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On Enantioselective Deprotonation: Synthesis and Crystal Structure of a Chiral Amidolithium Tetrahydrofuran Complex

Andrew J. Edwards, Susan Hockey, Francis S. Mair,* Paul R. Raithby, and Ronald Snaith

University Chemical Laboratory, Lensfield Road, Cambridge, CB2 1EW, U.K.

Nigel S. Simpkins

University of Nottingham, Department of Chemistry, University Park, Nottingham, NG7 2RD, U.K.

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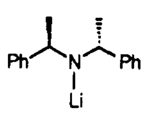
Summary: The enantioselective base (*R,R'*)-bis(1-phenylethyl)amidolithium (1) was crystallized from THF/hexane and characterized by X-ray crystallography as a bis-THF-solvated cyclic dimer which adopts a conformation that maximizes methyllithium contacts, inconsistent with previous rationalizations of its enantioselectivity in enolizations of cyclic ketones.

Enantiomerically pure chiral amidolithium reagents are emerging as powerful new tools for asymmetric synthesis.[1] More specifically, the direct asymmetric transformation of cyclic prochiral ketones into nonracemic derivatives, particularly enol silanes, has attracted considerable attention.[2] Prominent among the chiral bases employed is (*R,R'*)-bis(1-phenylethyl)amidolithium (1), which has been used to selectively remove the highlighted hydrogens from ketones such as 2–4.[3] A rationalization of such "enantioselective deprotonations" using base 1 was recently proposed by Majewski and Gleave.[2c] Here, we describe the molecular structure of the THF complex of this increasingly important reagent 1, determined by crystallography,[4] which contradicts the structure used in the abovementioned rationalization and provides a basis for further mechanistic discussion.



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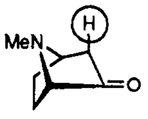

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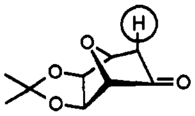

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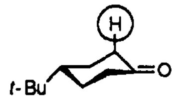

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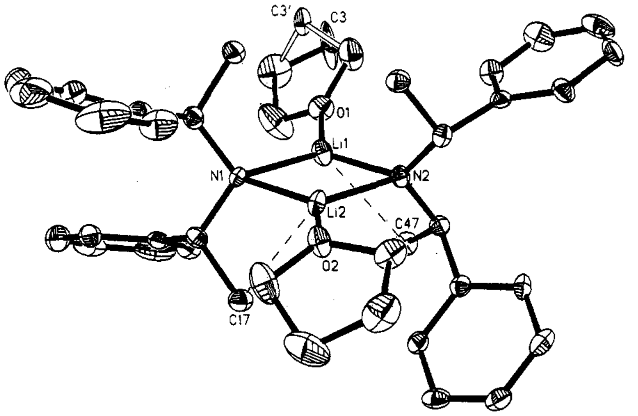

Figure 1. Thermal ellipsoid plot (40% probability) of the molecular structure of $(1\cdot THF)_2$. Hydrogen atoms are omitted for clarity. Selected bond lengths (Å): Li(1)–O(1), 1.984(13); Li(1)–N(1), 2.073(13); Li(1)–C(47), 2.78(2); Li(1)–N(2), 1.992(14); Li(2)–O(2), 1.952(12); Li(2)–N(2), 2.068(13); Li(2)–N(1), 2.031(13); Li(2)–C(17), 2.741(14). Selected bond angles (deg): N(1)–Li(2)–N(2), 107.0(6); N(1)–Li(1)–N(2), 108.3(6); Li(1)–N(1)–Li(2), 71.9(5); Li(1)–N(2)–Li(2), 72.8(5).

Reaction of the commercially available (*R,R'*)-bis(1-phenylethyl)amine[5] with BuLi in hexane/THF produced colorless crystals of amidolithium 1 in 40% yield.[5] The preparative advantages of isolation of pure, crystalline solids over use of solutions prepared *in situ* have been described by others.[6]

The crystallographically determined[7] molecular structure (Figure 1) of 1 shows similarities to the recently reported LDA–THF complex[6] with which it differs by replacement of a methyl group with a phenyl group. However, the reduced symmetry induces subtle structural points worthy of note. Li(1), Li(2), N(1), and N(2) lie in a plane (mean deviation = 0.004 Å) approximately orthogonal to the planes defined by the amido CNC units. The oxygen atoms of the THF ligands lie slightly above the Li_2N_2 ring plane (O(1) 6.0°, O(2) 5.4° above), and the plane defined by C–O(1)–C of a THF ring is bent a further 12.3° toward the "top" of the Li_2N_2 ring as drawn. The second THF is also slightly bent toward this side of the

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[1] For a recent review of the uses of homochiral lithium bases see: Cox, P. J.; Simpkins, N. S. *Tetrahedron: Asymmetry* **1991**, *2*, 1.

[2] (a) Bunn, B. J.; Simpkins, N. S. *J. Org. Chem.* **1993**, *58*, 533. (b) Honda, T.; Kimura, N.; Tsubuki, M. *Tetrahedron: Asymmetry* **1993**, *4*, 21. (c) Majewski, M.; Gleave, D. M. *J. Org. Chem.* **1992**, *57*, 1599. (d) Underiner, T. L.; Paquette, L. A. *J. Org. Chem.* **1992**, *57*, 5438. (e) Bambridge, K.; Simpkins, N. S.; Clark, B. P. *Tetrahedron Lett.* **1992**, *33*, 8141. (f) Cox, P. J.; Simpkins, N. S. *Synlett.* **1991**, 321.

[3] The ketones illustrated are simple examples of those enantioselectively enolized to date, all of which posses either bulky substituents or bridgehead atoms to fix a chairlike conformation with axial enolizable hydrogens.

[4] Only two chiral amidolithiums, both containing internal coordination sites, have been previously characterized by crystallography: (a) Barr, D.; Berrisford, D. J.; Jones, R. V. H.; Slawin, A. M. Z.; Snaith, R.; Stoddart, J. F. *Angew. Chem., Int. Ed. Engl.* **1989**, *28*, 1044. (b) Sato, D.; Kawasaki, H.; Shimada, I.; Arata, Y.; Okamura, K.; Date, T.; Koga, K. *J. Am. Chem. Soc.* **1992**, *114*, 761.

[5] Overberger, C. G.; Marullo, N. P.; Hiskey, R. G. *J. Am. Chem. Soc.* **1961**, *83*, 1374. Commercial quantities from Oxford Asymmetry, 57 Milton Park, Abingdon, Oxfordshire, U. K.

[6] Williard, P. G.; Salvino, J. M. *J. Org. Chem.* **1993**, *58*, 1.

[7] Space group $P2_1$, a = 9.682(2) Å, b = 13.358(3) Å, c = 14.241(3) Å, β = 98.69(3)°, cell volume = 1820.7(7) Å^3, Z = 2, D_{calc} = 1.107 Mg m^{-3}. A total of 5014 reflections were collected, of which 4768 were independent. Full-matrix least-squares refinement on F^2 for all reflections gave final agreement factors R = 0.0787 [for reflections with $I > 2\sigma(I)$], $wR2$ = 0.1906. All non-hydrogen atoms are anisotropic. Disorder in a carbon of one THF was modeled over two sites, which refined to occupancies of 49% and 51%. Data were not sufficiently accurate for an unambiguous absolute configuration determination.

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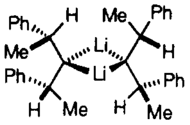
ring, giving an unusual "cisoid" ring geometry.[8] The most important structural point concerns the rotameric conformation of the four chiral *R* side groups of the two amido groups. The determining factor seems to be the maximization of methyl contacts to lithium. All four methyl groups are quite close to lithium centers, but C(17) and C(47) lie closest (C–Li 2.741(14), 2.78(2) Å, respectively). Both of these lie on one side of the ring, reinforcing the "cisoid" character generated by the positions of the THF ligands.

In the previous rationalization of the reactivity of 1 the dimeric structure **5** was proposed to explain the selectivity of deprotonations of *cis*-3,5-dimethylcyclohexanone. Figure 1 confirms that a dimeric structure predominates,[9] but the conformation suggested by Majewski and Gleave on the basis of molecular mechanics (gas phase) calculations appears to be incorrect. The error lies in the model used, which implicitly ignored the attractive term between the coordinatively unsaturated three-coordinate lithium and the methyl groups in the approximation of the Li_2N_2 ring to a cyclobutane.



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Assuming that in the most populated of possible transition-state structures the chiral side-groups adopt their lowest energy conformations, the structure presented in Figure 1 gives the best possible starting point on which to base mechanistic speculation.[10] However, the application of existing enolization models, both dimeric[11] and monomeric,[12] to this chiral case did not yield obvious explanations of the observed sense of enantioselectivity. Ideally, any new model should encompass added salt, added solvent, and *in situ* quench effects. We are currently seeking structural and mechanistic evidence in support of such a model for enantioselective deprotonation, which we believe must involve mixed aggregation effects of the type recently proven to affect *E*/*Z* selectivities in reactions of LDA.[13]

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Supplementary Material Available: Experimental procedure and characterization data for compound 1 (1 page). 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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(8) For a review of structural trends in amidolithium complexes, see: Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47.

(9) (a) While the extension of crytallographic results to the solution state is open to criticism, comprehensive studies on LDA in THF, a system closely related to that which we discuss here, prove that the ring dimer observed in the solid state is maintained in THF solution.[9b] Our own ^1H and ^7Li variable-temperature NMR investigations show no evidence for species other than dimeric $(1\cdot THF)_2$ in solution. (b) Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 794.

(10) The lack of any intermolecular contacts in the crystal suggests that the solid-state dimer is a reasonable model for the solution state. The amide geometry found experimentally is consistent with an early model of monomeric 1: Marshall, J. A.; Lebreton, J. *J. Am. Chem. Soc.* **1988**, *110*, 2925.

(11) (a) Romesberg, F. E.; Gilchrist, J. H.; Harrison, A. T.; Fuller, D. J.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 5751. (b) Romesberg, F. E.; Collum, D. B. *J. Am. Chem. Soc.* **1992**, *114*, 2112. (c) Williard, P. G.; Liu, Q.-Y. *J. Am. Chem. Soc.* **1993**, *115*, 3380.

(12) Ireland, R. E.; Mueller, R. M.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868.

(13) (a) Hall, P. L.; Gilchrist, J. H.; Collum, D. B. *J. Am. Chem. Soc.* **1991**, *113*, 9571. (b) Mair, F. S.; Clegg, W.; O'Neil, P. A. *J. Am. Chem. Soc.* **1993**, *115*, 3388.