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^{19}F NMR Monitoring of a S_NAr Reaction on Solid Support

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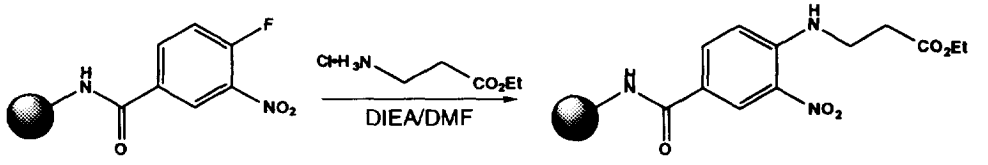
Abstract: Gel-phase ^{19}F and MAS ^{19}F and ^{13}C NMR for monitoring the progress of an on-resin S_NAr reaction is demonstrated.

Nucleophilic aromatic substitution (S_NAr) is an old and well studied process.[1] It has been applied recently to the formation of macrocyclic diphenyl ethers found in vancomycin,[2] teicoplanin,[3] bouvardin,[4] and K-13.[5] We wished to employ this efficient and versatile reaction for solid-phase synthesis of novel, bioactive substances. A common impediment to optimizing solid phase reactions is that monitoring reaction progress on the solid phase is problematic. In order to analyze solid phase reactions without resorting to cleavage, we have developed a number of methods for monitoring reactions on-resin.[6] One such method[6a] involves the application of magic angle spinning (MAS) NMR[7] of solvent-swollen resin as a complement to the well established gel-phase NMR techniques.[8]

In the case of S_NAr reactions, fluorine is frequently the leaving group, so ^{19}F NMR offers a window through which to observe reaction progress. To establish that ^{19}F NMR is in fact a good method for monitoring solid phase reaction kinetics, we examined the displacement of fluorine from 4-fluoro-3-nitrobenzamide by ethyl 3-aminopropanoate•HCl (see Scheme I).

Scheme I



1 **2**

Specifically, 1.0 g of polystyrene resin **1** (4-fluoro-3-nitrobenzamide linked to RinkAmide™ AM resin from Peptides International; loading = 0.44 mmol/g) in 20 mL DMF was treated with 10 equiv of ethyl 3-aminopropanoate•HCl and 20 equiv diisopropylethylamine (DIEA) at ambient temperature under argon. Aliquots (0.5 mL) were removed and rinsed with excess DMF and MeOH dried *in vacuo* to remove reagent and halt the reaction. The identity of **2**, the only product obtained, was established by on-resin MAS ^{13}C NMR (*vide infra*), on-resin FT-IR,[6c] and by ^{1}H NMR and MS of the benzamide cleaved off the resin.[9]

The time course of the S_NAr displacement of the fluorine atom was monitored for 2 hours by obtaining six ^{19}F gel-phase NMR spectra.[10] Shown in Figure 1 are ^{19}F gel-phase NMR spectra for two time points (15 and 30 min) during the course of the reaction.[10] The broad peak

in the spectrum arises from fluorine-containing components of the probe and it can be used as an external standard. A plot of reaction progress (Figure 2) shows that it is essentially complete in less than 2 hours.

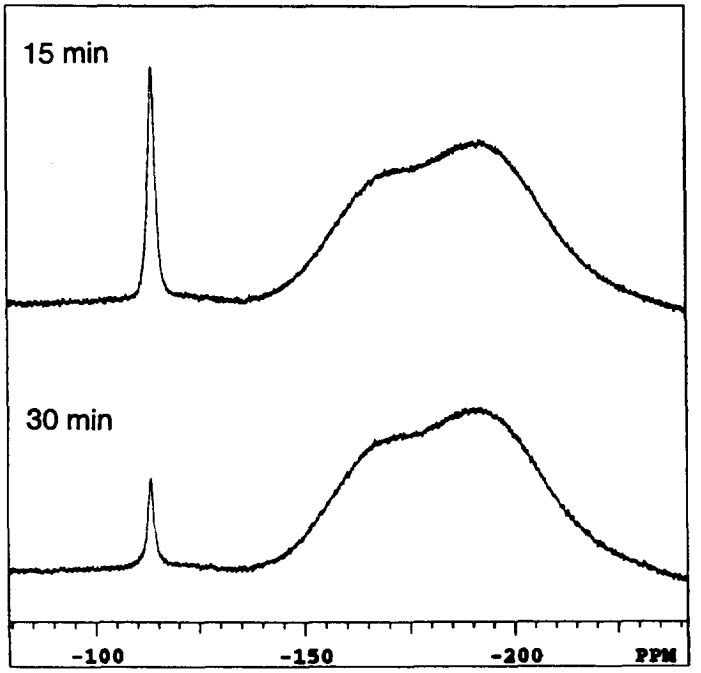


Figure 1. Gel-phase ^{19}F NMR spectra of benzene-d_6-swollen resin **1** at (a) 15 min and (b) 30 min after exposure to ethyl 3-aminopropanoate•HCl/DIEA. δ (**1**) = -115.3 ppm.

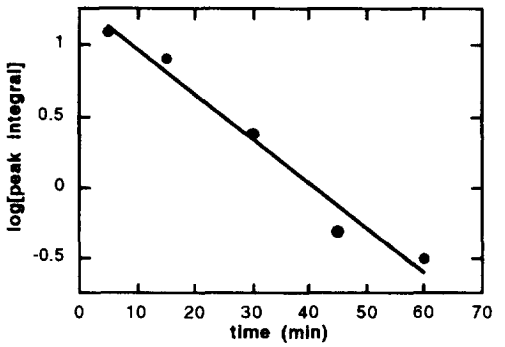


Figure 2. Plot of the peak integral of the ^{19}F resonance of resin **1** (δ = -115.3 ppm) *vs.* reaction time for the model reaction.

The reaction could also be conveniently monitored by MAS ^{19}F NMR using solvent-swollen resin.[11] The results obtained were analogous to those found for the ^{19}F gel-phase NMR data, where the disappearance of signal gives an indication of the reaction progress. The advantage of the MAS NMR is apparent in the time necessary to obtain satisfactory data. A typical spectrum, shown in Figure 3, required only 4 minutes to acquire.

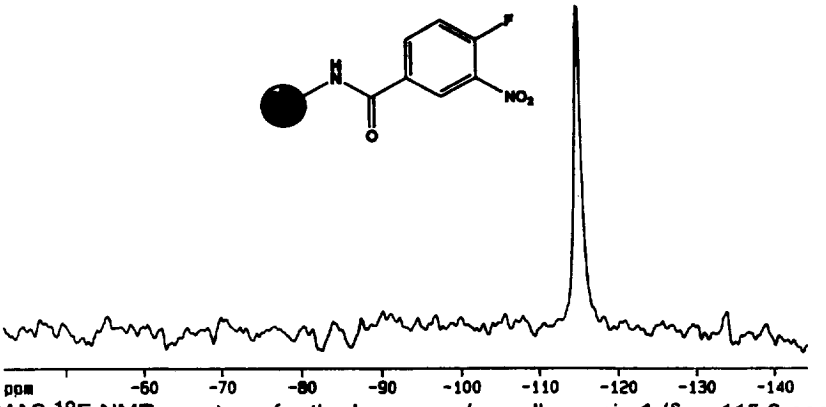


Figure 3. MAS ^{19}F NMR spectrum for the benzene-d_6-swollen resin **1** (δ = -115.3 ppm).

Alternatively, this reaction could be monitored using MAS ^{13}C NMR on the solvent-swollen resin. As shown in Figure 4, both the product and the linker to the resin have resolved methyl group signals. The appearance of the high-field methyl group resonance is indicative of product formation. As the reaction progresses, the high-field methyl signal grows and when the reaction is complete the signals have equal intensity.

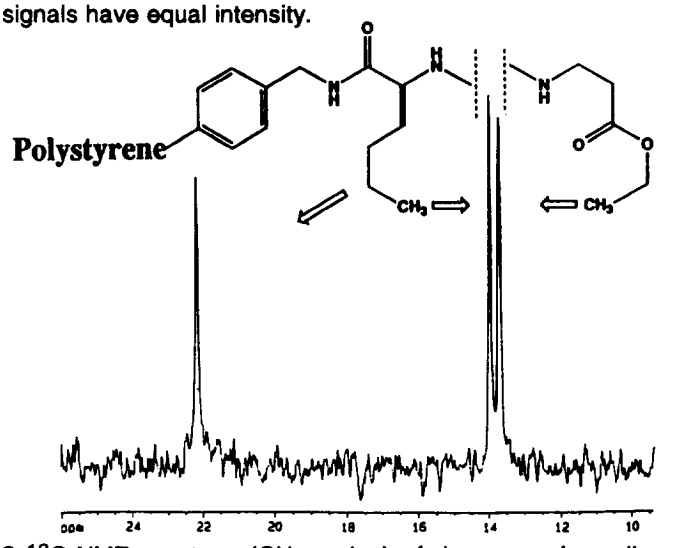


Figure 4. MAS ^{13}C NMR spectrum (CH_3 region) of benzene-d_6-swollen resin **2**. Part of the tether of the RinkAmide™ AM resin is shown on the left.

In conclusion, we have demonstrated several NMR methods that can be used to follow on-resin S_NAr reactions. The choice of method to monitor the reaction depends on the hardware available. For this reaction, ^{19}F MAS NMR spectroscopy on solvent-swollen resin appears to be the most-efficient technique.

References and Notes

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9. The reaction products were also followed by ^1H NMR after cleavage from the resin. The NMR spectra were consistent with the expected product from nucleophilic substitution of the fluorine atom: δ = 8.4 (d, 1H), 7.6 (dd, 1H), 6.3 (d, 1H), 3.9 (q, 2H) 3.0 (t, 2H), 2.1 (t, 2H), 1.0 (t, 3H).
10. For typical gel phase NMR spectra, it took 1 to 1.5 hours to acquire data sufficient to attain the signal-to-noise ratio shown in Figure 1. The sample was shown to be stable to the conditions by repeating the data acquisition for a sample sitting in solution for 4 days, obtaining the same results.
11. MAS NMR data were obtained on a Bruker DMX-400 widebore instrument using standard solution experiments in a 7 mm rotor with MAS at 4 kHz. The resin was swollen with benzene-d_6. The solvent-swollen powder was placed into a 7 mm rotor. The broad component from the probe background was removed by zeroing and linear predicting of the first 20 points of the FID. Gel-phase NMR data were obtained on a Bruker AC-300 spectrometer equipped with a 5 mm quad nucleus probe.

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