Crystal and Molecular Structure of 1-Lithio-3,6-diethoxy-2,5-dimethyl-1,2-dihydropyrazine, the Lithiated Bis-lactim Ether of the Diketopiperazine from Alanine

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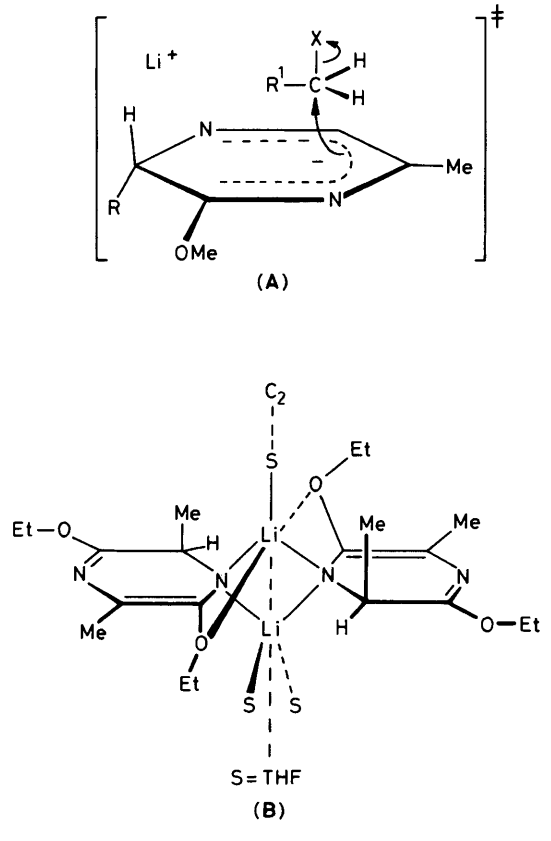
Crystals of a racemic sample of the title compound, grown from a tetrahydrofuran (THF) solution, contain dimeric aggregates of homochiral moieties in which the two lithium atoms and the two negatively charged nitrogens of the heterocycle form a four-membered ring; one lithium is co-ordinated by a single THF molecule, the other by two.

Recent advances in the development of stereoselective methods involving polar organometallic reagents[1] have stimulated interest in the structures of putative intermediates and in the underlying reaction mechanisms.[2,3] Among the more spectacular applications is the use of diketopiperazine derivatives for the asymmetric synthesis of amino acids by Schöllkopf and his group.[4] The mechanistic picture advanced by this school for alkylations induced by lithium is shown in Figure 1(A). Recent studies of the structures of lithium derivatives of carbanions[5] and of enolates[2,6] derived from ketones, carboxylic esters, and amides show, however, that the lithium atoms tend to be σ-bonded to the atom on which the negative charge of the anion is concentrated. Furthermore, aggregated structures (dimers, tetramers, or even hexamers) are the rule. Since neither of these features is taken into account in the above mechanistic proposal, we considered it important to have unambiguous experimental evidence on the structure of at least one such lithiated diketopiperazine derivative.



(A)

(B)

Figure 1. Proposed mechanism of alkylation of a lithiated diketopiperazine bis-lactim ether (A) (ref. 4) and actual dimeric structure (B) found in the crystal of LDP.

We have now determined the crystal structure of a tetrahydrofuran (THF) solvate of racemic 1-lithio-3,6-diethoxy-2,5-dimethyl-1,2-dihydropyrazine (LDP)† at 163 K [Figure 1(B) and Figure 2]. The structure has a number of novel features. (i) Although the dimeric molecule has no exact crystallographic symmetry, it has an approximate twofold axis, which means that the two organic moieties in each dimer are homochiral; the space group ensures that the crystal is racemic, *i.e.* that it contains equal numbers of enantiomers. (ii) The two lithium atoms in the dimer are not related by the approximate twofold axis but are situated on it. They are thus non-equivalent, and, indeed, as Figure 2 shows, they have quite different environments; Li(1) is bonded to the negatively charged nitrogens [2.06(1) Å] of the LDP molecules and to the oxygen atoms [1.98(1) Å] of two THF solvent molecules in approximately tetrahedral co-ordination. In contrast, Li(2) is bonded to the same two nitrogen atoms [2.05(1) Å], to the oxygens of the α-ethoxy groups [2.25(1) Å], and to the oxygen [1.92(1) Å] of a third THF molecule, in a distorted trigonal bipyramidal arrangement, with the ethoxy oxygens in the apical positions. The Li · · · Li distance is 2.61(1) Å, so that, depending on taste, one can regard these two atoms as being bonded to one another or not.

As far as we are aware, this is the first example of an organolithium dimer containing lithium atoms in chemically different surroundings. As is evident from Figure 2, the difference between the two diastereotopic faces of LDP is greatly accentuated in the dimeric complex.

Our cryoscopic experiments[10] show that in 0.06—0.10 M solutions, obtained by dissolving crystalline LDP in THF, the equilibrium mixture at −108 °C has an average degree of aggregation of 1.15, which would correspond to a 5 : 1 mixture

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† Racemic 2,5-diethoxy-3,6-dimethyl-3,6-dihydropyrazine was deprotonated at −78 °C with 1.1 equiv. of butyl-lithium in THF. After warming to 0 °C and addition of hexane, crystals were grown by gradually cooling the resulting solution (0.15 M hexane–THF 5 : 1) to −78 °C (the colourless solution turns violet above 0 °C). The short, rhomb-shaped translucent crystals, with a slight violet tinge, were washed with hexane and dried in high vacuum; they are stable under argon at room temperature. A single crystal *ca.* 0.3 mm in length was mounted in a glass capillary, with hexadecane as adhesive. All manipulations were carried out in an argon-filled glove bag. *Crystal data:* $(C_{10}H_{17}LiN_2O_2)_2 \cdot 3$ THF, $M = 624.72$, space group $P2_1/c$, $a = 10.719$, $b = 20.248$, $c = 17.639$ Å, $\beta = 77.94°$ at 163 K, $Z = 4$, $U = 3743.8$ Å³, $D_c = 1.11$ g cm⁻³. Intensities of 6564 unique reflections (3187 with $I > 3\sigma_I$) were measured with Mo-K_α radiation ($\lambda = 0.71069$ Å) for $\theta < 25°$. The structure was solved by MULTAN[7] and refined by full-matrix least-squares analysis with anisotropic vibration parameters for non-hydrogen atoms, isotropic for hydrogen atoms, to $R = 0.07$, $R_w = 0.074$ (modified exponential weights,[8] $r = 4$ Å²). Positions of THF hydrogens were calculated.

The atomic co-ordinates for this work are available on request from the Director of the Cambridge Crystallographic Data Centre, University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW. Any request should be accompanied by the full literature citation for this communication.

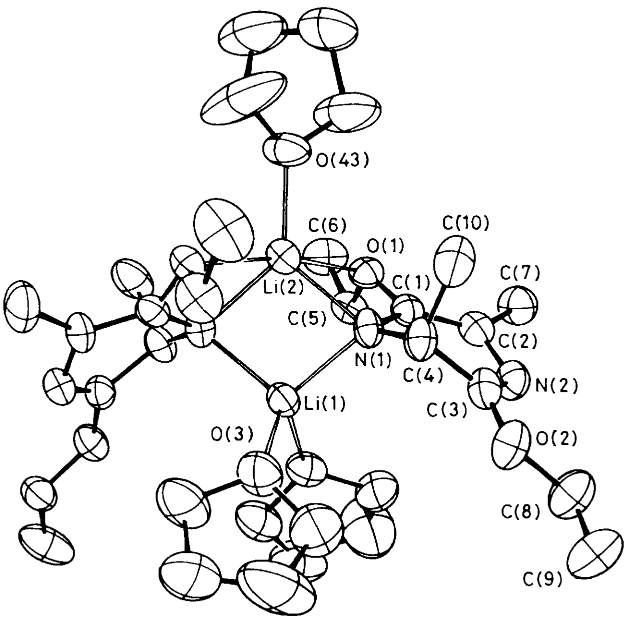

Figure 2. Structure of the complex LDP dimer with vibration ellipsoids drawn at the 50% probability level (ref. 9). Hydrogen atoms have been omitted for clarity. Important bond lengths (in Å) are: Li(1)-O(3) 1.98(1) [1.98(1)], Li(1)-N(1) 2.05(1) [2.06(1)], Li(1)-Li(2) 2.61(1), Li(2)-O(1) 2.25(1) [2.24(1)], Li(2)-N(1) 2.06(1) [2.04(1)], Li(2)-O(43) 1.92, C(1)-C(2) 1.36(1) [1.36(1)], C(3)-C(4) 1.51(1) [1.52(1)], C(2)-N(2) 1.41(1) [1.43(1)], C(4)-N(1) 1.45(1) [1.47(1)], N(2)-C(3) 1.27(1) [1.27(1)], N(1)-C(1) 1.36(1) [1.35(1)]. The two distances [one in brackets] refer to the two fragments related by the approximate twofold axis.

of monomer and dimer.‡ At present, we do not know which is the reacting species. If it is the dimer, the electrophilic reagent must first displace the solvent on the concave side of the molecule, since it is known[4] that attack occurs preferentially from this side (rel. topicity *ul*-1.4).[11]

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‡ At higher temperature, the content of the aggregated species may be higher. *C.f.* the butyl-lithium tetramer–dimer equilibrium in THF: D. Seebach, R. Hässig, and J. Gabriel, *Helv. Chim. Acta*, 1983, **66**, 308, 2269.

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