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Formation of hybrid polymethylene–poly(oxyethylene) macrocycles

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Abstract—Macrocyclisations, particularly those forming crown ethers, normally require high *dilution* conditions. However, treatment of 1,9-bis(sarcosylamino)nonane with α,ω-bis(oxiranylmethyl) ethers derived from oligomeric poly(ethyleneglycol)s of MW 400–600 Da under high *concentration* conditions was found to give excellent yields of 1:1 hybrid polymethylene–poly(oxyethylene) macrocyclic crown ether derivatives. The corresponding α,ω-bis(oxiranylmethyl) ether derived from poly(ethyleneglycol) of mean MW 1500 Da gave polymeric material only. The macrocycles were characterised by NMR, GPC and MS.

Currently, routes to macrocyclic polyethers, such as crown ethers, and hybrid hydrocarbon–polyether macrocycles require high dilution (or *pseudo* high dilution) conditions to avoid polymerisation.[1,2] There is strong interest in the development of new high-yielding methods avoiding very low concentration conditions for formation of large macrocyclic crown ether derivatives.[3–6] Adventitious macrocyclisations during attempted polymerisations are also being studied.[7] As part of a programme of preparation and evaluation of biodegradable polymers for applications in delivery of therapeutic and diagnostic agents to tumours,[8–11] we developed a polymerisation strategy for the synthesis of alternating co-polymers of peptide and poly(oxyethylene) (PEG) units.[12] For this polymerisation, we proposed the reaction of nucleophilic peptide α,ω-secondary amines with electrophilic PEG α,ω-diglycidyl ethers. The elegance of this approach is that the chemistry is an addition reaction, obviating the formation of co-products that have to be removed from the polymer. This method proved successful in polymerisation of α,ω-bis(methylamino)peptides[10] with PEG derivatives. However, as part of our model studies on this polymerisation process, the reactions of a simple α,ω-secondary amine, 1,9-bis(sarcosylamino)nonane **4**, with PEG α,ω-diglycidyl ethers were also investigated.

To provide a model for the α,ω-bis(methylamino)peptides, Cbz-sarcosine **1**[13] was firstly converted to its 2,4,5-trichlorophenyl ester **2**, which was used to acylate nonane-1,9-diamine **3** to give 1,9-bis(Cbz-sarcosinamido)nonane **4**[14] (Scheme 1). Deprotection by hydrogenolysis afforded 1,9-bis(sarcosylamino)nonane **5**.[14] The chain length of **5** corresponds closely to the typical dimensions of our tetrapeptide derivatives. We have previously described[12] the conversion of PEG 1500 **6c** into the corresponding electrophilic α,ω-bis(oxiranylmethoxy) derivative **7c** by treatment with epichlorohydrin and sodium hydroxide, in a modification of the general method of Gu et al.[15] This process has now been extended to the lower oligomers PEG 400 **6a** and 3,6,9,12,15-pentaoxaheptadecane-1,17-diol **6b**, giving **7a** and **7b**, respectively.[16] In this process, the polyether acts as both phase-transfer catalyst and substrate enabling conversion of the end-groups with >97% efficiency, as determined by ^{13}C NMR.

In our typical polymerisation procedure, a high concentration (10% w/v) of the two bifunctional reagents are stirred in refluxing ethanol for ca. 15 h. Surprisingly, reaction of α,ω-bis(oxiranylmethyl) PEG 400 **7a** with the diamine **5** under these conditions[17] gave a mixture of 1:1 macrocycles **8a** in excellent yield (Scheme 1). GPC analysis[18] (Fig. 1A) showed only material in the MW range 600–1000 Da for **8a**. However, the ^1H NMR spectrum[19] (Fig. 1B) demonstrated complete reaction of all end-groups as shown by the absence of epoxide resonances. The sarcosine CH_2 resonances appeared as a pair of doublets, reporting an asymmetric environment. Such an asymmetric environment is created when the oxirane is opened by the secondary amine, forming a secondary alcohol.

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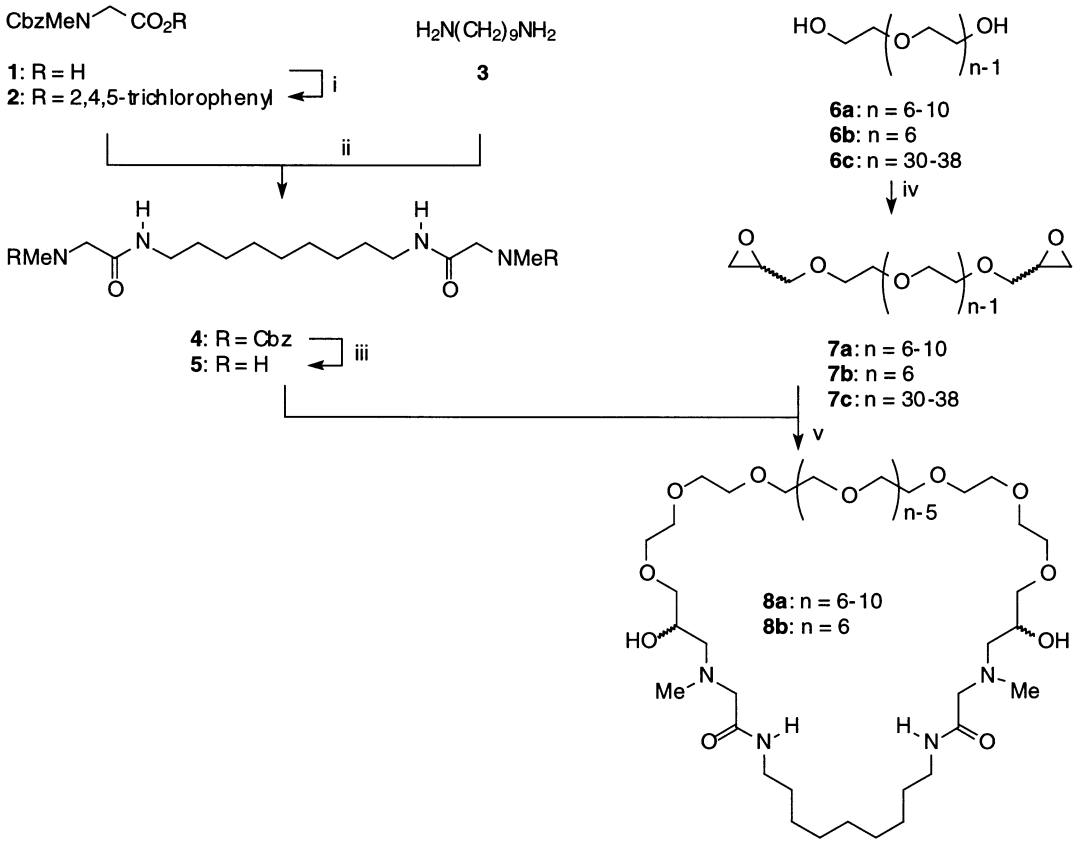

Scheme 1. Synthesis of the hybrid polymethylene–poly(oxyethylene) macrocycles **8a**,**b**. *Reagents and conditions*: i, 2,4,5-trichlorophenol, dicyclohexylcarbodiimide, EtOAc, 0°C, 4 h, 85%; ii. $Pr^{i}_{2}NEt$, DMAP, CH_2Cl_2, 7 days, 91%; iii, H_2, Pd/C, MeOH, 2 days, 99%; iv, epichlorohydrin, NaOH, water (trace), 65°C, 2 h, 68% (**7a**), 90% (**7b**), 76% (**7c**); v, EtOH (10% w/v solution), 15 h, reflux, 99% (**8a**), 97% (**8b**).

Electrospray and FAB mass spectroscopic analysis reconciled this apparent dichotomy. Ions corresponding to $[M+H]^+$, $[M+Na]^+$ and $[M+K]^+$ for the oligomeric macrocycles **8a** were observed (Fig. 1C). The relative abundances of these *pseudo*molecular ions fitted well with the oligomeric composition of the starting PEG 400 diglycidyl ether **7a**.

This interesting macrocyclisation prompted us to investigate the reaction of the monodisperse oligomer **7b** (a component of the PEG 400 derivative **7a**) and of the much longer polydisperse **7c**. Similar treatment of the defined-length oligomer **7b** afforded the corresponding 1:1 macrocycle **8b** in high yield as confirmed by ^1H NMR and MS. However, the analogous reaction of

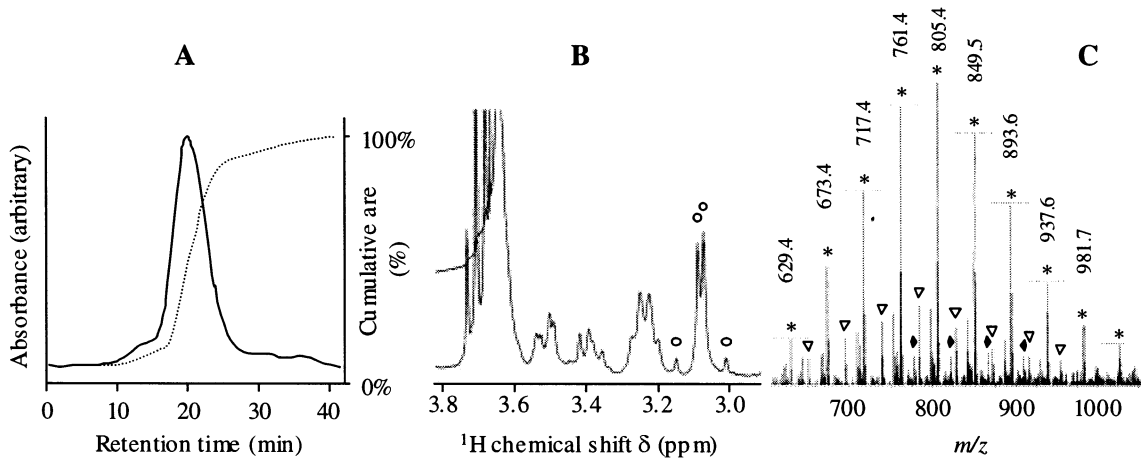

Figure 1. GPC trace (**A**), part of ^1H NMR spectrum (**B**) and electrospay MS (**C**) of **8a**. In **B**, signals marked ○ are assigned to the Sar-CH_2. In **C**, peaks marked ▽ are $[M+H]^+$, peaks marked * are $[M+Na]^+$ and peaks marked ♦ are $[M+K]^+$.

α,ω-bis(oxiranylmethyl) PEG 1500 **7c** with **5** was shown by GPC to give predominantly polymeric material.

The reaction proceeds by an initial addition of one secondary amine to one oxirane. Subsequently, it may be postulated that macrocyclisation occurs only when the polyether is pre-organised. It may be speculated that complexation to a sodium cation facilitates the movement of the remaining oxirane and secondary amine into close proximity. Such traces of sodium ions may be adventitiously present as a minor contaminant in **7a**,**b**. In this context, it is notable that the [M+Na] peaks are highly abundant for all oligomers of **7a** in the electrospray MS, whereas the [M+K] ions are of low abundance and are absent for the lower oligomers. In the case of **7c**, an analogous complexation would not bring about this favourable conformation.

This straightforward method of preparing hybrid polyether–hydrocarbon macrocycles opens avenues of approach to a wide range of functionalised hybrid macrocycles. Our continuing investigations are exploring the detail and the generality of the process.

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16. **Synthesis of 7a.** PEG 400 **6a** (5.00 g, 12.5 mmol) was added dropwise to epichlorohydrin (6.75 g, 75 mmol), NaOH (3.0 g, 7.5 mmol) and water (0.3 mL) and was stirred at 65°C for 2 h. The cooled suspension was filtered and the solids were washed with CH_2Cl_2. Drying and evaporation gave **7a** (4.49 g, 71%).
17. **Synthesis of 8a.** Compounds **5** (500 mg, 1.66 mmol) and **7a** (806 mg, 1.66 mmol) were heated at reflux in EtOH (10 mL) for 15 h. Evaporation gave **8a** (1.30 g, 99%) as a colourless gum.
18. Bruker LC 21/41 system; THF eluant at 1 mL min^{-1}; 'PL Gel' (Polymer Laboratories).
19. ^{1}H NMR data for **8a**: δ ($CDCl_3$) 1.29 (10 H, brs, $CH_2CH_2(CH_2)_5CH_2CH_2$), 1.49 (4 H, br, 2×NCH_2CH_2), 2.34 (6 H, s, 2×NMe), 2.42 (2 H, dd, J=13, 4 Hz) and 2.50 (2 H, dd, J=13, 8 Hz) (2×NCH_2CHOH), 3.05 (2 H, d, J=16 Hz) and 3.10 (2 H, d, J=16 Hz) (2×Sar-H_2), 3.23 (4 H, q, J=7 Hz, 2×NCH_2CH_2), 3.35–3.55 (4 H, m, 2×OCH_2CHOH), 3.62 (ca. 35 H, br, 9×OCH_2CH_2O), 3.91 (2 H, m, 2×$CHOH$), 7.45 (2 H, br, 2×NH).