matched literature values.

^{1}H NMR of **21**: 5.66 (m, 1 H), 4.89 (bs, 1 H), 4.74 (bs, 1 H), 2.34 (m, 2 H), 2.15 (m, 4 H), 1.68 (pent, $J = 6.0$ Hz, 2 H), 1.47 (sext, $J = 7.5$ Hz, 2 H), 0.90 (t, $J = 7.5$ Hz, 3 H). ^{13}C NMR: 143.77, 136.70, 127.34, 107.27, 35.19, 32.98, 26.46, 23.57, 21.85, 14.24. CIHRMS for $C_{10}H_{16}$: found 136.1243, calcd 136.1252.

Samples of **18** and **18-d_2** were pyrolyzed to nearly complete conversion and analyzed by ^{1}H NMR and GCMS analyses. ^{1}H NMR of **22**[11] matched literature values. The 360-MHz ^{1}H NMR spectrum of **23** is 2.22 (t, 4 H), 1.93 (bs, 4 H), 1.80 (pent, 2 H), 1.63-1.57 (m, 4 H), which is consistent with the lower field spectrum previously reported.[13] Hydrogen shift products **24** (and **24-d_2**) were identified by only GCMS. In analogy with **21**, structures **24** and **24-d_2** were assigned.

Acknowledgment. We thank the Department of Energy for support of this work.

Supplementary Material Available: ^{1}H NMR spectra of all new compounds (along with some ^{13}C NMR spectra) (18 pages). Ordering information is given on any current masthead page.

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Carbon Acidity. 79. Acidity of Enolate Equivalent Compounds: Oxime Ethers

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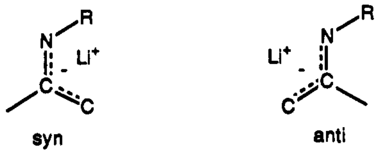
A series of benzylic oxime ethers were synthesized ($CH_3ON{=}C(CH_2Ar)_2$, Ar = phenyl (**1**), 4-biphenylyl (**2**), 1-naphthyl (**3**)), and the equilibrium ion pair acidities in THF were determined. The lithium ion pair acidity of **1** was found to be approximately 5 p*K* units lower than the corresponding cesium ion pair acidity. The oxime ethers are approximately 10 orders of magnitude less acidic than their corresponding ketones for cesium ion pairs. Thermodynamic parameters for the equilibrium acidities were measured and are consistent for contact ion pair monomers being the important species in solution. An aggregation study also indicates that these cesium oxime ether enolates exist mainly as ion pair monomers. The role of the gegenion in the stability of oxime ether anions is discussed.

The use of carbanion intermediates for the formation of carbon-carbon bonds is an important method in synthetic chemistry. A common source of these intermediates comes from the removal of the α-proton of a carbonyl compound by either a lithium amide or alkyllithium compound to produce an enolate ion. Much work have been dedicated to the chemistry of the enolate ion.[1] Recently, the use of carbonyl derivatives has attracted a great deal of attention for their uses as "enolate equivalents" in organic synthesis. The most important classes of these derivatives are the imines,[2] hydrazones,[3] and oxime ethers.[4,5] An interesting and useful aspect of these "enolate equivalents" is their preference for producing the syn configuration at the CCNR (R = R′, OH, OR′, NR′$_2$) partial double bonds.[5,6] This fact results in reactions of these anions being both highly regioselective and stereoselective.[7]

Table I. Spectrophotometric Data for Oxime Ether Anions in Tetrahydrofuran at -20 °C

O-methyloxime ether of	Cs$^+$ salt λ_{max}[a] (ϵ)	Li$^+$ salt λ_{max}[a]
1,3-diphenylacetone (**1**)	398 (24 100)	373[b]
1,3-di(4-biphenylyl)acetone (**2**)	473 (37 800)	450[b]
1,3-di(1-naphthyl)acetone (**3**)	505 (15 000)	*c*

[a] In nanometers. [b] Li$^+$ salt is not stable at these conditions so that an extinction coefficient could not be determined. [c] No absorbance from the Li$^+$ salt could be detected.



Although many studies on the reactivity and regiochemistry of these intermediates have been done,[8] relatively few physical studies are available discussing their acid-base behavior or the actual species that are involved in the reactions. Since these reactions are usually carried

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out in solvents of low dielectric constant such as diethyl ether or tetrahydrofuran, ions in solution would probably exist as ion pairs or higher aggregates. It has been suggested that the actual reacting species is the single ion pair.[9] However, little attention has been paid to the nature of the solution aggregates, and thus more research in this area is necessary. It is significant to understand the nature of the ions in solution because these aggregates and the coordination of the various metal gegenions can be used to control the regiochemistry and stereochemistry in the addition of the enolate ions to electrophiles.

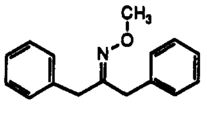
An extensive theoretical study is available for the lithium salts of oximes.[10] Accordingly, in the following work, the *O*-methyl oxime ethers of benzylic ketones were used as model compounds for which ion pair acidities were determined. These acidities are defined by the equilibrium constant of eq 1 in which the reference, R′H, is taken as the fluorenyl salt of lithium as a solvent separated ion pair (SSIP) or cesium as a contact ion pair (CIP) with both assigned the value of the ionic p*K* in dimethyl sulfoxide, 22.90 (per hydrogen).[11]

$$RH + R'^{-}M^{+} = R^{-}M^{+} + R'H \qquad (1)$$

The thermodynamic parameters for the ion pair equilibria with hydrocarbon indicators as well as with each other were determined. Experiments were also carried out with one of the anions of these compounds in solution to determine the extent of aggregation. The stabilities of the anions of these carbonyl compounds with various gegenions will also be discussed.

Results

The oxime ethers were prepared by condensation of the appropriate ketone with methoxylamine hydrochloride in ethanol/pyridine solvent (50:50).[12] Ketones were prepared with chromophoric groups attached to the carbonyl moiety (**1**–**5**) so that the carbanions from the derived oxime ethers would possess an absorption band above 340 nm (Table I). In this way, the oxime ethers can be used as indicators in a double-indicator measurement of the ion pair acidity constant.[13] Previously it had been demonstrated by isotopic exchange using a lithium amide base in THF that the acidic α-proton of the oxime ethers is syn to the alkoxy group.[4] No exchange at the anti position was observed. For this study, it is assumed that the acidity of the proton syn to the alkoxy group of the oxime ether is the quantity being measured.



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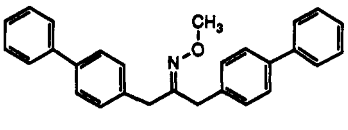

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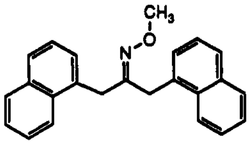

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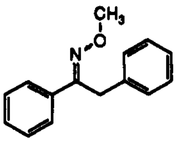

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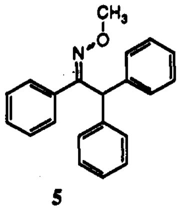

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Table II. Ion Pair Acidity Equilibrium Measurements of Oxime Ethers in Tetrahydrofuran at −20 °C[a]

R_1H[b]	R_2H	$\Delta pK_{Cs/THF}$	R_1H[b]	R_2H	$\Delta pK_{Cs/THF}$
TPP	2	0.43	1	9-PX	0.87
2	1	1.36	TPP	1	1.80
TPP	3	1.0[c]	1	PDDA	0.27

[a] On per hydrogen basis, assuming syn proton exchange only. Estimated error from internal consistency is 0.02. [b] R_1H is the more acidic compound. Abbreviations: TPP, 1,1,3-triphenylpropene; PDDA, 9-phenyl-10,10-dimethyldihydroanthracene. [c] Estimated error from internal consistency is 0.2.

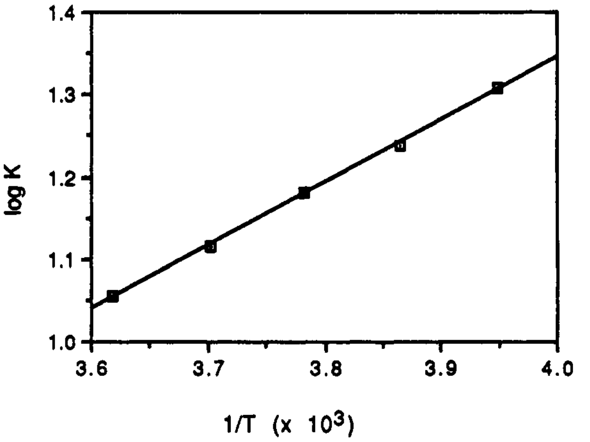

Figure 1. Determination of the temperature dependence of the cesium ion pair equilibrium constants for the reaction of 1,3-diphenylacetone *O*-methyloxime with PDDA.

Initial attempts to determine the cesium ion pair acidity constant in tetrahydrofuran at room temperature yielded no usable results because the anions of the oxime ethers decomposed too rapidly for measurements to be carried out. These results were confirmed by NMR spectroscopy. The resonance of the methoxy group of **1** vanished rapidly with time, resulting in the formation of a precipitate, presumably cesium methoxide. This was previously observed for other salts of oxime ethers[4] and has been utilized synthetically for the preparation of aziridine rings.[14,15]

Cooling to −20 °C prior to the formation of the anion solutions with diphenylmethylcesium resulted in solutions that were stable for the duration of the experiment for the symmetrical *O*-methyl oxime ethers (**1**–**3**). These measurements yielded internally consistent acidity values for these oxime ethers at −20 °C (Table II). However, the anions of the *O*-methyl oxime ethers of desoxybenzoin (**4**) and benzhydryl phenyl ketone (**5**) were still not stable at these lower temperatures and were not used. In all cases studied, the carbanions from the oxime ether with lithium as the gegenion were not stable enough at or above −20 °C for precise quantitative measurements to be carried out. An absorbance band from the lithium ion pair of **1** and **2** could be observed and was shifted by 25 and 23 nm, respectively, to shorter wavelengths than the corresponding cesium ion pair (Table I). The indicators used in this work were 1,1,3-triphenylpropene (TPP), 9-phenyl-10,10-dimethyldihydroanthracene (PDDA), and 9-phenylxanthene (9-PX).

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Table III. Thermodynamic Parameters for the Cesium Ion Pair Equilibrium of Oxime Ethers in Tetrahydrofuran and Comparison of Values with Previous Results[a]

R_1H[b]	R_2H	$\Delta H°$[c]	$\Delta S°$[d]	$\Delta pK_{Cs/THF}$[e]
TPP	2	−2.3 ± 0.2	−7.3 ± 0.3	0.12
2	1	−1.8 ± 0.1	−0.8 ± 0.2	1.14
1	PDDA	−1.4 ± 0.2	−4.3 ± 0.5	0.09
(TPP	PDDA	−5.5 ± 0.5	−12.4 ± 1.0	1.35)[f]
TPP	PDDA	−5.4 ± 0.6	−12.0 ± 1.0	1.34[g]

[a] On per hydrogen basis. [b] R_1H is the more acidic compound. See Table II for key to abbreviations. [c] In kilocalories per mole. [d] In entropy units. [e] At 25.0 °C, calculated from the thermodynamic data, because the anions of the oxime ethers rapidly decompose at room temperature. [f] Calculated from the data in this table. [g] Experimental data from ref 21a.

Table IV. pK_a Values for the Cesium Ion Pairs of Oxime Ethers in Tetrahydrofuran at 25 °C[a]

compd[b]	pK_a	compd[b]	pK_a
TPP	26.76[c]	1	28.0[d]
2	26.9[d]	PDDA	28.11[c]
3	27.4[e]	9-PX	28.73

[a] On per hydrogen basis. [b] See Table II for the key to the abbreviations. [c] From ref 16. [d] Calculated using the $pK_{Cs/THF}$ values reported in ref 16 and Table II. [e] Interpolated from the values at −20 °C, assuming similar thermodynamic parameters as for the other oxime ethers.

The ion pair equilibrium constants of the other oxime ethers could be measured at temperatures up to 3 °C without appreciable decomposition on the time scale of the experiment. Van't Hoff plots were generated from the oxime ether cesium ion pair equilibrium values at temperatures from −20 to 3 °C (Figure 1), and the thermodynamic constants were determined (Table III). It was possible to use the phenyl and *p*-biphenylyl derivatives (**1** and **2**) in the variable-temperature experiments, but the 1-naphthyl derivative (**3**) started to decompose at temperatures above −20 °C and could not be used. By using the thermodynamic data, values for the ion pair equilibrium constants could be extrapolated to 25 °C, for comparison with previously determined equilibrium values, and this allowed the placement of the oxime ethers on the cesium ion pair/tetrahydrofuran acidity scale (Table IV).[16] The calculated acidity constants for **1** and **2** are 26.9 and 28.0, respectively. A representative plot of the temperature dependence of the equilibrium of the anion of **1** with PDDA is shown in Figure 1. Van't Hoff plots for the other equilibrium systems were of similar quality.

The determination of the amount of aggregation of the anions of the oxime ethers was carried out by measuring the dependence of an ion pair equilibrium constant against the total concentration of the oxime ether anion. The slope of the log of the ion pair equilibrium constant plotted against the log of the anion concentration is equal to $(1 - \bar{n})/\bar{n}$, where $\bar{n}$ is the average aggregation number of the species.[17] The degree of aggregation was measured for 1,3-diphenylacetone *O*-methyloxime. The concentration of the anion was varied from 0.2×10^{-4} to 5.1×10^{-4} M, a 25-fold increase in concentration, with a slope of 5.2×10^{-2} (Table V). The aggregation number from this data was calculated to be 1.05, or essentially unaggregated. The biphenylyl (**2**) and naphthyl (**3**) derivatives are expected to be similarly unaggregated since the anionic charge in these compounds is more delocalized.

Table V. Dependence of the ΔpK_a of Cesium Ion Pairs of Oxime Ethers on the Change in Concentration of the 1,3-Diphenylacetone *O*-Methyloxime (1) Enolate Anion[a]

[anion], 10^4 M	ΔpK_a[b]	[anion], 10^4 M	ΔpK_a[b]
0.207	0.236	1.603	0.269
0.508	0.256	2.085	0.274
0.557	0.244	2.554	0.280
0.859	0.267	3.259	0.285
1.094	0.261	4.032	0.291
1.420	0.271	5.126	0.296

[a] At −20 °C in THF with PDDA indicator. [b] This minimal change in the equilibrium constant corresponds to an average aggregation number of 1.05, or the oxime ether anion exists mainly as the cesium ion pair in THF.

Discussion

We have described in this paper quantitative work involving representative oxime ethers. The anions of the oxime ethers with cesium as the gegenion, in general, do not appear to be stable at temperatures above −20 °C, with the exception of **1** and **2**. These two are stable indefinitely (>4 h) at −20 °C, but start to decompose at 0 °C. The lithium salts of these anions are much less stable. The lithium ion pair of **1** was not stable until the temperature was lowered to −60 °C, and even at this temperature significant decomposition took place.[4] Similar results have been reported with Grignard reagents as the base.[14] The stability of the ion pairs of oxime ethers appears to be dependent on the gegenion. The initial path of decomposition is presumed to be loss of a metal alkoxide (the loss of alkoxide ion is observed for the decomposition of oxime ether anions in the gas phase).[15,18] From these facts, it appears that metals which form strong complexes with oxygen, such as lithium or magnesium, cause an increase in the rate of oxime ether anion decomposition. Since cesium ion does not coordinate as well with oxygen or nitrogen, the oxime ether ion pairs with this gegenion are relatively more stable.

Even though no precise measurements were done with lithium ion pairs, one can make some significant conclusions from the available data. The absorbance band due to the lithium ion pair of **1** could be generated by using the lithium salt of benzo[*b*]fluorene (pK_a = 22.95) but not from the lithium ion pair of benzo[*c*]fluorene (pK_a = 19.29).[19] These results indicate that the lithium salt acidity of **1** should lie between these two, giving a pK_a of approximately 21–23. Oxime ether **1**, with lithium as the gegenion, is about 5 p*K* units more acidic than when cesium ion is employed. This large change in the ion pair acidity is consistent for comparing a lithium contact ion pair (LiCIP) of the oxime ether enolate with a lithium solvent separated ion pair (LiSSIP) of the hydrocarbon indicator.[17] The observed blue shift in the visible absorbance band of **1** and **2** (Table I) upon changing the gegenion from cesium to lithium also provides evidence for the formation of LiCIP with the oxime ether anions.[20]

The cesium ion pairs of the oxime ethers **1** and **2** were stable over a large enough temperature range to determine the thermodynamic parameters for the ion pair acidity equilibrium reaction. The enthalpy and entropy terms (Table III) are reasonable for the reactions of the oxime ethers with the indicators and with each other. In previous work it was shown that restricting the rotation of an aryl

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Table VI. Comparison of pK_a of Cesium Ion Pairs of Oxime Ethers with Corresponding Ketones[a]

compound	pK_a	compound	pK_a
1,3-diphenylacetone	17.95[b]	oxime ether (1)	28.0
1,3-di(1-naphthyl)acetone	17.78[b]	oxime ether (3)	27.4
1,3-di(4-biphenylyl)acetone	17.10[b]	oxime ether (2)	26.9

[a] On per hydrogen basis. [b] From ref 22.

substituent causes approximately a 3 eu (entropy unit) increase.[21] The large entropy term for the reaction of 2 with TPP is due to the fact that in neutral TPP, the three phenyl groups are free to rotate, but in the anion this rotation is now restricted. The small change in entropy for the reaction of 1 with 2 indicates that there is little change in rotational freedom as either neutral compound or anion are exchanged. The entropy change that is found can be attributed to the partial freezing of the rotation of the second phenyl ring of the biphenyl group, not present in 1, but the effect is small.

From pK_a measurements, it can be seen that the oxime ethers are approximately 10 powers of 10 less acidic than the ketones[22] for the cesium contact ion pairs from which they are derived (Table VI). This difference in acidity is clearly related to the charge distribution of the oxime anion and enolate ion. The theoretical studies show that the negative charge of the oxime anion resides mainly on the nitrogen atom,[10] and in the enolate ion the negative charge is located mainly on the oxygen atom.[23] Since oxygen is more electronegative than nitrogen, the enolate ion is relatively more stabile.

Conclusion

In this study we have provided quantitative data on the ion pair acidities of oxime ethers, an important class of synthetically useful compounds. These measurements allowed placement of the oxime ethers on the THF/cesium ion pair acidity scale and have shown that the lithium ion pairs to be approximately 5 pK units less basic than their cesium counterparts. Differences in the pK_a's and visible absorbance bands for the lithium and cesium ion pairs indicate formation of lithium contact ion pairs in THF solution. Along with measurements of the ion pair acidities, the thermodynamic parameters for cesium gegenions were determined for the reaction with hydrocarbon indicators. The absence of large effects in these parameters indicates that solvation of the oxime ether ion pairs and hydrocarbon ion pairs must be similar. No aggregation effects were observed for these delocalized oxime ether ion pairs in THF solvent over the concentrations used. Finally, differences in stabilities of the anions of the oxime ethers with various gegenions display the importance of the nature of the metal ion.

Experimental Section

General. Starting materials for syntheses were obtained from commercial suppliers and, when needed, were purified by recrystallization or distillation prior to use. Melting points (Pyrex capillary) were determined on a Büchi melting point apparatus and are uncorrected. Proton nuclear magnetic resonance (^1H NMR) spectra were determined on a UCB-200 (a superconducting 200-MHz instrument) operating in the FT mode. Chemical shifts are expressed as parts per million downfield from tetramethylsilane (internal standard). Variable-temperature studies made use of a Neslab RTE-4 refrigerated recirculating bath.

Equilibrium Measurements. The procedures used in the equilibrium acidity determinations have been previously described in detail.[13,19] The cesium ion pair indicator pK's used are those of the newly revised scale.[16]

Indicator Acids. The hydrocarbons used to determine the acidity of the compounds in this study were available from previous studies. The compounds were purified by column chromatography or multiple recrystallizations followed by vacuum sublimation. Purity was determined by a combination of NMR, melting point, or elemental analysis.

Tetrahydrofuran. Commercial THF (Fisher Scientific) was predried by distillation from $LiAlH_4$ and then processed by the method previously described.[19]

Oxime Ethers. The oxime ethers were prepared from the corresponding ketones.[12] Purification was accomplished by column chromatography on silica gel using 3% ethyl acetate in hexane as the eluent. Purity was assessed by NMR, elemental analysis, and melting points where possible. Assignment of *E* and *Z* isomers was determined using data available from literature.[24]

1,3-Diphenylacetone *O*-Methyloxime. A solution of 1.7 g of 1,3-diphenylacetone (Aldrich Chemical Co.) and 1.9 g of methoxylamine hydrochloride (Aldrich) in 5 mL of absolute ethanol and 5 mL of pyridine was refluxed for 16 h. The solvent was removed, the oily residue was taken up into CH_2Cl_2, and the solution was washed with 5% H_2SO_4 and water, dried, and distilled to give 1.5 g of the crude oxime ether. This was chromatographed on silica gel using 3% ethyl acetate in hexane as the eluent: ^1H NMR (200 MHz) δ 7.1–7.4 (10 H, m, phenyl), 4.96 (3 H, s, OCH_3), 3.58 (2 H, s, *syn*-CH_2), 3.41 (2 H, s, *anti*-CH_2).[4]

1,3-Di(1-naphthyl)acetone *O*-Methyloxime. From the reaction of 1,3-di(1-naphthyl)acetone[25] with methoxylamine hydrochloride: mp 79–80 °C; ^1H NMR (200 MHz) δ 7.1–8.1 (14 H, m, aromatic), 4.15 (3 H, s, OCH_3), 4.12 (2 H, s, *syn*-CH_2), 3.92 (2 H, s, *anti*-CH_2). Anal. Calcd for $C_{24}H_{21}NO$: C, 84.93; H, 6.24; N, 4.12. Found: C, 84.80; H, 6.36; N, 3.98.

1,3-Di(4-biphenylyl)acetone *O*-Methyloxime. From the reaction of 1,3-di(4-biphenylyl)acetone[26] and methoxylamine hydrochloride: mp 65.5–66 °C; ^1H NMR (200 MHz) δ 7.3–7.7 (18 H, m, aromatic), 4.10 (3 H, s, OCH_3), 3.72 (2 H, s, *syn*-CH_2), 3.49 (2 H, s, *anti*-CH_2). Anal. Calcd for $C_{28}H_{25}NO$: C, 85.90; H, 6.44; N, 3.58. Found: C, 85.51; H, 6.40; N, 3.47.

Diphenylmethyl Phenyl Ketone. To a solution of diphenylmethane in THF (3.0 g in 20 mL), 8 mL of 2.3 M *n*-butyllithium was added dropwise under N_2 at −78 °C, and the mixture was allowed to warm to rt. The solution turned deep red from the formation of the diphenylmethyl anion. The solution of (diphenylmethyl)lithium was added dropwise to 10 g of benzoyl chloride in 25 mL of THF at −78 °C under N_2. The color of the anion was immediately quenched upon addition to the acid chloride solution. After the addition was complete, the solution was warmed to rt, stirred for an additional 30 min, and carefully poured into an ice-cold, 10% NaOH solution, and the mixture was stirred overnight to hydrolyze the unreacted benzoyl chloride. The resulting mixture was extracted with diethyl ether, and the solvent was removed to give the crude ketone. The crude solid was recrystallized from hexane/ethanol to give 2.96 g (61% yield) of a pale yellow solid: mp 135–136 °C (lit.[27] mp 135–137 °C); ^1H NMR δ 7.96–8.05 (2 H, m, aromatic), 7.2–7.5 (13 H, m, aromatic), 6.06 (1 H, s, α-proton).

Diphenylmethyl Phenyl Ketone *O*-Methyloxime. From the reaction of diphenylmethyl phenyl ketone and methoxylamine hydrochloride. The isolated oil was a mixture of *E* and *Z* oxime ether isomers (47:53). The *E* and *Z* isomers were separated by repeated column chromatography on silica gel using ethyl acetate/hexane (5:95). *E* isomer: ^1H NMR δ 7.05–7.20 (15 H, m, aromatic), 6.03 (1 H, s, α-proton), 3.93 (3 H, s, OCH_3). Anal. Calcd

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for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.68; H, 6.48; N, 4.55. *Z* isomer: ^1H NMR δ 7.05–7.22 (15 H, m, aromatic), 5.32 (1 H, s, α-proton), 3.85 (3 H, s, OCH_3). Anal. Calcd for $C_{21}H_{19}NO$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.42; H, 6.38; N, 4.52.

Benzyl Phenyl Ketone *O*-Methyloxime. From the reaction of benzyl phenyl ketone (Aldrich) and methoxylamine hydrochloride. The isolated solid oxime ether was the *Z* isomer: mp 53–54 °C; ^1H NMR δ 7.2–7.4 (10 H, m, aromatic), 3.93 (3 H, s, OCH_3), 3.85 (2 H, s, CH_2). Anal. Calcd for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.21. Found: C, 80.04; H, 6.82; N, 6.18.

NMR Experiment. A solution of (diphenylmethyl)cesium was prepared in a septum-capped NMR tube by the addition of 0.02 g of diphenylmethane to 0.02 g of cesium metal in 0.5 mL of tetrahydrofuran-d_8 in a glovebox. This was allowed to stand 48 h to insure complete reaction of the diphenylmethane with the metal. 1,3-Diphenylacetone *O*-methyloxime was added immediately before the spectra were taken. Enough (diphenylmethyl)cesium was present to completely deprotonate the added oxime ether. Spectra were taken every 5 min, and within 15 min the resonance from a methoxy group was no longer present. When the tube was removed from the spectrometer, a white precipitate had formed.

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Registry No. 1, 2913-02-2; 1 Cs^+ salt, 132020-26-9; 1 Li^+ salt, 132020-27-0; 1 ketone, 102-04-5; 2, 132020-22-5; 2 Cs^+ salt, 132020-28-1; 2 Li^+ salt, 132020-29-2; 2 ketone, 15762-17-1; 3, 132020-23-6; 3 Cs^+ salt, 132020-30-5; 3 Li^+ salt, 132020-31-6; 3 ketone, 51042-38-7; (*Z*)-4, 132046-30-1; 4 ketone, 451-40-1; (*E*)-5, 132020-24-7; (*Z*)-5, 132020-25-8; 5 ketone, 1733-63-7; $CH_3ONH_2 \cdot HCl$, 593-56-6; diphenylmethane, 101-81-5.

Kinetics of Amine Addition to Benzylidenemalonodialdehyde in 50% Me_2SO–50% Water

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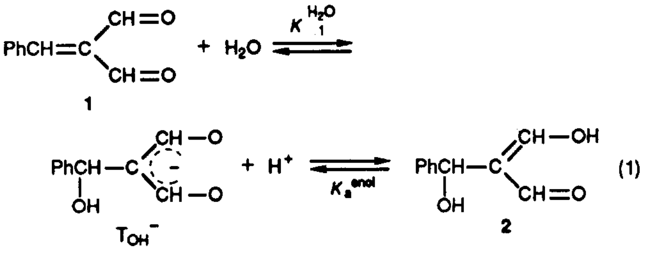
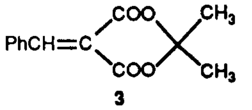
The kinetics of the reaction of benzylidenemalonodialdehyde with piperidine, morpholine, *n*-butylamine, 2-methoxyethylamine, glycinamide, glycine ethyl ester, cyanomethylamine, and semicarbazide have been determined in 50% aqueous Me_2SO at 20 °C. The reaction leads to a zwitterionic adduct, $PhCH(RR'NH^+)C(CHO)_2^-$ ($T_A^\pm$), that is in fast acid–base equilibrium with the anionic adduct, $PhCH(RR'N)C(CHO)_2^-$ (T_A^-). With strongly basic amines at high pH there is also attack of the amine on one of the carbonyl groups, which acts as a rapid preequilibrium. Rate constants for the formation of $T_A^\pm$ (k_1) and its reverse (k_{-1}), as well as equilibrium constants ($K_1 = k_1/k_{-1}$) and the pK_a of $T_A^\pm$, were determined for all the amines. Intrinsic rate constants ($k_0 = k_1 = k_{-1}$ when $K_1 = 1$) were calculated. The intrinsic rate constants are lower than those for amine addition to benzylidene Meldrum's acid. This is consistent with the greater role played by resonance in stabilizing $T_A^\pm$ derived from benzylidenemalonodialdehyde. However, k_0 for piperidine/morpholine addition to benzylidenemalonodialdehyde is much higher than for the reaction of benzylideneacetylacetone with the same amines, indicating that the rate-depressing effect of intramolecular hydrogen bonding in $T_A^\pm$ derived from benzylidenemalonodialdehyde is much smaller than that in $T_A^\pm$ derived from benzylideneacetylacetone. Even though semicarbazide is an α-effect nucleophile, no enhancement of k_1 was observed, but K_1, estimated on the basis of a structure–reactivity relationship, is larger than expected based on the pK_a of the amine. This result is attributed to a low β_{nuc}^n value.

Benzylidenemalonodialdehyde (1) is an unusually reactive electrophile whose first synthesis was reported only recently[1,2] and whose chemistry has not yet been fully explored.[2] 1 reacts with water to form an equilibrium mixture of 1 and 2[2a,3]; 2 may be considered as the hydrate (1,4-addition) of 1, or as the enol form of the protonated hydroxide ion adduct T_{OH}^-. In aqueous solution at 25 °C the equilibrium ratio is $[2]/[1] = K_1^{H_2O}/K_a^{enol} = 0.50$ while $[T_{OH}^-]/[1] = 1.0$ at pH 4.79 ($K_1^{H_2O} = 1.62 \times 10^{-5}$ M or p$K_1^{H_2O} = 4.79$, p$K_a^{enol} = 4.49$).[3]



The equilibrium constants for water ($K_1^{H_2O} = 1.62 \times 10^{-5}$ M) or OH^- addition to 1 ($K_1^{OH} = K_1^{H_2O}/K_w = 8.66 \times 10^8$ M^{-1}) are larger than the corresponding equilibrium constants for benzylidene Meldrum's acid 3 ($K_1^{H_2O} = 3.75 \times 10^{-6}$ M, $K_1^{OH} = K_1^{H_2O}/K_w = 2.00 \times 10^8$ M^{-1}),[4] but the *rate* constants[3] for water ($k_1^{H_2O} = 0.068$ s^{-1}) and OH^- addition to 1 ($k_1^{OH} = 223$ M^{-1} s^{-1}) are smaller than the corresponding rate constants for 3 ($k_1^{H_2O} = 0.55$ s^{-1}, $k_1^{OH} = 745$ M^{-1} s^{-1}).[4] This inverse relation between rate and equilibrium constants indicates that there is a lower *intrinsic* rate constant (k_0) (higher intrinsic barrier, ΔG^*_0[5] for water and hydroxide ion addition to 1 compared to 3. This difference in the intrinsic rate constants has been attributed to a larger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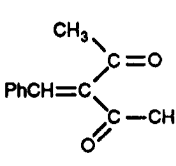
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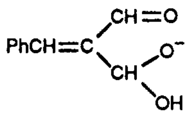
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[5] For a reaction with a forward rate constant k_1 and a reverse rate constant k_{-1}, k_0 is defined as $k_1 = k_{-1}$ when $K_1 = 1$. Similarly ΔG^*_0 is defined as $\Delta G^*_1 = \Delta G^*_{-1}$ when $\Delta G^0 = 0$. More on these definitions in the Discussion.