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Use of ^{19}F NMR Spectroscopy to Evaluate Reactions in Solid Phase Organic Synthesis

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Abstract: Gel-phase ^{19}F NMR spectroscopy has been used to characterize products from a variety of reactions of fluorinated aromatics linked to a TentaGel resin. High quality spectra were obtained in a few minutes using an ordinary NMR spectrometer, and the ^{19}F chemical shifts of the support-bound compounds closely matched those of soluble references. In addition, substantial chemical shift differences were obtained for almost all of the synthetic transformations, illustrating the potential of ^{19}F NMR for rapid monitoring of reactions in solid-phase organic synthesis.

Combinatorial chemistry allows efficient preparation of large numbers of structurally distinct molecules and is increasingly being applied for preparation of chemical libraries in medicinal chemistry.[1-4] Combinatorial organic chemistry performed on a solid support has many advantages over combinatorial chemistry in solution and is suitable for automation. Excess reagents can be used to drive reactions to completion since isolation and purification of support bound products is accomplished simply by washing of the solid phase. Future developments in combinatorial chemistry rely on adaption of both organic reactions and analytical techniques to conditions that are compatible with various solid supports.

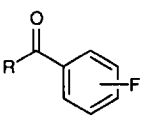
In view of its powerful applications in organic chemistry, NMR spectroscopy appears to be the analytical tool of choice also for solid phase organic synthesis and combinatorial chemistry. However, conventional ^{1}H and ^{13}C NMR spectroscopy of compounds attached to solid supports (gel-phase NMR) usually requires prolonged spectral aquisition, gives very broad resonances and is dominated by signals from the solid support.[5-7] Attempts to circumvent these problems include magic angle spinning,[6-10] use of selectively ^{13}C enriched building blocks,[11,9] presaturation of support signals,[12] and combinations of these techniques.[9] Drawbacks with these approaches are that magic angle spinning requires access to specialized and expensive NMR equipment, whereas the commercial availability of selectively ^{13}C-labelled starting materials is limited and these materials may also be costly.

Commonly used solid supports do not contain fluorine and consequently ^{19}F NMR offers an opportunity to monitor reactions on solid-phase involving fluorine containing compounds. ^{19}F Chemical shifts are spread over a wide frequency range and structural transformations even quite remote from the fluorine atom will affect the position of the ^{19}F NMR signal. A recent report[13] describing the use of ^{19}F NMR spectroscopy

for monitoring a nucleophilic aromatic substitution with fluorine as a leaving group prompts us to disclose our own results on the use of ^{19}F NMR spectroscopy for monitoring organic reactions performed on solid phase and for characterization of support bound products.

In a model study the commercially available *ortho*-, *meta*- and *para*-fluorobenzoic acids **1a-c** were coupled to a TentaGel S NH_2 resin to give the resin linked benzamides **2a-c** (Table 1). The 2-methoxyethyl benzamides **3a-c** were also prepared as low-molecular weight, soluble reference compounds. NMR spectroscopy revealed that the ^{19}F chemical shifts for the resin bound amides **2a-c** were almost identical to those for the soluble amides **3a-c** (Table 1). Furthermore, when the fluorine atom was located *ortho*- or *para*- to the carbonyl group the ^{19}F chemical shifts for the benzamides differed significantly from those of the corresponding acids, whereas the *meta*-position appeared to be less sensitive.

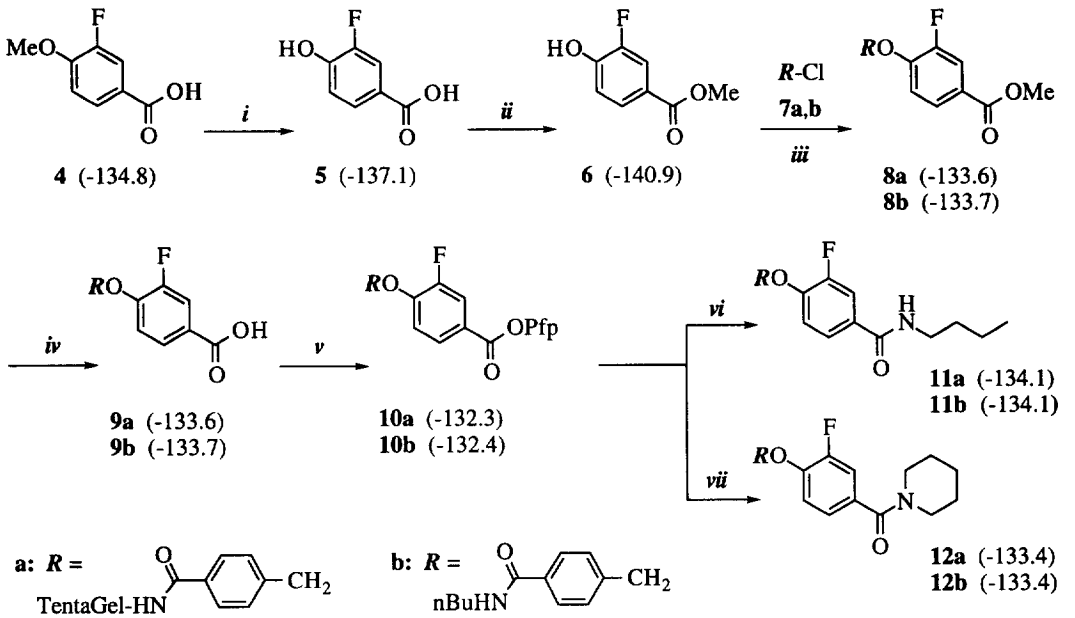
Table 1. ^{19}F-NMR chemical shifts (δ, ppm) for compounds **1a-c, 2a-c** and **3a-c**.[14]



	R	**a** (*ortho*)	**b** (*meta*)	**c** (*para*)
1	OH	-108.7	-112.5	-104.5
2	TentaGel-NH	-114.0	-112.4	-108.8
3	MeO⌒NH	-114.0	-112.9	-109.1

The use of ^{19}F NMR in solid phase synthesis was therefore further evaluated for the synthetic sequence leading to compounds **11** and **12** (Scheme 1).[15] The synthetic sequence was initiated from commercial 3-fluoro-4-methoxybenzoic acid **4** which was converted into **6** by demethylation with BBr_3[16] and then esterification with $TMSCHN_2$[17]. Nucleophilic substitution of the benzylic chloride in the solid support **7a** and the analogous, soluble butylamide **7b** [each obtained in two steps from 4-(hydroxymethyl)benzoic acid] with the phenol group of **6** gave the methyl benzoates **8**, which were hydrolyzed to the acids **9**. Activation of **9** as the pentafluorophenyl esters **10** then allowed formation of the butyl and piperidyl amides **11** and **12**.

Gel-phase ^{19}F NMR spectra of high quality were obtained for compounds **8a-12a** in less than 10 minutes on 50-200 mg of resin (cf. spectrum of **11a** in Figure 1a).[14] Linewidths for the compounds linked to the solid support (Figure 1b) approached those in solution (Figure 1c) and indicated that shift differences of ≤0.5 ppm can be detected. In contrast to a recent study[13] where ^{19}F NMR was used to monitor the kinetics for the substitution of an aromatic fluorine atom, no background signals were obtained from the probe of the NMR instrument. It is again noteworthy that the correlation between the ^{19}F chemical shifts for the support-linked compounds and the corresponding soluble references was excellent (≤0.1 ppm difference, cf. Scheme 1). Furthermore, there was a significant change in the ^{19}F chemical shift (≥1.0 ppm) for each conversion in the transformation of **4** into **12**, with exception of the hydrolyis of esters **8** to give acids **9**. It should also be pointed out that for each conversion performed on the solid phase no residua' peak from the starting material could be observed in the ^{19}F NMR spectrum, revealing that each step was quantitative (cf. transformation of **10a** into **11a**, Figure 1b).



Scheme 1. Synthesis of the resin linked and soluble butyl and piperidyl amides **11** and **12** with ^{19}F-NMR chemical shifts[14] in parenthesis for all compounds. *Reaction conditions*: (*i*) BBr_3, CH_2Cl_2, -78 °C → r.t., 96%; (*ii*) $TMSCHN_2$, CH_2Cl_2/MeOH, 86%; (*iii*) DBU, CH_3CN, reflux, **8b** 82%; (*iv*) LiOH, THF/EtOH/H_2O, 0 °C → r.t., **9b** 94%; (*v*) Pentafluorophenol, DIC, EtOAc, r.t., **10b** 84%; (*vi*) *n*-Butylamine, HOBt, r.t., **11b** 92%; (*vii*) Piperidine, HOBt, EtOAc, r.t., **12b** 98%. Yields after purification by flash column chromatography.

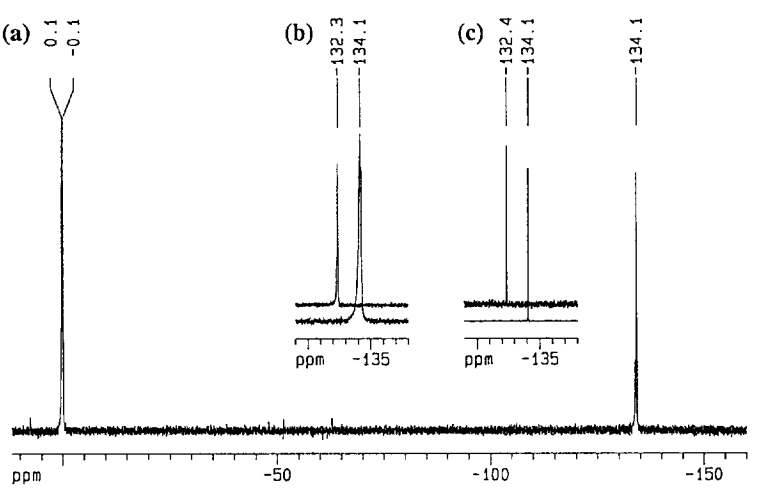


Figure 1. ^{19}F NMR spectra obtained at 375.5 MHz for: (a) the resin linked butyl amide **11a**, (b) conversion of **10a** into **11a** on solid phase, and (c) conversion of **10b** into **11b** in solution. Chemical shifts are given adjacent to the ^{19}F NMR peaks.

In summary, we have shown that ^{19}F NMR spectroscopy is a versatile technique for evaluation of a variety of reactions on solid phase which involve fluorinated aromatic compounds. A substantial ^{19}F chemical shift difference is usually observed on transformation of a reactant into product, and the chemical shifts on solid phase match those in solution. In addition, high quality spectra are obtained within minutes for solid-phase linked compounds using an ordinary NMR spectrometer, without any need[13] for magic angle spinning. A wide range of fluorine containing compounds are commercially available and we expect that ^{19}F NMR spectroscopy should find important applications in solid-phase combinatorial synthesis of small molecule libraries.

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14. Gel-phase ^{19}F NMR spectra were recorded with a Bruker ARX-400 spectrometer operating at 375.5 MHz for solutions in $CDCl_3$ or DMSO-d_6 with CCl_3F (δ_F 0.0) as internal standard. For the hydrogen bonding **9** and **11** a better chemical shift correlation between the support-bound and the corresponding soluble compound was obtained when DMSO-d_6 was used as solvent instead of $CDCl_3$.
15. Selected ^1H NMR data (400 MHz): **8b** δ ($CDCl_3$) 6.07 (1H, bs, N*H*), 5.24 (2H, s, OC*H*$_2$Ph), 3.89 (3H, s, OC*H*$_3$), 3.47 (2H, dt, *J*=7.1, 5.8 Hz, NC*H*$_2$), 0.96 (3H, t, *J*=7.3 Hz, CH$_2$C*H*$_3$). **9b** δ (DMSO-d_6) 8.49 (1H, bs, N*H*), 5.37 (2H, s, OC*H*$_2$Ph), 3.40 (2H, dt, *J*=7.1, 5.8 Hz, NC*H*$_2$), 0.93 (3H, t, *J*=7.4 Hz, CH$_2$C*H*$_3$). **10b** δ ($CDCl_3$) 6.16 (1H, bt, *J*=5.1 Hz, N*H*), 5.29 (2H, s, OC*H*$_2$Ph), 3.46 (2H, dt, *J*=7.2, 5.8 Hz, NC*H*$_2$), 0.96 (3H, t, *J*=7.3 Hz, CH$_2$C*H*$_3$). **11b** δ ($CDCl_3$) 6.16 (1H, bs, N*H*), 6.06 (1H, bs, N*H*), 5.21 (2H, s, OC*H*$_2$Ph), 3.49-3.39 (4H, m, 2 NC*H*$_2$), 0.95 (6H, 2 t, *J*=7.3 Hz, 2 CH$_2$C*H*$_3$). **12b** δ ($CDCl_3$) 6.21 (1H, bs, N*H*), 5.20 (2H, s, OC*H*$_2$Ph), 3.62 (2H, bm, NC*H*$_2$), 3.44 (2H, m, NC*H*$_2$), 3.40 (2H, bm, NC*H*$_2$), 0.96 (3H, t, *J*=7.3 Hz, CH$_2$C*H*$_3$).
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