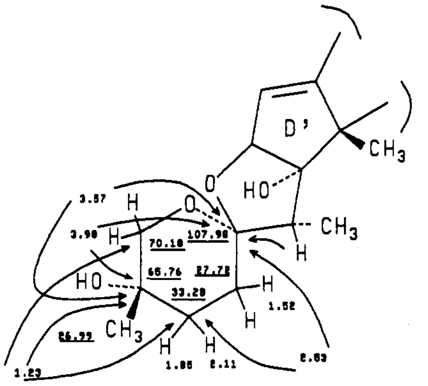
tively to cephalostatins 7–9. While the right-side moiety of pyridizines 7–9 proved identical with that of cephalostatin 1 (**1**), beyond the left-side C′-ring of each were found substantial differences. Structural elucidation of cephalostatin 7 (**3**) primarily by high field two-dimensional ^{1}H- and ^{13}C-NMR provides an appropriate illustration. Partial structure A for rings D′–F′ was derived from the result of heteronuclear multiple bond correlations (HMBC).[12] Application of comparable H,H-relayed COSY,[13] NOE, and HMBC experiments to cephalostatin 8 resulted in structure **4** as most consistent with the spectral data with only the stereochemistry at C-22′ remaining equivocal. The same approach was also successful with cephalostatin 9 (**5**) again excepting the stereochemistry at C-22′. The configuration of the C-23′ hydroxyl is likely *R* as shown, and established in cephalostatin 1 (**1**).



A

Cephalostatins 7–9 (**3**–**5**) displayed remarkable potency with TI$_{50}$ (molar) values of 10^{-9}–$<10^{-10}$ against a number of (e.g., non-small cell lung HOP 62, small cell lung DMS-273, renal RXF-393, brain U-251 and SF-295, and leukemia CCRF-CEM, HL-60, and RPM1-8226) cell lines and values of 10^{-8}–10^{-9} for the breast MCF-7 cell line; the "mean graphs" (see ref 10 for definition and interpretation) showing the patterns of relative cellular sensitivity across the panel of 60 cell lines were remarkably similar, if not essentially indistinguishable, for cephalostatins 1–4 and 7–9. By contrast, cephalostatins 5 and 6 (**2**) proved to be modestly cytotoxic against only two of these human cell lines (renal SN12K1 and CNS U-251) with potency reduced to GI$_{50}$ 10^{-7}–10^{-8} molar.

Discovery of cephalostatins 1–4 and 7–9 with potent cytotoxicity against certain human cancer cell lines suggests that the pyridizine right-side unit is essential for such biological activity. Minor configuration and substitution (including an additional methyl in cephalostatin 8) alterations in the left-side E′- and F′-rings appear to have little influence on cytotoxic activity, but aromatization of the C′-ring with concommitant bonding to the side-chain system (cf. **2**) markedly diminishes the potency. Perhaps cephalostatins 5 and 6 (**2**) represent a biosynthetic misadventure in the long evolutionary history[14] of *Cephalodiscus*.

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Supplementary Material Available: 400-MHz ^{1}H-NMR spectra of Cephalostatins 7–9 (6 pages). Ordering information is given on any current masthead page.

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Dependence of Aggregation on the Basicity of Some Cesium Enolates in THF[1]

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Summary: Equilibrium constants in THF for dimerization of several cesium enolates of benzylic ketones show a decrease as the ion-pair acidities of the parent ketones increase when steric factors are comparable.

Many enolate salts are known to be aggregated in synthetically important ethereal solvents such as THF.[2-4] With increasing delocalization of the carbanionic charge the enolate ion becomes less effective in solvating the cation compared to solvent dipoles and aggregation is expected to be less important. This principle has been established qualitatively[5] but not quantitatively. Arnett and Moe[4] have recently shown that aggregation numbers of some lithium enolates and related phenolates depend also on steric bulk and the type of acidic group. In the present work we present the first determinations of equilibrium constants for dimerization of some cesium enolates and show that the principle is established quantitatively for several ketones when steric effects are approximately constant.

The ketones selected for study are the aryl-substituted acetones, 1,3-diphenyl- (**1**), 1,3-di(1-naphthyl)- (**2**),[6] 1,3-di(4-biphenylyl)- (**3**),[7] and 1,1,3,3-tetraphenylacetone (**4**),[8]

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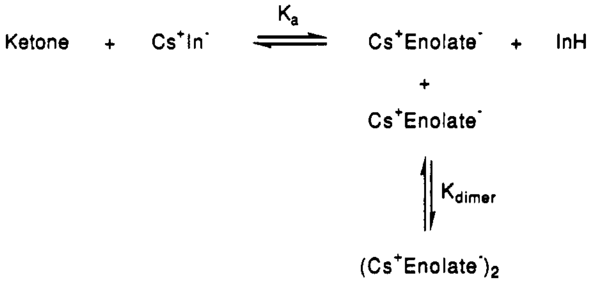
Table I. Cesium Ion-Pair Acidities and Ion Pair–Ion Pair Dimer Equilibrium Constants for Benzylic Ketones in Tetrahydrofuran at 25 °C[a]

compd	pK_a[b]	K_{dimer}[c]	λ_{max}[d] (ϵ)
1,3-diphenylacetone (1)	17.95	1870	337–342 (22400
1,3-di(1-naphthyl)acetone (2)	17.78	760	419–425 (14300)
1,3-di(4-biphenylyl)acetone (3)	17.10	595	393–398 (29800)
1,1,3,3-tetraphenylacetone (4)	16.57	570	348–351 (19200)
α,α-diphenylacetophenone (5)	17.56	2310	361–363 (14600)

[a] On a per hydrogen basis for the monomer relative to fluorene = 22.90. Indicators used were 9-*p*-biphenylylfluorene (p*K* = 17.72), 7-phenyl-7*H*-benzo[*c*]fluorene (p*K* = 15.62), and 9-phenylfluorene (p*K* = 18.15).[10] [b] The estimated error is of the order ±0.05 p*K* units. [c] Equilibrium constant for the formation of ion pair dimers from ion pair monomers, M^{-1}. From a total differential analysis, the error associated with the dimer/monomer equilibrium constants is on the order of 10%. [d] This is the range observed for the maximum absorbance wavelength of the mixture of monomer and dimer ion pairs for the cesium enolates in nm.

Scheme I



and α,α-diphenylacetophenone (**5**). The observed ion-pair acidity constant is dependent on the concentration of the enolate ion; the slope of a plot of the logarithm of the enolate concentration versus the observed p*K* is equal to $(n - 1)/n$, where n is the average aggregation number.[3] The plots of the cesium salts of **1–5** exhibit curvature indicating that the amount of aggregation of the enolate ion pairs changes with concentration, a feature not previously observed for such carbanion ion pairs. The change in the state of aggregation is also demonstrated by a dependence of the wavelength maximum on the concentration of the cesium enolate.[9] A blue shift of the λ_{max} of approximately 5 nm was observed as the concentration of the cesium enolate was increased over the range used (Table I). The slopes from each plot gave average aggregation numbers near 1 at low concentrations ($\sim 2 \times 10^{-5}$ M) and approximately 2 at the highest concentrations ($\sim 1 \times 10^{-3}$ M) used in this work. We make the reasonable assumption that the principal equilibria are between ion pair monomers and dimers.

A straightforward analysis of the equilibria in Scheme I leads to eq 1–5 from which the true acidity constant for monomers, K_a, and the equilibrium constant for dimerization, K_{dimer}, can be deduced from the experimental data.

$$K_a = [\mathrm{Cs^+enolate^-}][\mathrm{InH}]/[\mathrm{ketone}][\mathrm{Cs^+In^-}] \quad (1)$$

$$K_{dimer} = [(\mathrm{Cs^+enolate^-})_2]/[\mathrm{Cs^+enolate^-}]^2 \quad (2)$$

$$K_{a(obs)} = [\mathrm{Cs^+enolate^-}]_{total}[\mathrm{InH}]/[\mathrm{ketone}][\mathrm{Cs^+In^-}] \quad (3)$$

$$[\mathrm{Cs^+enolate^-}]_{total} = [\mathrm{Cs^+enolate}] + 2[(\mathrm{Cs^+enolate^-})_2] \quad (4)$$

$$K_{a(obs)} = K_a(1 + 0.5(1 + 8K_{dimer}[\mathrm{Cs^+enolate^-}]_{total})^{1/2}) \quad (5)$$

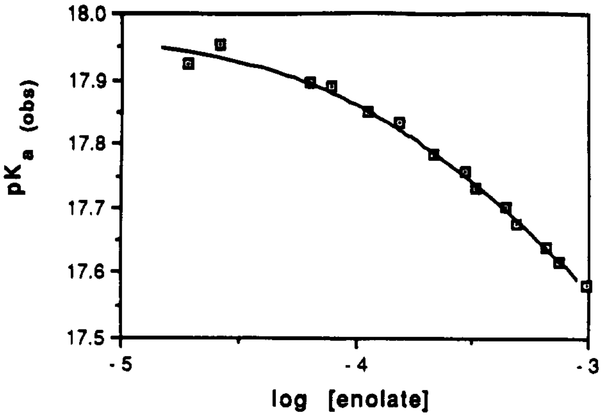


Figure 1. Aggregation plot for **1**. The curve shown is the theoretical curve for pK_a of the monomer = 17.97 and K_{dimer} = 1890 M^{-1}.

Note that the concentration of the enolate dimer is multiplied by 2 because the spectroscopic method does not distinguish among the different aggregated enolates and only measures the total amount of enolate in solution. The p*K* values for the indicators used have been reported previously.[10] The acidity values reported in Table I are for the formation of the monomer cesium ion pair from the ketone. An example of this analysis is given for **1** in Figure 1. The values for **1** and **4**, 17.95 and 16.57, respectively, compare favorably with those reported by Bordwell for the free ions in DMSO of 19.4 for **1** and 17.7 for **4**.[11] The fact that the relative ion pair p*K*s are lower than the DMSO values indicates that these cesium enolates are less dissociating to the free ions than the cesium salts of the indicators used.[12]

The data in Table I show that an increase in the size of the conjugated system (more delocalization) is accompanied by an increase in the acidity of the ketone; however, there is no general correspondence between the basicity of the enolate ion pair and its tendency to dimerize. Steric effects are undoubtedly also important in determining aggregation. Table I includes two pairs of systems whose steric environment in the enolate region are similar but whose acidities differ. In the cesium salt of **3**, the *p*-phenyl substituent results in significant delocalization without affecting the steric environment around the enolate group. In this comparison, a $\Delta G°$ of 1.2 kcal mol^{-1} change in acidity results in a $\Delta G°$ change of 0.7 kcal mol^{-1} in dimerization. Similarly, both enolates **4** and **5** are derived from benzhydryl ketones. For this pair a $\Delta G°$ change of 1.35 kcal mol^{-1} change in acidity is accompanied by a $\Delta G°$ change of 0.8 kcal mol^{-1} in dimerization.

The present results provide a quantitative demonstration that as cesium enolate ion pairs become less basic they are less likely to aggregate, when steric factors are comparable. This result may be general; it would be especially important to establish that it applies as well to synthetically more important lithium enolates.

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