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A NMR Investigation of α-Heterosubstituted Chloroethyllithiums in THF

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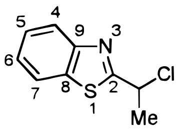
Introduction

Some of us have recently reported that certain heterosubstituted (α-chloroalkyl)lithiums behave as Darzens reagents, adding smoothly and stereoselectively to carbonyl compounds and imines to give heterosubstituted epoxides and aziridines, respectively.[1,2] To gain further insights into their structural features, rationalize the stereochemical pathway of their addition to electrophiles, and attempt to optimize stereoselectivity, we decided to undertake a detailed NMR investigation based on an approach developed for the study of α-heterosubstituted carbanions in DMSO.[3] In the present paper, we describe the generation and NMR study results of (2-(α-chloroethyl)benzothiazolyl)lithium (**1-Li**) and (4,4-dimethyl-2-(α-chloroethyl)oxazolinyl)lithium (**2-Li**). Semiempirical calculations have been included in order to complement and support the NMR results.

Results and Discussion

NMR Investigation of the Lithium Salts in THF. The **1-Li** and **2-Li** lithium salts of respectively α-chloro-2-ethylbenzothiazole (**1**) and α-chloro-2-ethyl-4,4-dimethyloxazoline (**2**) were studied in THF by means of ^{13}C and ^{15}N NMR spectroscopy. The salts were prepared from neutral precursors using lithium diisopropylamide (LDA) as a base. Lithium salts of carbanionic systems with the negative charge mainly residing on an oxygen or nitrogen atom generally exist as contact-ion pairs in ethereal solvents such as THF, with the lithium gegenion coordinated to the negatively charged heteroatom site.[4]



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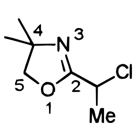

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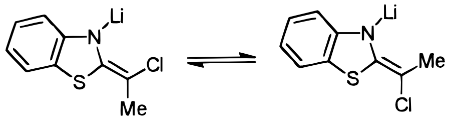
The ^{13}C and ^{15}N NMR shifts of compounds **1**, **2**, **1-Li**, and **2-Li** are shown in Table 1. The ^{13}C shift assignments in the neutral compounds **1** and **2** were based on the multiplicity of the patterns, coupling constants, and known heteroatom substituent effects operating in the heterocycle;[5] the assignments for the lithium salts **1-Li** and **2-Li** were based on the multiplicity of their patterns, using the anion of 2-benzylbenzothiazole as a model comparative compound for the former.[6] In both systems, the ^{15}N shift underwent a high-field displacement on going from the neutrals to the anions, in line with previous results obtained for pyridine-like nitrogen atoms.[6,7] This result is related to the increase in π-electron density on the N(3) atoms in the anions.

The ^{13}C NMR spectrum of **1-Li** shows the presence of two species, which are identified as the two geometric isomers (*E*)-**1-Li** and (*Z*)-**1-Li** along the bond linking the carbanionic carbon and the heterocycle. The absence of protons in suitable positions did not allow us to perform the NOE experiment that we have previously used[7b] to determine the double-bond configuration of benzylazine anions. As a consequence, the two series of signals shown in Table 1 have been labeled as belonging to two generic isomers **A** and **B** of the lithium salt **1-Li**. The composition of the equilibrium between the two species was found to be dependent on the time from the preparation of the anion, thus showing that slow equilibrium occurs in solution (Table 2). In particular, the molar ratio of a freshly prepared anionic solution is about 3:1, with isomer **A** being the predominant species; the relative concentration of the originally minor isomer **B** increases over time until it reaches almost the same molarity as that of isomer **A** after 24 h; and finally, the equilibrium shifts almost completely toward isomer **B** after 4 days. One of the two geometric isomers is therefore thermodinamically more stable, whereas kinetic equilibrium at least partially favors the formation of the other.



(*E*)-**1-Li** (*Z*)-**1-Li**

The slow equilibrium between the two $E-Z$ isomers suggests that the bond linking the carbanionic carbon and C(2) of the ring has a high double-bond character. We have previously reported[6] that the charge demand c (defined as the fraction of π-charge withdrawn by the heterocycle from an adjacent charged trigonal carbon atom) of the 2-benzothiazolyl ring in the anion of 2-benzylbenzothiazole is the highest among azoles containing one pyridine-like nitrogen atom and one of the highest among heterocyclic substituents. In the anion of 2-benzylbenzothiazole, almost 50% of the negative charge is delocalized into the heterocyclic ring, whereas about 15% of the charge resides on the phenyl ring. In anion **1-Li**,

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Table 1. $^{13}C^{a}$ and ^{15}N NMR Shifts^{b} (ppm) of 1 and 2 and Corresponding Lithium Salts 1-Li and 2-Li at −80 °C in THF^{c}

compd		C(2)	N(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)	CH/C−	α-CH_3	other groups
1		171.30	68.7	122.99	126.11	125.45	121.86	135.19	152.33	54.67	23.54	
1-Li	**A**	155.34	184.2^{d}	108.49	123.63	111.51	117.82	129.58	159.45	83.84	20.54	
	B	151.94		109.08	124.08	111.96	118.13	130.09	158.21	74.80	22.22	
2		163.21	130.1	^{e}	78.65					48.87	21.12	4-CH_3 = 27.17
2-Li		163.75	251.8	61.92	77.95					61.60	19.39	4-CH_3 = 28.78

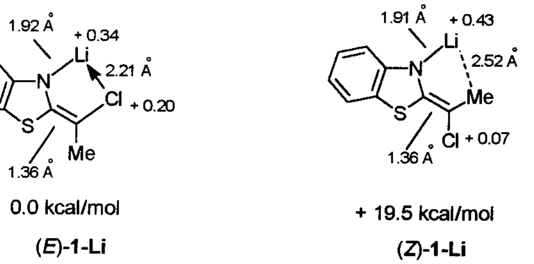
[a] Relative to Me_4Si (0.0 ppm). [b] Relative to neat nitromethane (0.0 ppm) (Witanowski, M.; Stefaniak, L.; Webb, G. A. *Ann. Rep. NMR Spectrosc.* **1986**, *18*, 3; **1993**, *25*, 3). [c] 0.50 M solutions. [d] Nitrogen of **1-Li** was detected in the first 4 h after deprotonation and assigned to isomer **A**. [e] Covered by solvent peak (THF: 66.5 ppm).

Table 2. Variation of Relative Ratio of the Two Geometrical Isomers of 1-Li with Time in THF at −80 °C.

ratio **1-Li A**:**1-Li B**	time (h)^{a}
75:25	1
50:50	24
10:90	96

[a] Time from preparation of the anion.

Scheme 1

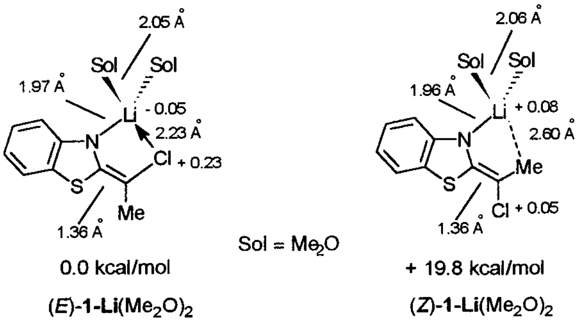


where the partitioning of the negative charge is reduced by the absence of the phenyl ring of the 2-benzylbenzothiazole anion, a larger amount of negative charge can be expected to be delocalized into the heterocyclic ring, leading[8] to the high π-character of the bond between the ring and the carbanionic carbon.

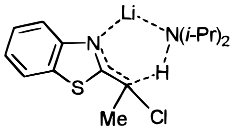
To identify the double-bond configuration of the thermodynamically more stable isomer and investigate the reasons for the inverse composition of the kinetically controlled equilibrium, semiempirical calculations[9,10] were performed. Although the MNDO semiempirical method for which the lithium parameters are known has been successfully applied to the investigation of Li−N interactions,[11] we preferred using the PM3 Hamiltonian because of the tendency of MNDO to overestimate C−Li bonds.[12] Furthermore, in combination and in comparison with electron-correlated ab initio computations, the PM3 method has recently been successfully applied to the investigation of lithium enolates in ethereal solvents.[13] The relative energies, selected geometric parameters, and calculated total charges are shown in Scheme 1.

Energetics show a strong preference for the *E* isomer, with coordination between the chlorine atom and the gegenion. Since this interaction may be overestimated in the computations because of the absence of the interaction between lithium and the solvent, we decided to repeat the geometry optimizations and PM3 energy calculations on the disolvated geometric isomers, (*E*)-**1-Li**($Me_2O)_2$ and (*Z*)-**1-Li**($Me_2O)_2$.[14] We chose dimethyl ether as a realistic model ether solvent molecule. The results shown in Scheme 2 fully confirm the considerable difference in energy between the two isomers.

Scheme 2



The solvation energies from **1-Li** to the disolvated species were calculated to be 18.9 for the *E* and 18.6 kcal/mol for the *Z* isomer, values that compare well with the PM3 solvation energies of lithium enolates in dimethyl ether.[13] We can therefore reasonably conclude that the thermodynamically more stable species of **1-Li** is the *E* isomer, as a result of an internal chelation involving the chlorine atom. In transition state **3** of the deprotonation reaction, internal chelation between the chlorine substituent and the lithium cation is no longer feasible because of the presence of the LDA nitrogen atom in the six-membered cycle. This may provide a rationale for the absence of any preference for the *E* isomer in the kinetically controlled equilibrium of **1-Li**.



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In the case of the lithium salt **2-Li** of the oxazolinyl derivative, only one set of ^{13}C NMR signals was detected, which may indicate either the presence of a single geometric *E* or *Z* isomer or a rapid interconversion (on the NMR time scale) between the two species. The charge demand of the 2-oxazolyl substituent in 2-benzyloxazole is much lower (0.35) than that of the 2-benzothiazolyl ring (0.47),[6] and we can expect the electron-withdrawing capacity of the partially saturated oxazolynyl ring to be further decreased. As a consequence, the double-bond character of the bond linking the carbanionic carbon to C(2) of the heterocyclic ring in **2-Li** should be smaller than that of **1-Li**. On the basis of these premises, we conclude that rapid interconversion between the two

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Table 3. Shielding Contributions A_i (ppm) of Substituents

substituent	A_i[a]
benzothiazol-2-yl	8.7[b]
4,4-dimethyloxazolin-2-yl	0.5[c]
Cl	2.1[d]
CH_3	10.6[e]

[a] Positive values mean low-field displacement. [b] Reference 6. [c] The same shielding contribution of the oxazol-2-yl substituent is assumed (ref 6). [d] Obtained from the difference between the ^{13}C chemical shift of C(1) of $CH_2{=}CHCl$ (124.9 ppm) (ref 5, p 199) and ethylene (122.8 ppm). [e] Obtained from the difference between the ^{13}C chemical shift of the C(2) of $CH_2{=}CHCH_3$ (133.4) (ref 5, p 192) and ethylene (122.8 ppm).

isomers (*E*)-**2-Li** and (*Z*)-**2-Li** is more likely to be the case. Once again, the unsolvated *E* isomer was semiempirically computed to be the most stable species.

***π*-Charge Mapping.** The application of relationships 1−4 allows the empirical calculation of *π*-electron densities on carbon and nitrogen atoms in anionic systems once the ^{13}C and ^{15}N NMR chemical shifts are known. These relationships have been validated by means of their successful application to a large number of anions of benzyl and methylene derivatives of primary organic functionalities,[15,16] pyridines,[7a,17] azines,[7] and azoles.[6] In particular, the *π*-charge/^{13}C-shift relationship (1) makes possible the empirical calculation of the *π*-electron density $q^{\pi}{}_{C}$ on a trigonal carbanionic carbon $XYZC^-$;[15a,18] relationship 2 (derived from relationship 1) allows the calculation of the variation in *π*-electron density for every carbon site on going from the neutral to the conjugate anionic system; and finally the *π*-charge/^{15}N-shift relationship (3)[6,7,8,16] can be used to compute the same local variation for a nitrogen atom.

$$\delta^{13}\mathrm{C} = 122.8 + \Sigma A_i - 160(q^{\pi}{}_{\mathrm{c}} - 1) \qquad (1)$$

$$\Delta\delta(^{13}\mathrm{C}) = -160\ \Delta q^{\pi}{}_{\mathrm{c}} \qquad (2)$$

$$\Delta\delta(^{15}\mathrm{N}) = -366.34\ \Delta q^{\pi}{}_{\mathrm{N}} \qquad (3)$$

$$q_{\mathrm{Het}} = q^{\pi}{}_{\mathrm{neutral}} + \Sigma(\Delta q^{\pi})_{\mathrm{ring}} \qquad (4)$$

Relationships 2 and 3 are valid for sites which do not experience a change in substitution pattern upon the deprotonation of the substrate. Relationship 1 requires the knowledge of the shielding contributions A_i of the substituents of the carbanionic carbon, which can be calculated following a previously described approach:[15c] the A_i values are listed in Table 3. The mapping of the local *π*-variation for each position of the heterocyclic rings is shown in Table 4. The total *π*-electron density of the heterocyclic ring in the anionic systems, calculated using relationship 4 (where $q^{\pi}{}_{\mathrm{neutral}}$ = number of *π*-electrons of the heterocyclic ring in the neutral substrate), and that of the carbanionic carbon (calculated using relationship 1) are shown in Table 5.

Table 4. Variations of the Local *π*-Electron Densities (Millielectrons) for Each *i*th Position Going from the Neutral Chloromethyl Heteroaryl Derivatives 1 and 2 to the Corresponding Lithium Salts 1-Li and 2-Li in THF[a]

compd		C(2)	N(3)	C(4)	C(5)	C(6)	C(7)	C(8)	C(9)
1-Li	**A**	100	315	91	16	87	25	35	−44
	B	121		87	13	84	23	32	−37
2-Li		−3	332						

[a] Positive values correspond to an increment of *π*-electron density.

Table 5. Experimental *π*-Electron Densities *q* (Electrons) for Lithium Salts 1-Li and 2-Li

compd		q_{Het}[a]	q_{C}[b]	$q_{\mathrm{Het}} + q_{\mathrm{C}}$[c]
1-Li	**A**	10.624	1.377	12.00[d]
	B	10.639[e]	1.434	12.07[d]
2-Li		4.329	1.465	5.79[f]

[a] *π*-Electron density residing on the heterocyclic ring. [b] *π*-Electron density residing on the carbanionic carbon. [c] Total *π*-electron density of the anionic system, excluding the chlorine atom. [d] To be compared with the theoretical value of 12 *π*-electrons. [e] Same $\Delta_{q^{\pi}\mathrm{N(3)}}$ of isomer A was assumed. [f] To be compared with the theoretical value of 6 *π*-electrons (difference to 6 is due to the absence of the contribution of $\Delta q^{\pi}{}_{\mathrm{O(1)}}$; see text and charge mapping in oxazole derivatives: ref 6).

Following conclusions based on previous calculations involving thiazole derivatives,[6] we have assumed that the sulfur atom of the benzothiazole ring in **1** does not accommodate any negative charge on going to anion **1-Li** (that is $\Delta q^{\pi}{}_{\mathrm{S}} = 0$), whereas the corresponding variation for the oxygen atom of the oxazolinyl derivative **2-Li** cannot be calculated because of the lack of any general charge/shift relationships for oxygen.

Analysis of the data shown in Tables 4 and 5 shows that a considerable amount of the negative charge is delocalized into the nitrogen sites of **1-Li** and **2-Li**. More than 60% of the negative charge formed upon deprotonation is withdrawn by the heterocyclic ring in **1-Li**, thus validating our previous considerations concerning the strong *π*-character of the bond between the carbanionic and C(2) carbon atoms; on the contrary, the oxazolinyl ring of **2-Li** only accepts 30% of the charge. It is therefore reasonable to conclude that rapid interconversion between the two geometric isomers occurs in solution.

Conclusions

Both the multinuclear NMR investigation at −80 °C in THF, with the application of shift/charge relationships, and semiempirical calculations on the lithium salts **1-Li** and **2-Li** of heteroaryl chloromethyl derivatives have provided interesting structural insights concerning the nature of the anionic systems. The lithium salt **1-Li** of the benzothiazolyl derivative exists in solution as a mixture of *E* and *Z* isomers, the relative concentration of which is inverted 4 days after deprotonation. Only one set of ^{13}C NMR resonances for the oxazolinyl derivative **2-Li**, in combination with the *π*-charge delocalization data, supports the hypothesis that in this case a rapid interconversion between the two geometric isomers takes place in THF solution at −80 °C. PM3 computations show that a stabilizing internal coordination between the gegenion and the chlorine atom is responsible for the higher relative stability of the *E* isomer of both sub-

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(14) Usually the lithium cation reaches stabilization in the tetracoordination, with the presence of three molecules of solvents (ref 4b). However, high-level ab initio computations have recently shown that in lithium enolates the most stable solvated species is the disolvated form—that is the lithium cation is formally tricoordinated—with the presence of an additional stabilizing internal chelation (ref 13).

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strates. Finally, empirical π-charge mapping indicates that a considerable portion of the negative charge (more than 60%) is delocalized into the **1-Li** benzothiazolyl ring, thus leading to the high π-character of the bond linking the heterocyclic ring to the carbanionic carbon. These data concerning the geometric and electronic structure of the two lithium salts in THF provide a valuable support for the design and control of important stereoselective reactions in which these species are involved as intermediates.[1,2]

Experimental Section

^{13}C and ^{15}N NMR investigations were carried out at −80 °C using 0.50 M solutions in THF. Spectral parameters and calibrations have been previously reported,[7b] with the exception of the ^{15}N measurement of **2-Li**, for which a pulse delay of 40 s was used. The 10-mm o.d. tubes for the THF solutions were equipped with an internal 4 mm coaxial tube containing acetone-d_6 for internal lock. Anhydrous THF was prepared by means of continuous distillation over sodium sand, in the presence of benzophenone and under nitrogen, until the blue color of sodium ketyl was permanent. Diisopropylamine was refluxed over CaH_2 for 4 h and distilled under nitrogen prior to use. 2-(1-Chloroethyl)-1,3-benzothiazole (**1**) and *tert*-butyl hypochlorite were prepared according to the literature.[19] 2,4,4-Trimethyl-2-oxazoline was purchased from Aldrich Chemical Co.

Preparation of 2-(1-Chloroethyl)-4,4-dimethyl-2-oxazoline (2). *tert*-Butyl hypochlorite (8.89 mL, 78.62 mmol) was added dropwise to a solution of 2,4,4-trimethyl-2-oxazoline (10 g, 78.62 mmol) in anhydrous carbon tetrachloride (60 mL) at 0 °C under nitrogen. The reaction was stirred at 0 °C for 30 min. Then, it was allowed to warm to room temperature and stirred for one night. The mixture was evaporated in vacuo, and the crude product was purified by distillation under reduced pressure (49 °C, 10^{-2} mmHg) to give 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline (**2**) (9.66 g, 76%) as a clear oil: ^1H NMR ($CDCl_3$) δ 1.28 (s, 3 H), 1.29 (s, 3 H), 1.72 (d, $J = 6.9$ Hz, 3 H), 4.01 (s, 2 H), 4.54 (q, $J = 6.9$ Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 21.89, 27.82, 27.85, 48.71, 67.24, 79.59, 163.98; MS m/z 163 ($M^+ + 2$, 15), 161 (M^+, 46), 148 (220), 146 (692), 120 (56), 118 (184), 96 (1000), 42 (275), 41 (363); IR (film) 2971, 1664, 1366, 999, 965, 696 cm^{-1}.

Preparation of the LDA Solution in THF for NMR Experiments. A solution of *n*-BuLi in hexane (1.6 M, 4.6 mL, 7.4 mmol) was added under nitrogen at room temperature to a solution of freshly distilled diisopropylamine (0.900 g, 8.9 mmol) in anhydrous THF (2 mL) in a 50-mL Schlenk flask fitted with an airtight septum cap and stopcock. Formation of LDA is considered quantitative. After the mixture was stirred for 15 min at room temperature, the solvent and the excess diisopropylamine were removed by evaporation under high vacuum and dry nitrogen was then added. Anhydrous THF (5.3 mL) was added to give a 1.4 M solution of LDA in THF.

Preparation of the Anions for NMR Experiments. The anions were prepared adopting a procedure already described for the preparation of anions in DMSO.[18] Samples were prepared directly in a 10-mm NMR tube fitted with an airtight septum cap. A 2.0 M solution of the neutral substrate in anhydrous THF (0.5 mL) was added to a 1.4 M solution of LDA in THF (1.5 mL) under nitrogen at −78 °C. The resulting solution (2.0 mL) was 1.0 M in base and 0.5 M in anionic substrate. The 2-fold excess of base was used in order to ensure complete deprotonation of the substrate. The NMR tube was kept dipped in crushed dry ice (−80 °C), and spectra were recorded after 0.5 h from preparation of the anionic substrate.

Supporting Information Available: ^1H and ^{13}C NMR ($CDCl_3$) spectra of compound **2** (2 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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