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X-ray Crystal Structure Analysis of (*N*-Isopropylbenzamide)lithium Tetrahydrofuran: An Aza Analogous Ketone Lithium Enolate

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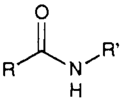
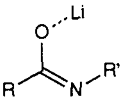
Abstract: The first X-ray crystal structure of a lithium azaenolate derived from a carboxylic acid amide is presented. A hexameric aggregate of lithium *N*-isopropylbenzamide crystallizes from a THF/TMEDA/hexane mixture at room temperature. Six lithiums and six oxygens form a slightly skewed hexagonal prism, providing three coordination sites for each Li. The fourth ligand on four of the six Li is an amide nitrogen, such that essentially planar four-membered ring chelation (Li–O–C–N) results; the other two Li are coordinated to THF oxygens. Three C_2-symmetry-related pairs of amide moieties are present, the chelating ones have *E* configurations and the nonchelating one has *Z* configuration. The structure is discussed in connection with the lithiation of oligopeptides and is compared with that of lithium carboxylates.

Crystalline ketone,[3,4] ester,[5] and amide lithium enolates[4,6] are exclusively metalated on oxygen. Depending on the solvent or ligand added, dimeric, tetrameric, or hexameric[7] aggregates may be formed. As yet, no crystal structure has been available for a lithium azaenolate derived from a carboxylic acid amide (A); the question arises as to whether the metal is coordinated only to oxygen (B)[8], only to nitrogen (C), or to both heteroatoms (D, E).[9]



A



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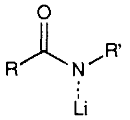

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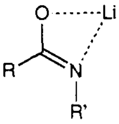

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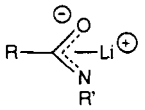

E

This question has special significance for investigations of deprotonated oligopeptides.[10] In such polylithiated oligopeptides, particular amino acid residues may be selectively α-alkylated in the presence of lithiated amide groups of the type derived from A ($pK_a < 20$). Obviously, polar interactions determine the shape and conformation of the peptide chain and, in turn, the stereoselectivity and yield of such reactions. Generally, both the selectivity and yield are increased by adding lithium salts (LiBr, $LiClO_4$, or $LiOSO_2R$),[11,12] a phenomenon that most likely results from a mixed lithium aggregate of the deprotonated species.

Preparation and X-ray Crystal Structure Analysis of Lithiated *N*-Isopropylbenzamide

N-Isopropylbenzamide was deprotonated with 1 equiv of *n*-butyllithium in THF. The lithium derivative crystallized at ambient temperature from THF/hexane in the presence of 1 equiv of TMEDA as a hexameric aggregate with a crystallographic 2-fold axis; see Figures 1 and 2.

The central unit is made of six lithium and six oxygen atoms as vertices of a hexagonal prism in an alternate manner. The six-membered rings are slightly skewed.

In this way, three lithium ligand sites[13] are already occupied within the central coordination unit. This is also the case for tetrameric organolithium compounds where a cube (a square prism) forms the central coordination sphere.[3] For two pairs of symmetrically equivalent lithium atoms (Li1, Li1A and Li2, Li2A, respectively), the fourth ligand site[14] is occupied by a nitrogen atom (N1, N1A and N2, N2A, respectively) so that four-membered chelate rings are formed within the amide units. The third pair of lithium atoms (Li3, Li3A) is coordinated to a THF molecule (O4, O4A) instead of an amide nitrogen (N3, N3A). The third pair of symmetrically equivalent amide units is therefore metalated only on oxygen (O3, O3A). The origin of this phenomenon—the incorporation of THF instead of intramolecular coordination of the remaining nitrogen atoms (N3, N3A)—is probably a mere packing effect. (There are no apparent steric interactions among phenyl and isopropyl groups of neighboring amide units in the same six-membered ring; see **1**, **2A**, and **1A**, **2**, respectively, in Figure 1.) If there were three chelated amide units in each six-membered ring of the central Li–O cage, there would be too much empty space in the axial and equatorial regions. The planes O3–C31–C37 and O3A–C31A–C37A of the nonchelated amide units are almost perpendicular to the planes of the six-membered Li–O rings, so that the phenyl groups occupy the axial space and the isopropyl groups the equatorial space in this hexameric complex (see **3** in Figure 2).

Four additional THF molecules per unit cell are incorporated into the crystal lattice. However, they are disordered. The phenyl groups of the amide units **2**, **2A** are disordered too. Therefore, these two fragments of the structure were refined as rigid groups

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[1] Part of the Ph.D. Thesis of T.M., ETH, Zürich, Dissertation No. 9206 (1990).

[2] Part of the Diplomarbeit of C.P.H., ETH, Zürich, 1989.

[3] (a) Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**, *64*, 2617–2621. (b) Seebach, D.; Amstutz, R.; Dunitz, J. D. *Ibid.* **1981**, *64*, 2622–2626.

[4] Laube, T.; Dunitz, J. D.; Seebach, D. *Helv. Chim. Acta* **1985**, *68*, 1373–1393.

[5] Seebach, D.; Amstutz, R.; Laube, T.; Schweizer, W. B.; Dunitz, J. D. *J. Am. Chem. Soc.* **1985**, *107*, 5403–5409.

[6] Bauer, W.; Laube, T.; Seebach, D. *Chem. Ber.* **1985**, *118*, 764–773.

[7] (a) Williard, P. G.; Carpenter, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 3345–3346. (b) Williard, P. G.; Carpenter, G. B. *Ibid.* **1986**, *108*, 462–468.

[8] Compare the structure of a Reformatsky reagent, where in a dimeric aggregate the zinc atoms are coordinated to oxygen and the α-carbon, respectively: (a) Dekker, J.; Boersma, J.; van der Kerk, G. J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 553–555. (b) Dekker, J.; Budzelaar, P. H. M.; Boersma, J.; van der Kerk, G. J. M.; Spek, A. L. *Organometallics* **1984**, *3*, 1403–1407.

[9] For a crystal structure of a vinylogous hydrazide in which such bridging is observed, see: Wanat, R. A.; Collum, D. B.; Van Duyne, G.; Clardy, J.; DePue, R. T. *J. Am. Chem. Soc.* **1986**, *108*, 3415–3422.

[10] Review article: Seebach, D. *Angew. Chem.* **1988**, *100*, 1685–1715. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624–1654.

[11] Seebach, D.; Estermann, H. *Helv. Chim. Acta* **1988**, *71*, 1824–1839; Seebach, D.; Estermann, H. *Tetrahedron Lett.* **1987**, *28*, 3103–3106.

[12] Seebach, D.; Thaler, A.; Beck, A. *Helv. Chim. Acta* **1989**, *72*, 857–867.

[13] Lithium prefers to have a tetrahedral ligand sphere. Setzer, W. N.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353–451.

[14] In a similar structure of a hexameric (pinacolone)lithium enolate the outer ligand site remains unoccupied. This organolithium compound was crystallized from a nonpolar solvent (heptane) in the absence of a donor ligand.[7] This ketone enolate crystallized from THF as a tetramer[3] and from TriMEDA/hexane as a dimer.[4]

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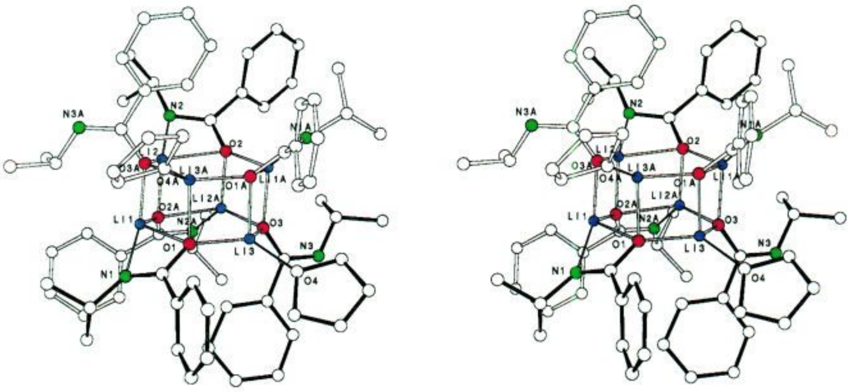

Figure 1. Stereodrawing of the crystal structure of the title compound. Three symmetrically independent amide units **1–3** and THF are drawn with bold bonds.

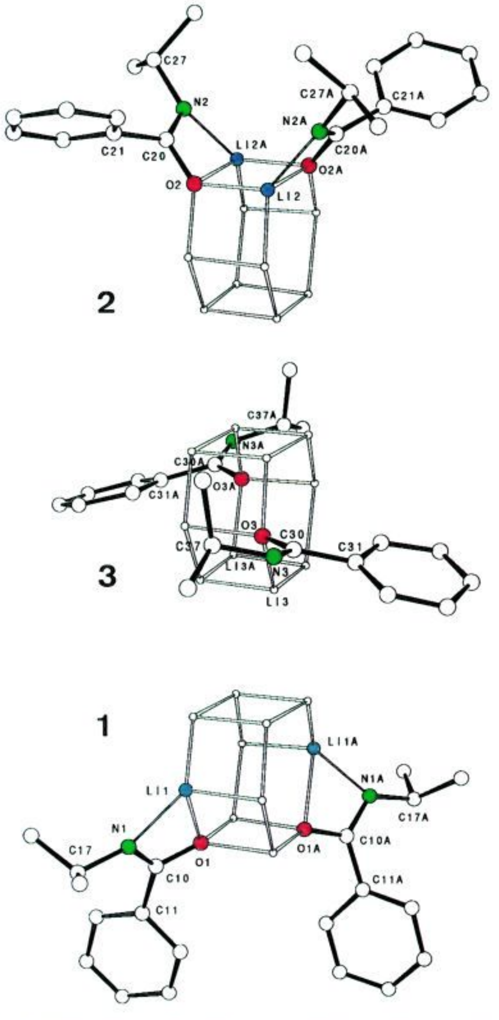

Figure 2. Separate drawing of each of the three independent pairs **1–3** of lithiated amide units that are related by the crystallographic C_2-axis (running vertically through the central Li–O cage of the hexameric complex).

with an idealized geometry. As a consequence of this disorder, there is considerable uncertainty in the bond lengths and angles of the amide units **2**, **2A**. The bond lengths and angles are shown in Figure 3.

To form a four-membered chelate ring, the two amide units **1**, **1A** and **2**, **2A** must have the *E* configuration about the C–N bond and the O-metalated amide units **3**, **3A** that do not participate in chelation must have *Z* configuration about the azaenolate double bond. The C–O bond lengths are comparable to those of lithium enolates (1.31 Å), aluminum azaenolate (1.33 Å),[15] and imino esters (1.34 Å).[16] The C–N bond lengths are longer than in the aluminum azaenolate (1.26 Å) and imino esters (1.26 Å),[16] but shorter than in carboxylic acid amides (1.34 Å).[17] (The C–N bond length of 1.34 Å in the amide units **2**, **2A** appears "too long" due to disorder in this fragment.)

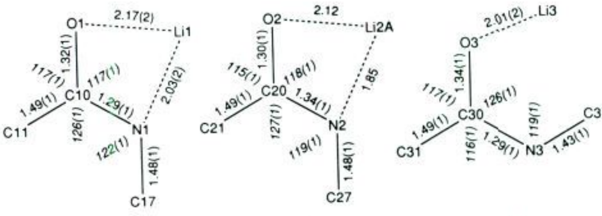

Figure 3. Bond lengths (Å) and angles (deg) of the three symmetrically independent lithium amide units **1–3** (standard deviations in parentheses).

The nitrogen atoms in the amide units **1**, **1A** and **2**, **2A** have trigonal-planar geometry. The torsion angles about the C–N bonds are approximately 180° in the amide units **1**, **1A** and **2**, **2A** and 0° in the amide units **3**, **3A**.

Discussion of the Structure

The X-ray crystal structure analysis presented here describes two particularly remarkable structural features.

The crystals were grown at room temperature from a solution of THF/hexane in the presence of TMEDA. Despite the demonstrated affinity of TMEDA for lithium, as shown by many X-ray crystal structure analyses,[13] this bidentate ligand is not incorporated in the crystals. To our knowledge, this is the first hexameric complex of this nature that was not crystallized from a pure hydrocarbon solvent.[7,10]

The second noteworthy feature of this hexameric structure is that there exist two configurations about the C–N double bonds in the same complex, depending upon the presence or absence of chelation. Furthermore, the absence of chelation observed in two of the six amide units suggests that packing effects might compete with intramolecular complexation.

Conclusions

The first crystal structure analysis of a lithiated carboxylic acid amide is presented. It reveals that cosolvents even as effective as TMEDA may be displaced in favor of the formation of higher aggregated complexes. In the case of a lithium carboxylate, a 1,3-dioxa allylic system, one might expect that the tendency to form chelate four-membered rings should be even higher. How-

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(15) Kai, Y.; Yasuoka, N.; Kasai, N.; Kakudo, M. *Bull. Chem. Soc. Jpn.* **1972**, *45*, 3388. See also: Kai, Y.; Yasuoka, N.; Kasai, N.; Kakudo, M. *J. Organomet. Chem.* **1971**, *32*, 165.

(16) Mean value of 18 structures of the CSD.[19]

(17) Mean value of 43 structures of the CSD.[19]

(18) If the lithiated *N*-isopropylbenzamide is crystallized from TMEDA/hexane and the crystals are quenched with CD_3OD/CD_3COOD, the ^1H NMR spectrum shows that again no TMEDA is incorporated.

ever, among the 50 lithium carboxylate structures of the CSD[19] (crystallized from polar solvents such as water, methanol, or DMSO) no such case could be found. These systems tend to form intermolecular Li–O bridges. Lithium benzoate itself, when crystallized from DMSO, forms one-dimensional chains.[20]

Finally, it is possible to solubilize lithiated oligopeptides by adding lithium salts. Here, one can argue that the intramolecular chelate rings are disrupted and that each ligand site of the peptide is independently occupied by lithium. These lithium atoms again may be involved in locally mixed aggregates with the lithium salt and further donor solvent molecules, promoting dissolution of the complete molecular aggregate.[10]

Experimental Section

To a solution of *N*-isopropylbenzamide (1.14 g, 7.03 mmol) and TMEDA (1.11 mL, 7.4 mmol) in 2.5 mL of THF was added under argon at −10 °C *n*-butyllithium (4.40 mL, 1.6 M in hexane, 7.03 mmol). The slightly yellow solution was transferred immediately into a beaker in a desiccator. The atmosphere of the desiccator was saturated with hexane. Twenty-four hours later the colorless cubic crystals were isolated and mounted in a capillary with hexadecane.

X-ray Crystal Structure Analysis of $(C_{10}H_{12}NOLi)_6 \cdot 3C_4H_8O$. A crystal (0.3 × 0.3 × 0.4 mm) was fixed under nitrogen (glove bag) in a capillary (ϕ 0.5 mm) and mounted on an Enraf-Nonius CAD4 four-circle diffractometer with graphite monochromator. Data: monoclinic, space group $C2/c$, a = 23.36 (2) Å, b = 13.70 (2) Å, c = 25.38 (4) Å, β = 111.5 (1)°, V = 7556 Å^3, M = 1231.23, Z = 4, D_{calcd} = 1.08 g·cm^{-3}, μ = 0.39 cm^{-1}, $F(000)$ = 2640. Data were collected at 24 °C with Mo Kα radiation (λ = 0.7101 Å) in the 2θ range of 3–40°. Intensities of 3510 independent reflections were measured, and 1556 with $I > 3\sigma(I)$ were used for the refinement. Absorption corrections were not applied. The structure was solved by direct methods (SHELXS-86[21]). The carbon atoms of the isopropyl groups, four atoms in the phenyl ring of amide unit **1**, and N2 and N3 were refined anisotropically; the rest of the non-hydrogen atoms were refined isotropically. A riding model with idealized geometry was employed for H atom refinement. The phenyl group of amide unit **2** and the noncoordinated THF molecule were refined as rigid groups with idealized geometry (SHELX-76[22]). Two hundred seventy-three parameters were refined and a weighting scheme ($w^{-1} = \sigma^2 F_o$) was used. The final values for R and R_W were 0.093 and 0.104, respectively, with the final Fourier difference map showing a maximum of 0.35 e Å^{-3} and a minimum of −0.41 e Å^{-3}. The crystallographic figures were prepared with ORTEP.[23]

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Supplementary Material Available: Table listing the X-ray crystal structure analysis, a figure, with atom numbering, and tables of the atomic coordinates and thermal parameters, bond lengths, and angles (6 pages). Ordering information is given on any current masthead page. The list of coordinates of the crystal structure has been deposited with the Cambridge Crystallographic Data center.[19]

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(20) Mason, R. P.; Harriman, J. E. *J. Chem. Phys.* **1976**, *65*, 2274–2287.

(21) Sheldrick, G. M. SHELXS-86. Program for the Solution of Crystal Structures. University of Göttingen, Germany, 1986.

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(23) Johnson, C. K. ORTEP-II. Report ORNL-5138. Oak Ridge National Laboratory, TN, 1976.