Communication

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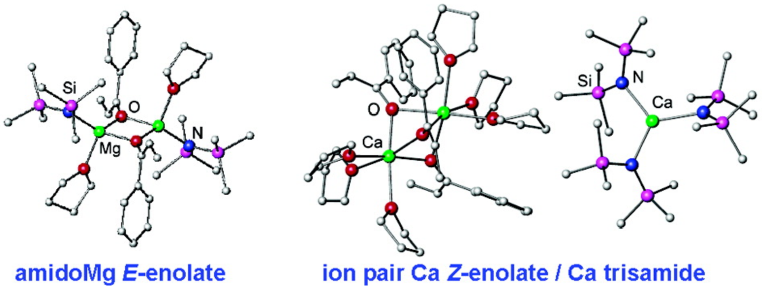

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Stereoselective Enolizations Mediated by Magnesium and Calcium Bisamides: Contrasting Aggregation Behavior in Solution and in the Solid State

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The selective deprotonation of ketonic substrates to generate enolate synthons is a reaction of central importance in organic chemistry.[1] Lithium-mediated transformations dominate this area, and a good deal of their success can be traced to elucidating the nature of the intermediates present in these reactions.[2,3] Recently, increasing interest has been directed toward the development of alternative metal-base systems that may be advantageous in specific transformations.[4] Magnesium amides in particular have proved to be exceptional reagents in a growing number of synthetically useful reactions, notably regioselective metalations[5] and enantiotopic deprotonations.[6] However, even fundamental questions regarding the identity of the metal enolates have yet to be answered. Also, the utility of the heavier alkaline earth metal analogues in synthesis remains largely undeveloped.[7] Nevertheless, applications of these metals are quickly emerging, such as catalysts for the polymerization of lactides[8] and styrene.[9] Herein, we demonstrate the use of magnesium and calcium bis(hexamethyldisilazide), **1** and **2**, in the stereoselective deprotonation of propiophenone, **3**, and delineate the aggregation and dynamic behavior of the resulting metal enolates.

Ketone **3** is a classic substrate for assessing the stereoselectivity of reagent systems, and the structural characterization of the enolate complexes of both Mg and Ca was targeted for study.[10] Addition of **3** to a slight excess of **1** (1.1 equiv) in hexane solution at ambient temperature produced a yellow solid that dissolved on addition of 1 equiv of THF. A mixture of small crystals and amorphous solid was deposited on cooling this solution at −20 °C for several weeks (∼20% yield). Crystallographic analysis revealed the dimeric amidomagnesium enolate complex $[\{(Me_3Si)_2NMgOC(Ph){=}CHMe\cdot THF\}_2]$, **4**, shown in Figure 1.

A key feature of **4** is the presence of both the *E*- and the *Z*-isomers within the crystal, which was refined to a relative ratio of 65:35. In synthetic terms, the predominance of the *E*-isomer was a surprise considering that lithium hexamethyldisilazide, LHMDS, is known to be highly *Z*-selective in ketone enolizations (2:98 *E*/*Z* for the reaction of LHMDS with **3** in THF).[11] Moreover, to the best of our knowledge no Li amide system has exceeded 50% *E*-selectivity for the enolization of **3**.[12]

^1H NMR monitoring of the reaction of **1** with **3** (0.75 equiv) in toluene-d_8 showed complete consumption of the ketone within 3 h at ambient temperature. Depletion of ketone ensued with the appearance of four quartets in the region δ 5.0−5.4 due to the newly formed vinylic CH groups and four trimethylsilyl signals in the region δ 0.33−0.43. Variable concentration studies (0.2−0.02 M) in conjunction with integration analyses were consistent with these signals arising from a pair of stereoisomeric amidomagnesium enolates, each of which exhibits a monomer−dimer equilibrium. The spectra simplified over time, such that after ∼3 days only two distinct sets of signals were present, including a pair of quartets centered at δ 5.33 and 5.09 in a ratio of 70:30. NOE experiments assigned the dominant solution species to be the *E*-isomer, consistent with the solid-state structure of **4**.

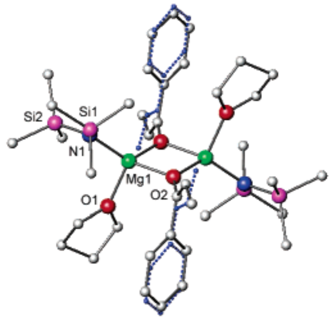

Figure 1. Molecular structure of amidomagnesium enolate **4** depicting the major *E*-isomer, with the minor Z-isomer superimposed (blue dashes). Key bond lengths (Å) and angles (deg): Mg1−O1 2.017(2), Mg1−O2 1.999(2), Mg1−O2* 1.975(2), Mg1−N1 2.006(3), O2−Mg1−O2* 82.43(10), Mg1−O2−Mg2* 97.57(10), N1−Mg1−O1 106.46(11), N1−Mg1−O2 126.88(11).

Attempts to prepare the silyl enol ether derivatives to confirm the enolate geometry with authentic samples proved problematic due to the very slow reaction of the Mg enolate with TMSCl in neat toluene. This issue was successfully resolved by development of a transmetalation strategy, where the Mg enolates were reacted with excess BuLi/THF followed by trapping with TMSCl. This approach resulted in near-quantitative conversion to the silyl enol ethers with stereoselectivity identical to that noted in solution. Repeating the reaction of **1** with **3** (0.75 equiv) in toluene-d_8 in the presence of HMPA (2 equiv) resulted in preferential formation of the *Z*-enolate, in accord with previous studies.[13] The use of HMPA also dramatically accelerated the trapping reactions, giving near-quantitative conversions to the *Z*-silyl enol ether after only 1 h at ambient temperature.

Turning to the calcium derivatives, high quality crystals were prepared from the equimolar reaction of **2** with **3** at −78 °C in THF, followed by warming the reaction mixture to ambient temperature and then storing the resulting solution to −20 °C for 24 h (21% crystalline yield). X-ray analysis of these crystals revealed the unexpected solvent-separated ion pair complex $[Ca_2\{OC(Ph){=}CHMe\}_3\cdot 6THF]^+[Ca\{N(SiMe_3)_2\}_3]^-$, **5**, with all three enolates in the *Z*-configuration (Figure 2). Repeated unit cell checks of different batches of crystals confirmed that **5** was the sole isolated product. The $[Ca(HMDS)_3]^-$ anion has not previously been characterized, but it is reminiscent of related magnesium trisamides.[14] The cation, with hexacoordinate calcium centers and three μ^2-bridging enolates, is entirely unprecedented in calcium coordination chemistry and is also a new structural motif for a metal enolate aggregate.[2,7b]

^1H NMR monitoring of the equimolar reaction of **2** with **3** in toluene-d_8 indicated complete consumption of the ketone within a few minutes, demonstrating the substantially greater reactivity of

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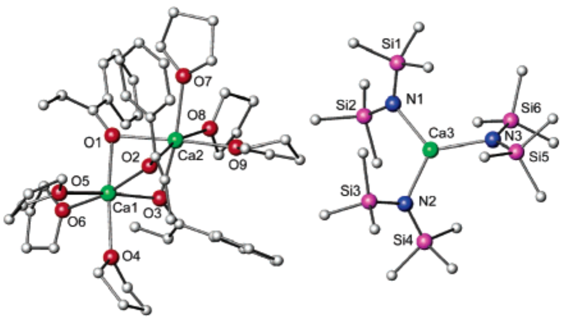

Figure 2. Molecular structure of **5**, showing the $[\mathrm{Ca_2\{OC({=}CHMe)Ph\}_3}]^+$ cation and the $[\mathrm{Ca(HMDS)_3}]^-$ anion. Key bond lengths (Å) and angles (deg): Ca1−O1 2.286(2), Ca1−O2 2.291(2), Ca1−O3 2.310(2), Ca3−N1 2.304(3), Ca3−N3 2.308(3), Ca3−N2 2.319(3), O1−Ca1−O2 80.14(8), O1−Ca1−O3 78.62(8), O2−Ca1−O3, 78.62(9), O1−Ca2−O2 77.97(8), O1−Ca2−O3 76.79(8), O2−Ca2−O3 76.30(8), N1−Ca3−N3 119.58(12), N1−Ca3−N2 117.75(11), N3−Ca3−N2 122.67(12).

2 compared to that of **1**. However, the highly complex spectra obtained did not simplify adequately for useful interpretation. Using pyridine-d_5 as solvent media for this reaction or alternatively for the dissolution of crystalline **5** proved more amenable. Both gave similar ^{1}H NMR spectra displaying two major sets of independent signals for the trimethylsilyl groups at δ 0.35 and 0.34 and for the enolate, including a pair of vinylic CH quartets centered at δ 5.26 and 5.11. NOE experiments determined both quartets to be *Z*-isomers, consistent with the solid-state studies. The high frequency quartet was assigned as a calcium bisenolate complex by independently preparing this species via the reaction of 2 equiv of **3** with **2** in pyridine-d_5. Further support for this scenario comes from the signal at δ 0.34 corresponding to calcium bisamide **2**, that is, the dismutation partner of the bisenolate.

In an attempt to determine if the remaining major set of signals was due to an ion pair complex, the independent preparation of the calcium trisamide anion was pursued. This was accomplished by the synthesis of $[\mathrm{K{\cdot}(18\text{-}C\text{-}6){\cdot}THF{\cdot}tol}]^+[\mathrm{Ca\{N(SiMe_3)_2\}_3}]^-$, **6**, from the equimolar reaction of KHMDS, **2** and 18-crown-6 in toluene/THF solution. Ion pair formation was confirmed by X-ray analysis (see the Supporting Information). The ^{1}H NMR of **6** in pyridine-d_5 showed a single trimethylsilyl signal at δ 0.55. This did not correspond with the remaining major signal in the spectra of **5** but did match the position of a much smaller signal, with a relative integral of ∼5% the combined total of the two major peaks. The correspondence between these signals was confirmed by similar chemical shift positions in their ^{13}C and ^{29}Si NMR spectra. These results indicate the presence of an ion pair in pyridine-d_5 solution but only in relatively low quantities. The sole precipitation of **5** must therefore be a consequence of the relative solubilities of the solution species present.[15] The remaining major species in pyridine solution is most likely a heteroleptic amidocalcium enolate. This is consistent with the relative ratio of the integrals of the vinylic CH at δ 5.11 and the trimethylsilyl signal at δ 0.35.

Further evidence for this composition comes from the characterization of the *Z*-configuration, heteroleptic, monomer $[\mathrm{(Me_3Si)_2NCa\{OC(Ph){=}CHMe\}{\cdot}PMDETA}]$, **7** (Figure 3). Complex **7** was prepared in a manner similar to **5** but with the addition of 1 equiv of the tridentate donor solvent PMDETA (43% crystalline yield). The ^{1}H and ^{13}C NMR spectra of **7** in pyridine-d_5 are essentially identical to that discussed above for **5**.

The Ca enolates were trapped in THF and pyridine by TMSCl within 1 h at 0 °C, with *E*/*Z* ratios of 4:96 and 2:98, respectively. Similar reactions in neat toluene resulted in ∼55% conversion after 36 h, with an *E*/*Z* ratio of 12:88. Interestingly, repeating this reaction followed by transmetalation with BuLi/THF after 3 h gave quantitative conversion to the silyl enol ethers but with an *E*/*Z* ratio of 60:40. This suggests that an isomerization process and perhaps preferential trapping is occurring over time.[16]

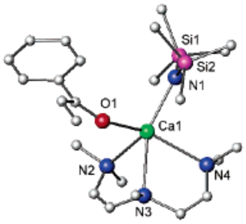

Figure 3. Molecular structure of the monomeric amidocalcium enolate **7**. Key bond lengths (Å) and angles (deg): Ca1−O1 2.1701(10), Ca1−N1 2.3283(12), Ca1−N2 2.6271(12), Ca1−N3 2.5550(12), Ca1−N4 2.6438(14), O1−Ca1−N1 102.74(4), N2−Ca1−N3 72.90(4), N3−Ca1−N4 69.06(4).

These results lead to speculating which, if any, of the newly discovered species will be active components in subsequent reactions. This is a key question if the rational design of highly selective reagents is to be realized. Identification of calciate **5** is of particular significance since magnesiate formation is known to dramatically increase the reactivity of organomagnesium complexes.[17] We are presently conducting kinetic studies of these systems to address these issues. Also, the high *Z*-selectivity achieved using **1** and **2** in the presence of polar solvents establishes their synthetic utility. Moreover, the surprising *E*-selectivity of both **1** and **2** with **3** in arene solution outperforms any reported Li amide system[11,12] and illustrates the considerable potential for further developments in the use of group 2 bases.

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Supporting Information Available: Full experimental and XRD data (CIF, PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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