MicroDRIFT: Rapid and Efficient IR Analysis of Solid Phase Organic Chemistry Reactions

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Diffuse reflectance FTIR (DRIFT) analyses of Solid Phase Organic Chemistry (SPOC) resins using a DRIFT cup with a reduced sample volume, the DRIFT microcup, are presented. The use of this microcup only requires <1 mg of resin. The spectra are comparable with DRIFT spectra acquired using a conventional DRIFT accessory, but the amount of sample consumed in analysis is appreciably less. The use of a DRIFT accessory with a smaller sample compartment strongly reduces the time required for nitrogen purging. This, combined with the acquisition of spectra with a lower resolution and fewer scans, results in an over tenfold reduction of total analysis time without the loss of relevant spectral information. This technique is a useful alternative and/or complement to IR microscopic analysis of SPOC resins and other IR sampling techniques. A number of reactions analysed by this technique is presented.

Combinatorial Chemistry (CC) is currently receiving much attention as an approach to drug discovery[1][2]. Solid phase organic chemistry (SPOC) is often used as a tool for CC in order to generate libraries of organic compounds. During the initial stages, before constructing a library, the conditions for the reaction on the resin beads have to be optimised. Since relatively little knowledge has been obtained on organic reactions on solid supports besides peptide and nucleic acid synthesis, this is one of the bottlenecks in constructing libraries of organic compounds[3]. The optimisation is usually done by performing a sequence of reactions on a single compound tethered to the resin. However, when working with SPOC, the organic chemist cannot use his favourite analytical tools, solution state NMR and TLC to monitor the optimisation of the reactions. IR spectroscopy using KBr pellet spectra has widely been used as an analytical tool for SPOC[4][5][6][7][8]. The KBr pellet method suffers from the drawback that the water present in the KBr obscures the 3400−3000 cm^{-1} region of the spectrum. Since this is one of the few available windows unperturbed by the peaks of the resins, the KBr pellet method is not particularly suitable in this case. Moreover, the KBr pellet method consumes multimilligram quantities of resin beads. Recently it was reported that IR microscopy[9][10][11][12][13] can efficiently be used, consuming only a single bead in analysis. However, IR microscopes are not widely available, expensive and their operation is not trivial. DRIFT is a more widely accessible and economical IR technique. A drawback of this technique is that it requires more material for analysis. We demonstrate the use of a DRIFT cup with a reduced sample volume, the DRIFT microcup, as an alternative because it consumes less material than a conventional DRIFT cup. A number of reactions analysed by this technique is discussed.

Figure 1 displays the microDRIFT spectra of the intermediates of the reaction sequence depicted in Scheme 1 involving an L-fucose derivative coupled to a Merrifield resin. This reaction sequence was chosen because it is particularly suitable to illustrate the potential of microDRIFT. Figure 1A shows the hexane dithiol functionalised resin. Although the S−H stretch peak is expected at about 2565 cm^{-1}, which is a region of the spectrum unperturbed by the peaks of the resin[14], no peak is observed here. This is probably due to the low intensity of this band in IR[15]. In the first reaction, the acetylated fucose imidate is coupled, using trimethylsilyl triflate (TMSOTf) in dichloromethane, to the resin, This results in the appearance of the strong acetyl ester bands at 1750 cm^{-1} and 1240 cm^{-1} originating from the carbonyl stretch and C−O stretch vibrations respectively (B). Subsequently, the acetyl groups were removed using KOtBu in a mixture of DMF and MeOH. This is evident by the disappearance of the ester carbonyl bands at 1750 cm^{-1} and the emergence of a broad OH peak centered at 3400 cm^{-1} (C). The disappearance of the ester carbonyl allows for a semiquantitative following of the reaction: comparison with the spectrum of the starting material indicates that the ester carbonyl band decreased over 80%. Two of the three OH groups were then converted to an isopropylidene moiety by treatment with dimethoxyisopropanol in dichloromethane resulting in a strongly reduced OH peak (D). Finally, the benzoylation of the last remaining hydroxyl an arylchloride in pyridine was monitored by the emergence of a strong benzoylester carbonyl peak at 1730 cm^{-1} (E).

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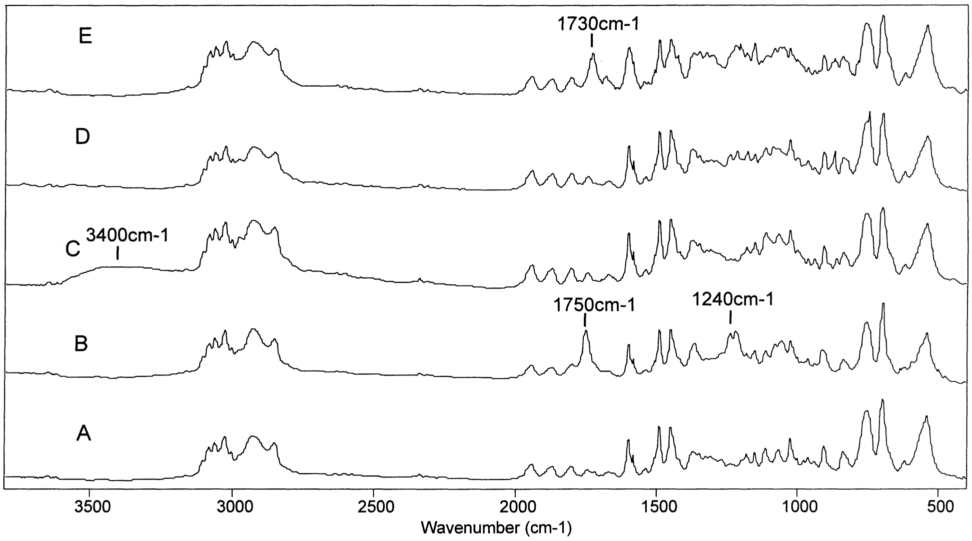
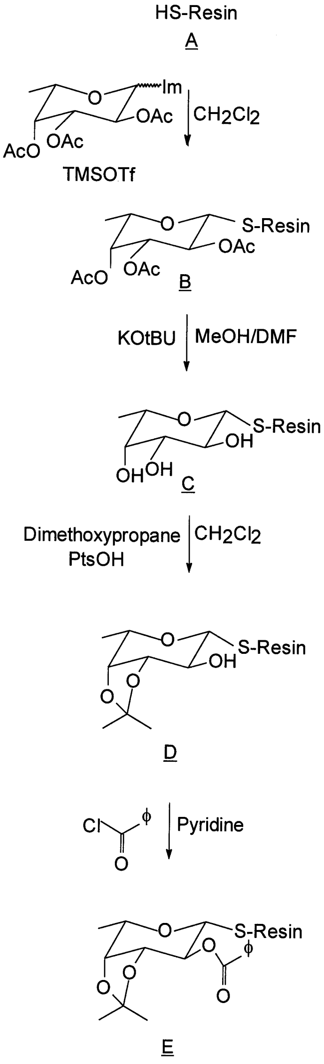
Figure 1. MicroDRIFT spectra of the reaction sequence displayed in Scheme 1; characteristic frequencies have been marked



Scheme 1. Reaction sequence studied by MicroDRIFT shown in Figure 1; the Merrifield resin was used

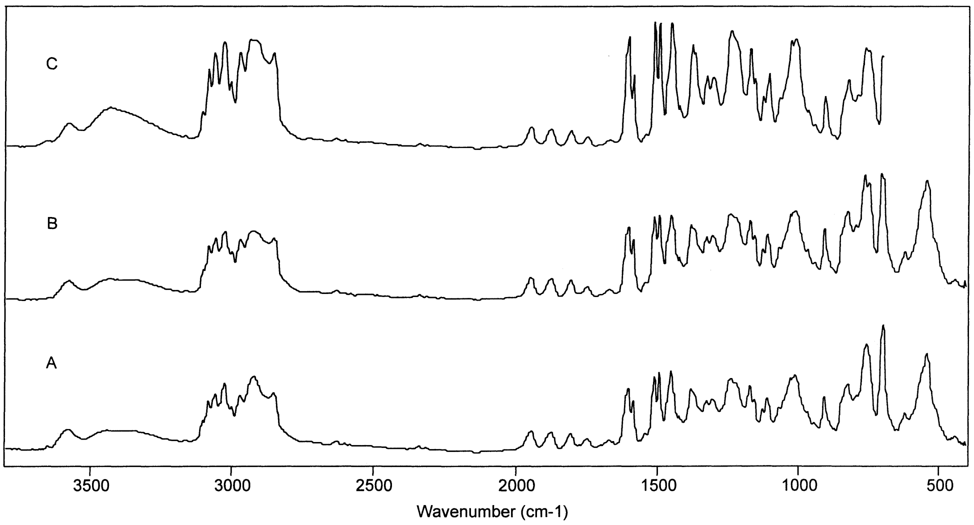


To compare MicroDRIFT with IR microscopy and conventional DRIFT, and to try improving the method, several experiments were done using an unfunctionalised Wang resin as a model.

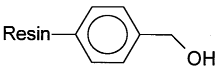
Figure 2 shows spectra obtained with microDRIFT (A), conventional DRIFT (B) and an IR microscope (C) on an unfunctionalised Wang resin (Scheme 2). For the conventional DRIFT measurement, 5.2 mg of resin was used, compared to 0.7 mg (500−1000 beads) for the microDRIFT measurement. The IR microscope spectrum was obtained on a single bead. Although the microDRIFT spectrum was obtained with only a fraction of the amount of material used to acquire the conventional DRIFT spectrum, the spectra are of comparable quality. Figure 2C shows the IR spectrum of a single bead using an IR microscope. The microDRIFT spectrum and the spectrum obtained by the IR microscope are of similar quality, although the IR microscope spectrum shows a slightly better resolution. The spectrum of the resin mainly consists of peaks originating from polystyrene. The hydroxyl group in the starting material give rise to bands at ca. 3570 and 3430 cm^{-1} originating from free and hydrogen bonded O−H stretch vibrations respectively[13].

The analysis time could be further reduced by using a DRIFT accessory with a smaller sample compartment. This has the advantage that the time required for thoroughly purging the sample compartment is much shorter. To further reduce analysis time, 32 instead of 128 scans were obtained and a resolution of 4 cm^{-1} was used. Figure 3 shows a comparison between the spectrum obtained this way (A) and a spectrum acquired with 128 scans, using a resolution of 2 cm^{-1} (B). The spectra are virtually identical. Reduction of digital resolution is acceptable since the peaks of the resin and the resin bound compounds are broad: reduction of the digital resolution will not affect the information content of the spectrum since the spectral resolution

Figure 2. A: MicroDRIFT spectrum of an unfunctionalised Wang resin (Scheme 2); B: conventional DRIFT spectrum; C: IR microscope spectrum



Scheme 2. Unfunctionalised Wang resin; the IR spectrum is shown in Figure 2



is low. Reduction of the number of scans and resolution combined with measurement in a smaller sample compartment results in a total analysis time of less than 1 minute instead of 10 minutes (including purge).

Thus it has been shown that microDRIFT allows the acquisition of IR spectra of <1 mg of SPOC resin. The quality of the spectra is comparable to those obtained by conventional DRIFT and with those obtained by IR microscopy. The amount of sample required is larger than when using IR microscopy (500 − 1000 beads instead of one), but five to tenfold lower than when using a conventional DRIFT cup. Using microDRIFT, reactions and reaction sequences could be qualitatively assessed. In some cases it is possible to obtain semiquantitative results. The ease of operation allows the acquisition of the spectra by synthetic organic chemists themselves instead of analytical chemists, ensuring fast feedback on reaction optimisation. In our lab, 15 − 20 microDRIFT analyses a day are carried out this way, using microDRIFT as the equivalent of TLC for the analysis of SPOC reactions. Recently, attenuated total reflection (ATR)[16] was also proposed as a sampling technique.

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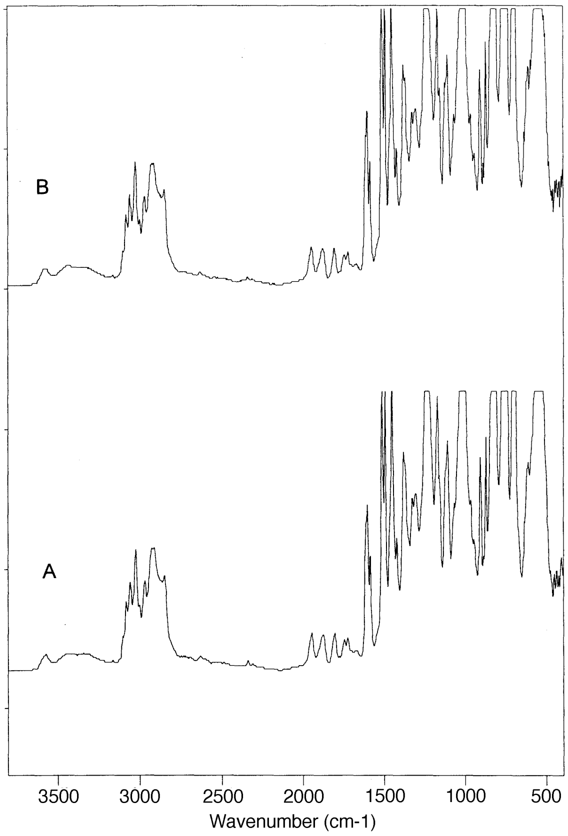
Figure 3. A: MicroDRIFT spectra obtained on an unfunctionalised Wang resin (Scheme 2), recorded using a smaller sized sample compartment, a resolution of 4 cm^{-1}, acquiring 32 scans and B: using a purged sample compartment, a resolution of 2 cm^{-1} and acquiring 128 scans; the vertical scale has been expanded to allow comparison



Experimental Section

Wang or Merrifield resin were used for this study. For the microDRIFT measurements, typically 0.5−1 mg of the resin was ground with ca. 30 mg KBr with an agate pestle and mortar. The sample was then transferred to a SPECTRATECH microDRIFT cup and placed into a SPECTRATECH DRIFT cell in a nitrogen-purged sample compartment. For conventional DRIFT measurements, ca.

5 mg of resin was mixed with ca. 400 mg KBr, ground and transferred to a normal DRIFT cup. Spectra were collected on a BIORAD FTS-60 IR, FTS-135 or FTS-175C FTIR spectrometer. Typically, 128 scans were collected with a resolution of 2 cm^{-1}. The IR microscope spectra were acquired on a SpectraTech IR-plan microscope interfaced with BIORAD FTS-175 spectrometer, acquiring 64 scans with a resolution of 4 cm^{-1}.

The spectra acquired with a DRIFT accessory with a reduced sample compartment were measured using the Harrick 'Praying Mantis' DRIFT accessory on a BRUKER VECTOR22 FTIR spectrometer; 32 scans were obtained with a resolution of 4 cm^{-1}.

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[1] M. A. Gallop, R. W. Barret, W. J. Dower, S. P. A. Fodor, E. M. Gordon, *J. Med Chem.* **1994**, *37*, 1233–1251; E. M. Gordon, R. W. Barret, W. J. Dower, S. P. A. Fodor, M. A. Gallop, *J. Med. Chem.* **1994**, *37*, 1385–1417.

[2] F. Balkenhohl, C. von dem Bussche-Hünnefeld, A. Lansky, C. Zechel, *Angew. Chem.* **1996**, *108*, 2436–2487.

[3] P. H. H. Hermkens, H. C. J. Ottenheijm , D. Rees, *Tetrahedron* **1996**, *52*, 4527–4554.

[4] J. M. Frechet, C. Schuerch, *J. Am. Chem. Soc.* **1971**, *93*, 492–496.

[5] M. J. Kurth, L. A. Ahlberg Randal, C. Chen, C. Melander, R. Bryan Miller, *J. Org Chem..* **1994**, *59*, 5862–5864.

[6] J. K. Young, J. C. Nelson, J. S. Moore, *J. Am. Chem. Soc.* **1994**, *116*, 10841–10842.

[7] J. R. Hauske, P. Dorff, *Tetrahedron Lett.* **1995**, *36*, 1589–1592.

[8] G. E. A. Deben, T. H. M. van Wijk, E. van Doornum, P. H. H. Hermkens, E. R. Kellenbach, *Microchim. Acta* **1997**, *14*, 245–246.

[9] B. Yan, G. Kumaravel, H. Anjaria, A. Wu, R. C. Petter, C. F. Jewell, J. R. Wareing, *J. Org Chem.* **1995**, *60*, 5736–5738.

[10] B. Yan, G. Kumaravel, *Tetrahedron* **1996**, *52*, 843–848.

[11] K. Russel, D. C. Cole, F. M. McLaren, D. E. Pivonka, *J. Am. Chem. Soc.* **1996**, *118*, 7941–7945.

[12] B. Yan, J. B. Fell, G. Kumaravel, *J. Org. Chem.* **1996**, *61*, 7467–7472.

[13] B. Yan, Q. Sun, R. Wareing, C. F. Jewell, *J. Org. Chem.* **1996**, *61*, 8765–8770.

[14] J. Rademan, R. R. Schmidt, *Tetrahedron Lett.* **1996**, *37*, 3989–3990.

[15] D. Lin-Vien, N. B. Colthup, W. G. Fateley , J. G. Grasselli, *Infrared and Raman Characteristic Frequencies of Organic molecules,* Academic Press, San Diego, **1991**, 226–227.

[16] H.-U. Gremlich, S. L. Berets, *Appl. Spectrosc.* **1996**, *50*, 532–536.

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