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EVIDENCE SUPPORTING A SINGLE ELECTRON TRANSFER PATHWAY IN THE REDUCTION OF AROMATIC KETONES BY METAL ALKOXIDES. LITHIUM ISOPROPOXIDE, AN EXCELLENT REDUCING AGENT FOR AROMATIC KETONES.

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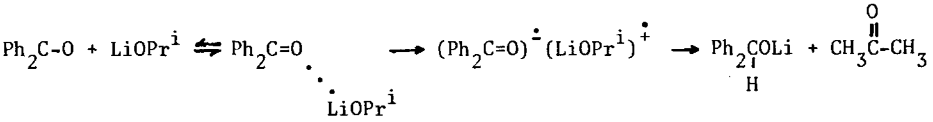
SUMMARY: Reactions of various metal alkoxides with aromatic ketones have been shown to produce radical intermediates. Lithium isopropoxide has been found to be an excellent reducing agent for aromatic ketones and reduces benzophenone at a faster rate than does aluminum isopropoxide.

The degree of polar and radical character exhibited in reactions of typical nucleophilic reagents with organic substrates has been the subject of recent interest.[1,2] The mechanisms of these reactions have been proposed mainly on the basis of stereochemical observations, kinetics, product formation studies and radical anion trapping. Recently, we proposed the possible involvement of a single electron transfer (SET) pathway in reactions of lithium amides and lithium (and potassium) alkoxides with organic substrates such as alkyl halides and polynuclear hydrocarbons.[3] The basis of the proposed SET mechanism was the appearance of radical intermediates (observed by EPR spectroscopy) and product formation studies using cyclizable probes. More recently, we have shown that the reduction of $Ph_2C=O$ with $LiNPr^i{}_2$ proceeds via a radical intermediate.[4] Russell[5] has generated fluorenone ketyl by reacting alkoxides with flourenone however, he did not observe reduction product. On the other hand, Screttas[6] has observed reduction product in the case of benzophenone and alkoxide, but did not directly observe the ketyl precursor. In view of these results, we decided to study the mechanism of reduction of ketones with metal alkoxides, not only lithium and potassium alkoxides, but also $Al(OPr^i)_3$ involving the classic Meerwein-Ponndorf-Verley reduction[7] which has been well recognized to proceed via a polar mechanism.

We have observed the formation of radical intermediates in the reactions of aromatic ketones [benzophenone and mesitylphenylketone (MPK)] not only with metal alkoxides such as $LiOPr^i$, $LiOBu^n$, $LiOBu^t$, $LiOCH_2{}^tBu$ and KO-t-Bu, but also with $Al(OPr^i)_3$, (eq. 1). The reduction product (Ph_2CHOM), of course, is only formed in the reaction of alkoxide reagents containing α-hydrogen atoms.

When a solution of freshly prepared lithium alkoxide, LiOR(I) (where R = i-Pr, n-Bu, t-Bu and CH_2-t-Bu) and KO-t-Bu(II) was mixed with $Ph_2C=O$ in THF under nitrogen at room temperature, a blue colored solution developed slowly in every case. These solutions were found to be paramagnetic (showed complex EPR spectra), indicating the formation of an intermediate radical species. Interestingly, the solutions of different alkoxide reagents provided a different EPR spectrum (see Figures 1a, 1b and 2), thus suggesting that the radical intermediate is not the free ketyl. This point was further confirmed by comparing the spectra of the various reactions with those of the free ketyls prepared independently. The amounts of the radical intermediates were found to increase slowly with time and the rate of increase was found to be dependent on the nature of the alkoxy group of the reagent. The rate of radical formation followed the trend: i-Pr > CH_2-t-Bu > n-Bu > t-Bu in the lithium alkoxide series. Thus while $LiOPr^i$ generated a reasonable concentration of radical intermediate ($\sim$5%) within ten hours only a trace amount of radical was detected in reactions involving $LiOBu^t$. Interestingly, $KOBu^t$ was observed to react with $Ph_2C{=}O$ to produce a radical intermediate at a much faster rate than $LiOBu^t$. No reduction product was formed in those cases where no α-hydrogen is present in the alkoxides although electron transfer is observed.

The importance of the steric requirement of the reagent (alkoxy groups) as well as the substrate (aromatic ketone) was also observed in the product formation studies. In the reactions of a sterically bulky ketone (MPK) with sterically bulky alkoxide reagents (such as $LiOCH_2OBu^t$) either none or only a trace amount of reduction product was formed even after warming to 50°C. This observation suggests that the hydrogen transfer step of the reaction is affected significantly by the steric demands of the intermediates. The total observations reported above can be best explained by the mechanism represented by equation 1.



$$Ph_2C\text{-}O + LiOPr^i \rightleftarrows \underset{\cdot\cdot\, LiOPr^i}{Ph_2C{=}O} \longrightarrow (Ph_2C{=}O)^{\dot{-}}(LiOPr^i)^{\dot{+}} \longrightarrow Ph_2\underset{\underset{H}{|}}{C}OLi + CH_3\overset{\overset{O}{\|}}{C}\text{-}CH_3 \qquad (1)$$

In the reaction of $LiOPr^i$ and $Ph_2C{=}O$ in 2:1 molar ratio in THF at room temperature, the highest concentration of radical intermediate was 14% after one day. While the radical concentration was increasing with time, the product of the reaction continuously formed and after one day about 45% reduction product was isolated. After the radical concentration reached a maximum, the EPR signal slowly decreased and after 3 days disappeared completely. At this time, no starting benzophenone was detectable in the reaction mixture and the product was formed in essentially quantitative yield.

In view of the above results involving lithium alkoxides, we decided to carry out the classic Meerwein-Ponndorf-Verley reduction involving $Al(OPr^i)_3$ as the reducing agent. When freshly distilled $Al(OPr^i)_3$ (trimer or tetramer) and

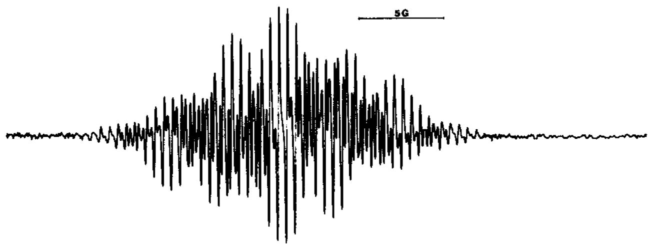


Figure 1A: EPR spectrum of the intermediate formed in the reaction of benzophenone with lithium isopropoxide in THF at room temperature

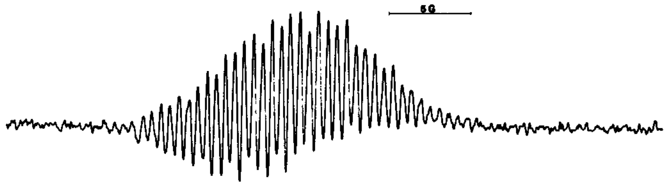


Figure 1B: EPR spectrum of the intermediate formed in the reaction of benzophenone with lithium neopentoxide in THF at room temperature.

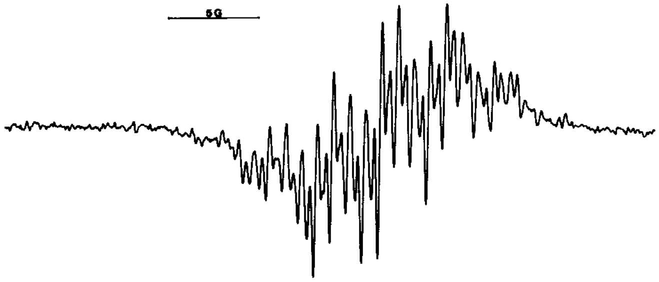


Figure 2: EPR spectrum of the intermediate formed in the reaction of benzophenone with potassium t-butoxide in THF at room temperature.

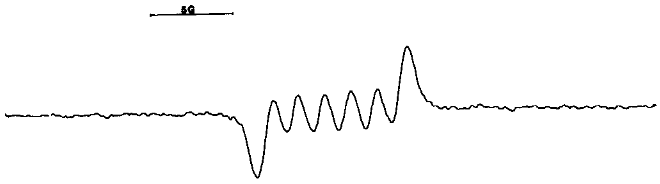


Figure 3: EPR spectrum of the intermediate formed in the reaction of benzophenone with $Al(OPr^{i})_3$ in THF at room temperature.

$Ph_2C=O$ or MPK were mixed in THF, an EPR signal (Fig. 3) was observed immediately. The intensity of the signals indicated the concentration of radicals to be $\sim$1%. The EPR signal resembled that of the expected radical cation. These signals decayed slowly and completely disappeared within two hours. When the reaction mixture was heated to 50°C for 7 hours, a new signal developed (trace amount) which resembled that of the radical anion (e.g., in the case of MPK, a quartet with 4-5 G spacing, appeared which can be explained as the splitting due to ortho- and para protons of the phenyl ring). In the case of $Ph_2C=O$, reduction product was obtained whereas MPK gave only a trace amount of reduction product after 7 days. It is quite possible that if the radical mechanism is operative here, the rates of the first step (electron transfer) and the second step (coupling of radicals) are comparable so that little or no radical concentration can develop. We did not observe the formation of the trityl radical in the reaction of $Al(OPr^i)_3$ with Ph_3CBr whereas $LiOPr^i$ did react to form the trityl radical ($Ph_3C\cdot$)[3]. Similarly, no radical could be detected in the reaction of $Al(OPr^i)_3$ with polynuclear hydrocarbons.

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