Supports for solid-phase synthesis with high fluidity and high functionality

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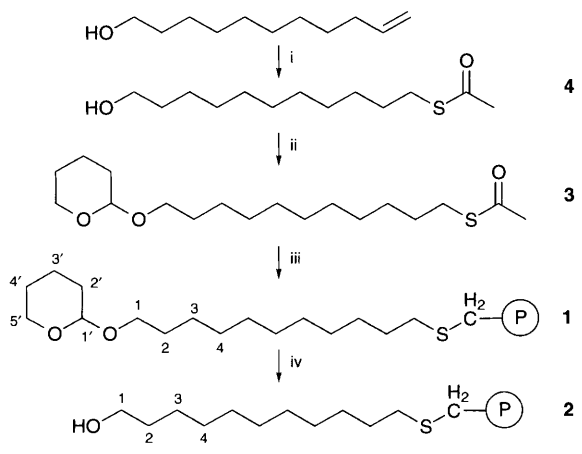
A support for solid-phase synthesis is described, characterised both by a high level of functionality and liquid-phase-like fluidity.

Impressive developments in solid-phase organic synthesis have been made recently, driven largely by the impetus of combinatorial and parallel syntheses in drug development.[1] The solid supports commonly in use include conventional Wang and Merrifield resins,[2] mixed polymers from ethylene glycol and styrene (*e.g.* Tentagel),[3] porous glass[4] and polystyrene pins functionalised with acrylamide side-chains by γ-irradiation.[5] For much of this work, the loading of reagent or analyte on to the solid support is quite low, being typically in the range of 0.1 to 0.5 mmol g^{-1}. At higher loadings, if practicable, there may be disadvantages due to the reduced mobility of functional groups at the interface and lowered accessibility of the reaction sites. But in many cases it will be desirable to present a higher concentration of supported reaction sites, for example to enable the course of reactions to be followed directly and avoid the need for tagging of beads,[6] and current methodology is deficient in this respect. We present a promising approach.

In earlier work we had demonstrated that long-chain analogues of polystyrene supported cation-exchange resins functioned as micellar catalysts, and a related principle was used to develop the present work.[7] Chloromethylpolystyrene (63% substituted, 2% crosslinked, 40–63 μ) was reacted[8] with the salt of sulfide **1**, itself prepared by the sequence shown in Scheme 1. The product was formed quantitatively, and we were pleased to discover that high quality ^{13}C NMR spectra, assignable on literature precedent,[9] were readily obtained in a short time without special techniques, provided that the spectrum was recorded with the beads suspended in a solvent which swelled the polymer (*e.g.* $CDCl_3$, CD_2Cl_2, [$^2H_7$]DMF). The ^{13}C NMR spectrum of the initial product **1** is shown in Fig. 1(*a*), and this was also the technique of choice for monitoring transformations of the beads, for instance the deprotection to primary alcohol **2**. Under microscopy, the beads were discrete translucent spheres, although **2** was free-flowing and **1** quite sticky. It was observed that Disperse Red 1 dye distributed evenly through the beads and was completely washed out within seconds by CH_2Cl_2.



Scheme 1 Synthesis of polymers; i, MeCOSH, $(PhCO_2)_2$, CH_2Cl_2, 97%; ii, dihydropyran, *p*-TsOH, CH_2Cl_2, 99%; iii, poly-$ArCH_2Cl$, NaH, THF, 96%; iv, HCl, MeOH, CH_2Cl_2, 99%

Determination of ^{13}C spin lattice times was of considerable interest, since it provided a probe of the fluidity and homogeneity of the interior of the gel.[10] For comparison, T_1 measurements were also carried out on the related monomers **3** and **4**, under closely related conditions. The results are shown in Fig. 2, which compares the observations for monomers and polymers. As expected, the fluidity of the polymer is lower, leading to shorter recovery times than for the corresponding monomer, but the difference is surprisingly small. More importantly, the T_1 values for both polymers demonstrate a homogeneity of side-chain environment; the fluidity of the interior of the bead is identical to that of the surface region.[11] For the THP ethers, the trends in T_1 for the polymer **1** around the pyran ring mirror those for the monomer **3**. The information is, however, limited by a lack of resolution of the internal chain carbons of the polymer beyond C2 in the ether and C4 in the alcohol, illustrated by the broad signals flanking of methylene carbons flanking the sulfide. The reduction in mobility of polymer relative to monomer is greater for the polymer alcohol **2** than for the THP ether **1**.

The hydroxy group of polymer **2** is easily functionalised, and to illustrate simply the potential of this new class of supports in synthesis, a peptide coupling sequence was carried out as shown

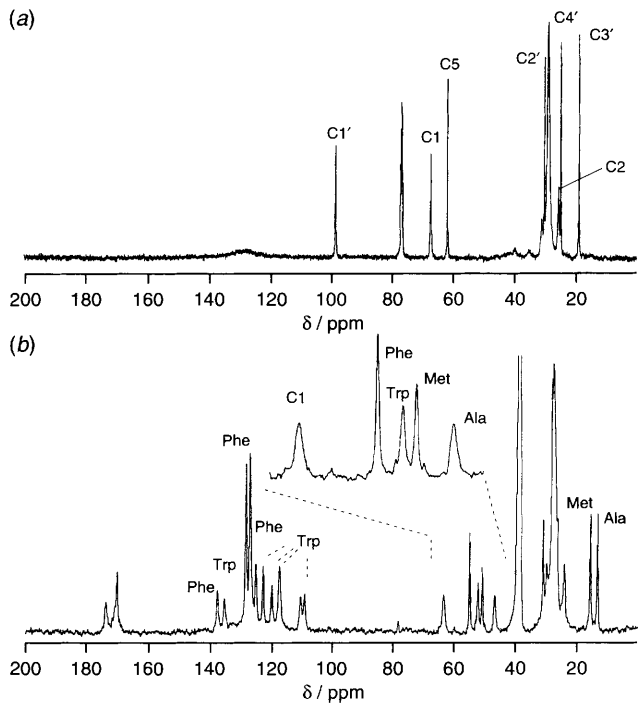


Fig. 1 ^{13}C NMR spectrum at 126 MHz (*a*) of polymer **1** (*ca.* 100 mg) suspended in $CDCl_3$, 300 K, 980 scans, 25 min; (*b*) of polymer **5** (*ca.* 100 mg) suspended in [$^2H_6$]DMSO; 323 K, 2340 scans, 1 h (δ 44–64 region inset)

in Scheme 2. Esterification of the polymer with the Fmoc derivative of L-alanine by the acid fluoride route[12] occurred quantitatively. Release of the protecting group followed by successive couplings with L-tryptophan, L-methionine and L-phenylalanine gave **5**. At each stage of the synthesis, progress could easily be monitored by ^{13}C NMR, and as the attached peptide chain increased in length the resonances broadened concomitantly; for the product **5** better results were obtained by recording the spectrum in [$^2H_6$]DMSO, where presumably any inter-chain aggregation induced by H-bonding is vitiated. Even at this level of complexity the polymer can be assayed by a single ^{13}C NMR determination (1 h, 50 °C) which confirms the identity of all four amino acid residues with baseline separated peaks [Fig. 1(*b*]. A tentative assignment of Cα carbons can be made based on the shifts observed during the synthetic sequence, and if correct then there is a correlation between line widths and the distance from the anchoring chain.

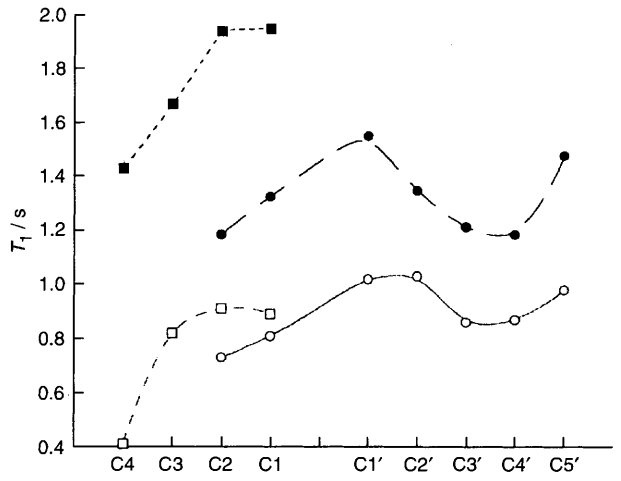
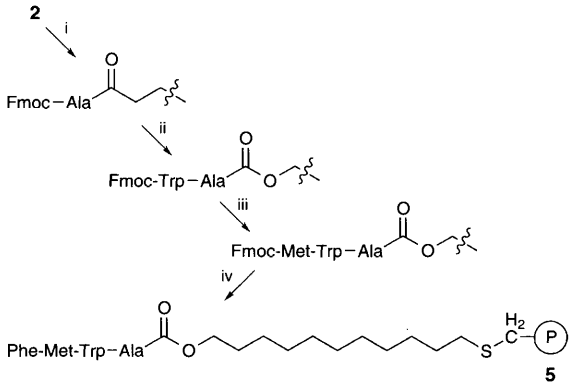


Fig. 2 ^{13}C NMR T_1 relaxation times of polymers **1** and **2** compared to monomers **3** and **4** in $CDCl_3$ (300 K) measured by the inversion-recovery method (14 points, 768 scans per point for **1**, **2**; 16 scans per point for **3**, **4**); ○ polymer **1**; □ polymer **2**; ● monomer **3**; ■ monomer **4**. (T_1/2 for C1′).



Scheme 2 Peptide synthesis sequence, average yield <95%; i, Fmoc–AlaCOF, DMAP, CH_2Cl_2, then $C_5H_{11}N$, DMF; ii–iv, Fmoc–(AA)OH, DICI, HOBt, CH_2Cl_2 then $C_5H_{11}N$, DMF. (AA) = amino acid.

In summary, we have developed a class of polystyrene-based solid supports which promise to make a distinctive contribution to solid-phase chemistry, for which further applications will be reported in due course.

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