

Multinuclear NMR characterisation of the complexes between chiral 3-aminopyrrolidine lithium amides and *n*-butyllithium

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RÉSUMÉ

L'étude du transfert de chiralité, dans la réaction de condensation du *n*-butyllithium sur les aldéhydes aromatiques en présence d'amidures de lithium dérivés d'une série de 3-aminopyrrolidines optiquement actives, est abordée *via* la détermination de la structure du complexe formé entre amidure et *n*-BuLi par RMN haut champ ^1H , ^{13}C et ^6Li dans des conditions proches de celles de la réaction.

mots-clés : RMN du ^6Li , ^{13}C , ^1H ; amidure de lithium chiraux; 3-aminopyrrolidine; structure, complexes amidure de lithium-alkyllithium.

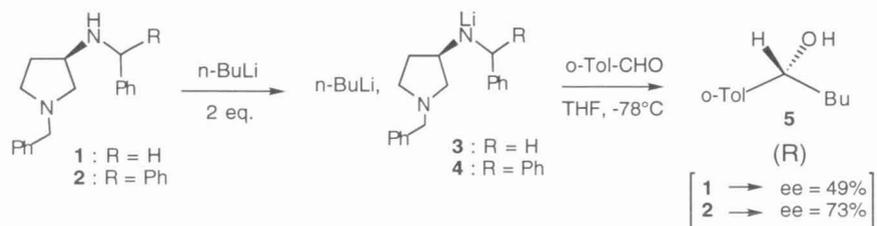
ABSTRACT

From a set of one- and two-dimensional ^1H , ^{13}C and ^6Li NMR experiments, we propose the formation of a well organised 1:1 tight complex between substituted 3-aminopyrrolidine lithium amides and *n*-butyllithium. This complex is probably at the origin of the stereoselection observed in the asymmetric condensation of *n*-butyllithium onto aromatic aldehydes.

key words : ^6Li , ^{13}C , ^1H NMR; chiral lithium amide; 3-aminopyrrolidine; structure, lithium amide-alkyllithium complexes.

INTRODUCTION

We have developed several accesses to N-substituted chiral 3-aminopyrrolidines [1a, 2] and have recently applied their lithium amides as chiral inductors in the asymmetric condensation of n-butyllithium onto aromatic aldehydes (Eq.1) [1b, 2a]. We have observed that, provided a cumbersome group is present on the 3-amino moiety, e.e. up to 77% can be obtained. The analysis of the mechanism ruling the chirality transfer in such a reaction requires an insight on the structure of the reactive species in solution [2b]. Spectacular achievements [3] have proved multinuclei high-field NMR spectroscopy to be a very potent tool in the structural analysis of lithium amides into solutions [4]. However, only very recently has a chiral amide and its complex with n-BuLi been studied [5].



RESULTS

We first studied the formation of lithium amides **3** and **4** by adding, directly into the NMR tube, n-Bu⁶Li [6] to a THF-d₈ solution of the corresponding amine at -78°C. Despite the structural analogy between **1** and **2**, the NMR data collected for lithium amides **3** and **4** are dramatically different. While amide **3** pyrrolidinic ring undergoes only minor changes with respect to its amino precursor **1**, amide **4** presents a norbornyl-like bridged structure organized around Li⁺ (Fig. 1). This structure has been deduced from a set of one- and two-dimensional ¹H, ¹³C and ⁶Li NMR experiments similar to these used for the structural elucidation of the final complex (*vide infra*).

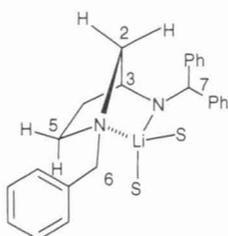


Figure 1: Norbornyl-like structure of **4** in THF-d8.

This conformation explains the strong splitting observed between the gem H² (H²:2' 2,91; 2,15 ppm) [7] and the significant ¹³C chemical shift on C² (7 ppm downfield). The Li⁺ chelation by the ring nitrogen also stiffens the benzylic moiety, rendering both gem H⁶ (H⁶:6' 3,93; 3,12 ppm) and gem H⁵ (H⁵:5' 2,77; 1,91 ppm) chemically non-equivalent.

When one supplementary equivalent of n-Bu⁶Li was added to **4**, a 1:1 complex was formed in which the two protons α to Li in BuLi are diastereotopic (at -70°C) and appear as coupled multiplets at -0,73 and -0,83 ppm as shown on the ¹H-¹H COSY spectrum (Fig. 2a). Moreover, intermolecular dipolar interactions between these two protons and those of the pyrrolidinic ring, as observed in the ¹H-¹H NOESY experiment (Fig. 2b), led us to propose the formation of a tight complex between one lithium amide **4** molecule and one n-BuLi.

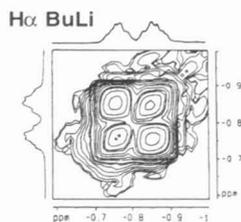


Figure 2a: ¹H-¹H COSY (THF-d8; 203 K ;500.13 MHz).

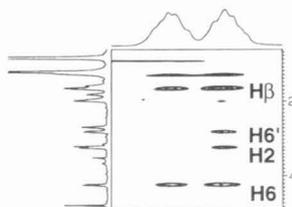


Figure. 2b: ¹H-¹H NOESY in **4** -BuLi 1:1 complex (THF-d8; 203 K; τ=1s; 500.13 MHz).

Complementary, the ^1H decoupled ^{13}C signal of the methylene carbon α to Li in BuLi is a 1/2/3/2/1 quintet, indicating its coupling ($J=7.9\text{Hz}$) with two lithium cations ($I=1$). On the other hand, the ^6Li spectrum displays two singlets at 2,25 and 2,07 ppm correlating with α and β methylene protons, H^2 and aromatic protons (Fig.3a). Finally, both ^6Li - ^6Li COSY and EXSY (Fig. 3b) experiments indicate that the two lithium cations belong to the same complex and exchange their positions.

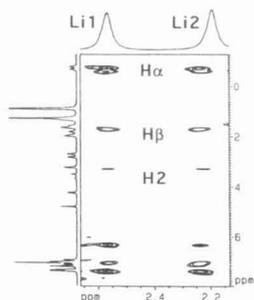


Figure 3a: ^1H - ^6Li HOESY (THF- d_8 ; 203 K; $\tau=2\text{s}$; 500.13 - 73.58 MHz).

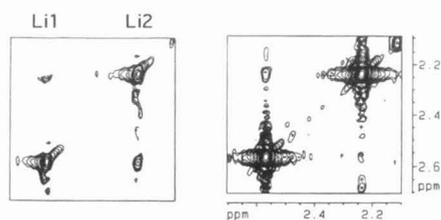


Figure 3b: ^6Li - ^6Li COSY and EXSY of 4 -BuLi (THF- d_8 ; 203 K; $\tau=1\text{s}$; 73.58 MHz).

It is worth emphasizing that the structural differences between amides **3** and **4** are no more observed when they are complexed with BuLi. Very similar spectra are indeed obtained, except for the diastereotopicity of the α methylene protons, indicating a possible difference in the rigidity of the system. Theoretical DFT calculations fully support the structures deduced from our NMR data [8]. From all these observations, we suggest the enantioselectivity to be a consequence of the interactions between the aldehyde and these complexes during the docking process.

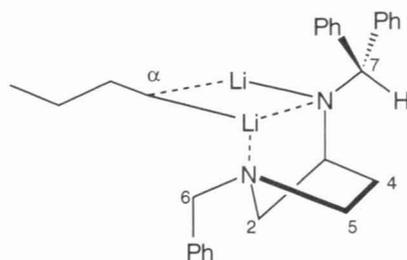


Figure 4: Proposed conformation for BuLi - **4** complex in THF-*d*8 solution at 203 K

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