Available online at www.sciencedirect.com

Tetrahedron Letters 46 (2005) 1827–1829

Tetrahedron Letters

# Oligomeric ethylene glycols as sorting tags for parallel and combinatorial mixture synthesis

Craig S. Wilcox* and Serhan Turkyilmaz

*Department of Chemistry, University of Pittsburgh, Pittsburgh, PA 15260, USA*

Received 22 December 2004; accepted 21 January 2005

**Abstract**—Sorting tags for chromatography allow mixtures of substrates to be carried through parallel chemical processes and then separated. The first sorting tags were fluorocarbons. An enabling characteristic of fluorous sorting tags is the predictable incremental increase in retention time with increasing fluorocarbon chain length. Here we describe a general approach to sorting tags and report our discovery of a second class of chromatographic tags. The new tags are oligomeric ethylene glycol (OEG) derivatives.

Solid phase chemical synthesis methods revolutionized protein and polynucleotide synthesis and are now an important method for small molecule chemical discovery.[1] The benefits of employing solid support methods include the ease of first-pass purification of the tethered products and the possibility of generating very large libraries through systematic diversification strategies. These benefits come with a cost. Reaction conditions that have been developed for homogeneous ('solution phase') reactions can require substantial re-optimization for use on solid supports.[1a] Also, some solution phase reactions are not transferable to solid phase because of the needed temperatures or pressures, or the need to have rapidly diffusing reactive intermediates,[2] may be incompatible with high molecular weight supports. Monitoring reaction progress and characterizing products still bound to the support is challenging.[3] Expensive, specialized equipment is often employed, and scale-up of the optimized solid phase process is not feasible.

To circumvent some of these difficulties with solid phase methods, researchers have pursued alternative solution phase methods such as liquid phase combinatorial synthesis,[4] indexed combinatorial libraries,[5] template-based libraries,[6] precipitons,[7] and fluorous mixture synthesis (FMS).[8] In FMS, substrates attached to perfluorinated sorting tags of differing lengths are mixed, taken through a certain number of reactions as a mixture and demixed (i.e., separated) using fluorous chromatography. This approach to accelerated chemical synthesis has significant promise.

An enabling characteristic of fluorous tags used for chromatographic separations is the predictable incremental increase in retention time with increasing fluorocarbon chain length. We sought to develop a second class of chromatography tags to complement the fluorous tags. To have at hand different classes of sorting tags could amplify the power of mixture synthesis. In this letter we wish to communicate our development of oligomeric ethylene glycol (OEG) derivatives as chromatographic sorting tags.

This project was focused on OEG derivatives (**1**) that contain five or fewer ethylene glycol subunits. OEG derivatives (named 'lariat ethers' in the seminal work by Gokel et al.[9]) form complexes with group IA cations such as $Li^+$, $Na^+$, and $K^+$. The magnitudes of the formation constants ($K_f$) for these complexes differ with the length of the OEG unit.[9,10] For this reason we surmised that OEG tags might work well as sorting tags on standard chromatography columns or on columns doped with group IA cations. The low cost of starting materials for these tags further encouraged us to investigate the potential of these molecules as sorting tags.

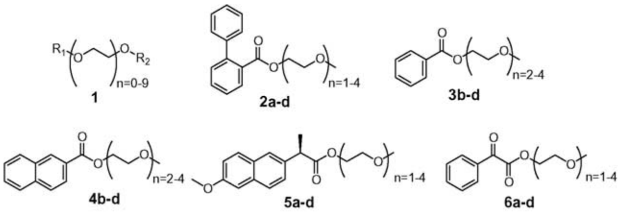
Esters **2a**–**6d** were prepared via conventional methods from commercially available starting materials. A mixture containing 18 of these esters was prepared and separation was tested on several chromatographic columns.

---

*Keywords*: Parallel synthesis; Sorting tags.

* Corresponding author. Tel.: +1 4126248269; fax: +1 4126248611; e-mail: daylite@pitt.edu

0040-4039/$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2005.01.109



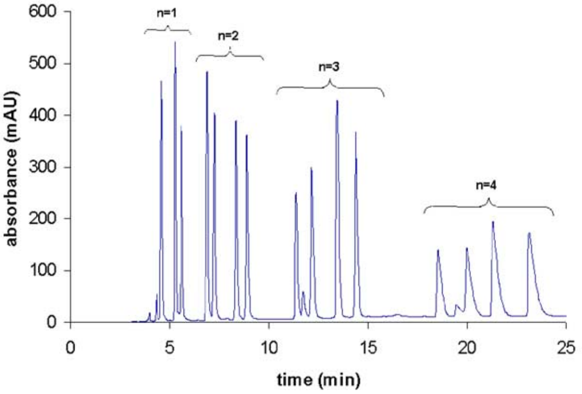


**Figure 1.** Separation of **2a**–**6d** on a 5μ Supelcosil™ column (gradient: 3:7 EtOAc–hexane to 8:2 EtOAc–hexane in 20 min, flowrate: 1 mL/min).

**Table 1.** Separation of esters **5a**–**d** by TLC under various conditions

| Entry | $[M^+]$ (mol/cm$^2$)[a] | **5a**[b,h] | **5b**[b,h] | **5c**[b,h] | **5d**[b,h] | Eluent |
|---|---|---|---|---|---|---|
| 1 | 0 | 0.70 | 0.60 | 0.46 | 0.34 | EtOAc |
| 2 | $1.72 \times 10^{-5}$ ($Li^+$) | 0.75 | 0.64 | 0.33 | 0.18 | EtOAc |
| 3 | $3.73 \times 10^{-5}$ ($Li^+$) | 0.76 | 0.63 | 0.34 | 0.19 | EtOAc |
| 4 | $6.63 \times 10^{-5}$ ($Li^+$) | 0.70 | 0.6 | 0.34 | 0.16 | EtOAc |
| 5 | $8.73 \times 10^{-5}$ ($Li^+$) | 0.71 | 0.59 | 0.22 | 0.11 | EtOAc |
| 6 | $1.09 \times 10^{-4}$ ($Li^+$) | 0.70 | 0.59 | 0.22 | 0.10 | EtOAc |
| 7 | $8.9 \times 10^{-5}$ ($Na^+$) | 0.75 | 0.63 | 0.48 | 0.38 | EtOAc |
| 8 | $6.1 \times 10^{-5}$ ($K^+$) | 0.78 | 0.68 | 0.53 | 0.33 | EtOAc |
| 9 | 0 | 0.50 | 0.29 | 0.15 | 0.08 | [c] |
| 10 | $8.73 \times 10^{-5}$ ($Li^+$) | 0.56 | 0.34 | 0.08 | 0.03 | [c] |
| 11 | $8.73 \times 10^{-5}$ ($Li^+$) | 0.59 | 0.48 | 0.30 | 0.20 | [d] |
| 12 | $8.73 \times 10^{-5}$ ($Li^+$) | 0.78 | 0.75 | 0.68 | 0.62 | DME |
| 13 | $8.73 \times 10^{-5}$ ($Li^+$) | 0.58 | 0.45 | 0.23 | 0.11 | [e] |
| 14 | $8.73 \times 10^{-5}$ ($Li^+$) | 0.64 | 0.58 | 0.50 | 0.39 | THF |
| 15 | 0 | 0.73 | 0.65 | 0.51 | 0.38 | [f] |
| 16 | 0 | 0.75 | 0.64 | 0.61 | 0.58 | [g] |
| 17 | $3.73 \times 10^{-5}$ ($Li^+$) | 0.78 | 0.65 | 0.43 | 0.30 | [g] |

[a] Conc. of metal ions on the surface of the TLC plate.

[b] $R_f$ values.

[c] 1:1 EtOAc–hexane.

[d] 1:1 DME–hexane.

[e] 1:1 THF–hexane.

[f] 0.1 M $LiClO_4$ in EtOAc.

[g] 1 M $LiClO_4$ in EtOAc.

[h] Variation in $R_f$ values was ±0.05.

In a single pass on a normal silica column (5μ Supelcosil), 17 of the 18 esters were separated (Fig. 1). Identification of individual peaks was accomplished by comparing the retention times of pure compounds to the retention times of components in the mixture and by analyzing the UV–vis spectra of the component peaks.

The esters were separated into four major subregions based on the length of the OEG moiety. Within each subregion, the separation was dependent on the structure of the acid component portion. The elution order was conserved within each subregion (**2**–**6**). Similar chromatograms were obtained on another silica column (10μ VersaPak) and on a cyclodextrin column (5μ Cyclobond I).

We anticipated that additions of group IA cations to the chromatography medium would modify the retention times of OEG tagged molecules. To test this, a number of TLC plates were prepared by immersing standard analytical silica plates in aqueous solutions of different salts and then drying the plates at 150 °C.

The $R_f$ values for **5a**–**d** on these treated and untreated TLC plates and with a number of eluents were recorded (Table 1, Fig. 2). It was found that improved separation was obtained for $8.73 \times 10^{-5}$ mol/cm$^2$ concentration of $Li^+$ (entries 1–6). The retarding effect is larger for the longer OEGs **5c** and **d** than for the shorter tagged esters **5a** and **b**. The comparative lack of effect of $Na^+$ and $K^+$ salts (entries 6–7) agrees with the known $K_f$ values for OEG/$Li^+$ and OEG/$Na^+$ complexes.[10] Both DME and THF caused the esters to elute closer to each other (entries 9–14). Equilibria that may affect the retention of these esters are illustrated in Figure 3. The effects of soluble lithium salts (entries 15–17) indicate the complex (c) may be more mobile than free ligand (Fig. 3).

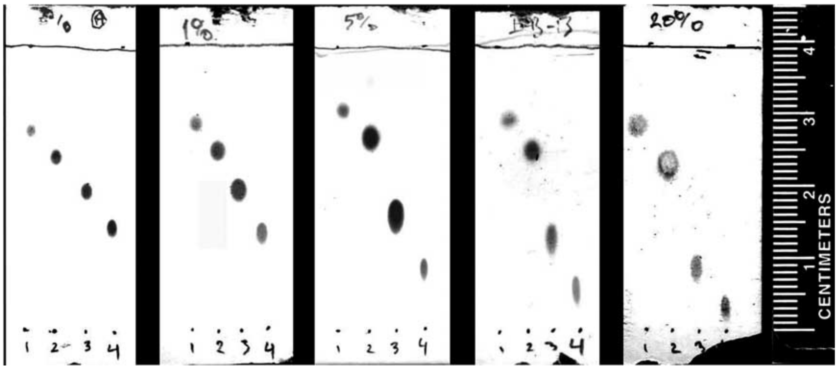


**Figure 2.** TLC results for esters **5a**–**d**. Plates were immersed in 0, 1.3, 2.6, 3.9, and 5.2 M aqueous LiCl (respectively, from left to right) and then dried prior to development with EtOAc.

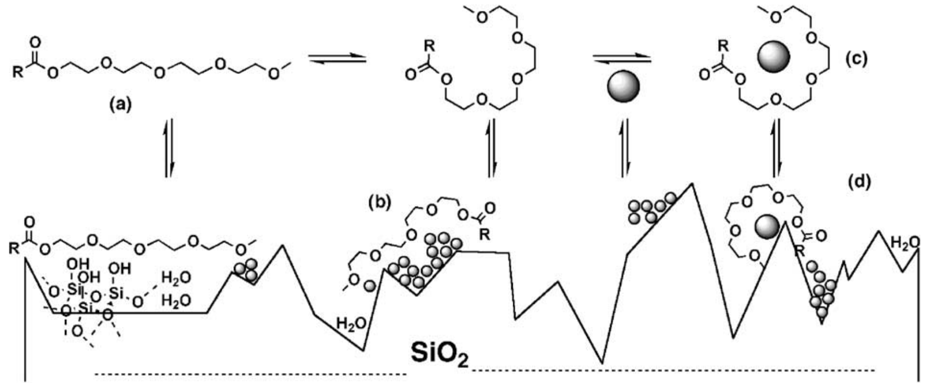


**Figure 3.** Representations of physical processes that may affect elution characteristics.

We conclude from this study that OEG derivatives can be useful sorting tags for chromatography. They are not expensive and separations can be achieved with standard laboratory equipment (we have used a HPLC and flash columns) on regular silica media. OEG tags can be used together with fluorinated tags to further the scope of mixture synthesis.

Unlike fluorinated tags, OEG tags have an NMR fingerprint (4.2–3.0 ppm in $^1$H NMR), which might interfere with the characterization of some OEG-bound substrates, but we do not expect this to prohibit OEG tag use because often analytically important hydrogen resonances lie outside this region. OEG tags could decompose under conditions that cause PEG depolymerization. Judicious choice of reaction conditions should minimize the impact of this limitation. Further studies of the properties of OEG tags and their synthetic applications are currently underway in our laboratory.

## Acknowledgements

We thank the National Institute of General Medical Sciences for support of this work.

## Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2005.01.109.

## References and notes

1. (a) Seneci, P. *Solid phase synthesis and combinatorial technologies*; Wiley-Interscience: New York, NY, 1998; (b) Thompson, L. A.; Ellman, J. A. *Chem. Rev.* **1996**, *96*, 555–600; (c) Lam, K. S.; Lebl, M.; Krchnak, V. *Chem. Rev.* **1997**, *97*, 411–448.
2. Honigfort, M. E.; Brittain, W. J.; Bosanac, T.; Wilcox, C. S. *Macromolecules* **2002**, *35*, 4849–4851.
3. Yan, B. *Acc. Chem. Res.* **1998**, *31*, 621–630.
4. (a) Han, H.; Wolfe, M. M.; Brenner, S.; Janda, K. D. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 6419–6423; (b) Gravert, D. J.; Janda, K. D. *Chem. Rev.* **1997**, *97*, 489–509.
5. (a) Pirrung, M. C.; Chen, J. *J. Am. Chem. Soc.* **1995**, *117*, 1240–1245; (b) Pirrung, M. C.; Chau, J. H.-L.; Chen, J. *Chem. Biol.* **1995**, *2*, 621–626.
6. (a) Cheng, S.; Tarby, C. M.; Comer, D. D.; Williams, J. P.; Caporale, L. H.; Myers, P. L.; Boger, D. L. *Bioorg. Med. Chem.* **1996**, *4*, 727–737; (b) Cheng, S.; Comer, D. D.; Williams, J. P.; Myers, P. L.; Boger, D. L. *J. Am. Chem. Soc.* **1996**, *118*, 2567–2573; (c) Boger, D. L.; Tarby, C. M.; Comer, D. D.; Myers, P. L.; Caporale, L. H. *J. Am. Chem. Soc.* **1996**, *118*, 2109–2110.
7. (a) Bosanac, T.; Yang, J. M.; Wilcox, C. S. *Angew. Chem., Int. Ed. Engl.* **2001**, *40*, 1875–1879; (b) Bosanac, T.; Wilcox, C. S. *J. Am. Chem. Soc.* **2002**, *124*, 4194–4195.
8. (a) Luo, Z.; Zhang, Q.; Oderaotoshi, Y.; Curran, D. P. *Science* **2001**, *291*, 1766–1769; (b) Curran, D. P.; Oderaotoshi, Y. *Tetrahedron* **2001**, *57*, 5243–5253; (c) Curran, D. P.; Furukawa, T. *Org. Lett.* **2002**, *4*, 2233–2235; (d) Zhang, Q.; Rivkin, A.; Curran, D. P. *J. Am. Chem. Soc.* **2002**, *124*, 5774–5781.
9. Gokel, G. W.; Dishong, D. M.; Diamond, C. J. *Chem. Commun.* **1980**, *22*, 1053–1054.
10. Chan, L. L.; Wong, K. H.; Smid, J. *J. Am. Chem. Soc.* **1970**, *92*, 1955–1963.