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Fibre optic ATR-IR spectroscopy at cryogenic temperatures: in-line reaction monitoring on organolithium compounds†

Daniel Lumpi,*[a] Christoph Wagner,[b] Matthias Schöpf,[a] Ernst Horkel,[a] Georg Ramer,[b] Bernhard Lendl[b] and Johannes Fröhlich*[a]

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A reliable methodology, utilising an ATR-IR fibre probe, for in-line monitoring of low temperature reactions is presented. The application of this convenient set-up enables a fast and safe exploration of highly reactive substrates. Hence, *in situ* monitoring of lithiation reactions is realised and the potential to investigate sensitive intermediates is being demonstrated.

Reaction conditions in synthesis are commonly optimised using off-line methods to determine operation parameters.[1] However, on-line or especially in-line methods such as time resolved spectroscopy can provide highly relevant information for process optimisation and scale-up.[1] Still, dynamic reaction analysis in order to monitor highly reactive species at low temperatures (*e.g.* lithiation chemistry) remains a challenging task.

Organolithium compounds gained outstanding importance as powerful reagents and key intermediates in organic synthetic chemistry.[2] Therefore, since the discovery by Schlenk and Holtz,[3] lithiation chemistry has grown into a well established technique also receiving attention in modern industrial synthesis.[4] As a consequence of the highly reactive intermediates such lithiation reactions are generally performed at low temperatures of approximately −60 to −80 °C, in some cases even below −100 °C.[2]

Encouraged by recent studies,[5] a mid-IR fibre optic probe comprising an attenuated total reflection (ATR) element was selected for a fast and safe in-line monitoring of lithiation reactions. The major advantage of this *in situ* technique *versus* off-line approaches is that monitoring takes place inside the reaction system, thus eliminating risks of sample alteration during probing. This method proved to be a versatile and effective tool to explore intermediates at elevated temperatures,[6] however, to the best of our knowledge, no examples of applications towards reactive metal halogen (inter-)exchange reactions at cryogenic temperatures have been reported up to date.

In this contribution a reliable methodology in order to realise probe applications at cryogenic temperatures is being developed. The demonstrated investigations on organolithium intermediates outline their potential impact on routine synthetic steps and also to derive kinetic data of highly complex multi-step reactions suitable for mechanistic considerations.

A key challenge in spectroscopic measurements in reaction mixtures at cryogenic temperatures is that dynamic processes can easily lead to the sample spectra being acquired at substantially different temperatures than the background. Applying the aforementioned mid-IR fibre optic probe exothermic effects, and also simple reactant addition in the course of the synthesis, resulted in spectra heavily overlaid with (co-)sine-type artifacts, rendering the acquired spectra useless for detailed interpretation.

These artifacts are attributed to differing thermal expansion coefficients of the probe material and the diamond ATR crystal and probably represent a common problem preventing the application of IR monitoring in fast dynamic processes at low temperature. Various standard correction approaches[7] were applied to reduce these fringes, but none yielded satisfactory results. Thus, a dedicated procedure based on Fast Fourier Transformation (FFT) was developed and implemented to the data evaluation process. In this approach the correction was realised by applying an FFT on the recorded spectra, which deconvolutes the data into a linear combination of sine and cosine functions of different frequencies. To remove the introduced artifacts the Fourier coefficients of the corresponding low frequencies were set to zero. After an application of this high pass filter and retransformation by inverse FFT, the fringes in the spectra were significantly reduced.

The number of removed Fourier coefficients can be adjusted individually, depending on the encountered temperature differences for each spectrum specifically. Errors in absorption and frequency values observed during the FFT correction as well as further information and limitations of this strategy are given in the ESI.† Applying the FFT filter rendered it possible to acquire reliable IR spectroscopic data of organolithium compounds during reaction progress at temperatures even below −80 °C covering a spectral range from 600 to 1800 wavenumbers.

To follow the formation of organolithium species, integrated values (areas) under strong non-interfered absorption bands were evaluated subsequently to the FFT correction.[8] As a first step the metal halogen exchange reaction on aryl halides was investigated as mentioned above.[8] The results show very high

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[a] *Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163-OC, 1060 Wien, Austria. E-mail: daniel.lumpi@tuwien.ac.at, johannes.froehlich@tuwien.ac.at; Fax: +43 1 58801 154 99; Tel: +43 1 58801 163 719*
[b] *Institute of Chemical Technologies and Analytics, Vienna University of Technology, Getreidemarkt 9/164-AC, 1060 Wien, Austria*

† Electronic supplementary information (ESI) available: Experimental details, additional information regarding the FFT correction procedure and the double-sided halogen dance reaction as well as spectral data. See DOI: 10.1039/c2cc16016a

reaction rates in THF at −86 °C reaching a steady state in the phenyllithium concentration within 1.0 min for bromobenzene, and within 30 s when using iodobenzene.[8] In comparison, protocols published in the recent literature report reaction times of 30–60 min for bromobenzene and *n*BuLi in THF at −78 °C.[9] This clearly illustrates the potential to effectively optimise reaction times also in relatively fast processes under cryogenic conditions. Metal halogen exchange reactions investigated on bromothiophene derivatives are presented in the ESI.†

Slower lithiations were observed using Et_2O as the solvent, yielding no reaction of bromobenzene and a significantly lower reaction rate for iodobenzene at −86 °C (Fig. 1). Consequently, an increase in the reaction temperature also yielded good results for the FFT method. In Et_2O at −40 °C bromobenzene is consumed relatively slowly; in contrast the reaction of iodobenzene is accomplished in less than 1.0 min. Reasonable conversion rates of bromobenzene in Et_2O could be observed at 2 °C (state of equilibrium: ~1400 s). These results correspond to data previously reported at various temperatures or by applying other techniques (*e.g.* rapid-injection NMR[10]).[2] The significant temperature dependence of reaction rates clearly points out the importance of in-line monitoring, as both sampling and standard bypass approaches cannot ensure constant thermal conditions in the course of analysis, thus leading to erroneous readings—especially when directly compared to the actual (batch) process. In contrast the application of IR probe spectroscopy allows monitoring of highly sensitive reactants both *in situ* and in real-time.

The Halogen Dance (HD) reaction[11] represents a powerful tool, especially in heterocyclic chemistry, to reliably achieve specific substitution patterns. In a preliminary study we intended to clarify the influence introduced by the migrating halogen on the lithiation. Therefore, the activating effects of the bromine group on the metallation reaction of thiophene moieties were studied for a lithium diisopropylamide (LDA) induced lithiation of 2- and 3-bromothiophene, respectively (Scheme 1).

As obvious from Fig. 2 a strong activating effect of the bromine was determined. In THF at −86 °C no reaction progress could be observed on thiophene; in comparison using 2- and 3-bromothiophene good conversion rates were detected. This highly increased reactivity exerted by inductive effects of the halogen substituent is surprising especially in the case of 2-bromothiophene; the faster conversion of 3-bromo- compared to 2-bromothiophene is attributed to a stronger inductive effect of the bromine substituent in the *ortho*- compared to the *para*-position. Metallation of thiophene in THF was observed at −40 °C.

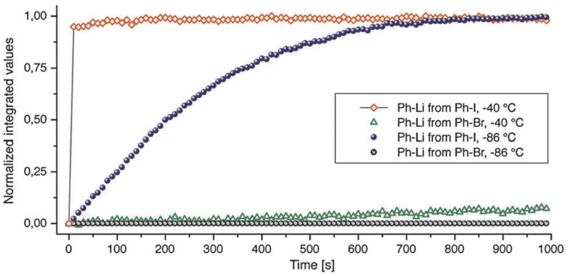
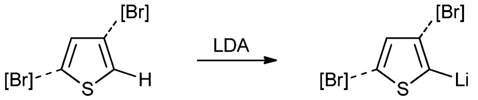


Fig. 1 Metal halogen exchange reaction of bromo- and iodobenzene at different temperatures (*n*BuLi, −86 °C and −40 °C, Et_2O).



Scheme 1 Investigation on activating effects; metallation reactions using LDA on (bromo-)thiophene derivatives.

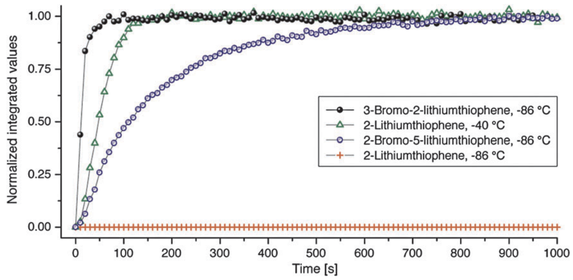
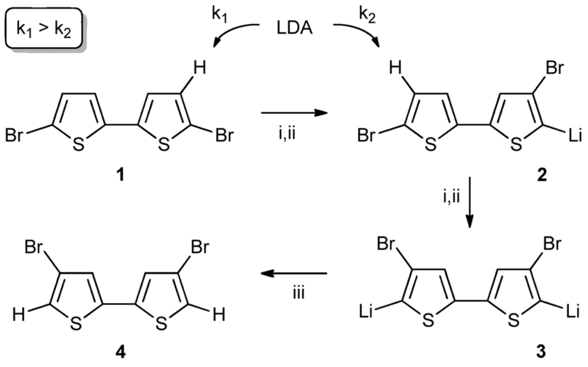


Fig. 2 Effects of activating halide groups on thiophene moieties in metallation reactions using LDA at −86 °C and −40 °C (solvent: THF).

In previous work we examined halogen migrations on 5,5′-dibromo-2,2′-bithiophene focusing on the selectivity of double- *vs.* single-sided HD reactions (Scheme 2). In this multi-step sequence the first metallation and the HD are expected to proceed faster, leading to accumulation of **2** before the second lithiation towards **3** occurs.[12] However, kinetic data of the *in situ* formation of **2** during a double-sided Halogen Dance are of great value for synthetic aspects and possible application of this reaction.

By in-line ATR-IR monitoring, again applying FFT correction, the accumulation of **2** can be clearly observed (Fig. 3A). With the results indicating a very good agreement of the time constants (31.8 s for LDA *vs.* 31.1 s for **2**), the comparison of the kinetic parameters of LDA consumption and intermediate formation confirms the formation of **2** as being the first step in the sequence (Fig. 3B). This proves that in the first reaction step LDA is exclusively consumed to form **2**; the second HD is realised in a next step leading to **3**. Complementarily,[8] we investigated the ratio of single- and double-sided HD (**2** and **3**, respectively) depending on the amount of LDA *via* NMR spectroscopy, supporting the assumption (Scheme 2) of the metallation being the rate determining step in this HD reaction; the migration of the halogen proceeds relatively fast (no accumulation of 3-lithiothiophene species, for details see ESI†).

Accessing kinetic parameters for the formation of intermediate **3** required multivariate data analysis due to overlapping of absorption bands of **3** (~1017 cm^{-1}) with an LDA absorbance



Scheme 2 Double-sided Halogen Dance reaction on 5,5′-dibromo-2,2′-bithiophene utilising LDA (2.5 equiv.) at −40 °C. (i) Metallation reaction, (ii) Halogen Dance reaction, (iii) excess of methanol.

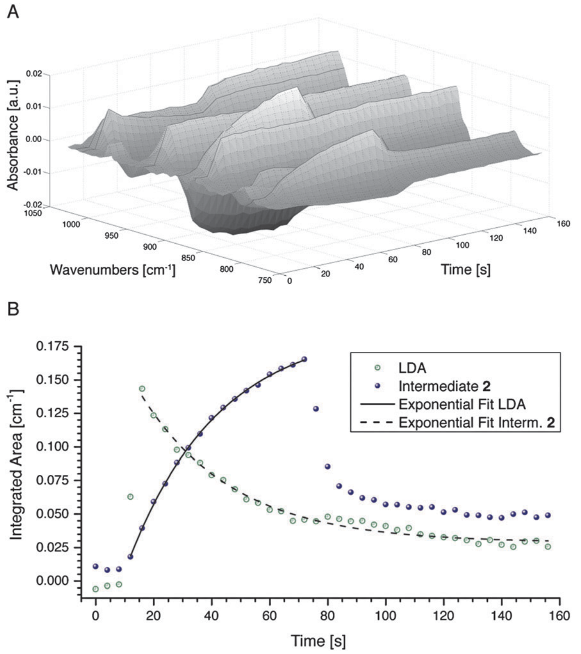


Fig. 3 In-line IR sensor spectra during the double-sided Halogen Dance reaction (−40 °C, $t = 0$ s: **1** already included, $t = 12$ s: LDA addition); (A) 3D plot of spectra (750–1050 cm^{-1}) recorded during reaction progress (0–160 s), (B) monitoring of Li-species LDA and intermediate **2**; exp. fit LDA (τ_1: 31.8 s, R^2: 0.99), exp. fit **2** (τ_1: 31.1, R^2: 0.99).

at ~1008 cm^{-1}. Hence, multivariate curve resolution using alternating least squares (MCR-ALS)[13] algorithm was applied to the spectral data set (Fig. 3A). This method decomposes the data into species spectra and their corresponding concentration profiles. Fig. 4 shows the result of the MCR-ALS analysis for intermediate species **2** and **3** including bi-exponential fits to the data points. The results again outline the good match of kinetic parameter between the consumption of **2** and the formation of **3**, approving the aforementioned conclusions. Moreover, the good agreement of data in the first reaction step between integrated areas (Fig. 3B) and the MCR-ALS algorithm (Fig. 4) underlines the applicability of this multivariate tool.

Summarising, a reliable methodology enabling successful monitoring of reactions under cryogenic conditions in real-time is presented. It was shown that this in-line technique utilising an FFT correction procedure is suitable for a convenient and safe exploration of (hetero-)aromatic lithium compounds. In addition, the possibility to disclose kinetic data, also of sensitive reaction intermediates, was demonstrated to be an important factor for *e.g.* mechanistic considerations or process optimisation.

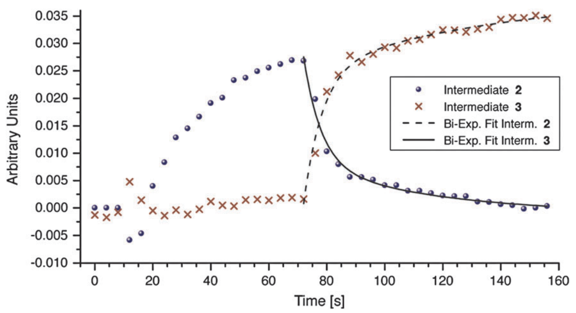


Fig. 4 Intermediate **3** formation as extracted from the spectral data set *via* MCR-ALS algorithm; bi-exp. fit **2** (τ_1: 6.9 s, τ_2: 2.5 × 10^{-6} s, R^2: 0.98), bi-exp. fit **3** (τ_1: 6.8 s, τ_2: 3.3 × 10^{-6} s, R^2: 0.98).

In conclusion not only information about lithiation reactions is presented but also a methodology, based on an FFT procedure, for an effective reaction monitoring at cryogenic temperature widely applicable in the field of chemistry is developed. This is in particular true since mid-IR fibre optic probes are nowadays commercially available.[14] Potential applications in the field of organic synthetic chemistry are widespread; for example aromatic substitution, oxidation and selective hydrogenation as well as reactions of sensitive substrates in general are of great interest concerning investigations at low temperatures. Furthermore, the compatibility to heterogeneous reaction mixtures, high pressure conditions and biotechnological applications expands the scope of this technique.

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