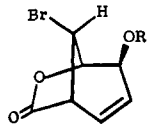
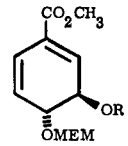
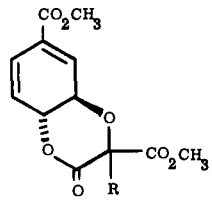
Chart I



3 R = H
4 R = MEM
5 R = $CH(CO_2CH_3)_2$
6 R = $C(CO_2CH_3)_2CH_2N(CH_3)_2$
7 R = $C(CH_2)CO_2CH_3$



8 R = H
9 R = $CH(CO_2CH_3)_2$



10 R = H
11 R = $CH_2N(CH_3)_2$
12 R = $CH_2\overset{\oplus}{N}(CH_3)_3\,{}^{\ominus}OSO_2F$

Next, a one-pot hydrolysis, decarboxylation, and β elimination in base was expected to create the enol pyruvate appendage. Indeed, when **12** was stirred with a measured quantity of base (1.5 equiv of NaOH–H_2O, 90 min, 0 °C) the initially clear solution became turbid, and $CDCl_3$ extraction gave a nearly pure sample of dimethyl chorismate **1b** in 37% yield from **12** (25% after preparative SiO_2 TLC at 5 °C). This material was spectroscopically indistinguishable from an authentic sample of the optically active diester **1b**,[11] which we and Berchtold et al.[6] have independently reconverted to **1a** (NaOH, THF–H_2O, 0 °C); 10–30%). Under fully homogeneous conditions (NaOH, THF–H_2O, 0 °C), the hydrolysis of **12** produced chorismic acid directly to complete the synthesis in 12 steps from 1,4-dihydrobenzoic acid.

Pseudochorismic acid **2a** was also readily available from allylic alcohol **3** via malonate **5** and Mannich base **6** according to the above mentioned protocol [$N_2C(CO_2CH_3)_2$, $Rh_2(OAc)_4$, 70%; $CH_2{=}{}^{+}N(CH_3)_2I^-$, CH_2Cl_2, reflux, 84%]. Quaternization of **6** (CH_3I, CH_2Cl_2, reflux), then thermolysis in Me_2SO (95 °C, 8 h) gave the bicyclic enol pyruvate **7** (mp 121–122 °C) in 73% yield from **6**. Saponification of **7** (3 equiv of NaOH, 3:1 THF–H_2O, 0 °C, 2 h; room temperature, 12 h) with concomitant HBr elimination furnished **2a** as a solid (89% yield) contaminated with variable amounts of *m*-hydroxybenzoic acid. Recrystallization from EtOAc–hexane gave pure **2a** (72%; mp 125–127 °C). As might be expected, the NMR characteristics of **1** and **2a** were remarkably similar.

Further aspects of the chemistry and biochemistry of **1a** and **2a** will be reported in due course.

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Registry No. (±)-**1a**, 80657-95-0; (±)-**1b**, 80631-87-4; (±)-**2a**, 83573-29-9; (±)-**3a**, 65825-61-8; (±)-**4**, 83573-19-7; (±)-**5**, 83573-26-6; (±)-**6**, 83573-27-7; (±)-**7**, 83573-28-8; (±)-**8**, 83573-20-0; (±)-**9**, 83573-21-1; (±)-**10** (β-COOMe), 83573-22-2; (±)-**10** (α-COOMe), 83602-87-3; **11**, 83573-23-3; **12**, 83573-25-5; $CH_2{=}N^+(CH_3)_2{\cdot}CF_3CD_2^-$, 25468-31-9; dimethyl diazomalonate, 6773-29-1; methyl *m*-enolypyruvylbenzoate, 16929-33-2.

Supplementary Material Available: Listing of physical and spectral data and experimental details for key intermediates (4 pages). Ordering information is given on any current masthead page.

(11) Ife, R. J.; Ball, L. F.; Lowe, P.; Haslam, E. *J. Chem. Soc., Perkin Trans. 1*, in press.

Evidence for a Single-Electron-Transfer Mechanism in Aldol Condensation Reactions

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The condensation of an aldehyde or ketone in the presence of a base (Aldol condensation) is an important synthetic reaction, the mechanism of which is considered to be polar in nature.[1,2] Nevertheless, the ability of enolate anions to transfer a single electron to various organic substrates is well documented.[3-6] Recently, we reported the involvement of a single-electron-transfer (SET) mechanism in reactions of various nucleophiles with aromatic ketones.[7-9] We now report evidence consistent with the involvement of a SET mechanism in aldol condensation reactions involving enolate nucleophiles with aromatic ketones.

When the lithium enolates of 2,2-dimethyl-3-butanone (pinacolone, A) and 2,2-dimethyl-3-pentanone (B) were allowed to react with benzophenone (C), 2,4-dimethylbenzophenone (D), and mesityl phenyl ketone (E), EPR active species were generated in all cases. For example, when enolate B was allowed to react with benzophenone in a 1.5:1 mole ratio, respectively, in THF at 25 °C, a blue color appeared within a few hours. This colored solution gave rise to a well-resolved EPR spectrum, as well as a visible spectrum (λ_{max} 632 nm), both of which are similar to the EPR and visible spectra recorded for an authentic sample of lithium benzophenone ketyl (prepared by the rxn of lithium metal with benzophenone in THF). The concentration of the free ketyl (H) reached a maximum after 1 week and was calculated to be approximately 10% relative to benzophenone.[10] After this period of time when the reaction was quenched, benzophenone was recovered in nearly quantitative yield.

In contrast, the reaction of enolate A with benzophenone under exactly the same conditions gave a high yield (90%) of the condensation product, 4,4-dimethyl-1,1-diphenyl-1-penten-3-one (F) in 3 days. EPR analysis of the reaction mixture showed the existence of a paramagnetic species formed in small (~0.1%) concentration. The signal was too weak to resolve. Figure 1 shows

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(2) Caine, D. S. In "Carbon-Carbon Bond Formation"; Augustine, R. L., Ed.; Marcel Dekker: New York, 1979; Vol. I.
(3) Russell, G. A.; Janzen, E. G.; Strom, E. T. *J. Am. Chem. Soc.* **1964**, *86*, 1807.
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(5) Kornblum, N. *Angew, Chem., Int. Ed.* **Engl. 1975**, *14*, 734.
(6) Bunnett, J. F.; Singh, P. *J. Org. Chem.* **1981**, *46*, 5022 and references cited therein.
(7) Ashby, E. C.; Goel, A. B.; DePriest, R. N. *Tetrahedron Lett.* **1981**, *22*, 4355.
(8) Ashby, E. C., Goel, A. B.; Park, W. S. *Tetrahedron Lett.* **1981**, *22*, 4209.
(9) Ashby, E. C.; Goel, A. B.; Argyropoulos, J. N. *Tetrahedron Lett.* **1982**, *23*, 2273.
(10) The standard used was 2,2,5,5-tetramethylpyrrolidine-3-carboxamide 1-oxy in THF. The peak heights of the ketone radical and standard were compared.

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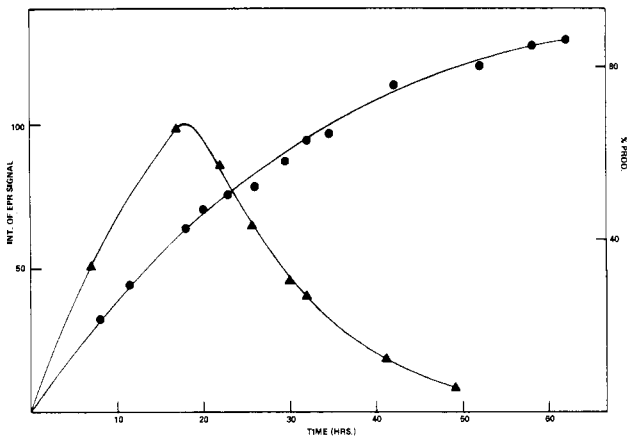


Figure 1. Reaction of benzophenone (0.08 M) with the lithium enolate of pinacolone in THF: (▲) intensity of EPR signal (mm) vs. time, where 1 mm = 0.001% radical; (●) condensation product (%) vs. time (h).

that the intensity of the EPR signal reaches a maximum at 18 h, beyond which decay proceeds in a first-order fashion over a period of 2 days. The concentration of benzophenone decreases rapidly during the time that the signal for the paramagnetic species is increasing, and after 18 h the rate of formation of product is the same as the rate of decay of the paramagnetic species.

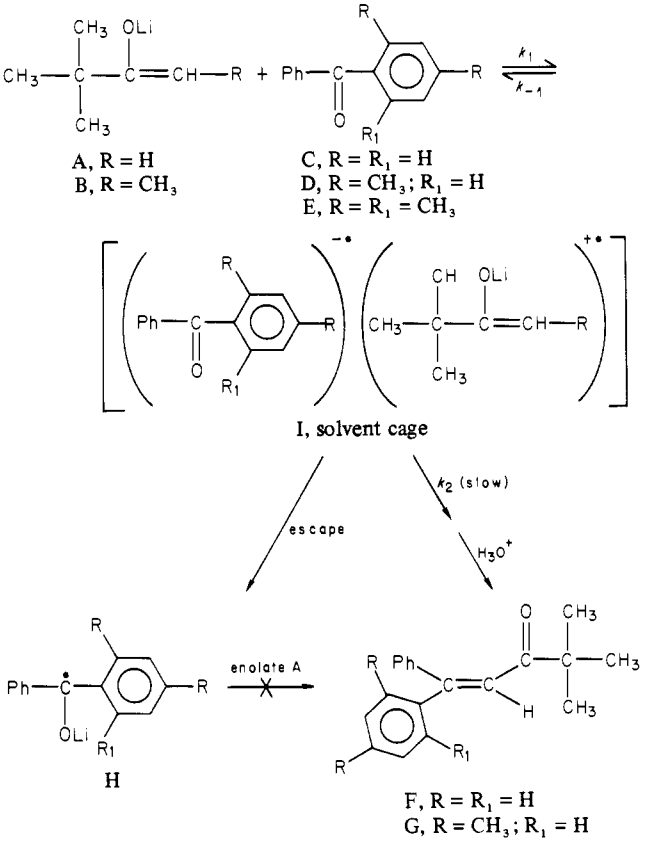
On the basis of the results of these two reactions, a mechanistic scheme (Scheme I) involving a radical anion–radical cation pair as the intermediate is proposed. When enolate B was allowed to react with benzophenone, coupling of the radical anion–radical cation did not occur to give condensation product (presumably due to steric reasons), and in time, the radical anion escaped from the solvent cage leading to a large buildup of the free, stable radical anion of benzophenone. However, when the less sterically hindered enolate A was allowed to react with benzophenone, condensation product did form. The first-order decay of the radical intermediate in this reaction suggests that it is the radical anion–radical cation pair (I) instead of the free ketyl (H). The first-order rate constant k_2 for the disappearance of the paramagnetic intermediate is 2.3 $\times 10^{-5}$ sec^{-1}. As seen from Scheme I, the free ketyl (H) does not react with enolate A, since the lithium ketyl of benzophenone prepared independently did not react with pinacolone enolate to give product. Furthermore, when dicyclohexylphosphine was used in 10 mol % relative to benzophenone, no effect on the rate of formation of product was observed, thus providing further evidence that the free ketyl (H) is not involved in the product-forming step.[11] The overall reaction was second order with a rate constant of 4.5 $\times 10^{-5}$ s^{-1} M^{-1} at 25.0 °C.

The possibility that a radical-chain mechanism may be operating in the reaction of benzophenone with enolate A was investigated by carrying out reactions under normal laboratory light, in the dark, and in the presence of 5 mol % *p*-dinitrobenzene. In all the cases the rate of formation of product was essentially the same. The effect of 10% HMPA or Me_2SO in THF on the reaction of enolate A with benzophenone was also studied. In these solvents the rates of formation of the radical intermediate and product are greater than in pure THF. This observation is consistent with an expected accelerated rate for the formation of the intermediate and product in solvents of higher dielectric constant.

Enolate A was also allowed to react with 2,4-dimethylbenzophenone in THF in the hope of increasing the amount of radical intermediate by slowing down k_2 (Scheme I). The condensation product (G) formed in 30% yield over a period of 9 days. The maximum amount of radical generated in this reaction was approximately 10 times greater than the amount of paramagnetic intermediate generated when benzophenone and enolate A were allowed to react. The reaction of enolate A with mesityl phenyl ketone gave an even larger amount of paramagnetic intermediate

(11) Dicyclohexylphosphine was shown to be an efficient trap for benzophenone ketyl, yielding benzhydrol quantitatively.

Scheme I



(5% free ketyl); however, no product was formed in the reaction. A similar observation was made when mesityl phenyl ketone was allowed to react with enolate B. Such observations are consistent with the mechanism presented in Scheme I.

In conclusion, it has been demonstrated by ESR spectroscopy that typical enolate anions react with aromatic ketones by an electron-transfer process to produce a paramagnetic intermediate. A kinetic analysis shows that the paramagnetic intermediate formed in the reaction of enolate A with benzophenone disappears at the same rate that the condensation product forms.[12] A steric effect seems to be operating in the reaction of benzophenone and its substituted derivatives with the lithium enolates studied that governs not only the rate of formation of condensation product but also the amount of radical generated. Large amounts of free ketyl are observed when the pathway to condensation product is blocked by steric hindrance (k_2 step in Scheme I). When the product is observed, the amount of paramagnetic intermediate is much smaller though dependent on the rate at which product forms. We are now pursuing further characterization of the ESR active species that arise in these reactions as well as extending the work reported here to other carbonyl compounds and lithium enolates.

Registry No. A, 70367-67-8; B, 64869-29-0; C, 119-61-9; D, 1140-14-3; E, 954-16-5; F, 844-39-3; G, 83511-33-5; I, 83511-31-3; lithium benzophenone ketyl, 16592-10-2; lithium mesityl phenyl ketone ketyl, 59671-59-9; lithium 2,4-dimethylbenzophenone ketyl, 83511-32-4; dicyclohexylphosphine, 829-84-5; *p*-dinitrobenzene, 100-25-4; benzhydrol, 91-01-0.

(12) With the assumption that the reaction is at equilibrium after 18 h, the following analysis can be made:

$$d[F]/dt = k_2[I] = k_2K[A][C] = k'[A][C]$$

$$-d[I]/dt = k_2[I] + k_{-1}[I] - k_1[A][C] = k_2[I]$$

$K = k_1/k_{-1} = 0.99$ was estimated by calculating the extent of electron transfer between benzophenone and various lithium enolates where radical intermediate but no condensation product was formed. Hence $k' = 4.5 \times 10^{-5}$ s^{-1} M^{-1} $\approx$ 2.3×10^{-5} s^{-1} M^{-1} = k_2K.