# Single Electron Transfer in Aldol Condensation. The Reaction of Lithium Enolates with Diaryl Ketones

E. C. Ashby* and J. N. Argyropoulos

*School of Chemistry, Georgia Institute of Technology, Atlanta, Georgia 30332*

*Received August 27, 1985*

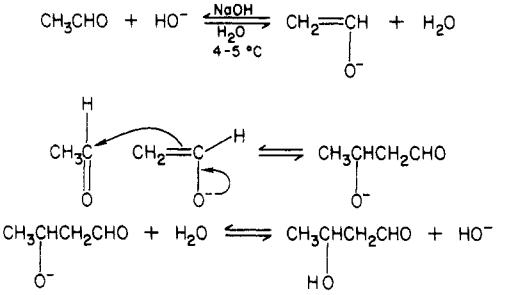
It has been determined by EPR spectroscopy that typical enolate anions react with diaryl ketones by an electron-transfer process to produce paramagnetic intermediates. A kinetic analysis shows that the paramagnetic intermediate formed in the reaction of the lithium enolate of methyl *tert*-butyl ketone (pinacolone) with 2-methylbenzophenone decreases, exhibiting a first-order rate constant which is approximately equal to the pseudo-first-order rate constant for formation of condensation product. A steric effect appears to be operating in the reaction of benzophenone and its more highly substituted derivatives on reaction with the more highly substituted lithium enolates. This steric effect governs not only the rate of formation of condensation product but also the amount of radical generated. Large amounts of free ketyl are formed when no condensation product is observed. When the product is observed, the amount of paramagnetic intermediate is much smaller though dependent on the rate at which product forms. The above observations are consistent with a single-electron-transfer pathway, although it is not possible to rule out the possibility of a competing polar process.

The addition of an enolate anion to the carbonyl group of an aldehyde or ketone constitutes an important reaction in organic chemistry known as the aldol condensation. The reaction has been widely used for the construction of carbon–carbon bonds.[1] More recently, the reactions of preformed enolate anions with aldehydes or ketones have provided a method for introducing chirality into molecules.[2]

The accepted mechanism[1a] for the base-catalyzed aldol condensation is illustrated by the series of equilibria shown in Scheme I. Several lithium enolates were allowed to react with several diaryl ketones in order to evaluate the possible involvement of a single-electron-transfer (SET) pathway in aldol condensation reactions. Due to the sufficiently positive reduction potentials ($E_{redn}$) of diaryl ketones, these substrates have been frequently used in reactions with nucleophiles in order to determine whether a process involving an initial electron-transfer step is plausible. For example, the addition of Grignard reagents to diaryl ketones[3] and, more recently, the reaction of lithium dimethylcuprate with diaryl ketones[4] have been shown to proceed by a pathway involving an initial electron-transfer step. In the former case the SET pathway was detected by a cyclizable radical probe, and in the latter case SET was suggested on the basis of the large concentration of ketyl observed when the cuprate was allowed to react with benzophenone and mesityl phenyl ketone.

The ability of enolate anions to transfer a single electron to various organic substrates was reported by Russell in 1964.[5] In this report, Russell showed that the potassium enolate of propiophenone reacted with a variety of unsaturated systems to give rise to paramagnetic species. Examples of some electron acceptors employed by Russell were *p*-dinitrobenzene, azobenzene, and fluoren-9-one. Although only the presence of an ESR signal was used to indicate electron transfer, Russell speculated on the "importance of electron-transfer processes in the synthetically important addition and condensation reactions of carbanions." More recently it has been shown[6] that the lithium enolate of pinacolone reacts with ethyl *p*-nitrobenzoate in THF at room temperature to give a solution which is EPR active. The concentration of the paramagnetic species generated in the reaction was shown to decrease with an apparent first-order rate constant which was approximately equal to the apparent first-order rate constant for the formation of the Claisen condensation product.

**Scheme I**



The present study addresses the question of whether lithium enolates can react with diaryl ketones by an SET process. The study was approached by (1) utilizing EPR spectroscopy in an attempt to identify the paramagnetic intermediates and follow their appearance and disappearance with time, (2) characterizing the condensation products, whenever possible, and (3) determining for each reaction the amount of product formed with respect to time by GLC analysis. An attempt was then made to determine whether or not the paramagnetic intermediate was actually on the reaction pathway to condensation product.

## Results and Discussion

When the lithium enolates of pinacolone (**1**), 2,2-dimethyl-3-pentanone (**2**), and 2,2,4-trimethyl-3-pentanone (**3**) were allowed to react with benzophenone (**4**), 2-methylbenzophenone (**5**), and mesityl phenyl ketone (**6**), EPR active species were generated in all cases. Hence the lithium enolates were shown to be good one-electron donors toward diaryl ketones other than fluoren-9-one.

In particular, the reaction of the lithium enolate of pinacolone (**1**) with benzophenone (**4**) in THF at 25 °C in

(1) (a) House, H. O. "Modern Synthetic Reactions", 2nd ed.; W. A. Benjamin: Menlo Park, CA, 1972; Chapter 10. (b) Nielson, A. T.; Houlihan, W. J. In "Organic Reactions"; Cope, A. C., Ed.; Wiley; New York, 1968.

(2) Evans, D. A.; Nelson, J. V.; Taber, T. R. In "Topics in Stereochemistry"; Allinger, N. L., Eliel, E. L., Wilen, S. H., Eds.; Wiley: New York, 1982.

(3) Ashby, E. C. *Pure Appl. Chem.* **1980**, *52*, 545 and references cited therein.

(4) House, H. O.; Chu, C.-Y. *J. Org. Chem.* **1976**, *41*, 3083.

(5) Russell, G. A.; Janzen, E. G.; Strom, E. T. *J. Am. Chem. Soc.* **1964**, *86*, 1807.

(6) Ashby, E. C.; Park, W. S. *Tetrahedron Lett.* **1983**, *24*, 1667.

0022-3263/86/1951-0472$01.50/0 

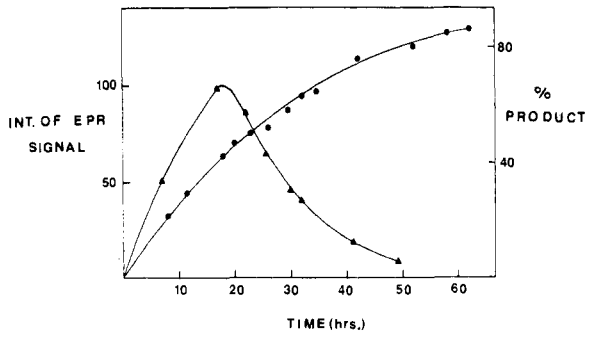



**Figure 1.** Reaction of benzophenone (4) (0.08 M) with the lithium enolate of pinacolone (1) in THF: (▲) intensity of EPR signal (mm) vs. time (h), where 1 mm = 0.001 % radical; (•) condensation product (%) vs. time (h).

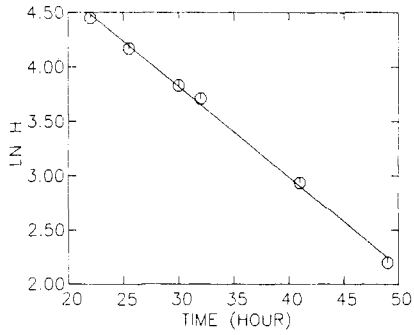



**Figure 2.** Plot of ln $H$ vs. time for the first-order decay of radical intermediate in the reaction of enolate 1 with benzophenone (4).

a 1.5:1 molar ratio, respectively, gave a high yield (90%) of condensation product 7 in 60 h as shown in Figure 1. EPR analysis of the reaction mixture showed the existence of a paramagnetic species formed in low concentration; however, the EPR signal was too weak to resolve. The concentration of the paramagnetic species reached a maximum after 18 h (0.10% relative to $Ph_2CO$) (Figure 1) beyond which it decreased in a first-order fashion (Figure 2) with $k = 2.3 \times 10^{-5}$ s$^{-1}$. The first-order decay of the radical intermediate suggests that it is the radical anion–radical cation pair as shown in Scheme II. The condensation product 7 was formed in a second-order fashion with $k = 4.5 \times 10^{-5}$ s$^{-1}$ M$^{-1}$.

Enolate 1 was also allowed to react with ketones 5 and 6 in the hope of retarding the rate at which condensation product forms. The steric bulk of the two *o*-methyl groups of ketone 6 causes the molecule to adopt a conformation in which the trisubstituted phenyl ring is perpendicular to the plane of the carbonyl group.[7] In this conformation, the two *o*-methyl groups shield both sides of the carbonyl carbon atom and hence should decrease the reactivity of ketone 6. To a lesser extent, ketone 5 should also be less reactive toward enolate 1 compared to benzophenone. Thus by decreasing the value of $k_2$ (Scheme II), the concentration of the paramagnetic intermediate should increase in going from ketone 4 to ketones 5 and 6, provided the first step in Scheme II (the SET step) is unaffected. Since the reduction potentials of ketones 4, 5, and 6 are similar ($E_{redn}$ values range from −1.80 to −1.97 V)[4] then the SET step should not be adversely affected by the steric bulk of the methyl groups.

The reaction of enolate 1 with 2-methylbenzophenone (5) in a 1.5:1 molar ratio, respectively, in THF at 25 °C gave rise to a paramagnetic species whose concentration reached a maximum after 44 h (1.0% relative to ketone

(7) Newman, M. S. In "Steric Effects in Organic Chemistry"; Newman, M. S., Ed.; Wiley: New York, 1956; pp 240–242.

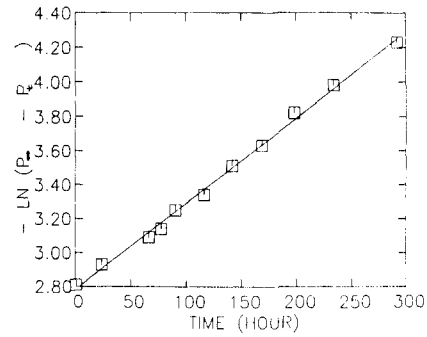



**Figure 3.** Plot of ln $(P_\infty - P_t)$ vs. time for the pseudo-first-order formation of enone 8.

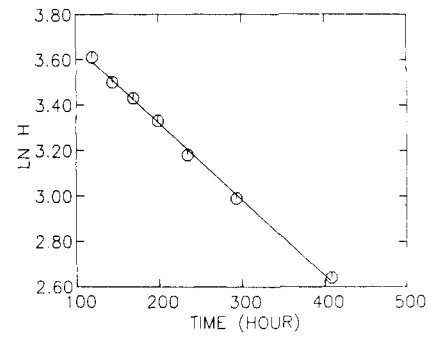


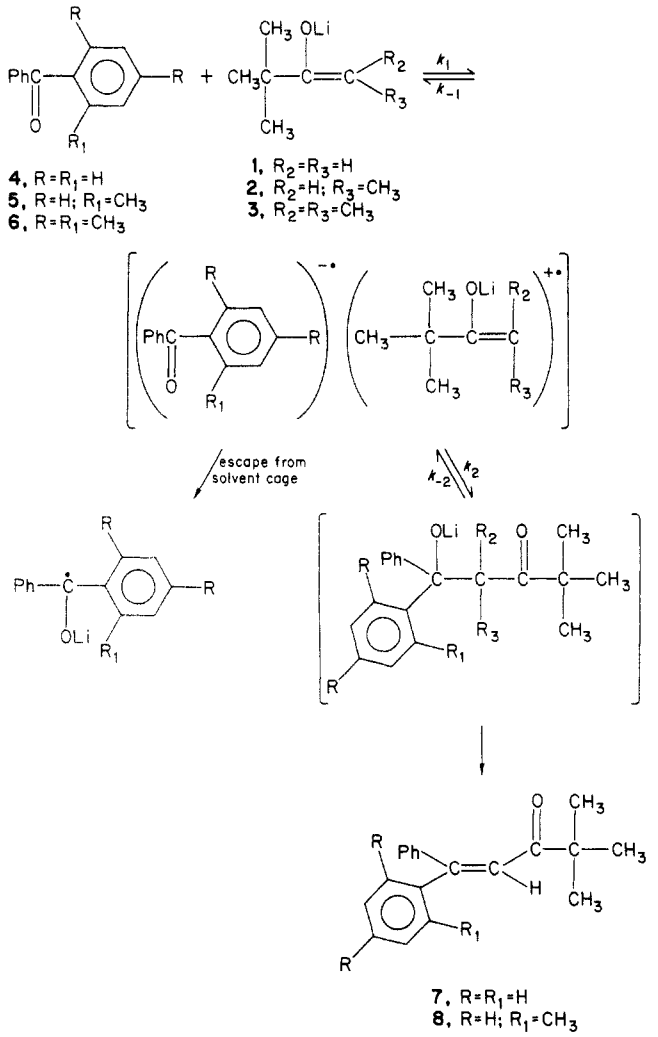

**Figure 4.** Plot of ln $H$ vs. time for the first-order decay of radical intermediate in the reaction of enolate 1 with 2-methylbenzophenone (5).

5). Though the solution gave rise to a strong EPR signal (approximately 10 times more intense compared to the case of benzophenone and enolate 1), the signal could not be fully resolved. The condensation product 8 formed very slowly in 30% yield over a period of 9 days. When enolate 1 was allowed to react with mesityl phenyl ketone (6) under similar conditions, no condensation product was observed. Nevertheless, the reaction gave rise to a red solution and a strong EPR signal ($g$ = 2.0020). The paramagnetic species (5.0% relative to ketone 6 at its maximum) gave a well-resolved EPR spectrum which was identical with the lithium ketyl of 6. By increasing the steric requirement of the ketone so that carbon–carbon bond formation is slow, sufficient time exists for the ketyl to escape the solvent cage. The above results lend credence to the steric argument and hence support the mechanistic pathway depicted in Scheme II.

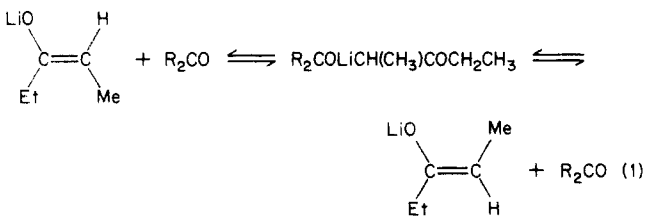
In an attempt to make the reaction of enolate 1 with ketone 5 amenable to kinetic analysis, compounds 1 and 5 were allowed to react in a 5:1 molar ratio, respectively, in THF:DMF (9:1 by volume) at 25 °C. The condensation product 8 appeared more readily than in the previous case exhibiting pseudo-first-order kinetic behavior (Figure 3) with $k = 1.4 \times 10^{-6}$ s$^{-1}$. The concentration of paramagnetic intermediate reached a maximum after 23 h and then decreased in a first-order fashion (Figure 4) with $k = 9.0 \times 10^{-7}$ s$^{-1}$. A comparison of the first-order rate constants (approximately equal within experimental error) shows that the paramagnetic species is decreasing during the same time period that the condensation product is being formed (Scheme II).

When enolates 2 and 3 were allowed to react with benzophenone in a 1.5:1 molar ratio, respectively, in THF at 25 °C, a blue solution appeared slowly in both cases. The colored solutions gave rise to well-resolved EPR spectra, as well as visible spectra ($\lambda_{max}$ 632 nm), all of which were similar 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

**Scheme II**




THF). The concentration of ketyl in each case reached a maximum after 1 week and was calculated to be approximately 10% relative to benzophenone. After this period of time, the reactions were quenched and benzophenone was recovered quantitatively. The inability to observe condensation product in each of these reactions does not rule out the possibility that the aldol-type intermediate was formed. In fact, Rathke[8] has reported that stereoisomeric enolates from 3-pentanone can react with benzophenone or 3-pentanone to give an equilibrium mixture of enolates. It was suggested that the most likely isomerization mechanism was reversible aldol condensation as shown in eq 1. Hence, if enolates **2** and **3** are reacting




with benzophenone to give an aldol intermediate which undergoes facile retroaldolization, then on the basis of Scheme II, a large concentration of ketyl should develop since significant escape of the paramagnetic intermediate from the solvent cage can occur over a long period of time.

(8) Fataftah, Z. A.; Kopka, I. E.; Rathke, M. W. *J. Am. Chem. Soc.* **1980**, *102*, 3959.

**Scheme III**

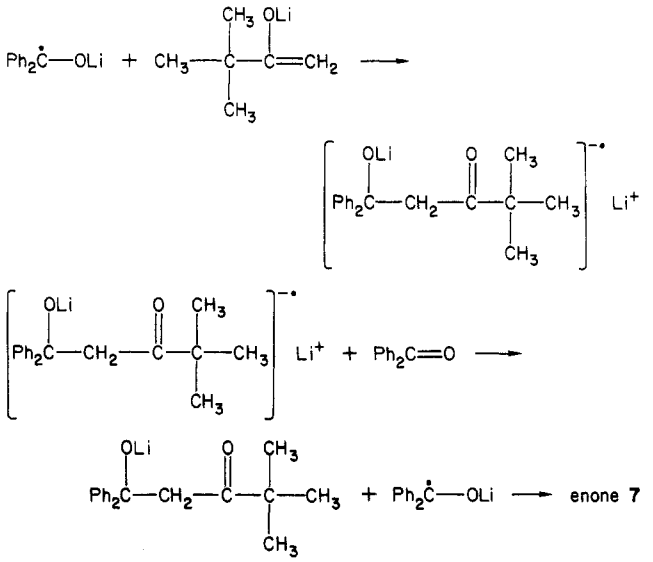



**Table I. Effect of Light, Absence of Light, and Radical Scavengers on the Reaction of the Lithium Enolate of Pinacolone (1) with Benzophenone (4)[a]**

| time, h | enone 7, % light | no light | 0.10 equiv of DNB[b] | 0.10 equiv of DCPH[b] |
|---|---|---|---|---|
| 13 | 22 | 21 | 20 | 21 |
| 24 | 40 | 42 | 31 | 38 |
| 68 | 83 | 89 | 79 | 80 |

[a] See Experimental Section for details. [b] Equivalents based on benzophenone.

This was observed. It is interesting to note that an alternate pathway to the isomerization mechanism proposed by Rathke for the equilibration of stereoisomeric enolates from 3-pentanone may exist. It has been suggested[9] that the interconversion of geometrically isomeric enolates can occur via an $\alpha$-keto radical which is generated when the enolate donates an electron to some acceptor. Since the above results indicate that benzophenone readily accepts an electron from enolates **1**, **2**, and **3**, then the pathway involving an $\alpha$-keto radical is a viable explanation for the results that Rathke obtained with benzophenone.

The possibility that enolate **1** is reacting with benzophenone via an $S_{RN}1$ pathway as shown in Scheme III was also investigated. Reactions were carried out under ambient fluorescent light, in the absence of light, and in the presence of 10 mol % *p*-dinitrobenzene. As shown in Table I, the rate of formation of condensation product **7** was unaffected. Hence the reaction of enolate **1** with benzophenone was found to be insensitive to the factors that normally influence an $S_{RN}1$ pathway. Furthermore, when dicyclohexylphosphine (DCPH) was used in 10 mol % in the above reaction, the rate of formation of condensation product **7** was also unaffected (see Table I) and benzhydrol was not observed. In an independent experiment, DCPH was shown to act as a hydrogen atom donor and trap the lithium ketyl of benzophenone to give benzhydrol (on hydrolysis), quantitatively. Since an $S_{RN}1$ process necessitates the presence of the paramagnetic intermediate (ketyl) outside of the solvent cage where it can be trapped, the results with DCPH provide further evidence that the reaction pathway depicted in Scheme III is not in operation.

(9) See ref 1a, p 564.

An alternate pathway for the disappearance of paramagnetic intermediate in the reaction of benzophenone with enolate 1 is illustrated in eq 2. The disproportion-

$$2(Ph_2CO)^{\cdot-}\,Li^+ \rightleftharpoons Ph_2C{=}O + (Ph_2CO)^{2-}\,2Li^+ \quad (2)$$

ation of benzophenone ketyl to give a small concentration of benzophenone and the corresponding dianion is known.[10] Benzophenone may then react with enolate 1 to give condensation product by a polar process (Scheme I) and hence shift the equilibrium in eq 2 to the right. This mechanistic pathway was ruled out by observing no condensation product (enone 7) after 48 h, when enolate 1 was allowed to react with benzophenone ketyl (generated by reacting lithium metal with benzophenone in THF) in a 2:1 molar ratio, respectively, in THF. The above result lends further support to the mechanistic scheme depicted in Scheme II.

It has been recognized for a long time that the observation of a reactive intermediate and even following its rate of appearance and disappearance does not necessarily prove that the intermediate is directly involved in the reaction. For example, according to eq 3, reactants A and B react to form the intermediate (I) which can then form product in a first-order fashion. However the formation

$$P \leftarrow A + B \rightleftarrows I \rightarrow P \quad (3)$$

of I could simply be a blind step and the product (P) is formed by direct reaction of A and B. Such a situation could describe the reaction in question where A = enolate, B = ketone, and I = radical anion–radical cation. What this work shows is not conclusive proof that aldol condensation involving an enolate and an aromatic ketone proceeds by single-electron transfer, but that a paramagnetic intermediate is formed and a single-electron transfer pathway is consistent with all the data obtained in this study and is a viable alternate pathway for aldol condensation involving aromatic ketones. Except for the report by Russell in 1964 in which numerous nucleophiles and substrates were allowed to react in the cavity of an ESR spectrometer and an ESR signal was observed for the reaction of the potassium enolate of propiophenone with fluoren-9-one, there is no other report suggesting that aldol condensation might take place by an electron-transfer process.

## Experimental Section

**Materials.** Reagent-grade *N,N*-dimethylformamide (DMF) from Aldrich was distilled from $CaH_2$ under nitrogen at reduced pressure. Reagent-grade tetrahdyrofuran (THF) from Fisher was distilled under nitrogen from a deep purple solution of benzophenone ketyl. Pinacolone from Aldrich and 2,2-dimethyl-3-pentanone and 2,2,4-trimethyl-3-pentanone from Wiley Organics were distilled from $CaH_2$ under nitrogen prior to use. Benzophenone (4) and 2-methylbenzophenone (5) were purchased from Aldrich and distilled under vacuum. Mesityl phenyl ketone (6) was available from a previous study[11] and distilled under vacuum prior to use.

**General Procedures.** Methods of manipulation of reagents under an inert atmosphere and instrumentation were discussed in a previous paper.[12] Melting points were measured by a Mel-Temp apparatus and were corrected. EPR spectra were obtained on a Varian E-109ES spectrometer. Visible spectra were recorded on a Varian DMS-90 spectrophotometer. GLC yields were determined by utilizing internal standards and comparing peak areas which were corrected for response factors. For quantitative GLC analyses, the following columns and conditions were used (retention times are given relative to the internal standard): column A, 5% Carbowax 20M on Chromosorb G, 2.5 ft × $^1/_4$ in., 190 °C, benzophenone (0.74), 2-methylbenzophenone (0.74), mesityl phenyl ketone (1.00), 7 (1.70), 8 (1.72); column B, DB-1 fused silica capillary column, 30 m, 50 °C for 4 min to 150 °C at 15° per min, 2,2-dimethyl-3-pentanone (0.56), *n*-decane (1.00).

**Preparations. Enone 7.** To a cold (−78 °C) solution of LDA, prepared from 1.7 mmol of MeLi, 1.9 mmol of diisopropylamine, and 5.0 mL of THF was added dropwise and with stirring during 5 min 0.17 g (1.7 mmol) of pinacolone in 2.0 mL of THF. The resulting solution was stirred at −78 °C for 1 h and then brought slowly to room temperature under vacuum to remove the solvent and other volatile components. The resulting white solid was then redissolved in 8.0 mL of freshly distilled THF and 0.20 g (1.1 mmol) of benzophenone in 3.0 mL of THF was added all at once. The solution was stirred for 3 days at room temperature and then quenched with 1 M HCl (10 mL) and extracted twice with 30-mL portions of hexane. The combined hexane layers were washed successively with saturated $NaHCO_3$ and brine, dried, and concentrated. The residual oil was dissolved in a small portion of ether and then subjected to preparative GLC (5% Carbowax 20M on Chromosorb G, 2 ft, 170 °C) to give 0.23 g (79%) of enone as a pale-yellow solid: mp 65–66 °C [lit.[13] mp 66 °C]; $^1$H NMR ($CCl_4$) δ 1.2 (s, 9 H), 6.8 (s, 1 H), 7.1–7.3 (m, 10 H); IR ($CCl_4$) 3040, 2980, 1690, 1595 1570, 1080, 695 cm$^{-1}$; mass spectrum, *m/e* (relative intensity) 264 ($M^+$, 0.4), 208 (18), 207 (100), 179 (26), 178 (36), 152 (5), 105 (18), 77 (5).

**Enone 8.** To a cold (−78 °C) solution of LDA, prepared from 9.0 mmol of MeLi, 10 mmol of diisopropylamine, and 5.6 mL of $Et_2O$, was added dropwise and with stirring during 10 min 0.90 g (9.0 mmol) of pinacolone in 5.0 mL of THF. The resulting solution was stirred at −78 °C for 1 h and then brought slowly to room temperature under vacuum. The resulting white solid was then redissolved in 16 mL of THF and 2.0 mL of DMF, and 0.35 g (1.8 mmol) of 2-methylbenzophenone was added all at once. The solution was stirred for 7 days at room temperature and then quenched with 1 M HCl (20 mL) and extracted twice with 50-mL portions of hexane. The combined hexane layers were washed 3 times with water, dried, and concentrated. The residue was dissolved in a small portion of ether and then subjected to preparative GLC as described above to give 0.16 g (32%) of enone as a pale-yellow oil: $^1$H NMR ($CCl_4$) δ 1.2 (s, 9 H), 2.2 (s, 3 H), 6.8 (s, 1 H), 7.1–7.3 (m, 9 H); IR ($CCl_4$) 3040, 2980, 1690, 1595, 695 cm$^{-1}$; electron-impact mass spectrum, *m/e* (relative intensity) 263 (2), 222 (15), 221 (100), 178 (24), 119 (40), 115 (80), 105 (29), 91 (33), 77 (6), 65 (8), 57 (10); chemical-ionization mass spectrum, *m/e* 279 ($M^+ + 1$).

Anal. Calcd for $C_{20}H_{22}O$: C, 86.27; H, 7.98. Found: C, 86.40; H, 7.69.

**Product Studies. Reactions of Enolate 1 with Ketones 4 and 5.** For the reaction profile studies, enolate 1 was allowed to react with ketones 4 and 5 as described in the previous sections except that each reaction was 0.080 M in ketone. The solutions were maintained at 25 ± 0.5 °C by use of a constant-temperature water bath. The progress of each reaction was followed with time by taking 0.50-mL aliquots from the reaction mixtures and quenching them in vials containing saturated $NH_4Cl$. Mesityl phenyl ketone was then added as the internal standard and the organic layer was extracted with hexane (2 × 2.0 mL). The combined hexane layers were washed twice with water, dried, and then analyzed by GLC for enones 7 or 8 by utilizing column A. A plot of ln $(P_\infty - P_t)$ vs. time, where $P_\infty$ represents the maximum concentration of the condensation product and $P_t$ represents the concentration at some time *t*, yielded a straight line (Figure 3) for the reaction of enolate 1 with 2-methylbenzophenone. A plot utilizing eq 4, where *a* and *b* are the initial concentrations of ketone

$$\frac{1}{b - ra}\left\{\ln\left(\frac{a}{a - x}\right) - \ln\left[\frac{(b/r)}{(b/r) - x}\right]\right\} = kt \quad (4)$$

4 and enolate 1, respectively, $r = 1.0$, and $x$ is the moles per liter of ketone 4 which have reacted at time *t*, yielded a straight line

(10) (a) Demortier, A.; Bard, A. J. *J. Am. Chem. Soc.* **1973**, *95*, 3495. (b) Jensen, B. S.; Parker, V. D. *J. Chem. Soc., Chem. Commun.* **1974**, 367.
(11) Ashby, E. C.; Boone, J. R. *J. Am. Chem. Soc.* **1976**, *98*, 5524.
(12) Ashby, E. C.; Argyropoulos, J. N. *J. Org. Chem.* **1985**, *50*, 3274.
(13) Kohler, E. P. *Am. Chem. J.* **1907**, *38*, 511.

for the reaction of enolate 1 with benzophenone.[14]

**EPR Studies. Reactions of Enolate 1 with Ketones 4 and 5.** For the EPR studies, the above-named reactions were performed in quartz EPR tubes equipped with ground glass stopcocks under identical conditions used in the product studies. Immediately after mixing the reagents, the measurements of the EPR signal intensities were made at appropriate time intervals. The plot of ln $H$ vs. time, where $H$ represents the height of the first-derivative EPR signal obtained at high modulation and measured in mm, yielded a straight line in the region where the intensity of the EPR signal was decreasing (see Figures 2 and 4). The concentration of radical species was estimated by a comparison of the peak height of the first-derivative EPR signal generated in the reaction being studied with the peak height of the signal obtained from a standard solution of 2,2,5,5-tetramethylpyrrolidine-3-carboxamide-1-oxyl.

**Reaction of Enolate 2 with Benzophenone (4).** To a cold (−78 °C) solution of LDA, from 2.5 mmol of MeLi, 2.8 mmol of diisopropylamine, and 5.0 mL of THF, was added dropwise and with stirring during 5 min 0.29 g (2.5 mmol) of 2,2-dimethyl-3-pentanone in 2.0 mL of THF. The resulting solution was stirred from −78 to 0 °C for 1 h and the solvent was then evaporated under vacuum. The resulting white solid was redissolved in 14 mL of THF and 0.31 g (1.7 mmol) of benzophenone (4) in 3.0 mL of THF was added all at once. After allowing the solution to stir for 24 h at 25 °C, a 0.50-mL aliquot was taken from the reaction mixture and worked up as described previously. GLC analyses utilizing columns A (for benzophenone) and B (for 2,2-dimethyl-3-pentanone) indicated that no reaction had occurred. After 1 week, the remainder of the reaction mixture was worked up, and the residual oil was placed under vacuum for 4 h. The NMR spectrum was then obtained ($CH_3NO_2$ in $CCl_4$ as the internal standard) and found to be that of $Ph_2CO$ (96%).

**Effect of Light, *p*-Dinitrobenzene, and Dicyclohexylphosphine on the Reaction of Enolate 1 with Benzophenone (4).** The effect of light and the presence of *p*-DNB and DCPH on the rate of reaction of enolate 1 with benzophenone (4) was determined by carrying out four sets of reactions. One set was carried out under ambient laboratory light, another was carried out in a reaction tube wrapped with aluminum foil, and the others were performed in the presence of either 10 mol % *p*-DNB or DCPH (added to a solution of enolate 1 prior to the addition of $Ph_2CO$) under laboratory light. Aliquots taken from each reaction at appropriate times were worked up and analyzed as described in a previous section. The results of the study are given in Table I.

**Acknowledgment.** We are indebted to the National Science Foundation (Grant CHE 78-00757) for support of this work. We also thank G. Richard Meyer for his assistance in the kinetic studies.

**Registry No.** 4, 119-61-9; 5, 131-58-8; 7, 844-39-3; 8, 63382-94-5; pinacolone, 75-97-8; 2,2-dimethyl-3-pentanone, 564-04-5.

(14) Castellan, G. W. "Physical Chemistry", 2nd ed.; Addison-Wesley: Reading, MA, 1971; pp 737-739.

# Polar Effects in Free-Radical Reactions. Selectivity and Reversibility in the Homolytic Benzylation of Protonated Heteroaromatic Bases

Francesco Minisci,* Elena Vismara, Giampiero Morini, Francesca Fontana, Silvio Levi, and Marco Serravalle

*Dipartimento di Chimica del Politecnico, 32 Milano, Italy*

Claudio Giordano

*ZAMBON CHIMICA S.p.A., 26 Cormano, Italy*

*Received July 2, 1985*

The homolytic benzylation of protonated 4-cyanopyridine, quinoline, 2-methyl- and 4-methylquinoline, isoquinoline, and quinoxaline is investigated. The great influence of the polar effect and of the reversibility of the addition of the benzyl radical on the reaction selectivity is discussed. It is put forward the hypothesis that the HSAB principle can be extended to free-radical reactions when the polar effect is the dominant factor.

The substitution of protonated heteroaromatic bases by nucleophilic carbon-centered radicals has very large synthetic involvements, which substantially reproduce the numerous aspects of the aromatic Friedel–Crafts alkylation and acylation but with opposite reactivity and selectivity.[1] Since there is a strict relationship between stability of carbonium ions and nucleophilic character of carbon-centered radicals, generally all the Friedel–Crafts reagents useful in aromatic substitution can be utilized, as corresponding radicals, for the selective substitution of protonated heteroaromatic bases.

Recently a quite similar behavior has been observed with different aromatic substrates bearing a positive charge in the aromatic nucleus, the pyrilium salts,[2] further supporting our interpretation that the polar effect is the dominant factor in determining the reactivity of these free-radical reactions. From the regioselectivity and the kinetic behavior (negative activation energy) we have previously obtained evidence[3] that the reactions with *tert*-alkyl and acyl radicals can be reversible and that therefore the equilibrium and the rate of the rearomatization step can play an important role in determining the selectivity.

(1) Minisci, F. *Synthesis* **1973**, 1; *Top. Curr. Chem.* **1976**, *62*, 1; "Fundamental Research in Homogeneous Catalysis"; Plenum Press: New York, 1984; Vol. 4, p 173. Minisci, F.; Citterio, A.; Giordano, C. *Acc. Chem. Res.* **1983**, *16*, 27. Vismara, E. *Chim. Ind. (Milan)* **1983**, *65*, 34.

(2) Doddi, A.; Ercolani, G., personal communication, Symposium of Organic Chemistry, Sirmione, Italy, Sept 22–27, 1985.

(3) (a) Arnoldi, A.; Bellatti, M.; Caronna, T.; Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *Gazz. Chim. Ital.* **1977**, *107*, 491. (b) Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960. (c) Citterio, A.; Minisci, F.; Franchi, V. *J. Org. Chem.* **1980**, *45*, 4752. (d) Minisci, F.; Giordano, C.; Vismara, E.; Levi, S.; Tortelli, V. *J. Am. Chem. Soc.* **1984**, *106*, 7146.

0022-3263/86/1951-0476$01.50/0 