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Synthesis, Isolation, and Structure of an LDA–THF Complex

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Summary: Crystals of a dimeric 1:1 LDA–THF complex are prepared as described. A single crystal of this substance was subjected to X-ray diffraction analysis while being maintained at ∼−100 °C in a stream of dry nitrogen. The crystalline LDA–THF aggregate is a bis-solvated dimer.

Kinetic deprotonation of ketones and other carbonyl compounds by alkali metal amide bases is vitally important in organic synthesis. Although lithium diisopropylamide (LDA) in tetrahydrofuran is the most widely utilized amide base for deprotonation of weakly acidic organic compounds, relatively little detailed information concerning the structure of this base existed until very recently.[1] Cryoscopic measurements in THF were interpreted by Seebach[2] implicating a monomer–dimer equilibrium; however, more recent extensive NMR studies by Collum et al.[3] indicate that the dimer is the exclusive species in THF solution. Several X-ray crystal structures of related alkali metal amide bases are known[4] including polymeric forms of LDA.[5] We now provide structural details obtained from X-ray diffraction analysis for the dimeric, 1:1 LDA–THF complex 1.

We prepared crystals of the dimeric LDA–THF complex 1 as described below. A single crystal of this substance was subjected to X-ray diffraction analysis while being maintained at ∼−100 °C in a stream of dry nitrogen.[6] Direct-methods structure solution followed by least-squares refinement led to the dimeric aggregate structure depicted in Figure 1.

The following procedure was utilized for preparing and isolating a single crystal of the LDA–THF complex according to Figure 2. A round-bottom flask purged with argon is charged with Li metal (659 mg, 94 mmol), anhydrous ether (50 mL), diisopropylamine (13 mL, 94 mmol), and freshly distilled styrene (5.4 mL, 47 mmol). The reaction mixture is warmed to reflux until all of the Li metal disappears. The reaction solvent is removed in vacuo and the remaining white powdery residue is washed with several portions of anhydrous pentane to remove trace impurities. After careful evaporation of the remaining pentane, one obtains 6.6 g (62 mmol) of a white, pyrophoric powder which we believe is unsolvated LDA (2). This

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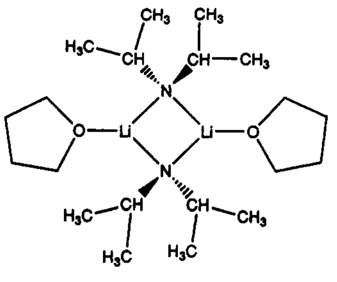

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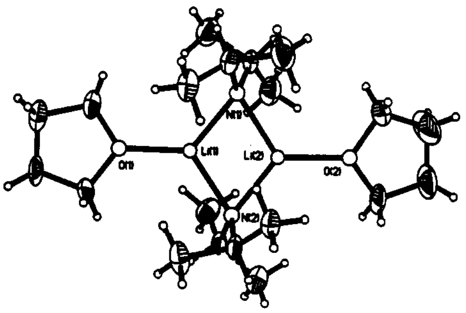

Figure 1.

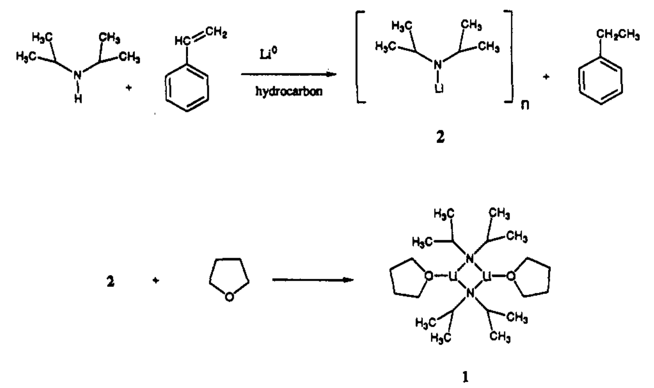

Figure 2.

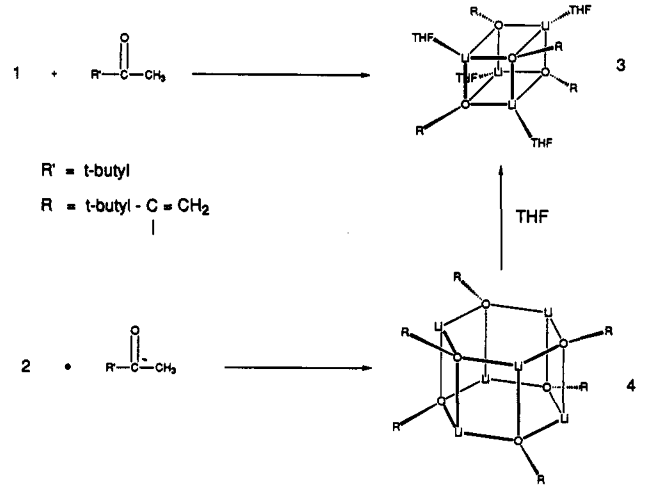

Figure 3.

powder can be stored in a dry, oxygen-free atmosphere at subambient temperatures for long periods of time or alternatively it can be complexed with a stoichiometric quantity of THF and recrystallized from pentane below 0 °C to form the 1:1 LDA–THF complex 1.[7] Our preparation of the LDA–THF complex directly from Li metal represents an extension of reported procedures in that a stable and preparatively useful complex is isolated and purified.[8]

For routine reactions, use of a preformed LDA–THF complex may not offer an advantage over the widely utilized in situ preparation of LDA from *n*-butyllithium and diisopropylamine. However, for accurate measurement of stoichiometric quantites of base and for reactions requiring LDA on a scale > 0.5 mol, the use of a purified, solid reagent that can be accurately weighed is advantageous. We find it convenient to prepare and to isolate the LDA–THF complex on a preparative scale and to dispense this reagent as any other oxygen- and moisture-sensitive compound, e.g., $NaNH_2$. This procedure also provides an efficient route to isotopically labeled ^{6}LDA, whose preparation for use in subsequent NMR studies provided the stimulus for our initial investigation.

It is noteworthy that enolization of pinacolone with 1 in hydrocarbon solution leads to a tetrameric, THF solvated enolate 3.[9] A differently aggregated enolate 4 is obtained when THF is excluded from the reaction and unsolvated LDA (2) is used in place of 1.[9a] Consequently, it is not surprisingly that the THF-solvated tetramer 4 is formed when the THF-solvated LDA dimer 1 is utilized in the enolization reaction.

An intriguing aspect of lithium amide crystal structures is their relationship to the reactive species responsible for deprotonation of carbonyl compounds in solution. The structure of two unenolized esters coordinated to the lithium hexamethyldisilazide dimer[10] as well as the structures of a ketone and an amide enolate complexed

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[6] The LDA–THF complex 1 crystallized in the monoclinic space group $P2_1/c$ with unit cell parameters a = 14.433 (6) Å, b = 10.082 (8) Å, c = 24.952 (18) Å, and β = 101.24 (5)°. The unit cell contained four asymmetric units of molecular formula $[(C_6H_{14}NLi)\cdot(C_4H_8O)]_3$ in a volume of 3566.2 (4.0) Å^3. This produces a calculated density of 1.00 g/cm^3. A total of 3744 reflections were recorded using the ω-scan routine and graphite-monochromated Mo Kα radiation in the range 3.5° $\leq 2\theta \leq$ 42°. All computer programs belonged to the SHELXTL 4.1 system. The final agreement factors are R = 0.0740 and Rw = 0.0764 for 352 parameters and 2574 unique observed reflections. A complete summary of the diffraction results are given in the supplementary material. The author has deposited atomic coordinates for 1 with the Cambridge Crystallographic Data Centre. The coordinates can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

[7] The pure, dry, unsolvated LDA is extremely reactive, and care should be taken to avoid exposure to the atmosphere or excessive heating. After extensive private discussions with Prof. D. Collum at Cornell University, we have noted that this material has different solubility properties than that prepared by the procedure outlined in ref 9a in that it can by solubilized by warm hydrocarbons such as hexane or heptane immediately after preparation. However, LDA prepared either by this procedure or by the procedure outlined in ref 9a yields the same 1:1 complex with THF. For the recrystallization from THF, a quantity of ~0.035 mol of the solid, unsolvated LDA is suspended in 8.5 mL of anhydrous pentane or hexane. This suspension is chilled to 0 °C in an ice bath, and a slight excess (~0.036 mol) of dry THF is added slowly so that no discernible color change is observed. The suspension is removed from the ice bath and warmed slowly with swirling until a solution is obtained (approximately 5–10 min). The LDA–THF solution is placed in a freezer at −25 to −30 °C overnight whereupon large colorless crystals of 1 are obtained.

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with trimethylenediamine (TriMEDA)[11] provide useful models for the pre- and postdeprotonation reaction intermediates. We believe that the dimeric LDA–THF complex 1 is certainly involved in enolization reactions and that there is increasing experimental evidence for the involvement of aggregated intermediates in the enolization reactions of LDA.[12]

Addition of Lewis bases to solutions of LDA affects both deprotonation rates and pK_a.[13] As more structural information about the lithium amide bases becomes available, undoubtedly a more complete picture will emerge to explain these experimental observations. Of special interest with respect to structure reactivity correlation are reactions such as the recently reported enantioselective deprotonation of ketones with chiral lithium amide bases and the enantioselective elimination of epoxides to form allylic alcohols.[14]

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Supplementary Material Available: Details of X-ray structure determination (8 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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