Effective Reaction Monitoring of Intermediates by ATR-IR Spectroscopy Utilizing Fibre Optic Probes

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1. Introduction

The use of reaction monitoring in order to determine operation parameters in organic synthesis and pharmaceutical chemistry still commonly relies on off-line approaches. However, application of on-line or in particular in-line methodologies provides highly valuable data with respect to process optimization and scale-up (Bakeev, 2005; Rubin et al., 2006). This statement is especially true for time-resolved spectroscopic *in-situ* techniques, which allow to gain insights into key intermediate formation or structures, and therefore also provide valuable information for mechanistic considerations (Minnich et al., 2007; Wiss et al., 2006).

One of the major advantages of in-line techniques (both *in-situ* and real-time) over off-line approaches is that the investigation occurs inside the reaction system, thus eliminating sample alterations prior to analysis. These alterations during probing, including the loss of inertness or changes of reaction conditions, may result in erroneous readings; especially when directly compared to the (batch) process. This dramatically affects investigations at low temperatures. Both sampling and standard bypass approaches, which do not ensure constant thermal conditions in the course of analysis, potentially lead to incorrect results. For obtaining real-time information on chemical composition of samples in gas, liquid or solid phase, mid-infrared (IR) spectroscopy proved to be highly versatile, especially when performed with the attenuated total reflectance (ATR) technique (Grunwaldt & Baiker, 2005; Marziano et al., 2000; Minnich et al., 2007; Zogg et al., 2004).

In this chapter, we focus on in-line monitoring of both highly sensitive and reactive organic key intermediates (reagents) by mid-IR fibre probes based on the ATR technique (Fig. 1). At first, we give a short introduction to mid-IR spectroscopy (also briefly commenting on alternative spectroscopic methods), outline advantages of IR fibre optics as well as ATR technologies and provide a brief overview of fibres suitable for mid-IR fibre applications. The last part is intended to introduce the interested reader to fibre-optic probes available and typical characteristics, referring to literature about chemical and physical properties of modern IR fibre materials, showcasing potential areas of application.

Fig. 1. Mid-IR fibre and ATR probe (left) and IR probe focused on the ATR element (right).

In the second part, we report on recent results of in-line investigations successfully utilizing mid-IR fibres on organometallic species. Hence, explorations on the formation of sodium alkoxy intermediates (performed in our group, Lumpi et al.) and their impact on reaction optimizations towards monodisperse oligo (ethylene glycols) are outlined. Subsequently, we switch to monitoring of organolithium compounds. In these projects Weymeels et al. as well as Gupta et al. were able to demonstrate ATR-IR fibre probe applications on metallation reactions and Lumpi et al. on metal halogen exchange reactions under cryogenic conditions.

2. Monitoring by mid-infrared spectroscopy

Spectroscopy in the mid-infrared of a spectral range from approximately 4000 cm^{-1} to 400 cm^{-1} (2.5 µm to 25 µm) emerged as an effective tool for both qualitative and quantitative analysis. Within this range most of the fundamental molecular vibrations, the first overtones and combination frequencies occur. These typically relatively sharp absorption bands generally possess high absorption coefficients. Not only do these desirable spectroscopic properties facilitate an identification of molecules by its specific spectral "fingerprint", but also comprise valuable structural information (e.g. functional groups, substitution patterns, etc.) (Melling & Thomson, 2002).

The distinctive absorption bands associated with individual molecules enable the analysis of individual components in even complex mixtures by either evaluating isolated bands or by applying modern chemometric methods (e.g. Principal compound analysis), which process the entire spectral information. As a consequence, mid-IR spectroscopy represents a widely applicable tool for investigations of dynamic processes (e.g. chemical reactions, phase transitions, sedimentations, etc.). Moreover, information about interactions of the analyst with the surrounding media can be acquired because vibrational modes tend to be affected by the molecule's environment (Raichlin & Katzir, 2008).

Therefore, from many perspectives, mid-IR spectroscopy provides clearly more information than spectroscopy in other regions of the spectrum, such as the visible or the near-infrared range (Raichlin & Katzir, 2008).

2.1 Mid-infrared optical fibre probes

Modern-technology fibre optics offers important and versatile tools in spectroscopy. In the field of vibrational spectrometry fibre optics had a great influence on near-IR and Raman spectroscopy. The development of mid-IR transparent fibres (discussed in chapter 2.3) in the last decades had a significant impact on IR methods (Lendl & Mizaikoff, 2002). The fibre application makes it possible to overturn the established method of analyzing samples

within the typically stationary IR spectrometer by enabling the direct placement of the fibre-optic probe inside the reaction system of interest (Melling & Thomson, 2002).

The technologies of mid-IR spectroscopy providing highly relevant physico-chemical information, and the flexibility of fibre-optic probes offering new possibilities of application to measure samples in gas, liquid and solid phase, result in a breakthrough in molecular spectroscopy. Nowadays, spectroscopy utilizing IR fibre probes is routinely used in research laboratories, process development facilities and industrial quality control. This routine application can be explained by the fact that data, often not available by other methods, can be conveniently acquired (Melling & Thomson, 2002).

Additionally, ATR-based mid-IR fibre optic probes represent an entirely non-invasive technique, which has recently been shown to be a promising tool e.g. for biotechnological applications (Mazarevica, 2004) and, even more impressively, for obtaining spectroscopic information *in vivo* (Brancaleon et al., 2000).

In principle, the sensor constructions rely on five basic sensing schemes: transmission, reflection, grazing angle reflection, attenuated total reflection (ATR), and a variant of the ATR effect known as the fibre-evanescent wave sensor (FEWS) (Melling & Thomson, 2002). The investigations described in chapters 3 and 4 are based on the use of the ATR technique, focusing on its advantageous properties, especially in terms of mechanical robustness.

2.2 Attenuated total reflection

The majority of reported mid-IR fibre probes rely on the well-established attenuated total reflection (ATR) technique, revealing many advantages in the general applicability over e.g. absorption measurements in short pathway flow cells. In the ATR method only a thin film (a few micrometers) at the proximity of the ATR element is subject to the measurement. The thickness of the analyzed film is defined by the penetration depth of the evanescent field (Fig. 2).
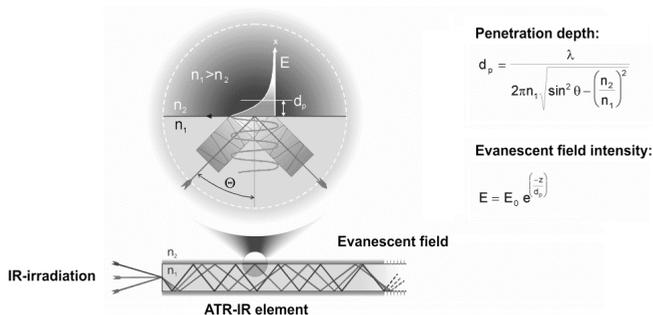

Penetration depth:

$$d_p = \frac{\lambda}{2\pi n_1 \sqrt{\sin^2\theta - \left(\frac{n_2}{n_1}\right)^2}}$$

Evanescent field intensity:

$$E = E_0\, e^{\left(\frac{-z}{d_p}\right)}$$

Fig. 2. Principle of total reflection of an infrared beam at the boundary of the ATR element to a medium with lower refractive index $n_2 < n_1$ (n_1, n_2, refractive indices; θ, angle of incidence; E, exponentially decaying evanescent field; d_p, penetration depth; λ, wavelength of incident radiation). Figure reproduced from Mizaikoff & Lendl, 2002.

The interactions of the incident and the internally reflected electromagnetic waves generate an exponentially decaying evanescent field, which penetrates the adjacent medium to a

certain depth. The depth of penetration depends on the irradiation wavelength, the incident angle and the refractive indices of both the ATR element and the contact medium. The equations describing this behavior are given in Fig. 2 (Mizaikoff & Lendl, 2002).

2.3 Infrared transparent fibres

This chapter gives a brief insight into the most important, for the main part commercially available, IR fibre optics. Detailed reviews on IR fibres are given in the literature by J.A. Harrington (Harrington, 2010) and, with a special focus on mid-IR applications by B. Lendl and B. Mizaikoff (Lendl & Mizaikoff, 2002).

The basic requirements for mid-IR fibres include physical properties such as transparency over the spectral range requested for the intended investigations, robustness (mechanically), stability (thermally and chemically) as well as adequate flexibility (Lendl & Mizaikoff, 2002). The characteristic of the optical transparency is typically evaluated by focusing on relevant loss mechanisms. The most important losses include intrinsic and extrinsic losses, Fresnel losses and bending losses (Sanghera & Aggarwal, 1998, as cited in Lendl & Mizaikoff, 2002). Available mid-IR fibre optics meet these challenges to different extents.

First developments on non-silica based IR transparent fibres from chalcogenide glasses, mainly arsenic sulphide, were published in 1965, exhibiting losses higher than 10 dB/m (Kapany & Simms, 1965, as cited in Harrington, 2010). Due to an elevated demand for IR fibres in short-haul applications increased research efforts were reported from the mid-1970s onwards (Harrington, 2010). Up to date, both optical and mechanical characteristics of IR fibres cannot compete with silica fibres (which are not applicable in the mid-IR region due to a transmission only up to approximately 2.5 µm). Losses in the range of a few decibels per meter still limit these to short-haul applications. Nevertheless, modern mid-IR fibres for short-haul have already enabled a broad variety of developments in spectroscopy and important usage in practical (e.g. medical) applications (Minnich et al., 2007, and references therein).

A logical categorization of the most important IR fibres can be illustrated as follows: glass, crystalline and hollow waveguides. Table 1 outlines this categorization also providing further subdivision based on materials and structures (Harrington, 2010).

Main	Subcategory	Examples
Glass	Heavy metal fluoride (HMFG) Germante Chalcogenide	ZrF_4-BaF_2-LaF_3-AlF_3-NAF (ZBLAN) GeO_2-PbO AsS_3 and AsGeTeSe
Crystal	Polycrystalline (PC) Single crystal (SC)	AgBrCl Sapphire
Hollow waveguide	Metal/dielectric film Refractive index <1	Hollow glass waveguide Hollow sapphire at 10.6 µm

Table 1. Categories of the most important of IR fibers; data reproduced from Harrington, 2010.

A graphical comparison of attenuation losses of the most relevant mid-IR fibres is given in Fig. 3. Among these, materials suitable for optic chemical sensor applications in liquid phase
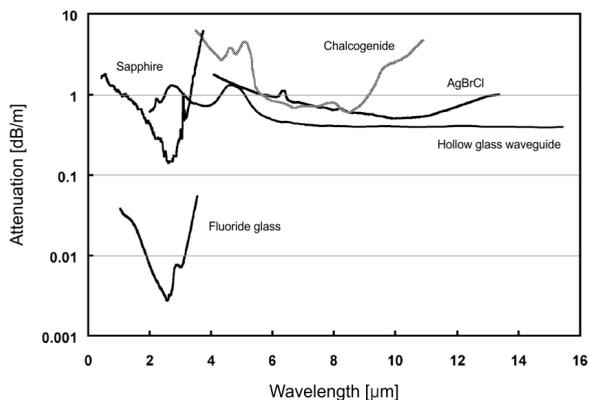
Fig. 3. Composite loss spectra for some common IR fibre optics: ZBLAN fluoride glass , SC sapphire, chalcogenide glass, PC AgBrCl, and hollow glass waveguide; plot reproduced from Harrington, 2010.

(e.g. reaction mixtures), relying on the evanescent wave principle, are AgBrCl, sapphire, chalcogenide and HFMG (Harrington, 2004). Polycrystalline silver halide fibres have been shown to be a promising candidate for mid-IR (ATR) fibre probes, especially for measurements at wavelength > 10 µm (Brandstetter, 2009).

The combination of the flexible structure and IR transmission of AgBrCl fibres ensures a convenient analytical approach; thus, also being applied in investigations presented later in this chapter.

2.4 Alternative spectroscopic methods for reaction monitoring

Besides IR spectroscopy, RINMR (rapid injection nuclear magnetic resonance) experiments also received considerable attention in the field of spectroscopic investigations of highly reactive species, especially under cryogenic conditions. The RINMR methodology, often based on the developments of J. F. McGarrity (McGarrity, 1981), C. A. Ogle and H. R. Loosli was successfully applied by several research groups to investigate reactive intermediates also at low temperatures and short time scales. In contrast to conventional NMR studies the rapid injection design relies on a piston-driven syringe injection assembly above the vessel inside the bore of the spectrometer magnet. This setup simultaneously provides turbulent mixing in the sample. In their first studies McGarrity et al. could establish that butyllithium in THF exists in equilibrium of the tetramer and the dimer complex with the proportion of dimer increasing as the temperature is decreased (McGarrity, 1985a). Moreover, kinetic examination proved that the dimeric butyllithium is more reactive toward the applied electrophiles than the tetramer by a factor of 10 (McGarrity, 1985b). Improved designs of RINMR systems implementing features such as multiple reactant and faster rapid injection were developed in the last decade by P. J. Hore et al., H. J. Reich et al. and S. E. Denmark et al.

In conclusion, RINMR is a powerful tool for monitoring reactive intermediates, directly providing highly relevant structural data. However, the experimental complexity of this technique, in contrast to ATR-IR fibre probe applications, certainly limits its versatility.

2.5 Reaction monitoring of organometallic compounds

As mentioned before, the scientific results discussed in this contribution focus on monitoring of reactive organometallic species by ATR-IR spectroscopy utilizing mid-IR fibre probes. While alkoxide species, the conjugated base of an alcohol, are rather generally applied in synthetic chemistry (e.g. bases, nucleophiles and ligands) organolithium compounds require further introduction.

Since W. Schlenk and J. Holtz reported on the first syntheses of organolithium species in 1917 these powerful reagents or intermediates have gained enormous importance in the field of synthetic and pharmaceutical chemistry (Rappoport & Marek, 2004; Wu & Huang, 2006). Synthetic operations are generally carried out at low temperatures as a consequence of the high reactivity of lithium reagents; in some specific examples even below -100 °C (Rappoport & Marek, 2004). Nowadays, modern lithiation chemistry represents a well-established technique also receiving considerable attention in industrial processes (Rathman & Bailey, 2009; Wu & Huang, 2006). Despite the broad application of cryogenic temperature reactions dynamic analysis in order to monitor reactive lithium species remains a challenging task.

3. *In-situ* IR monitoring of alkoxides

In this chapter, we focus on monitoring the formation of alkoxides, as this is an important intermediate for the synthesis of ether and ester containing substances. The conventional approach is to transform deprotonated moieties, followed by classical analytical methods (e.g. thin layer chromatography, HPLC or NMR spectroscopy). There are only limited descriptions of in-line methods in the literature, therefore an investigation is of high interest.

3.1 Introduction

A study (Lumpi et al., 2009) is presented in detail, where the usage of in-line ATR-IR was demonstrated in order to optimize the synthesis of monodisperse oligo(ethylene glycols) (OEG). This substance class has a wide range of applications in many fields of science and industry. They can be used as synthons for crown ether-type derivatives, as non-ionic surfactants, as templates for the synthesis of porous inorganic materials, and, more recently, functional mono-layers were applied to develop biocompatible material. The physical and chemical properties of these modified materials often depend to a large extent on the number of repetition units of the OEG moiety. For a systematic investigation of the influence of chain length, novel polystyrene-oligo(oxyethylene) graft copolymers containing monodisperse OEG units have been synthesized (Braunshier et al., 2008). For the preparation of these resins, access to well-defined oligo(ethylene glycols) of up to 12 units was required. Despite the widespread utility of OEGs, their synthesis remains a challenging task. The published synthetic methods for commercially unavailable or expensive representatives (n>4) are usually time-consuming and/or include extensive purification procedures. The most efficient strategy for synthesis of OEGs is based on bidirectional chain elongation (Keegstra et al., 1992).

Based on this approach, the key steps should be optimized in order to shorten reaction times from periods as long as several days to more acceptable values. The formation of corresponding alkoxides by deprotonation of mono-trityl protected glycols **1a-b** (first

1a-b: k=2,4   **2a-b**: m=2,4   **3a-d**: n=6,8,10,12
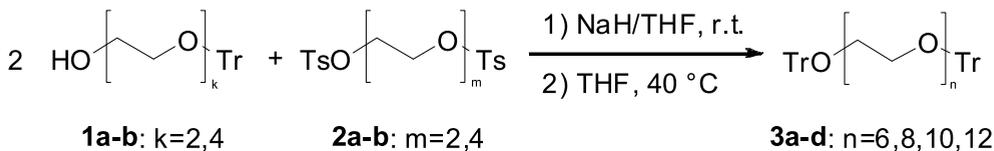
Scheme 1. Synthesis of glycols **3a-d**. Scheme reproduced from Lumpi et al., 2009.

reaction step shown in Scheme 1) is reported to take at least 18 h to reach completion. To prove this information, it was necessary to monitor the conversion in an inert, anhydrous reaction medium. Due to the lack of other proper methods of analysis, a mid-IR fibre optic probe was chosen for fast in-line monitoring of the chemical reaction under investigation.

3.2 Technical details

The ATR fibre system was built up by a FT-IR spectrometer Bruker Matrix F® in connection with an ATR fibre probe (A.R.T. Photonics, Berlin; Ø 12 mm) and a MCT (mercury cadmium telluride) detector (Belov Technology, Co., Inc.). The probe was directly inserted through the ground neck of the reaction vessel and comprised two 1 m silver halide fibres (Ø 1 mm) connected to a conical two bounce diamond ATR element housed in a rod of hastelloy. Using this set-up it was possible to follow the reactions to be studied in real-time covering a spectral range from 600 to 2000 wavenumbers.

3.3 Inline monitoring

Two possibilities for the analysis of the obtained data have been applied. Single band analysis on the one hand, and multivariante curve resolution on the other hand.

3.3.1 Single band analysis

Determination of reaction progress by tracking changes in absorbance values at selected wavenumbers is described. Absorbance values at characteristic wavenumbers for the substrate and the product respectively are plotted against reaction times in Figure 4.
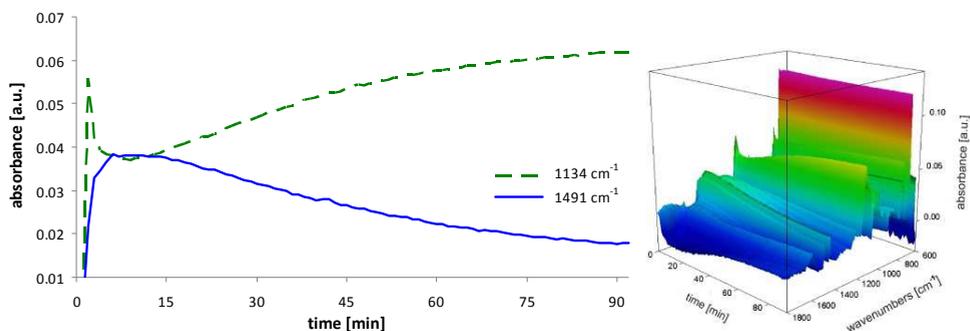

Fig. 4. (a) Left: ATR-IR in-line monitoring for the deprotonation of 13,13,13-triphenyl-3,6,9,12-tetraoxatridecanol (substance **1b**). Distortions for t ≤ 10 min are attributed to equilibration effects (temperature and concentration). (b) Right: Representative 3-D example of measurement. Figure reproduced from Lumpi et al., 2009.

The blue curve derives from the starting alcohol; the green graph originates from the deprotonated moiety. The graph clearly shows that after 90 min no significant changes of absorption values can be observed, thus being an indication for the end of the reaction.

3.3.2 Multivariate curve resolution

Multivariate curve resolution – alternating least squares (MCR-ALS) – was additionally applied for the analysis of the IR data set. MCR-ALS is a modern chemometric method for the resolution of multiple component responses in unknown unresolved reaction mixtures (Tauler, 1995). This technique decomposes the recorded data set into smaller matrices containing information on the spectra and the concentration profiles of each component involved in the reaction. MCR-ALS can be applied to the analysis of a global instrumental response such as a set of mid-IR spectra recorded from a chemical reaction over time. In this case a matrix D (n x w) is obtained with n being the number of spectra and w representing the number of wavelengths. The MCR technique has the target to decompose D into the pure contributions of the components of the reaction according to the equation:

$$D = CS^T + E \qquad (1)$$

C contains the concentration profiles for all involved compounds and S^T represents the corresponding spectra. MCR-ALS solves this equation in an iterative, alternating least squares manner by minimizing the residual matrix E. For the MCR analysis the data matrix D may be augmented with pure component spectra. Furthermore, several data sets may be analyzed simultaneously. During calculation meaningful constraints may be applied with the aim to guide the iteration process toward a mathematically as well as chemically meaningful solution.

Despite all advantages, MCR-ALS algorithms written in MATLAB have the disadvantage of how the selected constraints are implemented in the execution of the MATLAB routine. This process can be troublesome and sophisticated, particularly in complex cases where several data matrices are simultaneously analyzed and/or different constraints are applied. In order to overcome these difficulties and taking advantage of the better MATLAB tools to create graphical user interfaces, an improved MCR-ALS toolbox with a user-friendly graphical interface was presented by Jaumont et al., 2005.

Examples for meaningful constraints in the chemical system under investigation in the paper by Lumpi et al., 2009 are non-negativity of concentrations and spectral intensities as well as unimodality. As a result, quantitative information on the amount of spectral contribution of each component in every spectrum of the data set is obtained. 99.72 % of the spectral variance of the recorded data could be explained with two components. Therefore it was concluded that the two components needed to be considered in modeling the data set, as shown in Figure 5. The reaction under study came to completion after 90 minutes.

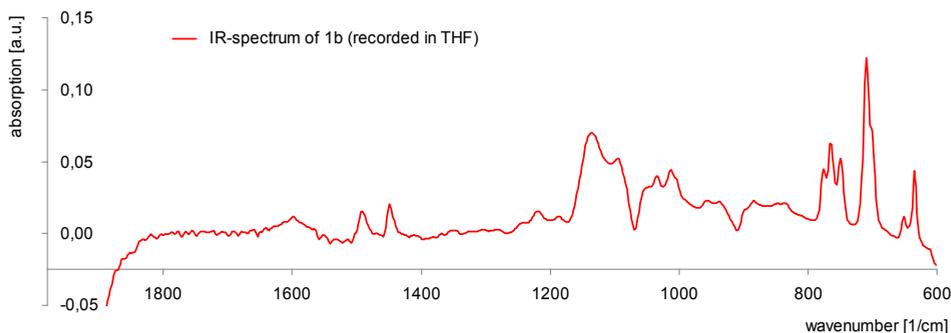### 3.4 Results and discussion

Both techniques for IR data analysis presented, showed clearly that time for deprotonation is much shorter than described in the literature. The subsequent nucleophilic reaction of the alkoxides with the tosylated glycols **2a-b** lead to substances **3a-d**.
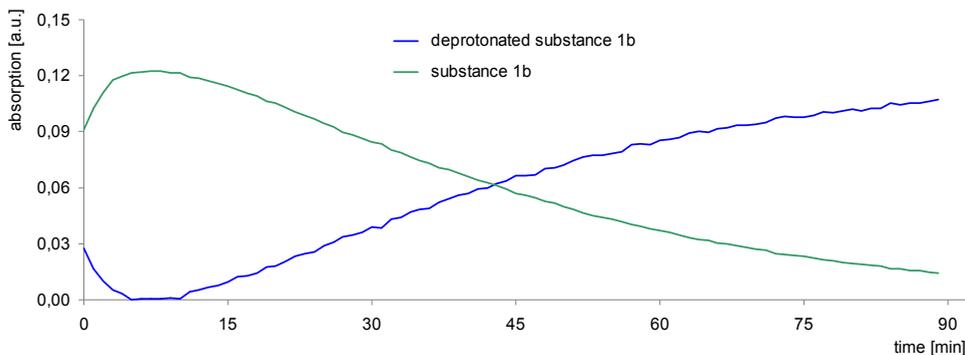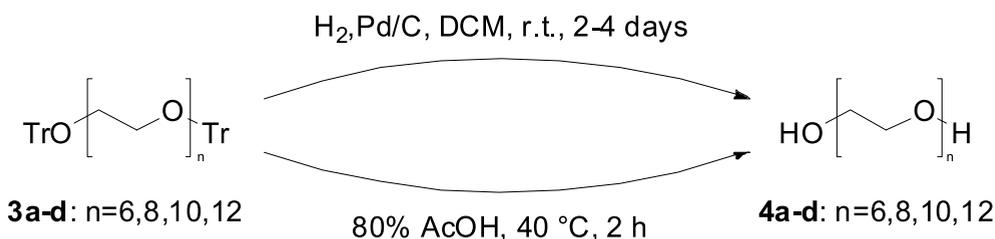
(a)
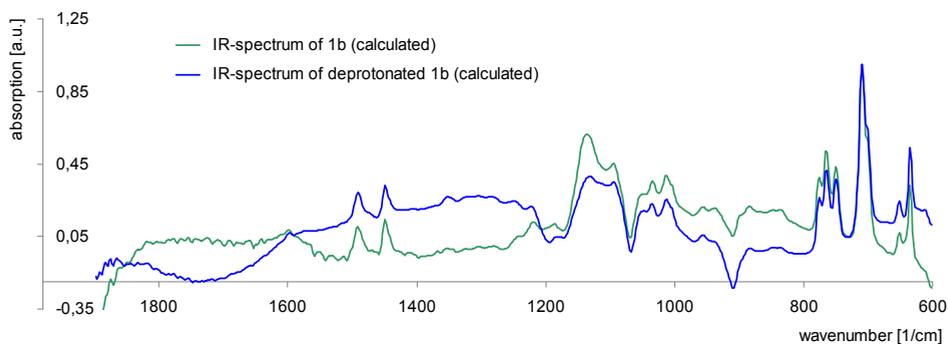
(b)

(c)

Fig. 5. MCR-ALS calculations of the deprotonation of trityl-protected 1b; (a) calculated absorption profiles, (b) spectra calculations, (c) pure substance 1b spectrum. MCR-ALS-Parameters: [efa_matrix]=efa(dep10,90); min value of log efa plot=1; number of factors=2; als2004; Data matrix=dep10; Init estimate=efa_matrix; Non negative Concentration nnls; number of spec with non neg=2; spec equal height; Plots are optimum in the iteration Nr. 935 Std.dev of residuals vs. exp. data=0.0011238 Fitting error (lack of fit, lof) in %(PCA)=2.8319e-014 Fitting error (lack of fit, lof) in %(exp)=4.881 Percent of variance explained at the optimum is=99.7618. Figure reproduced from Lumpi et al., 2009.

Entry	Glycol	Tosylate	Time	Product	Yield
	1	2	h[a]	3	%
1	**1a**	**2a**	4/84	**3a**	98
2	**1a**	**2b**	4/84	**3b**	97
3	**1b**	**2a**	2/60	**3c**	98
4	**1b**	**2b**	2/60	**3d**	95

Table 2. Reaction times and yields for the preparation of substances **3a-d**. [a]Times given refer to deprotonation and overall reaction time respectively. Modified from Lumpi et al., 2009.

To obtain the target compounds (OEGs **4a-d**), the protecting groups have to be cleaved off. Virtually all published procedures use hydrogenolysis under high-pressure conditions in the presence of palladium for several days to achieve this final transformation. Apart from long reaction time, this procedure suffers from some more disadvantages. The most serious one is the need for equipment allowing to perform gas reactions under high pressure, which might be a limiting factor. Moreover, the use of halogenated organic solvents, e.g. dichloromethane and transition metal catalysts, might become troublesome, if the final product is intended to be used in the field of pharmaceutics or biology, especially when the procedure is performed on industrial scale.

H_2,Pd/C, DCM, r.t., 2-4 days

TrO$\left[\right.$O$\left.\right]_n$Tr

3a-d: n=6,8,10,12

80% AcOH, 40 °C, 2 h

HO$\left[\right.$O$\left.\right]_n$H

4a-d: n=6,8,10,12

Scheme 2. Synthesis of glycols **4a-d**; hydrogenolysis *vs*. acidic cleavage. Scheme reproduced from Lumpi et al., 2009.

In the work presented, this deprotection step was substituted for a safe, fast and inexpensive procedure. Acidic cleavage by acetic acid in water for only 2 h was performed to obtain the pure OEGs. Comparing this new protocol to hydrogenolysis, the advantages are the following: dramatically shortened reaction times (2 h *vs*. 4 days), easier work-up and higher product quality. In summary, an optimized protocol for the synthesis of monodisperse OEGs up to 12 units has been reported. In contrast to other approaches described in the literature, neither special equipment for high pressure hydrogenolysis nor any chromatographic purification is needed for the key steps of the sequence. In-line ATR-IR spectroscopy was shown to be a powerful analytical tool for the effective monitoring of such "problematic" processes.

4. *In-situ* monitoring in organolithium chemistry

4.1 Introduction

In this chapter, we describe monitoring in organolithium chemistry, one of the most important fields within organic synthesis, especially for the functionalization of

heteroaromatic substances. They are applied in many fields of chemistry, either for pharmaceuticals or as building blocks for various applications within materials science, e.g. in Organic Light Emitting Transistors (OLET). As a matter of fact, extensive efforts have been applied to a variety of synthetic methodologies. The most prominent strategy is based on lithium moieties, formed through deprotonation, which allows multiple functionalizations. Organolithium chemistry is known to be highly sophisticated due to the fact that analytical methods for the monitoring of reactive intermediates, often only stable at low temperatures, are rare. Furthermore, side reactions related to the aggregation state and structures of the reactive species are common. Over the last years, only a few studies on monitoring of metallation by in-situ infrared spectroscopy have been carried out (Kondo et al., 1999; Sun & Collum, 2000; Pippel et al., 2001; Zhao & Collum, 2003). One reason might be that IR spectroscopy is preferred mostly for strong absorbing groups, like carbonyl moieties, which are often missing in heteroaromatics. Some of the most important reagents for lithiation are n-butyllithium (BuLi), lithium tetramethylpiperidine (LTMP) and lithium diisopropylamide (LDA), which have been selected in the following examples.

4.2 *In-situ* infrared studies applying BuLi and LTMP

Here, the work of Weymeels et al., 2005, in which the kinetics and mechanism of the deprotonation of 3,5-dichloropyridine by lithium tetramethylpiperidine (LTMP) and n-butyllithium (BuLi) were investigated.

4.2.1 Technical details

The IR spectra were recorded with a ReactIRe4000 equipped with a DiComp ATR probe (ASI Applied Systems, Mettler Toledo). The following steps of the experiments have been performed: (1) THF was cooled to -75°C; (2) the spectral baseline was reset to zero and the spectra recording was started; (3) the substrate was added; (4) the base was added dropwise; and (5) the reaction was quenched by deuterium oxide.

4.2.2 Results and discussion

The absorption bands of 3,5-dichloropyridine instantly decreased upon the addition of the base. As a result, the absorbance values associated with the aryllithium species appeared. By comparing the absorbance bands obtained using LTMP (Fig. 6(a)) and BuLi (Fig. 6(b)), it is clearly visible that two values (753 and 1007 cm^{-1}) out of the three attributed to 3,5-dichloro-4-pyridyllithium are identical, while the third (1139 cm^{-1} using LTMP and 1143 cm^{-1} using BuLi) is different. A possible explanation was that lithium bears different ligands, which is even more sophisticated due to the presence of the ring nitrogen atom. Studies comparing the consumption of LTMP and BuLi respectively for achieving quantitative protonation have been applied. It was assumed that a competitive formation of a complex between the generated aryllithium and LTMP could be responsible for different consumptions (1,25 equiv. LTMP *vs* 1,0 equiv. BuLi). To sum up, transition structures between the substrate and the lithio derivative could be detected by using IR in-situ monitoring. Moreover, IR monitoring assured that reaction conditions (time, temperature, number of equivalents) had been selected in a right way. This is a crucial requirement to circumvent overestimation, which can be a source of degradation and/or competitive reactions.
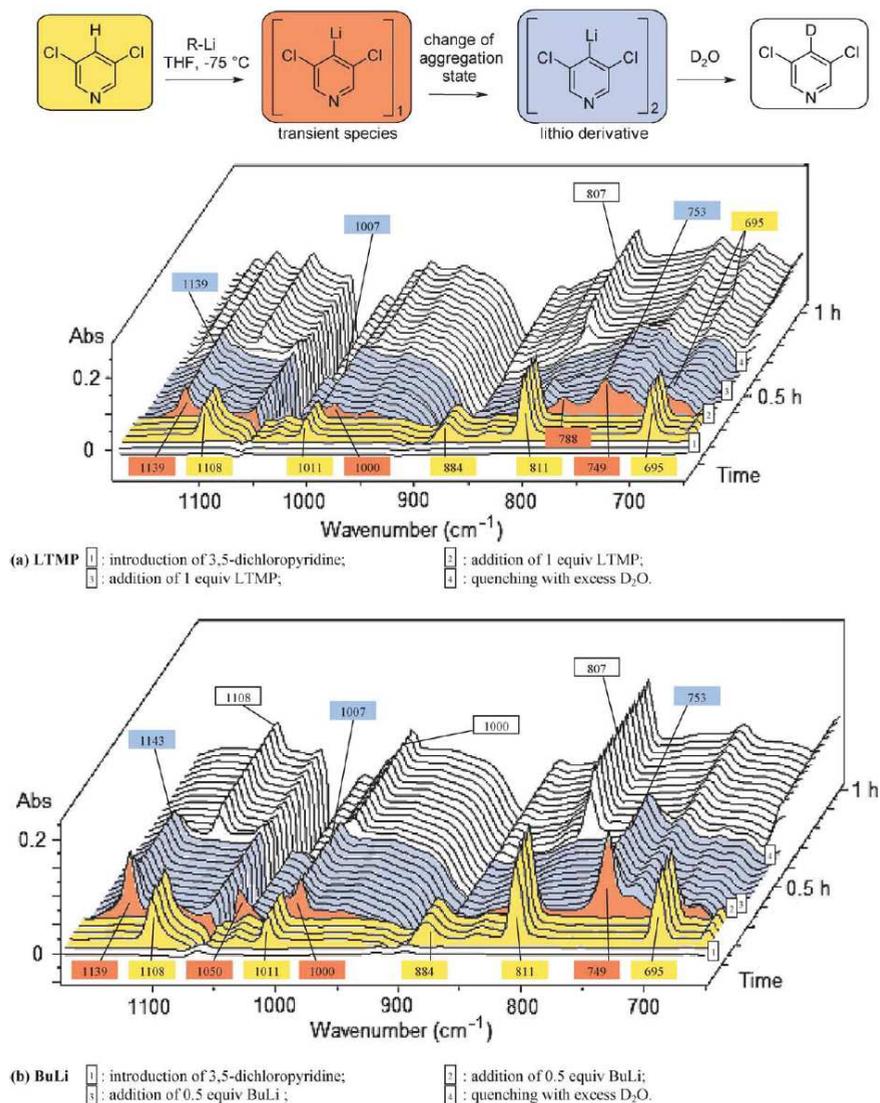
Fig. 6. Progression of the reaction between 3,5-dichloropyridine and (a) LTMP or (b) BuLi, and subsequent deuteriolysis. Figure reproduced from Weymeels et al., 2005.

4.3 *In-situ* studies applying LDA

Lithium diisopropylamide (LDA) is the most prominent and preferred reagent for reactions requiring a strong non-nucleophilic base, therefore being one of the most important reagents in organic chemistry (Collum et al., 2007). The central importance of LDA motivated several research teams to examine mechanism and transition state as well. Based on ATR-IR spectroscopy Collum et al. presented some studies on lithiation reaction.

The topic of the presented contribution (Gupta et al., 2008) is ortholithiation on a range of arenes mediated by LDA in combination with catalytic amounts of LiCl (0,5% relative to LDA). The lithiation reactions were monitored using in-situ IR spectroscopy following both the disappearance of the arene and the formation of the resulting aryllithium moiety. In addition, ^{19}F NMR spectroscopic analysis was performed, providing comparable results. The challenge was to monitor the Li-species as sensitive key intermediate, only stable at cryogenic temperatures. Therefore classical analytical methods could not be applied.

4.3.1 Technical details

The spectra were recorded by applying an in-situ IR spectrometer fitted with a 30-bounce, silicon-tipped probe. The spectra were acquired in 16 scans, and a representative reaction was carried out as follows: The IR probe was inserted into an oven-dried, cylindrical flask fitted with a magnetic stir bar and a T-joint. The T-joint was equipped with a septum for injections and a nitrogen line for inertness.

4.3.2 Results and discussion

Reaction rate studies investigating the effect of the LiCl and other lithium salts as catalyst were performed. Furthermore, the effect of the influence of the substrate was part of the study. In conclusion, despite some detected irregularities, the obtained results might be important for industrial application. Rate variations that go undetected in the lab could give way to unexpected and potentially costly variations on production scales. A representative example of in-situ monitoring is shown in Figure 7. A significant difference in the half-lives ($t_{1/2}$) can be identified, indicating an acceleration of the lithiation by addition of LiCl.
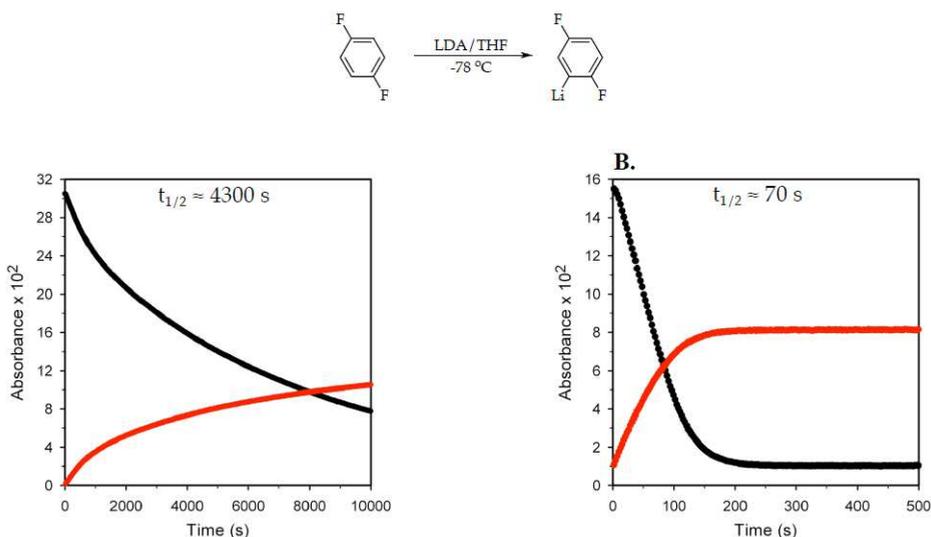

Fig. 7. Plot of IR absorbances (black – 1507 cm^{-1}, red – 1418 cm^{-1}) versus time for the ortholithiation of 1,4-difluorobenzene (0.10 M) with LDA (0.12 M) in THF at -78 °C: (A) no added LiCl; (B) 0.5 mol% LiCl. Figure reproduced from Gupta et al., 2008.

4.4 Investigations of metal halogen exchange reactions

In contrast to the previous chapters dealing with the deprotonation (metallation) of the substrate this chapter focuses on metal halogen exchange reactions towards the desired organolithium intermediates using BuLi. This type of reaction is of particular importance for the selective synthesis of certain substitution patterns (Rappoport & Marek, 2004).

The outlined contribution (Lumpi et al., 2012) presents investigations on metal halogen exchange reactions by inline monitoring of organolithium species under both inert and cryogenic conditions. Starting from relatively simple substrates the exploration of a complex Halogen Dance reaction sequence was realized, which allows the convenient synthesis of precursors for e.g. thiophene ring-opening reactions (Bobrovsky et al., 2008). In order to acquire reliable spectroscopic data *via* an optical ATR-IR fibre probe a procedure to correct the effects of (co-)sine type fringes, which are observed during the fast and exothermic metal halogen exchange reactions, has been developed.

4.4.1 Technical details

The instrumental setup was identical to the setup described in chapter 3.2. The fibre probe was mounted through a ground neck into a 4-neck round bottom flask, which was subsequently charged with dry solvent and cooled *via* a cooling bath. After a steady temperature in the vessel was reached a background spectrum was recorded, the measurement started and the lithium species added. Finally, the respective reactant was rapidly added *via* a syringe.

4.4.2 FFT correction procedure

Temperature deviations between the sample spectra and the background acquired during dynamic reaction processes represent one of the major challenges in IR spectroscopy at cryogenic temperatures. During these investigations the application of an ATR-IR fibre probe to relatively fast and exothermic metal halogen exchange reactions resulted in spectra heavily overlaid with (co-)sine-type artifacts. The introduced fringes lead to spectral data not utilizable for further interpretation.

To overcome these limitations a correction procedure based on fast Fourier transformation (FFT) was implemented to the data evaluation process. This high pass filter significantly reduced the fringes (attributed to differing thermal expansion coefficients of the probe materials) and rendered it possible to achieve a reliable monitoring of metal halogen exchange reactions at temperatures even below –80 °C.

4.4.3 Results and discussion

An application of the developed methodology to simple substrates for metal halogen exchange reactions but also to metallation procedures afforded reliable results. Thus, the technique was utilized for a detailed kinetic investigation of a double-sided Halogen Dance (Fig. 8, A) reaction towards 4,4'-dibromo-2,2'-bithiophene (Bobrovsky et al., 2008).

In this multi-step sequence (Fig. 8, A) the first metallation could be shown to proceed faster than the second lithiation towards **3** leading to an accumulation of intermediate **2** (Fig. 8, B). This assumption of the first reaction step exclusively consuming LDA to form **2** and the second Halogen Dance being realized in a next step leading to **3** could be verified by a
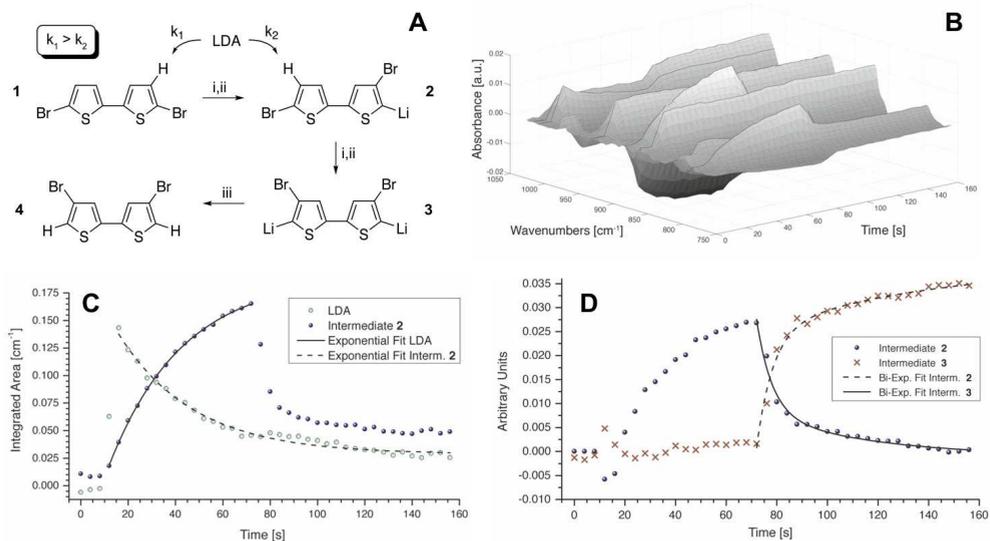
Fig. 8. Double-sided Halogen Dance reaction; A: reaction scheme; LDA (2.5 equiv.), -40 °C. i: metallation reaction, ii: Halogen Dance reaction, iii: excess of methanol; B: 3D plot of spectra (750 - 1050 cm^{-1}) recorded during reaction progress (0 - 160 s); C: monitoring of Li-species LDA and intermediate **2**; D: intermediate **3** formation as extracted from the spectral data set *via* MCR-ALS algorithm. Figure reproduced from Lumpi et al., 2012.

good agreement of kinetic parameters of LDA consumption and intermediate formation (Fig 8, C).

Due to overlapping absorption bands the MCR-ALS algorithm (chapter 3.3.2.) was applied to the spectral data set prior to analysis in order to compare the consumption of intermediate **2** and the formation of product **3** (Fig 8, D). The results again disclose a good agreement of kinetic data supporting the aforementioned conclusion, being highly valuable for potential application of this reaction (e.g. sequential Halogen Dance).

In summary, a methodology utilizing an FFT based correction procedure for a convenient monitoring of metal halogen exchange (but also metallation) reactions is presented. By applying this technique a mechanistic investigation of a complex double-sided Halogen Dance reaction could be realized.

5. Conclusion

In conclusion, it has been demonstrated that mid-infrared (ATR) spectroscopy utilizing modern optical fibre probes is an effective methodology for in-line monitoring of highly reactive species. Therefore, this non-invasive technique has emerged as a versatile tool for direct reaction monitoring, which was outlined using the example of organometallic intermediates.

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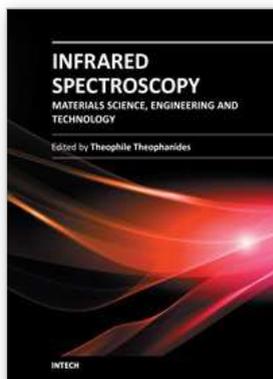
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The present book is a definitive review in the field of Infrared (IR) and Near Infrared (NIR) Spectroscopies, which are powerful, non invasive imaging techniques. This book brings together multidisciplinary chapters written by leading authorities in the area. The book provides a thorough overview of progress in the field of applications of IR and NIR spectroscopy in Materials Science, Engineering and Technology. Through a presentation of diverse applications, this book aims at bridging various disciplines and provides a platform for collaborations among scientists.

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