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A Likely Intermediate during the CO_2-Induced Activation of 2-Alkylindoles toward Electrophilic Substitution: Structure of a Unique Tetramer Formed by Joining Two Boat-Shaped $(LiOCO)_2$ Rings

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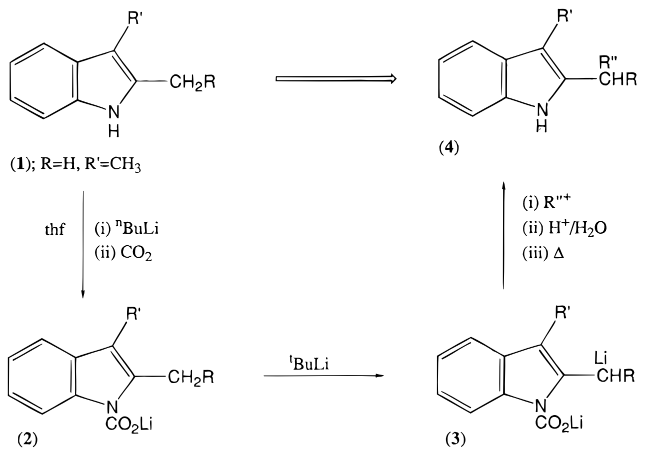
Summary: Reaction of 2,3-dimethylindole in thf with ^{n}*BuLi and* CO_2 *gives a lithium carbamate complex* (**2**·*thf*)$_n$*, which has a unique tetrameric solid-state structure* (n = 4) *containing two boat-shaped (−LiO-COLiOCO−) rings joined by four inter-ring Li−O connections. The two-coordinate O atoms of these rings are near to the 2-Me groups of the indolyl residues, suggesting an explanation for second lithiation (and subsequent electrophilic substitution) of 2-alkylindoles and related heterocyclics occurring specifically at the 2-alkyl position.*

Much is now known about the one-off structures of lithiated organic molecules prepared specifically for such structural examination (alkyls, amides, and enolates, for example).[1] Given this, it is timely to examine like species as they occur as intermediates during multistep organic syntheses.[2] There, understandably enough, one-pot conversions (often very specific ones, regio- and/or stereoselectively) of precursors to products are usually described by linked equations which cite the generation of lithiated molecules, their treatment with electrophiles, and then workup. Lithium intermediates are typically shown as monomers (rare in practice) and as unsolvated (unlikely, since polar media are normally used). The route—let alone the detailed mechanism—must be speculative, and in particular the origins of any selectivity remain unclear. Recently therefore we have begun to examine a series of organic protocols which involve lithiations, by isolating, identifying, and structurally characterizing lithium intermediates.[3] Here we report preliminary results of this approach as applied to an important method[4] for the specific electrophilic substitution of 2-alkylindoles at the 2-alkyl position (Scheme 1).

Scheme 1[4]



The key mechanistic feature proposed for this protocol is that, after lithiation in thf, CO_2 insertion (**1** to **2**) serves both to protect the N−H position and to somehow direct second lithiation (**2** to **3**) to the 2-alkyl position. We reacted a chilled (−78 °C) solution of 2,3-dimethylindole (**1**) in thf with 1 equiv of ^{n}BuLi, warmed to room temperature to give a dark orange solution, and then treated this with CO_2. Chilling of the solution afforded pale yellow cubic crystals of the lithium carbamate, (**2**·thf)$_n$, in 67% first batch yield.[5] X-ray crystallography[6] has revealed a tetrameric structure (n = 4) unprecedented in alkali metal coordination chemistry (Figure 1).

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(1) For reviews, see for example: (a) Setzer, W.; Schleyer, P. v. R. *Adv. Organomet. Chem.* **1985**, *24*, 353−541. (b) Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 1624−1654. (c) Mulvey, R. E. *Chem. Soc. Rev.* **1991**, *20*, 167−209. (d) Gregory, K.; Schleyer, P. v. R.; Snaith, R. *Adv. Inorg. Chem.* **1991**, *37*, 47−142. (e) Weiss, E. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1501−1523. (f) Sapse, A. M., Schleyer, P. v. R., Eds. *Lithium Chemistry: A Theoretical and Experimental Overview*; John Wiley & Sons: New York, 1995.

(2) For reviews, see for example: (a) Wakefield, B. J. *Organolithium Methods*; Academic Press: London, 1988. (b) Brandsma, L. *Preparative Polar Organometallic Chemistry*; Springer-Verlag: Berlin, 1990; Vol. 2. (c) Fieser, M. *Reagents for Organic Synthesis*; Wiley-Interscience: New York, 1990; Vol. 15. (d) Williard, P. G. In *Comprehensive Organic Synthesis*; Pergamon: New York, 1991; Vol. 1. (e) Thompson, C. M. *Dianion Chemistry in Organic Synthesis*; CRC Press: Boca Raton, FL, 1994.

(3) (a) Ball, S. C.; Cragg-Hine, I.; Davidson, M. G.; Davies, R. P.; Edwards, A. J.; Lopez-Solera, I.; Raithby, P. R.; Snaith, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 921−923. (b) Ball, S. C.; Cragg-Hine, I.; Davidson, M. G.; Davies, R. P.; Raithby, P. R.; Snaith, R. *J. Chem. Soc., Chem. Commun.* **1996**, 1581−1582.

(4) Katritzky, A. R.; Akutagawa, K. *J. Am. Chem. Soc.* **1986**, *108*, 6808−6809.

(5) A solution of 2,3-dimethylindole, **1** (0.725 g, 5.0 mmol), in dry thf (8 mL) was chilled to −78 °C and *n*-butyllithium solution (3.2 mL of a 1.6 mol dm^{-3} hexane solution, 5.0 mmol) was added. Warming to room temperature gave a clear dark orange solution which was then treated with gaseous CO_2, turning the solution to pale yellow. Partial removal of solvent (to 5 mL) and refrigeration (5 °C) for 2 days afforded pale yellow cubic crystals identified as (**2**·thf)$_n$. The first batch yield was 0.89 g, 67%. Continued refrigeration of the filtrate over 2 further days gave more of the product, the yield then being increased to 91%. Anal. Calcd for $C_{15}H_{18}LiNO_3$: C, 67.42; H, 6.74; N, 5.24. Found: C, 66.82; H, 6.81; N, 5.25. Further characterization data are given in the Supporting Information.

(6) Crystallographic data for (**2**·thf)$_4$: $C_{60}H_{72}Li_4N_4O_{12}$; M_r = 1068.98, tetragonal, $I4_1/a$; a = 16.288(4), c = 21.674(6) Å; V = 5750(3) Å^3; d_{calc} = 1.235 Mg/m^3; Z = 4; $F(000)$ = 2272; μ(Mo Kα) = 0.084 mm^{-1}; T = 153(2) K. The data collection was carried out on a Stoe four-circle diffractometer equipped with an Oxford Cryostream crystal cooling apparatus, using graphite-monochromated Mo Kα radiation (λ = 0.710 73 Å) and an ω/θ scan technique. A total of 3277 reflections were collected in range 3.54 < θ < 25.00°. The data were corrected for Lorentz and polarization effects. The final cycle of refinement included 201 parameters with unweighted R_1 = 0.0499 on data with $I > 2\sigma(I)$ and weighted wR_2 = 0.1216 on all data. All calculations were performed on a Viglen 486 PC using SHELXTL-PLUS and SHELXL93 software. Atomic coordinates, bond lengths and angles, and vibrational parameters have been deposited at the Cambridge Crystallographic Data Centre.

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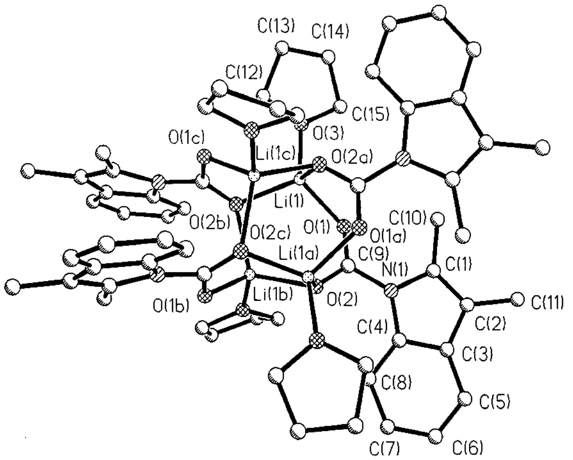

Figure 1. View of the molecular structure of (**2**·thf)$_4$ with hydrogen atoms omitted for clarity.

From symmetry and by inspection of bond lengths, the core of the structure is best viewed (west to east) as comprising two eight-membered boat-shaped (−LiOCOLiOCO−) rings joined by four inter-ring Li−O connections [north to south: Li(1c)−O(2a), O(2b)−Li(1), O(2c)−Li(1a), Li(1b)−O(2)] all of length 1.966(3) Å. This core is shown more clearly in Figure 2. Apart from the inter-ring Li−O connections (shown as open bonds) and a bond to thf [1.905(3) Å], each Li$^+$ is attached within its own ring to a two-coordinate [Li−O, 1.908(3) Å] and to a three-coordinate [Li−O, 1.993(3) Å] carboxylate oxygen, the latter being the oxygen involved in the inter-ring bonding. Eight-membered (−LiOCO−)$_2$ rings have been found before, in the molecular chair-shaped dimer (Ph$_2$NCO$_2$Li·tmeda)$_2$[3a] and in various polymeric hydrated lithium carboxylates.[7] However, we can find no structures having two such rings joined together, as in (**2**·thf)$_4$.

The final noteworthy structural feature in (**2**·thf)$_4$ may have mechanistic implications, especially regarding the conversion of **2** to **3** (Scheme 1) and precisely how the CO$_2$ unit directs and/or stabilizes second lithiation at the 2-alkyl position. Thus, each merely two-coordinate oxygen in the structure is positioned quite close to a 2-methyl group [e.g., O(1a)−C(10) in Figure 1; all such O−C distances are 2.758(3) Å].[8] Such oxygen centers may therefore complex the added second equivalents of butyllithium, bringing them nearby the 2-methyl groups, and/or they may complex the second lithium centers postlithiation. Of course, such further reaction occurs in solution. It is impossible to prove conclusively that (**2**·thf)$_4$ is the major or the only species present in solution, awaiting further lithiation and subsequent electrophilic substitution. It could be that a complex of general type (**2**·$x$thf)$_n$, with $x \neq 1$ and $n \neq 4$, remains in solution. It could also be that such a complex merely crystallizes as (**2**·thf)$_4$ [i.e., that this is the lowest energy solid-state formulation] and that, by implication, (**2**·thf)$_4$ reverts to (**2**·$x$thf)$_n$ on dissolution in thf. However, notwithstanding these critical qualms, we have gathered two pieces of evidence which suggest that specifically (**2**·thf)$_4$ is the most likely dominant solution species. First, although the initial yield of this solid complex is only 67%, continued refrigeration of the reaction solution affords more of it (91% final yield), with no other solid species being isolable. Second, ^{7}Li NMR spectra (25 °C, 155.5 MHz) of solid (**2**·thf)$_4$ dissolved in dmso and of the filtrate (plus dmso) left after isolation of the first batch of (**2**·thf)$_4$ both show a single, very sharp resonance at the same frequency (δ 0.98 relative to Ph^{7}Li in dmso). It can be noted finally that even if solid (**2**·thf)$_4$ is present in solution as a dimer, (**2**·2thf)$_2$, or as a monomer, (**2**·3thf), the above-noted short O···CH$_3$ contacts would likely be retained.

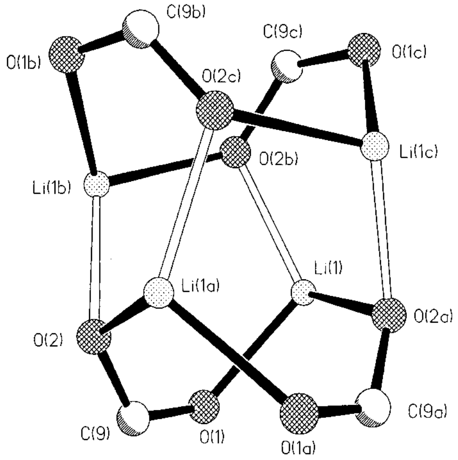

Figure 2. Core of the structure of (**2**·thf)$_4$ showing the Li−O connections (open bonds) between the two boat-shaped (−LiOCOLiOCO−) rings.

In conclusion, the study illustrates the value of isolating, identifying, and structurally characterizing lithiated species proposed to occur during organic syntheses involving deprotonations by lithium bases. Here, the proposed simple unsolvated monomer **2** (Scheme 1) prepared by lithiation and carboxylation of 2,3-dimethylindole (**1**) is shown to be a complicated tetrameric and solvated structure, (**2**·thf)$_4$. The precise structural features of this indicate much more clearly than hitherto why second lithiation is directed to the 2-methyl position. We are now attempting to isolate and to structurally characterize this dilithiated intermediate **3**.

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Supporting Information Available: Text describing experimental, spectroscopic, and analytical data for compound (**2**·thf)$_n$ and tables giving details of the X-ray structure determination, positional and thermal parameters, and bond distances and angles (6 pages). Ordering information is given on any current masthead page.

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(7) (a) Smith, G.; O'Reilly, E. J.; Kennard, C. H. L. *Acta Crystallogr., Sect. C.* **1986**, *42*, 1329−1331. (b) Küppers, H. *Ibid.* **1988**, *44*, 2093−2095. (c) Chen, X.-M.; Mak, T. C. W. *J. Crystallogr. Spectrosc. Res.* **1993**, *23*, 291.

(8) The sum of the van der Waal's radii of C and O is *ca.* 3.20 Å. In hydrogen-bonded systems involving CH···O units, a short C···O distance, taken to imply a significant interaction, is in the range 3.0−3.5 Å.