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EVIDENCE FOR SINGLE ELECTRON TRANSFER IN CLAISEN CONDENSATION.

THE REACTION OF ETHYL p-NITROBENZOATE WITH THE LITHIUM ENOLATE OF PINACOLONE

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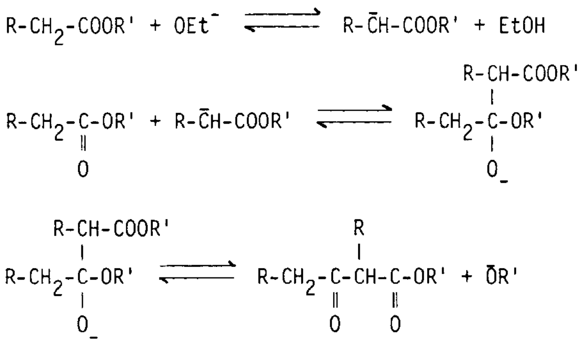
Abstract: The paramagnetic intermediate in the reaction of ethyl p-nitrobenzoate with the lithium enolate of pinacolone is shown to be on the reaction pathway for the formation of the condensation product, 4,4-dimethyl-1-(4-nitrophenyl)-1,3-pentanedione.

Claisen condensation is considered one of the most fundamental reactions in synthetic organic chemistry.[1] It involves the reaction of an ester containing an α-hydrogen with a strong base (e.g., sodium ethoxide), to form a β-keto ester. The mechanism of this reaction is considered to be well established[2] and is represented by Scheme I.

Scheme I



$$R\text{-}CH_2\text{-}COOR' + OEt^- \rightleftharpoons R\text{-}\bar{C}H\text{-}COOR' + EtOH$$

$$R\text{-}CH_2\text{-}\underset{\underset{O}{\|}}{C}\text{-}OR' + R\text{-}\bar{C}H\text{-}COOR' \rightleftharpoons R\text{-}CH_2\text{-}\overset{\overset{R\text{-}CH\text{-}COOR'}{|}}{\underset{\underset{O^-}{|}}{C}}\text{-}OR'$$

$$R\text{-}CH_2\text{-}\overset{\overset{R\text{-}CH\text{-}COOR'}{|}}{\underset{\underset{O^-}{|}}{C}}\text{-}OR' \rightleftharpoons R\text{-}CH_2\text{-}\underset{\underset{O}{\|}}{C}\text{-}\overset{\overset{R}{|}}{C}H\text{-}\underset{\underset{O}{\|}}{C}\text{-}OR' + \bar{O}R'$$

Recently we have reported the involvement of a single electron transfer (SET) mechanism in reactions of various nucleophiles with aromatic aldehydes[3] and ketones.[4-7] Since we have shown that Aldol Condensation involving aromatic ketones proceeds by SET,[6] we thought that Claisen Condensation might proceed by a similar mechanistic pathway. We therefore decided to investigate this possibility by allowing the preformed lithium enolate of pinacolone to react with ethyl p-nitrobenzoate ester in THF.

We have approached this study in the following ways: (1) the detection of a paramagnetic intermediate by EPR spectroscopy and resolution of the corresponding spectrum

(2) kinetic analysis to correlate the rate of disappearnance of the paramagnetic intermediate to the rate of formation of the condensation product and (3) kinetic analysis to correlate the rate of appearance of the paramagnetic intermediate to the rate of disappearance of the reactants.

When ethyl p-nitrobenzoate (A) was allowed to react with the lithium enolate of pinacolone (B) in THF at room temperature, a dark brown color developed rapidly and the solution was found to be EPR active. The concentration of the EPR active species was ~6% relative to the initial concentration of starting ester.[8] A resolved EPR spectrum of the radical species generated in the reaction carried out in THF solvent was similar to that of the radical anion of ethyl p-nitrobenzoate reported in the literature.[9] However, when the same reaction was carried out in THF/HMPA (9:1 ratio) solvent, a very well-resolved and well-defined spectrum was obtained (Fig. 1).

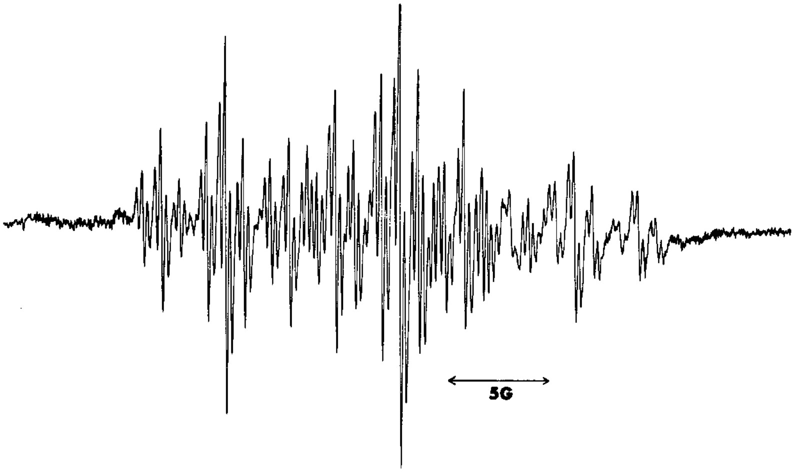


Fig. I: EPR spectrum of the intermediate formed in the reaction of ethyl p-nitrobenzoate with lithium enolate of pinacolone in THF/HMPA (9:1) at room temperature.

The intensity of the EPR signal obtained in the title reaction increased rapidly to a maximum, beyond which it decreased slowly in a first order fashion with the concurrent formation of the condensation product, 4,4-dimethyl-1-(4-nitrophenyl)-1,3-pentanedione (P)[10] (Fig. 2). The first order rate constant of this radical intermediate decay process observed by EPR spectroscopy was k_1 (epr) = $-1.13 \times 10^{-4}\mathrm{sec}^{-1}$ (correlation coeff. = 0.9891) in a time interval from 30 min to 240 min. During the same time interval where the radical intermediate (I) decayed in a first order fashion, the rate of formation of condensation product, monitored by NMR, also exhibits first order behavior with the rate constant of k_1 (P) = $0.9 \times 10^{-4}\mathrm{sec}^{-1}$ (correlation coeff. = 0.9258). Comparison of these two first order rate constants suggests that the major decay process of the intermediate radical is on the pathway to form the condensation product, P. Based on the above observations, a mechanistic scheme involving a radical anion-radical cation pair as the intermediate is proposed (Scheme II).

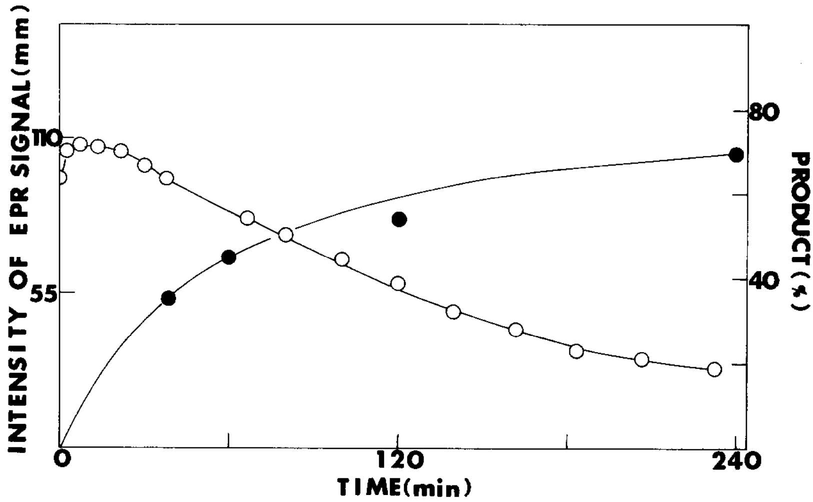
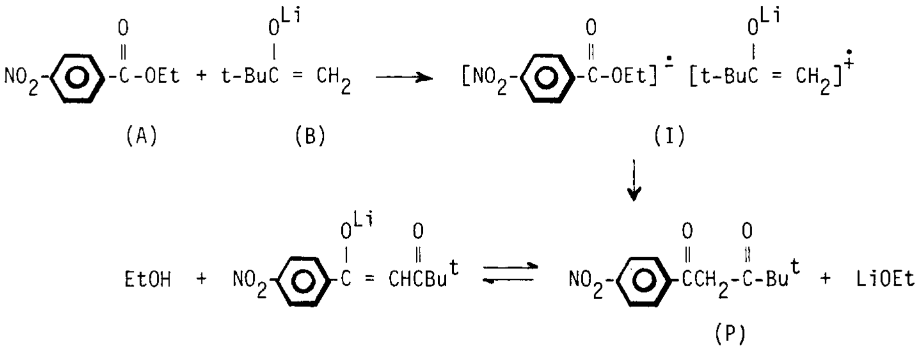


Fig. 2: Reaction of ethyl p-nitrobenzoate (A) with lithium enolate of pinacolone (B) in THF at room temperature: (o) intensity of EPR signal (mm) vs. time (min), where A:B = 0.10M: 0.01M; (●) condensation product (%) vs. time (min), where A:B = 0.20M:0.40M.

Scheme II



For the purpose of comparison of the rate of disappearance of reactants with the rate of formation of intermediate (I), the rate of disappearance of A was monitored by GLPC in the same reaction under pseudo-first order conditions (A:B = 0.02M:0.20M), and the pseudo-first order rate constant for disappearance of A was calculated: k_1 (pseudo) = $-4.25 \times 10^{-3} \mathrm{sec}^{-1}$ (correlation coeff. = 0.9997). Since the decrease of the intermediate should be involved early in the reaction, the pseudo-first order rate constant of I formation was estimated at the earliest measurable portion of the same reaction (3 min → 4 min by EPR spectroscopy:

k_1 (pseudo) (per) = 3.50 x 10^{-3}sec^{-1}. These two rate parameters, again, suggest that the formation of I is on the major pathway of the disappearance of reactants. Thus the SET mechanism is the major pathway of this condensation reaction as has been demonstrated by kinetic analysis correlating the rate of reactant disappearance to the rate of appearance of the intermediate and the rate of disappearance of the intermediate to the rate of product formation.

In conclusion, it has been demonstrated that the reaction of p-nitrobenzoate esters with the lithium enolate of pinacolone takes place mainly via a single electron transfer pathway. Further studies concerning the involvement of SET pathways in reactions involving more common aromatic esters and different kinds of nucleophiles are being conducted.

References

1. C. R. Hauser and B. E. Hudson Jr., Org. React., 1, 266 (1942)
2. J. March, Advanced Organic Chemistry, McGraw Hill, Inc. p. 443-445 (1972)
3. E. C. Ashby, D. T. Coleman III, and M. P. Gamasa, Tetrahedron Lett., submitted for publication.
4. E. C. Ashby, A. B. Goel, and R. N. DePriest, Tetrahedron Lett., 22, 4355 (1981)
5. E. C. Ashby, A. B. Goel, and W. S. Park, Tetrahedron Lett., 22, 4209 (1981)
6. E. C. Ashby, A. B. Goel, and J. N. Argyropoulos, Tetrahedron Lett., 23, 2273 (1982)
7. E. C. Ashby, J. N. Argyropoulos, R. Meyer, and A. B. Goel, J. Am. Chem. Soc., in press
8. The Standard used was 2,2,5,5,-Tetramethylpyrrolidine-3-carboxamide-1-oxyl in THF.
9. P. B. Ayscough, F. P. Sargent, and R. Wilson, J. Chem. Soc., 5418 (1963)
10. NMR:δ 16.30 (1H, broad singlet), 8.05-8.33 (4H,AB quartet), 6.30 (1H, singlet), and 1.23 (9H, singlet). m.p. 105-107°, matched well with lit.[11] values.
11. D. C. Nonhebel, Tetrahedron, 24(4), 1869-74 (1968)

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