Ion Pair Acidities and Aggregation of Some Amide and Oxazoline Enolates in THF[†,‡]

Antonio Facchetti and Andrew Streitwieser*

Department of Chemistry, University of California, Berkeley, California 94720-1460

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Equilibrium lithium ion pair acidities at 25 °C have been determined in THF for the following acetamides: *N*,*N*-dimethyl-(4-biphenylyl)acetamide (**1**) (19.69), *N*,*N*-diethyl-(4-biphenylyl)acetamide (**2**) (20.30), *N*,*N*-dimethyl-diphenylacetamide (**3**) (20.76), *N*,*N*-diethyl-diphenylacetamide (**4**) (21.99), and 1-(diphenylmethylcarbonyl)pyrrolidine (**5**) (21.08). These acidity data compare well with those previously reported for the corresponding cesium enolates. Lithium and cesium ion pair acidities in THF are reported for two oxazolines: 2-(4-biphenylylmethyl)oxazoline (**6**) (Li, 21.53; Cs, 25.49) and (*E*)-(4S,5R)-2-(4-biphenylylmethyl)-4-methoxymethyl-5-phenyloxazoline (**7**) (Li, 20.10; Cs 24.21). Studies of their acidities over a wide range of concentrations indicate that all of the lithium and cesium enolates of **1**−**7** are essentially monomeric at concentrations ranging from 10^{-3} to 10^{-4} M. Traces of dimer were detected for the lithium enolates of amides **1** and **2** and for the cesium enolate of oxazoline **6**. Their dimerization constants (M^{-1}) were found to be about 450, 200, and 150, respectively. All of the other lithium and cesium enolate probably form small amounts of dimer, but the dimerization constant of <100 M^{-1} is below the limit of precision of our spectroscopic method.

Introduction

Metalated derivatives of carboxamides possessing α-aryl or other carbanion-stabilizing groups are well-known compounds, and their simple alkylation and addition reactions have been investigated.[1] Lithium enolates of N,N-disubstituted carboxamides are frequently chosen as nucleophiles because these anions are particularly stable and react with a large variety of electrophiles. These reactions became particularly interesting when asymmetric synthesis was demonstrated.[2] Recent papers have reported the stereochemistry of Michael reactions[3] and additions to epoxides[4] of amide enolates and describe the effects of structural change in the amide and in the electrophile on the stereoselectivity of the reactions. More recently, lithium carboxamide enolates have found application in the synthesis of 10-membered rings via an aza-Claisen rearrangement.[5] Metalated chiral 2-substituted oxazolines are also useful reagents in asymmetric carbon−carbon bond formation, including synthesis of some chiral α-substituted alkanoic acids.[6]

It is also well established that many metal enolates of ketones, esters, and other carbonyl derivatives are frequently aggregated[7] in nonpolar or weakly polar solvents such as hydrocarbons and ethers; dimers, tetramers, and higher aggregates are the usual species present in such solutions. Recently, we reported that cesium enolates of several aryl-*N*,*N*-dialkylamides are essentially monomeric in THF, although small amounts of dimer were detected.[8] The establishment of reaction mechanisms in such systems has synthetic significance because of the potential role of such aggregates in reactivity and stereoselectivity. Mechanistic interpretations have been advanced to explain the regio- and stereochemical behavior of enolate ion reactions, but these theories usually consider the nucleophilic system only in the monomeric state.

In this paper, we report the lithium ion pair acidities of the *N*,*N*-dialkylamides **1**−**5** and the aggregation of the lithium enolates in THF, and we compare them with previous results obtained on the corresponding cesium systems.[8] In addition, this study also included the lithium and cesium enolates of oxazolines **6** and **7**. The amide **8** is a known compound, and its lithium enolate has been studied at low temperature.[9] Accordingly, we hoped to include its enolates in the present study. Unfortunately, we found that the enolates are not stable at room temperature and could not be studied by our techniques.

[†] Carbon Acidity. 105.

[‡] This paper is dedicated to Professor Giorgio A. Pagani on the occasion of his 60th birthday.

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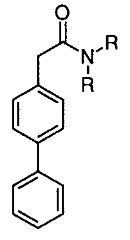

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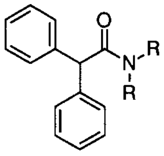

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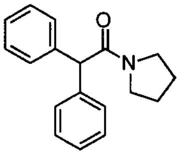

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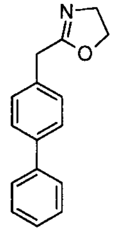

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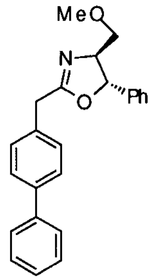

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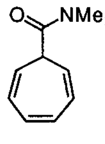

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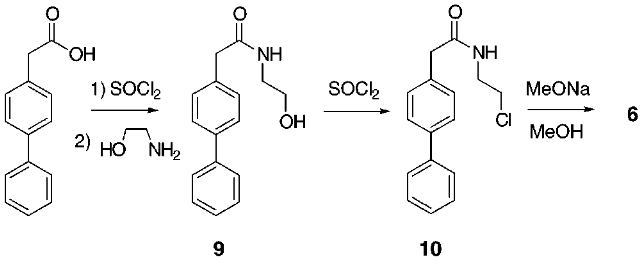
Results and Discussion

Synthesis. Compounds **6** and **7** appear to be unknown in the literature and have been prepared following two of the several procedures[10] for the synthesis of 2-oxazolines. The synthesis of **6** started (Scheme 1) from (4-biphenylyl)acetic acid, which was converted to the corresponding acid chloride with $SOCl_2$ and treated with 2-aminoethanol to give the amide **9** in good yield (85%). Replacement of the OH group of **9** by chlorine with $SOCl_2$ gave **10**, and the final base-catalyzed (MeONa) cyclization afforded the target compound **6**.

Scheme 1



The chiral system **7** was readily prepared following the synthetic route in Scheme 2.

Scheme 2

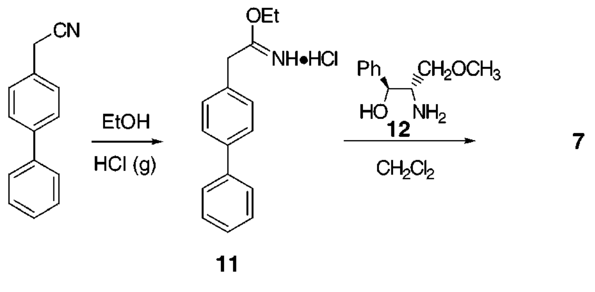


Table 1. Spectroscopic Data for Lithium and Cesium[a] Enolates of 1−7 in THF at 25 °C

compds	counterion	λ_{max} (nm)	ϵ (cm^{-1} M^{-1})
1	Li	408−413[b]	32 500
		396[c]	30 500
	Cs	412[c]	35 600
2	Li	420−422[b]	34 600
	Cs	416[c]	36 600
3	Li	378	18 400
	Cs	392	19 400
4	Li	380	19 600
	Cs	398	18 700
5	Li	377	20 000
	Cs	388	19 000
6	Li	435	53 000
	Cs	442	47 600
7	Li	427	45 900
	Cs	437	47 700

[a] For compounds **1**−**5** from ref 8, otherwise this work. [b] Depending on the concentration. [c] Data are for the isosbestic point.

4-Biphenylylacetonitrile was treated with gaseous HCl in ethanol to give the iminoether **11**. Condensation of the latter compound with the chiral amino alcohol **12** afforded **7** in 67% yield.

Ion Pair Absorption Spectra. All of the cesium and lithium enolates of amides **1**−**5** and oxazolines **6** and **7** absorb in the visible or near-UV region. For each ion pair, a series of 24−30 absorption spectra at different concentrations were recorded for determination of the extinction coefficient. The absorption spectra of enolates Li-**1** and Li-**2** were found to be slightly concentration dependent. A shift of 5 nm was observed for Li-**1**, but only 2 nm for Li-**2**. No appreciable shift in the maximum absorption (λ_{max}) was observed for the other systems. Extinction coefficient measurements of Li-**1** at varying concentrations revealed an isosbestic point at 396 nm (Figure S1, Supporting Information). A clear isosbestic point could not be detected for Li-**2**, probably because the concentration dependencies of its spectra are smaller than the experimental error in the measurements. The spectroscopic data for the metalated enolates M-(**1**−**7**), λ_{max} and extinction coefficients at λ_{max} and/or at the isosbestic point, are summarized in Table 1. Note that the lithium enolates have λ_{max} at shorter wavelength than the corresponding Cs salts, indicating that these Li enolates are CIP.[11]

Singular value decomposition (SVD) was applied to Li-**1** to give the spectra of two components assumed to be monomer and dimer (Figure S2, Supporting Information); however, since the total variation in λ_{max} is so small these spectra could have large systematic errors. In other work, we have found such SVD analyses to have important limitations.[11] Nevertheless, each of the spectra was deconvoluted in terms of these monomer and dimer spectra to give the composition of each mixture from which $K_{1,2}$ was determined as 6.9×10^2 M^{-1}. This value is the average of the three best runs and has a precision of better than 5%; however, because of possible systematic errors in the SVD analysis only the order of magnitude is secure.

Ion Pair Acidity. Ion pair acidities are defined as the transmetalation equilibria in eq 1 (M = Li, Cs) using indicators, InH, of known p*K* values in THF;[12,13] the

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resulting Δp*K*'s are converted to absolute numbers[14] by setting the p*K* of fluorene equal to its ionic p*K* of 22.9 (per hydrogen) measured in DMSO.[15]

$$\mathrm{Ind^-M^+ + AH \overset{K}{\rightleftharpoons} IndH + A^-M^+}$$

$$\Delta pK = -\log K, \quad pK(\mathrm{AH}) = pK(\mathrm{IndH}) + \Delta pK \quad (1)$$

If the ion pairs from AH form aggregates, as in eq 2, the equilibrium (1) is displaced toward the right, resulting in lower measured p*K* values for AH.

$$n(\mathrm{A^-M^+}) \rightleftharpoons (\mathrm{A^-M^+})_n \quad (2)$$

A simple relationship has been previously reported[16] relating the average aggregation number to the measured p*K* values and the ion pair concentration.

The existence of suitable absorption spectra for the ion pairs of compounds **1**−**7** allows the use of the double-indicator method of acidity determination,[17] in which the concentrations of the ion pairs are determined by linear least-squares fitting of the spectra of the separate species (enolate and indicator) to the spectra of the equilibrium mixtures. Details of this method are reported elsewhere.[12−14]

The lithium acidities of the aryl-substituted carboxamides and oxazolines in THF were measured against the following indicators:[13] 3,4-benzofluorene (3,4-BF, p*K* = 19.29) for **1**−**3**, 9-isopropylidenefluorene (IPF, p*K* = 22.33) for **4**, and 1,2-benzofluorene (1,2-BF, p*K* = 19.70) for **5**−**7**. The cesium acidities of the oxazolines **6** and **7** were measured against the indicator 1,5-diphenyl-1,3-pentadiene (DP5, p*K* = 25.62).[12] For each experiment, the initial concentration of the indicator salt ($\mathrm{Ind^-M^+}$) as well as the amounts of compound added were varied to provide a variation in the concentration of the enolate (AM). We have shown[14] that the dissociation constants of lithium salts of a typical hydrocarbon indicators in THF are relatively constant at 1×10^{-5} M. This value is sufficiently large that eq 1 can be effected by the much lower dissociation constants in CIP of lithium enolates **1**−**7** (vide infra). We made a correction considering the lithium carboxamide salts to be effectively undissociated. Since the dissociation constants of cesium ion pairs of these indicators are lower than that for lithium salts,[14] the presence of free ions may be neglected and no correction is required at the concentrations used. The acidities were measured over a large range of anion concentration to determine the extent of ion pair aggregation. The average aggregation number, $\bar{n}$, was obtained from eq 3,

$$pK = \frac{(1-\bar{n})}{\bar{n}} \log[\mathrm{A^-M^+}]_t + b \quad (3)$$

where p*K* is the experimentally measured acidity, $\bar{n}$ is the average aggregation number, $[\mathrm{A^-M^+}]$ is the total formal ion pair concentration, and *b* is a constant for a specific set of AH and IndH.

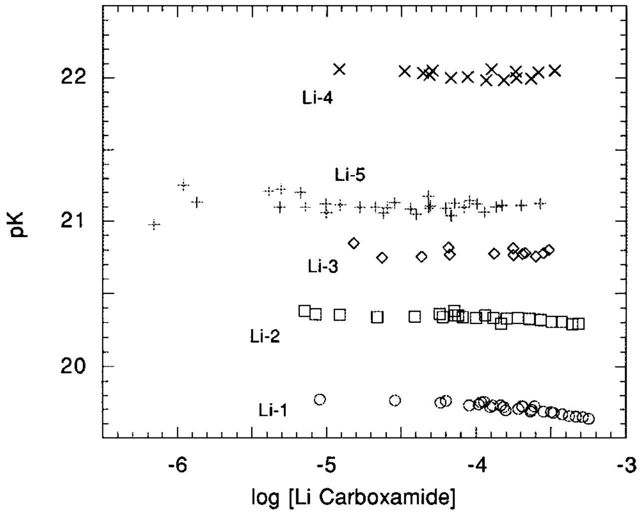

Figure 3. Aggregation of lithium carboxamides by p*K* measurements as a function of concentration. The slope near log[enolate] = −4 of Li-**1**, −0.119, corresponds to $\bar{n} = 1.13 \pm 0.01$; that for Li-**2**, −0.045, corresponds to $\bar{n} = 1.05 \pm 0.01$. The other slopes are close to zero and corrrespond to $\bar{n} = 1.01 \pm 0.01$.

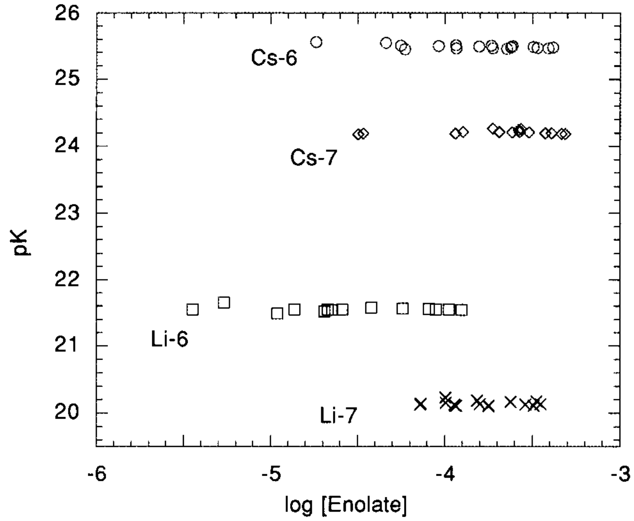

Figure 4. Lithium and cesium ion pair acidity of oxazolines **6** and **7** in THF as a function of anion concentration at 25 °C. Slopes are Cs-**6**, −0.050 ± 0.016; Li-**6**, −0.012 ± 0.021; Cs-**7**, 0.011 ± 0.023; Li-**7**, 0.010 ± 0.037.

If a given anion is aggregated in solution, the apparent p*K* varies with the concentration of metal enolate and the average degree of aggregation is determined by the slope of a plot of p*K* vs log $[\mathrm{A^-M^+}]$.

The observed ion pair acidities at 25 °C are presented in Figure 3 (lithium enolates of **1**−**5**) and Figure 4 (lithium and cesium enolates of **6** and **7**). Compounds Li-**1** and Li-**2** show slight aggregation with $\bar{n} = 1.13 \pm 0.01$ and 1.05 ± 0.01, respectively. All of the other compounds show slopes hardly distinguishable from zero, indicating that they are present wholly as monomers. The only exception is Cs-**6**, which shows slight aggregation. These aggregation numbers are summarized in Table 2, and the experimental data are given in Table S3 (Supporting Information).

An alternative way of expressing the data is by a plot of K_{obs} vs [enolate]/K_{obs}. Such a plot is linear for a

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[12] Streitwieser, A.; Ciula, J. C.; Krom, J. A.; Thiele, G. *J. Org. Chem.* **1991**, *56*, 1074.

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Table 2. Dimerization Constant ($K_{1,2}$) and Average Aggregation Numbers for Ion Pairs of Lithium and Cesium Enolates of 1−7 in THF at 25 °C

		$K_{1,2}{}^{a}$ (M^{-1})	
enolate	$\bar{n}$ (±0.01)	Li	Cs
1	1.13	453 ± 31	470[b]
2	1.05	202 ± 32	440[b]
3	1.01	13 ± 99	120[b]
4	1.01	5 ± 91	83[b]
5	1.01	22 ± 179	69[b]
6	1.01 1.05[c]	51 ± 279	139 ± 71
7	0.99 1.00[c]	−37 ± 107	−11 ± 60

[a] Calculated dimerization constant from acidity data. [b] From ref 8. [c] For cesium.

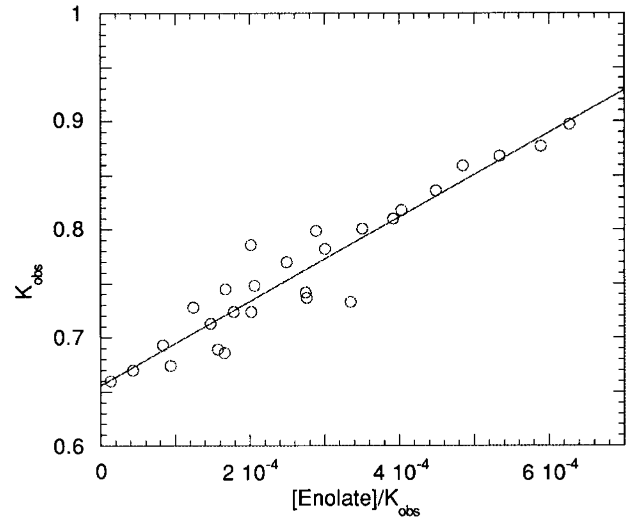


Figure 5. Aggregation plot for Li-**1**. The line shown is 0.656 ± 0.008 + (390 ± 27)x; $R^2 = 0.897$.

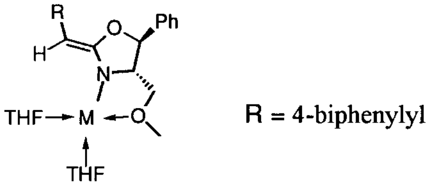
monomer−dimer mixture; the intercept gives K_o for the monomer (from which its pK is determined), and the slope is $2K_{1,2}K_o{}^2$.[17] Such a plot is shown for Li-**1** in Figure 5. The intercept gives $K_o = 0.656$ or pK of the monomer = 19.77 (statistically corrected by 0.30 for the two methylene hydrogens). From the slope, $K_{1,2} = 453 \pm 31$. We consider this to be a more reliable value than that derived by SVD. Note that if higher aggregates were involved significantly the plot would curve upward; the linearity found shows that the aggregation equilibrium is that of monomer−dimer. Similar plots for the other compounds also give linear correlations (Figure S6, Supporting Information) with values for $K_{1,2}$ summarized in Table 2. Note that most of the values are meaningless because the errors are about 10^2 M^{-1}. $K_{1,2} = 100$ M^{-1} means that monomer and dimer concentrations are equal when [monomer] = 0.01 M or the total formal concentration of enolate ([M] + 2[D]) = 0.03 M. These concentrations are much higher than those used in our UV−vis measurements for which the maximum [enolate] is closer to 0.001 M. Thus, for $K_{1,2}$ of the order of 100 or less, other techniques, such as IR or NMR, are more appropriate, as used in the aggregation of lithiated phenylacetonitrile.[18]

The ion pair acidities of the lithium and cesium monomers of the enolates of **1**−**7** are summarized in Table 4. On the basis of reproducibility and our previous experience, these pK values probably have errors of about ±0.1 pK units. The lithium enolates are uniformly 4−5 pK units less basic than the corresponding cesium derivatives, in common with the enolates of ketones.[11] This result is consistent with the spectroscopic data. Both sets of enolates are contact ion pairs, and lithium cation is more tightly bound by the oxygen charge. The trend of the acidities of M-(**1**−**7**) is the same for both the lithium and cesium counterions. The biphenylylacetamides M-(**1**,**2**) are more acidic than the diphenyl derivatives M-(**3**−**5**), although diphenylmethane is more acidic than *p*-methylbiphenyl. The difference is clearly a matter of steric hindrance to conjugation in the anion. Similarly, the *N*,*N*-dimethyl amides M-(**1**, **3**) are more acidic than the *N*,*N*-diethyl and pyrrolidine amides M-(**2**, **4**, **5**) for the same reason; the larger ethyl substituents interfere with conjugation of the aryl group with the amidate anion. A particularly interesting result is that both lithium and cesium enolates of the chiral oxazoline **7** are more acidic than the parent system **6** by about 1.5 units. The only reasonable explanation of this substantial difference is the internal chelation at the metal provided by both the methoxy group and the nitrogen atom which stabilizes the metalated form M-**7**.

Table 4. Ion Pair Acidity[a] of Lithium and Cesium Enolates of 1−7 in THF at 25 °C

compds	pK_{Li}	p$K_{Cs}{}^{b}$
1	19.77	24.87
2	20.36	25.26
3	20.78	25.48
4	22.02	26.09
5	21.11	25.85
6	21.55	25.51
7	20.13	24.20

[a] Ion pair acidity of the conjugate acid with respect to the monomeric ion pair. The pK's are statistically corrected per acidic hydrogen and have estimated uncertainties of about ±0.1 pK units. [b] For compounds **1**−**5** from ref 8.



M-7

What is remarkable and unexpected is that the stabilization of this chelation (about 2 kcal mol^{-1}) is about the same for Li$^+$ and for the much larger Cs$^+$. Such chelation of Li$^+$ was hypothesized by Meyers to explain the stereoselectivity in reactions of oxazolines of the type **7** to produce chiral amino acids[6] and now finds a quantitative confirmation. Note that M-**7** is formulated with two moles of solvent; this is an assumption based on a 4-coordinate lithium cation because our experimental methods give no direct information about solvation. For the related enolates of ketones, temperature effects suggest that the cesium cation is substantially solvated by THF[11a] and that the lithium cation in the monomer is solvated by 2 mol of THF,[11b] a conclusion that agrees with some computational results.[7f] Comparable solvation probably applies to the amide enolates.

Finally, the comparison between amides **1** and **6** shows that biphenylylmethyl carbanions are better stabilized

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(18) Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Corset, J.; Castella-Ventura, M.; Froment, F. *J. Org. Chem.* **1998**, *63*, 3287−94.

by a dialkylaminocarbonyl than by a 2-oxazolinyl substituent. The difference in acidity between the two systems is substantial, especially on the lithium scale (carbonyl vs imino functions).

Conclusions

The spectra of the lithium salts of the amides **1**−**5** and oxazolines **6** and **7** indicate that they are contact ion pairs in THF as are the corresponding cesium salts. The lithium ion pair acidities have p*K*'s ranging from 20 to 22 units. These values are 4−5 p*K* units lower than the corresponding cesium ion pair p*K*'s, indicating that the lithium enolates have dissociation constants to the free ions 10^{-4}−10^{-5} that of the cesium compounds. Both the cesium enolates Cs-(**1**−**5**) and the corresponding lithium compounds Li-(**1**−**5**) show low tendencies to aggregate; only for the biphenylyl enolates **1** and **2** were small amounts of dimer found at concentrations of about 10^{-4} M. Similar studies of the lithium enolates of **3**−**5** showed that their dimerization constants are too low to be accurately detected using our UV−vis method.

Two new 2-(4-biphenylyl)oxazolines **6** and **7** have been synthesized, and the ion pair acidities of their lithium and cesium enolates were determined. Their p*K*'s are about 20−21 and 24−25 on the lithium and cesium scale, respectively. These ion pair acidities are almost invariant with concentration, showing that the enolates of **6** and **7** are essentially monomeric. The results show that a dialkylaminocarbonyl group is more acidifying than a 2-oxazolinyl group. Internal coordination of the alkali cation by the methoxy group in **7** provides stabilization of about 2 kcal mol^{-1} for both the lithium and cesium derivatives.

Experimental Section

General Procedures. Melting points (Pyrex capillary) were determined on a Buchi melting point apparatus and are uncorrected. Elemental analysis and HRMS were by Analytical Services, College of Chemistry, University of California, Berkeley. Spectral measurements were with the glovebox-spectrometer facility described previously.[8]

Materials. Starting materials for synthesis were obtained from commercial suppliers and were purified by crystallization or distillation prior to use. All of the amides **1**−**5** are known compounds and were available from our previous study. The purity of these compounds was monitored by combination of ^{1}H NMR, GLC, mp, and elemental analysis.

***N*-(2-Hydroxyethyl)-4-biphenylylacetamide.** A mixture of biphenylylacetic acid (3.5 g, 16.49 mmol) and thionyl chloride (25 mL) was stirred at 60 °C for 3 h. The excess thionyl cloride was removed in vacuo to yield the crude chloride as a brown oil (3.4 g). A solution of the acid chloride in methylene chloride (30 mL) was added dropwise to a solution of 2-aminoethanol (1.66 g, 27.16 mmol) in the same solvent (6 mL) at 0 °C. After being stirred overnight at room temperature, the solution was filtered and washed with water (50 mL) and the solvent was evaporated to give the amide as a white solid (3.57 g, 13.98, 84.8%): mp 184 °C from MeOH; ^{1}H NMR (acetone-d_6) δ 8.56 (broad, 1H), 7.63 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.1 Hz, 2H), 7.48−7.38 (m, 4H), 7.32 (t, J = 7.2 Hz, 1H), 3.59−3.50 (m, 4H), 3.31−3.22 (m, 2H). Anal. Calcd for $C_{16}H_{17}NO_2$: C, 75.25; H, 6.72; N, 5.49. Found: C, 75.34; H, 6.61; N, 5.22.

***N*-(2-Chloroethyl)-4-biphenylylacetamide.** A solution of *N*-(2-hydroxyethyl)biphenylylacetamide (3.50 g, 13.70 mmol) in thionyl chloride (5 mL) was stirred at room temperature for 20 h. The solution was then poured into dry ether (30 mL), and the chloride was precipitated and collected by filtration. The white solid was washed twice with ether (20 mL) to afford the pure product (2.28 g, 8.33 mmol, 60.8%): mp 173 °C from *i*-PrOH; ^{1}H NMR ($CDCl_3$) δ 7.63−7.56 (m, 4H), 7.47−7.32 (m, 5H), 5.90 (s broad, 1H), 3.64 (s, 2H), 3.62−3.53 (m, 4H). Anal. Calcd for $C_{16}H_{16}NOCl$: C, 70.20; H, 5.89; N, 5.12. Found: C, 70.06; H, 6.05; N, 5.00.

2-(4-Biphenylylmethyl)oxazoline, 6. *N*-(2-Chloroethyl)-biphenylylacetamide (1.00 g, 3.65 mmol) was dissolved in 30 mL of 1 M MeONa in MeOH and the solution was refluxed. After being stirred for 2 h, the solution was poured onto water (100 mL) and the precipitate was collected by filtration. The crude oxazoline (750 mg) was chromatographed on silica gel (1:1 CH_2Cl_2/AcOEt) to afford the pure compound as a white solid (340 mg, 1.43 mmol, 39.2%): mp 87 °C (after sublimation); ^{1}H NMR ($CDCl_3$) δ 7.63−7.51 (m, 4H), 7.48−7.30 (m, 5H), 4.27 (t, J = 9.3 Hz, 2H), 3.87 (t, J = 9.2 Hz, 2H), 3.66 (s, 2H). Anal. Calcd for $C_{16}H_{15}NO$: C, 80.97; H, 6.38; N, 5.90. Found: C, 81.00; H, 6.41; N, 5.89.

(*E*)-(4*S*,5*R*)-2-(4-Biphenylylmethyl)-4-methoxymethyl-5-phenyloxazoline, 7. Dry hydrogen chloride was passed into a solution of biphenylylacetonitrile (300 mg, 1.55 mmol) and EtOH (75 mg) in dry toluene (8 mL). After one night at 0 °C, dry ether (15 mL) was added and ethyl iminobiphenylyl acetate hydrochloride precipitated (420 mg, 1.52 mmol, 98.2%): ^{1}H NMR (DMSO-d_6) δ 7.69−7.57 (m, 4H), 7.48−7.32 (m, 5H), 4.37 (q, J = 6.9 Hz, 2H), 3.98 (s, 2H), 1.28 (t, 3H). The white solid was washed twice with ether and used in the following step without further purification.

(1*S*,2*S*)-1-Phenyl-2-amino-3-methoxy-1-propanol (250 mg, 1.38 mmol) was added in one portion to a solution of the imino ether hydrochloride (420 mg) in dry methylene chloride (5 mL) at 0 °C. After being stirred for 7 h at 0 °C, the white turbid mixture was poured into ice−water (10 mL). The methylene chloride layer was separated, and the aqueous solution was extracted twice with methylene chloride (20 mL), dried ($MgSO_4$), and concentrated to give a brown oil (0.501 g). Flash chromatography on silica gel (1:1 Et_2O/ETP) gave **7** as a colorless oil (330 mg, 0.92 mmol, 66.9%). Kugelrohr distillation gave a pure sample for the glovebox studies: ^{1}H NMR ($CDCl_3$) δ 7.65−7.15 (m, 9H), 5.38 (d, J = 6.6 Hz, 1H), 4.17 (m, 1H), 3.84 (s, 2H), 3.68−3.47 (m, 2H), 3.42 (s, 3H); HRMS mass calcd for $C_{24}H_{23}NO_2$ 357.1729, found 357.1734.

Ethyl 1,3,5-Cycloheptatriene-7-carboxylate.[19] 7-Cyano-1,3,5-cycloheptatriene (3 g, 25.61 mmol) was refluxed under nitrogen in methanol (45 mL) containing concentrated H_2SO_4 (9 g) for 35 h. The bulk of the solvent was removed in vacuo, and the residue was poured into water (120 mL). The solution was extracted with petroleum ether (3 × 20 mL), the extract was dried over $MgSO_4$, and the solvent was evaporated to give the crude ester (3.03 g). Two distillations under reduced pressure afforded the pure ester as a colorless oil (1.78 g, 11.85 mmol, 46.3%): ^{1}H NMR ($CDCl_3$) δ 6.70−6.61 (m, 2H), 6.33−6.26 (m, 2H), 5.41−5.34 (m, 2H), 3.34 (s, 3H), 2.59 (t, J = 5.5 Hz, 1H).

1,3,5-Cycloheptatriene-7-carboxylic Acid.[19] A solution of ethyl 1,3,5-cycloheptatriene-7-carboxylate (1.00 g, 6.65 mmol) in methanol (8 mL) was added to a solution of $NaHCO_3$ (0.76 g, 9.05 mmol) in water (6 mL). The reaction mixture was refluxed for 2 h and then poured into water (25 mL). The alkaline solution was washed with petroleum ether (2 × 25 mL) to remove the unreacted ester, acidified (pH = 1) with H_2SO_4 (30%, ca. 1 mL) and finally extracted with ether (3 × 20 mL). The organic layer was dried over $MgSO_4$, and the solvent was removed under reduced pressure to afford the pure acid as a colorless oil that crystallized on standing in the refrigerator (0.67 g, 4.92 mmol, 74.0%): ^{1}H NMR ($CDCl_3$) δ 6.70−6.60 (m, 2H), 6.35−6.22 (m, 2H), 5.46−5.27 (m, 2H), 2.59 (t, J = 5.7, 1H).

***N,N*-Dimethyl-1,3,5-cycloheptatriene-7-carboxamide.**[10] A mixture of 1,3,5-cycloheptatriene-7-carboxylic acid (0.5 g, 3.67 mmol) in thionyl chloride (4 mL) was stirred at room temperature for 42 h. The excess of thionyl chloride was removed at 60 °C under reduced pressure, leaving the acid

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[19] Betz, W.; Daub, J. *Chem. Ber.* **1972**, *105*, 1778

chloride as a brown oil. The chloride was dissolved in dry ether (20 mL), and an excess of dimethylamine was bubbled for 1 h. The timing of this step is important; shorter or longer times led to lower yields. The dimethylamine hydrochloride formed was filtered, and the filtrate was concentrated in vacuo to give a brown oil (0.67 g) that was chromatographed on silica gel (ether/ETP 7:3) to afford a colorless oil (0.32 g). The pure amide (0.26 g, 1.59 mmol, 43.32%) was obtained as a white solid (mp 62 °C) after Kugelrohr distillation: ^{1}H NMR ($CDCl_3$) δ 6.70−6.58 (m, 2H), 6.31−6.18 (m, 2H), 5.52−5.38 (m, 2H), 3.01 (s, 3H), 2.91 (s, 3H), 2.42 (t, $J = 6.4$ Hz, 1H).

Deprotonating Agents. The solution of cesium diphenylmethane used to prepare the cesium enolates was obtained using our previously reported procedure.[20] Trimethylsilylmethyllithium was prepared following the method described by Saljoughian.[21] After sublimation, it was transferred into the glovebox and used as a solid to prepare the lithium enolates.

Extinction Coefficient Measurements. A solution of known concentration of **1**−**7** in THF was prepared in a UV cuvette, and an excess of base was added to completely deprotonate the neutral compound. The solution was successively diluted with known amounts of THF, and the spectrum was recorded after each dilution.

Acidity Measurements. The method used is substantially that of the double indicator method described previously. A known amount of both an appropriate hydrocarbon indicator and a substrate (**1**−**7**) were transferred into a thermostated 0.1 cm quartz cell containing a known amount of THF. At this point, two procedures were followed depending on whether the equilibrium between the indicator and the substrate was reached rapidly or slowly. In the first case, a small amount of base was added, and the spectrum of the solution was immediately recorded. In the second, the base was added until the absorbance of the solution reached 1.5−2.0 absorbance units, and then the mixture was allowed to reach equilibrium. Spectra at different anion concentrations were obtained by successive addition of base in the first case or by dilution with known amounts of THF in the second.

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Supporting Information Available: Figures S1, S2, and S6 and Table S3. This material is available free of charge via the Internet at http://pubs.acs.org.

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[21] Saljoughian, M. *Monatsh. Chem.* **1984**, *115*, 519.