Synthesis of New Poly(ethyleneglycol)s with a High Loading Capacity[1]

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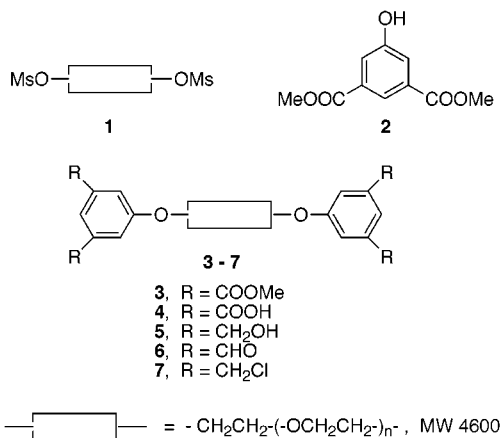
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The use of soluble polymeric matrixes as supports for the synthesis of small organic molecules is currently receiving a great deal of attention.[2] Organic synthesis on soluble polymers profits from both the advantageous features of homogeneous solution chemistry (high reactivity, lack of diffusion phenomena,[3] analytical simplicity) and of solid phase methods (easy isolation and purification of the products). In addition, soluble polymers are generally much less expensive than insoluble ones.[4]

However, the use of soluble polymers should not be considered the panacea in the field of polymer-supported synthesis, since it still presents some drawbacks. Among these, a major one is the low number of functional groups per gram of polymer (loading, expressed in mequiv/g). For instance, the widely employed poly(ethylene glycol) monomethyl ether of MW 5000 (MeOPEG$_{5000}$)[2,5−7] has a loading as low as 0.2 mequiv/g, and thus relatively large *weight* amounts of polymeric material are required to handle relatively small *mole* quantities of nonpolymeric substance.[8]

The problem of low loading can be overcome by combining the basic principles of dendrimer chemistry[9] with that of

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(1) Presented in part by M.B. at the 12th International Congress on Organic Synthesis (ICOS-12), Venice, Italy, June 28−July 2, 1998.

(2) Reviews: (a) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489. (b) Pillai, V. N. R.; Mutter, M. *Acc. Chem. Res.* **1981**, *14*, 122. (c) Bonora, G. M. in *Seminars in Organic Synthesis*; Cozzi, F., Ed.; Societa' Chimica Italiana, Roma, 1998; pp 117−142. For recent reviews on the use of polymeric supports in organic synthesis, see: (d) Früchtel, J. S.; Jung, G. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 17. (e) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555. (f) Hermkens, P. H. H.; Ottenhejm, H. C. J.; Rees, D. *Tetrahedron* **1996**, *52*, 4527.

(3) For a recent discussion of the effects of the polymer structure on the kinetics of solid phase organic reactions, see: Li, W.; Yan, B. *J. Org. Chem.* **1998**, *63*, 4092.

(4) For instance, by comparing the prices of different polymers functionalized with primary OH groups, and considering the number of functional groups per gram of polymer, PEG polymers cost 10−500 times less than other commercially available polymeric matrixes.

(5) For recent syntheses of organic molecules anchored to MeOPEG$_{5000}$ and related polymers not included in ref 2, see: (a) Zhu, J.; Hegedus, L. S. *J. Org. Chem.* **1995**, *60*, 5831. (b) Park, W. K. K.; Auer, M.; Jaksche, H.; Wong, C. H. *J. Am. Chem. Soc.* **1996**, *118*, 10150. (c) Sauvagnat, B.; Lamaty, F.; Lazaro, R.; Martinez, J. *Tetrahedron Lett.* **1998**, *39*, 821. (d) Molteni, V.; Annunziata, R.; Cinquini, M.; Cozzi, F.; Benaglia, M. *Tetrahedron Lett.* **1998**, *39*, 1257. (e) Dreef-Tromp, C. M.; Willems, H. A. N.; Westerduin, P.; van Veelen, P.; van Boeckel, C. A. A. *Biorg. Med. Chem. Lett.* **1997**, *7*, 1175. (f) Blettner, C. G.; Konig, W. A.; Stenzel, W.; Schotten, T. *Synlett* **1998**, 295.

(6) For recent immobilization of ligands and reagents on PEG and other soluble polymers not included in refs 2 and 5, see: (a) Han, H.; Janda, K. D. *J. Am. Chem. Soc.* **1996**, *118*, 7632. (b) Han, H.; Janda, K. D. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1731. (c) Gerlach, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 741. (d) Wipf, P.; Venkatraman, S. *Tetrahedron Lett.* **1996**, *37*, 4659. (e) Wentworth, P.; Vandersteen, A. M.; Janda, K. D. *J. Chem. Soc., Chem. Commun.* **1997**, 750. (e) Hori, M.; Janda, K. D. *J. Org. Chem.* **1998**, *63*, 889. (f) Felder, M.; Giffels, G.; Wandrey, C. *Tetrahedron: Asymmetry* **1997**, *8*, 1975.

(7) For recent developments of a linker connecting small organic molecules to PEG, see refs 2, 5, 6, and (a) Jung, K. W.; Zhao, X.; Janda, K. D. *Tetrahedron Lett.* **1996**, *37*, 6491. (b) Zhao, X.; Jung, K. W.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 977. (c) Zhao, X.; Janda, K. D. *Tetrahedron Lett.* **1997**, *38*, 5437. (d) Jung, K. W.; Zhao, X.; Janda, K. D. *Tetrahedron* **1997**, *53*, 6645.

(8) A soluble, non-cross-linked polystyrene (loading 0.3 mequiv/g) has been recently used as support for the total synthesis of prostaglandin F$_{2\alpha}$: Chen, S.; Janda, K. D. *Tetrahedron Lett.* **1998**, *39*, 3943.

Scheme 1

3, R = COOMe
4, R = COOH
5, R = CH$_2$OH
6, R = CHO
7, R = CH$_2$Cl

$\square$ = - CH$_2$CH$_2$-(-OCH$_2$CH$_2$-)$_n$- ,   MW 4600

PEG polymers to generate new, soluble PEG supports of expanded functional group capacity. We report here some preliminary results along this line.

The bismesylate **1**, obtained from PEG$_{4600}$ in 98% yield by a modification of a reported procedure,[7c] was reacted (Scheme 1) with dimethyl 5-hydroxyisophthalate (**2**) and Cs$_2$CO$_3$ (3.0 mol equiv of each reagent/OMs group) in DMF (50 °C, 15 h) to afford the tetraester **3** in 95% yield.[10] Hydrolysis of this (10 mL of 2 M aqueous KOH/g of **3**, rt, 15 h) followed by acidification gave the tetraacid **4** in 70% yield. Reduction of the ester **3** with 2 N DIBALH in CH$_2$Cl$_2$ (2.5 mol equiv/COOMe group, −78 °C to rt, 15 h) afforded the tetraol **5** in 83% yield. From this compound, which features four easily removable benzylic hydroxyl groups, the tetraaldehyde **6** was synthesized by oxidation with MnO$_2$ (4.0 mol equiv/OH group, CH$_2$Cl$_2$, rt, 72 h, 71% yield), and the tetrachloride **7** by reaction with SOCl$_2$ (3.0 mol equiv/OH group) in the presence of pyridine (1.2 mol equiv/OH group) in refluxing toluene (15 h, 60% yield). Thus five different functionalities amenable to a variety of synthetic manipulations could be easily attached to the polymer backbone.

To demonstrate the possibility of performing on this polyfunctionalized PEG some synthetically relevant chemistry, the reaction sequence reported in Scheme 2 was then carried out. Thus, the tetraol **5** was transformed into the tetra-*N*-Boc glycinate **8** by reaction with *N*-Boc glycine, DCC, and DMAP (1.6 mol equiv of each reagent/OH group, refluxing CH$_2$Cl$_2$, 15 h, 94% yield). Removal of the protecting group (30 mL of a 2:1 TFA:CH$_2$Cl$_2$ mixture/g of polymer, rt, 2 h; then aqueous NaHCO$_3$) gave the tetramine **9** in 83% yield.[11]

This was transformed into imine **10** by two different procedures, both occurring in quantitative yield. One method[5d] involved reaction with neat benzaldehyde (3.0 mol equiv/

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(9) (a) Tomalia, D. A.; Durst, H. D. *Top. Curr. Chem.* **1993**, *165*, 193. (b) Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* **1995**, *132*, 875. (c) Zeng, F.; Zimmermann, S. C. *Chem. Rev.* **1997**, *97*, 1681. (d) For a recent example of dendrimer-supported combinatorial chemistry, see: Kim, R. M.; Manna, M.; Hutchins, S. M.; Griffin, P. R.; Yates, N. A.; Bernick, A. M.; Chapman, K. T. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 10012.

(10) The yields of compounds **3**−**11**, **13**, and **14** were determined assuming a MW of 4600 Da for the PEG fragment. The supported products were purified by precipitation in Et$_2$O and removal of the excess nonimmobilized reagents by Et$_2$O washings. Their purity was determined by 300 MHz ^{1}H NMR analysis in CDCl$_3$ (with presaturation of the CH$_2$ signals of the polymer at 3.63 ppm) exploiting the PEG−OC*H*$_2$CH$_2$O−Ar signal at 3.87 ppm as internal standard. The estimated integration error is ± 7%. The PEG−OCH$_2$C*H*$_2$O−Ar signal of compounds **3**−**11**, **13**, **14** resonates at 4.20 (for compounds **3**, **4**, **6**), 4.16 (**5**), 4.12 (**7**), 4.08 (**8**), 4.15 (**9**), 4.10 (**10**, **13**), 4.12 (**11**), 4.13 (**14**) ppm, respectively.

(11) Tetraamine **9** was generally stored as its *N*-Boc derivative or trifluoroacetate salt and liberated immediately before use.

Scheme 2
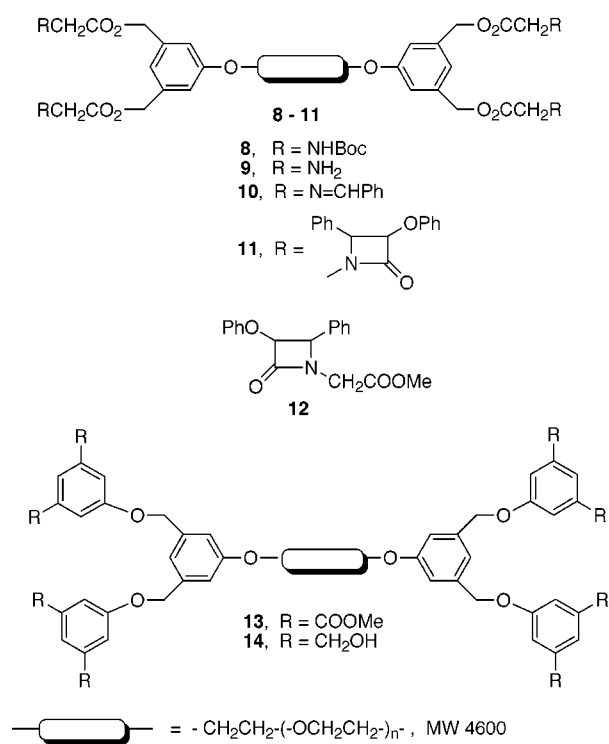
NH$_2$ group) at 80 °C for 2 h, followed by in vacuo removal of the excess benzaldehyde; the other[12] required reaction with benzaldehyde (2.0 mol equiv/NH$_2$ group) in a 7:3 (MeO)$_3$-CH:CH$_2$Cl$_2$ mixture as solvent (10 mL/g of polymer) for 15 h at rt.

Among the variety of different synthetic applications that exploit the imine functionality, β-lactam formation was selected because of its relevance.[13] Thus, imine **10** was reacted in a Staudinger cycloaddition process with phenoxy-acetyl chloride and TEA (10 mol equiv each/imino group) in CH$_2$Cl$_2$ at rt for 18 h to afford the tetralactam **11** in 81% yield.[14] Release of the azetidinones from the polymer was

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(12) Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937.

(13) Two other syntheses of β-lactams on a polymer matrix have been reported, see ref 5d (on MeOPEG$_{5000}$) and Ruhland, B.; Bhandari, A.; Gordon, E. M.; Gallop, M. A. *J. Am. Chem. Soc.* **1996**, *118*, 253 (on Sasrin).

attempted in different conditions. The best, yet unoptimized result (57% yield of isolated **12**) was obtained using TEA in MeOH (1:3 mixture, 5 mL/g of polymer, 50 °C, 18 h).[15,16] Remarkably, in these conditions the functionalized polymeric support, namely the tetraol **5**, could be recovered and recycled; furthermore, it must be noted that throughout the reaction sequence the modified polymer support retained its usual solubility/insolubility properties.

Finally, the possibility of further expanding the loading capacity of these new PEG materials was investigated. To this end, tetrachloride **7** was reacted with phenol **2** (3.0 mol equiv/Cl group) in the presence of Cs$_2$CO$_3$ (3.0 mol equiv/Cl group) in DMF (50 °C, 48 h) to afford the octaester **13** in 71% yield. Reduction of this with an excess of DIBALH (see above) gave the octaol **14** in 65% yield.

In conclusion, the synthesis of some highly loaded PEGs featuring different functional groups has been performed using very simple chemical transformations. These derivatives retain the solubility/insolubility features of the commonly used PEG supports, as demonstrated by the synthesis of β-lactam **12**. Work is in progress to extend the use of these new polymeric matrixes to other soluble polymer-supported syntheses.

Supporting Information Available: Complete experimental details for the preparation of all the products; ^{1}H NMR and IR spectral data for the modified PEG compounds **3**−**11**, **13**, **14**; mp, ^{1}H and ^{13}C NMR, IR, and elemental analytical data for β-lactam **12** (4 pages).

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(14) 300 MHz ^{1}H NMR analysis showed that the β-lactams in **11** were obtained in the cis configuration ($J_{H3/H4} = 4.5$ Hz).

(15) A control experiment showed β-lactam **12** to be both chemically and stereochemically stable in the removal conditions. This was a new compound (mp 130−131 °C) that gave elemental analysis and spectral data (^{1}H and ^{13}C NMR, IR) in agreement with the proposed structure (see Supporting Information).

(16) A β-lactam having the same substituents at C-3 and C-4 featured by **12** was obtained in 52% overall yield (for the cycloaddition and removal steps) starting from an imine immobilized on MeOPEG$_{5000}$ (ref 5d). Taking into account the loading of MeOPEG$_{5000}$ (0.2 mequiv/g), that of PEG **9** (0.8 mequiv/g), and the overall yield of the same steps by which **12** has been obtained in this work (46%), it can be concluded that the use of PEG **9** allowed almost a 4-fold increase in the yield of the β-lactam with respect to the use of MeOPEG$_{5000}$.