The Crystal Structures of a Chiral Aminoalkoxide Cluster and Its Adduct with Benzyllithium

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Mixed aggregates between alkyllithium bases and coordinating auxiliaries, such as lithium alkoxides or aminoalkoxides, are becoming more and more important for two main reasons. First, these aggregates often reveal an enhanced proton-abstracting power toward substrates of low reactivity (superbasic properties). Furthermore, chirality can be introduced by the use of enantiomerically pure auxiliaries (leading to chiral bases or nucleophiles). In the meantime, many examples applying this principle have been developed, involving various amides and alkoxides of metals of groups 1 and 2.[1] Optically active variations have been introduced into enantioselective synthesis.[2]

The dominating structural principles for alkoxides or amino-alkoxides are the ladder, the ring-ladder, and the stacked-ring architecture.[3] The mixed aggregates with alkyllithiums can often be described as tetramers and hexamers, where alkoxy groups have been exchanged for alkanide units.[2a] Since a strong structure/reactivity relation is assumed for mixtures of this type,[4] these structural associations have been the basis for several NMR studies in solution.[2a] This work shows that a surprising structural motif might have been neglected up to now.

The lithium alkoxide of 1-methyl-(S)-2-(hydroxymethyl)pyrrolidine [(S)-2] has been used in combination with alkyllithiums as a chiral complex base.[2,5,6] However, especially the applied molar ratio between alkoxide and the alkyllithium has been a source of ongoing controversial discussions. We report herein on the crystal structure of the enantiomerically pure alkoxide (S)-2 and its reactivity enhancement on n-butyllithium in the deprotonation of toluene. The resulting striking crystal structure of the adduct (S)-3 represents the first 6:1 aggregate between a lithium alkoxide and an alkyl-lithium that is not formed by the exchange of alkoxy groups for alkanide units, thus representing a previously unconsidered type of structure.

When (S)-1 is reacted with tert-butyllithium (molar ratio of 1:1 or excess of base) in n-pentane, colorless single crystals of the hexameric aggregate of the aminoalkoxide (S)-2 are obtained in almost quantitative yield. When n-butyllithium is used (molar ratio of 1:1), an insoluble alkoxide is formed which, in contrast to the tert-butyllithium case, dissolves when an excess of n-butyllithium is added. The addition of toluene to this solution leads to the precipitation of the aggregate (S)-3 as pale yellow crystals, where the hexameric aminoalkoxide is capped by one molecule of benzyllithium, resulting from the deprotonation of toluene by n-butyllithium (Scheme 1).
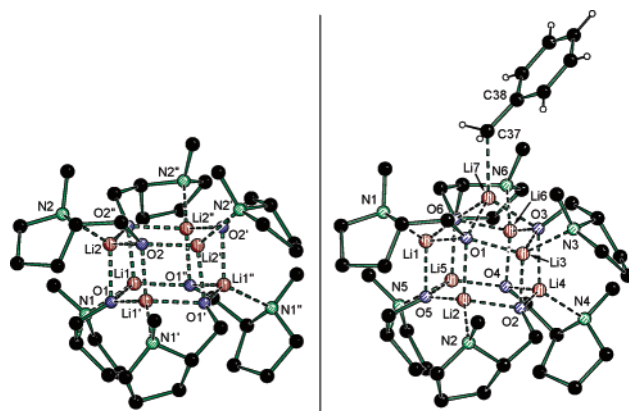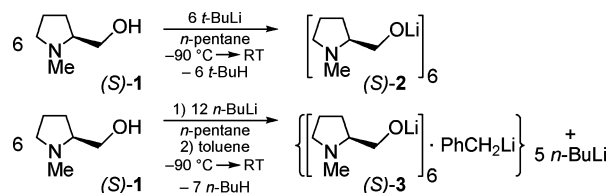
Scheme 1

Figure 1. Molecular structures of (S)-2 and (S)-3 in the crystal (*Schakal* plots[9a]). Selected bond lengths (Å) and angles (deg) of (S)-2: Li(1)−O(1) 1.964(5), Li(1)−O(1)″ 1.886(6), Li(1)−O(2)″ 1.953(5), Li(1)−N(1) 2.158-(6), Li(2)−O(2) 1.947(6), Li(2)−O(2)″ 1.886(6), Li(2)−O(1) 1.962(5), Li-(2)−N(2) 2.162(6); (S)-3: Li(1)−O(5) 1.895(4), Li(1)−O(6) 1.945(4), Li(1)−O(1) 1.963(4), Li(1)−N(1) 2.130(4), Li(7)−O(3) 1.999(4), Li(7)−O(6) 2.058(4), Li(7)−O(1) 2.060(4), C(37)−Li(7) 2.302(4), C(37)−C(38) 1.440(3), C(38)−C(37)−Li(7) 133.7(2).

Figure 1 shows the molecular structure of (S)-2 in the solid state, which crystallized as a hexamer from n-pentane in the hexagonal crystal system, space group R3 (cocrystallized tert-butane has been omitted for clarity).[7] The asymmetric unit contains two aminoalkox-ides, the hexamer (S)-2 being formed by a C_3 symmetry operation. The central structural motif is a ring-ladder, consisting of two stacked six-membered rings [Li−O distances between the rings amount to 1.953(5) and 1.962(5) Å], which can also be found in similar aggregates.[8] These rings are formed by alternating lithium and oxygen centers, two adjacent centers formally belonging to the same monomeric unit [Li−O distances of adjacent centers amount to 1.886(6) and 1.955(6) Å]. Moreover, a slight chair conformation is observed, as evidenced by the sum of the angles of 710.7° for the ring built up by Li(2) and O(2) and 711.2° for that constructed from Li(1) and O(1) (720° for an ideally planar hexagon). The lithium centers each have four contacts: two Li−O contacts within the same six-membered ring, one Li−O contact to the second ring, and one Li−N contact to the nitrogen center of the 1-methylpyrrolidine unit. All six methyl groups of the pyrro-lidine units are pointing in the same direction, which is most probably due to steric reasons, since otherwise two pyrrolidine units would show significant steric interactions. By this specific arrange-ment, a more 'closed' "bottom side" and a more 'opened' "top side" of the chiral hexameric aggregate is formed (Figure 1).

Figure 2 shows a ball-and-stick model of the molecular structure of (S)-2 in the crystal, where the electrostatic potential has been projected onto a Connolly surface[9b,10] [coordinates of the crystal structure used as input orientation, single-point DFT calculation B3LYP/6-31+G(d);[11] Connolly surface generated with a spherical probe radius of 0.60 Å (Li+)]. The "top side" (on the left) is less
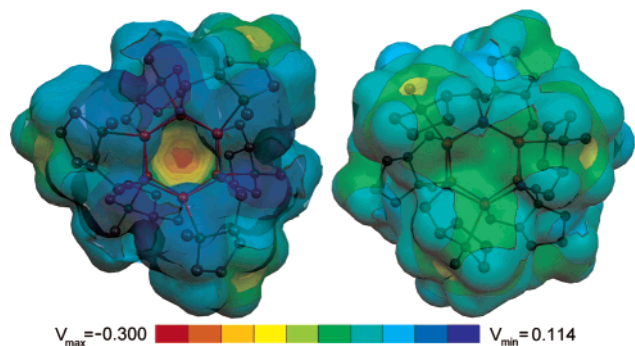
Figure 2. Visualization of the electrostatic potential of (*S*)-**2** [B3LYP/6-31+G(d)], projected onto a Connolly surface (*Molekel* plot[9b]); "top" view on the left, "bottom" view on the right.

shielded by the methyl groups which are pointing in this direction, as evidenced by the exposed negative potential in the center of the visualization plot. The "bottom side" of (*S*)-**2** (on the right) is more shielded by the pyrrolidine rings, giving rise to a more neutral potential in the center (Figure 2).

The good accessibility from the "top side" together with the charge distribution in (*S*)-**2** is well suited for the complexation of an alkyllithium base, as proven by the crystal structure of compound (*S*)-**3** (Figure 1). The aggregate which can be regarded as an adduct between (*S*)-**2** and benzyllithium, crystallized from an *n*-pentane/toluene mixture in the monoclinic crystal system, space group $P2_1$.[7]

The additional lithium center Li(7) of the monomeric benzyllithium is capping the hexameric alkoxide framework from the "top side" by three Li−O interactions, two of which [Li(7)−O(1) and Li(7)−O(6)] are equal while one [Li(7)−O(3)] is slightly shorter. The lithium−carbon distance Li(7)−C(37), which amounts to 2.302-(4) Å, is significantly longer than in comparable crystal structures, where corresponding Li−C distances between 2.15(3) and 2.210-(5) Å can be found.[12] The reason for this observation might be the steric demand of the particular ligand in (*S*)-**2**. The sum of the angles of 340.7° at C(37) proves that the carbanionic unit is far from being planar, which is in contrast to the findings of many crystal structure determinations on ordinary benzyllithium systems.[13] As a result of the coordination to the lithium center Li(7), a slight distortion of the alkoxide framework is observed. A more distinct chair conformation is the result, giving rise to a smaller sum of the angles of 686.9° of the six-membered ring next to Li(7), the second ring almost unchanged with a value of 710.1°. The lithium cuprate [Li₇-(O*t*-Bu)₆][Cu₂{Si(SiMe₃)₃}₃] also shows this particular structural motif of a lithium center capping three oxygen centers of a ring-ladder system, but is only marginally comparable.[14]

In the literature, several aggregates have been described where the oxygen centers of such alkoxide or aminoalkoxide clusters have been replaced on reactions with alkyllithiums.[2a,15] Unexpectedly, in (*S*)-**3** the alkoxide framework acts as a ligand to the alkyllithium and remains intact. Computational studies by Goldfuss et al. on alkoxide cubes show that the integration of alkoxide ligands is favored but limited by the steric demand of these ligands.[15c] Thus, in the case of (*S*)-**3**, the following two factors might play an important role: The steric demand of the alkoxide ligand within the hexameric framework is small enough *not* to favor a substitution of alkoxides by benzyllithiums *and* the deaggregation of benzyllithium in noncoordinating solvents is more facile than of other alkyllithiums (due to the delocalization/stabilization of the negative charge by the aromatic ring system). It would appear that the special property of the aggregate of (*S*)-**2**—an unshielded coordination site in a chiral pocket which is only accessible from one side—leads to the observed defined 6:1 adduct formation of (*S*)-**3**.

In a preliminary addition reaction between (*S*)-**3** and benzaldehyde at −90 °C in toluene, an enantiomeric ratio of the addition product of 62:38 was observed by the use of the NMR shift reagent Eu(tfc)₃. This value shows that a reactive aggregate between the alkyllithium and the chiral alkoxide exists in solution; however, this might not necessarily be the one we find in the solid state.

Our crystallographic studies of compounds (*S*)-**2** and (*S*)-**3** reveal a new coordination mode between a lithium aminoalkoxide and an alkyllithium compound which has not been considered significantly in past studies. Moreover, the 6:1 adduct of (*S*)-**3** can help to better understand the effects of the applied stoichiometries on the distribution of regio- or stereoisomers. In a recent article, Plaquevent et al. claim that "chiral alkali alkoxides [...] appear to be a powerful class of chiral basic auxiliaries [...] and seem to be excellent candidates for future asymmetric syntheses".[5] We believe that the determination and the consideration of the crystal structures will greatly help in understanding the reactivity of this new generation of chiral bases or nucleophiles, respectively.

Supporting Information Available: X-ray crystallographic data in CIF format; experimental and computational data. This material is available free of charge via the Internet at http://pubs.acs.org.

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