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SPECIFIC ^{14}C-LABELED SURFACTANTS. THE ADDITION OF HOMOGENEOUS POLYOXYETHYLENE GLYCOLS TO p-(1,1,3,3-TETRAMETHYLBUTYL)PHENOL

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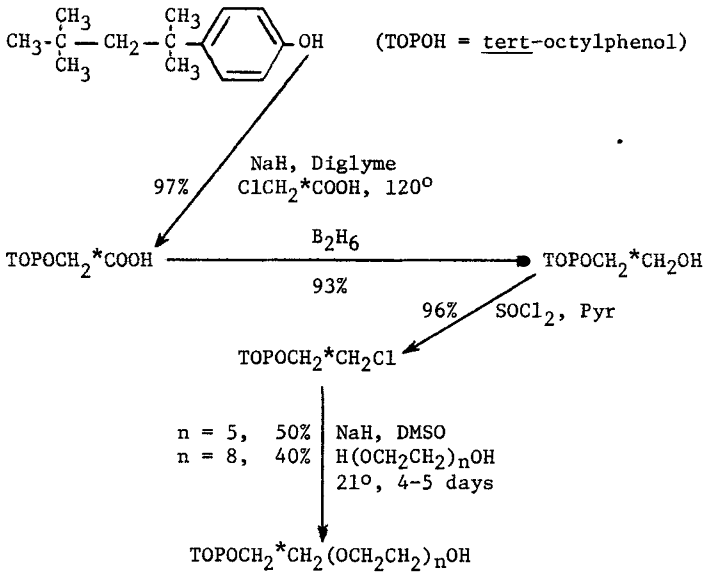
SUMMARY

Two surfactants, one containing a six and the other containing a nine unit polyoxyethylene glycol side chain attached to p-(1,1,3,3-tetramethylbutyl)phenol (TOPOH), were prepared with specific ^{14}C-labeling. The radioactive label was introduced into the first ethylene oxide unit attached to the aryl moiety, $TOPOCH_2{*}CH_2(OCH_2CH_2)_nOH$, by coupling chloroacetic-^{14}C-1 acid with TOPOH. A 4-step reaction scheme was utilized in the synthesis, and all reactions gave excellent yields except for the final Williamson coupling reaction. A competing elimination reaction occurred in the final reaction to afford a vinylic by-product, TOPOCH=CHCl, which was identified by spectroscopic methods. The overall yields for $TOP(OCH_2CH_2)_6OH$ and $TOP(OCH_2CH_2)_9OH$ were 42 and 33 per cent, respectively.

INTRODUCTION

The synthesis of specific ^{14}C-labeled surfactants of 2,6,8-trimethyl-4-nonanol (TMNOH) with homogeneous polyoxyethylene glycol moieties was reported$^{(1)}$. These detergents were prepared for investigations into the metabolism and environmental fate of nonionic surface active agents. The synthesis and study of specific ^{14}C-labeled nonionic aryl detergents is an important extension of these investigations. A reaction sequence was prepared for the synthesis of ^{14}C-labeled homogeneous poly(ethoxy)ethanol containing detergents of p-(1,1,3,3-tetramethylbutyl)phenol (TOPOH). We had hoped to utilize the same experimental conditions that were reported for the TMNOH surfactant synthesis; however, those conditions proved unsatisfactory for all reactions except for the diborane reduction. Therefore, the reactions given in Scheme 1 were developed for the synthesis of homogeneous nonionic aryl surfactants.



Scheme 1

EXPERIMENTAL

Materials and Methods. The p-(1,1,3,3-tetramethylbutyl)phenol was purchased from K & K. This material was recrystallized from n-hexane to yield a product of greater than 99% purity by gas-liquid chromatography (GLC). Chloroacetic-^{14}C-1 acid (6 mCi, purity 99%) with a specific activity of 26.3 mCi/mmol was obtained from New England Nuclear. The specific activity was reduced to 8 mCi/mmol by addition of nonradioactive chloroacetic acid. The source, purification, and drying of all other chemicals were as previously described(1).

Equipment and general operating conditions for GLC were the same as previously reported in the alkyl detergent synthesis. In Table I are given some specific conditions and the retention times of the surfactants and the intermediates of TOPOH.

Table I

3% OV-1, °C	Compound	ml/min, N_2	Retention, min
190°	TOPOH	80	3.7
190°	$TOPOCH_2COOCH_3$	80	10.3
190°	$TOPOCH_2CH_2OH$	80	8.3
300°	$TOP(OCH_2CH_2)_6OH$	85	10.5
335°	$TOP(OCH_2CH_2)_9OH$	85	16.8
10% DC-LSX-3-0295, °C			
210°	$TOPOCH_2CH_2Cl$	85	9.0

The nuclear magnetic resonance (NMR) spectra were taken in deuteriochloroform with tetramethylsilane as the internal reference. Only the data involving the alkoxyl side chain of the surfactant intermediates were reported. Interpretation of the NMR spectra of the aromatic ring and tert-octyl side chain protons was reported by Stolzenberg, Zaylskie and Olson(2).

The procedures for verification, purification, and radioactive counting of the aryl detergents derived from TOPOH were the same as those utilized in the TMNOH detergent synthesis. The two purified aryl surfactants were estimated as having a radiochemical purity of greater than 99% by thin-layer chromatography and autoradiography. The specific activity of the surfactants was verified to be 8 mCi/mmol by GLC and liquid scintillation counting.

Purification of $TOPOCH_2COOH$. Separation of TOPOH from the aryloxyacetic acid was accomplished on a phosphate-buffered silica gel(3) chromatographic column. To prepare the buffer solution, a saturated aqueous solution of sodium dihydrogen phosphate was adjusted to pH 4, and 40 ml of this solution was added to 60 g of silica gel. The buffer and silica gel were thoroughly mixed, and then a slurry was prepared by the addition of water-washed chloroform to the silica gel mixture. The chromatographic column was prepared by firmly packing a 50-ml buret with the buffered silica gel(3). $TOPOCH_2COOH$-^{14}C in chloroform solution was placed on the column, and elution was initially performed with 250 ml of water-washed chloroform. Elution of the column was continued with 200 ml of ethyl ether; $TOPOCH_2COOH$ was recovered in the ether fraction. A significant fraction of the product remained in the chloroform eluate after the initial passage through the column. Therefore, the chloroform fractions were combined, concentrated, placed on the column, and the elution sequence with chloroform and ether was repeated. By passing the material through the column 4 times, 97% (0.704 mmol) of the radioactive product was recovered in this separation procedure.

Mineral oil from the sodium hydride dispersion prevented all the aryloxyacetic acid from remaining on the column during elution with chloroform. In trial studies with pure materials, the acid was easily separated from the phenol with a single passage through the column. To improve this separation, the alkoxide of TOPOH should be prepared without using a dispersion in mineral oil. However, the use of sodium and potassium metal or sodium methylate did not prove as convenient, reliable, or give as high a yield as did the sodium hydride dispersion. Therefore, the best method to avoid mineral oil interference at the purification step appears to be to wash the sodium hydride dispersion free of mineral oil with an inert solvent prior to synthesis.

Synthesis of $TOPOCH_2COOH$. Into a modified Kjeldahl flask(1) was added 0.6 g (3 mmol) of TOPOH, 0.16 g (4 mmol, 57% dispersion in mineral oil) of sodium hydride, and 5 ml of anhydrous diglyme. After the initial vigorous reaction at ambient temperature, the mixture was heated at 120° for about 20 min to ensure complete conversion of the substituted phenol to the sodium salt. The reaction was cooled to room temperature, and

70.9 mg (0.75 mmol, 6 mCi) of chloroacetic-^{14}C-1 acid dissolved in 1 ml of dry dioxane was slowly added to the phenolic salt solution with stirring. The addition funnel was washed with a small portion of anhydrous ethyl ether. Then the addition funnel was removed, the side arm stoppered, and the flask manually shaken to ensure complete neutralization of the chloroacetic acid. The ether was removed from the reaction by heating the mixture at gentle reflux, and the reaction was then maintained at 120° for 3 hr. After allowing the mixture to cool, the solution was made acidic with 5 ml of 10% (v/v) sulfuric acid in water. The product was extracted from the reaction mixture with aliquots of n-hexane. NMR, 4.61 (2H, singlet, $-OC\underline{H}_2C-$ group), 11.22 ppm (H, singlet, $-COO\underline{H}$ group). Yield 97%.

The aryloxyacetic acid was separated from the aryl phenol before reduction (cf. Purification of $TOPOCH_2COOH$). After purification, all traces of water were removed from the sample by azeotropic distillation with benzene in a micro soxhlet extractor(1).

Synthesis of $TOPOCH_2CH_2OH$. An apparatus for the external generation of diborane(4) was assembled for this synthesis as previously described(1). The reaction vessel contained 186 mg (0.704 mmol) of $TOPOCH_2COOH$-^{14}C in 15 ml of anhydrous tetrahydrofuran (THF). In the generation flask was placed 1.5 ml (1.66 g, 11.7 mmol) of boron trifluoride etherate in 4 ml of dry diglyme. The addition funnel was charged with 180 mg (4.71 mmol) of sodium borohydride dissolved in about 14 ml of diglyme. The entire system was flushed with dry nitrogen, and then diborane was generated by dropwise addition of the sodium borohydride solution over a 20 min period. The diborane was swept into the reaction vessel with a gentle flow of nitrogen. The generation flask was heated for 1 hr at 70-80°, and then the material in the reaction vessel was held at gentle reflux for 2 hr. Both flasks were allowed to cool, and the generator flask was disconnected. Hydride in the generator flask was destroyed by careful addition of water, and excess diborane in the reaction vessel was decomposed by slow addition of 15 ml of water followed by 5 ml of 6 M hydrochloric acid. The THF was removed by rotary evaporation, and the product was extracted from the aqueous phase with n-hexane. The sample was dried by the azeotropic distillation method(1). NMR, 2.30 (H, singlet, -O$\underline{H}$ group), 3.98 ppm (4H, multiplet, -OC$\underline{H}_2$C$\underline{H}_2$OH group). Yield 93%.

Synthesis of TOPOCH$_2$CH$_2$Cl. Into a 25-ml pear-shaped flask was added 164 mg (0.655 mmol) of TOPOCH$_2$CH$_2$OH-^{14}C and 74 mg (75 µl, 0.9 mmol) of cold anhydrous pyridine. Then 0.82 g (0.5 ml, 6.9 mmol) of purified thionyl chloride was slowly pipetted into the reaction vessel. A reflux condenser with drying tube was fitted onto the pear-shaped flask, and the reaction was heated at reflux for 2 hr. The solution was cooled to ambient temperature and transferred into a separatory funnel containing about 20 ml of n-hexane. Cold water was added to decompose the excess thionyl chloride. The aqueous layer was extracted with additional portions of hexane. The hexane fractions were combined and washed 2 times with aqueous 5% sodium bicarbonate and 3 times with distilled water. The product sample was then dried by the azeotropic distillation method. NMR, 3.74 (2H, triplet, J = 5.5 Hz, -CH$_2$C$\underline{H}_2$Cl group), 4.20 ppm (2H, triplet, J = 5.5 Hz, -OC$\underline{H}_2$CH$_2$Cl group). Yield 96%.

Synthesis of TOP(OCH$_2$CH$_2$)$_n$OH. A 25-ml round bottom flask was equipped with a pressure equalizing addition funnel and a calcium chloride drying tube. In the flask, 59 mg (1.4 mmol) of sodium hydride dispersion was suspended in 2 ml of dry ethyl ether. A solution of pentaethylene glycol (1.67 g, 7 mmol) dissolved in 3 ml of anhydrous dimethylsulfoxide was added dropwise to the sodium hydride. The mixture was stirred at ambient temperature for 15 min followed by an additional 15 min of stirring at 75°. Using the addition funnel, 84.7 mg (0.315 mmol) of TOPOCH$_2$CH$_2$Cl-^{14}C in ethyl ether (1 ml) was added to the reaction vessel. After addition, the funnel was rinsed with a small portion of ether and then removed from the flask. The ether was carefully removed from the solution with a rotary vacuum evaporator. The flask was then stoppered and stirred magnetically at ambient temperature for 4 days. The mixture was transferred into 25 ml of dichloromethane and hydrolyzed with 25 ml of 5 N aqueous sodium chloride and 5 ml of 6 N hydrochloric acid. Successive portions of dichloromethane were used to extract the product. Yield 50%.

For the preparation of $TOP(OCH_2CH_2)_9OH$, the same procedure described above for $TOP(OCH_2CH_2)_6OH$ synthesis was utilized. In this reaction 2.6 g (7 mmol) of octaethylene glycol was employed, and the mixture was allowed to stir at ambient temperature for 5 days. Yield 40%.

DISCUSSION

In the initial Williamson coupling of TOPOH with chloroacetic acid, the highest yield was obtained when diglyme was used as solvent. THF or dioxane gave lower yields, and dioxane also caused the solution to foam considerably during reflux, making the reaction difficult to control. The addition of chloroacetic acid to a hot solution of the phenolic salt in diglyme resulted in a 5 per cent reduction in yield during preliminary studies.

The final Williamson coupling of $TOPOCH_2CH_2Cl$ with the monosodium salt of penta- or octaethylene glycol gave the lowest yield of all the reactions. The highest yield achieved for this reaction was 50 per cent, and all attempts to improve the yield above this level failed. Kolobielski(5) obtained only a 12 per cent yield of para-nonylphenoxydeca(ethoxy)ethanol using sodium methylate in the final coupling reaction. Consequently, preliminary studies were attempted with potassium hydride to improve the product yield by use of a more reactive alkali metal. By this approach, however, very inconsistent yields of 22 to 38 per cent were achieved. Yields were improved by using sodium hydride with pentaethylene glycol at reaction conditions of 125° for 18 hr, 170° for 5 hr, and 40° for 18 hr. Using these reaction conditions yields ranged from about 30 to 50 per cent. In trial studies the final coupling reaction was also carried out at ambient temperatures. Aliquots were removed daily from the ambient temperature reactions and increases in yield were observed through the third day. Since yields were neither improved nor more consistent at elevated temperatures, the final coupling reaction was carried out at ambient temperatures.

Attempts were made to determine the reason for the low yields that were obtained in the final Williamson coupling. Upon purification of the detergents, approximately 40 to 50 per cent of the radioactivity was observed to migrate near the solvent front of the thin-layer chromatogram. This material was isolated from the thin-layer plates for identification. Infrared spectroscopy of the unknown material showed two absorption bands in the middle frequency region that were not present in the spectrum of TOPOH. The absorption band at 1650 cm^{-1} was a weak, but very sharp, band and was apparently due to C=C stretching vibration. The absorption band at 1720 cm^{-1} was more diffuse and appeared to result from the C-H overtone of the vinyl group. The NMR spectrum of the unknown material did not show the two triplets at 3.74 and 4.20 ppm which were due to the two methylene groups between the oxygen and chlorine of $TOPOCH_2CH_2Cl$. The characteristic pair of doublets for para substitution on the aromatic ring was also partially obscured by other peaks. Integration of the aromatic region indicated that approximately 6 protons were present, and vinylic protons attached to two polar atoms would be expected to appear in this region of the spectrum. Conclusive evidence was obtained by mass spectrometry. A molecular ion at m/e 266 was observed with an isotopic cluster indicating the presence of one chlorine atom. Therefore, the molecular ion was two mass units less than that of $TOPOCH_2CH_2Cl$ (m/e 268), and the fragmentation pattern was identical with that of $TOPOCH_2CH_2Cl$ except each fragment that contained the alkoxyl side chain was two mass units less. The physical data clearly indicated that the by-product of the coupling reaction was TOPOCH=CHCl, and the formation of the vinyl chloride was apparently in competition with the coupling reaction. The chemical results were also in agreement with the physical evidence. With the formation of a vinyl chloride, the chloro group would become very unreactive in a Williamson ether synthesis. Experimental conditions to avoid the elimination reaction could not be determined.

Temperature did not appear to be an important factor since approximately the same yields were achieved for the synthesis when experiments were performed from ambient temperature to 170°.

All the reactions given in Scheme 1, except for the final coupling reaction, gave excellent yields. If the yield of the last coupling reaction could be improved, an excellent overall yield of labeled detergent could be obtained by this synthetic scheme. In addition, it appears possible that the buffered silica gel column could be utilized for the separation of the alkoxyacetic acid from TMNOH since similar compounds were being separated. This could improve the recovery of material at that step in the alkyl detergent synthesis.

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† Mention of a trademark or proprietary product does not constitute a guarantee or warranty of the product by the U. S. Department of Agriculture and does not imply its approval to the exclusion of other products that may also be suitable.

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