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Plasmachemical surface functionalised beads: versatile tailored supports for polymer assisted organic synthesis

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Plasmachemical surface modification of porous polystyrene beads with allylamine or diaminopropane provides reactive amine functionality exclusively at accessible surface sites, allowing faster reactions than classically prepared materials.

Solid supported synthesis has become a widely used technique in organic chemistry. Whilst a range of inorganic materials such as clays, silicas and controlled pore glass are used, the vast majority of supports are insoluble organic polymers. Most commonly, lightly crosslinked swellable resins (1–2% crosslinker) are used. These are relatively cheap and easy to handle, but are limited to use with solvents that cause the swelling required to give access to the reactive sites contained within the interior of the bead. In contrast, highly crosslinked macroporous resins are accessible to all solvents but access to the interior of the bead is limited by diffusion and for larger molecules, size exclusion principles.[1] Moreover much of the desired functionality is located within the polymer matrix and not accessible to any reagent, *vide infra*. In this report we describe a solution to these problems through the preparation of tailored macroporous beads in which the reactive functionality is located specifically on the surface of the bead and is therefore accessible to all reagents.[2]

A popular strategy for the functionalisation of SPOS (Solid phase organic synthesis) supports is through the use of functional monomers which affords little control in the distribution of reactive sites.[3] Although grafting techniques can be used to increase control, this process is frequently accompanied by considerable side reactions leading to a deterioration of the support performance.[4] We envisaged that by using recently developed techniques in plasma-assisted surface functionalisation we could modify the surface of the bead to introduce the desired functionality in a precise and controlled fashion.[5] In polymer modifications, the result is minimal degradation of both the functionalising monomer and polymer surface and functionalisation only at accessible sites.[6] Using this technique a range of different functional groups has been incorporated onto a broad range of surfaces including wafers, films, fibres, pellets *etc*.[5,7]

As an initial demonstration of this concept we prepared surface-loaded amine-functionalised polymer beads (“plasmabeads”) and explored their application in solid phase synthesis. Simple polystyrene beads, the properties of which are easier to control than functionalised beads, were prepared possessing both high pore volume and high average pore size by careful optimisation of crosslinker and porogen ratios, polymerisation temperatures and reactor stirring speeds. Prior to functionalisation, the beads were sorted into particle size ranges by sieving and then assayed by nitrogen adsorption/desorption analysis and mercury porosimetry. Plasmachemical surface treatment was carried out on a 250 mg scale, using either allylamine (AA) or diaminopropane (DAP) as the functionalising agent, in a rotating glass reactor at 0.4 mbar pressure with a continuous wave plasma ignited at 20 W for 20 min. Loading of amine residues was established by standard Fmoc analysis (0.06[for 90–125 μm diameter beads]–0.10[20–38 μm] mmol g^{-1}). Although relatively low, analysis of the distribution of the functional groups by C≡N Raman mapping of a sample of cross-sectioned beads following exhaustive coupling with 4-cyanobenzoic acid confirmed that loading of these plasmabeads had been achieved through the near exclusive functionalisation of a highly accessible peripheral shell approximately 3–4 μm in depth, Fig. 1. The effective Fmoc loading in this region can therefore be estimated as being 0.12, 0.16 and 0.39 mmol g^{-1} for a 26, 48 and 88 μm diameter bead respectively.[8]

With these novel surface-loaded supports in hand their utility was investigated in both classical solid phase synthesis and in polymer assisted solution phase synthesis. Various synthetic schemes including peptide couplings and Suzuki cross coupling reactions were undertaken demonstrating the viability of the plasmachemical functionalised beads, Scheme 1. Although the low overall loadings generated limited the amount of material recovered, the yields produced were comparable with those obtained using standard bead systems.

Having demonstrated utility in standard SPOS applications we then turned to applications in which the exclusive surface

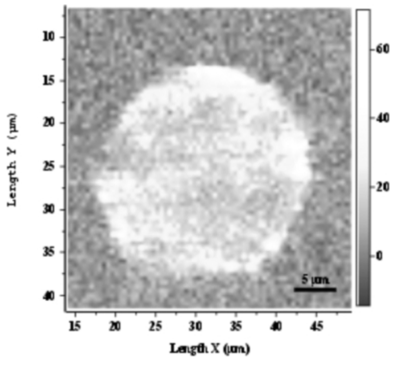
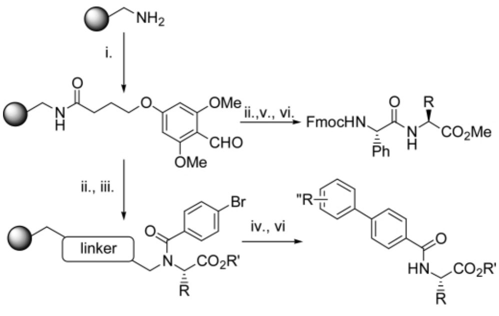


Fig. 1 Raman microscopy of cross-sectioned allylamine functionalised polystyrene bead after coupling with 4-cyanobenzoic acid. Bright regions correspond to the integrated cyanoband intensity (2210–2260 cm^{-1}).



Scheme 1 ***Reagents:*** i. $HO_2C(CH_2)_3OC_6H_2(OMe)_2CHO$, DIC, DIPEA, DMF; ii. NH_2CHRCO_2Me, $NMe_4BH(OAc)_3$, DMF; iii. 4-BrC_6H_4COCl, DIPEA, DCM; iv. $PhB(OH)_2$, $Pd(Ph_3)_4$, Na_2CO_3, EtOH, H_2O; v. Fmoc-PheOH, PyBOP, DIPEA; vi. TFA, DCM (36–78% HPLC purities ≥ 85%).

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distribution of functionality could be advantageous and examined the use of these materials in simple scavenging processes.[9] In common with polymer supported synthesis it has been accepted that polymer supported scavenging is relatively slow and requires a significant excess of the scavenging agent.[10] We compared commercially available amine functionalised resins with our amine functionalised plasmabeads using benzoyl chloride as a model electrophile. The rate and extent of the scavenging process was followed by monitoring the UV absorbance of the electrophile remaining in solution ($\lambda_{\max} = 246$ nm). Initial experiments conducted by removing aliquots over time revealed that such simple acylation reactions are fast, even on solid phase, and we therefore developed a simple flow through cell to monitor reactions more precisely. Preliminary studies showed that contrary to conventional practice, there is little significant benefit in having a large excess of scavenging reagent, Fig. 2. In this case, a minimum of two equivalents of amine are required to achieve complete scavenging and large excesses of amine afford minimal increases in reaction rate. More significantly, initial rate measurements demonstrated that, provided there are sufficient reactive sites available, these reactions are very rapid. Moreover, in a comparison of various bead types, the plasmabeads exhibited the fastest rates of scavenging ($v_{\text{init}} = 1.52 \times 10^{-3}$ dm^3 mol^{-1} s^{-1}), Fig. 3. We attribute this to the surface functionalised nature of these beads, which does not require diffusion into the interior of the bead to access the active sites. This contrasts with the lower rates in classically prepared beads in which the large majority (~97%) of the reactive functionality is contained within the interior of the bead.[11] As above, the use of allylamine plasmas provides material with lower efficiencies than diaminopropane treated beads.

In conclusion, we have shown for the first time that surface functionalised macroporous beads can be readily prepared by plasmachemical functionalisation and used in a variety of synthetically useful applications. Although the current levels of loading of these plasmabeads are lower when compared with conventional supports for classical SPOS, the rates of reaction with surface located functionality are higher. Coupled with this ability to control the location of functionality, plasmabeads provide advantages in situations in which access to the reactive groups *e.g.* with macromolecules (enzymes) or supported catalysis is a critical factor.[12] This plasmachemical modification strategy offers a number of other advantages including solventless processing, low energy consumption, negligible waste, and the need for very small amounts of reagents. Moreover, the ability to functionalise any surface by plasmachemical methods means that a greater range of materials can now be considered as supports for polymer supported chemistry and permits the nature of the support to be better tailored to the chemistry required. Studies that confirm these suggestions are in progress and will be reported in due course.

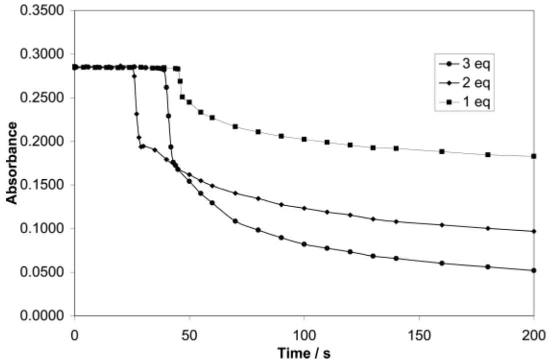

Fig. 2 Scavenging of PhCOCl functionalised DAP polystyrene resin.

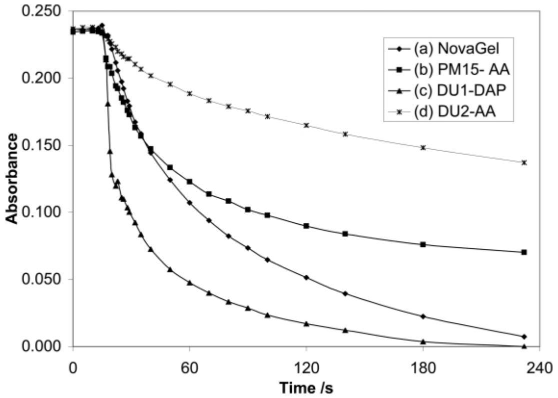

Fig. 3 Scavenging of PhCOCl with (a) NovaGel aminomethyl polystyrene resin $v_{\text{init}} = 2.12 \times 10^{-4}$ mol dm^{-3} s^{-1}(b) plasmachemical functionalised AA–Biosearch PM15 PS resin $v_{\text{init}} = 3.87 \times 10^{-4}$ mol dm^{-3} s^{-1} (c) plasmachemical functionalised DAP–PS resin $v_{\text{init}} = 1.52 \times 10^{-3}$ mol dm^{-3} s^{-1} (d) plasmachemical functionalised AA–ozonolysed PS resin $v_{\text{init}} = 8.74 \times 10^{-5}$ mol dm^{-3} s^{-1}. [DU = in-house prepared resins, see ESI].

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Notes and references

1 T. Groth, M. Grotli and M. Meldal, *J. Comb. Chem.*, 2001, **3**, 461.
2 For a recent approach towards this end see A. N. Cammidge, S. Downing and Z. Ngaini, *Tetrahedron Lett.*, 2003, **44**, 6633.
3 (*a*) J. Rademann, M. Barth, R. Brock, H. J. Egelhaaf and G. Jung, *Chem. Eur. J.*, 2001, **7**, 3884; (*b*) J. Kress, R. Zanaletti, A. Rose, J. G. Frey, W. S. Brocklesby, M. Ladlow and M. Bradley, *J. Comb. Chem.*, 2003, **5**, 28.
4 C. Viklund, A. Nordstrom, K. Irgum, F. Svec and J. M. J. Frechet, *Macromolecules*, 2001, **34**, 4361.
5 F. Denes, *Trends Polym. Sci.*, 1997, **5**, 23.Whilst beads (particulates) have been functionalised in this way there has not been a study on the effect of bead structure nor of applications in SPOS. A similar strategy has previously been employed to functionalise polyethylene filter discs for oligonucleotide synthesis. R. V. Devivar, S. L. Koontz, W. J. Peltier, J. E. Pearson, T. A. Guillory and J. D. Fabricant, *Bioorg. Med. Chem. Lett.*, 1999, **9**, 1239.
6 S. L. Koontz, R. V. Devivar, W. J. Peltier, J. E. Pearson, T. A. Guillory and J. D. Fabricant, *Colloid Polym. Sci.*, 1999, **277**, 557.
7 (*a*) Epoxides— C. Tarducci, E. J. Kinmond, J. P. S. Badyal, S. A. Brewer and C. Willis, *Chem. Mater.*, 2000, **12**, 1884; (*b*) fluorocarbons— S. P. Godfrey, E. J. Kinmond, J. P. S. Badyal and I. R. Little, *Chem. Mater.*, 2001, **13**, 513; (*c*) anhydrides— C. A. Fail, S. A. Evenson, L. J. Ward, W. C. E. Schofield and J. P. S. Badyal, *Langmuir*, 2002, **18**, 264.
8 Analysis of the beads by scanning electron microscopy suggested that filling of the smaller pores was occurring on allylamine plasmachemical treatment limiting the surface available for reaction. G. Øye, V. Roucoules, A. A. Cameron, L. J. Oates, N. R. Cameron, P. G. Steel, J. P. S. Badyal, B. G. Davis, D. Coe and R. Cox, *Langmuir*, 2002, **18**, 8996.This could be attributed to side reactions involving the unreacted alkenyl units arising from the divinylbenzene crosslinker used. R. V. Law, D. C. Sherrington and C. E. Snape, *Macromolecules*, 1997, **30**, 2868.Although N_2 adsorption and Hg porosimetry measurements indicated that ozonolytic treatment of the resin prior to plasmachemical functionalisation did give an increased proportion of larger pores this had no significant effect on the overall loading.
9 R. J. Booth and J. C. Hodges, *Acc. Chem. Res.*, 1999, **32**, 18; J. Eames and M. Watkinson, *Eur. J. Org. Chem.*, 2001, 1213.
10 D. Walsh, D. Q. Wu and Y. T. Chang, *Curr. Opin. Chem. Biol.*, 2003, **7**, 353.
11 This is consistent with similar observations made using commercially available TentaGel beads in which functionality in the outer region exhibited faster coupling rates—see ref. 3b. Interestingly with some simple PS gel type beads, the reactions of both interior and surface functionality is reported to occur simultaneously. S. Rana, P. White and M. Bradley, *J. Comb. Chem.*, 2001, **3**, 9.The difference between these observations and those described here can be related to the high levels of crosslinking used to prepare macroporous beads known to retard the rate of diffusion.
12 A. Y. Bosma, R. V. Ulijn, G. McConnell, J. Girkin, P. J. Halling and S. L. Flitsch, *Chem. Commun.*, 2003, 2790; S. D. Debenham, P. W. Snyder and E. J. Toone, *J. Org. Chem.*, 2003, **68**, 5805; J. Kress, R. Zanaletti, A. Amour, M. Ladlow, J. G. Frey and M. Bradley, *Chem. Eur. J.*, 2002, **8**, 3769.