Single Electron Transfer in the Cannizzaro Reaction

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Resolved ESR spectra of substituted benzaldehyde radical anions produced in the reactions of substituted benzaldehydes with either NaOH or KO-*t*-Bu, qualitative correlation of these ESR active species with product formation, high yield of Cannizzaro products under similar conditions in most cases, and isolation of dimer products, which have been shown to probably arise from a radical process, all suggest that the Cannizzaro reaction, under the conditions and with the aldehydes studied, proceeds by a single-electron-transfer mechanism at least to some extent.

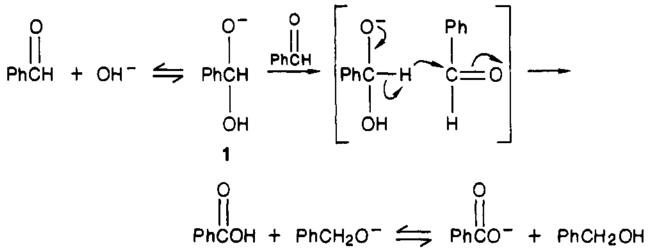
Introduction

The Cannizzaro reaction is considered one of the most fundamental reactions in organic chemistry.[1] It involves the reaction of an aldehyde possessing no α-hydrogens with a strong base (generally NaOH in high concentration) to form an equimolar mixture of the corresponding alcohol and the salt of the corresponding carboxylic acid. Alkoxides also have been used, in which case esters are formed instead of acids. Although aliphatic aldehydes possessing no α-hydrogen have been employed in the Cannizzaro reaction, aromatic aldehydes have been most often utilized. A variety of mechanisms have been proposed for this reaction,[2] but the generally accepted mechanism involves hydride transfer in its rate-determining step (Scheme I). Radical chain mechanisms have been suggested;[3] however, they have been discounted on the basis that neither radical initiators nor inhibitors have a decisive effect on the reaction rate.[4]

Recently, however, Chung has shown that radical intermediates may be involved in the reaction.[5] The reaction of benzaldehyde-α-d_1 in alkaline aqueous dioxane or dioxane with 18-crown-6 produced a substantial amount of benzyl alcohol-α-d_1 in addition to the normal product, benzyl alcohol-α-d_2. The monodeuteriated alcohol was believed to arise from hydrogen abstraction from the solvent by the radical anion of benzaldehyde. An electron-transfer pathway as shown in Scheme II has been proposed.[5,6]

It has been shown that hydroxide and alkoxide anions are capable of transferring an electron to a variety of electron acceptors including alkyl halides,[6,7] ketones,[8] polynuclear hydrocarbons,[7b] and cyano- and nitro-substituted substrates.[6,9] To explore whether electron transfer is occurring in the Cannizzaro reaction, the reaction was thoroughly studied by ESR spectroscopy in an attempt to detect the existence of paramagnetic species. Careful study of the reaction for the presence of byproducts, which would provide evidence for radical intermediates, the use of cyclizable probe substrates or nucleophiles, and the effect of additives on the reaction also were explored.

Scheme I



Scheme II

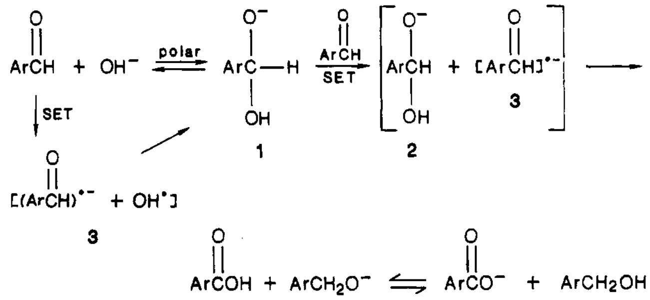
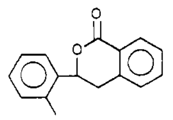


Table I. Reactions of Aromatic Aldehydes with NaOH in THF/HMPA (9:1) at 25 °C

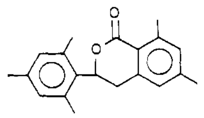
		% yield			
benzaldehyde	ESR signal	alcohol	acid	other	total
p-Cl	resolved	47.5	45.8	0	93.3
p-CF_3	resolved	46.5	43.3	0	89.8
p-CN	resolved	41.0	44.2	0	85.2
p-H	unresolved	29.3	26.2	*a*	84.5
p-NO_2	resolved				
o-CH_3	unresolved	35.2	33.1	*b*	78–83
2,4,6-$(CH_3)_3$	no signal	32.5	28.0	*c*	75–80
$(CH_3)_3CC(O)H$	no signal				

[a] 13.7% recovered aldehyde and 15.3% benzyl benzoate.

[b] 10–15%



[c] 15–20%



Results and Discussion

Evidence for the existence of paramagnetic species during the Cannizzaro reaction was obtained by ESR spectroscopic examination of the reaction solutions. Benzaldehyde and a number of substituted benzaldehydes

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(1) Geissman, T. A. *Org. React.* (*N.Y.*) **1944**, *II*, 94.

(2) Swain, C. G.; Powell, A. L.; Sheppard, W. A.; Morgan, C. R. *J. Am. Chem. Soc.* **1979**, *101*, 3576.

(3) (a) Weiss, J. *J. Chem. Soc., Trans. Faraday Soc.* **1941**, *37*, 782. (b) Haber, F.; Willstätter, R. *Chem. Ber.* **1931**, *64*, 2851. (c) Kharasch, M. S.; Foy, M. *J. Am. Chem. Soc.* **1935**, *57*, 1510.

(4) (a) Alexander, E. R. *J. Am. Chem. Soc.* **1947**, *69*, 289. (b) Geib, K. H. *Z. Phys. Chem. Abt. A.* **1934**, *169*, 41.

(5) Chung, S. K. *J. Chem. Soc., Chem. Commun.* **1982**, 480.

(6) Ashby, E. C.; Coleman, D. T., III; Gamasa, M. P. *Tetrahedron Lett.* **1983**, *24*, 851.

(7) (a) Ashby, E. C.; Bae, D.-H.; Park, W. S.; DePriest, R. N.; Su, W.-Y. *Tetrahedron Lett.* **1984**, *25*, 5107. (b) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *J. Org. Chem.* **1981**, *46*, 2429.

(8) (a) Screttas, C. G.; Cazianis, C. T. *Tetrahedron* **1978**, *34*, 933. (b) Ashby, E. C.; Argyropoulos, J. N. *Tetrahedron Lett.* **1986**, *27*, 465. (c) Screttas, C. G.; Micha-Screttas, M.; Cazianis, C. T. *Tetrahedron Lett.* **1983**, *24*, 3287.

(9) Blyumenfel'd, L. A.; Bryukhovetskaya, L. V.; Fomin, G. V.; Shein, S. M. *Zh. Fiz. Khim* **1970**, *44(4)*, 931 and references therein.

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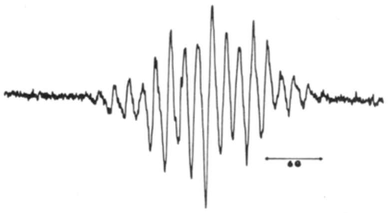

Figure 1. ESR spectrum of the intermediate formed in the reaction of 4-chlorobenzaldehyde with KO-*t*-Bu in THF/HMPA (9/1) at room temperature.

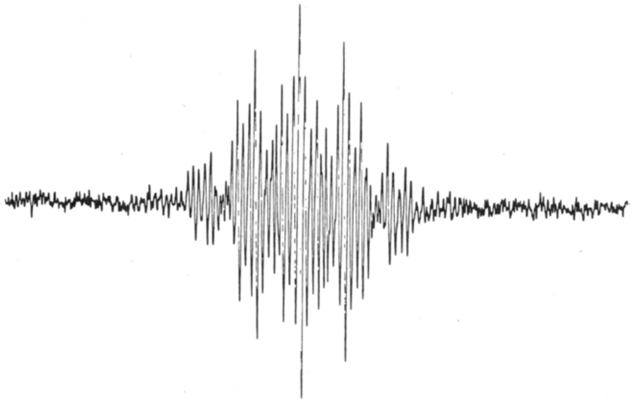

Figure 2. ESR spectrum of the intermediate formed in the reaction of NaOH with 4-(trifluoromethyl)benzaldehyde in THF/HMPA (9/1) at room temperature.

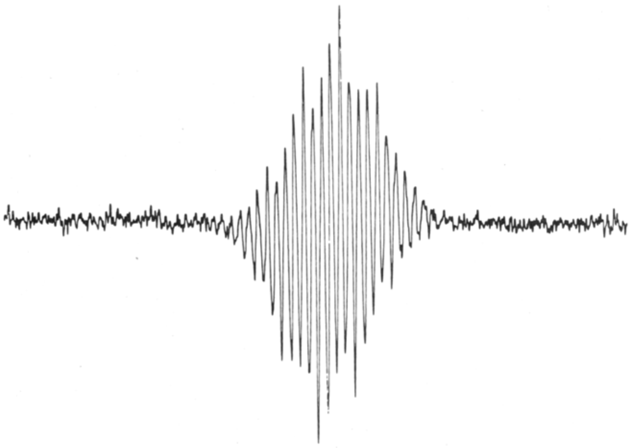

Figure 3. ESR spectrum of the intermediate formed in the reaction of NaOH with 4-cyanobenzaldehyde in THF/HMPA (9/1) at room temperature.

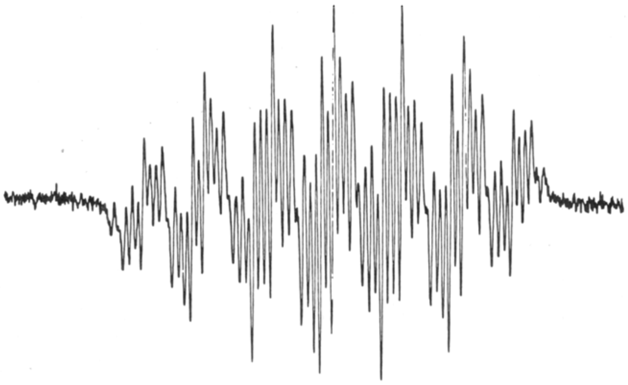

Figure 4. ESR spectrum of the intermediate formed in the reaction of 4-nitrobenzaldehyde with NaOH in THF/HMPA (9/1) at room temperature.

were allowed to react with NaOH in THF/HMPA (9:1 ratio), and the resulting heterogenous mixtures were studied by ESR spectroscopy (Figures 1–3). The results of these studies are tabulated in Table I. In three cases (4-chloro-, 4-(trifluoromethyl)-, and 4-cyanobenzaldehyde) the ESR spectra of the reaction solutions were well resolved, and the spectra obtained were identical with the spectra obtained when sodium metal was allowed to react with each respective aldehyde in the same solvent system. This suggests that the radical obtained in the NaOH reactions with each aldehyde is the radical anion of the respective aldehyde.

In the case of 4-nitrobenzaldehyde, the spectrum (Figure 4) was interpreted and found to be similar to the spectrum of the radical anion of 4-nitrobenzaldehyde. Of the seven aromatic aldehydes studied, only 2,4,6-trimethylbenzaldehyde failed to produce a radical signal by ESR spectroscopy. 2,2-Dimethylpropanal also was allowed to react under the same conditions, but no ESR signal was observed, presumably due to the higher reduction potentials of aliphatic aldehydes compared to aromatic aldehydes.

It was thought possible that the radical species observed in the Cannizzaro reactions studied might be semidione radical anions formed from the coupling of two radical anions of the aldehyde followed by the loss of the α-hydrogens in some manner. Bis(4-chlorophenyl)ethandione was allowed to react with sodium to form the corresponding semidione to explore this possibility, and the ESR spectrum of this species was compared to the ESR spectrum obtained from the reaction of NaOH or sodium with 4-chlorobenzaldehyde. The ESR spectrum of the semidione of bis(4-chlorophenyl)ethanedione was quite different from the spectrum obtained from the reaction of NaOH or sodium with 4-chlorobenzaldehyde, thus evidently semidione formation does not occur to any great extent under these conditions.

Due to the insolubility of NaOH in the solvent system used, the reactions carried out in ESR tubes did not proceed 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, Me_2SO) or the use of KOH in the presence of 18-crown-6 were not successful. Therefore, larger scale stirred reactions of the aromatic aldehydes (studied by ESR) were carried out by using the same concentrations and conditions as those used in the ESR studies. The isolated yields are given in Table I. The Cannizzaro reaction proceeds well to give good yields in the cases of 4-chloro-, 4-cyano-, and 4-(trifluoromethyl)benzaldehydes; benzaldehyde itself is complicated by the formation of the ester from the corresponding alcohol but gives reasonable yields. As reported by others, 4-nitrobenzaldehyde gives poor yields of the normal Cannizzaro products.[10]

The two aldehydes that have methyl groups at the ortho position gave lower yields (55–70%) of their respective alcohols and acids, but a dimeric product also was observed. In the case of 2-methylbenzaldehyde, 3,4-dihydro-3-(2-methylphenyl)-1*H*-2-benzopyran-1-one (**4**) was isolated (eq 1), and in the case of 2,4,6-trimethylbenzaldehyde, 3,4-dihydro-6,8-dimethyl-3-(2,4,6-trimethylphenyl)-1*H*-2-benzopyran-1-one (**5**) was isolated (eq. 2). Both **4** and **5** are believe to arise upon acid workup of the respective hemiacetals, **6** and **7**.

The proposed reaction scheme for the formation of the dimer product is given in Scheme III. The ortho methyl group is acting as an internal hydrogen atom donor, which is not surprising since methyl groups on aromatic com-

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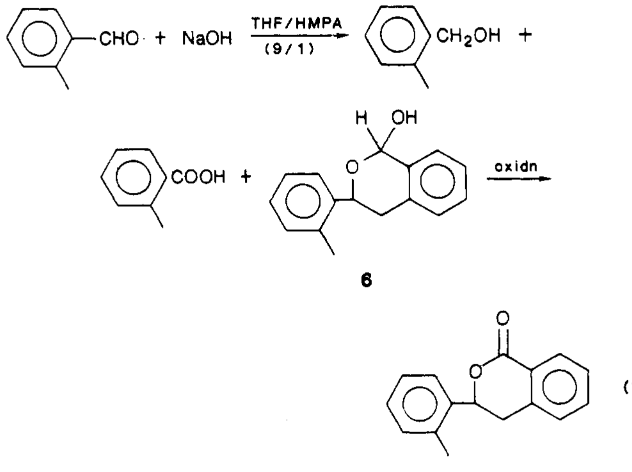
[10] (a) Kislina, I. S.; Vinnik, M. I. *Akad Wauk SSSR, Dokl. Chem.* **1972**, *206*(5), 797. (b) Vinnik, M. I. *Kinet. Kat.* **1974**, *15*(2), 311.



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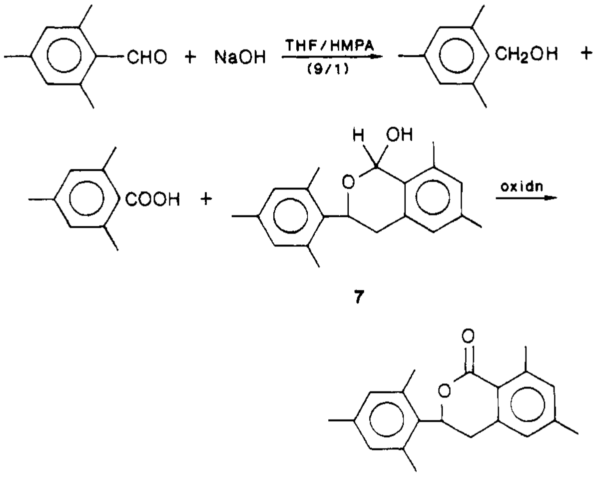
(1)



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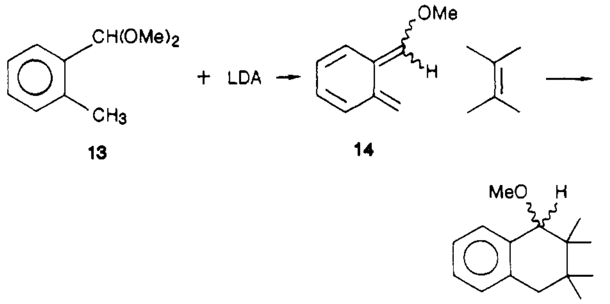
(2)

pounds are known to be reasonably good hydrogen atom donors, and the methyl group would be in close proximity to the oxygen radical (**9**). This oxygen radical could be formed by the transfer of an electron from base–aldehyde adduct **8** to another aldehyde molecule. The substituted methyl radical **11** formed from the hydrogen abstraction would still be in the solvent cage with benzaldehyde radical anion **10**, and these two radicals could couple to give dimeric product **12**. The closing of the six-membered ring could occur immediately by attack of the oxygen anion of **12** to eliminate OH^- as shown or later in the reaction solution or workup. The hemiacetal **6** is air oxidized upon acidic workup to produce the lactone **4**, which is isolated.

Deuterium exchange experiments were performed to determine whether an anionic pathway could be involved in the formation of **6** and **7**. The aldehyde, 2-methylbenzaldehyde, was allowed to react with either NaOH or NaOD in the presence of an excess of D_2O under the reaction conditions similar to those used in the other studies. No change in the deuterium content by GLC/MS was observed over the time period the reaction normally takes place.

Another experiment was conducted in an attempt to trap anion intermediates in the reaction. It has been reported in the literature that when strong bases such as LDA are allowed to react with ortho methyl compounds such as **13** (eq 3) that have good leaving groups, Diels–Alder like reactions can take place between such compounds and alkenes as shown (eq 3).[11]



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(3)

2-Methylbenzaldehyde was allowed to react with NaOH under normal reaction conditions with the exception that a 20-fold excess of norbornene was present to investigate whether a similar mechanism could account for the dimer product 4. Norbornene was chosen because it was the most effective alkene in trapping the intermediate species **14**. There was no significant difference in product yields, nor were any additional products observed in this reaction as compared to the reaction without alkene.

Although neither the deuterium incorporation or alkene trapping experiments are completely unequivocal, they decrease the likelihood that an anionic intermediate is involved. Additionally, it has been shown that **4** and its precursor **6** were formed photochemically from 2-methylbenzaldehyde in the presence and absence of oxygen, respectively.[12] All of the reactions studied were protected from light; therefore the dimers were not due to a photochemical reaction. However, the fact that such a product is formed photochemically suggests that it is possible to form the dimer by a radical process since often there is a similarity between thermal radical processes and photochemical processes.

Resolved ESR signals of the substituted benzaldehyde radical anions, the high yields of Cannizzaro products under similar conditions in many cases, and the isolation of dimer products **4** and **5** in the reactions of benzaldehydes that are methyl substituted at the ortho position all suggest that the Cannizzaro reaction in the cases studied form radical intermediates presumably by a single-electron-transfer mechanism.

Alkoxides. In an attempt at a more direct correlation between the appearance and disappearance of the radical intermediate with the appearance of products, similar reactions involving soluble alkoxides possessing no β-hydrogens and aromatic aldehydes were investigated. The product of the reaction of alkoxides with aromatic aldehydes is a 50/50 mixture of the appropriately substituted benzyl alcohols and benzoate esters as illustrated in eq 4.

$$2ArCHO + {}^-OR \rightarrow ArCH_2O^- + ArCO_2R \xrightarrow{H_2O} ArCH_2OH + ArCO_2R \quad (4)$$

Potassium *tert*-butoxide (KO-*t*-Bu) was the first base chosen for study because its rate of reaction was convenient to study. Initially the study was plagued by inconsistent results with respect to radical formation and maximum concentrations achieved, but once special steps to purify and handle KO-*t*-Bu as outlined in the experimental procedure were taken, the systems became well-behaved and reproducible data resulted.

When KO-*t*-Bu was allowed to react with 4-chloro-, 4-nitro-, 4-cyano-, 2-methyl-, 2,4,6-trimethylbenzaldehyde and benzaldehyde in THF/HMPA (9:1 ratio), significant ESR signals were produced (Figures 1–4). A detailed study of 4-chlorobenzaldehyde with KO-*t*-Bu was made in the

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[11] Moss, R. J.; Rickborn, B. *J. Org. Chem.* **1984**, *49*, 3694.

[12] Findlay, D. M.; Tchir, M. F. *J. Chem. Soc., Chem. Commun.* **1974**, 514.

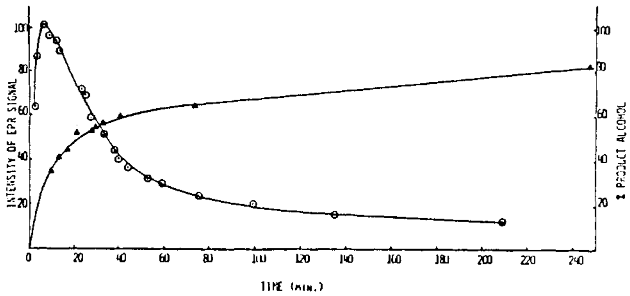
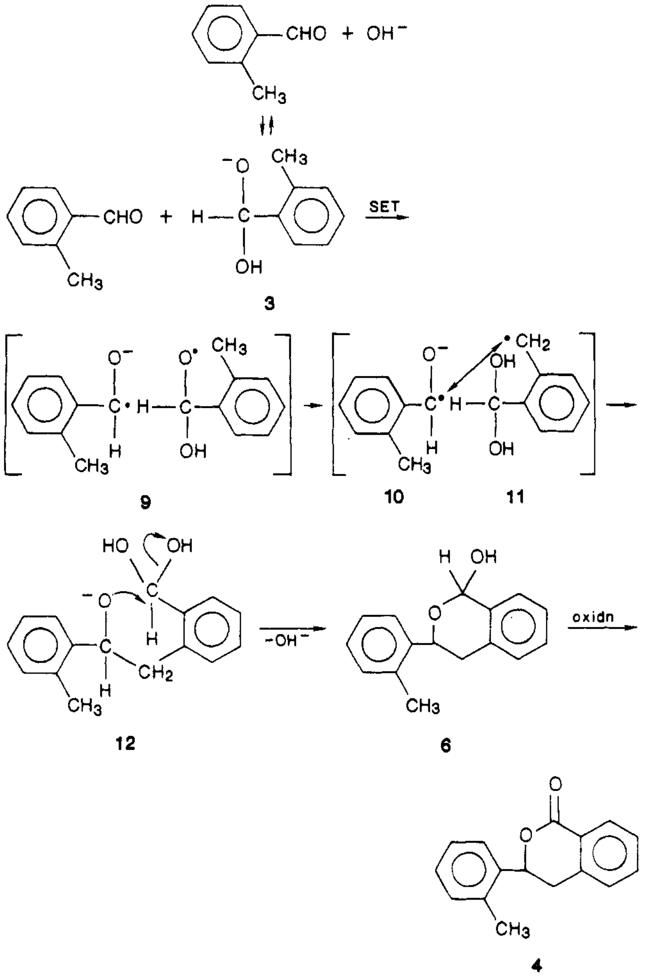


Figure 5. Rate of appearance and disappearance of the paramagnetic intermediate (⊙) and the rate of appearance of product (▲) in the reaction of 4-chlorobenzaldehyde (0.17 M) with KO-*t*-Bu in 2:1 ratio in THF/HMPA (9:1 ratio) at room temperature.

Scheme III. Formation of Dimeric Product



hope of relating the rate constants for radical occurence with product formation; however the kinetics of the reaction proved too complex to resolve. The reaction yields were quite good, and a qualitative relationship between product formation and radical appearance and disappearance was demonstrated as shown in Figure 5.

The reaction was carried out under pseudo-first-order conditions by using a large excess of 4-chlorobenzaldehyde (20 to 1 aldehyde to alkoxide) in an attempt to simplify the reaction kinetics for a quantitative comparison of rate constants for radical disappearance and product formation. The alkoxide of 2-methyl-2-hexanol was used instead of KO-*t*-Bu to allow for ease of analysis of the alcohol from the alkoxide after quenching. Unfortunately, the product alcohol, 4-chlorobenzyl alcohol, is in the base form until hydrolysis as shown in eq 4. This alkoxide continued to react, producing 4-chlorobenzyl 4-chlorobenzoate, and kept the radical concentration constant until all the aldehyde was consumed.

Radical Probe Studies. Several studies were carried out in which either the aldehyde or alkoxide could function as a radical probe by a cyclization process, if radical intermediates were involved. The hindered aldehyde probe, 2,2-dimethyl-5-hexen-1-al, was allowed to react with either NaOH or KO-*t*-Bu in THF/HMPA (9:1 ratio) and the products observed for the presence of cyclized products. No evidence of the formation of any cyclized products was observed. This may be due to the unfavorable reduction potential of the aliphatic aldehyde, or if a radical anion is formed, it may have a short lifetime. It was hoped that if electron transfer took place, the steric hinderance of the aldehyde would impart a longer lifetime for the intermediate. This longer lifetime would provide a greater opportunity for cyclization, thus providing evidence for electron transfer involving an aliphatic aldehyde.

The aromatic aldehyde probe, 2-(2-propenyl)benzaldehyde, was studied next by allowing it to react with NaOH in THF/HMPA (9:1 ratio). It was thought that a more easily reduced aromatic aldehyde might yield cyclized products. Unfortunately, the double bond isomerized in order to be conjugated with the aromatic ring. This isomerization could be a simple base isomerization or a radical process in which hydrogen atom abstraction from the allylic position is followed by isomerization of the double bond. Whatever the mechanism of isomerization, the result is that no cyclic compounds were detected.

In order to investigate whether radical anion formation was due to direct electron transfer between alkoxide or hydroxide and aldehyde, the alkoxide of 2-methyl-5-hexen-2-ol was allowed to react with 4-chlorobenzaldehyde in THF/HMPA (9:1 ratio). This probe had the possibility of cyclizing if an oxygen radical was formed as a result of electron transfer from the alkoxide to the aldehyde. The reaction yielded only the normal Cannizzaro products with no evidence of any cyclized nucleophile. The lack of cyclization in this study was inconclusive since the oxygen-based radical again may not have a sufficient lifetime to cyclize in comparison to competing reactions.

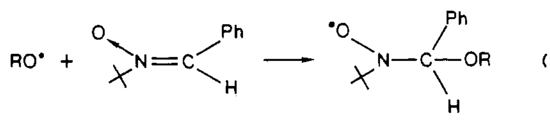
Additives. As noted earlier, a radical chain mechanism had been proposed for the Cannizzaro reaction[3] but later excluded due in part to the lack of effect of inhibitors, such as hydroquinone and diphenylamine, on the reaction rate.[4a] A number of additives were explored for their effect on reaction rate and product formation to test the effect of radical inhibitors on the Cannizzaro reaction under the conditions of this study. The model system for this study involved the reaction of 4-chlorobenzaldehyde with KO-*t*-Bu under the conditions employed for the earlier studies.

Di-*tert*-butylnitroxyl radical, a free radical trap, was added in a concentration of 10% relative to the aldehyde. No inhibiting effect was observed; however, lowered yields of the normal products and inconsistent results were obtained. The nitroxyl radical did react in some manner since by ESR the radical was observed to be stable in the presence of KO-*t*-Bu, but upon addition of 4-chlorobenzaldehyde the concentration of radical rapidly decreased (the singlet of the radical became a triplet). What exactly did occur in the reaction to cause this result is unclear, and definitive conclusions could not be drawn from this study.

Hydrogen atom donors, cyclohexadiene and dicyclohexylphosphine (DCPH), in a fivefold excess with respect to aldehyde were studied for their effect on these reactions. If radical anions are involved in a chain process, hydrogen atom donors would be expected to inhibit the reaction.

They did not inhibit the reaction rate, but, again, product yields of alcohol and ester were reduced. Stability studies showed no evidence that either the aldehyde or alkoxide reacts with either of the hydrogen atom donors employed separately. Therefore, the radical trap is involved somehow in altering the reaction of the aldehyde with the alkoxide.

The spin–trap, *N*-*tert*-butyl-α-phenylnitrone, has been shown to be effective in trapping oxygen-based radicals such as shown in eq 5. The R group could be *t*-Bu or Ar(*t*-BuO)CH, and if oxygen-based radicals are trapped, the stable radical **15** would be formed, which would be observable by ESR spectroscopy. In this connection the spin–trap, *N*-*tert*-butyl-α-phenylnitrone was added in a concentration of 40% relative to KO-*t*-Bu, and the Cannizzaro reaction with 4-chlorobenzaldehyde was studied by ESR spectroscopy. A weak ESR spectrum was obtained that had a similar appearance to the literature spectra of oxygen radicals trapped by this nitrone. However, the radical species were stable for only a few minutes and then disappeared. No other radical intermediates including the radical anion of the aldehyde were observed. This reaction, on a large scale, yielded the normal products in good yields. The disappearance of the nitrone trapped radical species is not surprising since it is a nitroxyl radical similar to di-*tert*-butyl nitroxyl radical which was shown earlier to rapidly react during the reaction to form nonradical products. What is surprising is the lack of an ESR spectrum for the aldehyde radical anion. It is possible that the radical anion of the aldehyde was trapped by the nitrone; however, if so, it would seem probable that a significant decrease in normal Cannizzaro products would have been observed.



(5)

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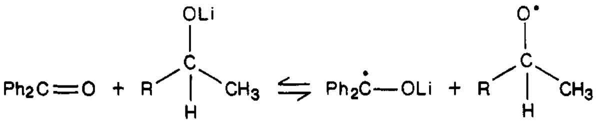
It was found in the case of the reduction of benzophenone by lithium isopropoxide (eq 6–8) that a key step in the reaction involves the abstraction of a β-hydrogen from the alkoxide by the radical anion of benzophenone (eq 7).[8b] Lithium benzhydrolate and the radical anion of acetone are formed and the source of the radical anion of benzophenone is due to electron transfer between isopropoxide and benzophenone.



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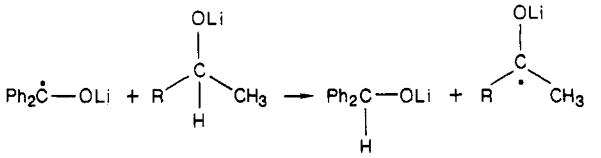

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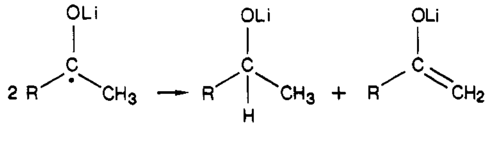
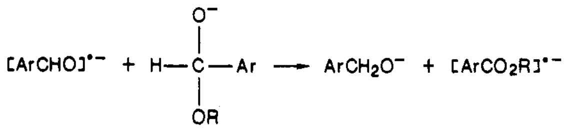


(8)

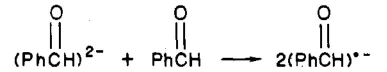
A similar mechanism could be proposed for the Cannizzaro reaction as illustrated by eq 9 and 10. The mechanism as written is a chain process. Although hydrogen atom donors did not decrease the rate of reaction as would be expected if a chain process was involved, two additional experiments were investigated to provide more evidence for or against this mechanism. A solution of benzaldehyde in THF containing 1% to 2% benzaldehyde radical anion relative to the total concentration of benzaldehyde was produced by reaction with sodium metal. This solution, which was stable for days as determined by ESR spectroscopy and product analysis, was allowed to react with KO-*t*-Bu and studied by ESR spectroscopy and product analysis over a period of time. The radical concentration initially increased and then decreased over a period of time; however, product analysis showed no appreciable acceleration in reaction rate, and product yields were reduced. The presence of radical anion at the start of the reaction evidently does not catalyze the reaction and, in fact, leads to lower yields. The same is true when NaOH was used instead of KO-*t*-Bu.



$$[\mathrm{ArCHO}]^{\bullet-} + \mathrm{H}-\underset{\mathrm{OR}}{\overset{\mathrm{O^-}}{\mathrm{C}}}-\mathrm{Ar} \longrightarrow \mathrm{ArCH_2O^-} + [\mathrm{ArCO_2R}]^{\bullet-} \quad (9)$$

$$[\mathrm{ArCO_2R}]^{\bullet-} + \mathrm{ArCHO} \rightleftharpoons \mathrm{ArCO_2R} + [\mathrm{ArCHO}]^{\bullet-} \quad (10)$$

In order to explore whether the dianion of the aldehyde is formed in the reaction solution and thus the dianion is transferring an electron to the starting aldehyde to form the radical anions (eq 11) observed by ESR spectroscopy, the product alcohol 4-chlorobenzyl alcohol was added to excess KO-*t*-Bu/DO-*t*-Bu in THF and NaOD/D_2O in THF/HMPA (9:1 ratio). Any evidence of deuterium incorporation was determined by GLC/MS. A slight increase in deuterium incorporation was observed after 1 month; however, this value is within experimental error of the determination (±1%). No evidence of deuterium incorporation was observed after 1 week.



$$(\mathrm{Ph\overset{\overset{\textstyle O}{\|}}{C}H})^{2-} + \mathrm{Ph\overset{\overset{\textstyle O}{\|}}{C}H} \longrightarrow 2(\mathrm{Ph\overset{\overset{\textstyle O}{\|}}{C}H})^{\bullet-} \quad (11)$$

The lack of effect of hydrogen donors on the rate, the negative effect of added radical anion, and the unlikelihood of significant dianion formation all suggest a reaction mechanism similar to the one observed for the reaction of benzophenone with lithium alkoxides (eq 6–8) is unlikely. Although very little in the way of additional evidence to support SET as the reaction pathway was obtained, none of the results above were inconsistent with the reaction pathway outlined in Scheme II. The scheme suggests that the base–aldehyde adduct **1** is in equilibrium with the free aldehyde. This adduct is the electron donor to benzaldehyde if electron transfer is the rate-determining step; however, direct electron transfer between base and aldehyde is also possible as a souce of the radical anion observed. If **1** is the electron donor, then the radical anion of the aldehyde and an oxygen-based radical (**2**) are formed in the solvent cage. It is interesting that Weiss in 1941 proposed that such an electron transfer does take place, but that a radical chain process was initiated as part of the mechanism.[3a] The radical anion then abstracts the β-hydrogen of the oxygen radical (**2**) to form the alkoxide and the acid.

It has been debated whether oxygen anions are capable of transferring an electron to substrates such as aldehydes in the time frame of the reactions involved. Using Marcus theory and literature values, Eberson concluded that electron transfer was not possible in the case of the Cannizzaro reaction and a number of other reactions involving oxygen-based nucleophiles.[13] Putting aside the fact that

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[13] Eberson, L. A. *Acta Chem. Scand., Ser. B* 1984, *6*, 439.

no attempt was made to include solvent effects and that broad assumptions were made on the similarity of nucleophiles, there would seem to be some real doubt as to the ability of oxygen nucleophiles to undergo electron transfer in reasonably fast reactions. Blyumenfel'd offers a possible solution to this dichotomy.[9] In a number of reactions, he and his co-workers have observed very strong evidence of $HO^•$ being produced by reactions of hydroxide ion with various acceptors. He suggests that although electron transfer from OH^- to acceptor was thermodynamically unlikely as a singular process, if the electron transfer was followed by an instantaneous second step in the solvent cage between $HO^•$ and another molecule, the reaction could be overall thermodynamically possible. In the system studied by Blyumenfel'd, the instantaneous reaction in the solvent cage could be between $HO^•$ and the radical anion of the acceptor or between either $HO^•$ or the radical anion of the acceptor and a thrid molecule of OH^-, acceptor or solvent. The nature of the instantaneous second step would of necessity have to influence the transition state of the first step. In the Cannizzaro reaction, the hydrogen atom abstraction from **2** by the radical anion could be the instantaneous second step that influences the transition state of the first step (**1** + aldehyde). The observed radical anion could be due to the oxygen radical **2** of the base–aldehyde adduct abstracting hydrogen from solvent or reacting in some other manner allowing the radical anion to escape from the solvent cage, be detected by ESR spectroscopy, and eventually react in some manner (Scheme II).

Experimental Section

Materials. Diethyl ether was distilled from $LiAlH_4$ and THF, benzene, and hexane were distilled from $NaAlH_4$. HMPA, from Aldrich, was distilled over sodium under reduced pressure.

N-*tert*-Butyl-α-phenylnitrone, 4-chlorobenzoyl chloride, 3-bromo-1-propene, *p*-toluenesulfonic acid, 2-methyl-2-propanol-d_1, sodium deuteroxide (40 wt % in D_2O), and 18-crown-6 from Aldrich were used as received. The compounds 4-(trifluoromethyl)-, 2-bromo-, 4-cyano-, 2-methyl-, and 2,4,6-trimethylbenzaldehyde, 2,2-dimethylpropanal, benzyl alcohol, *tert*-butyl alcohol, 2-methyl-2-hexanol, obtained from Aldrich, and 2-methyl-5-hexen-2-ol, from Wiley Organics, were distilled from CaH_2 under nitrogen or reduced pressure and stored under nitrogen. After distillation, 4-chlorobenzaldehyde from Aldrich was sublimed and stored under N_2 in a glovebox. After recrystalization, 4-nitrobenzaldehyde from Aldrich was doubly sublimed to give pure white material. Potassium *tert*-butoxide from Aldrich was allowed to reflux with distilled *tert*-butyl alcohol followed by removal of the alcohol under reduced pressure. The *tert*-butoxide was then triply sublimed and stored under N_2 in a glovebox. All transfers of the alkoxide reagent were carried out under the oxygen free atmosphere of a glovebox. Sodium hydroxide from Fischer was finely ground under nitrogen and allowed to reflux with dry, oxygen free benzene to azeotrope any water present. The benzene was then removed, and the NaOH was ground again to a fine powder and stored under an oxygen-free nitrogen atmosphere.

Authentic samples of *tert*-butyl 4-chlorobenzoate and 4-chlorobenzyl 4-chlorobenzoate were obtained by reaction of the respective alcohols with 4-chlorobenzoyl chloride. All products exhibited consistent NMR and mass spectra. An authentic sample of benzyl benzoate was obtained by the reaction of benzyl alcohol with benzoyl chloride and exhibited an NMR and IR spectrum identical with the previously reported spectra.[14] By a method reported earlier,[15] 5,5-dimethyl-1-hexen-6-ol was oxidized by pyridinium chlorochromate to give, after distillation, analytically pure 2,2-dimethyl-5-hexenal which exhibited NMR, IR, and mass spectra identical with those previously reported.[16]

General Procedures. All glassware and syringes were oven-dried at 150 °C, and the glassware was additionally flame-dried under high vacuum and then flushed with nitrogen. Syringes were flushed with nitrogen and kept under positive nitrogen pressure while cooling until used. Transfer of reagents was performed by using calibrated syringes equipped with stainless steel needles. Reactions were carried out in round-bottom flasks equipped with T-bore stopcocks attached to male 24/40 standard taper joints and were stirred with Teflon-coated magnetic stirring bars. Storage and transfer of CuI and $CuBr{\cdot}SMe_2$ took place in a glovebox equipped with a recirculating system consisting of manganese oxide columns to remove oxygen and liquid nitrogen traps to remove solvent vapors.

Proton NMR spectra were recorded on either a Varian T-60A or Bruker WM-300 instrument with chemical shifts reported relative to tetramethylsilane (Me_4Si) or nitromethane. Mass spectral analyses were performed on a Varian MAT-112S spectrometer. IR spectra were recorded on a Perkin-Elmer 299 infrared spectrophotometer. Elemental compositions were determined either by microanalysis (Atlantic Microlabs, Inc. of Atlanta, GA) or by high resolution mass spectrometry.

Quantitative NMR studies were carried out by using nitromethane as the internal standard. Quantitative GLC analyses were determined by utilizing internal standards and comparing peak areas corrected for response factors. For quantitative analysis, a 30-m DB-1 fused silica capillary column was heated 20°/min from 80 °C to 280 °C and kept at that temperature for 10 min. Retention times (relative to the internal standard) were as follows: for the reactions of 4-chlorobenzaldehyde, decane (1.00), 4-chlorobenzaldehyde (1.22), 4-chlorobenzyl alcohol (1.47), *tert*-butyl 4-chlorobenzoate (1.88), 4-chlorobenzyl 4-chlorobenzoate (3.28); and for the benzaldehyde reactions, benzaldehyde (0.91), decane (1.00), benzyl alcohol (1.03), *tert*-butyl benzoate (1.50), benzyl benzoate (2.56).

Preparations. 3,4-Dihydro-3-(2-methylphenyl)-1*H*-2-benzopyran-1-one (1). To 0.11 g of NaOH was added 1.0 mL of HMPA, followed by 9.0 mL of 0.40 M 2-methylbenzaldehyde in THF. The reaction was allowed to stir for 2 days in the dark at room temperature. The reaction was diluted with water and extracted immediately with ether three times. The water layer was acidified with dilute HCl and extracted three times with ether. The ether extractions were combined, washed three times with water, and dried over $MgSO_4$, and the ether was removed. Titration of the residue to a phenolphthalein endpoint yielded an insoluble material which was filtered from the aqueous solution and after drying gave 0.080 g (19% base on aldehyde) of >90% pure **1** by NMR. By repeated careful precipitation from hexane, an analytically pure sample was obtained which exhibited the following: mp 117.5–118 °C (lit.[12] mp 100–102 °C); ^1H NMR ($CDCl_3$) δ 2.20 (s, 3 H), 2.83–3.20 (m, 2 H), 5.50 (dd, 1 H), 6.83–8.00 (m, 8 H); IR ($CHCl_3$) 3020, 2960, 2930, 1725, 1610, 1460, 1280, 1220, 1120, 910 cm^{-1}; mass spectrum, *m/e* (relative intensity) 238 (M^+, 14). Anal. Calcd for $C_{16}H_{14}O_2$: C, 80.65; H, 5.94. Found: C, 80.54; H, 5.93.

3,4-Dihydro-6,8-dimethyl-3-(2,4,6-trimethylphenyl)-1*H*-2-benzopyran-1-one (2). In 0.11 g of NaOH was added 1.0 mL HMPA, followed by 9.0 mL of 0.40 M 2,4,6-trimethylbenzaldehyde in THF. The reaction procedure was the same as for **1** and 0.10 g (19%) of oxide product was obtained which was carefully precipitated from hexane to give an analytically pure sample which exhibited the following: mp 107–109 °C; ^1H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.27 (s, 3 H), 2.32 (s, 6 H), 2.62 (s, 3 H), 2.68 (dd, 1 H), 3.49 (dd, 1 H), 5.74 (dd, 1 H), 6.86–7.24 (m, 4 H); IR ($CHCl_3$) δ 3010, 2960, 3930, 1715, 1610, 1430, 1255, 1205, 1075, 905 cm^{-1}; mass spectrum, *m/e* (relative intensity) 294 (M^+, 11). Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.56; H, 7.62.

2-(2-Propenyl)benzaldehyde. In a solution of 25 g of distilled 2-bromobenzaldehyde, 20 mL of ethylene glycol, and 50 mL of benzene was dissolved 100 mg of *p*-toluenesulfonic acid. After the solution was allowed to reflux for 8 h in a Dean-Stark apparatus until no more water was collected, the reaction mixture was cooled to room temperature, diluted with ether, and washed

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[14] (a) Pouchert, C. J. *Aldrich Library of IR Spectra*, 2nd, ed.; Aldrich Chem. Co.; Milwaukee, WI, 1975. (b) Pouchert, C. J. *Aldrich Library of NMR Spectra*, 2nd ed.; Aldrich Chem. Co.: Milwaukee, WI, 1983.

[15] Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1985**, *50*, 3274.

[16] House, H. O.; Liang, W. C.; Weeks, P. D. *J. Org. Chem.* **1974**, *39*, 3102.

with 10% $NaHCO_3$ solution, water, and saturated NaCl. After drying, removing the solvent, and distilling under reduced pressure (89 °C at 0.1 mmHg), a near quantitative yield a 2-bromobenzaldehyde ethylene glycol acetal was obtained which gave a NMR spectrum identical with that previously reported.[17] To an ether solution of 10 g of the acetal cooled to −80 °C was added dropwise an equivalent amount of *tert*-butyllithium in hexane. After stirring for 2 h, 10 mL of 3-bromopropene was added. The reaction was allowed to warm slowly to room temperature and stirred overnight before being quenched with saturated NH_4Cl solution. After standard workup and distillation (95 °C at 0.2 mmHg), 7 g (84% yield) of pure 2-(2-propenyl)benzaldehyde ethylene glycol acetal was obtained. The product exhibited an NMR spectrum identical with that previously reported.[17] Treatment of an acetone solution of this acetal with a small amount of concentrated HCl followed by dilution with water yielded, after distillation (89 °C at 2 mmHg), 4.6 g (85% yield) of the title aldehyde which exhibited NMR, IR, and mass spectra in agreement with those previously reported.[17]

General Procedure for Product Studies. Reactions of NaOH with Aldehydes. All reactions were carried out under N_2 at room temperature and protected from light. The aldehyde concentrations were equal to 0.36 M in THF/HMPA (9 to 1) and the aldehyde to NaOH ratio was 2.0 to 1.5. Reactions were stirred 24 h except for benzaldehyde which was stirred 36 h, and both 2-methyl- and 2,4,6-trimethylbenzaldehyde were stirred for 48 h. Reactions were diluted with water and extracted three times with ether. These ether extracts were combined, washed three times with H_2O, and dried using $MgSO_4$. The solvent was removed to yield the respective alcohol product (in some cases the substituted benzyl esters). Yields were determined by NMR spectroscopy after the products were shown to be identical with the known NMR and IR spectra.[14] The aqueous layer from the ether extractions was acidified with dilute HCl and extracted three times with ether, and the ether extracts were combined. The extracts were then washed three times with water and dried using $MgSO_4$, and the solvent was removed to yield the acid. Yields were determined by base titration, and IR and NMR spectra were identical with the published spectra.[14] Compounds **1** and **2** were isolated as previously detailed in the preparation section.

Reactions of Alkoxides with Aldehydes. Equal portions of 0.22 M potassium *tert*-butoxide (KO-*t*-Bu) in THF and 0.44 M of the respective aldehyde in THF were mixed with sufficient HMPA to give a solution 0.1 M in KO-*t*-Bu, 0.2 M in aldehyde, and a 9 to 1 ratio of THF to HMPA. Reactions carried out without HMPA were at the same concentrations of alkoxide and aldehyde. Reactions were quenched with saturated NaCl solution, extracted with ether, and dried using $MgSO_4$. The yields were determined by quantitative GLC analysis as detailed in the general procedures.

The lithium alkoxides of 2-methyl-5-hexen-2-ol and 2-methyl-2-hexanol were prepared by the addition of an equimolar ammount of MeLi in Et_2O to a solution of the alcohol in THF at 0 °C. After stirring and allowing to warm to room temperature, HMPA and the aldehyde in THF were added to give a solution 0.2 M in aldehyde, 0.1 M in alkoxide, and with a THF to HMPA ratio of 9 to 1.

Deuterium Incorporation Studies. To a solution of 0.143 g of 4-chlorobenzyl alcohol in 9.0 mL of THF and 1.0 mL of HMPA was added 0.25 mL of 30 wt % NaOD in D_2O. To a solution of 5.0 mL of THF, 1.0 mL of HMPA, 0.24 g of KO-*t*-Bu, and 0.96 mL of 2-methyl-2-propanol-d_1 was added 4.0 mL of 0.253 M 4-chlorobenzyl alcohol in THF. To a solution of 0.12 mL (1.04 mmol) of 2-methylbenzaldehyde in 9.0 mL of THF and 1.0 mL of HMPA was added 0.15 mL of 30 wt % NaOD in D_2O. Samples were withdrawn by syringe after 1 and 7 days for all the reactions and also after 1 month for the last two reactions. All the samples were analyzed for deuterium incorporation by GLC/MS.

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Registry No. *p*-Chlorobenzaldehyde, 104-88-1; *p*-(trifluoromethyl)benzaldehyde, 455-19-6; *p*-cyanobenzaldehyde, 105-07-7; benzaldehyde, 100-52-7; *p*-nitrobenzaldehyde, 555-16-8; *o*-methylbenzaldehyde, 529-20-4; 2,4,6-trimethylbenzaldehyde, 487-68-3; 2,2-dimethylpropanal, 630-19-3; potassium 4-chloro-α-*tert*-butoxybenzenemethanol, 109432-63-5; potassium 4-(trifluoromethyl)-α-*tert*-butoxybenzenemethanol, 109432-64-6; potassium 4-cyano-α-*tert*-butoxybenzenemethanol, 109432-65-7; potassium 4-nitro-α-*tert*-butoxybenzenemethanol, 109432-66-8; 3-(2-methylphenyl)dihydroisocoumarin, 53830-88-9; 2,2-dimethyl-5-hexen-1-al, 52278-99-6; 2-(2-propenyl)benzaldehyde, 62708-42-3; 2-methylhex-5-en-2-ol, 16744-89-1.

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(17) Kampmeier, J. A.; Harris, S. H.; Mergelsberg I. *J. Org. Chem.* 1984, *49*, 621.