# The synthesis and solid-state and solution structures of an unprecedented mixed chiral α-amino lithium alkoxide–lithium alkoxide aggregate

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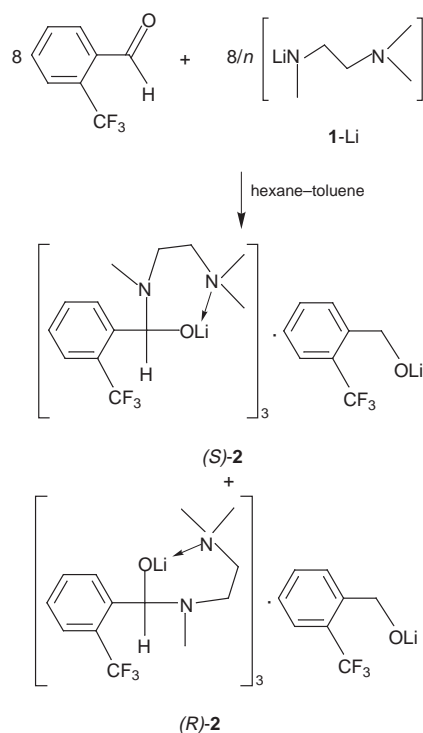[b] *Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, UK CB2 1EW;*
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**L e t t e r**

Lithium $N,N,N'$-trimethylethylenediamide, $LiN(Me)(CH_2)_2NMe_2$, reacts with 1 equiv. of 2-trifluoromethylbenzaldehyde, $2\text{-}F_3CC_6H_4CHO$, to afford a surprising tetranuclear mixed aggregate containing three chiral α-amino lithium alkoxide molecules which associate in a highly unusual fashion, the fourth molecule, the benzyl alkoxide reduction product, forming by an inter-molecular LiH transfer.

Extensive use is made of chiral organolithium reagents in organic synthesis.[1] In particular, chiral α-amino lithium alkoxides have been shown to be of use in the regiospecific metallation of arylaldehydes.[2] Typically, the reaction of a lithium dialkylamide with heterocyclic arylaldehydes[3] and variously substituted benzaldehydes[2,4] has been employed to afford species which contain not only a good aldehyde protecting group, but also one capable of directing a second equivalent of lithium to the *ortho*-ring position. In spite of their proven utility, the nature of such chiral lithiated intermediates has gone largely unexplored, with only a handful of solid-state,[5] solution[5,6] and calculational studies[7] being published prior to our recent report of the first X-ray structural characterisation of a chiral α-amino lithium alkoxide.[8] In light of the novel structure displayed by this species, we have studied ring-substituent effects extensively, in order to establish whether metal stabilisation by the amino moiety N-centres varies with the choice of ring-substituents.

We report here the solid-state and solution structures of an unusual mixed tetranuclear species, afforded in high yield by the 1 : 1 reaction of lithium $N,N,N'$-trimethylethylenediamide, **1**-Li, with 2-trifluoromethylbenzaldehyde in non-donor media (Scheme 1). X-ray crystallography† shows that the resulting compound $\mathbf{2}\cdot0.5C_6H_{14}$ contains chiral α-amino lithium alkoxide and alkoxide reduction product in a 3 : 1 ratio, the unit cell containing two tetranuclear aggregates which, since they are inversion related, are each enantiomerically pure (Fig. 1). Stabilisation of the metal centres by the $N,N,N'$-trimethylethylenediamino moieties[9] is not of a nature previously recorded in α-amino lithium alkoxides, where both α-N-mono- and concomitant α- and δ-N-bis-coordination modes have been reported, their occurrence depending on ligand chirality.[8] Instead, the solid-state structure of $\mathbf{2}\cdot0.5C_6H_{14}$

shows only δ-N-mono-coordination of the metals, affording seven-membered chelates, demonstrating *anti*-isomerism about the α-N–C bond. In either pseudo-cube three chelating alkoxide ligands are arranged such that, unusually, the aggregate cannot be regarded as a dimer–(mixed-dimer) stack. Two of the seven-membered rings [which incorporate the significantly different Li(1)–N(1) = 2.215(6) Å and Li(3)–N(5) = 2.155(6) Å bonds] adopt the orientations expected of a conventional staggered double dimer stack, *i.e.*, ring O(1)–Li(2)–O(3)–Li(3) on top of ring Li(1)–O(2)–Li(4)–O(4). However, the remaining chelate [incorporating Li(2)–N(3) = 2.198(6) Å] is orientated perpendicularly, straddling what would be the two stacking planes. This unusual ligand orientation presumably minimises ligand interactions between the three alkoxide moieties, and results from the inclusion in the structure of the reduced alkoxide ligand. The remaining tri-coordinate metal centre [Li(4)] is, however, isolated from
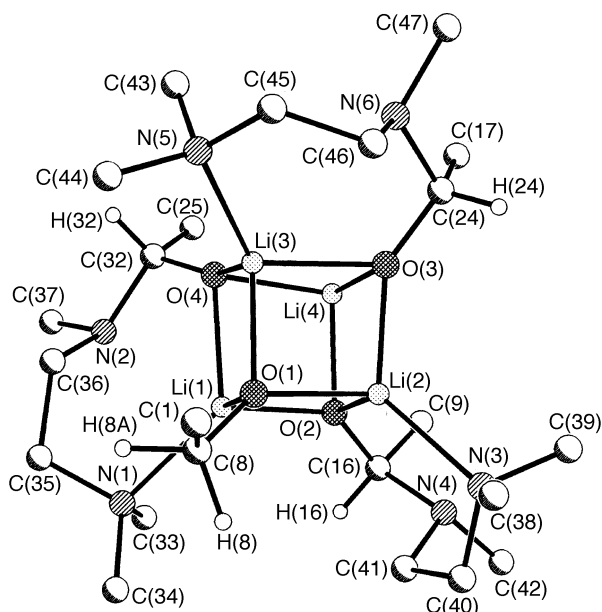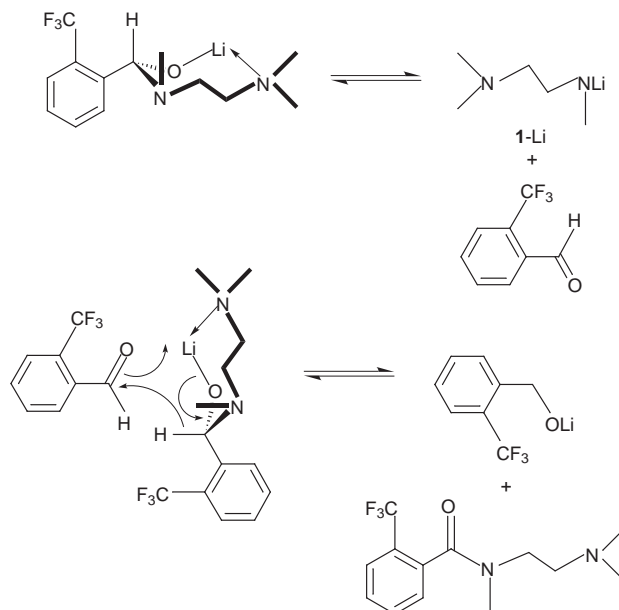


**Scheme 1**

**Fig. 1** Structure of the (*S*)-**2** mixed aggregate core with key atoms labelled; lattice hexane and hydrogen atoms (except the protected aldehyde hydrogens) have been omitted for clarity and only the *ipso*-carbon atoms of the aromatic rings are shown. Selected bond lengths (Å): Li(1)–N(1) = 2.215(6), Li(1)–O(1) 1.999(5), Li(1)–O(2) 1.900(5), Li(1)–O(4) 2.215(6), Li(2)–N(3) = 2.198(6), Li(2)–O(1) 1.937(5), Li(2)–O(2) 2.113(5), Li(2)–O(3) 1.945(5), Li(3)–N(5) 2.155(6), Li(3)–O(1) 1.954(5), Li(3)–O(3) 2.044(5), Li(3)–O(4) 1.935(5), Li(4)–O(2) 1.883(6), Li(4)–O(3) 1.916(5), Li(4)–O(4) 1.911(5)

this ligand, the O-centre of which [O(1)] is located at the *opposite* vertex of the pseudo-cube.

The presence of the reduced alkoxide unit, 2-$F_3CC_6H_4CH_2OLi$, implies that LiH transfer is afforded during the reaction of the aldehyde with the lithium dialkylamide. In this context, it has been noted[10] that $\alpha$-amino lithium alkoxides partially dissociate at low concentrations in non-donor media, affording equilibrium mixtures of the aldehyde and lithium dialkylamide (**1**-Li in this case) precursors, as well as intact $\alpha$-amino lithium alkoxide (in **2**·$0.5C_6H_{14}$ this behaviour is observable by ^{1}H NMR spectroscopy at *ca.* 1.0 mg ml$^{-1}$). Logically, the (2-trifluoromethyl)benzyl lithium alkoxide (and organic amide by-product) must result from the reaction of trace aldehyde with undissociated $\alpha$-amino lithium alkoxide (Scheme 2).

Multinuclear NMR spectroscopy indicates the solution behaviour of **2**·$0.5C_6H_{14}$ to be very complex. While ^{1}H NMR spectroscopy indicates the presence of many species in non-donor solution, the relative proportions of the four dominant ones (excluding those which result from $\alpha$-amino lithium alkoxide dissociation) showing *no* concentration dependence in [[2]H$_6$]benzene over a 1.0–30.0 mg ml$^{-1}$ range, the solution complexity prevents integrals from being easily interpreted. The protected aldehyde resonance is observed in the ^{1}H NMR spectrum as a complex multiplet in its characteristic[8] position at $\delta$ 6.05–5.51. Surprisingly, however, overlapping with the protected aldehyde resonances is that of the alkoxide CH$_2$ unit. The complexity of the ^{1}H NMR spectrum can be overcome by the employment of nuclear Overhauser spectroscopy. NOESY[11] allows not only the assignment of the reduced lithium alkoxide signals but also indicates the solution structural motifs displayed by the $\alpha$-amino lithium alkoxide molecules, for which it appears that $\delta$-N–Li bonded *anti*-isomers are retained, with the seven-membered rings adopting three geometries in solution. The observation of NOE cross-peaks between the protected aldehyde and the $\alpha$-NMe group for all three of these species in the NOESY spectrum at ambient temperature (Fig. 2) indicates that the latter adopts an *endo*-

**Scheme 2**



orientation with respect to the seven-membered ring in each of the solution motifs, thus presumably minimising steric interactions with the aromatic ring. However, the behaviour of the $\delta$-NMe$_2$ group is more variable. In the dominant species it adopts an *endo*-orientation with respect to the seven-membered ring, affording a boat conformation [Fig. 2(a) and Scheme 3(#1)], resulting in the observation of an NOE cross-peak with the main protected aldehyde signal ($\delta$ 5.62). Other salient through-space interactions observed for this conformer involve the four methylene protons in the seven-membered ring. One of these protons, for reasons as yet not fully understood, is anomalously deshielded and can be seen at $\delta$ 3.93. However, the signal is probably attributable to the axial $\gamma$-H (the question of how closely it approaches the protected aldehyde proton will be considered below). Finally for this conformer, the equatorial $\gamma$-H (it and the two $\beta$-H protons afford a multiplet in the range $\delta$ 2.43–2.11) also demonstrates an NOE with the main protected aldehyde proton. The second solution conformer demonstrates through-space interactions
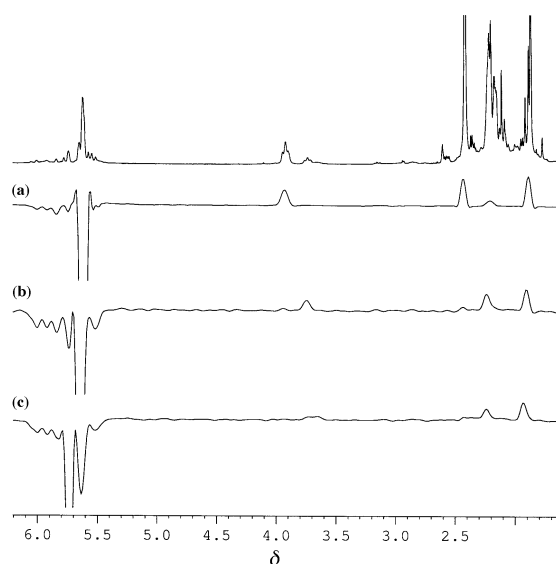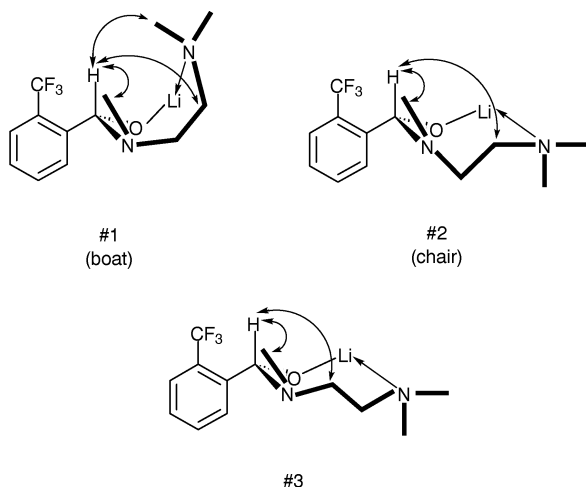


**Fig. 2** Part of the room temperature ^{1}H NMR spectrum of **2**·$0.5C_6H_{14}$ in [[2]H$_6$]benzene (top) with selected columns from the room temperature NOESY spectrum ($\tau_m$ = 1.5 s). (a) Column through the diagonal at $\delta$ 5.62; (b) column through the diagonal at $\delta$ 5.65; (c) column through the diagonal at $\delta$ 5.74

#1
(boat)

#2
(chair)

#3

**Scheme 3**

akin to those seen for the boat ($\#1$) notwithstanding the absence of a NOESY cross-peak between the protected aldehyde proton ($\delta$ 5.65) and the $\delta$-NMe$_2$ moiety [Fig. 2(b)]. Plainly this suggests the re-orientation of the latter group, affording a chair conformer in which the methylene groups remain essentially unchanged [Scheme 3($\#2$)] relative to their orientations in the boat. The ratio of boat ($\#1$) : chair ($\#2$) can be calculated to be 4 : 1 in non-donor solution based on the observation of the deshielded axial $\gamma$-H resonance for the latter species at $\delta$ 3.74. The remaining conformer shows NOESY cross-peaks between a small protected aldehyde signal ($\delta$ 5.74) and at least one methylene proton and the $\alpha$-NMe group [Fig. 2(c)]. The $\delta$-NMe$_2$ group again adopts an *exo*-orientation, making this species [Scheme 3($\#3$)] another chair conformer. Probably it is achieved by a re-orientation of the two methylene groups in the seven-membered ring such that the observable NOESY correlation is due to the two $\beta$-methylene protons. Also worth mentioning is the observation that Fig. 2(b) and (c) show significant chemical exchange cross-peaks between the two chair conformers in non-donor solution, indicating that at ambient temperature they are capable of inter-converting with relative facility. The second chair conformer ($\#3$) is, in fact, that observed in the solid-state structure of $2 \cdot 0.5C_6H_{14}$, allowing the likelihood of through-space interactions between the protected aldehyde and methylene protons to be gauged. An analysis of the distances between axial and equatorial $\beta$-methylene protons and the protected aldehyde proton in each of the six $\alpha$-amino lithium alkoxide molecules in the unit cell affords average through-space distances of 2.515 and 2.735 Å respectively. Both of these values fall easily within the range of through-space distances which have previously been reported to afford NOEs.[12] Finally, models suggest that the $\gamma$-methylene protons can adopt similar proximities to the protected aldehyde function in the boat conformer.

**Table 1** Cryoscopic data for $2 \cdot 0.5C_6H_{14}$ in benzene in the concentration range 2.3–40.4 mg ml$^{-1}$

| Conc./mg ml$^{-1}$ | Av. mol. mass | $n^a$ |
|---|---|---|
| 2.3 | 361 ± 40 | 1.5 ± 0.2 |
| 4.2 | 423 ± 32 | 1.8 ± 0.2 |
| 8.1 | 460 ± 20 | 1.9 ± 0.1 |
| 12.2 | 453 ± 13 | 1.9 ± 0.1 |
| 20.3 | 523 ± 11 | 2.2 ± 0.1 |
| 30.4 | 535 ± 8 | 2.2 ± 0.1 |
| 40.4 | 540 ± 7 | 2.3 ± 0.1 |

$^a$ Average formula mass for the monomer, based on 6[2-F$_3$CC$_6$H$_4$C(H)(OLi)N(Me)(CH$_2$)$_2$NMe$_2$] + 2[2-F$_3$CC$_6$H$_4$CH$_2$OLi] + hexane = 238.

The observation that, contrary to solid-state structural evidence, the boat conformer represents the preferred stereochemical form of the $\alpha$-amino lithium alkoxide molecules in non-donor solution is rather surprising and presumably has its origins in the more effective stabilisation of the lithium centre by the boat conformer. While at ambient temperature in [$^2$H$_6$]benzene only one signal is observed for the $\delta$-NMe$_2$ group ($\delta$ 2.43) in the boat conformer, suggesting rapid interchange of the two methyl groups and, therefore, *fast* dissociation–reformation of the $\delta$-N–Li interaction, at $-50$ °C in [$^2$H$_8$]toluene this process is observed in the *slow* exchange limit, the dominant $\delta$-NMe$_2$ signal having decoalesced into two resonances ($\delta$ 2.74 and 2.04) *both* of which show NOESY correlations with the dominant protected aldehyde signal. This last observation indicates either that chemical exchange of the two methyl groups is still rapid relative to the NOE build-up time ($\tau_m$ = 1.5 and 0.4 s at ambient temperature and $-50$ °C respectively) or alternatively that exchange is slow and that the NOE is being relayed (the fact that the NOEs and chemical exchange peaks are in phase at $-50$ °C makes it impossible to discriminate). At low temperature the two $\delta$-NMe$_2$ methyl groups show distinct cross-peaks between themselves, the observation that these cross-peaks are *out of phase* with NOEs in the ROESY[13] ($\tau_m$ = 0.2 s) spectrum at $-50$ °C in [$^2$H$_8$]toluene demonstrating clearly that they result from chemical exchange and, therefore, that NOE build-up time is slow relative to NOESY mixing-time.

While the $\alpha$-amino lithium alkoxide molecules demonstrate clear intra-molecular variations it is clear from cryoscopy in benzene (Table 1) and $^7$Li NMR spectroscopy in [$^2$H$_6$]benzene (at ambient temperature) and [$^2$H$_8$]toluene (at low temperature) that extensive variable aggregation state behaviour is also manifest, though the complexity of this system largely precludes a confident discussion of its nature. It is possible to suggest tentatively that at low concentrations (ca. 2.3 mg ml$^{-1}$) the tetranuclear aggregate almost totally dissociates to give a 1 : 1 mixture of dimers and mixed-dimers, affording an average formula mass in solution of 361 ± 40 {an average formula mass of 238 would result from complete dissociation [to 2(dimer) + 2(mixed-dimer) + hexane]}. However, at higher concentrations the dimers and mixed-dimers associate. Hence, at 30.4 mg ml$^{-1}$ an average formula mass of 535 ± 8 is observed (the majority of NMR spectroscopy using ca. 30.0 mg ml$^{-1}$ samples). While this is in close agreement with the value of 531 expected for a complex [dimer + mixed-dimer + 3(3 : 1 tetranuclear aggregate) + 2(hexane)] mixture, it must be emphasised that this figure is arrived at assuming that the reassociation of dimer and mixed dimer affords a 3 : 1 tetranuclear aggregate of the type observed for $2 \cdot 0.5C_6H_{14}$ in the solid state. However, it is possible that the association of *two dimers* or of *two mixed-dimers* might afford the purely $\alpha$-amino lithium alkoxide tetramer or a 2 : 2 tetranuclear aggregate respectively.

## Experimental

### Preparation of $2 \cdot 0.5C_6H_{14}$

*n*-Butyllithium (3.76 ml, 1.6 M in hexanes, 6.0 mmol) was added to *N,N,N'*-trimethylethylenediamine (**1**-H, 0.76 ml, 6.0 mmol) in hexane–toluene (1.0 ml : 0.5 ml) at $-78$ °C under nitrogen. After stirring for 10 min, 2-trifluoromethyl-benzaldehyde (0.79 ml, 6.0 mmol) was added and the resultant yellow suspension was stirred for a further 10 min at $-78$ °C. Warming to room temperature gave a white suspension, which afforded a yellow solution on gentle heating. After storage at room temperature for three days colourless, rectangular crystals of $2 \cdot 0.5C_6H_{14}$ were deposited, mp, 110–112 °C, yield, 62% (given the stoichiometry of the product this is based on 20% dissociation in Scheme 2). Found: C, 54.85; H, 6.23; N, 7.60. Calc. for

$C_{100}H_{134}F_{24}Li_8N_{12}O_8$ : C, 56.02; H, 6.26; N, 7.84%. ^{1}H NMR spectroscopy (500.133 MHz, [$^2H_6$]benzene), $\delta$ 8.45 [d, 0.2H, 6-$Ar$CH$_2$, $^3J_{HH} = 7.80$ Hz), 8.30 [d, 0.2H, 6-$Ar$C(H)(O) N$\#$3, $^3J_{HH} = 8.02$ Hz], 7.99 [d, 0.2H, 6-$Ar$C(H)(O)N$\#$2, $^3J_{HH} = 7.29$ Hz], 7.77 [d, 0.6H, 6-$Ar$C(H)(O)N$\#$1, $^3J_{HH} = 7.79$ Hz], 7.62 (d, 0.2H, 3-$Ar$CH$_2$, $^3J_{HH} = 7.34$ Hz], 7.57 [d, 0.2H, 3-$Ar$C(H)(O)N$\#$2], 7.55 [d, 0.2H, 3-$Ar$C(H)(O)N$\#$3], 7.54 [d, 0.6H, 3-$Ar$C(H)(O)N$\#$1, $^3J_{HH} = 7.57$ Hz], 7.40 (dd, 0.2H, 5-$Ar$CH$_2$, $^3J_{HH} = 7.48$ Hz), 7.34 [dd, 0.2H, 5-$Ar$C(H)(O) N$\#$3, $^3J_{HH} = 7.47$ Hz], 7.06 (dd, 0.2H, 4-$Ar$CH$_2$, $^3J_{HH} = 7.30$ Hz), 7.01 [d, 0.2H, 3-$Ar$C(H)(O)N$\#$2], 6.99 [dd, 0.2H, 4-$Ar$C(H)(O)N$\#$3, $^3J_{HH} = 7.29$ Hz], 6.88 [dd, 0.2H, 5-$Ar$C(H) (O)N$\#$2, $^3J_{HH} = 7.14$ Hz], 6.81 [dd, 0.6H, 4-$Ar$C(H)(O)N$\#$1, $^3J_{HH} = 7.60$ Hz], 6.53 [dd, 0.6H, 5-$Ar$C(H)(O)N$\#$1, $^3J_{HH} = 7.45$ Hz], 6.05–5.51 [m, 1.2H, ArC($H$)(O)N, ArC$H_2$], 3.93 (t, 0.8H, NCH$_2$), 3.74 (t, 0.2H, NCH$_2$), 2.43, 2.23–2.11 [m, 9H, N(CH$_3$)$_2$, NCH$_2$], 1.97–1.89 (m, 3H, NCH$_3$), 1.71–0.92 (m, 2.3H, hexane). ^{7}Li NMR spectroscopy (155.508 MHz, [$^2H_6$]benzene, 0 ppm = PhLi in [$^2H_6$]benzene at 25 °C) $\delta$ −0.93 (s, 1Li), −1.24 (s, 5Li), −0.27 (sh, 2.5Li).

## Acknowledgements

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