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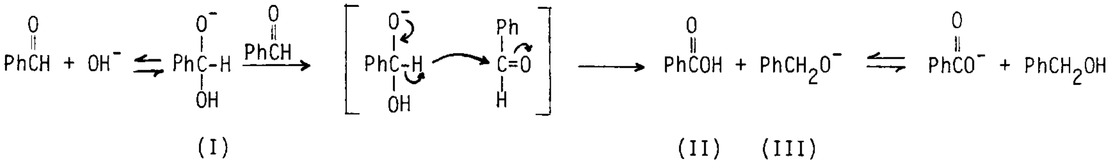
EVIDENCE SUPPORTING A SINGLE ELECTRON TRANSFER PATHWAY IN THE CANNIZZARO REACTION

E. C. Ashby,* David T. Coleman III and M. Pilar Gamasa
School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332 USA

Abstract: Radical species are observed by EPR spectroscopy in the Cannizzaro reaction involving various substituted benzaldehydes with NaOH in THF/HMPA (9:1). The radical species have been identified as the aldehyde radical anions corresponding to the particular aldehyde studied.

The Cannizzaro reaction has been considered one of the most fundamental reactions in organic chemistry.[1] It involves the reaction of an aldehyde, devoid of α-hydrogens, with a high concentration of a strong base (e.g. NaOH) to form an equimolar mixture of the corresponding primary alcohol and the salt of the corresponding carboxylic acid. Thus substituted aromatic aldehydes are prime candidates for this oxidation-reduction reaction. A variety of mechanisms for this reaction have been proposed,[2] however the mechanism presently accepted invokes a hydride transfer (Scheme I). Radical chain mechanisms have been suggested, but have been discounted on the basis that neither radical initiators nor inhibitors have a decisive effect on the rate of reaction.[3] Recently, however, Chung has shown[4] a possible involvement of radical intermediates in the Cannizzaro reaction involving benzaldehyde-α-d in alkaline aqueous dioxane and dioxane alone. His conclusion was based on the fact that a substantial amount of benzyl alcohol-α-d_1 was produced in the reaction in addition to the normal product, benzyl alcohol-α-d_2. The monodeuterated product suggests the formation of the benzaldehyde radical anion followed by hydrogen atom abstraction from the solvent.

Scheme I



We have studied the Cannizzaro reaction by EPR spectroscopy and have obtained evidence for the existence of paramagnetic species in solution. Benzaldehyde and a number of substituted benzaldehydes were allowed to react with NaOH in THF/HMPA (9:1 ratio) and the resulting mixture studied by EPR spectroscopy. The results of these studies are tabulated in the Table. In three cases (p-chloro-, p-trifluoromethyl-, and p-cyanobenzaldehyde) the EPR spectra of the

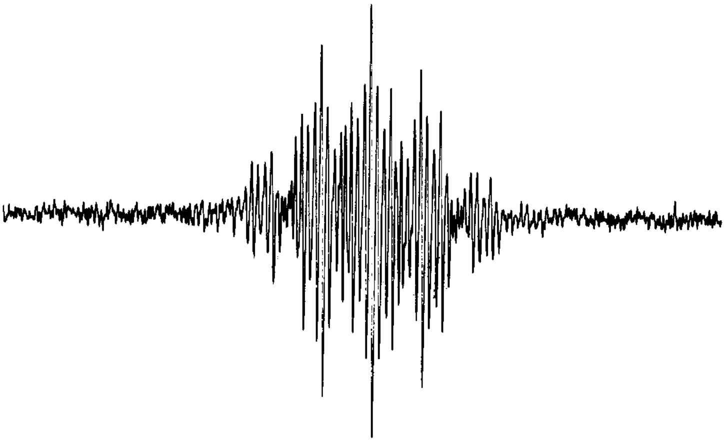


Figure 1: EPR spectrum of the intermediate formed in the reaction of NaOH with p-trifluoromethylbenzaldehyde in THF/HMPA (9:1) at room temperature.

Table. Reactions of aromatic aldehydes with NaOH in THF/HMPA (9:1 ratio) at 25°C.

Benzaldehyde	EPR Signal	% Yield Products		
		Alcohol[c,d]	Acid[c,e]	Total
p-Cl	resolved[a]	95.0	91.6	93.3
p-CF_3	resolved[a]	93.0	86.6	89.9
p-CN	resolved[a]	82.1	88.4	85.3
p-H	unresolved	58.5	52.4	84.5[f]
p-NO_2	resolved[b]			
o-CH_3	unresolved			
2,4,6-$(CH_3)_3$	no signal			
$(CH_3)_3C\overset{O}{\overset{\|}{C}}H$	no signal			

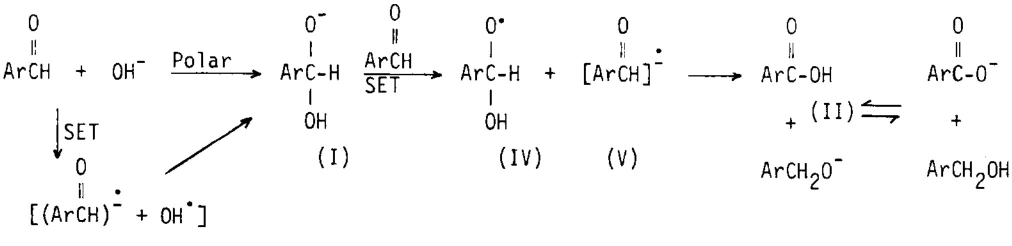
All reactions were carried out in the dark, under N_2 with [aldehyde] = 0.36M in HMPA/THF solution (1:9 ratio) and the ratio of aldehyde:NaOH was 2:1.5. Reaction times were 24 hrs for all reactions except benzaldehyde, which was allowed to react for 36 hrs. All aldehydes were distilled from CaH_2 except p-nitrobenzaldehyde which was doubly sublimed, THF was distilled from Na/benzophenone and HMPA was distilled from sodium. [a]Spectrum was compared to a spectrum of the reaction product obtained from the reaction of sodium with the aldehyde in the same solvent system. [b]Spectrum is similar to the free radical anion of p-nitrobenzaldehyde. [c]Alcohol and acid yields based on 1/2 of the total moles of starting aldehyde. [d]Yield determined by NMR. [e]Yield determined by base titration and the acid identified by neutralization equivalent and comparison of the IR spectrum with that of an authentic sample [f]Total yield based on starting aldehyde includes 13.7% of recovered aldehyde and 15.3% of benzyl benzoate. Aldehyde and ester yields were determined by NMR.

reacting solutions were well resolved and the spectra obtained are identical to the spectra produced from the reaction of sodium metal with each respective aldehyde in the same solvent system.[5] This suggests that the radical obtained in the reaction of NaOH with each of the aldehydes is the free radical anion of the respective aldehyde. The EPR spectrum of the intermediates formed on reaction of p-trifluoromethylbenzaldehyde with NaOH in THF/HMPA is given in the figure. In the case of p-nitrobenzaldehyde, the spectrum was interpreted and found to be similar to the radical anion of p-nitrobenzaldehyde. Of the seven aromatic aldehydes studied, only 2,4,6-trimethylbenzaldehyde failed to produce a radical signal by EPR spectroscopy. α-α-α-Trimethylacetaldehyde was also allowed to react under the same conditions, but no EPR signal was observed presumably due to the high reduction potential of aliphatic aldehydes compared to aromatic aldehydes.

Due to the insolubility of NaOH in the solvent system used, the reactions carried out in the EPR tubes did not go to completion. Attempts to increase the solubility of NaOH to a satisfactory level by use of a variety of different aprotic solvents (DMF, DME, HMPA, DMSO) and of KOH in the presence of 18-crown-6 were not successful. Therefore, stirred larger scale reactions of p-chloro, p-trifluoromethyl-, p-cyanobenzaldehyde, and benzaldehyde were carried out using the same concentrations and conditions as those used in the EPR tube reactions. The isolated yields are given in the Table. The Cannizzaro reaction proceeds well to give reasonable yields of the acid and alcohol products with the exception of benzaldehyde which is complicated by the formation of the ester from the alcohol and acid.

Resolved EPR signals of the substituted benzaldehyde radical anions and high yields of Cannizzaro products under similar conditions suggest that the Cannizzaro reaction in these cases is proceeding by a single electron transfer mechanism. Unfortunately a more direct correlation relating the appearance and disappearance of the radicals with the appearance of the products was not possible due to the insolubility of NaOH in the solvents used. However all of the data presented here indicate that aromatic aldehydes react with NaOH under the conditions described here to form Cannizzaro product by a SET pathway. The suggested mechanism is presented in Scheme 2.

Scheme 2



It can be seen that intermediate (I) can be formed by either of two pathways. We feel confident that the SET pathway is possible since we have independent evidence that OH^- is a good single electron donor. In this connection we have allowed NaOH in THF to react with both trityl bromide and p-dinitrobenzene. Significant amounts of trityl radical and p-dinitrobenzene radical anion were observed by EPR spectroscopy. The reaction of (I) with the aromatic aldehyde by a SET pathway is also reasonable since we have already shown that alkoxides can transfer an electron to alkyl halides,[6] ketones[7] and polynuclear hydrocarbons.[8] It is presumably at this stage that we are observing the aldehyde radical anion. The aldehyde radical anion (V) can then abstract a hydrogen atom from IV to produce the Cannizzaro products.

In conclusion, these studies indicate the the Cannizzaro reaction involving aromatic aldehydes is proceeding at least to some extent by a single electron transfer pathway. Further studies are underway.

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