Mixed Aggregates: Lithium Enolate of 3-Pentanone and a Chiral Lithium Amide

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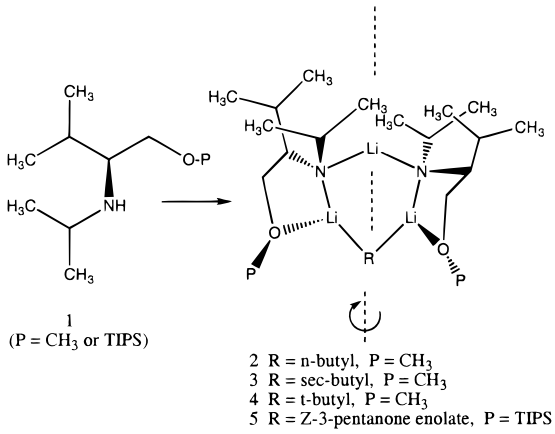
Chiral lithium amides have been utilized as bases in asymmetric deprotonation reactions and as chiral auxiliaries in other reactions.[1] Koga and others have shown that chiral lithium amides can lead to high stereoselectivities in aldol and related reactions.[2] The effect of these chiral lithium amides in aldol reactions, generally referred to as the Li-amide effect,[3] is likely to arise from mixed aggregates containing both lithium enolates and lithium amides. Consequently, identification of these aggregates, including their structural details, are important for designing and choosing chiral amines and for probing the origin of the stereoselectivity in asymmetric reactions involving these species. Previously, we isolated and characterized by X-ray diffraction mixed aggregates containing Li-enolates and achiral Li-amides.[4] We and others have suggested the importance of these species in enolate reactions.[5] We now wish to report definitive evidence for a simple enolate, chiral lithium amide complex that we've purposefully designed.

Recently we discovered unsolvated, mixed 2:1 stoichiometric complexes containing Li-amide ultimately derived from (*S*)-*N*-isopropyl-*O*-protected valinol (**1**) and alkyllithium reagents depicted in Scheme 1 as **2**−**4**.[6] The similarities in size, anionic nature and potential to form mixed aggregates lead us try to replace the alkyllithium derived groups in **2**−**4** with an enolate. Initial attempts to form mixed aggregates were carried out using 2 equiv of the Li amide derived **1** and one equiv of Li-enolate of pinacolone or other simple ketone enolates such as from 2-butanone, 3-pentanone, and 2-methyl-3-butanone in hydrocarbon solvents. With pinacolone only the known unsolvated hexameric Li-enolate of pinacolone was obtained.[7] We also tried to prepare mixed aggregates between these enolates and the Li amide reagents similar to **1** synthesized from alanine or phenylalanine in a systematic approach. We achieved success in observing a mixed aggregate with the enolate of 3-pentanone which crystallized as the 2:1 stoichiometric Li-amide/Li-enolate mixed aggregate trimer **5**[8] (Figure 1).

Scheme 1. Mixed 2:1 Chiral Amide/Anion Complexes



The structure **5** possesses a crystallographic 2-fold axis of symmetry if the enolate is not considered. This 2-fold rotation symmetry is analogous to that found in the Li amide/alkyllithium structures **2**−**4**. Since the enolate of 3-pentanone does not possess the 2-fold rotation axis symmetry, refinement of the crystallographic model included disorder which makes it impossible to determine the stereochemistry of the enolate olefin.[9] To define this stereochemistry unambiguously, crystals of the mixed aggregate were generated, separated from the solution, dissolved in pentane, and then trapped with TMS-Cl. The TMS enol ethers obtained in this manner provided unequivocal evidence that the enolate in the crystal was (*Z)* and not (*E)*.[10] Proton and ^{13}C NMR showed mostly *cis*-silyl enol ether and only trace amount of *trans* product, the amount of which varied slightly from sample to sample. When TMS-Cl was added immediately after the addition of 3-pentanone into the solution of Li amide **2** in pentane, that is, without generation of the crystals, a 32:68 ratio of *E*:*Z* enolates was obtained.[11] This observation leads to the conclusion that crystallization of the pure *Z* enolate occurs preferentially from solution.

A ^{6}Li-enriched crystalline complex of **5** was dissolved in toluene-d_8 and the ^{6}Li NMR spectrum was recorded at −78 °C,

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(8) X-ray data were collected in 0.3° steps on a four circle diffractometer in the ϕ-scan mode equipped with a Bruker SMART CCD 1K detector (Mo Kα radiation, $\lambda = 71.073$ pm). The structure of 1 was solved by direct methods and refined with full matrix least squares on all reflections based on F_2 using the SHELXTL programs commerically available from Bruker Analytical Instruments. Crystallographic data for aggregate 1: crystallographic asymmetric unit $C_{19.5}H_{42.5}Li_{1.5}NO_{1.5}Si$; Mr = 353.55; clear, colorless crystal of dimension 0.04 × 0.04 × 0.055 mm mounted on a quartz fiber under a stream of dry N_2 gas at −40 °C; trigonal space group $P3_221$; $a = b = 12.01$ (0.9) Å, $c = 31.58$ (1.3) Å; $V = 3846.2$ (5) Å^3; $Z = 6$; $\rho_{calcd} = 0.893$ g cm^{-3}; $\mu = 0.096$ mm^{-1} (no correction applied); 15256 reflections collected, 3910 independent ($R_{int} = 0.0787$); θ range 1.93−23.74°, 98.1% completeness; 241 parameters (4 restraints due to enolate disorder); $R_1 = 0.0887$, wR2 = 0.2143 [$I > 2\sigma(I)$] for 3910 data; max/min +1.140 and −0.309 eÅ^{-3}; H atoms located in density maps and refined in fixed idealized positions.

(9) The crystallographic 2-fold rotation symmetry requirement is satisfied for the enolate by a model with the enolate oxygen atom and C-3 of 3-pentanone located on the symmetry axis. The other four carbons in the enolate residue adopt the expected conformations for 3-pentanone. Only one of the two occupied sites of the enolate residue is shown for clarity. Note that the C2 symmetry of the overall aggregate **5** renders the two enolate sites virtually identical so this disorder should not adversely affect enolate enantioselectivity. This disorder is identical to that found in the aggregates 2−4.

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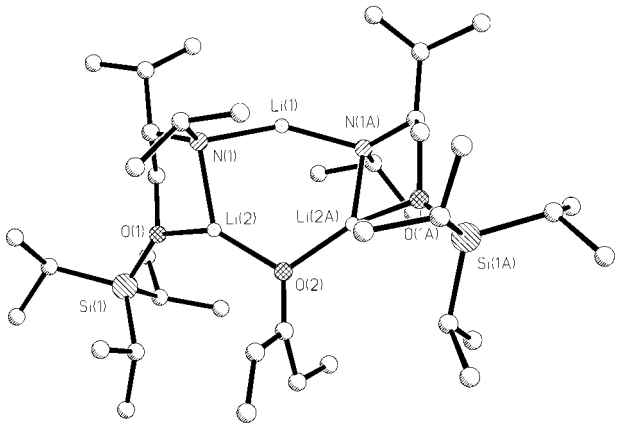

Figure 1. Structure of mixed 1:2 aggregate derived from (*S*)-*N*-isopropyl-*O*-triisopropylsilyl valinol.

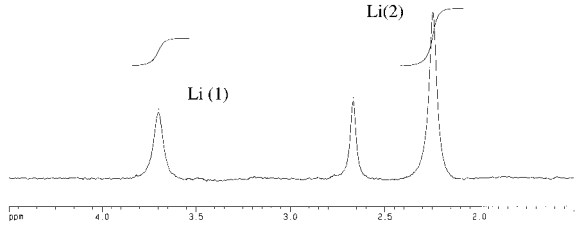

Figure 2. ^{6}Li NMR of aggregate 5 in toluene-d_8 at −78 °C.

see Figure 2. This spectrum exhibited three single peaks at δ 3.73, 2.70, and 2.27 ppm. The peak at 2.70 ppm was assigned as an aggregate of pure Li-amide derived from **1** by mixing only a stoichiometric equivalent amount of (*S*)-*N*-isopropyl-*O*-triisopropylsilylvalinol (**1**) and Bu^{6}Li. Integration of the other two singlets at δ 3.73 and 2.27 ppm showed a 1:2 ratio. A ^{6}Li−^{6}Li EXSY experiment at 10 °C revealed cross-peaks for these two ^{6}Li peaks strongly indicating that these lithium signals arise from the same complex (Figure 3). These two peaks are assigned to Li (1) and Li (2) respectively in complex **5** by comparison with our NMR determination of the solution structure of Li-amide/*n*-BuLi aggregates **2**−**4**.[12] This solution of **5** was stable at −78 °C overnight, but warming it up to room temperature resulted in an increase of the Li-amide peak at δ 2.70 and a decrease of the other two peaks, while cooling it back down did not return the original spectrum. This suggests that decomposition of **5** at higher temperatures occurred. The ratio of the peaks at δ 3.73 and 2.27, however, remained at 1: 2 as expected. We are currently investigating this decomposition.

Complexes containing Li-amides can aggregate in many different ways although we expected to see the trimeric structure **5** on the basis of our observation of the trimeric alkyllithium/Li-amide complexes **2**−**4**. It seems important to have four *iso*-propyl groups (excluding those on the silicon) present in these trimers, two from each valinol derived ligand. Substitution of the *N*-*i*-propyl group by *N*-ethyl or the *i*-propyl group from valine by methyl, for example from an alanine derivative instead of valine, apparently will not form a trimeric aggregate either in the solid phase or in solution. We've confirmed this by NMR. It is noteworthy that Hilmerson and Davidsson found a mixed 1:1 dimer containing one lithium amide ligand and *n*-BuLi in ethereal solvents in which one of the lithium atoms is solvated by THF or Et_2O.[13] Without this solvation, the unique lithium atom in **2**−**5**, that is, Li(1), is internally dicoordinated. We suggest that internal coordination and the steric hindrance to solvation by the *N*-isopropyl and valine iso-propyl groups hinder additional solvation by external solvents and lead to the formation of the trimeric aggregates. To date our attempts to obtain structural evidence of mixed 2:1 aggregates derived from alanine or other simple amino acid derivatives containing either alkyllithiums or lithium enolates have failed. We are in the process of determining the stereoselectivity in the reactions involving the enolate anion in complexes **2**−**5** as well as the generality of the formation of analogous trimeric aggregates with other lithium enolates and organolithium compounds.

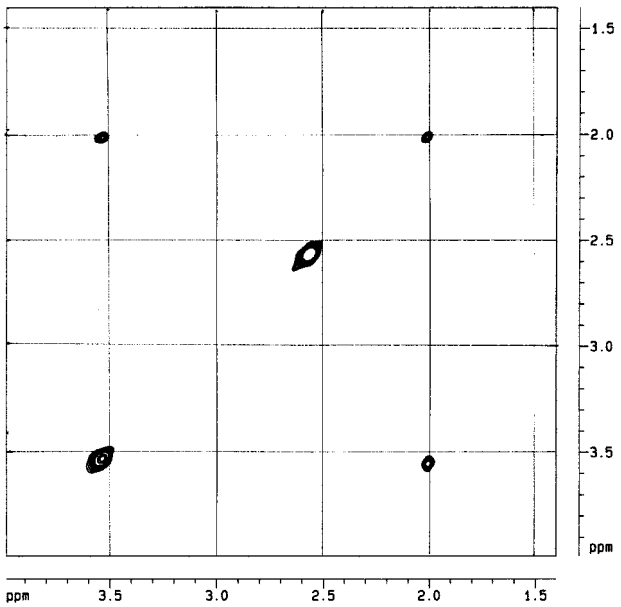

Figure 3. ^{6}Li−^{6}Li EXSY spectrum of 5 in toluene-d_8 at 10 °C.

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Supporting Information Available: Tables (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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