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The Aldol Reaction of Lithiopinacolonate with Substituted Benzaldehydes. Solvent and Structure Effects on Aggregation, Electrochemistry, and Heat of Reaction

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Abstract: The reaction of lithium pinacolonate with seven para-substituted benzaldehydes has been examined in tetrahydrofuran and acetonitrile. Reactions were clean, complete, and instantaneous at 25 °C, and heats of reaction were determined by titration calorimetry. Fairly good ($R = 0.96$) correlations between heats of reaction and the usual Hammett σ_P substituent parameters were obtained although the ionization of substituted benzoic acids is scarcely an appropriate model for the aldol reaction in nonpolar media. The question of electron transfer as a feasible mechanism was tested by using Eberson's criterion for estimating the free energy of activation from the free energy of electron transfer using the oxidation potential of lithium pinacolonate and the reduction potentials of the aldehydes by second harmonic alternating current voltammetry (SHACV) and cyclic voltammetry (CV). Calculated barriers are sufficiently endergonic to eliminate the SET pathway on the basis of this criterion. The effect of lithium perchlorate as a supporting electrolyte suggests a significant interaction between the lithium ion and the aldehyde group, which in fact, was detected through the chemical shifts of ^{13}C NMR spectra of the benzaldehydes upon the addition of lithium perchlorate. Unusual, and unexplained, effects on the oxidation potential were observed from varying the working electrode from platinum to glassy carbon. Aggregation numbers for the initial reactants and for the aldolate product were determined in both solvents by means of vapor pressure osmometry, cryoscopy, and ^{6}Li NMR.

Introduction

During the past quarter century the base-catalyzed aldol reaction has assumed a position of major importance to synthetic chemistry, primarily through the use of lithium enolates in nonpolar media at low temperatures (e.g., −80 °C).[1] During most of its previous 125 years the reaction was performed in aqueous or alcoholic solution at room temperature or above and was too poorly controlled to be of general value.

At first the rapidly developing empirical data base of stereochemical results was treated quite simply in terms of six-membered chelated transition states produced by the addition of the monomeric lithium enolate to the carbonyl acceptor.[1a–f,2] Recent studies have indicated however, that although this simple mechanism is still possible, there are many complexities which could accomodate or require alternative mechanisms.

It is now well known that the tendency for organolithium compounds to form aggregates (dimers, tetramers, hexamers) in nonpolar media is the rule and that monomers are only to be expected for chelated enolates such as those formed from β-dicarbonyl precursors.[3] In the hands of Jackman,[4] Williard,[5] Seebach,[1a,6] and others,[7,8] detailed structures of lithium aggregates have been determined both in the crystalline state and in solution. Solvent change may have a striking effect upon the nature of the aggregates.[9] Furthermore, the addition of lithium salts, or their production during the reaction of a lithium enolate with an alkyl halide may cause the reactive species in solution to pass through a wide spectrum of structural states many of which are viable candidates for the role of the reactive intermediate that forms the transition structure.[8,10] Among these possibilities it is still reasonable that one edge of the aggregated enolate could take the place of the previously proposed monomeric enolate in constructing the classical six-membered cyclic transition state.[6c]

While information about aggregates has been developing, questions regarding the actual nature of the electron-transfer

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process have come increasingly to the fore. Ashby has presented several lines of evidence through rate studies, ESR spectra and "radical clock" reactions which provide strong, but inconclusive evidence[11] that many organometallic additions to carbonyl groups proceed along single-electron transfer pathways. Eberson[12] has provided a careful examination of the various criteria for assigning single-electron transfer mechanisms and authoritative arguments for the difficulty of *proving* that a given reaction follows such pathways by means of the presently employed techniques. He has proposed a reasonable method for the prediction of reaction rates for single-electron transfer reactions by application of the Marcus equation.[12,13]

In cases where the rate constant for a given process can be measured and compared with that predicted by the Marcus equation from the redox potentials of the donor and acceptor, it is possible to decide whether or not a single electron pathway (SET) is at least feasible. Recently Bordwell and Harrelson have applied this technique to the ostensibly nucleophilic displacement reactions of a series of carbanions on several types of substituted alkyl halide substrates and found a considerable number of cases where the measured rate constants agreed closely (within an order of magnitude) with those predicted by the Marcus equation.[14]

Recently we have presented a complete thermochemical analysis fo the aldol reaction of lithiopinacolonate with pivalaldehyde in hexane at 25 °C and in cyclohexane at 25 and 6 °C in the presence and absence of several ligands.[9] Solution structures of reactants and products were determined by using colligative properties and heteronuclear Overhauser enhancement (HOESY) NMR spectra for the ^{6}Li enolate.

The present paper builds on this earlier study by using a series of para-substituted benzaldehydes as the carbonyl acceptors in reaction with lithiopinacolonate in tetrahydrofuran ($\epsilon = 7.58$) and acetonitrile ($\epsilon = 37.5$). As before, aggregation numbers of reactants and products have been determined by vapor pressure osmometry and cryoscopic determinations as a necessary accompaniment to calorimetrically measured heats of reaction.

In order to address the important question of feasible electron-transfer pathways, redox potentials have also been determined for the enolate and aldehyde in every case. The response of each property to variation of the aldehyde structure and of the solvent provides new perspectives on the modern aldol reaction.

Experimental Section

Materials and General Procedures. Tetrahydrofuran (THF; Fisher) was distilled from sodium benzophenone ketyl for calorimetry, vapor pressure osmometry, and cryoscopic measurements. However, because of the sensitivity of the BAS-100A Electrochemical Analyzer, the THF used in electrochemical measurements was distilled solely from sodium metal. Acetonitrile (Fisher) was dried first over potassium carbonate and distilled from phosphorus pentoxide (Fisher) after refluxing under argon for a minimum of 24 h. All air-sensitive compounds and solutions were handled either under argon with use of standard inert atmosphere techniques[15] or in a Vacuum Atmospheres HE-43-2 dry box equipped with a VAC HE-493 purification system. Acetonitrile-d_3 (Aldrich), benzene-d_6 (Aldrich), and THF-d_8 (Aldrich) were used as obtained from their commercially sealed ampules. Routine proton and ^{13}C NMR spectra were recorded on a Varian XL-300 NMR spectrometer at room temperature unless specified otherwise.

Purification of Benzaldehydes. All of the benzaldehydes were available from Aldrich. *p*-Nitro-, *p*-cyano-, *p*-chloro-, and *p*-bromobenzaldehyde were sublimed in vacuo and kept under vacuum for an additional 24 h before being transferred to a dry box for further manipulation. Benzaldehyde, *p*-methyl-, and *p*-methoxybenzaldehyde were vacuum distilled from phosphorus pentoxide and held under vacuum for a minimum of 24 h before being transferred under argon to a dry box. The purity of the aldehydes was checked by proton NMR in $CDCl_3$, and they were used immediately.

Syntheses of Lithium Compounds. Lithiopinacolonate and lithiopinacolonate·THF were isolated as solids.[9] Their purity was checked by ^{1}H and ^{13}C NMR before further manipulation. The lithium salt of 2,2-dimethyl-5-hydroxy-5-(4-chlorophenyl)-3-pentanone was prepared by the addition of 400 mg (2.85 mmol) of *p*-chlorobenzaldehyde to 300 mg (2.83 mmol) of solid lithiopinacolonate in 5 mL of *n*-pentane at 0 °C. Crystals were isolated by cooling to −78 °C and purified by washing with *n*-pentane. The aldolate salt was transferred to a dry box for further use: ^{13}C (^{1}H) NMR (75 MHz, CD_3CN, 25 °C) 225 (C=O), 176 (C-OLi), 143 (C-1′), 131.5 (C-4′), 130 (C-2′), 129 (C-3′), 122 ($-CH_2-$), 42 (*tert*-butyl C), 24 ($-(CH_3)_3$).

Syntheses of [^{6}Li]Lithium-Labeled Compounds. [^{6}Li]Lithium hexamethyldisilazide (LiHMDS) was prepared as described previously.[9] [^{6}Li]Lithiopinacolonate was prepared from 3,3-dimethyl-2-butanone (Aldrich) by reaction with [^{6}Li]HMDS in *n*-pentane at 0 °C and isolated as a crystalline solid at −78 °C. The [^{6}Li] salt of 2,2-dimethyl-5-hydroxy, 5-(4-chlorophenyl)-3-pentanone was prepared by using the purified [^{6}Li]lithiopinacolonate solid and 1 equiv of *p*-chlorobenzaldehyde at 0 °C in *n*-pentane and isolated at −78 °C as a solid with less than 1% residual *p*-chlorobenzaldehyde. Both [^{6}Li]lithium salts were transferred immediately under argon to a dry box for further manipulation.

Product Studies of the Aldol Addition Reactions. In order to ensure that the calorimetric aldol reaction was clean, the system was modeled in a 5-mm NMR tube. Para-substituted benzaldehyde (1 equiv, 10 mmol) was added to 1 equiv of the solid lithiopinacolonate in 0.5 mL acetonitrile-d_3. Proton NMR analysis indicated quantitative formation of the lithioaldolate product.

An alternative method was used to model the aldol reaction in THF. 3,3-Dimethyl-2-butanone (1 equiv, 2.5 mL, 20 mmol) was added to a 1.0 M solution of LiHMDS in THF (20 mL) at −78 °C. After the solution was warmed to 0 °C, 1 equiv of the para-substituted benzaldehyde was added and the subsequent solution was silylated by using 1.5 equiv of trimethylsilyl chloride (Aldrich).[16] The silylated aldol product from each para-substituted benzaldehyde was isolated and analyzed by using proton NMR in $CDCl_3$. All aldol addition reaction product studies showed quantitative formation of the silylated aldol product.

Calorimetry. All heats of reaction were determined at 25 °C by using a Tronac model 1250 solution calorimeter operated in the 450 isoperibol mode. Solutions of lithiopinacolonate (0.08 to 0.1 M) in THF and acetonitrile were prepared by using LiHMDS and 3,3-dimethyl-2-butanone. The solid lithiopinacolonate was isolated and transferred to a dry box where a 50-mL solution was prepared. This solution was transferred via a gas-tight syringe to an argon-purged Dewar calorimeter vessel. Titration calorimetry was used to introduce a precise amount of a para-substituted benzaldehyde solution (0.1 M) into the enolate solution. All benzaldehyde and benzaldehyde/lithium perchlorate (1:1 equivalent) solutions were prepared in the dry box. Clean, linear thermograms indicated that the exothermic reactions were complete and instantaneous at 25 °C. The heats of reaction were calculated by using the standard method.[17]

Vapor Pressure Osmometry. Aggregation numbers reported for lithiopinacolonate in both THF and acetonitrile and for the lithium salt of 2,2-dimethyl-5-hydroxy-5-(4-chlorophenyl)-3-pentanone in THF were determined by using a Wescor 5500-XR vapor pressure osmometer operating at 37 °C in a VAC dry box under purified argon. Calibration curves were obtained by using fluorene (Aldrich) and biphenyl (Aldrich) as standards with a least-squares analysis which generated correlation coefficients of 0.9900 as a minimum. All solutions were prepared within

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Table I. Reduction Potentials[c] of Para-Substituted Benzaldehydes in THF and Acetonitrile with Various Supporting Electrolytes

para substituent	0.5 M TBAP/THF			0.5 M LiClO4/THF			0.1 M TBAT/MeCN		
	$E_{1/2}$ (Pt)	E_{RED} (Pt)[b]	E_{RED} (GC)[b]	$E_{1/2}$ (Pt)	E_{RED} (Pt)[b]	E_{RED} (GC)[b,c]	$E_{1/2}$ (Pt)	E_{RED} (Pt)[b]	E_{RED} (GC)[b]
NO_2	−1908[b]	−1915[d,f]	−1901[d,f]	–	–	–	−1755[b]	−1797[d,f]	−1750[d,f]
CN	−1867[b,f]	−1865[f]	−1811[e]	−1436[a]	–	−1537	−1786[b]	−1773[f]	−1819[f]
Br	−1974[a]	−2167[d,e]	−2100[d,e]	−1730[a]	–	−1862[d]	−1878[a]	−2055[d,e]	−2011[d,e]
Cl	−1957[a]	−2212[d,e]	−2160[d,e]	−1709[a]	–	−1844[d]	−2071[a]	−2088[d,e]	−2099[d,e]
H	−2371[b]	−2382[f]	−2312[e]	−1939[a]	–	−1941	−2129[a]	−2267[e]	−2252[e]
CH_3	−2436[b]	−2437[f]	−2417[e]	−2051[a]	−1975[e]	−1970	−2330[a]	−2333[e]	−2339[e]
CH_3O	−2521[b]	−2536[f]	−2498[e]	−2116[a]	–	−2082	−2400[a]	−2455[e]	−2419[e]

[a] $E_{1/2}$ value obtained by using SHACV at a scan rate of 10 mV/s. [b] E_{RED} and $E_{1/2}$ values obtained by using CV at a scan rate of 100 mV/s. [c] All values reported with a standard deviation of 25 mV. [d] Two reduction peaks present in the voltammogram. [e] Irreversible cyclic voltammogram. [f] Reversible cyclic voltammogram.

the dry box and used immediately. Errors in aggregation numbers for compounds in acetonitrile and THF are ±10%.

Cryoscopic Measurements. Cryoscopy was performed with an apparatus similar to that of Mair et al.[18] The solution temperature was measured by a YSI precision thermistor and freezing curves were obtained with a Keithley 175 voltmeter. Calibration curves were obtained by using solutions of fluorene and biphenyl. Linear least-squares correlation coefficients of these plots were at least 0.9900. All solutions were prepared in a dry box and transferred to the cryoscopy cell via a gas-tight syringe.

Electrochemical Analyses. The acetonitrile solution of 0.1 M supporting electrolyte was made by using triply recrystallized (1:5 ethanol/ether) tetrabutylammonium tetrafluoroborate (TBAT) (Aldrich). The Bu_4NBF_4 salt was vacuum-dried at 110 °C for 24 h and transferred to a dry box before use.

The THF solutions of 0.1 M tetrabutylammonium perchlorate (TBAP, Fluka) and 0.5 M lithium perchlorate (Aldrich) were made by using triply recrystallized (1:1 ethanol/ethyl acetate) TBAP and triply recrystallized (ethanol) $LiClO_4$ respectively. Both salts were vacuum-dried at 110 °C for 24 h and transferred to a dry box before use.

The electrochemical measurements, cyclic voltammetry (CV) and second harmonic alternating current voltammetry (SHACV), were performed with a BAS-100A electrochemical analyzer equipped with a three-electrode assembly. The platinum working electrode (BAS) was polished with BAS polishing diamond suspension and rinsed with acetone before each run. The glassy carbon (GC) working electrode (BAS) was polished with BAS polishing alumina and rinsed with acetone before each use. The counter electrode was a platinum wire (BAS). The silver/silver nitrate and silver/silver tetrafluoroborate reference electrodes were made by inserting a silver wire (0 = 1 mm, Aldrich, 99.99+%) into a 0.1 M solution of silver nitrate or silver tetrafluoroborate which was isolated from the electrolyte solution by a fritted glass bridge (VYCOR membrane). The solvent for the silver nitrate solution was acetonitrile and THF for the silver tetrafluoroborate solution. The internal standard for all electrochemical measurements was the ferrocenium/ferrocene couple and its $E_{1/2}$ value was checked against the reference electrode before and after the measurements. A BAS-supplied electrochemical cell was used for all the measurements. The preparation of solutions and the detailed experimental conditions for individual compounds are given below.

Preparation of Solutions for Electrochemical Measurements. A sample of purified lithiopinacolonate solid sufficient for preparing 10 mL of a 50 mM solution or a sample of purified para-substituted benzaldehyde sufficient for preparing 10 mL of a 1.5–5 mM solution were weighed into cells inside a dry box. The cells were transferred immediately to the cell stand and flushed with high purity argon for a minimum of 2 min. The supporting electrolyte solution (10 mL) was added via a Hamilton airtight syringe and the electrochemical measurement obtained immediately after dissolution of the solid enolate or para-substituted benzaldehyde.

Methods and Conditions for Determining E_{OX}, E_{RED}, and $E_{1/2}$ Values. The techniques and conditions used for individual para-substituted benzaldehydes and lithiopinacolonate in THF and acetonitrile solutions are given in Tables I and II. In general, the error in CV measurements for scan rates of 25–100 mV/sec was ±25 mV. Errors in SHACV measurements for a scan rate of 10 mV/sec were ±30 mV.

^{13}C NMR Studies of Para-Substituted Benzaldehyde/$LiClO_4$ Complexes. In a dry box, 1 equiv of lithium perchlorate was added to a 1.0 mL (5-mm tube) solution of the para-substituted benzaldehyde in THF-d_8 for which a ^{13}C NMR spectrum had just previously been obtained. A ^{13}C NMR spectrum was determined immediately for this solution and both spectra were referenced to THF-d_8. The shift in the carbonyl carbon (Hz) due to coordination was calculated. The ^{13}C NMR control experiments were performed exactly as above substituting tetrabutylammonium perchlorate in place of lithium perchlorate.

Table II. Oxidation Potentials of Lithiopinacolonate in THF and Acetonitrile with Various Supporting Electrolytes at 25 °C

solvent system	E_{OX}, volts[a]	conditions
0.1 M TBAT/MeCN	0.138 ± 0.047	Pt electrode; CV
	0.033 ± 0.024	GC electrode; CV
	0.100 ± 0.028	Pt electrode; SHACV
0.5 M TBAP/THF	−0.086 ± 0.028	Pt electrode; CV
	−0.369 ± 0.087	GC electrode; CV
	−0.295 ± 0.043	Pt electrode; SHACV
0.5 M $LiClO_4$/THF	−0.061 ± 0.014	Pt electrode; CV
	−0.221 ± 0.015	GC electrode; CV

[a] All E_{OX} and $E_{1/2}$ values obtained at a scan rate of 100 mV/s for CV and 5 mV/s for SHACV by using a Pt wire auxiliary electrode at 25 °C.

Table III. Heats of Reaction for the Addition of Lithiopinacolonate to a Series of Para-Substituted Benzaldehydes in THF, Acetonitrile, and THF/$LiClO_4$ at 25 °C and Hammett Substituent Parameters

para substituent	σ_p[c]	ΔH_{rxn}[a]		
		THF	MeCN	THF/$LiClO_4$[b]
NO_2	0.78	−19.40 ±0.55	−20.36 ±1.4	−19.55 ±0.20
CN	0.66	−18.58 ±0.44	−19.44 ±0.97	−18.77 ±0.53
Br	0.24	−17.53 ±0.29	−18.19 ±0.84	−18.26 ±0.39
Cl	0.24	−18.04 ±0.44	−18.55 ±0.52	−17.90 ±0.18
H	0.00	−16.33 ±0.38	−16.95 ±0.82	−16.91 ±0.19
CH_3	−0.17	−16.13 ±0.54	−17.41 ±0.52	−16.51 ±0.17
CH_3O	−0.27	−15.73 ±0.39	−15.94 ±0.27	−15.38 ±0.25

[a] ΔH_{rxn} reported in kcal/mol. Errors reported as standard deviation. [b] $LiClO_4$ (1 equiv) added to para-substituted benzaldehyde solution before titration. [c] Values obtained from Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry*, 3rd ed.; Harper & Row: New York, 1987.

Variable-Temperature ^6Li NMR. All spectra were recorded on a General Electric GN-500 Spectrometer at 73.6 MHz. Samples were allowed to equilibrate at −80, −40, −20, 0, and 25 °C for 10 min prior to acquisition. All ^6Li chemical shifts were reported relative to an external standard [^6Li]Br/acetone-d_6. All samples were checked for decomposition at each temperature increment by using proton NMR.

Results

Calorimetry. Table III presents the heats of reaction for the addition of lithiopinacolonate to a series of para-substituted benzaldehydes. In addition to performing these reactions in THF (ϵ = 7.58), a series of the same reactions were run in acetonitrile (ϵ = 37.5) in order to see whether a solvent effect would be detectable. Although heats of reaction are remarkably similar in both solvents, in every case they are slightly more exothermic in acetonitrile. This is a clearly established trend although differences in most cases are scarcely outside those of the combined experimental errors.

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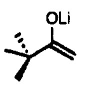
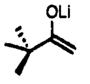
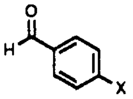
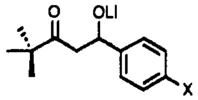
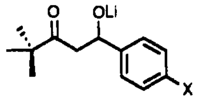
[18] Mair, B. J.; Glasgow, A. R., Jr.; Rossini, F. D. *J. Res. Natl. Bur. Stand.* **1941**, *26*, RP1397.

Table IV. Aggregation Numbers of the Lithium Enolate and Aldolate in THF and Acetonitrile

compd[a]	solvent	technique	aggregation number
	THF	VPO ^{6}Li NMR Cryoscopy	$n = 4.39 \pm 0.30$ – crystallizes
	MeCN	VPO Cryoscopy ^{6}Li NMR	$n = 6.24 \pm 0.74$ $n = 6.97$ one peak
	THF or MeCN	VPO	$n = 1.05 \pm 0.03$
	MeCN	VPO Cryoscopy ^{6}Li NMR	insoluble insoluble one peak
	THF	VPO Cryoscopy ^{6}Li NMR	$n = 1.69 \pm 0.19$ $n = 0.85$ one peak (broad)

[a] X = NO_2, CN, Cl, Br, H, CH_3, or CH_3O.

Table V. The Shift in the Carbonyl Carbon Resonance of the Para-Substituted Benzaldehydes due to Addition of Lithium Perchlorate in THF-d_8 at 25 °C when Using ^{13}C NMR

para substituent	carbonyl chemical shift (ΔH_z)[a]
NO_2	-24.90
CN	-33.46
Cl	-46.11
Br	-46.22
H	-77.17
CH_3	-86.42
CH_3O	-97.98

[a] Carbonyl carbon shift = ^{13}C (aldehyde) – ^{13}C (aldehyde/$LiClO_4$) in ΔH_z referenced to THF-d_8 ^{13}C resonances.

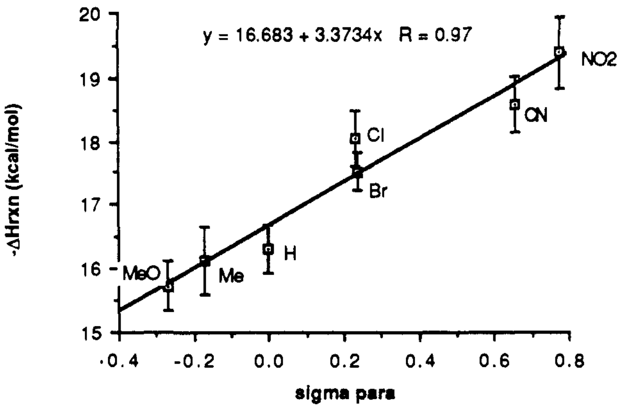


Figure 1. ΔH_{rxn} of lithiopinacolonate and para-substituted benzaldehydes in THF at 25 °C versus the corresponding σ_P values.

Since both the studies on aggregation number and electrochemistry imply considerable involvement of lithium in the reaction, the series was repeated in THF containing 1 equiv of lithium perchlorate before titration of the benzaldehyde into the calorimeter. Whatever contribution added lithium may make to the reaction it is clearly not reflected in the overall thermochemistry. In conformity with all of our previous observations on aldol thermochemistry[9] and rapid injection NMR studies,[8c,d,h] clean, sharp thermograms were obtained in every case indicating instantaneous reaction of the aldehyde with the enolate on the time scale of the titration reaction. Large exothermic values and the sharp titration thermograms indicate clearly that the reactions are also complete.

Aggregation and Structure in Solution. Table IV provides aggregation numbers as determined from vapor pressure osmometry at 37 °C, cryoscopy at −105 °C (THF), and −54 °C (acetonitrile).

^{6}Li NMR demonstrates that only one species of the lithium enolate and aldolate can be detected over the range from −40 to 20 °C in acetonitrile, or at −80 °C in THF. In order to test the interaction of lithium ion as a strong electrostatic acid with the aldehyde function the effect of lithium perchlorate in THF-d_8 at 25 °C on the ^{13}C chemical shift was examined and the results are tabulated in Table V.

Electrochemical Results. Table I presents the reduction potentials for the series of benzaldehydes in two different solvent/supporting electrolyte systems and with two different working electrodes—platinum and glassy carbon. Tetrabutylammonium perchlorate (TBAP) gave good SHACV and cyclic voltammagrams in THF although it is a very poorly conducting solvent. Tetrabutylammonium tetrafluoroborate (TBAT) was a good supporting electrolyte in acetonitrile. No attempt was made to compare TBAP with TBAT in that solvent. In view of the reasonable ion–dipole interaction of lithium ion with the aldehyde function, reduction potentials in THF were determined by using lithium perchlorate as a supporting electrolyte. Clearly this cation enables the reduction process to take place at a lower applied voltage and favors formation of the radical anion. Medium effects and electrode effects will be considered in the Discussion section. Table II summarizes the results for oxidation potentials of lithium pinacolonate as a function of solvent, supporting electrolyte, and electrode. The oxidation potentials are highly sensitive to these conditions for determining the electrode process.

Discussion

Calorimetry. Previous mechanistic studies of aldol additions have been limited almost exclusively to measurements of rates and, in a few cases, equilibria in hydroxylic solvents.[19] Except for the previous report[9] from this laboratory no thermochemical data are available which are directly relevant to the modern aldol reaction. Heats of reaction for the addition of lithiopinacolonate to the para-substituted benzaldehydes listed in Table III explore the effects of variation of structure, medium, and added salt at 25 °C. Here only the effect of changing aldehyde structure is significant.

Figure 1 presents a Hammett plot for the heats of reaction versus the conventional σ parameters. As might be expected the reactions become increasingly exothermic (from methoxy to nitro) in the same direction that the substituted benzoic acids become increasingly acidic in water at 25 °C. In both cases the reaction is favored by the presence of electron attracting groups. Beyond that the similarity of the two processes is so different that they can scarcely be compared.

In the aldol reaction one lithium aggregate (the enolate) is being converted into another (the aldolate) in a non-hydroxylic low-dielectric medium. In the case of the Hammett model reaction a neutral but polar reactant (a benzoic acid) is converted into a resonance-stabilized anion in a medium which is unusually favorable for such a process, by virtue of its polarity and hydrogen-bonding capabilities. Again, the thermodynamic properties are different, σ parameters being free energy terms, which we have plotted against enthalpies in Figure 1. Heats of ionization in water are notorious for their poor correlation with the corresponding free energy terms but their near compensation with entropy factors.[20] A plot of our heats of reaction in Table III versus

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[19] (a) Guthrie, J. P.; Dawson, B. A. *Can. J. Chem.* **1983**, *61*, 171. (b) Guthrie, J. P. *Can. J. Chem.* **1981**, *59*, 45. (c) Guthrie, J. P. *Can. J. Chem.* **1974**, *52*, 2037. (d) Guthrie, J. P.; Cooper, K. J.; Cossar, J.; Dawson, B. A.; Taylor, K. F. *Can. J. Chem.* **1984**, *62*, 1441. (e) Guthrie, J. P.; Cossar, J.; Cullimore, P. A.; Kamkar, N. M.; Taylor, K. F. *Can. J. Chem.* **1983**, *61*, 2621. (f) Guthrie, J. P. *Can. J. Chem.* **1978**, *56*, 962. (g) Agami, C.; Puchot, C. *J. Mol. Catal.* **1986**, *36*, 341. (h) Menon, B. C.; Kiehlmann, E. *Can. J. Chem.* **1971**, *49*, 3648. (i) Nondek, L.; Malek, J. *Coll. Czech. Chem. Comm.* **1980**, *45*, 1812. (j) Koudelka, L. *Chem. Zvesti* **1984**, *38*, 637. (k) Kandlikar, S.; Sethuram, B.; Rao, T. N. *J. Prakt. Chem.* **1979**, *321*, 131. (l) Kandlikar, S.; Sethuram, B.; Rao, T. N. *Ind. J. Chem.* **1978**, *16B*, 914. (m) Kandlikar, S.; Sethuram, B.; Rao, T. N. *J. Ind. Chem. Soc.* **1975**, *LII*, 1126. (n) Kandlikar, S.; Sethuram, B.; Rao, T. N. *Z. Phys. Chem.* **1975**, *95*, 87.

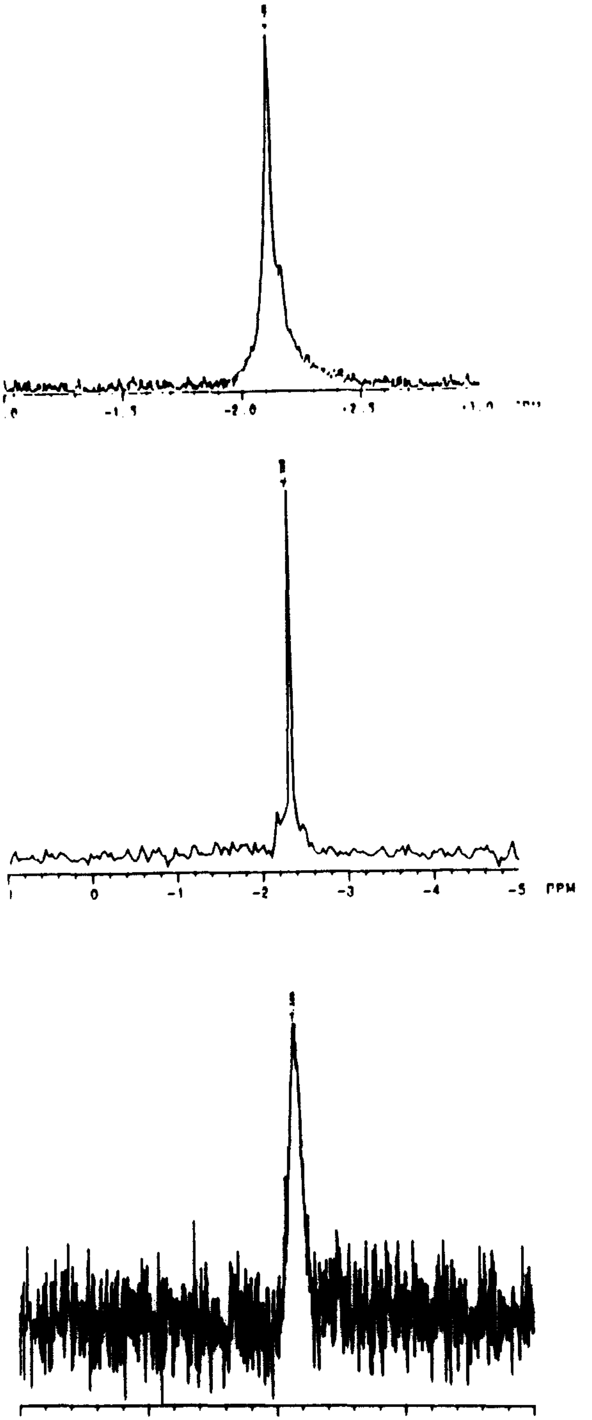

Figure 2. ^{6}Li low-temperature NMR of (A) lithiopinacolonate in acetonitrile-d_3 at -40 °C, (B) lithium salt of 2,2-dimethyl-5-hydroxy-5-phenyl-3-pentanone in acetonitrile-d_3 at -40 °C, (C) lithium salt of 2,2-dimethyl-5-hydroxy-5-phenyl-3-pentanone in THF-d_8 at -80 °C.

Hepler's heats of ionization[20b] (rather than σ) in water gives a complete scatter (R = 0.02) and correlation with Bolton's[20a] ΔH_i values only give R = 0.62. Thus, although it seems to be based on a far-fetched model, σ is the appropriate correlation parameter. For Figure 1 (R = 0.97) similar plots were made for the reaction in acetonitrile and in the presence of lithium perchlorate. Only minor differences in slope, intercept, or correlation coefficient were observed.

Table VI. Effect of Solvent and Supporting Electrolyte on the Reduction Potentials of Para-Substituted Benzaldehydes at 25 °C

			electrode	
para substituent	solvent THF vs MeCN[a]	supporting electrolyte $LiClO_4$ vs TBAP[b]	TBAP/ THF Pt vs GC[c]	TBAT/ MeCN Pt vs GC[d]
NO_2	153 (118)	-	14	47
CN	80 (93)	430	54	47
Br	96 (112)	245	67	45
Cl	114 (123)	248	51	11
H	242 (114)	432	69	15
CH_3	105 (104)	385	20	4
CH_3O	127 (81)	411	38	36
AV	131 (106)	359	45	29

[a] $E_{1/2}$ (THF/TBAP) - $E_{1/2}$ (MeCN/TBAT) using Pt or {E_{RED} (THF/TBAP) - E_{RED} (MeCN/TBAT) using Pt}. [b] $E_{1/2}$ (THF/TBAP) - $E_{1/2}$ (THF/$LiClO_4$) using Pt. [c] E_{RED} (THF/TBAP/GC) - E_{RED} (THF/TBAP/Pt). [d] E_{RED} (MeCN/TBAT/GC) - E_{RED} (MeCN/TBAT/Pt).

The only other thermometric study of a carbonyl addition reaction, of which we are aware, that is related to the present case is the Grignard addition of allylic Grignard reagents to simple ketones.[21] However, the reactants and conditions are too different to serve as a reasonable model.

Aggregation Numbers. As shown in Table IV, the initial state of the lithium pinacolonate varies from tetrameric in THF to hexameric in acetonitrile. The lithium aldolate may be monomeric or dimeric in THF since both colligative properties are close to unity. ^{6}Li NMR in Figure 2 shows no evidence of complex equilibria for either the starting pinacolonate or the product aldolate in both THF and acetonitrile. Not surprisingly, the initial aldehyde is monomeric in both solvents.

Electrochemistry. The addition of a nucleophile to a carbonyl compound can occur either by direct nucleophilic addition (polar process) or by initial single electron transfer (SET) followed by radical coupling. Both of these processes have been proposed for the aldol reaction and evidence exists to support each one depending on the reaction in question.[1,2,10c,d,22]

In our study of the base-catalyzed aldol reaction, the possibility of SET has not been overlooked. Previous papers by Ashby concluded that SET was the dominant pathway in the addition of the lithium enolate of pinacolone to benzophenone and ethyl p-nitrobenzoate in THF at 25 °C[10c,d] based on rate correlations by using ESR. The possibility does exist, however, that the radical observed by using ESR may not be the actual reactive intermediate in the reaction. Other methods (e.g. radical scavengers, stereochemistry, radical clocks, detection of radical products, etc.)[23] are also available to probe the possibility of SET, but once again the problem of determining whether the radical intermediate is indeed on the reaction pathway still exists.

The methodology of Eberson based on Marcus theory considers the energy difference between the initial and final states of the ET step to estimate the reaction barrier and determine the feasibility of the ET.[12,13] From the experimentally obtained oxidation potential of the nucleophile and the reduction potential of the carbonyl compound, the free energy of activation for the SET mechanism can be estimated. House used this type of calculation to determine whether SET was a possible pathway[24] for lithium organocuprate additions to α,β-unsaturated ketones. If a reaction is strongly endergonic, $\Delta G_{SET} > 23$ kcal/mol, it can be eliminated as an ET step; it will be too slow. If however, the reaction is strongly exergonic, $\Delta G_{SET} < -20$ kcal/mol, it can be assumed to be an extremely fast process. The feasibility of ET occurring is

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(20) (a) Bolton, P. D.; Fleming, K. A.; Hall, F. M. *J. Am. Chem. Soc.* **1972**, *94*, 1033. (b) Matsui, T.; Ko, H. C.; Hepler, L. G. *Can. J. Chem.* **1974**, *52*, 2906. (c) Larson, J. W.; Hepler, L. G. Heats and Entropies of Ionization. In *Solute-Solvent Interactions*; Coetzee, J. F., Ritchie, C. D., Ed.; Marcel Dekker: New York, 1969.

(21) Holm, T. *Acta Chem. Scand.* **1976**, *B30(10)*, 985.

(22) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2622.

(23) (a) House, H. O.; Weeks, P. D. *J. Am. Chem. Soc.* **1975**, *97*, 2770. (b) Ashby, E. C. *Acc. Chem. Res.* **1988**, *21*, 414. (c) Ashby, E. C.; Wiesemann, T. L. *J. Am. Chem. Soc.* **1978**, *100*, 3101. (d) Newcomb, M.; Burchill, M. T.; Deeb, T. M. *J. Am. Chem. Soc.* **1988**, *110*, 6528. (e) Newcomb, M.; Curran, D. P. *Acc. Chem. Res.* **1988**, *110*, 6528.

(24) House, H. O. *Acc. Chem. Res.* **1976**, *9*, 59.

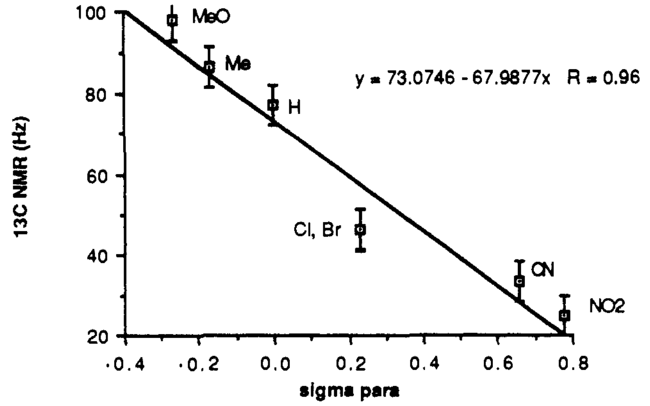

Figure 3. ΔHz of ^{13}C NMR of carbonyl resonance of para-substituted benzaldehydes due to addition of 1 equiv of $LiClO_4$ in THF versus the corresponding σ_P values.

uncertain when the calculated ΔG_{SET} is between these two extremes and a more refined theoretical treatment is needed. Since no general mechanism is required for the aldol reaction, it is desirable that each reaction be tested experimentally for the possibility of SET.

Accordingly, the reduction potentials of the para-substituted benzaldehydes and the oxidation potential of lithiopinacolonate in both acetonitrile and THF were obtained by using CV and SHACV. The results are shown in Tables I and II.

Upon determination of the reduction potentials of the para-substituted benzaldehydes, a dependence on the supporting electrolyte was found (Table VI). A more positive E_{RED} value was obtained in all cases when lithium perchlorate was the supporting electrolyte than with tetrabutylammonium perchlorate in THF. Since this could be a consequence of lithium ion interaction with the carbonyl oxygen dipole of the benzaldehyde, a study using ^{13}C NMR with 1 equiv of $LiClO_4$ added was performed (See Table V). As the para substituent becomes more electron donating (σ_P decreases), the carbonyl carbon is shifted further downfield as is consistent with tighter electrostatic binding to the lithium cation. This change in shift due to the electron-donating or electron-withdrawing character of the para substituent is represented in a plot of ΔH_z for the ^{13}C NMR resonance of the carbonyl carbon versus the σ_P value of the para substituent (see Figure 3). Since lithium ion interaction with the carbonyl withdraws electrons from the carbonyl compound and makes the carbonyl carbon more electropositive, it can be reduced more easily than if the lithium were not present. This is reflected in the E_{RED} values which are more positive in the THF/$LiClO_4$ solvent system. A similar effect has been reported for the polarographic reduction potentials of benzaldehydes in DMF.[25]

Reduction potentials of para-substituted benzaldehydes have been reported previously in various aprotic solvents such as sulfolane, DMSO, DMF, and acetonitrile.[26] However, only in sulfolane has a correlation between the reduction potential and σ_P value for the para substituent been determined. Of the benzaldehydes reported here, the nitro functionality was found to accept an electron prior to reduction of the carbonyl group.[27] Therefore, the electron-withdrawing ability of the substituent was markedly decreased from its σ_P value and did not correlate well with the other benzaldehydes. This was found to occur in this study as well and only the reduction potential of the carbonyl group is reported.

In addition to the nitro analogue, *p*-chloro- and *p*-bromobenzaldehyde also exhibited interesting behavior in sulfolane which was assigned to the reduction of the halogen substituents after the reduction of the carbonyl group.[28] This behavior was also observed in this study and again only the E_{RED} values of the carbonyl are reported. These values do not, however, deviate from the correlation due to reduction occuring after the carbonyl.

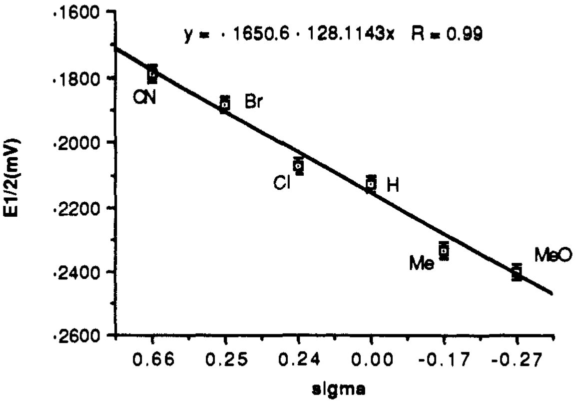

Figure 4. Reduction potentials of para-substituted benzaldehydes in 0.1 M TBAT/acetonitrile versus the corresponding σ_P values.

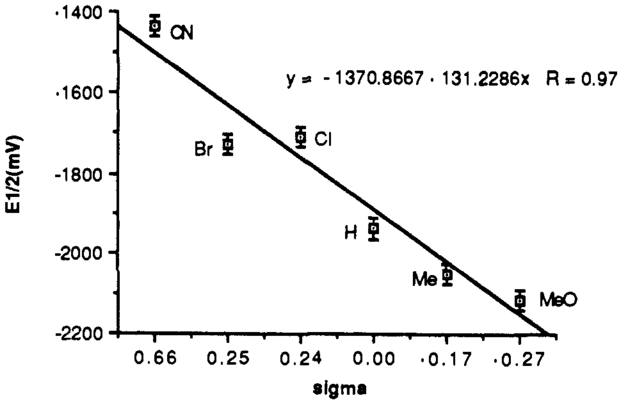

Figure 5. Reduction potentials of para-substituted benzaldehydes in 0.5 M $LiClO_4$/THF versus the corresponding σ_P values.

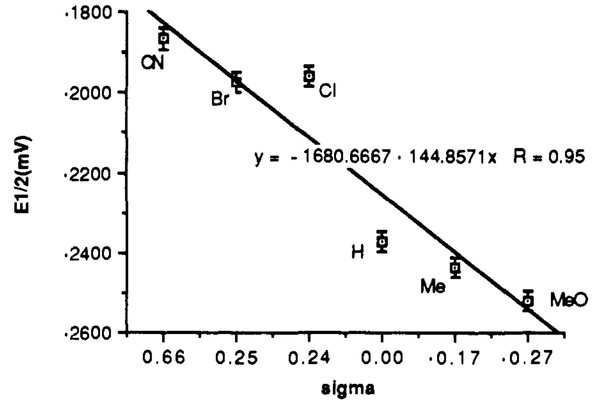

Figure 6. Reduction potentials of para-substituted benzaldehydes in 0.5 M TBAP/THF versus the corresponding σ_p values.

The E_{RED} values in all three solvent systems were plotted versus their respective σ_P values with the exception of the nitro analogue and correlation coefficients upwards of 0.95 were obtained which is identical with that obtained in sulfolane. (see Figures 4–6)

Upon determination of the oxidation potentials of lithiopinacolonate, a dependence on the supporting electrolyte was again found, but to a much smaller extent than for the benzaldehydes. However, a significant dependence on the working electrode was found which was not evident in the reduction potentials of the benzaldehydes. (See Table II) In all three solvent systems studied,

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(25) Kalinowski, M. K. *Chem. Phys. Lett.* **1971**, *8*, 378.

(26) (a) Fawcett, W. R.; Lasia, A. *Can. J. Chem.* **1981**, *59*, 3256. (b) Armstrong, N. R.; Quinn, R. K.; Vanderborgh, N. E. *Anal. Chem.* **1974**, *46*, 1759. (c) Wawzonek, S.; Gundersen, A. *J. Electrochem. Soc.* **1960**, *107*, 537. (d) Armstrong, N. R.; Vanderborgh, N. E.; Quinn, R. K. *J. Electrochem. Soc.* **1975**, *122*, 615. (e) Yeh, L. R. *J. Electroanal. Chem.* **1977**, *84*, 159.

(27) Kargin, V.; Kondrania, V.; Semakhima, H. *Tsvet. Akad. Nauk. Ser. Khim.* **1970**, *2*, 278.

(28) Kolthoff, I. M.; Lingane, J. J. *Polarography*, 2nd ed.; Interscience: New York, 1952; Vol. II, p 681.

Table VII. Calculated Free Energies of SET for the Aldol Addition Reactions of Lithiopinacolonate and a Series of Para-Substituted Benzaldehydes in THF and Acetonitrile with Various Supporting Electrolytes at 25 °C

para substituent	ΔG_{SET}		
	THF/TBAP	THF/$LiClO_4$	MeCN/TBAT
NO_2	37.19	–	38.16
CN	36.22	30.35	38.88
Br	38.71	37.84	41.00
Cl	38.33	37.43	45.45
H	47.87	39.66	46.79
CH_3	49.34	40.33	51.42
CH_3O	51.47	42.91	53.04

[a] ΔG_{SET} calculated from $E_{SET} = E_{RED} - E_{OX}$ (in volts) and $\Delta G_{SET} = -23.06E_{SET}$ (in kcal/mol). E_{SET} values reported with a standard deviation of ±25 mV.

the oxidation potential is more positive when the platinum electrode is used than when the glassy carbon electrode is used. In other words, the enolate will more readily donate an electron when the glassy carbon electrode is the working electrode. We know of no precedent for this result.

The effect of the medium on both the oxidation and reduction potentials was also determined by using tetrabutylammonium perchlorate in THF and tetrabutylammonium tetrafluoroborate in acetonitrile. This allows comparison of solvent without interaction of the supporting electrolyte. There is a substantial shift in the oxidation potentials of lithiopinacolonate due to the change in solvent using either Pt or glassy carbon electrode. The E_{OX} is more negative, and thus the lithium enolate donates an electron more readily in THF than in acetonitrile. Correspondingly, the reduction potentials in all cases are more positive, thus the carbonyl group accepts an electron more readily in THF than in acetonitrile. These results indicate that SET should occur more readily in the former solvent.

In order to determine if the ET step would be energetically feasible, the ΔG_{SET} was calculated from the aforementioned E_{OX} and E_{RED} values (see Table VII). The values for ΔG_{SET} were between 36 and 53 kcal/mol, depending on the solvent and supporting electrolyte. All of these calculations used only reversible $E_{1/2}$ values which were obtained by the SHACV technique using the Pt working electrode. The lowest values for ΔG_{SET} were found in the THF/$LiClO_4$ solvent system due to the effect of $LiClO_4$ on the reduction potentials of the para-substituted benzaldehydes.

Since all of the values of ΔG_{SET} calculated for the ET step are highly endergonic with $\Delta G_{SET} > 23$ kcal/mol, following Eberson, ET should be too slow to be considered as a possible pathway for this particular set of aldol reactions. However these calculations do not eliminate this mechanism for other aldol reactions utilizing different reactants and conditions.

Conclusions

1. The Hammett plots for heats of reaction as a function of para substituent are consistent with the formation of the lithium aldolate product although the ionization of benzoic acids in water would appear to be a poor model for the aldol reaction in nonaqueous media.

2. The addition of lithium perchlorate to solutions of the benzaldehydes produces a significant downfield ^{13}C shift consistent with a strong interaction between the lithium ion and carbonyl group.

3. Reduction potentials of the benzaldehydes are strongly dependent upon the nature of the para substituent, the solvent, and the supporting electrolyte. Oxidation potentials of the lithium enolate of pinacolone are strongly dependent on the solvent and the working electrode.

4. Application of Eberson's method for estimating the free energies of activation from the free energy of electron transfer and the Marcus equation leads to unacceptably high rate barriers for the SET mechanism for this set of reactions. Thus it is probably a polar addition to the monomeric aldehyde by either the free enolate anion or by one of several possible lithium aggregates.

Acknowledgment. This work was supported by National Science Foundation Grant CHE-8709249 for which we are most appreciative. In addition, we would like to thank Dr. Noel G. Harvey and Mr. Michael A. Nichols for their instruction in the use of the techniques used in this research and Professor C. A. Ogle at the University of North Carolina, Charlotte for preliminary rapid injection NMR studies.