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Reversible C–C bond formation: solid state structure of the aldol-like addition product of adamantanone to a 1,5-diazapentadienyllithium, and its solution state retro-aldol dissociation†

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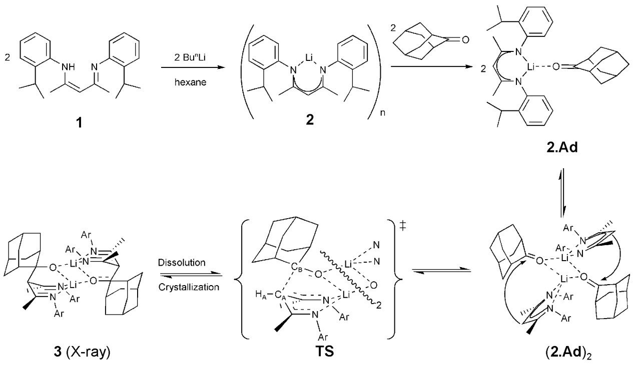
Analysis of crystals of the lithium complex of the tripodal ligand formed upon addition of adamantanone to a 1,5 diazapentadienyllithium complex reveals a long C–C bond which ruptures upon dissolution in non-co-ordinating solvents.

Among the most widely employed methods of C–C bond formation is the aldol addition. Since the 1970s it has been known to be reversible,[1] but despite intense and sustained interest and effort in controlling the stereoselectivity of asymmetric examples,[2] there remains only one example of an isolated and characterized lithium aldolate.[3] Given that transition states in these reactions tend to resemble reagents more than products,[4] there is value in investigation of its earlier stages, closer to the transition state. We have isolated and structurally characterized an aza-analogue of an aldolate, in which the newly formed C–C bond is long, and the reduced carbonyl single bond is short; retro-aldol dissocation occurs upon dissolution in even the least polar of solvents.

In view of the electronic stability of the 1,5 diazapentadienyl anion,[5] and the extreme difficulty of enolization of adamantanone, there was a possibility that the product of the reaction shown may contain unreacted adamantanone acting as a bridging ligand between two lithium atoms further ligated by terminal diazapentadienyl ligands (see Scheme 1). A similar structure is known where hexamethylphosphoramide acts as the bridge.[6] Furthermore, a computational study confirmed the capacity of carbonyls to bridge in lithium dimers.[7] Consequently, the target was the isolation of a model for the precursor of ketone enolization by amidolithium bases, in support of the hypothesis that such reactions proceed *via* bridging ketones.[7]

Reaction of **1** with Bu^nLi in hexane gave a precipitate of **2**, which redissolved on addition of adamantanone.† Slow cooling of the hot solution produced a crop of colourless blocks, which were found by crystallographic analysis‡ to be the dimeric lithium alkoxide-diimine **3** (Fig. 1). Enolization had indeed not occurred (see Scheme 1), but the diazapentadienyl fragment, so often adopted as an innocent spectator ligand, had here displayed its C-nucleophile reactivity: a new C–C bond had formed by addition of the carbanion across the C=O double bond. This reaction may be viewed as an aza version of the aldol addition. The only previously characterized lithium aldolate displayed normal C–C and C–O bond lengths in the tetrameric aggregated structure it assumed, such that it represented the terminus of the aldol addition reaction.[3] In contrast, the new C–C bond length in **3** was 1.644(2) Å averaged over the two monomers. While this is significantly longer than the standard C–C distance of 1.52 Å, it is not among the longest of such bonds.[8] Furthermore, the C–O bond was short (1.35 and 1.36 Å) in comparison to those from the analogous cumyl adamantanol and a tantalum-ligated adamantan-alkoxide, (both 1.44 Å).[9] Given the long C–C and short C–O bonds, it is tempting to view the structure of **3** as a transition state analogue for the aldol addition. However, computations on lithium aldols,[4] and aza-versions[10] more similar to the situation in **3**, all indicate a very early transition state, with C–C distance of 2.2–2.5 Å. Clearly, **3** is not a transition state analogue, but a ground state, albeit one in which the steric bulk of each reagent and the delocalization-derived stability of the reagent 1,5 diazapentadienyllithium has



Scheme 1

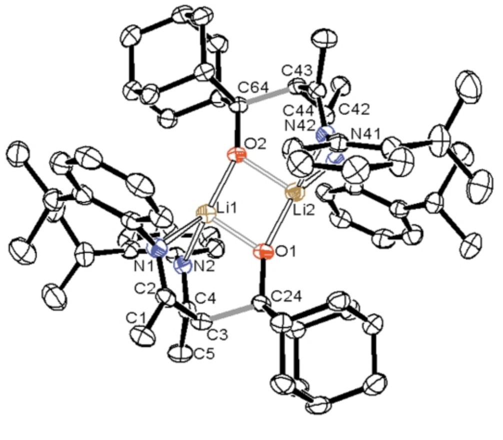


Fig. 1 Crystal and molecular structure of **3**. Ortep diagram, 50% probability ellipsoids. Hydrogens are omitted for clarity. The structure is crystallographically non-centrosymmetric; there are two independent monomers. Important bond lengths (Å): C(2)–N(1), 1.284(3); C(2)–C(3), 1.520(3); C(3)–C(4), 1.514(3); C(3)–C(24), 1.642(3); C(4)–N(2), 1.278(3); C(4)–C(5), 1.502(3); C(24)–O(1), 1.353(2); C(24)–C(25), 1.559(3); C(24)–C(29), 1.562(3); C(64)–O(2), 1.359(2); C(64)–C(65), 1.555(3); C(64)–C(69), 1.555(3); N(1)–Li(1), 2.090(4); N(2)–Li(1), 2.079(4); N(41)–Li(2), 2.100(4); N(42)–Li(2), 2.072(4); O(1)–Li(2), 1.812(4); O(1)–Li(1), 1.874(4); O(2)–Li(1), 1.795(4);O(2)–Li(2), 1.875(4). Angles (°): C(4)–C(3)–C(2), 115.02(17), C(4)–C(3)–C(24), 109.87(16), C(2)–C(3)–C(24), 109.25(16); O(1)–C(24)–C(25), 111.58(17), O(1)–C(24)–C(29), 111.23(15); C(25)–C(24)–C(29), 106.29(17); O(1)–C(24)–C(3), 108.48(16); C(25)–C(24)–C(3), 109.78(15); C(29)–C(24)–C(3), 109.45(16); O(2)–C(64)–C(65), 111.16(16); O(2)–C(64)–C(69), 111.27(15); C(65)–C(64)–C(69), 106.84(16); O(2)–C(64)–C(43), 107.92(15); C(65)–C(64)–C(43), 109.86(15); C(69)–C(64)–C(43), 109.80(16).

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† Electronic supplementary information (ESI) available: preparative and characterization details. See http://www.rsc.org/suppdata/cc/b2/b211745b/

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squeezed the reaction co-ordinate to the extent that the terminus of the reaction is separated from reagents by an extraordinarily small barrier. Among the other structural indications of this is the CC_AC angle, which at 116° lies between expected sp^2 and sp^3 angles.

Aside from the only other crystallized lithium aldolate,[3] there also exists structural data for a sodium enolate complexed by unenolized ketone.[11] Complex **3** represents a data point some way along the reaction co-ordinate for carbanion-addition to ketone, somewhere between these two extremes.

The dimeric structure is pseudocentrosymmetric. Lithium alkoxides, and their close relatives, lithium enolates, are known to exist in the solid state and in solution frequently as tetramers and hexamers.[11] Dimers are also not unusual, but are normally accompanied by extreme bulk and/or ancillary co-ordinating solvent ligands.[12] **3** is unusual in employing intramolecular imine nitrogen co-ordination in completing the lithium's co-ordination sphere, though a recent result almost duplicates this feature: the samarium-mediated (irreversible) reductive coupling of an α-diimine with benzophenone also gives a tridentate N, N, O ligand, though one of the imine nitrogens is reduced and carries an acidic proton.[13] Concerning the co-ordination environment of the lithiums, they are in a heavily distorted tetrahedral arrangement. Interestingly, the shortest Li–O distances link one lithium diazapentadienyl moiety with the oxygen of the 'other' unit. The lithium atom Li(2) lies only 0.18 Å above the plane of N(41), N(42) and O(1), (0.20 Å in the other monomer) such that if the dimer dissociated to form a monomer such as **2·Ad**, it could do so with minimal reorganization save for re-hybridization of C_A and C_B.

Solution state data points to just such a process of retro-aldol dissociation: The ^{1}H NMR resonance of H_A in deuterobenzene lies at 5.2 ppm, indistinguishable from its position in the complex **2**·(THF)$_2$,[14] and in accord with an environment attached to an sp^2 hybridized carbon. The resonance of the attached carbon, C_A, at 95 ppm, also maps closely to its position in **2**·(THF)$_2$. Furthermore, C_B, ostensibly the newly sp^3 hybridized alkoxide carbon, resonates at 227 ppm, representing a downfield co-ordinative shift from the carbonyl resonance of free adamantanone at 215 ppm. This evidence is strongly suggestive that **3** reverts in deuterobenzene to its precursor, either the monomer **2·Ad** or its dimer. To settle this question, cryoscopy was carried out in benzene. At all concentrations measured, the average molecular weight in solution implied that monomeric **2·Ad** was present,† with no contribution from dimer. In the solvent from which the crystals were harvested (hexane) it seemed possible that there might be a greater concentration of the dimeric species. However, the ^{1}H resonances in hexane were virtually unchanged from those in benzene. We postulate that the dimerization is closely linked to the aldol addition reaction: upon dimerization and the co-ordination of *two* lithium ions to the carbonyl oxygens, the greater polarization of the carbonyl facilitates carbanion attack. Dimerization would also push the two reactants together in the correct fashion, whereas in the monomer, close approach is unlikely. While a key feature of the postulated intermediate (**2·Ad**)$_2$, bridging carbonyls, has not been observed in lithium chemistry as yet, we have shown computationally that it is viable,[7] and it has been seen for heavier alkali metals.[15] To confirm that the anomalous shifts reported were not some strange spectroscopic phenomenon, solid-state ^{13}C CP-MAS experiments were carried out. The resonances for C_A and C_B at 95 and 227 ppm were absent, and were replaced by new resonances at 63 and 88 ppm, respectively, in perfect accord with expectation for coupled structure **3**.

The crystallographic observation of the aldol-like addition was not the result of a freak crystal selection. The single-crystal data collection was reproduced from different batches. Solid-phase infra-red (Nujol mull) and Raman (powder) spectra are also consistent with the single-crystal result, as is the ^{13}C CP-MAS NMR result. However, aqueous quenches on solutions of **3** produced recovered, uncoupled starting materials **1** and admantanone, a result entirely consistent with the solution-state spectroscopic results.

It is known that lithium aldol products are disfavoured by polar, strongly co-ordinating solvents,[1,2] though it remains surprising that scant evidence of coupled product is available even in hexane solution. It is further known that low temperatures favour aldols, though crystals of **3** can be grown at room temperature. The main factor in the equilibrium is therefore the transition from the solid to the solution state: the solid state favours higher aggregation states, and dimerization favours C–C coupling in this case; the greater entropy in solution reverses the process.

It should be recognized that the analysis of the structure of intermediates in lithium-mediated syntheses is infrequent. Had this not been done, neither the solution spectroscopic evidence nor the quenched product analysis would have indicated that any reaction had occurred. This leaves open the question of whether such phenomena may be common in reactions deemed to have 'failed'. It also suggests that solventless quenches on solid state products might be a worthwhile method of boosting yields.

Notes and references

‡ Crystal data: $C_{66}H_{86}Li_2N_4O_2$, M = 981.27, orthorhombic, a = 10.6269(3), b = 22.2662(3), c = 23.8287(4) Å, U = 5638.36(13) Å ^{3}, T = 150 K, space group $P2_12_12_1$ (no. 19), Z = 4, μ(Mo-K$_\alpha$) = 0.068 mm^{-1}, 37520 reflections measured, 10524 unique, including Friedel reflections (R_{int} = 0.0603), which were used in all calculations. The final $wR_2(F^2)$ was 0.0848 (all data). The Flack value {0.1(11)} was inconclusive. CCDC 199213. See http://www.rsc.org/suppdata/cc/b2/b211745b/ for crystallographic data in .cif or other electronic format.

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