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Commentary

(Special Topic)

Efficacious syntheses of alkylphenol ethoxylates and ethoxycarboxylates with long and single length PEG chain and their application to environmental fate study

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The Williamson alkylation of a phenolic hydroxyl group of a 4-*tert*-octylphenol by 2-[2-(2-chloroethoxy)ethoxy]ethanol in the presence of potassium carbonate afforded the corresponding 9-(4-*tert*-octylphenyl)-3,6,9-trioxanonan-1-ol (OP3EO) quantitatively. Using powdered sodium hydroxide in place of potassium carbonate in the presence of phase transfer catalyst, alkylation of the terminal hydroxyl group occurred to give a mixture of OP3EO, 18-(4-*tert*-octylpheny)-3,6,9,12,15,18-hexaoxaoctadodecan-1-ol (OP6EO), 27-(4-alkylphenyl)-3,6,9,12,15,18,21,24,27-nonaoxaheptacosan-1-ol (OP9EO) and so on. Many types of OPkEO (k=4, 5, 6···) could be obtained by using OP1EO and OP2EO as starting materials. The use of OPkEO with a long and single length polyethylene glycol (PEG) chain was effective for studying the environmental fate of APEOs. © Pesticide Science Society of Japan

Keywords: one-pot synthesis, alkylphenol ethoxylate, deuterium-labeled alkylphenol ethoxylate synthesis.

Introduction

APEOs, manufactured by sequential addition of ethylene oxide to appropriate alkylphenols, are commercially important non-ionic surfactants. Nonylphenol ethoxylate (NPEO) is the most prevailing surfactant and commercially available NPEO has a mixture of highly branched nonyl groups at the *para* position of the phenolic hydroxyl group with a small amount of *ortho* isomers. A less common but important APEO is octylphenol ethoxylate (OPEO), which has a monoisomeric 4-*tert*-octyl group at the *para* position of the phenolic hydroxyl group. These APEO have been widely used in domestic, agricultural, and industrial applications. It is known that APEO are easily biodegraded in the environment to give a complex mixture of metabolites.[1–5] The metabolites usually include the short (typically k=1–3) ethoxy chain length APkEO and corresponding carboxylated substances (APkEC.) The authors reported that APEO-degrading bacteria that degrade APEO to estrogenic AP2EO and AP1EO are distributed in farmland.[6,7] While the longer APkEO (k>3) lack estrogenic activity, the shorter APkEO (k=1, 2) and the original NP and OP cause an estrogenic response in fish and other aquatic organisms.[8–10] Moreover, these compounds are known to exist ubiquitously in the aquatic environment where they may undergo remobilization and biotransformation into the food chain.[11,12] It is necessary to know the precise environmental behavior of APEO and to estimate the toxicity of these metabolites not only for aquatic organisms but also for human health. This paper focused on the syntheses of APkEO and APkEC having long and single length PEG chain, and their application to APEO study.

1. Synthesis of APkEO and APkEC with Long and Single Length PEG Chain

The authors have already reported the synthesis of octylphenol oligoethoxylate (OPkEO, k=1–3).[7] The iteration of the alkylation of hydroxyl group by ethyl bromoacetate and subsequent lithium aluminium hydride reduction is the rational pathway for OPkEO, as shown in Fig. 1. The pathway is, however, invalid for OPkEO with long PEG chain, since it needs

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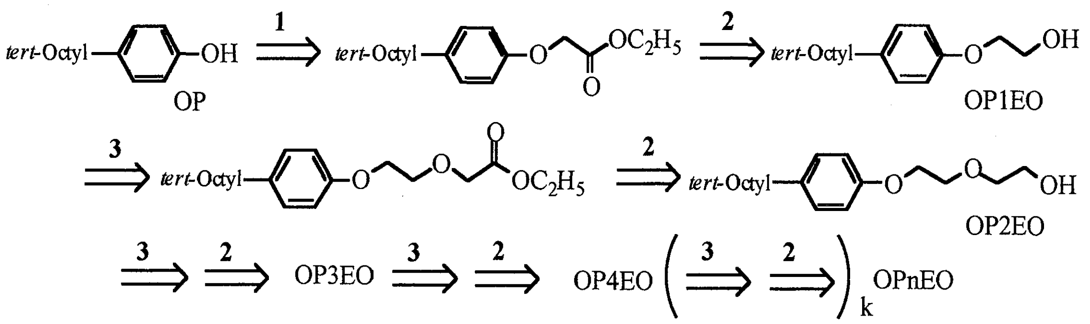
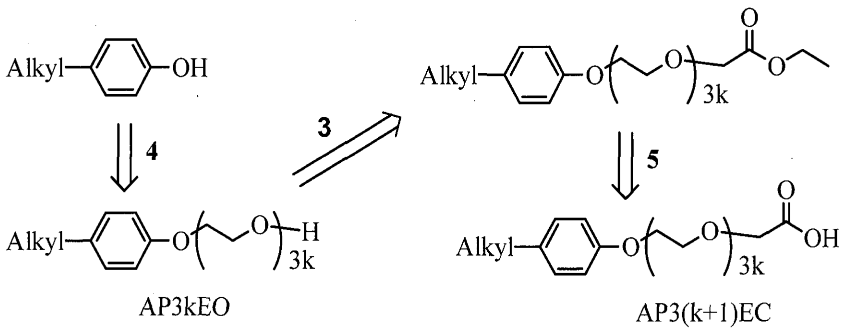
Abbreviations: APEO: alkylphenol ethoxylate, APkEO: alkylphenol ethoxylate with k units of ethylene glycol, OP1EO: 2-(4-*tert*-octylphenoxy)ethanol, OP2EO: 6-(4-*tert*-octylphenyl)-3,6-dioxahexan-1-ol, OPEC: octylphenol ethoxycarboxylate



(**1.** $BrCH_2COOEt$, K_2CO_3/ DMSO, **2.** $LiAlH_4$/THF, **3.** $BrCH_2COOEt$, NaH/ THF)

Fig. 1. Conventional synthesis of OPkEO (k=1, 2, ⋯).

twenty reaction steps for the synthesis of OP10EO. This means that a new synthetic strategy is necessary to synthesize OPkEO with a long and single length PEG chain. The authors previously achieved quantitative and one-step synthesis of AP2EO and AP3EO by direct alkylation of AP with 2-(2-chloroethoxy)ethanol or 2-[2-(2-chloroethoxy)ethoxy]ethanol, respectively (unpublished data). This reaction was pursued in DMSO in the presence of K_2CO_3. On the other hand, it is already known that the alcoholic hydroxyl group could be alkylated by alkyl halide in the presence of a strong base and phase transfer catalyst.[13] Figure 2 shows the one-pot synthesis of AP3kEO with a long and single length PEG chain using commercially available 2-[2-(2-chloroethoxy)ethoxy]ethanol and benzyltriethylammonium chloride in the presence of powdered sodium hydroxide. HPLC chromatograms of commercially available OPEO and synthesized OP3kEO (k=1, 2, 3, ⋯) are shown in Fig. 3. As the scale of the x-axis is the same in the two chromatograms, it is apparent that complete separation of the products could be achieved. Separation of the individual homologs was easily achieved even using open silica gel column chromatography, since the products differ by three ethylene glycol units. Eighteen reaction steps are needed to synthesize OP9EO by the conventional method. In contrast, we could obtain a series of OP3kEO by the one-step reaction and the conversion ratio of OP into OP3EO, OP6EO and OP9EO by this reaction was 25.5%, 19.0% and 12.5%, respectively. Moreover, by changing the starting material from OP to OP1EO or OP2EO, all series of OPkEO (k=4, 5, 6, ⋯) can be synthesized; however, the reaction of AP and 2-(2-chloroethoxy)ethanol gave only AP2EO, and AP2kEO (k=2, 3, ⋯) was not obtained. This phenomenon could be explained by the intramolecular cyclization of 2-(2-chloroethoxy)-ethanol to give 1, 4-dioxane. Figure 4 demonstrates the utility of this procedure. APkEO and APkEC with a long, single length and deuterium-labeled PEG chains were prepared by the same procedure using deuterium-labeled AP1EO as the starting chemical. Figure 5 indicates the MALDI-TOF mass spectra of NP9EO-d2 and OP10EO. As sodium iodide was used as the cationization reagent, the peaks of each compound were observed at *m/e* 641.42 (NP9EO-d2+Na^+) and *m/e* 669.19 (OP10EO+Na^+), respectively. Although the same procedure can be applied to NPkEO and NPkEC synthesis, complete separation was a little difficult because of the existence of many isomeric nonyl groups. New concept may be needed for the synthesis of pure NPkEO having long and single length PEG chains.



(Alkyl = Nonyl or *tert*-Octyl)

(**3.** $BrCH_2COOEt$, NaH/ THF, **4.** 2-[2-(2-Chloroethoxy)ethoxy]ethanol, NaOH, $BzEt_3N \cdot Cl$,
5. 3M NaOH in 50% EtOH)

Fig. 2. One-pot synthesis of AP3kEO and subsequent AP(3k+1)EC synthesis.

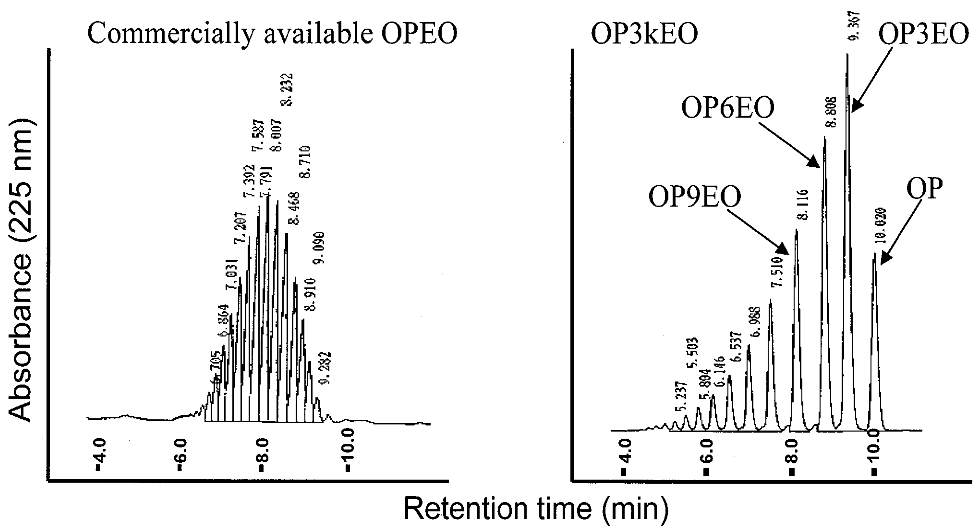
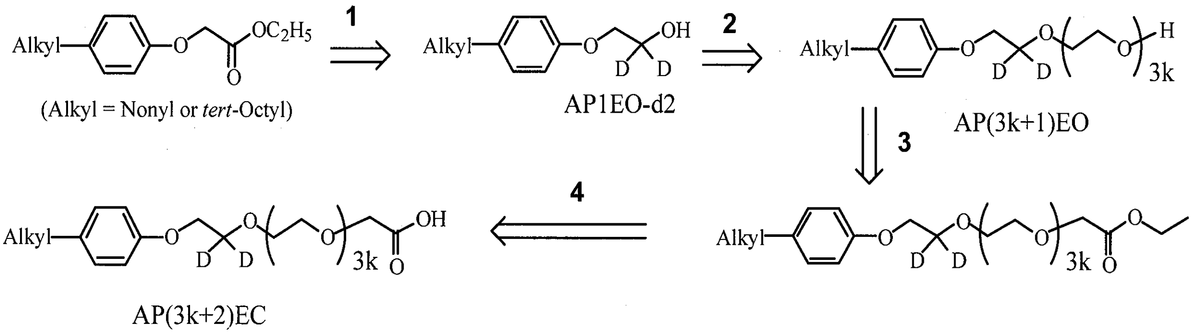


Fig. 3. HPLC chromatogram of commercially available OPEO and OP3kEO synthesized by the one-pot reaction of OP and 2-[2-(2-chloroethoxy)ethoxy]ethanol in the presence of PTC.



1. $LiAlD_4$/THF, **2.** 2-[2-(2-Chloroethoxy)ethoxy]ethanol NaOH, $BzEt_3N \cdot Cl$, **3.** $BrCH_2COOEt$, NaH/ THF, **4.** 2M NaOH in 50% EtOH

Fig. 4. One-pot synthesis of deuterium-labeled AP(3k+1)EO and subsequent AP(3k+2)EC synthesis.

2. Application of Prepared APkEO and APkEC Having Long and Single Length PEG Chains to Environmental Fate Study

Usually, APEO surfactants released into the environment are biologically degraded from the PEG side chain. The terminal ethylene glycol unit of the PEG chain is cleaved aerobically or anaerobically to give 1 unit shorter APkEO and C_2 compounds such as acetaldehyde, glyoxalic acid and glucolic acid.[14] Successive iterations of this process occur, leaving a remain the mixture of biodegradation products consisting of short chain APkEOs (k=1–3) and the corresponding carboxylic acid APkECs. The physicochemical properties of these metabolites largely differ according to their ethylene glycol unit number and the terminal functional group. It is difficult to decide the recovery rate of all metabolites using only a small number of typical surrogates. The use of deuterium-labeled APkEO and APkEC set plays an important role in identifying to know the precise environmental fate of APEOs.

Furthermore, the degradation mechanisms of PEG chain

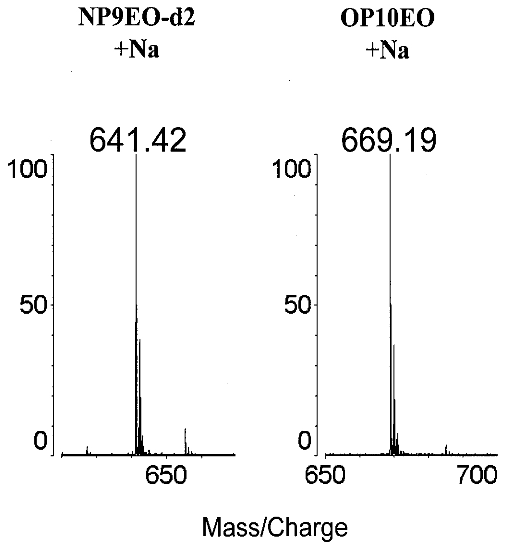


Fig. 5. MALDI-MS spectra of NP9EO-d2 and OP10EO using NaI as the cationization reagent.

are generally classified into two groups, exo-fission and endo-fission.[14] Endo-fission is usually called central fission and the ether bond of the PEG chain is randomly cleaved.[15] If we use commercial APEO as the substrate, we cannot distinguish the starting substrate and the corresponding product on the chromatogram; however, this discrimination between central fission and exo-fission can be achieved quite easily using APkEO with long and single length PEG chain. For example, *Pseudomonas putida* S-5 isolated from a paddy field was fed pure OP10EO as the sole carbon source to study its degradation mechanism. The peak area of one EO unit shorter homolog OP9EO gradually increased after 2 and 4 hr incubation by HPLC, as shown in Fig. 6. MALDI-TOF mass spectrum of the medium after 6 hr incubation is indicated in Fig. 7. This result and the detection of OP10EC, the oxidation product of OP10EO, suggest that oxidative degradation proceeded from the end of the PEG chain.

On the other hand, there are some soil samples from which we could not isolate degrading bacteria even by repeated experiments, although the soil samples had strong degradation activity in the enrichment culture. Usually, we could isolate many bacteria ubiquitously from soil samples that only oxidize the terminal hydroxyl group to the corresponding carboxylic acid. It is possible that in a combination of two kinds of bacteria, first group of bacteria can oxidize the terminal alcohol and the other oxidizes the α-carbon of carboxylic acid to glyoxylic acid and APkEO with shorter PEG chain by one ethylene glycol unit. The use of longer chain APkEC will make possible the isolation of such bacteria that constitute the microbial consortium with APkEO degrading activity.

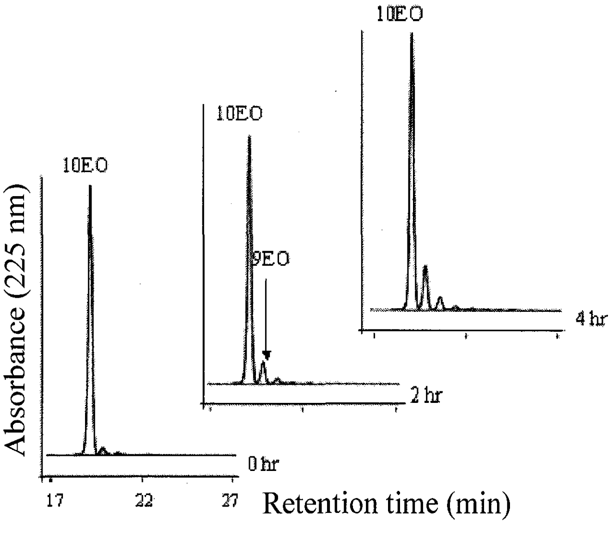


Fig. 6. Time-course feeding experiment of OP10EO to *Pseudomonas putida* S-5. HPLC conditions: column, Unison UK C-18; eluent, AcCN : H_2O=60 : 40 (v/v); flow rate, 0.8 ml/min; detection, 225 nm.

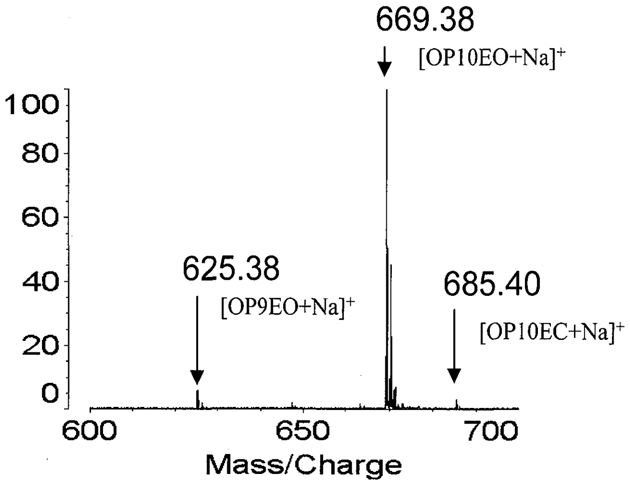


Fig. 7. MALDI-TOF mass spectrum of *P. putida* S-5 incubation fluid after 6 hr incubation. MALDI-TOF MS conditions: mode, reflectron and positive ion mode; matrix reagent, 2,5-dihydroxybenzoic acid; cationization reagent, sodium iodide.

Acknowledgments

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