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Evidence For A Single Electron Transfer Mechanism In The Reduction of Benzophenone with Lithium Alkoxides

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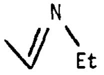
Summary: The reduction of benzophenone by lithium alkoxides gives rise to benzophenone ketyl which disappears in a first-order fashion and whose first-order rate constant is approximately equal to the pseudo-first-order rate constant for the formation of the product, benzhydrol.

The Meerwein-Ponndorf-Verley reduction of ketones is generally believed to proceed via a polar mechanism[1] involving a cyclic transition state.[2] Nevertheless, a single electron transfer (SET) pathway has been proposed for the reduction of ketones by metal alkoxides.[3-5] Recently however, the origin of benzophenone ketyl in the reactions of benzophenone with lithium dialkylamides has been questioned by Newcomb.[6] He proposed an alternate scheme involving fast concerted β-hydride reduction of benzophenone to give lithium benzhydrolate (eq. 1), the formation of dilithium benzophenone dianion from the deprotonation of lithium benzhydrolate by the lithium dialkylamide (eq. 2), and fast electron transfer from benzophenone dianion to benzophenone to give two molecules of ketyl (eq. 3). In support of the pathway depicted in equations 1-3, Newcomb showed that 10% benzophenone dianion was formed when lithium benzhydrolate was treated with a five fold excess of LDA for 22h at 22 °C. Lithium diisopropylamide was also found to rapidly reduce benzophenone to give approximately 55% lithium benzhydrolate (after the first few minutes with no significiant change in the yield of benzhydrol during the next 24 h). Conversely, the ketyl formed slowly and reached a maximum after 30 h, hence indicating that it is not the intermediate in the formation of the reduction product. Based on these results, Newcomb suggested that a similar pathway might be in effect for the reduction of benzophenone by alkoxides. With this

$$Ph_2CO \quad + \quad LiNEt_2 \longrightarrow Ph_2CHOLi \quad + \tag{1}$$



$$Ph_2CHOLi \quad + \quad LiNEt_2 \rightleftharpoons (Ph_2C\text{-}O)^{2-}\ 2Li^+ \quad + HNEt_2 \tag{2}$$

$$(Ph_2C\text{-}O)^{2-}\ 2Li^+ \quad + \quad Ph_2CO \rightleftharpoons 2(Ph_2C\text{-}O)^-\ Li^+ \tag{3}$$

background, benzophenone was allowed to react with lithium alkoxides in order to determine whether the Meerwein-Ponndorf-Verley reduction of benzophenone proceeds via a radical intermediate or by a polar process. Furthermore, the questions raised by Newcomb's study were also addressed.

When a solution of freshly prepared lithium alkoxide (LiOR where R = n-butyl, neopentyl, isopropyl, Ph_2CH, and tert-butyl) was allowed to react with benzophenone in THF at 22°C, a blue colored solution developed in all cases. The colored solutions gave rise to well-resolved EPR spectra as well as visible spectra (λ_{max} = 632 nm), all of which were identical to the EPR and visible spectra recorded for an authentic sample of lithium benzophenone ketyl (prepared by the reaction of lithium metal with benzophenone in THF).

In the reaction of lithium isopropoxide and benzophenone in a 20:1 molar ratio, respectively, in THF at 22°C, a blue colored solution developed in a few hours. The paramagnetic intermediate reached a maximum at about 8h and then decreased in an apparent first-order fashion with $k = 2.0 \times 10^{-5}$ sec^{-1}. The product of the reaction, benzhydrol, was formed quantitatively after two days in a pseudo-first-order fashion with $k = 2.5 \times 10^{-5}$ sec^{-1}. The rate of the above reaction was not affected by light or a catalytic amount of p-dinitrobenzene indicating a non-radical chain process; however, when the ratio of alkoxide:ketone:p-dinitrobenzene was 5:1:1, the rate of reaction was significantly decreased indicating the presence of the ketyl as an intermediate.

The reaction of lithium n-butoxide with benzophenone in a 20:1 molar ratio, respectively, in THF at 24°C also gave a blue colored solution in a few hours. The paramagnetic intermediate reached a maximum at 25h and then decreased in an apparent first-order fashion with $k = 5.0 \times 10^{-6}$ sec^{-1}. Benzhydrol also formed in a pseudo-first-order fashion with $k = 6.8 \times 10^{-6}$ sec^{-1}. The above kinetic analyses indicate that in each reaction lithium benzophenone ketyl is formed which decays with an apparent first-order rate constant which is approximately equal to the pseudo-first-order rate constant for the formation of product.

In order to further verify that the intermediate in the formation of reaction product (benzhydrol) is indeed benzophenone ketyl, benzophenone was allowed to react with lithium metal in THF and the resulting ketyl was transferred to a solution of lithium isopropoxide in THF (molar ratio of alkoxide to ketyl was 20 to 1, respectively). Interestingly, the concentration of ketyl decreased 1000-fold over a 60h period. The decay of the ketyl was monitored by EPR spectroscopy and found to be first order with an apparent first-order rate constant $k = 3.4 \times 10^{-5}$ sec^{-1}. When the ketyl was completely consumed, the reaction was quenched to give benzhydrol quantitatively. Hence the lithium ketyl of benzophenone in the presence of lithium isopropoxide was shown to behave in a similar manner to the paramagnetic intermediate formed in the reaction of benzophenone with lithium isopropoxide.

The possibility that benzophenone ketyl is originating from the disproportionation of benzophenone with its dianion (eq. 3) was also investigated. Lithium isopropoxide and benzhydrol were allowed to react in a 20:1 molar ratio, respectively, in THF at 22°C and the characteristic deep red color of the benzophenone dianion was not observed. Furthermore, an aliquot from the reaction mixture was treated with oxygen at time zero and 12h as described by Newcomb. Whitesides has shown that treatment of benzophenone dianion with oxygen gives benzophenone quantitatively.[7] No benzophenone was observed from time zero to 12h suggesting that the dianion was not present in detectable concentration. Hence lithium isopropoxide, unlike lithium dialkylamides, is not a strong enough base to deprotonate lithium benzhydrolate (eq. 2) to give a detectable amount of the dianion.

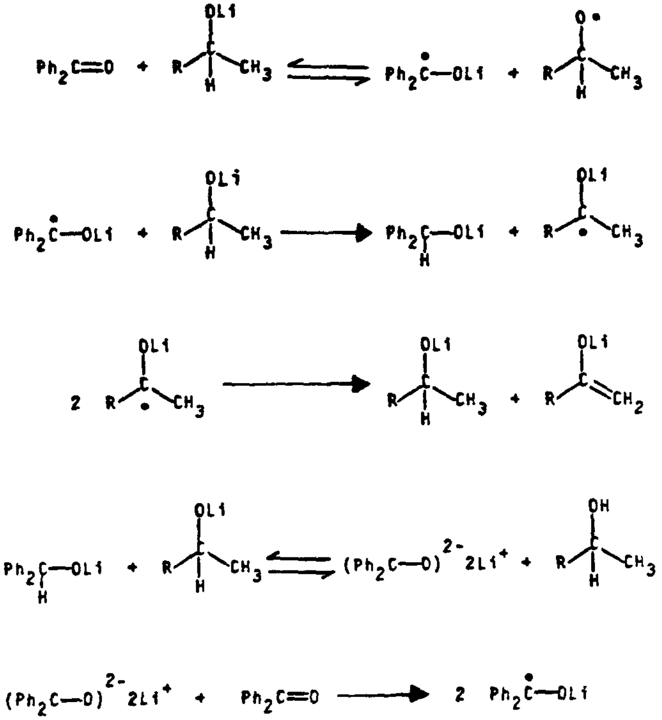
Nevertheless, if the rate of formation of benzophenone dianion from the deprotonation of lithium benzhydrolate is very slow, while the reaction of the dianion with benzophenone is fast, then the direct detection of dianion may not be possible. Hence lithium benzhydrolate and lithium isopropoxide were allowed to react in a 1:20 molar ratio, respectively, for 60h in the presence of 1.0 eq. i-PrOD in order to determine whether deuterated benzhydrol was formed by the trapping of the dianion with i-PrOD. The amount of deuterium incorporation was found to be very low (1.3%) by mass spectroscopy. These results suggest that a small amount of dianion can be formed by the deprotonation of lithium benzhydrolate with lithium isopropoxide. Thus the dianion is a possible intermediate in the formation of the ketyl in the reactions of benzophenone with lithium alkoxides containing β-hydrogens.

A second source of benzophenone ketyl in the reactions of benzophenone with lithium alkoxides are the alkoxides themselves. When lithium- or potassium t-butoxide (which do not contain a β-hydrogen needed for reduction) were allowed to react with benzophenone, the ketyl also formed in high concentration (3% relative to the ketone after 60h). Indeed, no reduction product was observed after 60h, yet the alkoxides gave EPR active solutions. Hence lithium alkoxides can act as one electron donors toward benzophenone to form the ketyl which was shown to react with the alkoxide to form the reduction product, benzhydrol.

Based on the above results, the reduction of benzophenone by lithium alkoxides is proposed to proceed by the pathway depicted in Scheme 1. The alkoxide can both initiate the reduction process as well as contribute to the formation of the ketyl throughout the course of the reaction. The product of the reduction (lithium benzhydrolate) can be deprotonated by the alkoxide, at least to some extent, to give dianion which can also contribute to the formation of ketyl. The lithium ketyl of benzophenone is converted to lithium benzhydrolate by abstracting a β-hydrogen atom from the alkoxide[8] as indicated by the kinetic studies. The alkoxide is thus converted to a lithium ketyl of an aliphatic ketone. Rautenstrauch[9] has shown that the lithium ketyls of aliphatic ketones containing β-hydrogens undergo a rapid disproportionation in THF to give a 1:1 enolate/alcoholate mixture as shown in Scheme 1.

In order to determine the fate of the alkoxide, the lithium salt of 2-heptanol was allowed to react with benzophenone in a 3:1 molar ratio, respectively, in THF at 24°C. A blue colored solution developed slowly and after 4 days benzhydrol was formed in 78% yield whereas 2-heptanone and 2-heptanol were formed in 15% and 84% yield respectively based on alkoxide used. Hence the alkoxide involved in the reduction was converted to 15% ketone and 11% alcohol. The ratio of ketone to alcohol is within experimental error of a 1:1 mixture which should result if the lithium ketyl of 2-heptanone is present and undergoes

Scheme 1



disproportionation to give a 1:1 enolate/alcoholate mixture. Further evidence that the ketone resulted from quenching the enolate was provided by a control study which showed that 2-heptanone in the presence of excess alkoxide undergoes condensation, and therefore is not stable over the time period of this reaction in the presence of excess alkoxide.

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