On the Mechanism of Lithiation of Hydric Aromatics: Direct NMR Evidence for Short H−Li Contacts in Mixed Aggregates[1]

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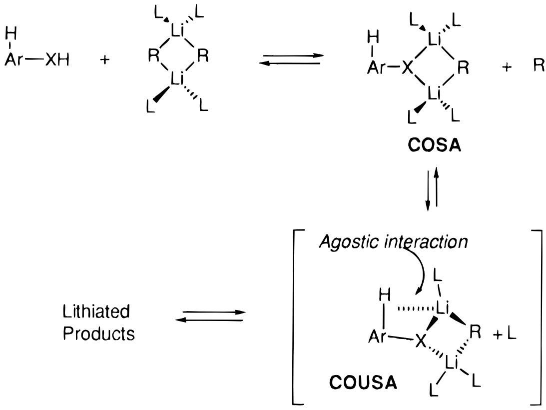
Received March 27, 1996

Two relevant aspects of the mechanism of the heteroatom-directed lithiation of aromatics are the matter of current debate.[2] The first is concerned with the necessity,[2,3] or not,[4] to invoke the formation of intermediate complexes as a step prior to the actual rate-determining deprotonation,[5] while the second refers both to the actual structure of such prelithiation complexes[6] and the detailed mechanism of activation[3−5] of the ortho (or appropriately located) hydrogens.[7] A number of studies have provided evidence, kinetic or otherwise, for such prelithiation complexes.[2,8,9] Unfortunately, direct NMR evidence has not been found. The working mechanistic models for lithiation of nonhydric[10] and hydric[11] aromatics are based on theoretical MNDO studies according to which ortho hydrogens are activated due to agostic interaction[12] with spatially close lithium atoms.[13] In particular, the lithiation of naphthols[11] and related compounds[14] has been rationalized on the basis of the mechanism illustrated in Scheme 1 (COSA and COUSA stand for coordinatively saturated and unsaturated mixed aggregates). Key issues raised by this proposal were as follows: (a) the lithiation of naphthols should involve a mixed aggregate showing dissimilar degrees of agostic interaction with ortho and peri protons, and (b) peri lithiation is actually favored because agostic interaction is stronger at this position. The NMR studies described below provide clear-cut evidence for the intermediacy of mixed aggregates of the general type $[(ArOLi)_m{\cdot}(RLi)_n]$ for the lithiation of hydric compounds. These mixed clusters undergo perceivable lithiation at ca. 30 to 50 °C at the most activated peri hydrogens,[15] which according to the ^{7}Li−^{1}H HOESY NMR spectra are the closest to the lithium atoms.[16]

Scheme 1. Proposed Mechanism for the Lithiation of Hydric Compounds



NMR titration studies commenced with solution A,[17] which showed one set of signals in the ^{1}H, ^{13}C, and ^{7}Li spectra corresponding to the expected lithium 1-naphtholate **1**,[18] a dimer according to the ^{7}Li quadrupole splitting constant (QSC = 111 kHz).[19,20]

1D (^{1}H, ^{13}C,[18] and ^{7}Li) and 2D (^{7}Li−^{1}H HOESY) NMR spectra of independently prepared B, C, and D solutions[17] revealed the formation of mixed organolithium−lithium naphtholate species **3**,[18] Scheme 2, as supported by (a) the presence of a set of duplicated signals both in the aromatic and aliphatic regions of ^{1}H (Figure 1) and ^{13}C[18] NMR spectra of solutions B−E; (b) the appearance of three lithium species in the ^{7}Li NMR spectra (Figure 1) corresponding to butyllithium homodimer (**2**; δ 1.09 ppm), lithium naphtholate homodimer (**1**; δ −0.51 ppm), and butyllithium−lithium naphtholate mixed dimer (**3**; δ 0.08 ppm), as proved by the ^{7}Li−^{1}H HOESY spectra (Figure 2) of **1** (cross peaks with H′-8 and H′-2 of the naphthalene skeleton) and **3** (with H-8 only, and the α and β hydrogens of the butyl chain), the ^{1}H−^{1}H COSY spectrum.[18] Interestingly, both **2** and the mixed cluster **3** were also found to be dimers ($m + n = 2$) as demonstrated by the multiplicity (heptuplets J_{CLi} = 20, 21.5 Hz, respectively) of the carbon-bearing lithium in the ^{13}C NMR spectra;[18] the ^{7}Li QSC value for **3** (QSC = 135 kHz) also agrees with **3** being a dimer in TMEDA. The equilibrium illustrated in Scheme 2 is almost completely displaced to the right when a 4:1 *n*-butyllithium:1-naphthol ratio is reached ($K \sim 2.5$), further addition of *n*-butyllithium (up to 8:1 ratio) not inducing further apparent changes.

In agreement with previous MNDO calculations,[11] the ^{7}Li−^{1}H HOESY spectrum of **3** (Figure 2) shows strong contacts for the peri hydrogen (δ 8.5 ppm) only, thereby suggesting that the ortho hydrogen must be further

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(1) Dedicated to Prof. Félix Serratosa "in memoriam".

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(16) See: (a) Bauer, W.; Schleyer, P. v. R. In *Advances in Carbanion Chemistry;* Snieckus, V., Ed.; JAI Press, Inc.: 1992; Vol. 1.

(17) Solutions containing 1:1 (A), 2:1 (B), 3:1 (C), 4:1 (D), and 8:1 (E) *n*-BuLi:1-naphthol ratios were prepared by adding 1-naphthol (1 mmol) in dry TMEDA (1 mL) to the appropriate amount of nBuLi in TMEDA, at −20 to 0 °C, under argon. *n*-BuLi in TMEDA was prepared from commercial 2.5M *n*-BuLi by removing the solvent with dry argon and the residue dissolved in 1 mL of TMEDA. Solvent suppression was achieved in all NMR spectra, except HOESY.

(18) Supporting information available.

(19) Jackman, L. M.; Scarmoutzos, L. M.; De Brosse, C. W. *J. Am. Chem. Soc.* **1987**, *109*, 5355 and references cited therein.

(20) The reliability of Jackman's method[19] depends on the uncertainties regarding the anisotropic rotational diffusion. QSC values for **1** and **3** (111 and 135 kHz, respectively) lie close to the ideal 120 kHz.

(21) Because γ_S/γ_I is >2.38 and τ_C can be assumed to be $\ll 1/\omega$. See: Neuhaus, D.; Williamson, M. P. *The Nuclear Overhauser Effect in Structural and Conformational Analysis;* VCH: New York, 1989.

S0022-3263(96)00570-1 CCC: $12.00

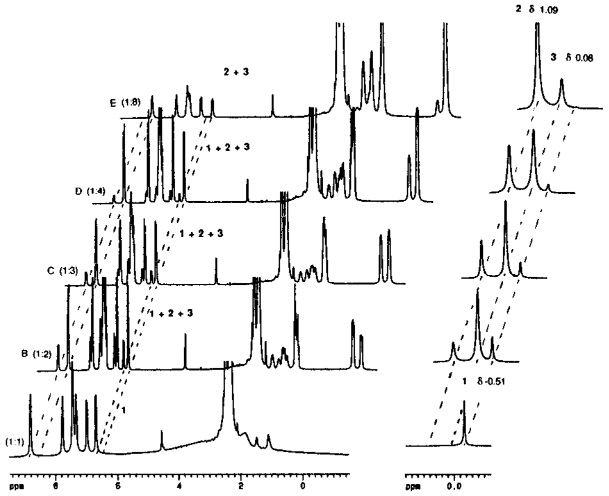
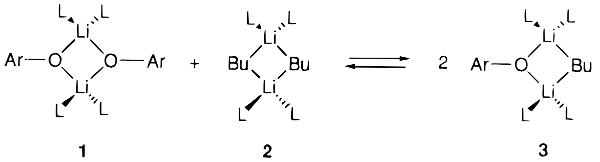


Figure 1. ^{1}H and ^{7}Li spectra of 1-naphthol:*n*-butyllithium mixtures A (1:1), B (1:2), C (1:3), D (1:4), and E (1:8) in TMEDA[18] at −20 °C.

Scheme 2. Equilibrium Formation of Mixed Aggregates from Alkyllithium and Lithium Aryl Oxides



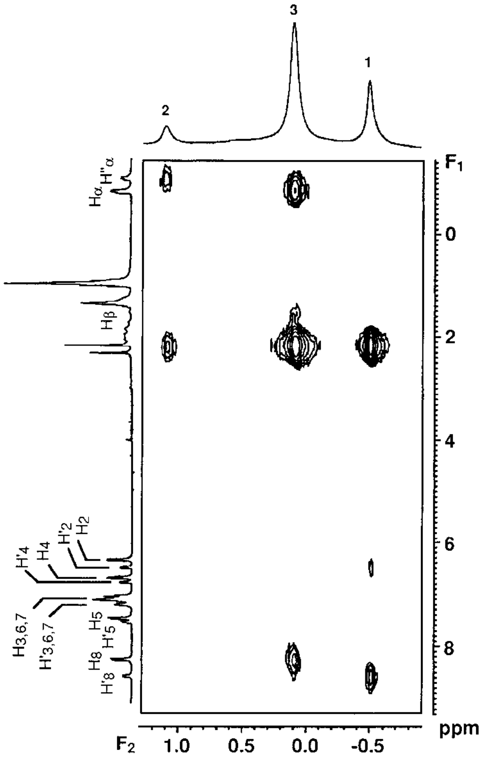


Figure 2. ^{1}H−^{7}Li HOESY NMR spectrum (mixing time 300 ms) of solution B[18] (see text) −20 °C. Assignments shown on F$_1$ are as follows: H_x for **3**, H'_x for **1**, and H''_x for **2**.

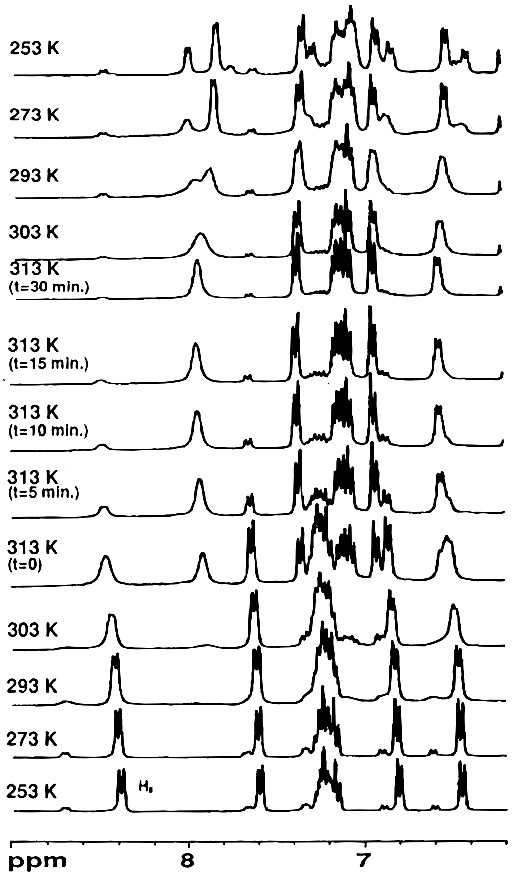


Figure 3. Peri lithiation of 1-naphthol:serial ^{1}H NMR spectra of a 1:4 1-naphthol:*n*-butyllithium mixture at increasing temperatures.[18]

away.[21] Relevant to our objectives, peri lithiation can be observed (Figure 3) in examining a series of NMR spectra of solution D at different temperatures. Complete lithiation is achieved at ca. 40 °C as shown by the disappearance of the peri hydrogen, the final spectrum exhibiting the expected AMX systems for 8-lithiated lithium 1-naphtholate.[7b] The structure of this compound is consistent with 1D and 2D spectra (COSY, HMQC, and HMBC),[18] quenching experiments.[7b]

In summary, the present work provides the first experimental evidence for the intermediacy of mixed aggregates[22] in the directed lithiation of hydric compounds. The excess of lithiating agent is required to displace the otherwise unfavorable equilibrium leading to their formation.[11,14] Close contacts observed in the ^{7}Li−^{1}H HOESY spectra of these mixed clusters show peri hydrogens to be the closest to lithium atoms. Since lithiation occurs on heating, it is tempting to conclude that complex-induced proximity effects play a key role in these reactions,[6,14] perhaps by activating the closest hydrogens by agostic interaction.[12,13] The definitive identification of the kinetically relevant species awaits the realization of careful kinetic studies.

Acknowledgment. Financial support by the DGICYT (Spain) is gratefully acknowledged. We thank Prof G. Boche (U. Marburg) for his invaluable help.

Supporting Information Available: 1D and 2D NMR spectra of 1-naphthol:*n*-butyllithium mixtures and a listing of NMR data for **1**−**3** (7 pages).

JO960570A

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