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Mechanistic Studies on the Base-Promoted Addition of Lithiopinacolonate to Several Aromatic Carbonyl Compounds in Nonhydroxylic Solvents†

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Abstract: An investigation of the reaction of lithium enolates with carbonyl compounds is continued by determining kinetic data for the aldol reaction of lithiopinacolonate with *o*- and *p*-methylbenzaldehyde in methylcyclohexane-d_{14} at −80 °C using rapid injection proton NMR spectroscopy. The data were fit to a second-order reaction model with half-lives of 43.2 and 12.7 s, respectively. The NMR spectra showed no evidence of free radicals participating in the CIDNP phenomenon. The question of electron transfer as a feasible mechanism was tested using Eberson's criterion of estimating the barrier to single electron transfer (SET) from the free energy of single electron transfer using the redox potentials of the reactants and Marcus theory. These values were obtained using cyclic voltammetry and second-harmonic ac voltammetry in tetrahydrofuran and acetonitrile at room temperature. In comparison to the observed free energy of activation, calculated from the observed rate at −80 °C, the electrochemical free energy of single electron transfer is sufficiently endergonic to eliminate the single electron transfer pathway according to this criterion. The same type of analysis was utilized for both the aldol reaction of lithiopinacolonate with benzophenone and its Claisen condensation with ethyl 4-nitrobenzoate in THF at room temperature. By this criterion, single electron transfer is also not a feasible process for either of these reactions. Three cyclizable probes were utilized to test further for a SET pathway in the aldol reactions and the Claisen condensation, namely, 7-iodo- and 7-bromo-2-methoxy-2-heptenenitrile and 8-iodo-3-methyl-3-octene. No cyclized products were found in any of the reactions tested. However, as expected, cyclized products were produced from reaction of the probes with tributyltin hydride and AIBN. Bulk electrolysis of the cyclizable probes leads to a complex mixture of products including the expected cyclized ones. None of the (admittedly questionable) criteria applied here to these reactions of lithiopinacolonate with these carbonyl electrophiles gave diagnostic evidence for an electron-transfer mechanism instead of the familiar nucleophilic addition. These results say nothing about the actual (free or aggregated) state of the lithium enolate in the transition structure.

Introduction

The addition of anionic reagents to carbonyl groups ranks in a leading position among the most useful reactions in chemistry. In recent years the power and adaptability of these reactions has been increased enormously by the use of lithium reagents in nonpolar media at low temperatures. Thanks to structural studies in a number of laboratories,[1-5] it is now established beyond doubt that most organolithiums exist in solution under synthetic conditions as clearly defined aggregates. A wide range of complex structures such as ion pairs, triple ions, dimers, tetramers, hexamers, octamers, and mixed aggregates of various types have been authenticated in crystal structures[2a-d,6-10] and in some cases related directly to those in solution.[2a,4b,f,5,6b,9,10] Several studies from this laboratory[5b-d] have dissected the thermochemistry of carefully chosen aldol reactions and related their thermodynamics to the structure changes. However, at this point, little definitive evidence is available about the mechanisms of aldol type reactions under modern synthetic conditions.

The traditional mechanisms proposed for such reactions[11-20] have involved the direct addition of the nucleophilic anion to the carbonyl electrophile usually through a six-membered chair transition state involving the metal cation as an organizing component of the ring. The state of aggregation, if any, of the organoalkali in the transition state is a widely recognized additional

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complication. Beyond that, a fundamental current question is whether the actual coupling of the anionic nucleophile to the carbonyl carbon is preceded by single electron transfer (SET) followed by radical coupling. The case for such a pathway in the aldol addition of lithiopinacolonate (LP) to benzophenone and in the Claisen condensation of LP with ethyl 4-nitrobenzoate was based by Ashby on strong precedents[21c-o] from other organometallic reactions and the appearance of a strong EPR signal which could reasonably be related to the ketyl product of electron transfer to the carbonyl function.[21a,b] Although the intensity of the EPR signal could not be related precisely to the rate of aldolate production, the kinetic behavior provided permissive evidence that the radical species produced by the SET step lay on the reaction coordinate to the products. However, Ashby appropriately advised caution on drawing this as a firm conclusion.

Electron-transfer processes are ubiquitous in chemistry. They may be demonstrated incontestably to take place between anions and carbenium ions of appropriate redox potentials,[21-24] and there is a growing body of evidence that at least some processes previously labeled as S_N2 reactions actually involve an initial SET step.[21,25-30] However, there is an enormous difference between finding permissive evidence for an SET process and proving the relevance of that evidence to the product-forming step on the reaction coordinate. Thus, the radicals produced by electron transfer may exist in a mechanistic blind alley that is not consummated in the final bond-forming step to give the product(s).[21d]

One requirement for an SET step is that the oxidation potential of the anion and the reduction potential of the carbonyl acceptor should be in a reasonable range to make electron transfer feasible. A criterion for such feasibility has been developed by Eberson[22] using Marcus theory to relate the free energy of electron transfer, which is readily determined by electrochemistry, to the free energy of activation and the rate constant for the electron-transfer step. If the electrochemical experiment implies a rate constant that is totally disparate from the observed rate of reaction, SET may be discarded as a reasonable mechanism. This approach has been applied successfully by House,[26] Bordwell and Harrelson,[25] and others. However, Eberson has been careful to point out limitations of this approach in cases where it clearly is misleading, and it cannot be considered as either a necessary or sufficient test for SET.[22]

Another popular diagnostic for SET mechanisms is the use of cyclizable probes: a special radical trapping technique. Most cyclizable probes are hexenyl halides which undergo a very fast intramolecular cyclization if the terminal halogen is removed by a free radical displacement reaction. In view of the fact that impurities or sources of free radicals other than those produced by SET can trigger the cyclization process, this test has become the focus of sharp controversy which has helped to improve the types of probes and to clarify their limits as diagnostic tools.[21c-f,31]

The study to be described below builds on a previous thermochemical and electrochemical examination of the aldol addition of LP to a series of substituted benzaldehydes.[5b] The effects of solvent and determination of aggregation states were included. Now the structural and thermodynamic investigation has been broadened by a rate study at −80 °C using rapid injection NMR (RINMR) spectroscopy. The observed rate constant has been compared with that estimated from the redox data by the Eberson–Marcus criterion. Three cyclizable probes under several conditions were applied to the LP–benzaldehyde aldol reaction

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and also to the two reactions of LP studied by Ashby referred to above.

Experimental Section

Purification and handling of materials and the use of standard instruments followed previously described procedures.[5b,c] Syntheses and purification of the cyclizable probes have been reported elsewhere,[21c,31g] but the following preparations and techniques require comment.

Preparation of 2-methoxy-2-heptenenitrile: In a 250-mL round-bottom flask fitted with a reflux condenser and an addition funnel under argon at room temperature was placed 900 mg (0.03 mol) of sodium hydride (80% dispersion in oil) in 75 mL of THF. To this suspension was added dropwise 6 g (0.029 mol) of diethyl ((cyanomethoxy)methyl)-phosphonate[32] in 40 mL of THF. After complete H_2 evolution, a solution of 3 mL (2.43 g, 0.028 mol) of valeraldehyde in 40 mL of THF was added dropwise. The resulting mixture was heated at reflux for 3 h. After cooling to room temperature, the reaction mixture was quenched with saturated aqueous ammonium chloride solution, and the THF layer was removed by rotary evaporation. The resulting solution was extracted with diethyl ether, and the combined ether layers were dried with magnesium sulfate. The product mixture (cis/trans isomers) was purified using column chromatography (silica gel, 6:1 hexane/ethyl acetate) to give 3.3 g of the cis/trans isomer mixture (85% yield): NMR ($CDCl_3$) 0.8–1.0 (6 H, t), 1.2–2.4 (12 H, m), 3.55 (3 H, s), 5.5 (2 H, t); mass spectrum, *m/e* (relative intensity) 157 ($(M + NH_4)^+$, 100), 140 (7), 124 (3), 113 (4).

Cyclizable probe product studies employed the following protocol. Into a 25-mL round-bottom flask under argon were placed 100 mg (0.5 mmol) of solid lithiopinacolonate (LP), isolated and purified as previously described,[5b,c] and 15 mL of THF at the specified temperature. To this solution were added all at once, via a glass-tight Hamilton syringe, 1 equiv (0.5 mmol) of the cyclizable probe and 1 equiv (0.5 mmol) of the electrophile in 10 mL of THF, which were prepared in a drybox under inert atmosphere and used immediately. The solution was stirred for the specified time interval (see tables). The resulting solution was quenched with saturated aqueous ammonium chloride, and the THF layer was removed by rotary evaporation. The remaining solution was extracted with diethyl ether, and the ether layers were combined, dried over magnesium sulfate, filtered, and concentrated. The products were analyzed immediately using ^1H ^{13}C APT NMR spectroscopy and GC/MS techniques and compared to published spectra. Any changes in reaction conditions are specified in the tables outlining the cyclizable probe product results.

The following protocol was used for sample preparation and operation[33] for rapid injection NMR spectroscopy. Solid LP was isolated, purified,[5b,c] and transferred to a drybox. Samples of approximately 100 mmol (in 0.30 mL of deuterated solvent) were prepared in 5-mm NMR tubes, and the purity of the samples was checked by proton NMR spectroscopy. An internal standard of tribenzylmethylsilane-d_{21} was used because its negative shift would not overlap reactant or product peaks. The NMR tube was placed in the previously equilibrated probe at the proper temperature. The experimental temperatures ranged from 0 to −100 °C depending on the solvent of interest.

A solution of the substituted benzaldehyde was prepared in a 1-mL volumetric flask and transferred to the gas-tight syringe of the injector system. The cap of the NMR tube was removed, and the injector system was placed in the magnet so that the Teflon tip of the injector capillary was just above the solution level in the NMR tube. The spinning rate of the tube was adjusted and final shimming completed.

Approximately 20 μL (1 equiv) of the benzaldehyde solution was injected as the computer was triggered externally. The first FID was acquired after an 85-ms delay for mixing and then every 85 ms up to 5 min. All reactions were shown previously to be complete on this time scale using proton NMR spectroscopy. No evidence for free radical intermediates by CIDNP was seen in the spectra.

Results

Previous studies have reported thermochemical data, colligative properties, and ^6Li, ^{13}C, and proton NMR results for reactions of LP with pivalaldehyde[5c,d] and a series of substituted benzaldehydes.[5b] Here we present a brief kinetic examination, using rapid injection NMR spectroscopy, and an electrochemical determination of the electron-transfer energy between LP and several carbonyl electrophile acceptors. Product studies from the corresponding reactions in the presence of several cyclizable probes are also offered as a test for the single electron transfer mechanism.

Table I. Rapid Injection NMR Data for Injection of *p*-Methylbenzaldehyde into Lithiopinacolonate[a] in Methylcyclohexane-d_{14} at −80 °C

time (s)	X (M)[b]	$a - X$ (M)[c]	$b - X$ (M)[d]	$[1/(a-b)]$ ln $[b(a-X)/a(b-X)]$
0	0.000	0.193	0.168	0.000
2	0.019	0.174	0.149	0.640
4	0.035	0.158	0.133	1.342
6	0.067	0.126	0.101	3.299
11	0.083	0.110	0.085	4.909
16	0.090	0.104	0.078	5.758
21	0.109	0.085	0.059	8.861
31	0.124	0.070	0.044	12.67

[a] The initial concentration of *p*-methylbenzaldehyde was 0.193 M, and the initial concentration of lithiopinacolonate was 0.168 M. [b] Reacted *p*-methylbenzaldehyde concentration reported in M. [c] Unreacted *p*-methylbenzaldehyde concentration reported in M. [d] Unreacted lithiopinacolonate concentration reported in M.

Table II. Rapid Injection NMR Data for Injection of *o*-Methylbenzaldehyde into Lithiopinacolonate[a] in Methylcyclohexane-d_{14} at −80 °C

time (s)	X (M)[b]	$a - X$ (M)[c]	$b - X$ (M)[d]	$[1/(a-b)]$ ln $[b(a-X)/a(b-X)]$
0	0.000	0.067	0.141	0.000
2	0.008	0.059	0.133	0.929
4	0.016	0.051	0.125	2.059
9	0.026	0.041	0.115	3.881
14	0.031	0.036	0.110	5.039
24	0.042	0.025	0.099	8.540

[a] The initial concentration of *o*-methylbenzaldehyde was 0.067 M, and the initial concentration of lithiopinacolonate was 0.141 M. [b] Reacted *p*-methylbenzaldehyde concentration reported in M. [c] Unreacted *p*-methylbenzaldehyde concentration reported in M. [d] Unreacted lithiopinacolonate concentration reported in M.

Table III. Reduction Potentials[a,e] of Ortho-Substituted Benzaldehydes in 0.5 M THF/Tetrabutylammonium Perchlorate with Two Working Electrodes at 25 °C

ortho subst	$E_{1/2}$ (GC)[c]	$E_{1/2}$ (Pt)	E_{red} (GC)[d]	E_{red} (Pt)[d]
NO_2	–	−2057[b,d]	−1997[b]	−2063[b]
Cl	–	−2015[d]	−2085	−2109
Br	–	−2029[d]	−1988	−2037
Me	−2365	−2372[c]	−2356	−2370
MeO	−2381	−2390[c]	−2371	−2388
2,5-Me_2	−2397	−2393[c]	−2377	−2384

[a] All values reported in millivolts with a standard deviation of ±25 mV. [b] Two reduction peaks present in the voltammogram. [c] $E_{1/2}$ values obtained using SHACV at a scan rate of 10 mV/s. [d] $E_{1/2}$ and E_{red} values obtained using CV at a scan rate of 100 mV/s. [e] 1.5–5 mM solutions of the substituted benzaldehyde.

Kinetics. The aldol reactions of LP with substituted benzaldehydes were monitored using RINMR spectroscopy in the laboratory of C.A.O. Several solvents were tried at temperatures mainly just above the freezing point of the solvent, but overlap of the reactant and product resonances prevented clean-cut results.

The most successful data were obtained using *p*- and *o*-methylbenzaldehyde in methylcyclohexane-d_{14} at −80 °C. Tables I and II present the data for their reactions with LP and the results of treatment by the usual second-order rate equation.[34]

Electrochemistry. The use of several voltammetric techniques for determination of the oxidation potential of LP and the series of para-substituted benzaldehydes as a function of solvent, supporting electrolyte, and working electrode has been reported.[5b] Comparable results for the ortho isomers are given in Table III. Because of their relevance to the role of a possible SET pathway for the lithium enolate addition to carbonyl acceptors,[21a,b] a similar

(32) Dinizo, S. E.; Freerksen, R. W.; Pabst, W. E.; Watt, D. S. *J. Org. Chem.* **1976**, *41*, 2846.

(33) (a) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805. (b) McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1810.

(34) Laidler, K. J. *Chemical Kinetics*, 3rd ed.; Harper & Row: New York, 1987.

Table IV. Reduction Potentials[a,b,g] of Ethyl 4-Nitrobenzoate and Benzophenone in THF and MeCN

	$E_{1/2}$			
compd	THF[c]	THF/HMPA[c,f]	MeCN[d]	$LiClO_4$/THF[e]
ethyl 4-nitrobenzoate	-2231 (Pt)	-2192 (Pt)	-1332 (Pt)	- (Pt)
	-2148 (GC)	-2077 (GC)	-1337 (GC)	-1311 (GC)
benzophenone	-2248 (Pt)	- (Pt)	- (Pt)	- (Pt)
	-2248 (GC)	- (GC)	- (GC)	-1867 (GC)

[a] Reported in millivolts with a standard error of ±25 mV. [b] Reversible cyclic voltammograms. [c] 0.5 M TBAP/THF electrolyte solution. [d] 0.1 M TBAT/MeCN electrolyte solution. [e] 0.5 M $LiClO_4$/THF electrolyte solution. [f] 0.8 equiv of HMPA added to electrolyte solution prior to electrochemical analysis. [g] 1.5–5 mM solutions of the electrophile.

Table V. Calculated Free Energies of SET[a,b] for the Reaction of Lithiopinacolonate with Ethyl 4-Nitrobenzoate (Claisen Condensation) and with Benzophenone (Aldol Addition) in THF and Acetonitrile at 25 °C

	ΔG_{SET}		
compd	THF[c]	THF/HMPA[c,d]	MeCN[e]
ethyl 4-nitrobenzoate	46.95	43.74	33.02
benzophenone	45.04	-	-

[a] ΔG_{SET} calculated from $E_{SET} = E_{1/2(red)} - E_{1/2(ox)}$ in volts and $\Delta G_{SET} = -23.06E_{SET}$ in kilocalories/mole. [b] E_{SET} values reported with a standard deviation of ±25 mV. [c] Potentials determined in 0.5 M THF/TBAP electrolyte solution with a platinum working electrode. [d] Enough HMPA added to generate a 9:1 THF/HMPA mixed solvent system. [e] Potentials determined in 0.1 M MeCN/TBAT electrolyte solution with a platinum working electrode.

study was performed on benzophenone and ethyl 4-nitrobenzoate, the results of which are given in Table IV and combined with the oxidation potential of LP to provide free energies of SET in Table V.

Table VI shows the redox potentials of four cyclizable probes used to test for the importance of the SET pathway in the reactions referred to above.

In order to examine the consequences of electrochemical oxidation and reduction of two of the cyclizable probes, we subjected them to bulk electrolysis in THF. The conditions are tabulated in Tables VII and VIII. Table IX reports product studies from the reactions of LP with benzaldehyde in the presence of three cyclizable probes under several reaction conditions, and Table X shows the corresponding control experiments for two of the probes in the absence of the benzaldehyde, under which circumstances no reactions occur. Tables XI–XIII report equivalent cyclizable probe product studies and control experiments for the aldol reaction of LP with benzophenone and for the Claisen condensation with ethyl 4-nitrobenzoate, systems for which Ashby has proposed

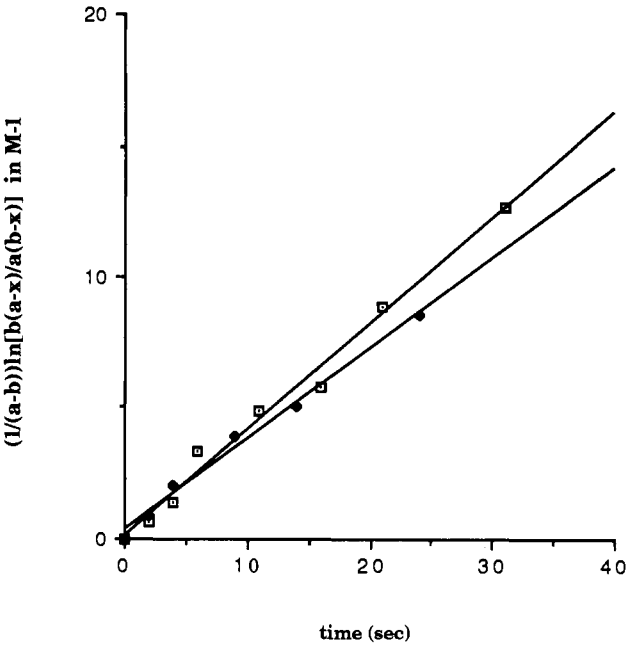


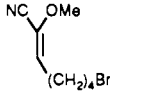
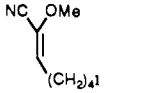
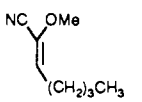
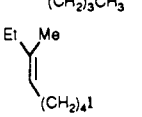
Figure 1. Overlay plot for the results of rapid injection proton NMR of lithiopinacolonate with *p*-methylbenzaldehyde ($y = 6.069 \times 10^{-2} + 0.407x$; $R^2 = 0.987$; $t_{1/2} = 12.7$ s) and *o*-methylbenzaldehyde ($y = 0.355 + 0.346x$; $R^2 = 0.991$; $t_{1/2} = 43.2$ s) in methylcyclohexane-d_{14} at −80 °C fitted to a second-order reaction model: ⊡, para; ◆, ortho.

SET as a primary mechanism.[21a,b] Finally, Table XIV demonstrates the effectiveness of two of the cyclizable probes for responding to bona fide radical-forming conditions.

Discussion

Our previous study[5b] found a fairly good correlation ($R = 0.97$, $\rho = 3.4$) between the heats of reaction of lithiopinacolonate (LP) with seven para-substituted benzaldehydes in THF and acetonitrile. In conformity with many now familiar precedents, the aggregation numbers of LP were found, using vapor pressure osmometry, to be 4.39 ± 0.30 in THF and 6.24 ± 0.74 in acetonitrile at 37 °C whereas that for benzaldehyde is 1.07 ± 0.03 and that for the lithium aldolate is 1.69 ± 0.19 in THF.[5b] Also, at −54 °C, the freezing point of acetonitrile, the aggregation numbers of the enolate and aldolate were 6.97 and 0.85, respectively, by freezing point depression. While it has been shown elsewhere that LP is hexameric in cyclohexane at 37 °C,[5c,d] we have no direct information regarding its aggregation state in methylcyclohexane at −80 °C, but would expect it to be at least tetrameric and perhaps hexameric. All evidence to date would predict that LP is highly

Table VI. Potentials[a] of Cyclizable Probes[e] in 0.5 M TBAT/THF Using Two Working Electrodes at 25 °C

cyclizable probe	reduction			oxidation (Pt)			
	$E_{1/2}$[c] (Pt)	E_{red}[b] (Pt)	E_{red}[b] (GC)	$E_{1/2}$[c] (1)	E_{ox}[b] (1)	$E_{1/2}$[c] (2)	E_{ox}[b] (2)
	−1737 ± 38	−1725 ± 14	−1483 ± 22	-	344 ± 20	-	-
	−1656 ± 25	−1647 ± 20	-	260 ± 25	31 ± 20	562 ± 25	449 ± 20
	*d*			*d*			
	-	−1623 ± 20	-	-	−119 ± 20	-	219 ± 20

[a] Reported in millivolts with standard deviation. [b] Irreversible potential obtained using CV at a scan rate of 100 mV/s. [c] Reversible potential obtained using SHACV at a scan rate of 10 mV/s. [d] No potential observed upon analysis. [e] 100 mM solution of cyclizable probe.

Table VII. Bulk Electrolysis[a,f] of 8-Iodo-3-methyl-3-octene at 25 °C

time (min)	E_{red}[b,c]	$E_{ox}(1)$[b,c]	$E_{ox}(2)$[b,c]	$\Delta E_{ox}(1)$	$\Delta E_{ox}(2)$
0	−1623	−119	219	90	104
68	*e*	−29	323	20	8
136	*e*	−9[d]	331[d]	114	102
204	*e*	105[d]	433[d]	14	4
259	*e*	91[d]	437[d]		

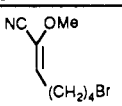
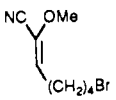
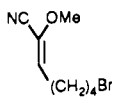
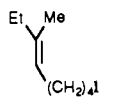
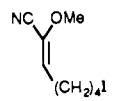
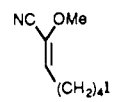
[a] 0.5 M TBAT/THF using platinum working electrode. [b] Irreversible potentials obtained using CV reported in millivolts. [c] Standard deviation of ±25 mV. [d] Coating observed on reference and auxiliary electrodes. [e] Not observed. [f] Initial cyclizable probe concentration of 40 mM.

Table VIII. Bulk Electrolysis[a,e] of 7-Iodo-2-methoxy-2-heptenenitrile at 25 °C

time (min)	E_{red}[b]	$E_{ox}(1)$[b]	$E_{ox}(2)$[b]
0	−1549	−61	295
68	*d*	−1061	587
136	*d*	−1153[c]	603[c]
204	*d*	*d*	615[c]

[a] 0.5 M TBAT/THF using a platinum working electrode. [b] Reversible potential obtained using OSWV reported in millivolts with a standard deviation of ±25 mV. [c] Coating observed on reference and auxiliary electrodes. [d] Not observed. [e] Initial cyclizable probe concentration of 40 mM.

Table IX. Cyclizable Probe Product Studies[a] with Three Cyclizable Probes in the Aldol Reaction of Lithiopinacolonate and Benzaldehyde

entry	probe added[b]	conditions	results[c]	
1		THF, 10 min, −78 °C	*d*	no cyclized product
2		THF, 10 min, 25 °C	*d*	
3		MeCN, 10 min, 25 °C	*d*	
4		THF, 1 h, 25 °C	*d*	
5		THF, 10 min, −78 °C	*d*	
6		THF, 10 min, 25 °C	*d*	

[a] Workup: Quench with saturated aqueous NH_4Cl, remove THF, extract with Et_2O, dry, filter, and concentrate. [b] Concentrations: 0.5 mmol of each reactant in 25 mL of solvent (23 mM). [c] Analyzed by ^1H ^{13}C APT NMR spectroscopy and GC/MS techniques. [d] Aldol and elimination products and cyclizable probe recovered.

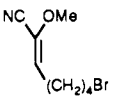
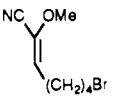
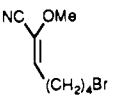
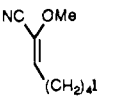
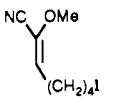
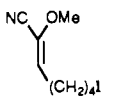
aggregated and that the lithium aldolate from reaction with benzaldehyde would probably be monomeric or dimeric in THF.

Although there are extensive rate and equilibrium studies for aldol additions in hydroxylic media,[35] we know of no direct precedent for a kinetic study under modern synthetic conditions at low temperatures with a lithium enolate in nonhydroxylic solvents. Many experiments with synthetic reactions and our calorimetric measurements show that such aldol reactions are highly exothermic and very fast. Accordingly, we have used the RINMR equipment at UNCC to obtain kinetics for the reaction of LP with o- and p-methylbenzaldehyde in methylcyclohexane-d_{14} at −80 °C. Despite a variety of technical problems, reasonably good second-order data were obtained (Tables I and II and Figure 1) giving for the para compound a second-order rate constant of 0.407 M^{-1} s^{-1} ($t_{1/2}$ = 12.7 s) and for the ortho isomer 0.346 M^{-1} s^{-1} ($t_{1/2}$ = 43.2 s).

The second-order rate data over several half-lives provide only inconclusive evidence for a simple pathway for this aldol reaction.

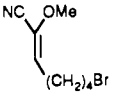
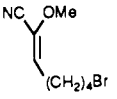
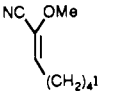
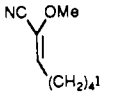
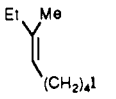
(35) Guthrie, J. P. *J. Am. Chem. Soc.* **1991**, *113*, 7249 and references cited therein.

Table X. Cyclizable Probe Product Studies[a] with Two Cyclizable Probes and Lithiopinacolonate

entry	probe added[b]	conditions	results[c]	
1		THF, 10 min, −78 °C	*d*	no cyclized product
2		THF, 10 min, 25 °C	*d*	
3		MeCN, 10 min, 25 °C	*d*	
4		THF, 24 h, 25 °C	*d*	
5		THF, 10 min, −78 °C	*d*	
6		THF, 10 min, 25 °C	*d*	

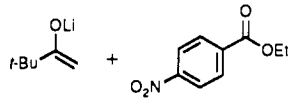
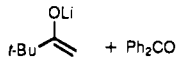
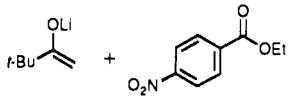
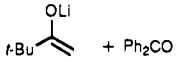
[a] Workup: Quench with saturated aqueous NH_4Cl, remove THF, extract with Et_2O, dry, filter, and concentrate. [b] Concentrations: 0.5 mmol of each reactant in 25 mL of solvent (23 mM). [c] Analyzed by ^1H ^{13}C APT NMR spectroscopy and GC/MS techniques. [d] No reaction; cyclizable probe recovered.

Table XI. Cyclizable Probe Product Studies[a] with Three Cyclizable Probes in the Aldol Reaction of Lithiopinacolonate and Benzophenone

entry	probe added[b]	reactn time[d] (h)	results[c]	
1		1	*e*	no cyclized product
2		60	*e*	
3		1	*e*	
4		60	*e*	
5		24	*e*	

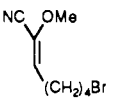
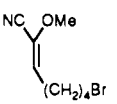
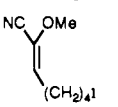
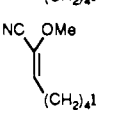
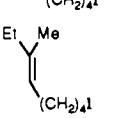
[a] Workup: Quench with saturated aqueous NH_4Cl, remove THF, extract with Et_2O, dry, filter, and concentrate. [b] Concentrations: 0.5 mmol of each reactant in 25 mL of solvent (23 mM). [c] Analyzed by ^1H ^{13}C APT NMR spectroscopy and GC/MS techniques. [d] Reaction run in THF at room temperature. [e] Aldol elimination product, unreacted ketone, and cyclizable probe recovered.

Table XII. Product Studies[a] with Lithiopinacolonate and Benzophenone (Aldol Reaction) and Ethyl 4-Nitrobenzoate (Claisen Condensation) at 25 °C and without Cyclizable Probes

entry	reactants[b]	reactn time[d] (h)	results[c]
1		1	*e*
2		1	*f*
3		4	*e*
4		60	*f*

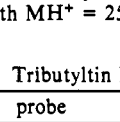
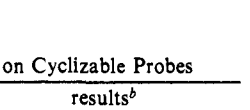
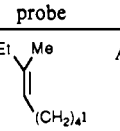
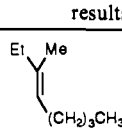
[a] Workup: Quench with saturated aqueous NH_4Cl, remove THF, extract with Et_2O, dry, filter, and concentrate. [b] Concentrations: 0.5 mmol of each reactant in 25 mL of solent (23 mM). [c] Analyzed by ^1H ^{13}C APT NMR spectroscopy and GC/MS techniques. [d] Reaction run in THF at room temperature. [e] Claisen condensation product and unrecovered ester recovered. [f] Aldol elimination product and unreacted ketone recovered.

Table XIII. Cyclizable Probe Product Studies[a] with Three Cyclizable Probes in the Claisen Condensation of Lithiopinacolonate and Ethyl 4-Nitrobenzoate at 25 °C

entry	probe added[b]	reactn time[d] (h)	results[c]	
1		1	*e*	no cyclized product
2		4	*e*	
3		1	*e*, *f*	
4		4	*e*, *f*	
5		4	*e*	

[a] Workup: Quench with saturated aqueous NH_4Cl, remove THF, extract with Et_2O, dry, filter, and concentrate. [b] Concentrations: 0.5 mmol of each reactant in 25 mL of solvent (23 mM). [c] Analyzed by ^1H ^{13}C APT NMR spectroscopy and GC/MS techniques. [d] Reaction run in THF at room temperature. [e] Claisen condensation product, unreacted ester, and cyclizable probe recovered. [f] Unknown GC peak detected with $MH^+ = 257$.

Table XIV. Tributyltin Hydride Reactions on Cyclizable Probes

entry	probe	conditions[a]	results[b]
1		AIBN, Bu_3SnH	
2		AIBN, Bu_3SnH	

[a] Reaction conditions were followed using the protocol of Newcomb et al.: Newcomb, M.; Park, S.-U.; Chung, S.-K. *J. Am. Chem. Soc.* **1986**, *108*, 240. [b] Analyzed by ^1H ^{13}C APT NMR spectroscopy and GC/MS techniques.

Table XV. Calculated Free Energies of SET[a,b] for the Aldol Addition Reactions of Lithiopinacolonate and a Series of Ortho- and Para-Substituted Benzaldehydes in THF and Acetonitrile at 25 °C

	ΔG_{SET}		
subst	THF/TBAP	THF/$LiClO_4$	MeCN/TBAT
p-NO_2	37.19	–	38.16
p-CN	36.22	30.35	38.88
p-Br	38.71	37.84	41.00
p-Cl	38.33	37.43	45.45
p-H	47.87	39.66	46.79
p-Me	49.34	40.33	51.42
p-OMe	51.47	42.91	53.04
o-NO_2	49.7	–	40.6
o-Br	45.7	–	39.9
o-Cl	46.9	–	39.6
o-Me	54.9	–	47.4
o-OMe	55.3	–	48.3
2,5-Me_2	55.2	–	48.3

[a] ΔG_{SET} calculated from $E_{SET} = E_{1/2(red)} - E_{1/2(ox)}$ in volts and $\Delta G_{SET} = -23.06E_{SET}$ in kilocalories/mole. [b] E_{SET} values reported with a standard deviation of ±25 mV.

At least there is no indication of an induction period or complex kinetics suggesting the formation of intermediates. Also, the spectra give no indication of CIDNP. However, Ashby's extensive and careful examination of the addition of organolithium and Grignard reagents to carbonyl acceptors raised the strong possibility that the aldol reaction might be proceeding via an electron-transfer route.[21]

Eberson's Test. An extensive electrochemical investigation of the reduction potentials of the benzaldehydes has been reported,[5b] and the derived free energies of electron transfer from LP at 25 °C are given in Table XV. By Eberson's criterion, an SET mechanism could be dismissed out of hand since the ΔG_{SET}s are all over 45 kcal/mol, far above the reasonable limit of 23 kcal/mol. The corresponding rates for the electron-transfer reactions were also calculated from the electrochemical data using the equation derived from Marcus theory,[22] k_d for the appropriate solvent,[36] and λ estimated from analogous reactions by Eberson.[22b] The k_{SET} for LP and *p*-methylbenzaldehyde is 2.1×10^{-26} s^{-1} and for LP and *o*-methylbenzaldehyde is 2.6×10^{-30} s^{-1} (which correspond to $t_{1/2}$(para) = 3.3×10^{25} s and $t_{1/2}$(ortho) = 2.6×10^{29} s, both of which are greater than present estimates for the age of the universe). These estimates for the SET process obviously conflict with the observed rapid rates at −80 °C.

Eberson[22a] has argued strongly against using any single diagnostic test to establish an SET mechanism, and the same should be said for disproving one. We doubt if Marcus theory could be so wildly erroneous as to account for such ridiculous disparities in rate constants as those cited above. However, one may question the suitability of electrochemical experiments using an electrode surface with a concentrated solution of supporting electrolyte in a polar solvent at room temperature as a conclusive mechanistic test for a process in a completely nonpolar medium at −80 °C.

Furthermore, both the lithium enolate and aldolate are highly aggregated under kinetic conditions, but their states at the electrode in the redox experiments are unknown. Also the question of whether the aldol transition state involves a free enolate anion or one bound to lithium on the side of an aggregate[37] is unknown at present. Thus, the relationship between the actual species involved in the electrochemical and kinetic experiments is tenuous. Finally, Eberson points to the large influence that errors in λ or "electrostatic factors" can have on cases similar to the present one.[22a]

The difficulty of classifying the present reaction within the polar/radical dichotomy is simply an example of a general problem for which there is presently no air-tight answer. Kinetically

(36) Gordon, A. J.; Ford, R. A. *The Chemist's Companion, A Handbook of Practical Data, Techniques, and References*; Wiley: New York, 1972.
(37) (a) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622. (b) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2618.

Table XVI. A Comparison of Observed Values and Calculated SET Values for the Addition of Lithiopinacolonate to a Carbonyl Acceptor

	observed			SET		
carbonyl	k_{obsd}[a]	$t_{1/2}$[b]	$\Delta G^{\ddagger}$[c]	k_{SET}[e]	$t_{1/2}$[h]	ΔG_{SET}[d]
p-methylbenzaldehyde	0.078[f]	12.7[g]	12.1	2.1×10^{-26}	3.3×10^{25}	49.34
o-methylbenzaldehyde	0.023[f]	43.2[g]	12.6	2.6×10^{-30}	2.6×10^{29}	54.9
ethyl 4-nitrobenzoate	0.9×10^{-4}[i]	7.7×10^{3}[g]	22.9	8.7×10^{-25}	7.9×10^{23}	46.95
benzophenone	3.6×10^{-6}[j]	2.8×10^{5}[h]	24.9	1.6×10^{-23}	4.3×10^{22}	45.04

[a] Reported in s^{-1}. [b] Reported in s. [c] Value calculated using the Eyring equation and reported in kilocalories/mole. [d] Obtained in 0.5 M TBAP/THF with a Pt working electrode and reported in kilocalories/mole. [e] Value reported in s^{-1}. [f] Second-order rate constant determined using RINMR spectroscopy at −80 °C in methylcyclohexane-d_{14}. [g] Value calculated for a second-order reaction. [h] Value calculated using the following equation: $t_{1/2} = \ln 2/k$ and reported in s. [i] Value taken from ref 21a for 25 °C in THF; determined using ^{1}H NMR spectroscopy. [j] Value taken from ref 21b for 25 °C in THF; determined using GLC techniques.

long-lived and thermodynamically stable prototypes of radicals, carbenium ions, and carbanions have been established beyond a doubt, but the identification of highly reactive intermediates close to the rate-limiting barrier along the reaction coordinate is quite another matter.

An important component of Ashby's studies of the reactions of LP with benzophenone and with ethyl 4-nitrobenzoate was the identification of strong EPR signals that appeared when the reactants were mixed and then faded at rates that were comparable to the rates of appearance of the products.[21a,b] Ashby was appropriately cautious about any final claims that the formed radicals necessarily lay on the reaction coordinate,[21d] although that is an attractive hypothesis. In the present case, the reaction was much faster than Ashby's, even at −80 °C, and we have no stopped-flow EPR equipment that might be used to detect free radicals directly at such a low temperature. All that may be said on that score is that there was no evidence for the CIDNP phenomenon in the observed RINMR spectra, which is far from definitive proof for the absence of transient free radicals.[38]

Cyclizable Probes. Another currently popular test for radical intermediates in SET reactions is the use of "cyclizable probes" which can undergo a type of intramolecular radical rearrangement that may provide qualitative evidence that a mechanism under study proceeds via the intermediacy of free radicals. The assumption in using cyclizable probes is that, after reaction with a radical in solution, the cyclizable probe will undergo a skeletal rearrangement under favorable conditions. Product analysis can then determine whether ET is occurring. However, Newcomb has subjected the use of this tool to extensive kinetic analysis[31b] and warned especially that radical chain processes triggered by adventitious traces of initiators can produce misleading results.

The application of this variant of radical trapping and the design of appropriate probes has been subjected to extensive discussion by Ashby,[21c-m] Newcomb,[31a-e,g] and Curran.[31c,f] Rather than judge the merits claimed for the various probes, we have used several examples recommended by Ashby and Newcomb for the reaction of LP and benzaldehyde, which are presented in Table IX. Results for some control experiments are given in Table X. By this criterion, there is again no evidence for a SET pathway for this reaction.

Tables VI–VIII and XIV report the conditions for bulk electrolysis and reaction with established radical-forming reagents, all of which show that these probes really do cyclize under SET conditions. These results, taken with the others given above, fail to give any evidence to support the SET route for the aldol reaction of LP with benzaldehydes. However, since none of the criteria used above is capable of providing conclusive mechanistic inference, their accumulated failure does not completely rule out SET as a viable route. Since there is no strong experimental reason at this point to support the SET option, the preferred mechanism remains the addition of some form of the lithium enolate as a nucleophile to the carbonyl group.

In view of Ashby's EPR study of the aldol addition of LP to benzophenone and the Claisen condensation of ethyl 4-nitrobenzoate,[21a,b] it was appropriate to apply Eberson's electrochemical test and also that of cyclizable probes against these closely related reactions. Tables IV and V present the electrochemical results for Ashby's reactions, and Tables XI–XIII present those for the corresponding probe experiments and the controls for those tests. Table XVI summarizes the results for Eberson's test applied to all three systems. Neither of these criteria gives evidence that either of Ashby's reactions proceeds by SET. Thereby, these support Ashby's concern that his observed radicals did not lie along the reaction coordinate.[21d]

At this point one could argue with strength either that none of these three carbonyl addition reactions of LP was going by SET or that they are such good candidates for SET mechanisms that their failure to support such a theory casts doubt on the value of these diagnostic tests. The results so far support the former position. We hope to pursue the application of cyclizable probes and of Eberson's criterion further by testing them against cases where electron transfer is indisputably occurring with the hope of determining some of the limits for this test.

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(38) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987; p 827.