SPECIFIC ^{14}C-LABELED SURFACTANTS. THE ADDITION OF HOMOGENEOUS POLYOXYETHYLENE GLYCOLS TO 2,6,8-TRIMETHYL-4-NONANOL

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SUMMARY

Two molecularly homogeneous nonionic detergents with specific-^{14}C labeling were prepared. Polyoxyethylene glycols of six and nine ethylene oxide units were coupled to 2,6,8-trimethyl-4-nonanol (TMNOH). The radioactive label was in the first ethylene oxide unit attached to the alkyl moiety, $TMNOCH_2{*}CH_2(OCH_2CH_2)_nOH$. All reactions employed in this synthesis gave good to excellent results. Two routes were developed for the reduction of an alkoxyacetic acid intermediate to the corresponding alcohol, and both methods gave excellent yields. The overall yields for $TMN(OCH_2CH_2)_6OH$ and $TMN(OCH_2CH_2)_9OH$ were 42 and 33 per cent, respectively.

INTRODUCTION

Nonionic surface active materials prepared from ethylene oxide condensations are widely used as detergents and emulsifiers. The most common method for the preparation of these nonhomogeneous surfactants is by the base catalyzed addition of ethylene oxide to either a long chain alcohol or to an alkylphenol. This method of synthesis leads to the production of molecular species having a Poisson distribution.

The synthesis of homogeneous surfactants with a definite number of ethylene oxide units has become desirable for the study of the

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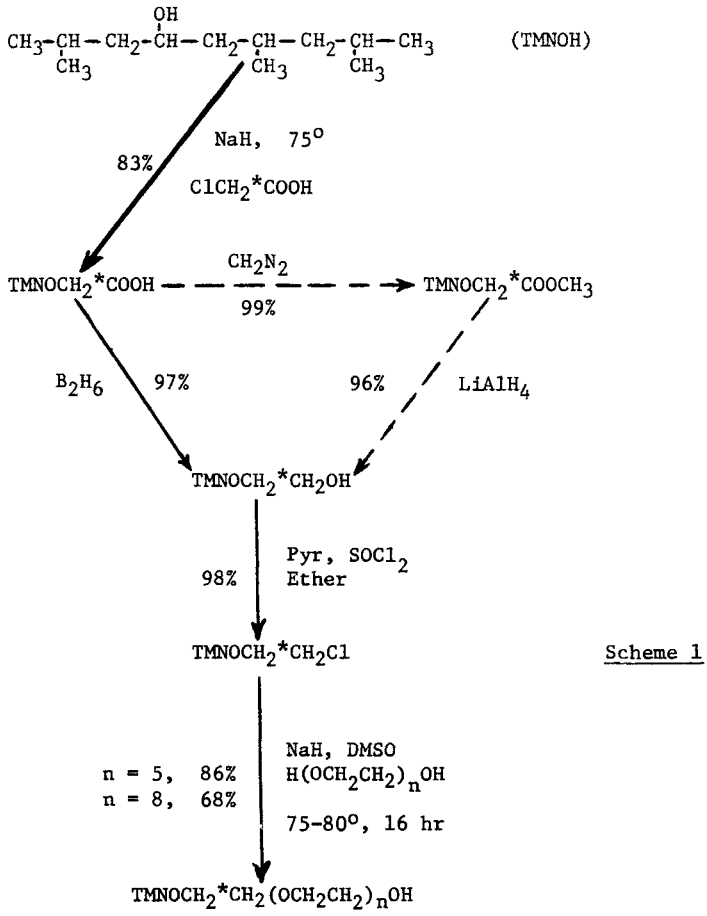
physical characteristics of these materials as well as for the determination of their fate under environmental conditions. Many workers have previously reported on the synthesis of homogeneous alkyl and aryl detergents[1-6]. These materials are generally prepared by coupling a homogeneous poly(ethoxy)ethanol moiety[7, 8] to an aryl or alkyl group by means of a Williamson type reaction.

Nooi et al.[9] prepared specific and random labeled-^{14}C surfactants of octadecanol by polymerization with ethylene oxide. Another specifically labeled nonhomogeneous surface active agent was prepared[10] by addition of ethylene oxide to dodecanol-^{14}C-1. To our knowledge, the synthesis of specifically labeled-^{14}C surfactants with molecularly homogeneous polyoxyethylene glycol side chains has not been reported. Therefore, the reaction sequence given in Scheme 1 was developed for the synthesis of homogeneous surfactants of 2,6,8-trimethyl-4-nonanol (TMNOH).



Scheme 1

In Scheme 1, the dotted arrows indicate an alternate route for the reduction of the carboxylic acid to the alcohol in excellent yield. In our case, the diborane reduction was selected because of slightly higher yields and greater ease of product isolation.

EXPERIMENTAL

Materials and Methods. Sodium hydride was used as a 57% dispersion in mineral oil. Dimethyl sulfoxide, bis(2-methoxyethyl) ether (diglyme), pentaethylene glycol, octaethylene glycol, and TMNOH were dried over molecular sieve 4A beads. Anhydrous ethyl ether was purchased in sealed metal containers, and freshly opened samples were used without further drying. Boron trifluoride etherate, after addition of a slight excess of ether, was redistilled over calcium hydride to yield a colorless liquid. Tetrahydrofuran was purified and dried by distillation from lithium aluminum hydride. Anhydrous pyridine was prepared by distillation over potassium hydroxide pellets, and thionyl chloride was redistilled from a small quantity of naphthalene and phosphorous pentachloride to yield a colorless product.

The 2,6,8-trimethyl-4-nonanol was purchased from Fluka and was approximately 99% pure (GLC). Pentaethylene glycol, with a purity of greater than 95%, was obtained from Chemical Samples Company. The octaethylene glycol[4] was kindly provided by Dr. R. L. West of Atlas-ICI, and this material had a purity of greater than 98%. Chloroacetic-^{14}C-1 acid (6 mCi, purity 99%) with a specific activity of 26.3 mCi/mmol was purchased from New England Nuclear. Unlabeled material was added to reduce the specific activity to 8 mCi/mmol.

Nuclear magnetic resonance (NMR) data were obtained on a Varian A-60A spectrometer. Samples were dissolved in deuteriochloroform, and tetramethylsilane was used as the internal reference. NMR data involving the TMN moiety were not reported, because structural changes were only performed on the alkoxyl side chain.

Gas-Liquid Chromatography (GLC). The determination of material purity and the estimation of product yield were performed on a Barber-Colman series 5000 gas chromatograph equipped with a flame ionization detector. Gas Chrom Q of 80 to 100 mesh was used as the solid support for the preparation of the chromatographic columns. Inlet and detector temperatures were held at least 25° higher than the column temperature. The operating conditions and retention times of the surfactants and the intermediates of TMNOH are given in Table I.

Table I

3% OV-1, °C	Compound	ml/min, N_2	Retention, min
150°	TMNOH	80	2.5
150°	$TMNOCH_2COOCH_3$	80	8.6
150°	$TMNOCH_2CH_2OH$	80	6.0
150°	$TMNOCH_2CH_2Cl$	80	6.0
275°	$TMN(OCH_2CH_2)_6OH$	85	7.5
310°	$TMN(OCH_2CH_2)_9OH$	85	14.4
10% DC-LSX-3-0295, °C			
185°	$TMNOCH_2CH_2OH$	70	5.1
185°	$TMNOCH_2CH_2Cl$	70	3.9

Each of the intermediates was synthesized in gram quantities to be used for reaction development. Purification of these intermediates was accomplished by vacuum distillation and thin-layer chromatography. The identity of each synthetic product was verified by NMR spectrometry. From these purified materials, standard solutions of known concentration were prepared for the estimation of reaction yields.

Purification of $TMNOCH_2COOH$. In the initial coupling reaction, TMNOH was not only one of the reactants, but also served as the solvent. Therefore, it was necessary to remove the product from a large excess of TMNOH. Purification was accomplished with a 2.5 x 38 cm column containing Whatman DE-52 microgranular cellulose (DEAE). A slurry of DEAE cellulose in aqueous methanol ($MeOH:H_2O$, 80:20 v/v) was used in

column preparation, and after packing, the column was washed with additional aqueous methanol. Flow rate of the column was held at 1.0 to 1.5 ml/min using a low pressure pump. Conversion of the column material to the acetate form was accomplished by elution with 1 N acetic acid (in degassed aqueous methanol) until the column eluate was of constant pH. The excess acetic acid was washed from the column with aqueous methanol. Although the capacity of the column was approximately 0.25 mmol, the $TMNOCH_2COOH$-^{14}C was applied in smaller quantities. Impurities were eluted first with about 155 ml of degassed aqueous methanol, and the $TMNOCH_2COOH$ was recovered from the column by elution with approximately 225 ml of 1 N acetic acid (in aqueous methanol). This method of separation would allow about 95% recovery of the applied material.

After elution with acid, a fraction of the alkoxyacetic acid was transformed to the methyl ester in the acidic eluate. Therefore, the acidic solution was made alkaline with potassium hydroxide, and the ester was hydrolyzed by refluxing for 4 hr. The alkoxyacetate salt was concentrated by rotary vacuum evaporation (under these conditions the methyl ester would codistill with methanol-water). After acidifying the solution with hydrochloric acid, the product was extracted with portions of n-hexane. A recovery of 0.386 mmol of $TMNOCH_2COOH$-^{14}C was obtained.

Purification of $TMN(OCH_2CH_2)_nOH$. The two alkyl surfactants were purified by thin-layer chromatography on plates of silica gel H (500 μ thickness) developed with water-saturated methyl ethyl ketone. Autoradiograms were taken in order to visualize the material on the thin-layer plates. The detergent in each case was removed from the chromatograms by vacuuming the silica gel into small soxhlet thimbles. Elution of the product from silica gel was accomplished in a micro soxhlet extractor with methanol. The two isolated surfactants were estimated as having greater than 98% radiochemical purity by thin-layer chromatography and autoradiography. Identity of the synthesized products was verified by comparison with authentic samples derived from commercial preparations.

Radioactivity measurements were carried out on a Packard model 3375 liquid scintillation spectrometer. The detergents after isolation were counted in a cocktail of 10 ml of Insta-Gel (Packard). Silica gel after extraction was removed from the soxhlet thimbles and counted as a gel suspension. The gel suspension was prepared by vigorously agitating 3 ml of distilled water with 10 ml of Insta-Gel. This analysis verified that after extraction, less than 1% of the radioactivity remained on the silica gel. Counter efficiency was estimated by the internal and external standard methods, and the results were in good agreement with each other.

Drying of Intermediates. It was mandatory that each intermediate be in an anhydrous condition before use in the next reaction. Trial experiments were performed using calcium sulfate, magnesium sulfate, and molecular sieve 4A as drying agents added directly into dilute solutions of the intermediates. Material losses ranged from 3% to as high as 80%, and the magnitude of the loss was largely dependent upon the intermediate being dried. The most effective method of sample drying was by azeotropic distillation of the water from the sample with benzene in a micro soxhlet extractor. By this technique, a dry sample could be obtained without material loss.

A 2 x 17 cm tube was used as the sample container to provide a long pathway to break up foam before it could reach the top of the flask. The sample was heated in an oil bath to avoid localized heating. The area of the soxhlet extractor between the sample tube and the condenser was wrapped with heating tape to lessen the heat on the sample required to reflux the benzene azeotrope into the soxhlet thimble. Anhydrous calcium chloride was placed in the thimble, and the sample was dissolved in about 20 ml of benzene. The benzene solution was held at reflux for 8 hr, and after drying the sample, the benzene was carefully removed by rotary evaporation.

Synthesis of $TMNOCH_2COOH$. A 10-ml Kjeldahl flask was modified by the attachment of a side arm, and both connections were terminated with ground

glass fittings. A calcium chloride drying tube was placed on the main taper of the flask, and an addition funnel with drying tube was fitted on the side arm. TMNONa was prepared by adding 0.3 g (7.1 mmol, 57% dispersion in mineral oil) of sodium hydride and 3.0 ml (2.46 g, 13.3 mmol) of TMNOH into the reaction vessel and heating the mixture in an oil bath at 130° for approximately 20 min. After the sodium hydride had completely reacted, the vessel was allowed to cool to ambient temperature. During this period, the addition funnel was charged with 70.9 mg (0.75 mmol, 6 mCi) of chloroacetic-^{14}C-1 acid dissolved in 1 ml of anhydrous dioxane. The radioactive chloroacetic acid solution was added to the TMNONa at ambient temperature, and the addition funnel was washed with about 1 ml of dry ether. The funnel was then removed, the side arm stoppered, and the flask manually shaken to ensure complete conversion of the chloroacetic acid to the neutralized salt. The reaction was heated for 16 hr at approximately 75°. During this period the ethyl ether was allowed to distill from the reaction vessel. The cooled mixture was made acidic with 20 ml of aqueous 10% sulfuric acid, and extraction of the acid product was accomplished with aliquots of n-hexane. The hexane fractions were combined, and the excess solvent was removed by rotary evaporation. NMR, 4.15 (2H, singlet, -OC$\underline{H}_2$- group), 11.20 ppm (H, singlet, -COO$\underline{H}$ group). Yield 83%.

Separation of TMNOH from TMNOCH$_2$COOH was required before reduction of the acid to the alcohol (cf. Purification of TMNOCH$_2$COOH). After purification of the intermediate, the sample was carefully dried (cf. Drying of Intermediates).

<u>Synthesis of TMNOCH$_2$CH$_2$OH.</u> An apparatus for external generation of diborane[11] was assembled using flasks of 50-ml volume for the generator and reaction vessels. The purified and dried sample of TMNOCH$_2$COOH-^{14}C (94.2 mg, 0.386 mmol) after removal of benzene was dissolved in 15 ml of anhydrous tetrahydrofuran (THF) and placed in the reaction vessel. Into the generation flask were added 1.0 ml of boron trifluoride etherate (1.11 g, 7.82 mmol) and 4 ml of dry diglyme.

The dropping funnel was charged with 120 mg (3.16 mmol) of sodium borohydride dissolved in approximately 10 ml of diglyme. The entire system was flushed with dry nitrogen. Diborane was slowly generated under an atmosphere of nitrogen by dropwise addition of the sodium borohydride solution over a 20 min period. The generated diborane was transferred into the reaction vessel with a gentle stream of nitrogen. To ensure complete transfer of the diborane, the generation flask was heated at 70-80° for 1 hr. Then the material in the reaction vessel was held at gentle reflux for 2 hr. After both flasks had cooled to ambient temperature, the generator flask was disconnected. Excess hydride in the generation flask was decomposed by slow addition of water until effervescence ceased. In the reaction vessel, the excess diborane was destroyed by carefully adding about 15 ml of distilled water. (If water was added too quickly, a rapid formation of foam would develop from the released hydrogen and the contents in the flask would overflow.) To complete hydrolysis, 5 ml of 6 M hydrochloric acid was added. The THF was removed by rotary evaporation, and the product was extracted with successive portions of n-hexane. The sample was then concentrated and dried. NMR, 2.50 (H, singlet, -OH group), 3.62 ppm (4H, multiplet, J = 3 Hz, $-O\underline{CH_2}\underline{CH_2}OH$ group). Yield 97%.

Synthesis of $TMNOCH_2CH_2Cl$. A 25-ml pear-shaped flask was equipped with a 30-cm air condenser, pressure equalizing addition funnel, and a calcium chloride drying tube. Then 86.2 mg (0.374 mmol) of $TMNOCH_2CH_2OH$-^{14}C, 49.2 mg (50 µl, 0.6 mmol) of dry pyridine, and 1 ml of anhydrous ethyl ether were added into the reaction vessel. To the solution was slowly added 0.5 ml (0.82 g, 6.9 mmol) of thionyl chloride dissolved in 1 ml of dry ether. Chlorination was accomplished by heating the reaction at approximately 100° for 4 hr. As the material refluxed, the ethyl ether was allowed to slowly escape from the reaction. The cooled solution was transferred into a separatory funnel containing 25 ml of n-hexane, and the excess thionyl chloride was decomposed by adding cold distilled water. Extraction of the aqueous layer was performed with

aliquots of hexane. The hexane fractions were combined and washed two times with aqueous 5% sodium bicarbonate. Following this treatment, the product was washed 3 successive times with distilled water and dried by the azeotropic distillation method. NMR, 3.61 (4H, two closely overlapping triplets, J = 3 Hz, $-O\underline{CH_2}\underline{CH_2}Cl$ group). Yield 98%.

Synthesis of $TMN(OCH_2CH_2)_nOH$. In preparation of $TMN(OCH_2CH_2)_6OH$, a 25-ml round bottom flask was fitted with an air condenser, addition funnel, and drying tube in the same manner as in the chlorination reaction. To 42 mg (1 mmol) of sodium hydride dispersion was added 2 ml of anhydrous ethyl ether. A solution of 1.2 g (5 mmol) of pentaethylene glycol dissolved in 2 ml of dry dimethylsulfoxide[12] (DMSO) was slowly added to the ether-sodium hydride suspension as the material was being magnetically stirred. The mixture was stirred for about 15 min until a clear solution was obtained, and the reaction was heated at 75° for an additional 15 min with stirring. Then 45.5 mg (0.183 mmol) of $TMNOCH_2CH_2Cl$-^{14}C dissolved in 1 ml of dry ethyl ether was placed in the addition funnel and added dropwise to the monosodium salt of pentaethylene glycol. An additional 1 ml of ether was used to rinse the dropping funnel. With continual stirring, the reaction mixture was heated at 75-80° for 16 hr. The reaction was cooled and transferred into a separatory funnel containing 25 ml of dichloromethane. Hydrolysis was achieved by addition of 25 ml of 5 N aqueous sodium chloride and 5 ml of 6 N hydrochloric acid. The product was extracted with dichloromethane. Yield 86%.

For the preparation of $TMN(OCH_2CH_2)_9OH$, the same procedure as described above was followed. For this synthesis, 1.9 g (5 mmol) of octaethylene glycol was used. Yield 68%.

ALTERNATE ROUTE TO $TMNOCH_2CH_2OH$

Synthesis of $TMNOCH_2COOCH_3$. Esterification of $TMNOCH_2COOH$ was achieved with an ethereal alcoholic solution of diazomethane prepared

from Diazald according to the procedure of de Boer and Backer[13]. A solution of 122 mg (0.5 mmol) of $TMNOCH_2COOH$ in 10 ml of anhydrous ethyl ether was placed in a 50-ml round bottom flask. The diazomethane solution was slowly added to the acid until the yellow color of the diazomethane persisted. The solution was then stirred for an additional 15 min. Excess diazomethane was destroyed by gently warming the sample in a water bath until the yellow color was no longer present. NMR, 3.74 (3H, singlet, $-OC\underline{H}_3$ group), 4.20 ppm (2H, singlet, $-OC\underline{H}_2C-$ group). Yield 99%.

Synthesis of $TMNOCH_2CH_2OH$. A 50-ml, 3-necked flask was fitted with a reflux condenser with drying tube, mechanical stirrer, and addition funnel. Into the reaction vessel was added 114 mg (3 mmol) of lithium aluminum hydride (LAH) and 20 ml of anhydrous ethyl ether. The mixture was heated at reflux with stirring for 1 hr. Then a solution of 129 mg (0.5 mmol) of $TMNOCH_2COOCH_3$ dissolved in 10 ml of ethyl ether was slowly added to the LAH solution. Following addition, the reaction was stirred at reflux temperature for 1 hr. Excess LAH was destroyed by carefully adding 5 ml of aqueous 10% sulfuric acid to the cooled reaction. The product was extracted with aliquots of ethyl ether. Yield 96%.

DISCUSSION

Initial attempts to prepare the alkoxide of TMNOH were carried out with sodium metal, but the rate of reaction was very slow. To increase the rate of alkoxide formation, metallic potassium was employed, but in this case dehydration of the alcohol was the primary result. Consequently, the most effective reagent for this reaction proved to be a dispersion of sodium hydride in mineral oil.

Two routes for the reduction of $TMNOCH_2COOH$ to the corresponding alcohol were developed. Both routes gave excellent yields. Esterification and reduction with LAH was initially developed because this method of carboxyl reduction was a commonly used approach. The diborane reduction

was developed next because this procedure would eliminate one reaction. The reduction with diborane was very reliable, easy to handle, and gave high product yields. But most important was the fact that this reaction allowed an easy separation of the product from the reactants. The LAH reduction at the 0.5 millimole level was still reported as an alternate approach because of its wide acceptance.

In the chlorination of the $TMNOCH_2CH_2OH$, a low boiling solvent was required to control the reaction temperature while thionyl chloride was being added to the pyridine and alcohol. A 10 per cent reduction in yield was observed during preliminary studies when ethyl ether was not present in the reaction mixture.

Parameters in the final Williamson coupling reaction were adjusted to give an optimum yield with excess pentaethylene glycol as reactant and solvent. Using dimethylsulfoxide[12] as solvent, however, the yield was immediately increased by about 14 per cent to give an 86 per cent reaction yield.

In summary, the reactions in the synthetic scheme gave excellent yields, and no loss occurred during the drying of each of the reaction intermediates. Therefore, if the loss of material had not occurred in the purification of the alkoxyacetic acid, an excellent overall yield of ^{14}C-labeled detergents would have been afforded by this sequence of reactions.

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REFERENCES

1. Gingras, B. A. and Bayley, C. H. - Can. J. Chem., 36: 1320 (1958).

2. Mulley, B. A. - J. Chem. Soc., 2065 (1958).

3. Mansfield, R. C. and Locke, J. E. - J. Amer. Oil Chemist's Soc., 41: 267 (1964).

4. Hartmann, L. and West, R. L. - J. Amer. Oil Chemist's Soc., 42: 65 (1965).

5. Kolobielski, M. - J. Amer. Oil Chemist's Soc., 45: 616 (1968).

6. Abe, Y. and Watanabe, S. - Fette.Seifen.Anstrichmittel, 74: 534 (1972).

7. Fordyce, R., Lovell, E. L., and Hibbert, H. - J. Amer. Chem. Soc., 61: 1905 (1939).

8. Bomer, B., Heitz, W., and Kern, W. - J. Chromatog., 53: 51 (1970).

9. Nooi, J. R., Testa, M. C., and Willemse, S. - Tenside, 7: 61 (1970).

10. Schmitz, J. - Tenside, 10: 11 (1973).

11. Zweifel, G. and Brown, H. C. - Org. Reactions, Vol. 13, Wiley, New York (1963), p. 31.

12. Smith, R. G., Vanterpool, A., and Kulak, H. J. - Can. J. Chem., 47: 2015 (1969).

13. deBoer, T. J. and Backer, H. J. - Org. Syntheses, Coll. Vol. IV, Wiley, New York (1963), p. 250.