Synthesis and Characterisation of New Monomethoxypoly(Ethylene Glycol) (mPEG) Carbonate Ester Surfactants

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New A B and A–B–A carbonate-esters, where A represents the hydrophilic part and B the lipophilic part, comprising monomethoxypoly(ethylene glycol) (mPEG) and a long chain carboxylic acid, have been synthesised. The synthetic approach to these compounds involved the alkylative esterification of aliphatic carboxylic acid as the key step. For the A B type compounds, the palmitic acid salt reacted chemoselectively with ambident α-chloroalkylcarbonates 8 in DMF provided cesium was the counter-ion. With methyl substitution on the alkyl halide the mode of reaction was slightly altered, leading to unravelling of the alkylating agent structure via a presumed interaction with DMF. The decomposition fragments were detected in HPLC and in NMR designed experiments. For the A–B–A analogue, the tetrabutylammonium salt of docosanedioic acid was first alkylated with an ethylthio derivative of chloromethyl chloroformate and then converted into the carboyl chloride that was used effectively to acylate mPEG alcohol. These new compounds have been studied to establish their properties as surfactants. Enzymatic hydrolysis studies have shown enhanced degradation of the carbonate ester function in comparison with ordinary esters.

Surfactants are useful additives in many industrial and pharmaceutical applications.[1] The chemical structures of most surfactants are amphiphilic, i.e. they contain both a hydrophilic and a hydrophobic part. Since most pharmaceutical applications involve aqueous solutions, non-ionic surfactants consisting of poly(ethylene glycol) (PEG) as the hydrophilic component are particularly attractive.[2] PEG presents outstanding physico-chemical and biological properties, such as solubility in water and organic solvents, ease of chemical modification,[3] lack of toxicity and absence of antigenicity and immunogenicity.[4] Commercially available surfactants that have PEG block lengths include ethers of the type $R(OCH_2CH_2)_nOH$ and esters of the type $RCO(OCH_2CH_2)_nOH$, where R represents a long-chain aliphatic group, and are marketed under the trade names Brij and Myrj, respectively.[5] By appropriately balancing the length of the hydrophobic fatty moiety and the degree of polymerisation of the hydrophilic poly(ethylene glycol) segment, a wide variety of surfactant properties may be achieved and have been used in many cosmetic, pharmaceutical and industrial applications, for example as emulsifiers, wetting agents, solubilisers, defoamers,

conditioning agents, lubricants and detergents.[1] Considering their widespread use it is desirable that PEG-based surfactants should exhibit a significant degree of biodegradability in order to minimise the risk of environmental accumulation. Whilst the ester linkage between PEG and fatty acid moieties will ultimately be hydrolytically cleaved, surfactants exhibiting a higher rate of hydrolysis may possess a number of significant advantages. It is with this consideration in mind that we undertook to design, synthesise and evaluate the carbonate ester surfactants 1 and 2 shown in Fig. 1. Both structures will be designated as A–B- and A–B–A-type surfactants. The degree of polymerisation of mPEG was

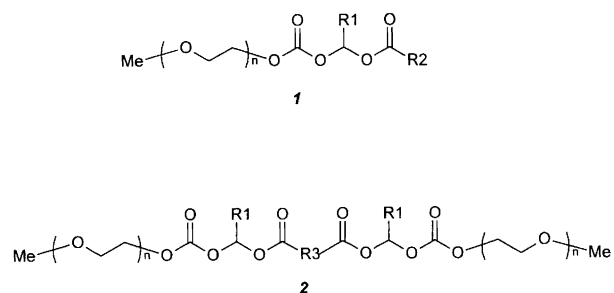*Fig. 1.* The designed target structures.

selected as $n = 12$, 22, 112, so as to cover a broad range of sizes. The lipophilic chain, R2, is palmitic acid, while R3 is a dicarboxylic acid component. Further, a single carbon atom, with or without substituent, links the carbonate and the ester functional groups. In this paper we present the results of our efforts to develop synthetic methods for these compounds. Also described are the surfactant properties of the mPEG carbonate ester derivatives. In the final section, this paper examines the biodegradability of these new amphiphilic molecules. It reports the rate of degradation of the double esters under enzymatic conditions. The results are compared with the degradation rate of the corresponding mPEG esters.

Results and discussion

Synthesis. Although other structural arrangements are possible, concern over the tolerability of the degradation products and the synthetic convenience weighed heavily in favour of the chosen target structures. The approaches towards the desired molecules are outlined in the retrosynthetic sketches shown in Fig. 2. These are: path (a) alkylative esterification of carboxylic acid **4** using the alkyl halide **3** and path (b) the acylation of monomethoxyPEG using the reagent **5**.

A–B-Type. First we attempted the synthesis of the A–B-type substances as shown in Scheme 1. Here, the halide required in the alkylation process was obtained by treating mPEG alcohol with chloroalkyl chloroformate in the presence of pyridine.[7–9] The results are summarised in Table 1 and as can be seen, mPEG of selected molecular weights reacted to afford the corresponding carbonates **8**. Analytical high-performance chromatography (HPLC)[10] served as a useful tool in monitoring the formation and purity of the products. Purification of products was easily accomplished by precipitation from ether solution of crude product by addition of pentane.[11] The yields of product were almost identical in all cases, but the time for completion of reaction varied according to the molecular weight of the PEG employed. The moderate yields obtained in these reactions were probably due to increased solubility of the derivatives **8** in
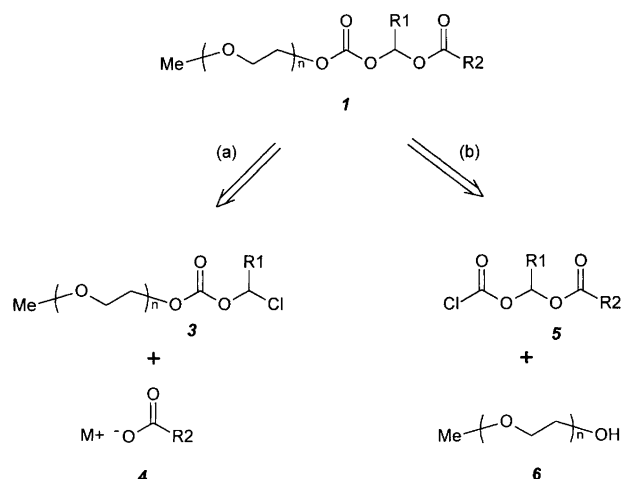
Fig. 2. Retroanalysis of target.

Table 1. Acylation of mPEG using chloroalkyl chloroformates.

Compound	n	R^2	Reaction time/h	Yield (%)
8a	12	H	3	59
8b	22	H	3	63
8c	112	H	72	61
8d	12	CH_3	3	67
8e	22	CH_3	3	68
8f	112	CH_3	72	73

the precipitation system and loss of material during the decantations. In addition, we observed that this acylation reaction of mPEG sizes was sensitive to the type of solvent employed. Thus, while THF was suitable solvent for acylation of mPEG of $n = 12$ and 22, no reaction took place when MPEG of $n = 112$ was employed. This large sized mPEG was eventually acylated in acetonitrile under standard conditions.

With the PEG chloroalkyl carbonate secured, *O*-alkylation of palmitic acid[12] was attempted. Several methods have been reported in the literature for efficient alkylative esterification carboxylic acids where a variety
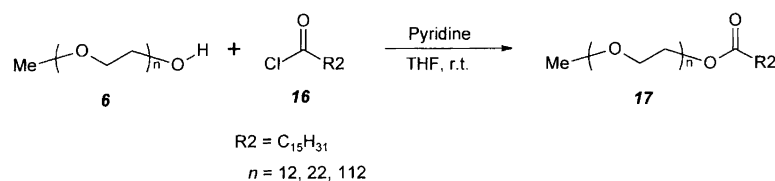
R1 = H, CH_3, R2 = $C_{15}H_{31}$

n = 12, 22, 112

Cesium Palmitate, DMF, r.t.
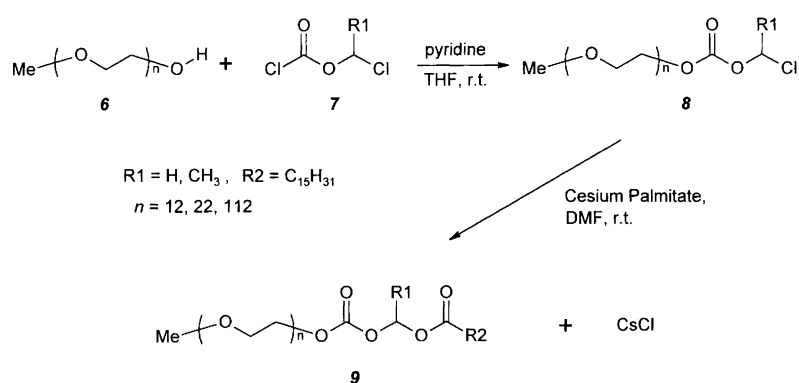
Scheme 1.

of their metal and non-metal salts reacted with simple alkyl halides or tosylates.[13] When *gem*-dihalides are employed structurally related diesters (acylals) have been obtained.[14] By contrast, our electrophilic α-chloroalkyl carbonates **8** are ambident in nature and carboxylate nucleophiles can attack at both the α-chlorocarbon and the carbonyl carbons, with the later leading to undesired products. Furthermore, heterolytic cleavage of the carbon–halogen bond in **8** is expected to result in high reactivity in nucleophilic substitution by S_N1 and S_N2 reactions.[15] However, we discovered that conventional metal and non-metal cations[16] such as Li^+, Na^+, K^+, Ag^+, $DBUH^+$, Et_3NH^+ as counter-ion on the palmitate failed to react and resulted in either the recovery of starting material or extensive decomposition. However, on the basis of earlier reports of success with cesium[17] as counter-ion in alkylation reactions, cesium palmitate was prepared and treated with the halide **8** in DMF. A highly chemoselective reaction took place and products were obtained in good yield. The results from the esterification reactions are listed in Table 2 and deserve some comments. Both mPEG chloromethyl carbonates and the 1-chloroethyl homologues reacted chemoselectively to afford the carbonate esters **9** in good to excellent yields. However, in contrast to the smooth reaction with chloromethyl carbonates, the alkylation with 1-chloroethyl carbonates gave a by-product which was observed as a peak on the HPLC chromatogram. From one reaction mixture this compound was isolated and spectroscopic data showed it to be mPEG alcohol. This was quite unexpected, since NMR analysis ruled out the presence of free mPEG alcohol as impurity in the starting halide. Because of the presence of mPEG alcohol in the reaction mixture, preparative HPLC was required in order to obtain the double esters **9d–f** in highly pure form. The appearance of mPEG alcohol in the reaction mixture was surprising, and we wanted to determine its origin and at the same time determine the optimal

conditions in terms of the effects of variables such as temperature and solvents in this alkylation process. Thus, the following NMR test-tube experiments were designed: treatment of cesium palmitate with mPEG ($n = 12$) 1-chloroethyl carbonate **8e** in deuteriated ($^2H_7$)DMF, ($^2H_4$)methanol and ($^2H_3$)acetonitrile. Spectral recordings were taken at intervals and analysed to monitor the disappearance of resonances from reactants and appearance of new ones from products. Briefly, the results of these explorations showed that: (1) the formation of product in DMF at 70 °C was completed within 3 h. Formation of product was accompanied by simultaneous formation of mPEG alcohol and acetaldehyde (δ 9.71–9.74 ppm (quartet) and δ 2.13–2.14 ppm (doublet), $J = 2.80$ Hz. This is shown in the ^1H NMR spectrum in Fig. 3. (2) No reaction at all took place in acetonitrile as the reactants remained unchanged even at 50 °C for 20 h. (3) In methanol at 50 °C for 20 h, reaction took quite an undesirable path and decomposition fragments traceable to the PEG alkylcarbonate were identified. On the basis of these findings the mechanism depicted in Scheme 4 in which DMF[18] plays the dual role of solvent and reactant is proposed. Thus, it is assumed that the nucleophilic[19] reaction follows a simultaneous S_N1 and S_N2 path. In this seldom but known mechanism,[20] the molecules of mPEG 1-chloroethyl carbonate that react by the S_N2 mechanism proceed through the accepted pentacoordinated intermediate **18** of the transition state to the expected product. On the other hand, for molecules that react by the S_N1 mechanism, the oxonium cation **19**, which is formed after the cleavage of the carbon–
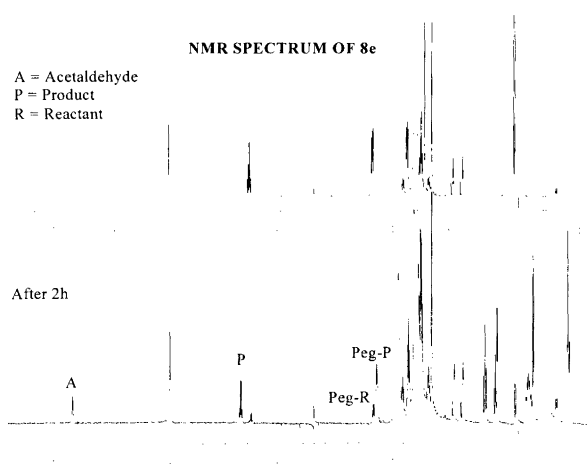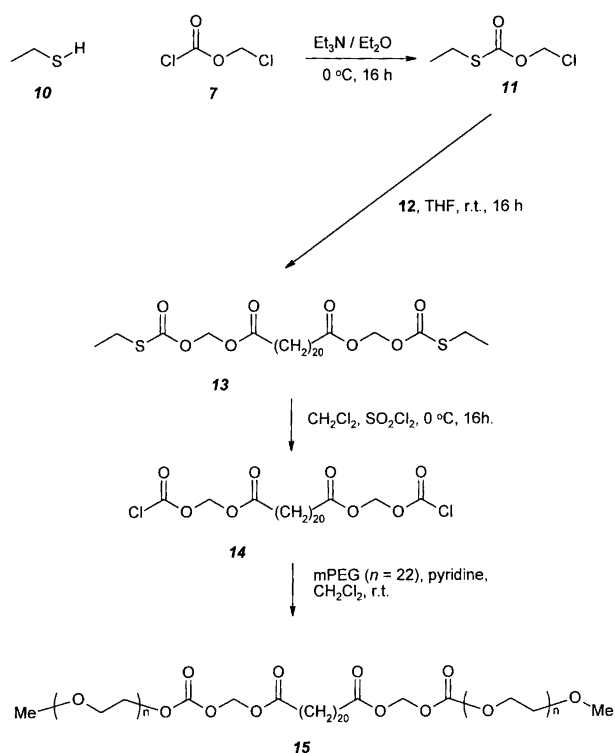
Table 2. Alkylation reaction between cesium palmitate and mPEG chloroalkyl carbonate derivatives **8**.

Compound	n	R^2	Reaction time/h	Yield (%)
9a	12	H	72	90
9b	22	H	72	63
9c	112	H	48	61
9d	12	CH_3	72	57
9e	22	CH_3	72	40
9f	112	CH_3	72	40

NMR SPECTRUM OF **8e**

A = Acetaldehyde
P = Product
R = Reactant

After 2h

Fig. 3. The NMR spectrum during reaction between **8e** and cesium palmitate.

$$Me \overset{O}{\underset{n}{\diagup}} O \diagdown^H + Cl \overset{O}{\diagup} R2 \xrightarrow[\text{THF, r.t.}]{\text{Pyridine}} Me \overset{O}{\underset{n}{\diagup}} O \overset{O}{\diagup} R2$$

6   **16**   **17**

R2 = $C_{15}H_{31}$

n = 12, 22, 112

Scheme 2.

Scheme 3.

carbon dioxide from the resulting arrangement **20** provides the driving force for the formation of mPEG alcohol (**21**) and acetaldehyde (**23**).

The superior reactivity of cesium over the other cations in the alkylation of the palmitate may be attributed to complexation by the oxygens of in the mPEG allowing it to act as template.[22] It has been suggested that other factors such as low charge/surface area ratio due to the large ionic diameter of cesium (3.3 Å) may be of significance[23] in enhancing this type of reaction. Compounds **17a–c** in Table 3 are esters obtained by treating palmitoyl chloride[24] with mPEG alcohol and were used for comparative biodegradability studies.

A–B–A-Type. Only one example of the **A–B–A** structural geometry was considered necessary for our present purpose of biodegradability studies. Docosanedioic acid was chosen for this purpose primarily because its size (22 carbons), sandwiched between two mPEG ($n = 22$) chain lengths, was sufficient to give a reasonable hydrophilic/lipophilic balance (HLB). However, in sharp contrast to the results obtained from our established alkylation

chloride bond, is intercepted by the oxygen of dimethylformamide, whose nucleophilicity is enhanced by association with cesium cation.[21] Subsequent expulsion of

Table 3. Esters from mPEG and palmitoyl chloride.

Compound	n	Reaction time/h	Yield (%)
17a	12	72	60
17b	22	24	61
17c	112	24	84
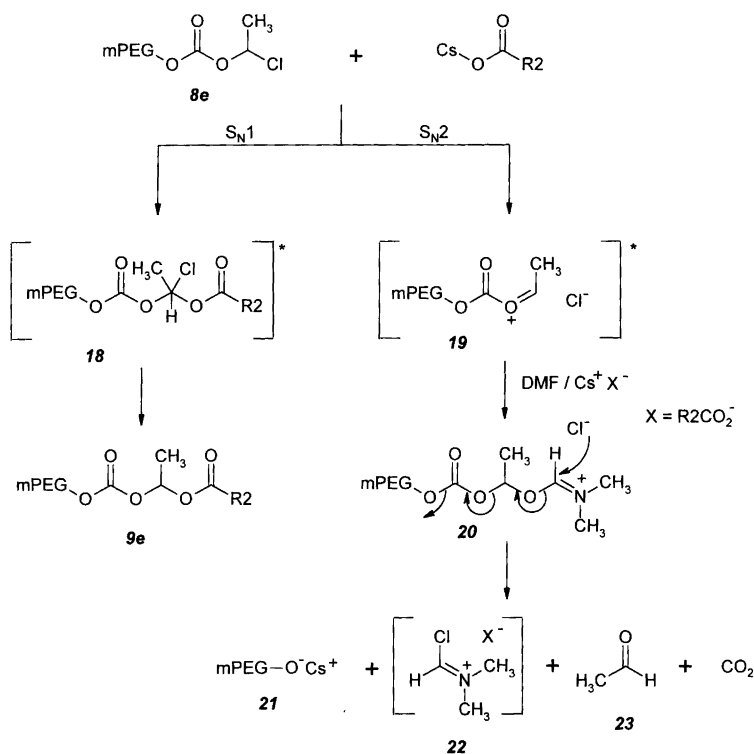
Scheme 4.

procedure, the cesium salt of docosanedioic acid[25,26] failed to react with our mPEG alkyl chloride **8**. The target compound was eventually obtained as outlined in Scheme 3, which is in accordance with path (b) in the retro-analysis in Fig. 2. The key intermediate **14** required in the final acylation step was obtained by sulfuryl chloride chlorination[27] of **13**, which in turn is the alkylation product of reaction between the bis(tetra-butylammonium) salt of docosanedioic acid **12** and the chloromethyl thiocarbonate **11**. Treatment of mPEG alcohol ($n = 22$) with the diacid chloride **14** in a dichloromethane–pyridine mixture afforded the double carbonate ester **15** in good yield.

Characterisation

NMR analysis. NMR was well suited in establishing the structural integrity of the carbonate esters. All the mPEG carbonate esters and ordinary esters presented well defined NMR spectra with characteristics which corresponded well to the composition of the products. For the A–B carbonate esters, proton NMR was efficient in determining the mPEG/palmitic acid ratios from the integration of resonances due to MPEG methylene at 4.28 ppm ($-OCH_2-CH_2-OCO_2-$ multiplet), carbonate ester linker at 5.75 ppm ($-O_2CO-CH_2-OCOR$, singlet) and palmitic acid at 2.36 ppm ($-OCOCH_2-$, triplet). When the linker is 1-ethylene, the resonance due to methine appears at 6.53 ppm as a quartet, ($-O_2CO-CHCH_3-OCOR$) and the methyl at 1.53 ppm ($-O_2CO-CHCH_3-OCOR$, doublet).

The important carbon atom assignments in the ^{13}C spectra are the resonances at 175.1 and 154.0 ppm, which correspond to the ester and carbonate carbonyl carbons, respectively. For the 1-ethylene analogue, these resonances are slightly shifted to 171.7 and 153.1 ppm. Definitive proof of the authencity of the proposed structures of the carbonate esters was obtained from hetero multiple quantum correlation experiments (HMQC), where long-range couplings were observed between the bridge proton and the carbonyl carbons from the fatty acid and the carbonate components.

Surface activity and critical micellar concentration (CMC). A fundamental property of surfactants is the ability to reduce the normally high surface tension of water. The surface activity of these new mPEG carbonate esters was established by measuring the surface tensions of their aqueous solutions. The data obtained by the Wilhemy plate method[28] on K1O ST (Kruss, Germany) tensiometer are reported in Fig. 4. As can be seen, low concentrations of the carbonate esters are sufficient to lower the surface tension of water from 73 to 35 mN m^{-1}. It is also clear from the figure that increasing the size of mPEG moiety leads to a corresponding decrease in the surface tension reducing ability of the surfactant. Plots of the surface tension reduction versus the logarithm of
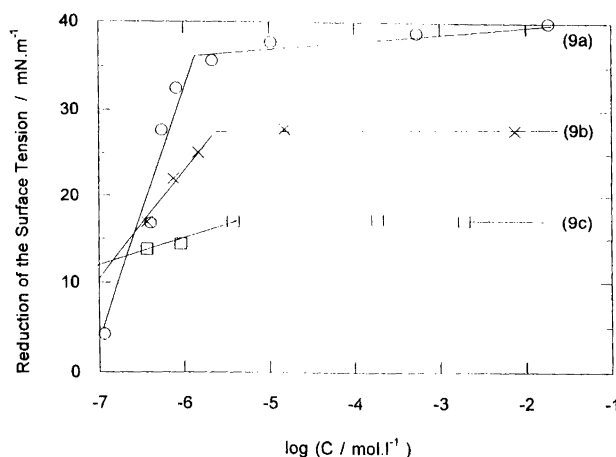
Fig. 4. The reduction of surface tensions for mPEG carbonate ester surfactants at various concentrations of aqueous solutions. The breaks correspond to the CMC values.

concentration gave sharp breaks corresponding to the CMC values[29] listed in Table 4.

Hydrolysis studies. Representative mPEG surfactants were selected for enzymatic hydrolysis studies. The experiments were performed in a pH-stat and carried out at ambient temperature in water containing DMF (8%) and the enzyme, pig liver esterase (PLE). Reactions were run at pH 8.2, with and without enzyme. Constant pH during hydrolysis was assured by simultaneous addition of 5 mM NaOH (titrant) from the autoburette. The rates, r mmol min^{-1} for the liberation of acidic metabolites (carbon dioxide and palmitic acid) from the hydrolysis by PLE were calculated from the amount of base consumed in the reaction, and verification of metabolites was supported by proving the presence of mPEG by HPLC and MALDI-MS. Some of the compounds studied and their associated degradation data are listed in Table 5. As can be seen from the data, all the compounds underwent faster hydrolysis in the presence of pig liver

Table 4. Determined CMC for mPEG carbonate ester surfactants.

Compound	CMC/mol dm^{-3}
9a ($n = 12$)	1.2×10^{-6}
9b ($n = 22$)	2.3×10^{-6}
9c ($n = 112$)	4.4×10^{-6}

Table 5. Rate values for enzymatic hydrolysis of some carbonate ester surfactants as determined by the pH-stat.

Compound	Rate of hydrolysis mmol min^{-1} at pH 8.2	
	PLE	Without PLE
9a	1.30	0.04
9e	0.70	—
17a	0.30	0.06
15	0.47	—

esterase than without esterase irrespective of whether they contained a single ester or a carbonate ester. However, while the single ester **17a** was hydrolysed 5 times faster than without esterase, hydrolysis was 32.5 times faster with the methylene-bridged carbonate ester **9b** under identical conditions. For the ethylene-bridged carbonate ester hydrolysis was ca. 20 times faster and 12 times faster in the case of the double carbonate ester variant, **15**.

Performing the hydrolysis at pH 8.2 is beneficial because it is above the pK_a values of both palmitic acid (pK_a 5.0) and HCO_3^- (pK_a 6.1) and thus eliminates the buffering capacity of these species. It also allows the sum of liberated metabolic carbon dioxide and palmitic acid to be determined by a simple neutralisation titration reaction.

In order to generate comparative data for rates of hydrolysis, the ideal condition is to use V_{max} values from Lineweaver–Burk plots.[30] With these surfactants exhibiting CMC values of 10^{-6} M, construction of Lineweaver–Burk plots would require substrate concentrations too low to be detected with proper accuracy. Therefore, a fixed amount of enzyme (100 μl) and a nearly constant weight of substrate (28–30 mg) were chosen, and the reaction was recorded from start to end with the pH-stat. Thus, the measured rate is an 'overall reaction rate' and not an expression of V_{max} for the enzyme–substrate couple. Despite the limiting factors mentioned above, the method was found appropriate to determine the reaction velocities when performed together with HPLC analysis.

In summarising, chloroformates have been found to acylate efficiently mPEG alcohols of various sizes in the presence of pyridine to yield the corresponding chloroalkyl carbonates. These PEG derivatives are useful alkylating agents in the esterification of palmitic acid provided cesium is the counter-ion of the carboxylate. Generally, the alkylation is thought to proceed by an S_N2 mechanism; however, a competitive S_N1 mechanism becomes dominant in the reaction of mPEG-1-chloroethyl carbonate with cesium palmitate and resulted in the reversal of this intermediate to the starting materials. By first alkylating the ditetrabutylammonium salt of docosanedioic acid using chloromethyl carbonothioate and conversion to the diacyl chloride, mPEG alcohol was acylated to afford **A–B–A** type molecular structure. These mPEG derivatives containing unique carbonate ester functions have been studied to establish their properties as surfactants and rates of hydrolyses. They were found to be hydrolysed considerably faster than the corresponding single ester in the presence of esterase. The proven properties should therefore make these surfactants attractive in the development of pharmaceutical applications as solubilisers, wetting agents and drug delivery matrices.

Experimental

General methods. HPLC analyses were performed using a C8 reversed-phase column (Beckman-ultrasphere)

under gradient conditions with a 75:25 mixture (v/v) of tetrahydrofuran–water and 0.1% trifluoroacetic acid. For preparative HPLC, 20 mm × 27.5 cm, RP-8 Lichroprep, 15–25 μm in a two-step gradient, (A) 48% acetonitrile in water and (B) 93% acetonitrile in water was used. The peak elusions were monitored with UV (280 nm) and RI coupled series. All NMR experiments were recorded on a Varian VXR-300S spectrometer using a broad band probe with 5 mm tube. Sample dissolved in $CDCl_3$ unless otherwise stated. Chemical shifts are reported relative to Me_4Si and $CDCl_3$. Liquid chromatography was performed using silica gel (Merck 230–400 mesh). Thin-layer chromatography (TLC) was performed on kieselgel 60 F_{254} precoated plates (0.25 mm), and spots were visualised with molybdophosphoric acid in ethanol after heating. mPEG was dried in a vacuum with P_2O_5 for 24 h or in activated 4-Å molecular sieves in appropriate solvents.

Materials. Ethyl acetate, petroleum ether and CH_2Cl_2 were used as received. DMF and THF were dried over 3 Å molecular sieves. Polyethylene glycols with one methoxy and one hydroxyl end group (mPEG) were purchased from shearwater Polymers, Inc.

General procedure

Carbonic acid chloromethyl ester mPEG ester (**8a–c**). To a stirred solution of dried monomethoxy polyethylene glycol (mPEG, $n=12$) (10.27 g, 10 mmol) in anhydrous tetrahydrofuran, THF (100 ml) and pyridine (3.40 ml, 40 mmol) was added chloromethyl chloroformate (3.60 ml, 40 mmol) at ambient temperature. Monitoring by HPLC showed that after 3 h 97% of product has been formed. The precipitated pyridinium hydrochloride salt was removed by filtration and the solvent removed by evaporation. The viscous oily residue was dissolved in ether (150 ml) or chloroform for mPEG ($n=112$) and the pegylated product was precipitated by addition of pentane (200 ml). Decantation of the solvents and drying of the residue under vacuum gave the pure product as a viscous oil, yield: 7.27 g (59%). ^1H NMR: δ 3.37–4.38 (m, mPEG), 5.73 (s, 2 H). ^{13}C NMR: δ 59.0, 68.1, 68.6, 70.5, 71.9, 72.2, 76.6, 153.3. IR (neat): 2873, 1767, 1450, 1349, 1256, 1110, 788 cm^{-1}.

Hexadecanoic acid mPEG–oxycarbonyloxymethyl ester (**9a–c**). A mixture of palmitic acid (0.40 g, 1.55 mmol) and cesium carbonate (0.65 g, 2.0 mmol) in dimethyl formamide, DMF (10 ml) was stirred at ambient temperature for 45 min before a solution of carbonic acid chloromethyl ester mPEG ($n=12$) ester (**8a**) (1.0 g, 1.55 mmol) in DMF (3 ml) was added. The reaction was monitored by HPLC, and after 72 h (95% conversion) the mixture was filtered and DMF removed under reduced pressure. The residue was dissolved in chloroform (30 ml) and extracted with saturated sodium bicarbonate solution (1 × 15 ml) and water (1 × 15 ml). Drying ($MgSO_4$), filtration and evaporation of the chlo-

roform phase gave the product as a white wax, 1.20 g (90%). ¹H NMR: δ 0.85–1.63 (m, 29 H), 1.60–1.63 (m, 2 H), 3.37–4.34 (m, mPEG), 5.75 (s, 2 H). ¹³C NMR: δ 14.1, 22.6, 24.5, 31.9, 33.8, 59.0, 61.5, 67.6, 68.6, 81.8, 154.0, 172.1. IR (neat): 2886, 1765, 1468, 1344, 1280, 1149, 1114, 947, 842 cm⁻¹.

Carbonic acid 1-chloroethyl ester mPEG ester (**8d–f**). To a stirred solution of dried mPEG (n = 22), (**6b**) (10 g, 10.00 mmol) in anhydrous, THF (150 ml) and pyridine (1.60 ml, 20.00 mmol) was added 1-chloroethyl chloroformate (2.20 g, 20.00 mmol) at ambient temperature. After 3 h the precipitated pyridinium hydrochloride salt was removed by filtration and the solvent removed by evaporation. The viscous oily residue was dissolved in ether (150 ml) or chloroform for mPEG5000 and the mPEG product was precipitated by addition of pentane (200 ml). Decantation of the solvents and drying of the residue under vacuum gave the pure product as a viscous oil, 7.55 g (68%). ¹H NMR: δ 1.83 (d), 3.54–4.36 (m, mPEG), 6.40–6.44 (q, 1 H). ¹³C NMR: δ 25.1, 59.0, 67.8, 68.6, 70.5, 70.6, 71.9, 84.6, 152.8. IR (neat): 2884, 1764, 1468, 1345, 1280, 1147, 1115, 965, 842 cm⁻¹.

Hexadecanoic acid 1-mPEG oxycarbonyloxyethyl ester (**9d–f**). Cesium palmitate was obtained by stirring a mixture of palmitic acid (0.50 g, 1.95 mmol) and cesium carbonate (1.0 g, 3 mmol) in water (20 ml) for 30 min. After evaporation of water, the residue was dried under high vacuum over P₂O₅/blue gel for 24 h. To a suspension of the cesium salt in dimethyl formamide, DMF (10 ml) was added a solution of carbonic acid 1-chloroethyl ester mPEG (n = 22) (**8e**) (2.16 g, 1.95 mmol) in DMF (3 ml) and stirred at ambient temperature for 45 min. The reaction was monitored by HPLC and after 72 h (65% conversion) the mixture was filtered and DMF removed under reduced pressure. The residue was then dissolved in chloroform (30 ml) and extracted with saturated sodium bicarbonate (1 × 15 ml) and water (1 × 15 ml). Drying (MgSO₄), filtration and evaporation of the chloroform phase gave the crude product as a white wax, 2.53 g (98%). Pure product was obtained by preparative HPLC as a white wax, 1.03 g (40%). ¹H NMR: δ 0.75–2.52 (m, 29 H), 1.29 (d, 3 H), 1.50 (d, 3 H, J = 6 Hz), 2.10 (m, 2 H), 3.07–4.34 (m, mPEG), 6.62 (q, 1 H, q, J = 6 Hz). ¹³C NMR: δ 14.0, 20.6, 22.5, 24.5, 32.8, 34.0, 59.1, 67.5, 67.6, 68.6, 81.8, 153.0, 169.1. IR (neat): 2887, 1765, 1468, 1344, 1280, 1149, 1114, 965, 947, 842 cm⁻¹.

mPEG palmitoyl ester (**17a–c**). Monomethoxy polyethylene glycol (mPEG, n = 22) (**6b**) (6.0 g, 6.0 mmol), pyridine (0.72 ml, 9.0 mmol) and palmitoyl chloride (**16**) (2.5 g, 9.0 mmol) were dissolved in THF (110 ml), and stirred at ambient temperature for 24 h. The precipitated pyridinium hydrochloride salt was filtered off and the solvent removed *in vacuo*. The residue was redissolved in chloroform (100 ml) and extracted once each with saturated NaHCO₃ (60 ml) and water (60 ml) dried (MgSO₄)

and evaporated. This residue was dissolve in ether (50 ml) or chloroform for mPEG (n = 112) and the derivatised mPEG product precipitated by addition of pentane (100 ml). Decantation of the solvents and drying of the residue under vacuum gave the pure product (**17b**) as a white compound, 4.50 g (60%). ¹H NMR: δ 0.85–0.91 (t, 3 H), 1.25–1.27 (m, 26 H), 1.51 (t, 2 H), 2.29–2.34 (t, 2 H), 3.37–3.39 (m, mPEG), 4.20–4.23 (t, 2 H). ¹³C NMR: δ 14.1, 22.5, 24.9, 29.1, 29.3, 31.9, 34.2, 59.0, 63.3, 69.2, 70.5, 71.9, 173.8. IR (neat): 2873, 1767, 1450, 1349, 1256, 1110, 788 cm⁻¹.

Thiocarbonic acid O-chloromethyl ester S-ethyl ester (**11**). A solution of EtSH (18.50 ml, 250 mmol) and Et₃N (34.65 ml, 250 mmol) in ether (100 ml) was added during 2 h to a stirred solution of chloromethyl chloroformate (22 ml, 250 mmol) in ether (450 ml) at 0 °C. Stirring was continued for 30 min at 0 °C and then for 16 h at ambient temperature. Filtration, evaporation of solvent and distillation of the residue gave the pure product as a colourless liquid, 11.69 g (30%): b.p. 50–54 °C/15 mbar. ¹H NMR: δ 1.35 (t, 3 H, J = 7 Hz), 2.93 (q, 2 H, J = 7 Hz), 5.77 (s, 2 H). ¹³C NMR: δ 14.70, 25.59, 34.44, 70.13, 72.52, 170.25.

Docosanedioic acid bis(ethylsulfanyl)carbonyloxymethyl ester (**13**). To a stirred suspension of docosanedioic acid (0.5 g, 1.35 mmol) in water (5 ml) was added tetrabutylammonium hydroxide solution (40%, 1.50 M, 1.80 ml, 2.70 mmol) at ambient temperature. The resultant clear and colourless solution was stirred at ambient temperature for 10 min and was lyophilised to afford a viscous oil. This oil **12**, dissolved freely in THF (10 ml) and was added dropwise to a stirred solution of **11** (0.40 g, 2.70 mmol) in THF (5 ml). The reaction was monitored by TLC. After 24 h the mixture was filtered, the precipitate washed with THF (3 ml) and the filtrate evaporated. The residue was triturated with ether (30 ml) and filtered again to remove more precipitate. Evaporation of the ether gave almost pure product as a white solid, 0.76 g, (93%). ¹H NMR: δ 1.25, 1.62 and 2.36 (m, 40 H), 1.40 (t, 3 H), 2.90 (q, 2 H), 5.80 (s, 2 H). ¹³C NMR: δ 14.7, 24.5, 25.4, 28.9, 29.2, 29.4, 29.6, 29.7, 33.9, 80.1, 170.7, 172.2. IR (neat): 2919, 2850, 1771, 1726, 1473, 1440, 1320, 1221, 1159, 1107, 1086, 1052, 965, 877 cm⁻¹.

Docosanedioic acid bis(chlorocarbonyl)oxymethyl ester (**14**). A stirred solution of docosanedioic acid bis(ethylsulfanyl)carbonyloxymethyl ester (**13**) (320 mg, 0.53 mmol) in CH₂Cl₂ (5 ml) was cooled to 5 °C (dry ice/methanol bath) and a solution of freshly distilled SO₂Cl₂ (0.14 g, 86 μl, 1.06 mmol) in CH₂Cl₂ (2 ml) was added dropwise through a syringe. The clear and colourless solution was stirred at 0 °C for 15 min followed by stirring at ambient temperature for 50 min. Evaporation of the formed EtSCl at ambient temperature and 20 mbar for 16 h gave **14** as a white substance, 262 mg, (89%). ¹H NMR: δ 1.23, 1.62, 2.40 (m, 40 H), 5.82 (s, 2 H). IR

(neat): 2918, 2850, 1785, 1474, 1440, 1130, 1107, 816, 731 cm^{-1}.

Docosanedioic acid bis(mPEG1000 carbonyl)oxymethyl ester (**15**). Crude docosanedioic acid bis(chlorocarbonyl)-oxymethyl ester (**14**) (0.25 mg, 0.45 mmol) was dissolved in CH_2Cl_2 (5 ml). A methylene chloride solution (10 ml) of mPEG1000 (0.91 g, 0.91 mmol) and pyridine (72 µl, 0.91 mmol) was added and the mixture stirred at ambient temperature for 3 days. The mixture was extracted once each with $NaHCO_3$ solution (10 ml) and water (10 ml). The organic phase was dried ($MgSO_4$), filtered and evaporated and the residue stirred for 2 h in ether (15 ml). After decantation of the ether and drying *in vacuo*, the crude product was obtained as a white substance, 904 mg, and pure product was obtained after preparative HPLC, 265 mg, (24%). ^{1}H NMR: [1.26, s, 1.64, m, 1.74, s, 2.37, t, 40 H], 3.39–4.35 (m, mPEG1000), 5.75 (s, 4 H). ^{13}C NMR: δ 24.5, 29.0, 29.2, 29.4, 29.6, 29.7, 33.9, 59.0, 67.6, 68.6, 70.7, 71.9, 81.8, 154.0, 172.1. IR (neat): 2919, 2852, 1765, 1468, 1345, 1280, 1148, 1114, 1061, 965, 947, 843 cm^{-1}.

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