Synthesis and novel structure of the first crystallographically characterised chiral α-amino lithium alkoxide

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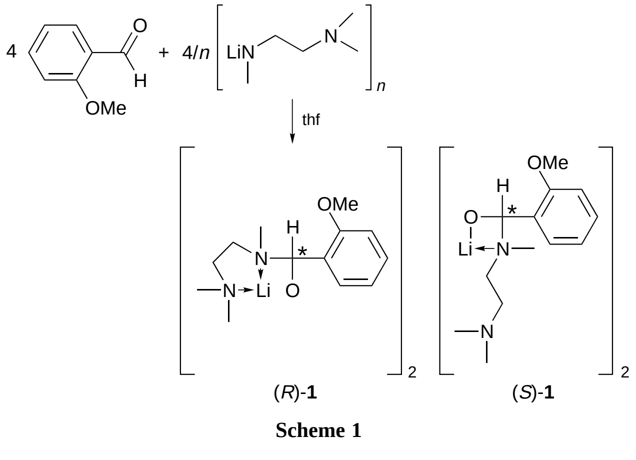
Lithium *N,N,N′*-trimethylethylenediamide, LiN(Me)(CH$_2$)$_2$NMe$_2$, reacts with *o*-anisaldehyde, *o*-MeOC$_6$H$_4$CHO, to afford a chiral α-amino lithium alkoxide 1, which in the solid state is a racemic tetramer with an 'open' pseudo-cubane core; the extent to which the *N,N,N′*-trimethylethylenediamido moieties internally solvate the Li centres varies with the chirality of the protected aldehyde groups.

Directed metallations of aromatic systems have been the subject of intensive research.[1] In particular, various carbonyl-derived directing groups have been applied to the problem of regiospecifically metallating arylaldehydes.[2] It has been reported that *in situ* protection of benzaldehyde derivatives[2,3] and heterocyclic arylaldehydes[4] *via* reaction with lithium dialkylamides, so giving α-amino lithium alkoxides, can be followed by ring lithiation, affording a convenient one-pot route to *ortho*-substituted arylaldehydes. Typically, a lithium dialkylamide is reacted with 1 equiv. of arylaldehyde (see, *e.g.* Scheme 1), yielding the corresponding chiral α-amino lithium alkoxide which is capable not only of protecting the formyl functionality but also of directing subsequent lithiation, in the presence of excess Bu^{n}Li, to the *o*-ring position. It is surprising that the nature of chiral lithiated intermediates in general has gone largely unexplored, with only a few examples of solution studies,[5] solid-state structures[5a,b] and theoretical investigations reported.[6] It is this scarcity of data which prompted us to investigate chiral α-amino lithium alkoxides, in order to establish precisely how the Lewis-base N-centres of the added amino moieties might stabilise the metal centres and, thereby, how subsequent lithiation might be directed.

We report here the isolation and structural characterisation of the first lithium α-amino alkoxide, **1**. It is obtained by the 1 : 1 reaction of *o*-anisaldehyde with *in situ* generated lithium *N,N,N′*-trimethylethylenediamide in thf† at −78 °C (Scheme 1). Warming affords a yellow solution, the storage of which at room temp. for 24 h yields colourless crystals of **1**. X-Ray crystallography‡ shows that in the solid state **1** is a novel tetramer based on an 'open' pseudo-cubane core (Fig. 1). The molecule sits on a crystallographic twofold axis which passes through the Li(1)O(2)Li(1A)O(2A) and Li(2)O(4)Li(2A)O(4A) planes of the cube. The Li centres each demonstrate fourfold coordination, although the fashion in which this is achieved is linked to the chirality of the protected aldehyde carbon. The observed exclusion of thf from the product is due to intramolecular stabilisation of the metal centres. This could occur *via* coordination by the α-N- or the δ-N-centres, or by both. Although there are several examples of intact (LiO)$_4$ pseudo-cubanes demonstrating intramonomer N-stabilisation[5a,b,10,11] of the metal centres, including two diastereomeric aggregates,[5a,b] it is nevertheless intriguing that in **1** the amino moieties are mono- or bis-chelating depending upon whether they are associated with (*S*)- or (*R*)-ligands, respectively. Opening of one end of the pseudo-cubane, which results from bis-chelation by the (*R*)-ligands, necessarily incurs significant variations in core Li–O bond lengths. Viewing the tetramer as an aggregate in which a dimeric pair of (*R*)-ligands lie next to a dimeric pair of (*S*)-ligands (Fig. 1, right to left), the inter-dimer Li–O distances vary between 1.909(8) Å [Li(2)–O(2)] and 1.852(8) Å [Li(1A)–O(4)]. The four-membered (LiO)$_2$ ring which is associated with dimerisation of the two (*S*)-ligands and constitutes the closed face of the pseudo-cubane, is likewise composed of two Li–O bond types. Those between the two (*S*)-monomers [*e.g.* Li(1)–O(2) 1.903(8) Å] are rather shorter than those present in the



(*R*)-**1** (*S*)-**1**

Scheme 1

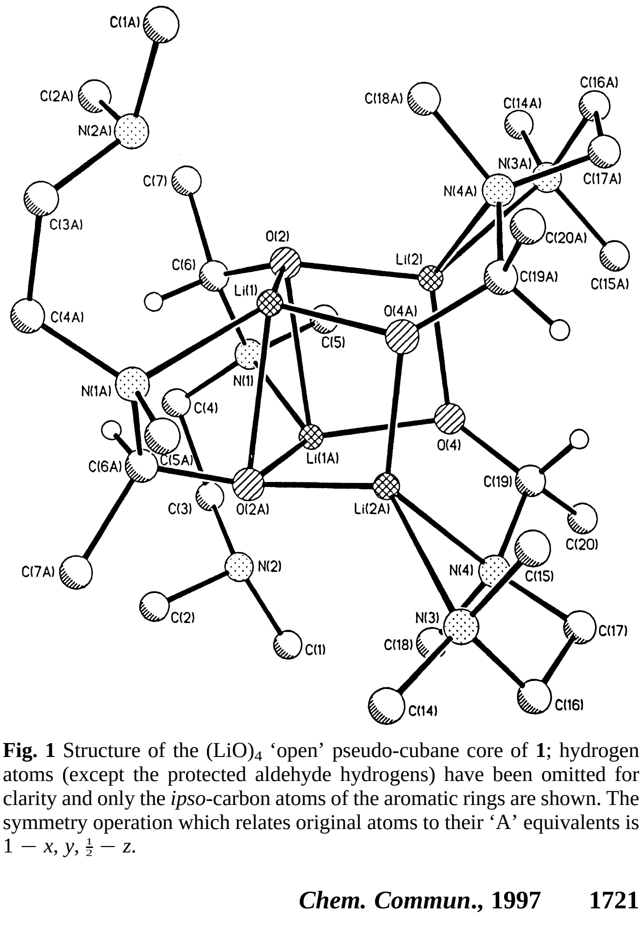


Fig. 1 Structure of the (LiO)$_4$ 'open' pseudo-cubane core of **1**; hydrogen atoms (except the protected aldehyde hydrogens) have been omitted for clarity and only the *ipso*-carbon atoms of the aromatic rings are shown. The symmetry operation which relates original atoms to their 'A' equivalents is $1 - x, y, \frac{1}{2} - z$.

four-membered chelate rings [*e.g.* Li(1A)O(2)C(6)N(1), Li(1A)–O(2) 2.303(8) Å] which result from mono-chelation of the α-amino moieties and which demonstrate *anti*-geometrical isomerism about the C–N bond. At 2.101(8) Å, the Li(1A)–N(1) distance is consistent with distances found in related mono-chelates.[5a,b,10] The two (*R*)-ligands behave in a bis-chelating fashion with both α- and δ-N-centres stabilising the metal centres. Concomitantly, two eclipsed intramonomer Li–O bonds in the pseudo-cubane core have cleaved [*i.e.* Li(2)···O(4A)]. The result is that instead of each (*R*)-ligand incorporating a four-membered Li–O–C–N chelate ring, both (*R*)-ligands combine with two intact edges of the open pseudo-cubane, yielding an eight-membered $(\mathrm{Li–O–C–N})_2$ ring in a boat conformation, in which geometrical isomerism about the C–N bonds is once again of the *anti*-form. The intact Li–O bonds [Li(2)–O(4)], at only 1.872(8) Å, are rather shorter than those in the (presumably) strained four-membered mono-chelate rings associated with the (*S*)-isomers. While the α-N–Li [Li(2)–N(4A)] distance, at 2.118(8) Å, is essentially unchanged from the analogous interactions in the mono-chelated (*S*)-ligands, the δ-N–Li [Li(2)–N(3A)] bond length is somewhat longer, at 2.365(8) Å.

At 2.723(8) Å, the non-bonded Li(2)···O(4A) distance is relatively short compared with that of 3.14 Å in $[\mathrm{PhOLi \cdot thf}]_4 \cdot \mathrm{PhOH}$, the only other known example of an ‘open’ $(\mathrm{LiO})_4$ pseudo-cubane.[12] However, unlike **1** this tetramer demonstrates opening of only one cubane bond, a phenomenon brought about by the inclusion of a non-lithiated phenol molecule whose hydroxyl group bridges one cubane edge. More extensive fragmentation, as seen in **1**, has been recorded in a lithium halide. Here, however, the fracture of intraaggregate bonds results from polymerisation,[13] $(\mathrm{LiBr \cdot thf})_\infty$ representing the only previous example of an ‘open’ pseudo-cubane in which, as for **1**, two eclipsed Li–X bonds are absent.

Multinuclear NMR studies suggest the solution behaviour of **1** to be of a complicated nature. Firstly, ^{7}Li NMR spectroscopy does not show two lithium environments in a 1 : 1 ratio. This suggests that the (*R*)- and (*S*)-monomers do not retain their solid-state differences in solution and that, therefore, either the tetramer is fluxional or it deaggregates. In fact, cryoscopy in benzene§ suggests that a monomer/dimer equilibrium is dominant in non-polar solution. Accordingly ^{7}Li NMR spectroscopy shows two major features in a 3.8 : 1 ratio at ambient temperature in [^{2}H$_6$]benzene (δ −0.35, −0.47). Variable-temperature ^{7}Li NMR spectroscopy in [^{2}H$_8$]toluene allows us to assign these as dimer and monomer respectively. The room-temp. spectrum shows peaks at δ −0.42 and −0.55 which are comparable to those observed in [^{2}H$_6$]benzene. However, at 193 K the high-field signal is absent, the low-field one having moved to δ −0.26.†

^{1}H NMR spectroscopy in [^{2}H$_6$]benzene at 298 K also reflects the complex behaviour of **1** in solution, showing as it does a dominant protected aldehyde signal at δ 6.48 along with five much smaller satellites in the range δ 6.12–6.01, all of which correlate with the protected aldehyde carbon centre at δ 88.60 (by HMQC spectroscopy).[14] Solution studies of **1** are ongoing.

We thank the UK EPSRC (A. E. H. W.) and The Royal Society (J. E. D., P. R. R.) for financial support.

Footnotes and References

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† Bu^{n}Li (1.88 ml, 1.6 M in hexanes, 3.0 mmol) was added to *N,N,N′*-trimethylethylenediamine (0.38 ml, 3.0 mmol) in thf (4 ml) at −78 °C under N$_2$. After stirring for 10 min, *o*-anisaldehyde (0.36 ml, 3.0 mmol) was added and the resultant colourless solution was stirred for a further 10 min at −78 °C. Warming to room temp. gave a white suspension, which afforded a yellow solution on gentle heating. Storage at room temp. for one day afforded colourless, rectangular crystals of **1**, mp, 160–161 °C, yield, 82%. ^{1}H NMR (500.13 MHz, 298 K, C$_6$D$_6$), δ 8.14 (d, 1 H, Ar), 7.18 (d, 1 H, Ar), 7.14 (dd, 1 H, Ar), 6.78 (dd, 1 H, Ar), 6.48–6.01 [m, 1 H ArC(*H*)(O)NR$_2$], 3.72–3.31 (m, 3 H, OCH$_3$), 2.75–2.69, 2.32 (m, 2 H, CH$_2$), 2.68–2.21 (m, 3 H, NCH$_3$), 2.53–2.49 (m, 2 H, CH$_2$), 2.41–1.92 [m, 6 H, N′(CH$_3$)$_2$].^{13}C NMR (100.61 MHz, 298 K, C$_6$D$_6$), δ 157.03, 135.83, 130.61, 126.83, 119.91, 110.01 (Ar), 88.60 [Ar*C*(H)(O)NR$_2$], 59.02 (CH$_2$), 54.86 (OCH$_3$), 52.13 (CH$_2$), 46.66–45.54 [m, N′(CH$_3$)$_2$], 36.87–34.73 (m, NCH$_3$). ^{7}Li NMR (155.51 MHz, 298 K, C$_6$D$_6$, ref. PhLi δ 0) δ −0.35 (s, 3.8 Li), −0.47 (s, 1 Li); (298 K, C$_6$D$_5$CD$_3$, ref. PhLi δ 0) δ −0.42 (s, 3.5 Li), −0.55 (s, 1 Li); (273 K) δ − 0.38 (s, 4.9 Li), −0.50 (s, 1 Li); (248 K) δ − 0.33 (s); (223 K) δ −0.29 (s); (193 K) δ −0.26 (s).

‡ *Crystal data* for **1**: $\mathrm{C_{52}H_{84}Li_4N_8O_8}$, monoclinic, space group *C*2/*c*, a = 21.795(6), b = 12.828(4), c = 20.754(7) Å, β = 105.19(2)°, M_r = 977.03, Z = 4, D_c = 1.159 Mg m^{-3}, μ(Mo-Kα) = 0.077 mm^{-1}, $F(000)$ = 2112. Data were collected by the ω–2θ scan method on a Rigaku AFC5R four-circle diffractometer at 150(2) K using the ‘oil drop mounting technique’.[7] Graphite-monochromated Mo-Kα radiation (λ = 0.710 69 Å) was used in the range $5.12 < 2\theta < 39.96°$, $\pm h$, $\pm k$, $+l$; 2707 reflections of which 2604 were independent (R_int = 0.0335) and used in all calculations. The structure was solved using direct methods[8] and subsequent Fourier-difference syntheses and refined[9] by full-matrix least squares on F^2 with anisotropic thermal parameters for all non-hydrogen atoms except Li. H-atoms were placed in geometrically idealised positions and refined using a riding model or as rigid methyl groups. Final $R(F)$ = 0.0536 for 2595 reflections with $[I > 2\sigma(I)]$, $wR(F^2)$ = 0.1412 for all data; 316 parameters; goodness of fit = 1.045. Maximum peak and hole in final Fourier difference map 0.172 and −0.186 e Å^{-3} respectively. CCDC 182/548.

§ Cryoscopy on **1** in benzene suggests that the average aggregation state varies from 1.3 to 1.5 (±0.1) in the concentration range 0.006–0.016 M (1.4–3.9 mg ml^{-1}). NMR spectroscopy used *ca.* 2 mg ml^{-1} samples.

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Received in Cambridge, UK, 23rd May 1997; 7/03573J