2 for isomer **18**. The positive solvent shift is thereby seen, in that the deshielding of H_a caused by the carbonyl group is less in C_6D_6 than in $CDCl_3$ for each isomer. The gross C_6D_6 deshielding of all isomers is probably a consequence of the polar benzenesulfonate substituent. See D. H. Williams and N. S. Bhacca, *Tetrahedron*, **21**, 2021 (1965)) for an extended discussion of benzene solvent shifts with carbonyl compounds.

(24) Dienone **49** could be isolated from several of the **17** → **51** reaction mixtures, but the major component was always dimer **51**.

(25) L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Oxford, 1969, p 185.

(26) (a) See ref 25, p 225; (b) H. B. Kagan, Ed., "Determination of Configurations by Spectrometric Methods," Vol. I. Georg Thieme Verlag, Stuttgart, 1977, p 59.

(27) Hoffmann has done a molecular orbital analysis of fragmentation reactions [R. Gleiter, W. D. Stohrer, and R. Hoffmann, *Helv. Chim. Acta*, **55**, 893 (1972)] and finds that, for those cases where the dihedral angle $\phi = 0°$, cyclobutane formation can be preferred. The cases in point (**41**-fold, **53**-fold) have $\phi \simeq 60°$, but the Hoffmann calculations do not give results other than for $\phi \simeq 0, 90, 180°$.

(28) Technical assistance for some of the 360-MHz NMR experiments by R. E. Santini, J. Dallas, and N. Nowicki is greatly appreciated.

(29) International Flavors and Fragrances, sold as *trans*-decahydro-β-naphthol.

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(33) (a) K. Taguchi and F. H. Westheimer, *J. Org. Chem.*, **36**, 1571 (1971); (b) H. Weingarten and W. A. White, *ibid.*, **32**, 213 (1967); (c) I. Moretti and G. Torre, *Synthesis*, 141 (1970).

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(38) (a) H. C. Brown, "Organic Synthesis via Boranes", Wiley-Interscience, New York, 1975, (b) H. C. Brown, A. K. Mandal, and S. U. Kulkarni, *J. Org. Chem.*, **42**, 1392 (1977); (c) H. C. Brown and N. Ravindran, *ibid.*, **42**, 2533 (1977).

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Mechanism of the Cannizzaro Reaction[1-4]

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Abstract: An ultimate technique for disqualifying compounds suspected of being intermediates is illustrated by the use of isotope dilution to prove that benzyl benzoate is not an intermediate in the Cannizzaro reaction of 0.5 M benzaldehyde-*p-t* (tritium labeled) with 0.25 M sodium hydroxide in 74% methanol–26% water at 100 °C. The adduct from hydroxide ion and two molecules of benzaldehyde that was thought to rearrange to benzyl benzoate could alternatively rearrange directly to the products, benzoate ion and benzyl alcohol. However, this mechanism also is disproved because methoxide ion acting instead of hydroxide ion should lead to benzyl methyl ether, but less than 1% is found. Two other mechanisms involving a proton transfer concerted with the hydride transfer are disproved by the k_{D_2O}/k_{H_2O} isotope effect of 1.9. The rate-determining steps can be represented by two hydride transfer reactions to C_6H_5CHO, from the adduct from $HO^- + C_6H_5CHO$ and from the adduct from $CH_3O^- + C_6H_5CHO$, or, equivalently, by two termolecular reactions, $HO^- + 2C_6H_5CHO$ and $CH_3O^- + 2C_6H_5CHO$.

The Cannizzaro reaction[6] is the disproportionation of an aldehyde to an equimolar mixture of primary alcohol and carboxylic salt. It is characteristic of aldehydes that have no *α* hydrogens, and therefore cannot undergo aldol condensation. The reaction is usually brought about in a homogeneous, strongly basic solution or in a heterogeneous system consisting of an organic phase and a strongly basic aqueous phase. A typical example is reaction of benzaldehyde (I) with concentrated sodium hydroxide in hot aqueous methanol to yield benzyl alcohol (II) and sodium benzoate (III). Formaldehyde disproportionates in acid solution also.[7] The Cannizzaro reaction was considered one of the most important synthetic reactions of organic chemistry prior to the discovery of $LiAlH_4$ in 1946, but has now been totally supplanted by metal hydrides for laboratory syntheses.

$$\underset{\text{I}}{2C_6H_5CHO} + NaOH \xrightarrow{CH_3OH} \underset{\text{II}}{C_6H_5CH_2OH} + \underset{\text{III}}{C_6H_5CO_2Na}$$

Benzyl benzoate (VI) was isolated from the reaction of I with NaOH in water or in homogeneous aqueous methanol solution when heating and excess NaOH were avoided.[8] In heavy water (D_2O), the alcohol produced from the reaction of I or formaldehyde contains no carbon-bound D;[9] this excludes all mechanisms involving a hydride transfer from or to oxygen atoms, for example, eq A or B.

The kinetic order with I and several derivatives in water, methanol, aqueous methanol, or aqueous dioxane is third:

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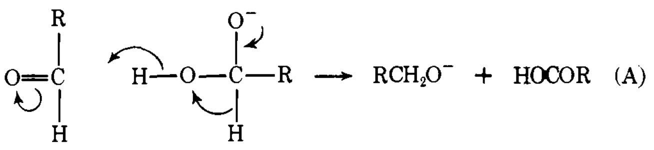
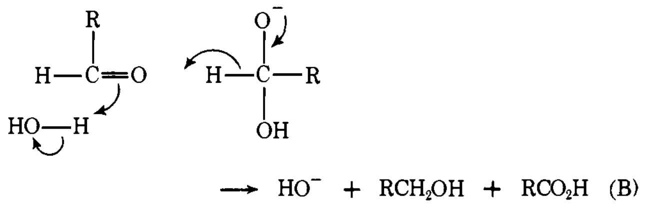

(A)

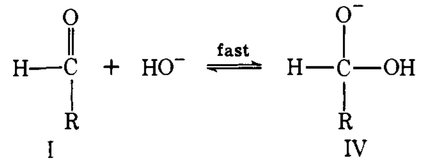

(B)

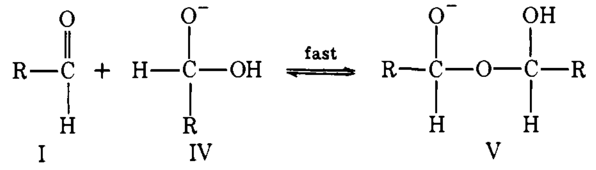
k_3[I]^2[base].[10] With furfural[11a,b] and formaldehyde[11c–e] the order varies from first to second in base, hence third to fourth overall depending on the conditions; sodium *m*-formylbenzenesulfonate also gives a fourth-order reaction, k_4[RCHO]^2·[base]^2, under certain conditions.[11f] The Hammett reaction constant for seven aromatic aldehydes with sodium hydroxide in 50% methanol at 100 °C is +3.76 (correlation coefficient 0.998).[10c,12]

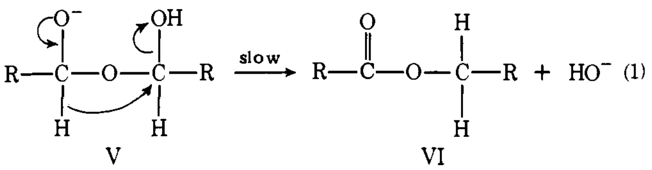
Under typical Cannizzaro reaction conditions, 0.6 M I and 0.25 M NaOH in 74% CH_3OH–26% water at 100 °C, the reactants exist predominantly as free I (not hydrate or hemiacetal), Na^+, and HO^-, the reaction is close to second order in I and first order in HO^-, and the principal products are II and III.[4] The purpose of this work was to investigate the main route by which II is formed under these conditions in order to exclude rigorously five of the six mechanisms (1–6) proposed.

Proposed Mechanisms. Radical-chain mechanisms have been proposed,[13] but are excluded under homogeneous conditions because radical initiators (benzoyl or sodium peroxide) or inhibitors (hydroquinone or diphenylamine) have no effect on the rate.[11a,14] Under heterogeneous conditions consisting of a benzaldehyde phase and a strongly alkaline aqueous phase, the reaction is a composite of two homogeneous reactions; the reaction in the organic phase is catalyzed by II produced by the slower reaction in the aqueous phase, but in both phases the reaction appears to be polar.[15]

Several mechanisms still consistent with the data so far presented have been proposed for the homogeneous Cannizzaro reaction. The first[6c,8,9a,10c,16] has eq 1 as its rate-determining step (R = phenyl).





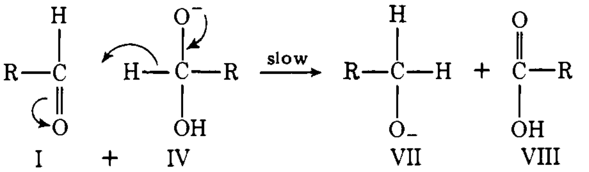

(1)

$$\mathrm{RCH_2OCOR} + \mathrm{HO^-} \xrightarrow{\text{fast}} \mathrm{RCH_2OH} + \mathrm{RCO_2^-}$$

VI II III

This mechanism involves formation of VI as an intermediate. Since ^{18}O exchange between water and I is much faster than the Cannizzaro reaction,[17] the rate-determining step cannot be formation of adduct IV or the mechanistically similar formation of adduct V, but it might be the rearrangement (eq 1) of V to VI. Ester hydrolysis is known to be fast under Cannizzaro conditions.[14]

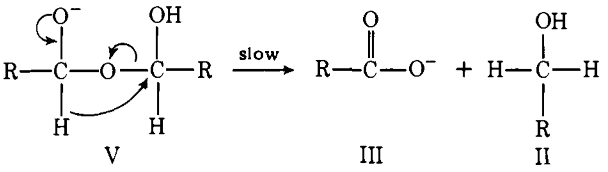
A second mechanism[18] is eq 2 with a prior equilibrium for IV as in mechanism 1. This mechanism involves a rate-determining intermolecular hydride shift, followed by fast proton transfer.

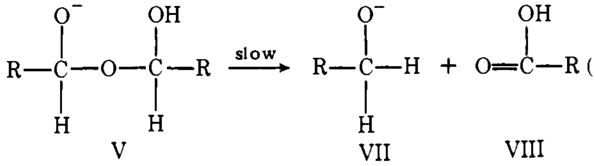

(2)

$$\mathrm{VII} + \mathrm{VIII} \xrightarrow{\text{fast}} \mathrm{RCH_2OH} + \mathrm{RCO_2^-}$$

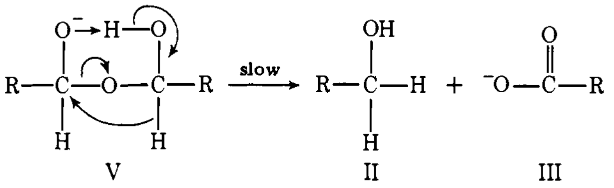
II III

Rearrangements of V that do not lead to formation of VI have also been proposed, as described by mechanism 3[19] or mechanism 4.[20] In (3), the stable products (II and III) are formed directly in the rate-determining step, while in (4) a fast proton transfer occurs after the rearrangement to form the stable products.

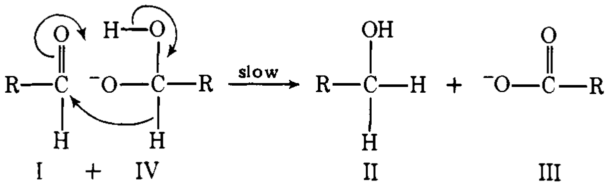

(3)


(4)

Another rearrangement of V, mechanism 5, involves a proton transfer in the slow step to produce the stable products.

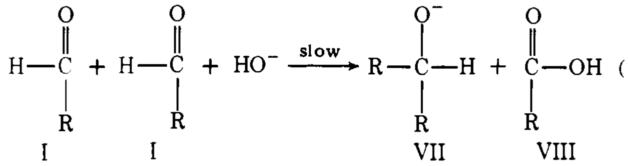

(5)

Similarly, the last two steps of mechanism 2 might be telescoped to (6).


(6)

In any solution of IV and I, there will be some V at equilibrium. In mechanisms 1, 3, 4, and 5, it is considered that V, in spite of its low concentration, reacts at a faster rate than more abundant reactants (I and IV) because V holds the migrating hydrogen in a favorable position for an intramolecular rearrangement. In mechanism 2 or 6 the necessary intermolecular hydride transfer cannot occur unless I and IV happen to collide with precisely correct orientations.

Mechanisms that are still simpler in the sense of bypassing IV can be proposed. Mechanism 7 is an example. Here IV is



$$\underset{\mathrm{I}}{\mathrm{H{-}C(=O){-}R}} + \underset{\mathrm{I}}{\mathrm{H{-}C(=O){-}R}} + \mathrm{HO^-} \xrightarrow{\text{slow}} \underset{\mathrm{VII}}{\mathrm{R{-}C(O^-)(R){-}H}} + \underset{\mathrm{VIII}}{\mathrm{R{-}C(=O){-}OH}} \quad (7)$$

a reversibly formed byproduct in equilibrium with the reactants, but not an intermediate along the main reaction path. General arguments against termolecular mechanisms are not valid at the high concentrations ordinarily used in the Cannizzaro reaction.[21] Termolecular mechanisms have been demonstrated in various systems experimentally.[22] Mechanism 7 could have the same transition state as mechanism 2.

Isotope effects using benzaldehyde-α-*t* (1.24–1.41)[2a,3a,23] and benzaldehyde-α-*d*[20,23] have been measured, and are in the normal direction for primary effects (though smaller than usual). However, they do not distinguish between mechanisms 1-7, which all involve a hydride or hydrogen atom transfer in the rate-determining step.

Isotope Dilution Applied to the Cannizzaro Reaction of Benzaldehyde-*p-t* in 74% Methanol–26% Water at 100 °C. Disproof of Mechanism 1. A promising technique for eliminating as an intermediate any suggested compound C that is stable when in pure form is to show that its actual concentration in the reacting system is less than would be required if it were an intermediate. This requires (a) measuring the rate of consumption of the suspected intermediate C under reaction conditions starting with it as a reactant, (b) calculating from this the concentrations of C that should be present at various times when none is added but on the assumption that it is formed as an essential intermediate along the main reaction path, and (c) showing that the measured concentrations of C are less than these calculated values. Since likely reaction intermediates are often very unstable under reaction conditions, this usually requires an extremely sensitive analytical method for measuring the concentration of C, especially when it originates from the usual reactants alone (as in part c). The most sensitive general analytical method known for hydrogen-containing C compounds involves the use of prior tritium labeling of C (in part a) or reactant (in part c), coupled with isotope dilution by a larger measured amount of unlabeled C, purification and analysis for radioactivity. The low cost of pure tritium (T_2) gas (ca. \$2 per curie) and the high sensitivity of radioactive counters make it practical to measure accurately concentrations of tritiated material as low as 10^{-14} M.[24,25] The following illustrates the use of this technique for proving that benzyl benzoate (VI) is not an intermediate in the Cannizzaro reaction of I.

In simultaneous base-catalyzed hydrolysis and methanolysis, methoxide ion is about three times more reactive than hydroxide ion toward acetyl L-phenylalanine methyl ester in 80% methanol–20% water[26a] and 45 times more reactive toward *p*-nitrophenyl acetate in dilute solutions of alcohol in water.[26b] When the rate of disappearance of 0.0625 M VI, partially labeled with tritium in the para positions of the rings, was determined under Cannizzaro conditions (0.125 M total base (methoxide + hydroxide), 74% methanol–26% water at 100 °C) by isotope dilution for unchanged VI, it was found that VI disappears by two parallel first-order reactions, with methoxide ion and with hydroxide ion, with the combined first-order rate constant of 0.37 s^{-1}. From these data and the third-order rate constant ($k_3 = 1.86 \times 10^{-4}\ M^{-2}\,s^{-1}$) for the Cannizzaro reaction of I, the concentration of VI that should be formed at various times in the Cannizzaro reaction, assuming that it is an essential intermediate as required by mechanism 1, was calculated by application of the steady-state approximation. Of course, some VI must form even if mechanism 2 operates, because the adduct of product benzyloxide ion VII to benzaldehyde I should be about as effective as IV as a hydride donor. However, IV is not formed initially if mechanism 2 is correct, whereas it is a necessary intermediate from the beginning in mechanism 1. Therefore, isotope-dilution measurements were restricted to the early part (6–19%) of the Cannizzaro reaction of benzaldehyde-*p-t*. The calculated concentrations of VI were at least 10–17.5 times the concentrations found. This shows that VI is not an essential intermediate along the main reaction path and excludes mechanism 1.

Product Analysis. Disproof of Mechanisms 3 and 4. Since methoxide ion is more reactive than hydroxide ion toward esters in methanol–water solutions,[26] there should be a considerable amount of reaction of I with CH_3O^- in Cannizzaro reactions carried out in alkaline methanol–water solutions. Mechanisms 1 and 2 would yield the same products with CH_3O^- as with HO^- since esters are rapidly hydrolyzed under the conditions. However, substitution of CH_3O^- for HO^- in mechanism 3 requires formation of benzyl methyl ether (IX), which should accumulate as a stable product. IX added to a Cannizzaro reaction mixture initially (0.25 M) was still present at the end (0.24 M), showing that this ether is not destroyed under Cannizzaro conditions. When none was added initially, less than 1% was found at the end by gas–liquid partition chromatography. This excludes mechanism 3.

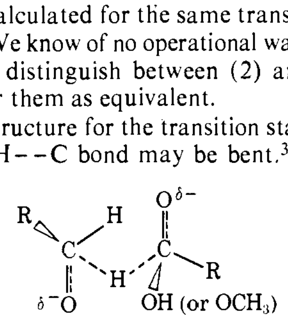
Mechanism 4 is forbidden as a concerted or one-step reaction by conservation of orbital symmetry rules. An equivalent two-step rearrangement via homolysis to a diradical or triplet carbene intermediate has been proposed[20] but seems excluded because thermal energy alone in the absence of light or free radicals should not break these strong bonds this rapidly, and products or rate should be affected by radical inhibitors if radicals were involved. Also, (4) provides no explanation for base catalysis since the homolytic rearrangement in (4) should proceed about as well with the neutral conjugate acid of V as with the monoanion.

Sovent Isotope Effect. Disproof of Mechanisms 5 and 6. Mechanisms 5 and 6 are excluded by our "solvation rule", which states that a proton being transferred between oxygens (or other atoms with unshared pairs) in the rate-determining step of an organic reaction (one with bond changes on carbon in the rate-determining step) should lie at a potential minimum (rather than maximum) at the transition state. This means that no primary kinetic isotope effect should be observed for any such hydrogen because it does not lose zero-point vibrational energy from ground state to transition state. Since its motion is not a critical part of the decomposition mode we should not include an arrow or arrows for its transfer in this step. This does not exclude the possibility of a favorable cyclic or hydrogen-bonded conformation for the transition state but does eliminate the more concerted mechanisms 5 and 6.

Experimental data on the Cannizzaro reaction, accumulated before this rule was formulated and tested by other reactions, leads to the same conclusion. The reactants of mechanism 2 in heavy water (D_2O) are DO^- and two molecules of aldehyde. At the transition state the DO^- bond has been replaced by a DO bond (uncharged). This equilibrium is more favorable with DO^- in D_2O than with HO^- in H_2O by a factor of about 2.0.[27,28] On the other hand, in mechanism 5 or 6 this should be more than offset by a primary isotope effect in the opposite direction from transfer of D rather than H in the rate-determining step, resulting in an equal or faster rate in H_2O. The observed k_{D_2O}/k_{H_2O} is 1.90. This excludes mechanisms 5 and 6 and shows that the proton is transferred after, rather than during, the rate-determining step.[29,30]

Mechanisms 2 and 7. These mechanisms are both still allowed. We know that the two molecules of reactant I are predominantly unsolvated and unassociated with hydroxide or methoxide in our solutions,[4] whereas the bonding of the hydroxide oxygen to carbon is complete or nearly so at the transition state (from the observed large values of k_{D_2O}/k_{H_2O} and the Hammett reaction constant ρ). We cannot say much about the sequence of events between reactants and transition state, whether the rate-determining reaction more usually involves two successive double collisions or one triple collision, because the same rate is calculated for the same transition state with either (2) or (7). We know of no operational way, experimental or theoretical, to distinguish between (2) and (7), and we therefore consider them as equivalent.

A reasonable structure for the transition state is illustrated by X. The C--H--C bond may be bent.[31] The carbonyl



X

oxygens of one or both aldehydes are likely to be polarized by hydrogen bonding to water or alcohol solvent molecules, and reasons have been given[27] for believing that such protons have normal bonds with normal zero-point energy at the transition state.

The fourth-order term observed with formaldehyde and certain other aldehydes may represent a transition state similar to X except that the hydroxylic proton has been transferred to a second hydroxide ion to form a separate water molecule.

Experimental Section[32]

Toluene-*p*-*t*. A Grignard reagent was prepared from 260 g (1.52 mol) of *p*-bromotoluene and 40 g (1.65 mol) of Mg in 370 mL of dry ether. Tritium chloride,[33] prepared from a heated mixture (25 °C to boiling point) of 1.0 g (0.11 equiv, 2.5 Ci) of tritiated water (see "Inorganic Chemicals"), 5.0 g (0.55 equiv) of H_2O, and 250 g of reagent grade C_6H_5COCl, was passed into the vigorously stirred Grignard mixture by a stream of purified N_2. After the ether had been removed from the resulting mixture, the pressure was reduced to 10 mm and the crude toluene-*p*-*t* was collected in a dry ice-acetone cooled flask. Distillation in a Vigreux column (16.5 cm × 2.5 cm o.d.) with a Claisen head gave 59 g (97%) of partially tritium-labeled toluene, bp 108-109 °C (lit.[34] for toluene, bp 111 °C).

Benzaldehyde-*p*-*t* (I-*p*-*t*). This toluene (59 g, 0.64 mol) was photochlorinated by a Sylvania RS sunlamp 15 cm from the flask. Hydrolysis[35] of the resulting benzylidene chloride gave partially tritium-labeled I, which was purified through the bisulfite addition product[35] and distilled under purified N_2 in a semimicro column,[36] bp 176-177 °C, $n^{25}{}_D$ 1.5424 (lit. for I, bp 179 °C,[35] $n^{20}{}_D$ 1.5446[37]), 26.4 g (39%).

Benzoic-*p*-*t* Acid and Benzyl-*p*-*t* Alcohol. A Cannizzaro reaction on this benzaldehyde (14 g, 0.13 mol)[38] gave 3.8 g (47%) of partially tritium-labeled VIII after recrystallization from water, mp 121-122 °C (lit.[39] for $C_6H_5CO_2H$, 122.38 °C), and 3.9 g (55%) of partially tritium-labeled II after distillation under N_2 in a semimicro column,[36] bp 109-110 °C (15 mm), $n^{25}{}_D$ 1.5366 (lit.[40] for II, bp 104-105 °C (20 mm), $n^{25}{}_D$ 1.5340).

Benzyl-*p*-*t* Benzoate-*p*-*t* (VI-*p*,*p*'-t_2) was prepared by a Tischtschenko reaction.[41] The partially labeled I (8.1 g, 0.076 mol) was treated with VII prepared from 0.033 g (0.0014 mol) of Na and 0.70 g (0.0065 mol) of the partially labeled II. The pasty, gelatinous mass resulting was treated with 40 mL of H_2O and 20 mL of ether to give three layers (H_2O, ether, and an oil) which were separated. The H_2O and oil layers were each washed with 20 mL of ether. The combined ether layers were dried over anhydrous Na_2SO_4. After the ether had been removed, the VI was distilled under N_2 in a semimicro column,[36] 5.1 g (63%), bp 133-134 °C (0.7 mm), $n^{25}{}_D$ 1.5664 (lit.[14] for VI, bp 133-135 °C (0.5 mm), $n^{24}{}_D$ 1.5672).

Benzaldehyde-α-*t* (I-α-*t*). The Reissert compound, 1-benzoyl-1,2-dihydroquinaldonitrile, was prepared from C_6H_5COCl, quinoline, and aqueous KCN and recrystallized twice from 95% ethanol as white needles, mp 154-154.8 °C (lit.[42] 154-155 °C). This was hydrolyzed in 2.5 M H_2SO_4 by refluxing 12 g in 108 g of a solution of 25.6 g of 96.5% H_2SO_4 (0.25 mol of H_2SO_4 + 0.05 mol of H_2O) in 84.6 g of tritiated water (4.70 mol) of 1.37 mCi/mol activity for 2 h under N_2. The solid crystals disappeared within 30 min. The product was steam distilled, extracted with ether, dried by azeotropic distillation with 15 mL of added C_6H_6, and distilled through a semimicro column,[36] 3.0 g, bp 74.0-74.4 °C (20-21 mm). The 2,4-dinitrophenylhydrazone, recrystallized twice from ethyl acetate, mp 241.0-242.2 °C (lit.[43] 237 °C), had an activity of 0.116 mCi/mol; the dimethone derivative, recrystallized twice from CH_3OH, mp 196.5-197.7 °C (lit.[44] 194-195 °C), had 0.120 mCi/mol; the semicarbazone, recrystallized twice from 50% ethanol, mp 220.2-221.1 °C (lit.[43] 222 °C), had 0.116 mCi/mol and changed less than 2% when it was dissolved in the minimum amount of 50% ethanol, refluxed for 1 h, and recrystallized to see if it exchanged with solvent; and VIII from $KMnO_4$ oxidation[45] of the compd recrystallized twice from water, mp 122.8-123.5 °C, had no significant tritium content (4.7 × 10^{-4} mCi/mol). I exchanges with tritiated H_2SO_4 less than 1% under these conditions: 5.0 mL of I refluxed with 52.2 g of a solution of 12.6 g of 96.5% H_2SO_4 in 42.3 g of tritiated water of 3.54 mCi/mol for 3 h under N_2 and worked up as above gave 3.86 g, bp 66.8 °C (15 mm), specific activity of semicarbazone 9.39 × 10^{-3} mCi/mol, of VIII 5.44 × 10^{-3} mCi/mol. These tritium analyses reported for water and organic compounds were done by the Mg[46] and Zn[47] reduction methods, respectively.

The isotope effect in this Reissert aldehyde synthesis is therefore k_H/k_T = (1.37 × 4.70 mCi)/0.116 mCi/mol × 10.0 equiv of H in H_2SO_4 solution = 5.6. A second synthesis with nine times the activity of the first gave 5.3.[48] This isotope effect does not prove that the proton transfer occurs in the rate-determining step, because there would be a selective competition between proton and triton donors even in a fast step unless it were diffusion controlled.

For the Cannizzaro reaction, the benzaldehyde-α-*t* was converted to semicarbazone, recrystallized, hydrolyzed back to aldehyde, and freshly distilled under N_2 before use, bp 69.0-69.7 °C (17-18 mm).

Methanol-*d* (CH_3OD) was prepared by decomposition of $Mg(OCH_3)_2$ with D_2O.[49] All the glassware was baked at 350 °C for several hours, assembled rapidly while hot, and immediately attached to Ascarite and Drierite towers to prevent introduction of CO_2 and moisture. ACS reagent grade CH_3OH was dried by the Mg method.[50] Mg (150 g) was added in small portions to 3.5 L of dry CH_3OH without exposing the system to the atmosphere. After the Mg had all dissolved and the solution had refluxed for 3 h, most of the CH_3OH was distilled and the residue was heated at 150-200 °C (1 mm) for 24 h. The system was allowed to cool to 25 °C and then dry, CO_2-free air admitted. D_2O (100 mL, >99.5%, degassed by bubbling purified N_2 through it for 30 min) was added and the resulting mixture was refluxed, with frequent shaking, for 4 days. The flask containing the reaction mixture was equipped for trap-to-trap distillation. Dry, CO_2-free air was admitted to the system while the distillation flask was cooled by liquid N_2. The system was then evacuated to 0.5 mm and the liquid N_2 bath was moved from the distillation flask to the receiver. After 24 h, dry, CO_2-free air was introduced and the distillate was allowed to warm to 25 °C. Mg (2 g) was added to the CH_3OD. After the Mg had all dissolved, the solution was refluxed for 3 h and the CH_3OD was distilled, bp 65 °C, 200 mL, GLC at 25 °C with two different columns (30% (by weight) 3-methyl-3-nitropimelonitrile on 60-100 mesh firebrick and 30% Carbowax 600 on 50-100 mesh firebrick in 8-mm Pyrex tubes 190 cm long) indicated total impurities of less than 0.1%. A determination of the D content by the falling-drop method[51] gave 24.65 atom % excess D (98.6% CH_3OD).

Methanol was prepared in the same manner as CH_3OD for comparison of rates in light and heavy 74% methanol, bp 63.5-64.0 °C. GLC indicated total impurities of less than 0.1%. CH_3OH for all the other runs was ACS reagent grade dried over Drierite.

Benzaldehyde (I), Eastman white label, was washed with 10% aqueous Na_2CO_3, dried over anhydrous Na_2SO_4 and freshly distilled under N_2 in a semimicro column[36] before use, bp 176-177 °C, $n^{25}{}_D$ 1.5432.

Benzyl benzoate (VI) and methyl benzoate (XII), Eastman white label, were redistilled under N_2 in a semimicro column:[36] VI, bp 121-122 °C (0.5 mm), $n^{25}{}_D$ 1.5653; XII, bp 75 °C (10 mm), $n^{25}{}_D$ 1.5122 (lit.[52] bp 83 °C (12 mm), n^{25}D 1.5155).

Benzyl benzoate (VI) used as the diluent for isotope dilution was recrystallized Eastman white label grade. A CH_3OH solution of VI was cooled in an ice-salt water bath; water was added to the cloud point and a seed crystal was introduced. The crystallized VI was collected on an ice-jacketed fritted-glass funnel, washed with a small amount of ice-cold CH_3OH, and air dried. After three such recrystallizations, it was recrystallized from a minimum of pure CH_3OH

Table I. Reaction of 0.5752 M I with 0.2875 M NaOD in 74% CH_3OD-D_2O at 99.8 ± 0.1 °C in Teflon Tubes

time, s	$[DO^-]$, M	% reaction	$k_3 \times 10^4$, $M^{-2}\,s^{-1}$
0	0.2872	0	
3600	0.2164	24.7	3.21
7200	0.1779	38.1	3.38
10 800	0.1599	44.9	3.12
18 000	0.1284	55.3	3.37
57 600	0.0753	73.8	3.57
			mean 3.33

Table II. Rate Constants for the Cannizzaro Reaction of I in Light and Heavy 74% Methanol-26% Water in Teflon Tubes

temp, °C	$[NaOL]_0$, M	$[I]_0$, M	water, L_2O	$k_3 \times 10^4$, $M^{-2}\,s^{-1}$
99.4	0.2850	0.5702	D_2O	3.76 ± 0.07
99.4	0.2609	0.5216	H_2O	1.79 ± 0.10
99.8	0.2685	0.5370	H_2O	1.86 ± 0.11
99.8	0.2875	0.5752	D_2O	3.33 ± 0.13

Table III. Cannizzaro Reaction of I in Glass Tubes

solvent, CH_3OH	temp, °C	$k_3 \times 10^4$, $M^{-2}\,s^{-1}$
50	100	2.33 ± 0.09[a]
67	100	2.22 ± 0.10[b]
74	98.3	3.31 ± 1.03[c]
74	98.6	2.45 ± 0.33[d]

[a] E. L. Molt;[10a] Tommila[10c] reported a frequency factor of 4.66 × 10^4 and an activation energy of 13.85 kcal for the Cannizzaro reaction of I in 50% CH_3OH. These gave a calculated k_3 of $3.47 \times 10^{-4}\ M^{-2}\ s^{-1}$ at 100 °C. [b] K. B. Wiberg.[23] [c] W. A. Sheppard.[2a] [d] I-*p*-*t*; I gave $2.36 \pm 0.16 \times 10^{-4}$ at 98.4 °C.

Table IV. Kinetics of the Alkaline Hydrolysis of 0.184 M VI with 0.177 M NaOH in 78% CH_3OH at 99.4 °C

time, s	$[HO^-]$, M	% reaction	$k_2{}^a \times 10^2$, $M^{-1}\,s^{-1}$
320	0.0577	67.4	3.4
600	0.0246	86.1	5.0
900	0.0145	91.8	5.6
1200	0.0109	93.9	5.5
1500	0.0092	94.8	5.0
1810	0.0089	94.9	4.2
			mean 5

[a] Based on total base consumed.

and dried over Anhydrone ($MgClO_4$) in a desiccator at 10 °C, mp 19.3-20.0 °C (lit.[53] mp 19.4 °C), $n^{25}{}_D$ 1.5672.

Benzyl methyl ether (IX), Eastman white label, was redistilled under N_2 in a semimicro column,[36] bp 169-170 °C (lit.[54] bp 170.5 °C).

Inorganic Chemicals. Purified nitrogen was prepurified N_2 freed of CO_2 and H_2O by passage through a series of towers containing Ascarite (NaOH on asbestos) and Drierite ($CaSO_4$). Tritiated water was prepared from T_2 gas (AEC, Oak Ridge) as described previously.[25] H_2O was laboratory distilled water which was redistilled from NaOH-$KMnO_4$ in an all-Pyrex apparatus.

NaOD was prepared by the dropwise addition of 100 mL of degassed D_2O (>99.5%) to 2.3 g (0.1 mol) of freshly cut reagent grade Na under an atmosphere of purified N_2 and then standardized. Analysis[51] of the solvent of the NaOD solution gave 99.14% D_2O. NaOH was prepared in the same manner as NaOD for the runs comparing rates in light and heavy 74% methanol. For the other runs, it was prepared either by the concentrated NaOH method[55] or by diluting 1 M Acculute and standardizing. CO_2-free H_2O was used in all these preparations.

Kinetic Procedures. The kinetics of the Cannizzaro reaction of I in 74% methanol was measured essentially by the method of Molt[10a] and Alexander.[14] The procedure was the same in light and heavy methanol. I (about 3 mL) was transferred by means of a 5-mL syringe and under an atmosphere of purified N_2 to a weighed 50-mL volumetric flask. The flask was reweighed and placed in a drybox, which was then flushed with purified N_2 for 20-30 min. Methanol (25 mL) was added to the flask, and 12.87 mL of 1 M NaOH was added from a buret with mixing by swirling. The volume was brought to the mark by addition of methanol. After the solution had been thoroughly mixed, it was drawn into a 50-mL syringe and seven aliquots of ca. 6 mL each were injected into Teflon tubes of ca. 7 mL capacity previously fitted snugly inside 18 × 150 mm Pyrex test tubes which had been constricted about 2.5 cm above the top of the Teflon to 4-5 mm. The tubes were protected from the atmosphere by tight-fitting rubber stoppers, removed from the drybox, cooled in an ice-water bath, sealed at the constriction, and placed in the constant temperature bath. After the tubes had been in the bath for 10 min, one was withdrawn, cooled in an ice-water bath, allowed to come to 25 °C, and opened. A 5-mL aliquot was pipetted into a known excess of 0.1 M standard HCl and back-titrated under purified N_2 to the phenolphthalein end point with 0.1 M NaOH. The constant was calculated from $k_3 = x(2a - x)/8ta^2(a - x)^2$, where a is the initial concentration of base at 10 min ($t = 0$) and x is the concentration reacted in time t. Data for a typical run are given in Table I, and the results for various runs in light and heavy 74% CH_3OH in Table II.

Teflon tubes were used in the later phases of this work because rapid attack of alkali on Pyrex tubes complicated the kinetics and gave poorer reproducibility in the earlier runs. Teflon tubes are convenient to use as described above and the solvent shows no tendency to distill out of the Teflon tube into the small space outside or under this tube (between the Teflon liner and the outer Pyrex tube) because the electrolyte (NaOH) is nonvolatile and keeps the vapor pressure below that of salt-free solvent. A difference in height of liquid inside and outside of over 30 m would be required for gravity to compensate this osmotic difference. Without these inert reaction vessels about one-quarter of the base was consumed by reaction with Pyrex under our conditions. Kinetic results of investigations in glass are reported in Table III.

In 74% CH_3OH-26% H_2O solutions at 100 °C CH_3O^- should attack VI to form methyl benzoate (XII) more rapidly than HO^- attacks VI or XII to form III.[26,27] Therefore the second-order rate

$$\begin{tikzcd}
C_6H_5COOCH_2C_6H_5 + CH_3O^- \arrow[r, shift left, "k_1"] \arrow[d, "k_2"', "HO^-"] & C_6H_5COOCH_3 + C_6H_5CH_2O^- \arrow[l, shift left] \arrow[d, "k_3"', "HO^-"] \\
C_6H_5COOH + C_6H_5CH_2O^- \arrow[d] & C_6H_5COOH + CH_3O^- \arrow[d] \\
C_6H_5COO^- + C_6H_5CH_2OH & C_6H_5COO^- + CH_3OH
\end{tikzcd}$$

$$k_1 > k_2 \text{ and } k_3$$

constant for hydrolysis of VI measured by the usual acid-base titration procedure should be nearly the same as that for XII. Since these esters hydrolyze rapidly even at 25 °C, the involved procedure for transferring samples under N_2, which was necessary for the Cannizzaro reaction runs, could not be used. Instead, as soon as the reaction solutions were prepared, samples were transferred as quickly as possible by means of a syringe to 7-mL ampules (15 × 125 mm Pyrex test tubes constricted in the middle to 4-6 mm) which were cooled in ice water and which had been previously flushed with purified N_2. The tubes were sealed quickly and placed in the constant temperature bath. At suitable intervals, one was withdrawn, cooled in ice water, and opened and then a 5-mL aliquot was pipetted into a known excess of 0.1 M standard HCl and back-titrated with 0.1 M NaOH. The second-order rate constant was calculated from the equation

$$k_2 = \frac{2.303}{t(a - b)} \log \frac{b(a - x)}{a(b - x)}$$

where a and b are initial VI and NaOH concentrations, respectively, and x is the amount of reactant consumed in time t. The kinetic results

Table V. Kinetics of the Alkaline Hydrolysis of 0.244 M XII with 0.235 M NaOH in 74% Methanol-26% Water at 99.4 °C

time, s	[HO$^-$], M	% reaction[a]	$k_2{}^a \times 10^2$, M^{-1} s^{-1}
300	0.0421	82.1	5.7
600	0.0121	94.8	9.4
900	0.0084	96.4	8.3
1200	0.0067	97.1	7.3
1500	0.0051	97.8	7.2
1800	0.0049	97.9	6.0
		mean	7

[a] Based on total base consumed.

for the hydrolysis of VI and XII as determined by acid-base titration are reported in Tables IV and V.

Despite the large errors inherent in measuring the rates of these very fast reactions, the close agreement of the second-order rate constant for VI (5×10^{-2} M^{-1} s^{-1}) with that for XII (7×10^{-2} M^{-1} s^{-1}) indicates that what is really being measured in the case of VI by the titration method is the attack of base on XII. The rate of disappearance of VI is very much faster, as reported below under "Isotope Dilution Technique".

The rate of disappearance of VI-*p,p'*-t_2 under Cannizzaro conditions was measured by determining the amount of unchanged ester at various times using isotope dilution. All transfers were made under purified N_2 to glassware that had been flushed with purified N_2. To a 50-mL volumetric flask containing 1.3256 g (0.006 25 mol) of VI (with tracer-level *p,p'*-t_2 labeling) was added 25 mL of CH_3OH. CO_2-free water (12.50 mL) was added from a buret. The temperature rose 10 °C and some ester separated as fine droplets. After the mixture had cooled to 25 °C, the volume was brought almost to the mark with CH_3OH, and the flask was swirled gently until the ester had dissolved. The volume was brought to the mark, and the resulting solution was thoroughly mixed by shaking. To a separate 50-mL volumetric flask containing 25 mL of CH_3OH was added 12.50 mL of 1.002 M NaOH from a buret. After the solution had cooled to 25 °C, the volume was brought to the mark with CH_3OH. The resulting solution was thoroughly mixed by shaking. A constant-delivery automatic syringe was used to deliver 3-mL aliquots of the 0.1250 M ester solution to one arm of inverted-Y-shaped Pyrex tubes. The tubes were stoppered with rubber stoppers. The syringe was cleaned by repeated rinsing with CH_3OH, dried, and then used to deliver 3-mL aliquots of the 0.2500 M NaOH solution to the other arm of the tubes. Eight tubes were loaded in this manner, cooled in ice water, and sealed so that the resulting third arm had about the same capacity as the other two. (Measurement, after the run, of the total capacity of each of seven of the tubes gave 17.1 ± 0.4 mL.) Some of the ester separated as fine droplets when the solutions were cooled. One of the tubes, the zero point, was opened and treated as described below under "Isotope Dilution Technique". To obtain each of the other points, a tube was placed in the constant temperature bath, held upright for 4-5 min to allow it to reach bath temperature, inverted (measurements on blanks showed that there was no rise in temperature when a 74% CH_3OH solution was mixed with an equal volume of 0.250 M NaOH in 74% CH_3OH), and shaken vigorously. At a suitable time, the tube was removed from the bath and plunged into ice water. The time was measured by means of a stopwatch from the instant the tube was inverted to the moment it was immersed in ice water. After the tube had been cooled, the sample was treated as described in the next section.

Isotope Dilution Technique. The 6-mL aliquots from the reaction of tritium-labeled VI with base under Cannizzaro conditions were washed with CH_3OH solutions containing known amounts of unlabeled VI. The solution was thoroughly mixed and the ester was purified by recrystallization five times. For the first three recrystallizations, the CH_3OH solutions were cooled in an ice-salt-water bath, water was added to the cloud point, and a seed crystal was introduced. The crystals were collected on an ice-jacketed fritted-glass funnel and washed twice with ice-cold CH_3OH. The fourth and fifth recrystallizations were from pure CH_3OH; filtration was used to remove the mother liquid and washings after the fourth, and decantation was used after the fifth. After the ester had been dried over Anhydrone in a desiccator kept at 10 °C, melting points were taken. The ester was liquefied and kept dry by allowing the desiccator to warm to 25 °C. Aliquots of the recovered ester were transferred to weighed counting bottles. After the amount of ester had been determined, 20 mL of scintillation solution (15 mg of diphenylhexatriene and 4 g of 2,5-diphenyloxazole/L of toluene) was added and the material was counted in a Packard Tri-Carb liquid scintillation spectrometer at 1200 V.

The amount of VI (A_0) in the aliquot of the reaction solution was found from $A_0 = AS/S_0$, where S is counts/min·g for recovered ester, S_0 is counts/min·g for undiluted VI, and A is g of untagged VI added to the aliquot. Self-quenching by the ester made it necessary to use different values of S_0 for different amounts of ester counted. Corrected S_0 values were obtained from a plot of S_0 vs. g of added VI.

The rate of consumption of VI under Cannizzaro conditions is slow enough to be measurable, as shown in Table VI. Although the ratio of total base (CH_3O^- + HO^-) to ester was 2:1 at zero time, the reaction was treated as first order since at 7 s the concentration of VI was 4.73×10^{-3} M while the total strong base concentration was 6.72×10^{-2} M. Accordingly, a plot was made of the logarithm of the concentration of VI vs. time. (Concentrations used were those after the fifth recrystallization.) The first-order rate constant k_1 of 0.37 s^{-1} obtained from the initial slope, which was constant from 0 to 20 s (four points), was interpreted as being that for the reactions of VI with HO^- and CH_3O^-. The fractions of the initial VI left after 7, 12,

Table VI. Reaction of Tritium-Labeled 0.0625 M VI with 0.1250 M NaOH in 74% CH_3OH at 99.8 ± 0.1 °C

time, s	A, g	no. of recrystns	mp, °C	sample counted, g	sample counts[a,b]	S,[c] counts min^{-1} g^{-1}	[VI],[d] M
0	5.532	4	19.2-19.7	0.0108	278 857 ± 717*	2.58×10^7	6.40×10^{-2}
7	5.490	4	19.0-19.8	0.1001	130 910 ± 525*	1.31×10^6	4.64×10^{-3}
		5	18.5-19.1	0.0999	133 870 ± 320*	1.34×10^6	4.73×10^{-3}
12	5.484	4	19.0-19.7	0.1007	17 006 ± 220*	1.68×10^5	6.0×10^{-4}
		5	18.0-18.5	0.1000	176 167 ± 1473	1.76×10^5	6.2×10^{-4}
20	5.499	4	18.8-19.8	0.0997	13 833 ± 118	1.34×10^4	4.7×10^{-5}
		5	18.0-18.7	0.1000	12 917 ± 185	1.24×10^4	4.4×10^{-5}
40	5.487	4	19.1-19.7	0.1001	9750 ± 168	9.22×10^3	3.8×10^{-5}
		5	18.0-18.5	0.1000	9465 ± 162	8.99×10^3	3.2×10^{-5}
90	5.490	4	18.7-19.5	0.1004	5683 ± 58	5.14×10^3	1.8×10^{-5}
		5	18.2-18.7	0.1000	5065 ± 64	4.59×10^3	1.6×10^{-5}
300	5.487	4	19.0-19.8	0.0996	1986 ± 51	1.47×10^3	5.2×10^{-6}
		5	18.2-18.9	0.1002	1550 ± 48	1.07×10^3	3.8×10^{-6}
3630	5.485	4	18.8-19.7	0.0999	2086 ± 31	1.57×10^3	5.6×10^{-6}
		5	18.4-19.0	0.1001	1551 ± 36	1.07×10^3	3.8×10^{-6}

[a] Asterisked counts are in 1 min; all others are in 10 min. [b] Mean value for ten trials with average deviation from the mean. After subtracting background, which was 518 ± 32 counts/10 min for samples after the fourth recrystallization and 480 ± 20 counts/10 min for samples after the fifth recrystallization. [d] Calculated using S_0 of 1.751×10^9 counts/min·g for zero point and S_0 of 1.215×10^9 counts/min·g for all other points. [c] Calculated initial concentration was 0.0625 M.

Table VII. VI Found by Isotope Dilution in the Cannizzaro Reaction of Tritium-Labeled 0.485 M I with 0.217 M NaOH in 74% CH_3OH at 100.5 °C

time, s	% reaction	A, g	no. of recrystns[a]	mp, °C	sample counted, g	sample counts[b,c]	S,[d] counts min^{-1} g^{-1}	$S_0 \times 10^{-9}$, counts min^{-1} g^{-1}	[VI], M × 10^7
0	0	0.5076	1		0.007 76	2620 ± 42	29 630		
			2		0.007 67	535 ± 19	2740	1.771	7.4
			3	18.7-19.2	0.043 72	1074 ± 15	1700	1.494	5.4
			4		0.016 91	7827 ± 129*	1500	1.692	4.
1800	5.9	0.4949	1		0.007 72	2532 ± 36	28 640		
			2		0.008 23	491 ± 18	2020	1.767	5.3
			3	18.7-19.1	0.048 20	989 ± 21	1360	1.471	4.3
			4		0.011 27	7345 ± 94*	1810	1.739	5.
3600	13.4	0.4923	1		0.009 43	2213 ± 56	20 060		
			2		0.007 43	458 ± 21	1790	1.772	4.7
			3	18.7-19.1	0.023 21	702 ± 27	1590	1.645	4.5
			4		0.012 76	7756 ± 125*	1930	1.725	5.
5400	18.7	0.4977	1		0.008 52	1826 ± 50	17 660		
			2		0.006 67	450 ± 20	1870	1.780	4.9
			3	18.7-19.1	0.014 18	547 ± 17	1510	1.715	4.1
			4		0.007 10	6056 ± 117*	1070	1.776	3.

[a] First recrystallization was from CH_3OH-H_2O with filtration; next three were from a minimum of pure CH_3OH with decantation. [b] Asterisked counts are for 100 min; all others are for 10 min. [c] Mean value for ten trials with average deviation from the mean. [d] After subtracting background, which was 321 ± 16 counts in 10 min for samples after the first recrystallization, 325 ± 29 counts in 10 min after the second recrystallization, 333 ± 16 counts in 10 min after the third recrystallization, and 5300 ± 140 counts in 100 min after the fourth recrystallization.

Table VIII. Concentration of VI in the Cannizzaro Reaction of Tritium-Labeled 0.485 M I with 0.2167 M NaOH in 74% CH_3OH at 100.5 °C

time, s	% reaction	[I], M	[VI] calcd, M	[VI] found,[a] M
0	0	0.4854	7.4×10^{-6}	$4. \times 10^{-7}$
1800	5.9	0.4596	6.6×10^{-6}	$5. \times 10^{-7}$
3600	13.4	0.4274	5.7×10^{-6}	$5. \times 10^{-7}$
5400	18.7	0.4042	5.1×10^{-6}	$3. \times 10^{-7}$

[a] See Table VII. The nonzero values are probably due mostly to labeled reactant I and product II impurities rather than VI because scavenging by unlabeled I and II was not used in this series of measurements.

and 20 s, respectively, were 7 (93% reacted), 1 (99% reacted), and 0.07% (99.93% reacted). A falling off of k_1 after 20 s (beyond 99.93% reaction) was attributed to significant back-reaction regenerating VI by reaction of VII with XII.

The amount of VI present at various times in a Cannizzaro reaction of 0.4854 M tritium-labeled I with 0.2167 M NaOH in 74% CH_3OH at 100.5 °C was determined using isotope dilution. The procedure for preparing the reaction solution and taking points has already been described under "Kinetic Procedure". Bromthymol blue was used as indicator. The third-order rate constant k_3 was calculated using

$$k_3 t = \frac{1}{(2b - a)^2}\left[\frac{(2b - a)2x}{a(a - 2x)} + \ln \frac{b(a - 2x)}{a(b - x)}\right]$$

where a is the initial concentration of benzaldehyde-*p*-*t* at 10 min ($t = 0$), b is the initial concentration of base at 10 min ($t = 0$), and x is the amount of base reacted in time t. The third-order rate constant obtained, $k_3 = 1.72 \pm 0.21 \times 10^{-4}\ M^{-2}\ s^{-1}$, does not differ significantly from that obtained in the solvent isotope effect runs (see Table II). After the 5-mL aliquots from the run had been titrated, they were made slightly acidic and a known amount of untagged VI was added. CH_3OH was added until all the VI had dissolved, and the resulting solutions were then treated as described above. Table VII gives the concentrations of VI found at various times in this run.

The concentration of VI that should accumulate in the Cannizzaro reaction at any time if it were an intermediate can be calculated using the steady-state approximation. The reactions involved are

$$2C_6H_5CHO + HO^- \text{ or } CH_3O^- \xrightarrow{k_3} C_6H_5COOCH_2C_6H_5\ (VI)$$

$$VI + HO^- \text{ or } CH_3O^- \xrightarrow{k_2} (C_6H_5COOCH_3 \text{ or } C_6H_5COOH) + C_6H_5CH_2O^-$$

Application of the steady-state approximation gives

$$d[VI]/dt = k_3[I]^2[B] - k_2[VI][B] = 0 \qquad (8)$$

$$[VI] = k_3[I]^2/k_2 \qquad (9)$$

where [B] is the total base concentration ($[CH_3O^-] + [HO^-]$) at any time in the Cannizzaro reaction, k_3 is the third-order rate constant for the Cannizzaro reaction in 74% methanol, and k_2 is the second-order rate constant for the reaction of VI with HO^- or CH_3O^- in the same solvent.

Equation 9 was used to calculate the concentration of VI that should have formed if it were an intermediate in the Cannizzaro reaction; $k_3 = 1.86 \times 10^{-4}\ M^{-2}\ s^{-1}$ was used since this value is considered the most accurate. k_2 as found above is $0.37/0.0625 = 5.92\ s^{-1}\ M^{-1}$. The calculated concentrations of VI, along with those actually found, are reported in Table VIII.

α-Hydrogen Isotope Effects. Our earliest work on the Cannizzaro reaction[2a,3a] utilized I-α-*t*. The procedure involved Pyrex ampules with 10-mL aliquots of 0.48 M I-α-*t* and 0.24 M NaOH in 74% CH_3OH under N_2 at 98.3 °C. After titration of 5 mL of the solution, the remainder was diluted with 4 mL of water and added to an excess of semicarbazide in a test tube. The mixture was thoroughly shaken, heated on a steam bath, and cooled to 5 °C. The white precipitate of I semicarbazone was filtered and recrystallized twice from 50% ethanol. Each sample was dried at 130 °C and less than 1 mm. The melting point (220–221 °C) and activity[46] were constant after the first crystallization. I-α-*t* was shown to exchange 3.5% of its tritium with NaOH solution in 12 h and 6.5% in 24 h, by separating the I-α-*t* remaining as the semicarbazone and assaying it. Thus, the rate of exchange is slow compared to the Cannizzaro reaction. The plot of log (activity) vs. log (fraction unreacted) deviated noticeably from a straight line for large fractions reacted for eight different samples of semicarbazone from 0 to 80% reaction.[2a] After correction of the activities for loss of tritium by exchange with the solvent it became linear; then from the slope of the least-squares line[56] the isotope effect k_H/k_T was found to be 1.24.[2a] This value is even lower than that found by Miklukhin for k_H/k_D from a similar competition experiment.[20]

Analysis for Benzyl Methyl Ether (IX). IX was shown to be stable under Cannizzaro conditions. A reaction mixture of I and NaOH with added IX in 74% CH_3OH was prepared. Four 6-mL aliquots were sealed in Teflon tubes and the tubes were placed in the bath at 99.5 °C. At suitable times, at the beginning and near the end of the reaction, tubes were withdrawn, cooled to room temperature, and opened. A 5-mL aliquot was pipetted into a 60-mL separatory funnel and extracted with two 10-mL portions of pure pentane. The pentane layers were combined and evaporated to 2 mL. This sample was washed into a 5-mL volumetric flask and diluted to the mark with pentane. The amount of ether was determined by GLC with 30% (by weight) Carbowax 600 on 50–100 mesh firebrick at 130 °C. Areas for three 15-μL aliquots of each sample were measured by planimeter a number of times and averages used. Values for the areas for the three 15-μL aliquots of a given sample were generally within 3% of each other. From known solutions of 0.0260–0.280 M IX in pentane, the ratio of area to concentration for the column was determined. This value was then used to calculate the concentration of IX in samples from the Cannizzaro reaction. There was no significant change in concentration of IX under Cannizzaro conditions: concentrations found in two samples taken after 10 min at 99.5 °C were 0.26 and 0.25 M; after 334 and 499 h they were 0.25 and 0.24 M.

After the final point from one Cannizzaro run (262 h, >90% reaction) had been titrated, the resulting solution was extracted with two 25-mL portions of pure pentane. The organic layers were combined and evaporated to 2 mL. This solution was washed into a 5-mL volumetric flask and diluted to the mark with pentane. GLC using Carbowax 600 showed no peak for IX. IX in pentane (0.0260 M, the amount that would have been present if 10% of the I had reacted with CH_3O^- ion by mechanism 3) was accurately measurable by this technique (area/concentration ratio within 1% of that for 0.26–0.28 M). Therefore certainly less than 1% of IX was present.

References and Notes

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(2) For further experimental details, cf. (a) W. A. Sheppard, Ph.D. Thesis, Massachusetts Institute of Technology, 1954; (b) C. R. Morgan, Ph.D. Thesis, Massachusetts Institute of Technology, 1963.

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