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Photoacoustic FTIR Spectroscopy, a Nondestructive Method for Sensitive Analysis of Solid-Phase Organic Chemistry

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The growing use of combinatorial chemistry for drug discovery has accelerated the development of analytical techniques for studying organic chemistry on the solid phase.[1−6] Although Fourier-transform infrared (FTIR) spectroscopy is most commonly used for detecting functional group changes of resin-bound compound,[1−3] the acquisition of quality spectra from resino compound by FTIR spectroscopy is complicated by light scattering and reflection.[7] Furthermore, methods for FTIR spectroscopy of derivatized resin are usually destructive and require inconvenient sample preparation.[1] Since spectral quality may be influenced by matrix homogeneity, the resin samples are typically examined in KBr pellets after thorough mixing.[1a] Single-bead FTIR microspectroscopy[2] and internal reflection FTIR spectroscopy[3] have recently been shown to offer advantages compared to conventional FTIR spectroscopy; however, these techniques require some sample preparation as well as mechanical contact with the sample.

We have explored the use of photoacoustic FTIR spectroscopy in order to develop a simple, rapid, nondestructive technique to monitor chemical reactions on solid support.[8] Photoacoustic FTIR (PA-FTIR) spectroscopy involves the measurement of oscillating pressure variations of a confined inert gas situated above the sample. This variation is caused by a thermal transfer from the sample to the surrounding gas upon absorption of modulated infrared radiation. The absorbed radiation diffuses as heat through the sample toward the surface where it heats a boundary layer of gas and induces a pressure change resulting in an acoustic wave. The acoustic wave is then detected by a sensitive microphone. Therefore, the photoacoustic signal is a direct measurement of the amount of absorbed radiation.

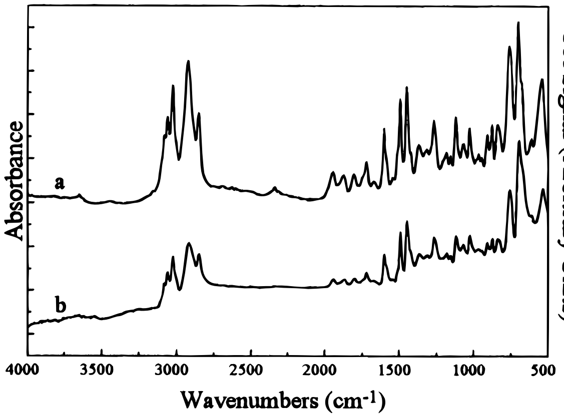

Figure 1. FTIR spectra of Merrifield's resin: (a) PA-FTIR; (b) FTIR of KBr pellet.

Photoacoustic FTIR spectroscopy offers a number of important advantages over conventional and the abovementioned surface-sensitive IR techniques. First, because only the absorbed radiation is measured, PA-FTIR spectroscopy eludes the effects of light scattering and reflection. Moreover, PA-FTIR spectroscopy does not require sample preparation. The sample is simply placed into a sample cup, introduced into the photoacoustic cell and purged with an inert gas (helium in the present experiments). Photoacoustic FTIR spectroscopy has been used to characterize many surfaces ranging from asbestos fibers to calcified tissues.[9−16] The technique is sensitive and nondestructive. Spectra can be recorded on a few milligrams of resin, which can be recovered, treated in chemical reactions, and reexamined repeatedly. To the best of our knowledge, we are the first to apply PA-FTIR spectroscopy to the analytical characterization of solid-phase organic chemistry.

In comparison with conventional FTIR spectroscopy, we have found that PA-FTIR spectroscopy produces spectra of superior quality as is clearly evidenced in the spectra of Merrifield's peptide resin (chloromethylated polystyrene[17]) that were obtained by using PA-FTIR spectroscopy[18] on neat resin (Figure 1a) and by employing standard FTIR spectroscopy[19] on the resin in a KBr pellet[20] (Figure 1b). The PA-FTIR spectrum is devoid of the light scattering and artifacts due to nonhomogeneity of the KBr pellet. Such effects generally require a baseline correction in order to obtain better quality spectra.

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(2) Single-bead FTIR microspectroscopy is presented in: (a) Yan, B.; Kumaravel, G.; Anjaria, H.; Wu, A.; Petter, R.; Jewell, C. F.; Wareing, J. R. *J. Org. Chem.* **1995**, *60*, 5736. (b) Yan, B.; Kumaravel, G. *Tetrahedron* **1996**, *52,* 843.

(3) Internal reflection FTIR spectroscopy of injection molded high density polystyrene ("Mega-Crowns") is described in: Gremlich, H.-U.; Berets, S. L. *Appl. Spectrosc.* **1996**, *50*, 532.

(4) Recent NMR techniques for the analysis of solid-phase synthesis resins are presented in: (a) Keifer, P. A. *J. Org. Chem.* **1996**, *61*, 1558. (b) Sarkar, S. K.; Garigipati, R. S.; Adams, J. L.; Keifer, P. A. *J. Am. Chem. Soc.* **1996**, *118*, 2305. (c) Garigipati, R. S.; Adams, B.; Adams, J. L.; Sarkar, S. K. *J. Org. Chem.* **1996**, *61,* 2911. (d) Anderson, R. C.; Jarema, M. A.; Shapiro, M. J.; Stokes, J. P.; Zilox, M. *J. Org. Chem.* **1995**, *60,* 2650. (e) Fitch, W. L.; Detre, G.; Holmes, C. P.; Shoolery, J. N.; Keifer, P. A. *J. Org. Chem.* **1994**, *59,* 7995.

(5) *In situ* mass spectrometry of solid-phase resins is presented in: (a) Egner, B. J.; Cardno, M.; Bradley, M. *J. Chem. Soc., Chem. Commun.* **1995**, 2163. (b) Egner, B. J.; Langley, G. J.; Bradley, M. *J. Org. Chem.* **1995**, *60*, 2652.

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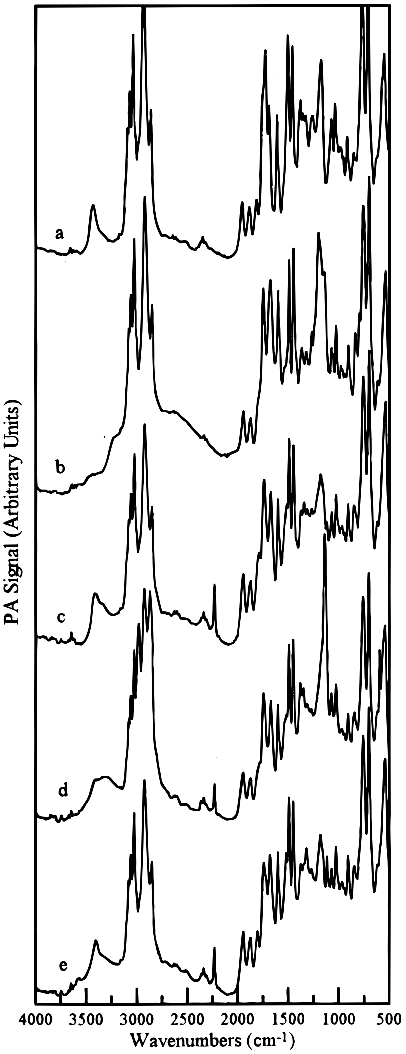
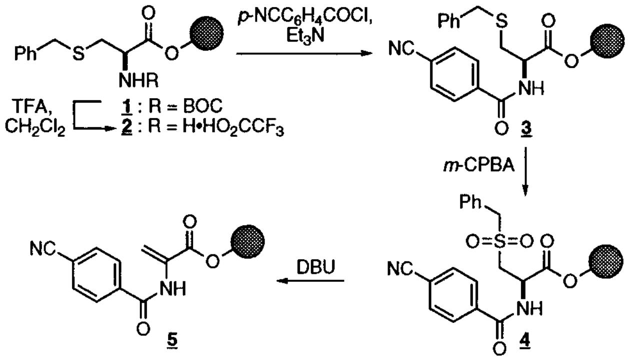


Figure 2. (a-e) PA-FTIR spectra of resino compounds **1**−**5**.

Three different resino amino esters were first examined by PA-FTIR spectroscopy.[21] We next monitored a sequence of reacctions using the same sample of resin.[22] Resino-*N*-(*p*-cyanobenzoyl)dehydroalanine **5** was synthesized in four steps from resino-(2*R*)-*S*-benzyl-*N*-(BOC)-cysteinate (**1**, Scheme 1).[23] The spectra were recorded on the same 10 mg sample. Resin **1** was first treated with TFA in dichloromethane and anisole to yield resino-(2*R*)-*S*-benzylcysteinate trifluoroacetate **2**. The formation of **2** was indicated by the disappearance of the carbamate carbonyl and NH bands at 1718 and 3420 cm^{-1}, respectively, and the appearance of the amine trifluoroacetate salt band at 1681 cm^{-1} (Figure 2a,b). Treatment of **2** with 4-cyanobenzoyl chloride in the presence of triethylamine in THF−CH_2Cl_2 afforded resino-(2*R*)-*S*-benzyl-*N*-(*p*-cyanobenzoyl)cysteinate **3** as determined by the appearance of the amide carbonyl band at 1674 cm^{-1}, the nitrile band at 2231 cm^{-1}, and the amide NH at 3413 cm^{-1} (Figure 2c). Oxidation of the thioether using excess *m*-CPBA in dichloromethane then yielded the resino sulfone **4** as observed by the appearance of the strong O=S=O stretch at 1140 cm^{-1} (Figure 2d).[24] The formation of resino-*N*-(*p*-cyanobenzoyl)dehydroalanine **5** on treatment of resino sulfone **4** with DBU was finally indicated by the disappearance of the sulfone stretch at 1140 cm^{-1} (Figure 2d,e).[25] As one can see from the results presented in Figure 2, useful PA-FTIR spectra were recorded on the same 10 mg sample of resino amino ester before and after each transformation. Moreover, no resin was lost.

Scheme 1. Synthesis of Resino Dehydroalanine 5



Effective ways to monitor chemical transformations on the solid phase are needed in order to ascertain reaction conversion and product purity during combinatorial chemistry. We have shown that PA-FTIR spectroscopy is superior than conventional FTIR spectroscopy for monitoring chemical reactions on the solid phase. By detecting only the absorption component of the IR beam, PA-FTIR spectroscopy eludes the effects of light scattering and reflection that complicate conventional FTIR methods. Because no sample preparation is required, PA-FTIR spectroscopy can be used to examine a sequence of reactions on the same resin sample without product loss. Photoacoustic FTIR spectroscopy should thus find general use as a convenient, nondestructive method for sensitive analysis of solid-phase organic chemistry.

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Supporting Information Available: Experimental details[23] as well as PA-FTIR and FTIR spectra (18 pages).

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[18] Spectra were taken on a Mattson Research Series FTIR spectrometer using an MTEC Model 300 photoacoustic cell. Less than 10 mg of the sample was placed in the sample cup. Samples were evaluated at a mirror speed of 0.098 cm/s (1.6 kHz) and a resolution of 8 cm^{-1}. Five hundred scans were co-added between 500 and 4000 cm^{-1}. Helium was used as the carrier gas. PA spectra were ratioed against carbon black spectra obtained from the reference from MTEC photoacoustics.

[19] Absorption spectra were taken on the spectrometer described in ref 18 using a DTGS detector with the samples pressed in KBr pellets. One hundred spectra were co-added at a mirror speed of 0.6 cm/s (10 kHz) and ratioed against the source emission spectrum. Beyond ratioing and in one case spectral subtraction, the spectra were subjected to no other mathematical treatment such as smoothing or base-line correction.

[20] KBr pellets were prepared according to the procedure described in ref 1a.

[21] Resino amino esters were prepared according to: Gisin, B. F. *Helv. Chim. Acta* **1973**, *56*, 1476. Characteristic bands and PA-FTIR spectra are reported in the supporting information.

[22] Assignments of spectral bands for different functional groups were made according to: Colthup, N. B.; Daly, N. H.; Wiberley, S. E. *Introduction to Infrared and Raman Spectroscopy*, 3rd ed.; Academic Press: San Diego, 1990.

[23] For a related synthesis of resino dehydropeptide see: Ojima, I.; Tsai, C.-Y.; Zhang, Z. *Tetrahedron Lett.* **1994**, *35*, 5785. For comparison, we prepared methyl *N*-(*p*-cyanobenzoyl)dehydroalanine from methyl *S*-benzylcysteinate hydrochloride; experimental details and spectral data for all intermediates are presented in the supporting information.

[24] The oxidation conditions were modified from: Kondo, K.; Nagishi, A.; Fukuyama, M. *Tetrahedron Lett.* **1969**, 2461.

[25] Kelly-Basetti, B. M.; Mackay, M. F.; Pereira, S. M.; Savage, G. P.; Simpson, G. W. *Heterocycles* **1994**, *37*, 529.