Mechanism of the Cannizzaro Reaction: Possible Involvement of Radical Intermediates

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The Cannizzaro reaction of [α-^{2}H]benzaldehyde in alkaline aqueous dioxan or dioxan alone produces a substantial amount of [α-^{2}H]benzyl alcohol together with the normal product, [α-$^2H_2$]benzyl alcohol, suggesting a possible partial involvement of radical intermediates.

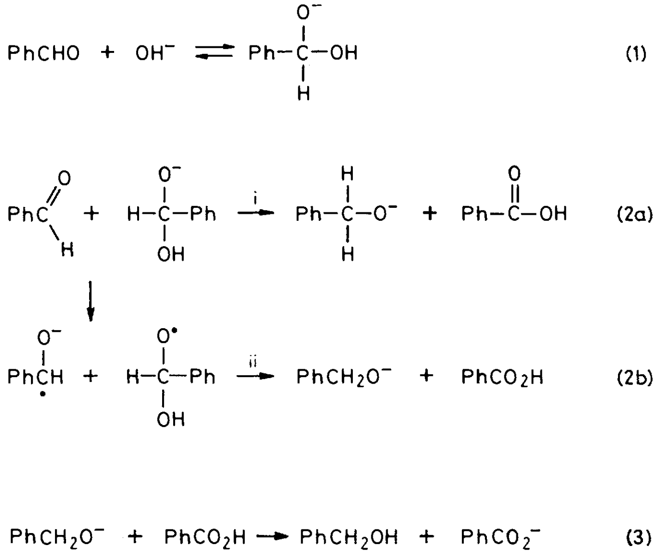
The Cannizzaro reaction is a disproportionation of aldehydes into an equimolar mixture of the corresponding alcohols and acid, and is normally carried out under strongly basic conditions.[1] Based on kinetic data, structure–reactivity relationships, and isotopic studies, a number of mechanisms have been proposed.[2] The generally accepted mechanistic process for the homogeneous Cannizzaro reaction involves a prior equilibrium addition of OH^- to the aldehyde and a rate-determining intermolecular hydride transfer (Scheme 1, pathway 2a) followed by fast proton transfer. A radical mechanism (Scheme 1, pathway 2b) has also been suggested,[3] but discounted largely because radical initiators and inhibitors have no significant effect on the reaction rate.[4]

In contrast to the previous observation that the alcohol obtained from the Cannizzaro reaction of benzaldehyde in D_2O did not contain any carbon-bound deuterium,[5] Swain *et al.*[6] recently reported that benzyl alcohol from the reaction of [α-^{2}H]benzaldehyde and NaOH in aqueous methanol at 100 °C included a substantial percentage of the [α-^{2}H]alcohol along with the expected [α-$^2H_2$]alcohol. This result was rationalized in terms of oxidation of the methoxide ion and the subsequent cross Cannizzaro reaction between formaldehyde and [α-^{2}H]benzaldehyde (Scheme 2).[6]

In view of our recent observation that a typical hydride transfer agent ($LiAlH_4$) could behave as donor of an electron as well as a hydrogen atom,[7] we considered that the hydrogen isotope incorporation into benzyl alcohol from H_2O–CH_3OH in the Cannizzaro reaction might be partially due to the intervention of radical intermediates. We report now some relevant results. It was rationalized that if the 'unusual' hydrogen isotope incorporation into the product from the solvent originated exclusively from the oxidation of the methoxide ion and the following cross Cannizzaro reaction, as explained by Swain *et al.*,[6] such an event would not be possible in other solvents such as aqueous dioxan and aqueous dimethylformamide. Since the Cannizzaro reaction is known to show the same kinetic behaviour in these solvents as in aqueous methanol,[2] the change of the solvent system is not likely to alter the reaction mechanism to a significant degree.

In a preliminary experiment with aqueous dimethylformamide at 100 °C, the substrate, [α-^{2}H]benzaldehyde (97% deuterium), showed a significant exchange of the aldehydic hydrogen with the solvent. On the other hand, the Cannizzaro reaction in aqueous dioxan did not show this. Thus, a number of Cannizzaro reactions were carried out with [α-^{2}H]benzaldehyde[8] in aqueous dioxan. The deuterium content in the benzyl alcohol product was analysed by g.l.c.–mass spectrometry on the product mixture containing benzaldehyde and the alcohol, and also by ^{1}H n.m.r. spectroscopy on the isolated alcohol product. In all runs, the alcohol product was found to consist primarily of $C_6H_5CD_2OH$ with varying amounts of C_6H_5-CHDOH depending on the relative concentration of the solvent mixture (Table 1). The g.l.c.–mass spectrometry analyses of the recovered benzaldehyde from each run clearly showed that there was no hydrogen exchange with solvent at the aldehyde stage. Control experiments also showed that no α-hydrogen exchange of benzyl alcohol occurred under the reaction conditions. In the determination of the percentage of C_6H_5CHDOH by the g.l.c.–mass spectrometry method, the measurement of the tropylium ion intensities at 70 eV was found to be somewhat more reliable than that of the molecular ion intensities at 15 eV. In addition, the independent determination of the percentage of C_6H_5CHDOH in the alcohol product by ^{1}H n.m.r. integration is in reasonable agreement with results from the g.l.c.–mass spectrometry method. Authentic samples of C_6H_5CHDOH and $C_6H_5CD_2OH$ were prepared by $NaBD_4$ reduction of C_6H_5CHO and C_6H_5CDO, respectively.

From the data in Table 1, it is clear that an appreciable amount of the benzylic hydrogen of the product alochol is derived from the solvent, even in aqueous dioxan or dioxan alone. Since it is well established that H_2O does not provide



$$\mathrm{PhCHO} + \mathrm{OH^-} \rightleftharpoons \mathrm{Ph{-}}\overset{\displaystyle O^-}{\underset{\displaystyle H}{\mathrm{C}}}\mathrm{{-}OH} \qquad (1)$$

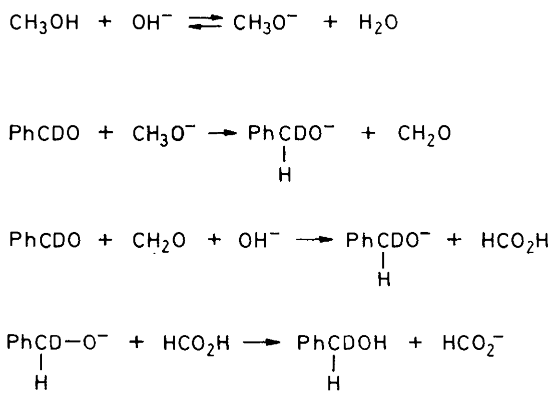
$$\mathrm{Ph}\overset{\displaystyle O}{\underset{\displaystyle H}{\mathrm{C}}} + \mathrm{H{-}}\overset{\displaystyle O^-}{\underset{\displaystyle OH}{\mathrm{C}}}\mathrm{{-}Ph} \xrightarrow{\text{i}} \mathrm{Ph{-}}\overset{\displaystyle H}{\underset{\displaystyle H}{\mathrm{C}}}\mathrm{{-}O^-} + \mathrm{Ph{-}}\overset{\displaystyle O}{\overset{\|}{\mathrm{C}}}\mathrm{{-}OH} \qquad (2a)$$

$$\big\downarrow$$

$$\mathrm{Ph}\overset{\displaystyle O^-}{\underset{\bullet}{\mathrm{C}}}\mathrm{H} + \mathrm{H{-}}\overset{\displaystyle O^\bullet}{\underset{\displaystyle OH}{\mathrm{C}}}\mathrm{{-}Ph} \xrightarrow{\text{ii}} \mathrm{PhCH_2O^-} + \mathrm{PhCO_2H} \qquad (2b)$$

$$\mathrm{PhCH_2O^-} + \mathrm{PhCO_2H} \rightarrow \mathrm{PhCH_2OH} + \mathrm{PhCO_2^-} \qquad (3)$$

Scheme 1. i, H^--transfer; ii, $H^\bullet$-transfer.



$$\mathrm{CH_3OH} + \mathrm{OH^-} \rightleftharpoons \mathrm{CH_3O^-} + \mathrm{H_2O}$$

$$\mathrm{PhCDO} + \mathrm{CH_3O^-} \rightarrow \mathrm{Ph}\underset{\displaystyle H}{\mathrm{C}}\mathrm{DO^-} + \mathrm{CH_2O}$$

$$\mathrm{PhCDO} + \mathrm{CH_2O} + \mathrm{OH^-} \rightarrow \mathrm{Ph}\underset{\displaystyle H}{\mathrm{C}}\mathrm{DO^-} + \mathrm{HCO_2H}$$

$$\mathrm{Ph}\underset{\displaystyle H}{\mathrm{C}}\mathrm{D{-}O^-} + \mathrm{HCO_2H} \rightarrow \mathrm{Ph}\underset{\displaystyle H}{\mathrm{C}}\mathrm{DOH} + \mathrm{HCO_2^-}$$

Scheme 2

Table 1

Run	Conditions[a]	% of C_6H_5CDHOH	
		G.l.c.–m.s.[b]	^1H n.m.r.[c]
1	H_2O–Dioxan (1 : 1)	4.4	6.0
2	H_2O–Dioxan (1 : 3)	8.7	11.0
3	HCHO[d]/H_2O–Dioxan (1 : 1)	35	32
4	H_2O–MeOH (1 : 1)	8.8	9.6
5	Dioxan–18-C-6[e]	18.8	16.0

[a] All reactions were run at 100 °C, in the dark, under N_2 with [α-^{2}H]benzaldehyde (1.0 M) and KOH (3.0 M). Use of freshly distilled dioxan (CaH_2) gave essentially identical results to those using a fresh bottle of dioxan (MCB, <0.005 % peroxides). [b] Determined by mass spectral analysis of *m/e* 92 and 93 peaks on a Hewlett-Packard g.l.c.–m.s. model 5982-A, corrected for the amounts of *m/e* 92 arising from proton loss of *m/e* 93, and expressed as a percentage. [c] Determined from the integral ratios of the benzylic hydrogen at δ 4.5 and the phenyl hydrogen at δ 7.3, and corrected for the initial proton content of ca.3% in [α-^{2}H] benzaldehyde. [d] Formaldehyde (1.5 M) was added. [e] 18-Crown-6 (0.5 M) was added in order to solubilize KOH in dioxan.

the benzylic hydrogen of the product,[5] the hydrogen, evidently, originates from dioxan, a good hydrogen atom donor. We suggest, therefore, that the most straightforward explanation for the observed production of [α-^{2}H]benzyl alcohol in the Cannizzaro reaction of [α-^{2}H]benzaldehyde in aqueous dioxan is the involvement of a ketyl radical anion intermediate, which is capable of abstracting the hydrogen atom from the ether solvent (and the crown ether in run 5). We further suggest that the nonchain radical process or an extremely short radical chain length is responsible for the negligible effect of radical initiators and inhibitors on the rate of the Cannizzaro reaction. Although the exact mechanism of the radical generation in this reaction is not yet clear, a thermal electron transfer between the benzaldehyde–hydroxide adduct (donor) and benzaldehyde (acceptor) appears possible.

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