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Dramatic Effect of Aggregation on Rates and Thermodynamics of Stereoisomerization of Magnesium Enolates

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One of the most powerful distinctions in understanding the selectivity of chemical reactions is that between thermodynamic selectivity (observed when the products can interconvert) and kinetic selectivity (observed when they cannot). For example, because the *E* or *Z* stereochemistry of a metal enolate is critical in determining the course of further reactions such as aldol additions or alkylations, the preparation of enolates in a highly selective manner continues to be an area of intensive research.[1] Systems in which high selectivity can be achieved on the basis of either kinetic or thermodynamic control have been observed.[2] However, despite the fact that alkali and alkaline earth metal enolates exist as mixtures of species differing in aggregation state and ancillary ligation,[3] the usual ways in which enolate stereoselectivity is measured (such as silylation and GC analysis of the silyl enol ethers) erase these distinctions.[2] This raises the question of whether stereoselectivity, particularly thermodynamic stereoselectivity, of such metal enolates is even a meaningful concept, since the chemical nature of the enolates present may well vary significantly depending on the reaction conditions.

Here we report on the thermodynamic stereocontrol of the (hexamethyldisilazide)magnesium enolates of propiophenone in THF.[4] The overall stereoselectivity proves to be very sensitive to concentration, since dimeric species with bridging enolates show no stereoselectivity while monomeric enolates show a very strong thermodynamic preference for the *Z* enolate. Kinetically, interconversion among aggregates is remarkably slow, whereas stereoisomerization of the monomer, even in the absence of a proton source such as ketone or amine, is remarkably fast. Both of these observations contrast with accepted views of such processes and have implications for understanding the identity and reactivity of metal enolates.

We recently reported a detailed kinetic and mechanistic investigation of the deprotonation of propiophenone by magnesium bis(hexamethyldisilazide), $Mg(HMDS)_2$, in toluene solution, which cleanly produces the two dimetallic stereoisomeric products (*E*)- and (*Z*)-[$(HMDS)_2Mg_2(\mu$-HMDS$)\{\mu$-OC(Ph)=$CHCH_3\}$] [(*E*)-**1** and (*Z*)-**1**].[5] Since more polar solvents such as ethers commonly simplify the solution behavior of early main-group organometallics,[3] we were surprised to find that addition of THF-d_8 to a toluene-d_8 solution of (*E*/*Z*)-**1** gives a complex series of enolate and Me_3Si signals in the ^{1}H NMR spectrum (Figure 1). Five distinct sets of enolate signals corresponding to four amidomagnesium enolate complexes are present, accompanied by four sets of Me_3Si signals [plus a set of Me_3Si signals corresponding to free $Mg(HMDS)_2$]. An intriguing observation is that the ratios of the relative integrals present are found to vary with both concentration and time, indicating the presence of a dynamic equilibrium between multiple solution species (Figure S3 in the Supporting Information). The related amide and enolate signals of the four individual heteroleptic aggregates were assigned from the correlated integral values upon alteration of the distribution over a range of times and concentrations. Nuclear Overhauser effect (NOE) studies (Figures S4 and S5) indicated that two of the enolate signals correspond to *E* isomers and the remaining three to *Z* isomers. Finally, both variable-concentration and pulsed gradient spin-echo (PGSE) studies (Figure S6 and Tables S1 and S2) indicated that the well-separated high-field quartet located at δ 4.71 is associated with a smaller aggregate than the other species, which are all of similar nuclearity. In combination, these studies are consistent with the formation of four independent 1:1 amidomagnesium enolate complexes: three stereoisomers of dimeric bis(enolate)-bridged [$(HMDS)Mg(\mu$-OC(Ph)=CHMe)(THF)$]_2$ [(*E*,*E*)-**2**, (*E*,*Z*)-**2**, and (*Z*,*Z*)-**2**] and monomeric [$(HMDS)Mg(OC(Ph)$=$CHMe)(THF)_2$] [(*Z*)-**3**], which is present only as the *Z* isomer. The assignment of the aggregates as dimers and a monomer is in accord with studies of related magnesium complexes, including the solid-state structural characterizations of monomeric [(HMDS)Mg{OC(Ph)=CHMe}·PMDTA] and dimeric **2**.[6]

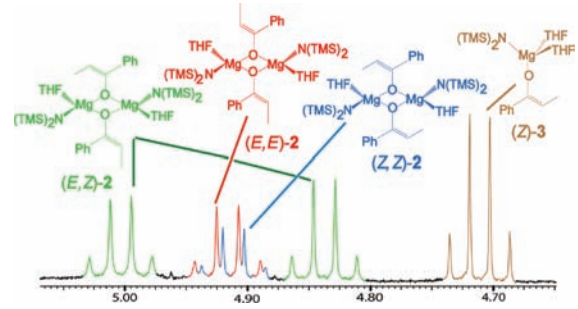

Figure 1. Enolate methine ^{1}H NMR signals upon addition of THF-d_8 to a toluene-d_8 solution of **1** (1:1 v/v, 0.086 M, 7 days, 20 °C).

Conspicuously, the *E* monomer (*E*)-**3** was not observed. A density functional theory study (B3LYP/6-31G*) of the full molecules was performed to examine the relative stabilities of the monomeric and dimeric complexes.[7] The absolute energies of the three dimeric isomers (*E*,*E*)-**2**, (*E*,*Z*)-**2**, and (*Z*,*Z*)-**2** are essentially identical, varying by <0.2 kcal/mol. However, the *E* monomer is less stable than the *Z* stereoisomer by 2.8 kcal/mol. This implies that the aggregation energy for the *E* monomer is significantly higher than that for the *Z* monomer (11.8 vs 5.6 kcal/mol of dimer, respectively). The calculations are therefore consistent with the NMR studies, indicating that the *E* monomer is thermodynamically disfavored. In addition, the calculated [B3LYP/6-311+G(2d,p)] ^{1}H NMR chemical shift values for the vinylic protons of the complexes closely match the experimental pattern: (*Z*)-**3** at δ 4.83, (*Z*,*Z*)-**2** at δ 5.31, (*E*,*E*)-**2** at δ 5.32, and (*E*,*Z*)-**2** at δ 5.42/δ 5.19. The absent *E* monomer signal was predicted to appear at δ 4.98, in a clear region of the spectrum.

The apparent instability of the *E* monomer implies that the *overall* *E*/*Z* ratio in the system should be highly sensitive to concentration, assuming that stereomutation of the enolate can be achieved in this system. To further elucidate this, the effects of concentration and time on the total *E*/*Z* ratio were investigated. Dissolution of

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crystalline samples of (*E*/*Z*)-**1** in toluene-d_8 allowed direct measurement of the *E*/*Z* ratio from the integrals of the dimetallic aggregates, which consistently showed that 60−65% *E* enolate was present. (The compositions of these solutions in toluene are stable for >1 month by NMR.) Dilution of these toluene-d_8 solutions into THF-d_8 (1:1 v/v) produced the THF adducts **2** and **3**. The overall *E* content of the enolates dropped immediately upon THF addition, with a larger drop in *E* content at increased dilution (Figure 2a).

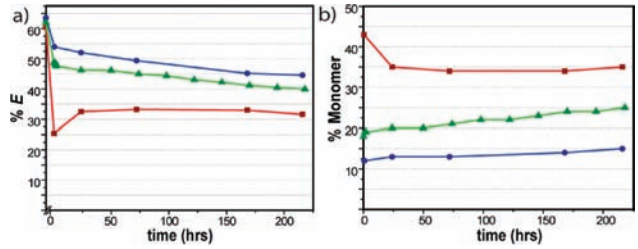
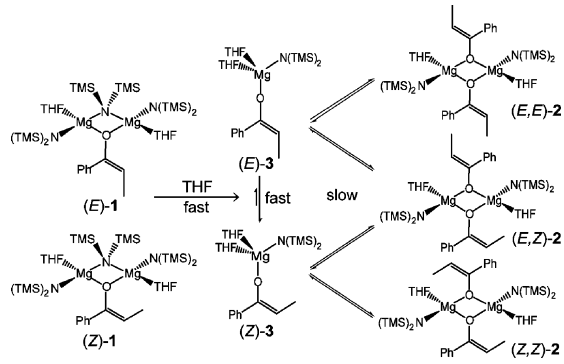


Figure 2. Equilibration of amidomagnesium enolates (initially 65% *E*) in 1:1 toluene-d_8/THF-d_8 at 20 °C (0.1720 M, blue ●; 0.0860 M, green ▲; 0.0430 M, red ■; averages of 2−3 runs): (a) percentage of *E* enolate; (b) percentage of enolate in monomeric form.

The initial fast drop in the %*E* present was then followed by remarkably slow equilibration (>1 week) of the two stereoisomers and the aggregation states present (Figure 2 and Figures S7 and S8). This resulted in equilibrium proportions of monomer, and hence *Z* enolate, that were enhanced at lower concentrations of magnesium. Production in situ of the magnesium enolates by reaction of propiophenone with $Mg(HMDS)_2$ resulted in the same equilibrium speciation as dissolution of (*E*/*Z*)-**1**, in either 1:1 toluene-d_8/THF-d_8 or neat THF-d_8 (Figure S2).

The initial burst of enolate stereoisomerization upon mixing with THF, followed by a much slower phase of isomerization, strongly suggests that stereomutation is rapid in the monomeric enolates but slow in the dimers. As dimetallic (*E*/*Z*)-**1** reacts with THF, it presumably dissociates to $Mg(HMDS)_2$ and monomeric **3**. Apparently, stereoisomerization of (*E*)-**3** is competitive with capture by another monomer to form dimeric (*E*,*E*)-**2** or (*E*,*Z*)-**2** (Scheme 1).

Scheme 1. Proposed Mechanism for the Isomerization and Equilibration of Amidomagnesium Enolates



The dimeric complexes are rather resistant to both stereoisomerization and deaggregation; it is most likely that both pathways involve dissociation to the stereochemically more labile monomeric complexes **3**. This scheme is consistent with the striking observation that at the very lowest concentrations studied, the initial drop in %*E* can actually overshoot the equilibrium value (Figure 2a and Figure S9). At such low concentrations, the monomer is long-lived enough to form a large amount of (*Z*)-**3**, which only slowly equilibrates with dimer (leading to rising %*E*).

Stereoisomerization of metal enolates is typically attributed to protonation/deprotonation by released amine or excess ketone present or to an aldol/retro-aldol sequence.[2,8] Neither mechanism can plausibly explain the rapid equilibration of (*E*)-**3** and (*Z*)-**3**, as crystalline (*E*/*Z*)-**1** contains no free amine or ketone. Even reaction with traces of these would not give the observed concentration dependence of the initial change in stereochemistry. A possible mechanism of isomerization is transient magnesiation, where the metal migrates from the oxygen to the carbon of the enolate, followed by bond rotation in the C-metalated enolate. While the stereoisomerization reaction in **3** is unexpectedly fast, the aggregation/deaggregation process, which is usually assumed to rapidly interconvert metal enolates, particularly in donor solvents such as THF, is in fact extremely slow.

Although it is widely appreciated that metal enolates may exist as multiple aggregates, the effect of this on enolate stereochemistry has not been appreciated. Here we have shown that metal enolates having different stereochemistry may have strikingly different thermodynamic and kinetic stabilities, depending on their aggregation states. This has several important implications: (1) Variation of overall enolate stereoselectivity with reaction conditions need not be an indication of kinetic control; if the aggregation (or ligation) of the enolates varies with the conditions, such variations may reflect changes in the stability of the (different) enolates. (2) Enolate composition may not be a simple barometer of subsequent selectivity, since rapid stereoequilibration (particularly in lower aggregates, which are generally believed to be more reactive) would lead to Curtin−Hammett effects on reactivity.[9] (3) Apparently thermodynamic distributions may in fact be far from equilibrium because aggregate interconversion can be extremely slow. The sensitivity of the system studied here to factors such as time, concentration, and solvation helps rationalize the extensive and seemingly contradictory literature data regarding metal-mediated stereoselective enolization reactions.[1,2,8]

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Supporting Information Available: Full experimental and computational details and complete author list for ref 7. This material is available free of charge via the Internet at http://pubs.acs.org.

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