

Application Note SC-XRD #501

2-Thienyllithium in the solid state and in solution – Insights from X-ray crystallographic and NMR spectroscopic data

Thiophene, the sulfur-containing five-membered aromatic heterocycle, is one of the most versatile scaffolds in various chemical areas spanning a wide range from organic synthesis via organo metallic chemistry and materials science to life science. Since the award of the chemistry Nobel Prize to Heeger, MacDiarmid, and Shirakawa for the discovery and development of conductive polymers in 2000, the polythiophenes (PTs) are one of the most flourishing areas in materials science. They are key candidates for conducting polymers, opto-electronical luminescent layers, sensors and many more applications.

Metallation fine tuning

In all these fields the lithiated species determines the product, which makes it essential to get information about the lithiated species, both in the solid state and in solution. Information concerning the latter can be very valuable because structural changes in solution like solvation and aggregation determine the reactivity and selectivity and hence the product range in organic, organometallic and inorganic syntheses. Accordingly, 2-monometallation needs

to be tuned, i.e. favoured or discriminated against 2,5-dimetallation, because that leaves the thienyl group either in a pendent or bridging position within the product.¹

Combined X-ray and NMR analyses

In his seminal case study on the relationship between solvation, aggregation and reactivity in organolithium chemistry, Collum stated "X-ray crystallography provides little insight into the thermodynamics of aggregation and solvation".² This is true as the crystal structure is commonly believed to represent the least soluble derivative in the pot and not necessarily the most abundant, let alone the most reactive species.³ Nevertheless, solid state investigations of such species can, in addition to structural information, provide the scope of potentially present species in solution. On the other hand, identification of the solution structure of these compounds can best be achieved by employing techniques of nuclear magnetic resonance (NMR) spectroscopy.

The solution provider

Bruker is able to provide solutions for both applications. A powerful X-ray source like Bruker's TURBO X-RAY SOURCE (TXS) equipped with HELIOS X-ray optics, a sensitive detector such as the APEX II and the APEX2 software suite, are required to get the excellent data quality needed for a successful structure determination of highly reactive lithium organics.

Insights into the solution state structures and dynamics can best be obtained using NMR spectroscopy. Bruker offers the most advanced high-frequency electronics technology in this field – the Avance III HD spectrometer – along with a wide variety of probes and automation accessories. Bruker's solution oriented software packages like the *CMC family* or *the Dynamics Center* assist the user in analysing the resulting data in the most efficient way.

To demonstrate the potential of a combined approach using both applications, various 2-thienyllithium derivatives were investigated in the solid state by X-ray diffraction and in solution by NMR techniques.⁴

Solid state investigations by X-ray crystallography

The tetrameric structure of $[(Et_2O)Li(C_4H_3S)]_4$ (**1**) is the starting point of the following X-ray diffraction data discussion (Figure 1). Compound **1** can be isolated from the parent reaction mixture upon storing the clear solution at 5 °C. As in all cases crystals were selected and applied to the diffractometer at cryogenic conditions applying the XTEMP-2 device.⁵ **1** crystallizes with one tetramer in the asymmetric unit. The four lithium atoms form a tetrahedron, a common structural motif for $[LiR]_4$ oligomers. All four almost equilateral Li_3 triangles are μ_3 -capped by the C_α -atom of the thienyl anion. THF is a much better donor to lithium in lithiumorganics than diethyl ether. Consequently, addition of THF to a diethyl ether solution of **1** gives crystals of the dimer

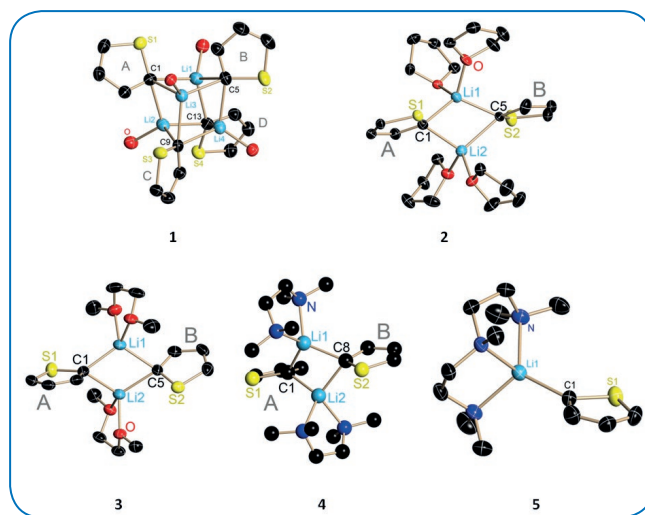


Figure 1: Molecular structures of $[(Et_2O)Li(C_4H_3S)]_4$ (**1**), $[(THF)_2Li(C_4H_3S)]_2$ (**2**), $[(DME)Li(C_4H_3S)]_2$ (**3**), $[(TMEDA)Li(C_4H_3S)]_2$ (**4**), and $[(PMDETA)Li(C_4H_3S)]$ (**5**). Anisotropic displacement parameters are depicted at the 50% probability level. Hydrogen atoms are omitted for clarity. Note that the thienyl substituents are rotationally disordered relative to the Li...Li vector, indicating no clear preference for additional Li...S interactions.

$[(THF)_2Li(C_4H_3S)]_2$ (**2**). As anticipated, the two THF donor molecules in the dimer **2** can readily be replaced by the chelating donor base DME. The structure retains the dimeric aggregation with a planar Li_2C_2 four-membered ring to give $[(DME)Li(C_4H_3S)]_2$ (**3**). Switching the DME donor base in **3** to TMEDA in $[(TMEDA)Li(C_4H_3S)]_2$ (**4**), has virtually no impact on the structural parameters. Providing more than two donor atoms in a single donor base changes the aggregation to monomeric. In $[(PMDETA)Li(C_4H_3S)]$ (**5**) the lithium atom is coordinated to the single C_α -atom in the ring plane like in other lithium aryl monomers.

Table 1: Selected crystallographic parameters obtained from the crystal structure determination of components **1**, **2**, **3**, **5**

	1	2	3	5
Space group	P-1	P-1	P-1	$P2_1/n$
Empirical formula	$C_{32}H_{52}Li_4O_4S_4$	$C_{24}H_{38}Li_2O_4S_2$	$C_{16}H_{26}Li_2O_4S_2$	$C_{13}H_{26}LiN_3S$
Formula mass	[u]	656.74	468.54	360.37
Unit cell lengths,				
a [Å]	10.086(2)	9.303(2)	8.625(2)	8.466(2)
b [Å]	11.779(2)	9.531(3)	10.471(2)	15.573(3)
c [Å]	17.970(3)	14.945(2)	12.749(2)	12.226(2)
Unit cell angles				
α [°]	85.97(2)	97.29(2)	76.66(2)	90
β [°]	73.83(2)	97.15(2)	81.73(2)	93.36(2)
γ [°]	66.45(2)	98.03(2)	67.47(2)	90
$R1, wR2$ [$I \geq \sigma(I)$]	0.0429, 0.1055	0.0362, 0.0916	0.0421, 0.1108	0.0332, 0.0814
$R1, wR2$ (all data)	0.0620, 0.1163	0.0410, 0.0943	0.0538, 0.1184	0.0467, 0.0863

Solution state investigations by high resolution NMR

These structures provide the starting point for the NMR investigations. Accordingly, the corresponding compounds were dissolved in non-coordinating deuterated toluene to offer the firm ground for Diffusion Ordered NMR spectroscopy (DOSY) as well as Heteronuclear Overhauser Enhancement NMR Spectroscopy (HOESY).

The ^1H -DOSY spectrum of $[(\text{PMDETA})\text{Li}(\text{C}_4\text{H}_3\text{S})]$ (**5**) in toluene- d_8 (Figure 2, left) clearly demonstrates that the thiophenyl group and the donor base form a stable complex in solution as protons from both units display the same diffusion coefficient ($1.23 \cdot 10^{-9} \text{ m}^2/\text{s}$). This value is in agreement with the molecular mass (263.37 g/mol) of the monomeric structure. A similar behaviour is observed in the ^1H -DOSY spectra of **3** ($D = 9.3 \cdot 10^{-10} \text{ m}^2/\text{s}$) and **4** ($D = 6.3 \cdot 10^{-10} \text{ m}^2/\text{s}$) (not shown). In contrast, in the solution of $[(\text{THF})_2\text{Li}(\text{C}_4\text{H}_3\text{S})]_2$ (**2**) the observed diffusion coefficient of THF ($1.7 \cdot 10^{-9} \text{ m}^2/\text{s}$) differs significantly from that of the metalated thiophene ($9.3 \cdot 10^{-10} \text{ m}^2/\text{s}$), but is still substantially lower than that of non-coordinating small molecules like hexane ($2.8 \cdot 10^{-9} \text{ m}^2/\text{s}$) (Figure 2, right). This indicates that in solutions of **2**, THF molecules partially dissociate from the lithiated thiophene structure possibly leaving Li atoms threefold-coordinated. In principle, higher thiophene aggregation would also set free THF molecules - in fact, a dimer-tetramer equilibrium is, for example, known to exist for *n*-BuLi in THF solution.

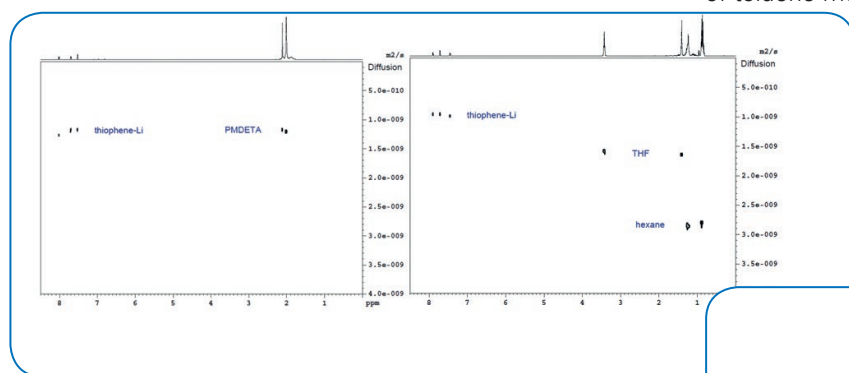


Figure 2: ^1H -DOSY spectra of $[(\text{THF})_2\text{Li}(\text{C}_4\text{H}_3\text{S})]_2$ (**2**) and $[(\text{PMDETA})\text{Li}(\text{C}_4\text{H}_3\text{S})]$ (**5**) in toluene- d_8 obtained on a Bruker Avance III HD 400 MHz NMR spectrometer and processed using *Dynamics Center* software package.

In addition, **1-5** were studied using the ^1H , ^7Li heteronuclear Overhauser effect (HOE). In this type of NMR experiment, only ^1H and ^7Li nuclear spins close in space are expected to show correlation peaks between each other. Since the crystal structures of these compounds contain several short proton-lithium distances (up to 4 \AA), cross-peaks are expected in ^1H , ^7Li HOESY spectra obtained in solution. Figure 3 depicts the ^1H , ^7Li HOESY NMR spectrum of **3** in toluene- d_8 as a representative example. In addition to the cross peaks to the neighbouring proton (H-3) of the thiophene moiety, each spectrum displays cross peaks to the

corresponding donor bases (Et₂O, THF, DME, TMEDA and PMDETA). Therefore, the solution HOESY NMR data of **1-5** is in agreement with the corresponding X-ray structures obtained in the solid state.

H...Li Distances Scaled to NOEs

Furthermore, nuclear Overhauser effect (NOE) build-up curves were recorded by varying the mixing time from 0.01 to 1.0 s. All curves feature an initial linear increase of the cross peak intensity, a maximum after approximately 0.5 s followed by a decay of the intensity at higher mixing times due to relaxation. Using the distance relation of Li...H NOE's (scales with a factor r^{-6}) allows gaining further insight in the aggregation degree of **1-5** in solution. Comparison of the slope provided by the linear region of the build-up curves and of the $(\sum r^{-6})$ calculated distances from the crystal structures offers a handle to judge on structure retention versus conversion in solution. Hereby, the structures of **3-5** are maintained in toluene solution. The data of **2**, however, indicates a partly dissociation or a rapid exchange between the vertices of a tetrameric core and free THF molecules. These observations are in agreement with the ^1H -DOSY data discussed above (Figure 2). Additional exchange spectroscopy (EXSY) investigations show that the ^1H signals of the thienyl substituents in **4** and **5** exchange to the corresponding signals of non-lithiated thiophene. This can be explained by exchange of the deuterium by a hydrogen atom via lithiation of toluene molecules followed by protonation.

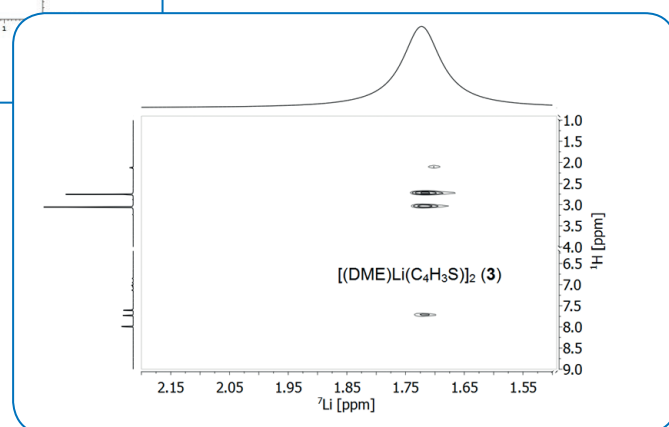


Figure 3: ^1H , ^7Li -HOESY spectrum (mixing time 0.5 s) of $[(\text{DME})\text{Li}(\text{C}_4\text{H}_3\text{S})]_2$ (**3**) in toluene- d_8 exhibiting cross-peaks between lithium and the related thienyl-moiety and the corresponding donor base, respectively. The data was recorded on a Bruker Avance III HD 400 MHz NMR spectrometer equipped with a broad-band observe probe.

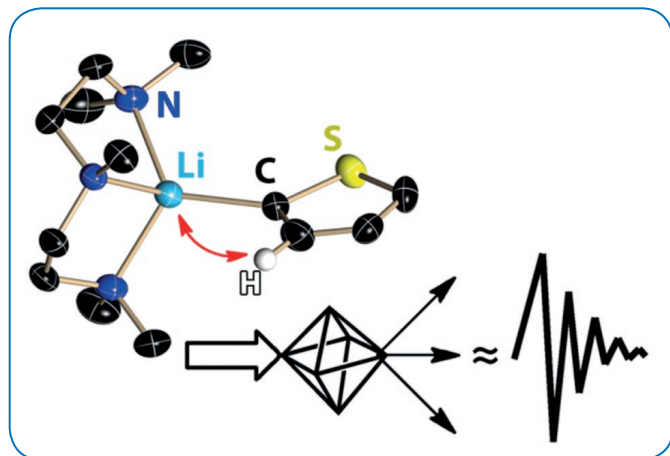


Figure 4: Li...H distances from XRD scaled to NOEs from NMR

References

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Conclusion

In conclusion, the combined approach of using both X-ray diffraction and NMR techniques allows insights to be gained into the similarities as well as the differences between the solid state and solution structures of these 2-thienyllithium derivatives (Figure 4). Bruker is well positioned to at providing optimal solutions for both applications.

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