

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Reactions Relating to Carbohydrates and Polysaccharides. LVI. The Synthesis of the Higher Polyoxyethylene Glycols¹

BY REID FORDYCE,² EDWIN L. LOVELL³ AND HAROLD HIBBERT

During the past ten years interest in the preparation and properties of long-chain polymers, of their derivatives and of co-polymers has been intensified because of their importance in the manufacture of plastics and synthetic fibers. One of the most important considerations has been the question of whether very high polymeric substances of the polyethylene oxide and cellulose types exist in solution as long macro-molecules, completely dispersed, or as aggregations of much shorter molecules associated in the micellar state.

One of the chief proponents of the former view, Staudinger⁴ has carried out an immense amount of invaluable work on the viscosity of solutions of such linear polymers. His conclusions regarding chain length have been based almost entirely on such measurements interpreted on the basis of the Staudinger viscosity relation, $\eta_{sp}/c = K_m M$.

Staudinger's researches in the high molecular weight range were admittedly carried out on polymeric mixtures obtained by fractional precipitation, because apart from the synthetic long chain polypeptides of Emil Fischer⁵ and Abderhalden and Fodor,⁶ no other chemically pure, homogeneous long-chain polymers were available.

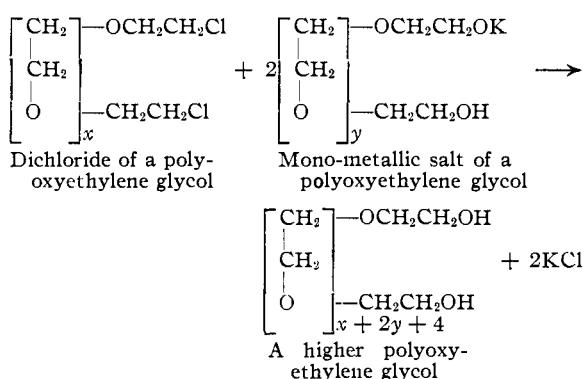
In view of this, an investigation was commenced ten years ago in this Division on the synthesis of pure homogeneous long-chain polyoxyethylene glycols, since it has been definitely established that these are identical in structure with Staudinger's polyethylene oxides.⁷

Considerable experimental difficulties have been encountered with increase in chain length and the present communication deals with the synthesis, purification and characterization of the

lower polymers, *viz.*, hexaoxyethylene glycol HO-(CH₂CH₂O)₆H, octadeca-oxyethylene glycol HO-(CH₂CH₂O)₁₈H and dotetracontaoxyethylene glycol HO(CH₂CH₂O)₄₂H.

Polyethylene glycols were first prepared by Lourenco⁸ and later by Wurtz⁹ who heated ethylene glycol with water.

However, the first direct method of synthesizing a given polyoxyethylene glycol was that of Perry and Hibbert.⁷ Their reaction may be written generally as



This method, with certain modifications, was used in the present work to synthesize the 6-, 18- and 42-membered polyoxyethylene glycols.

From the nature of the reaction it is essential that the mono rather than the dimetallic salt of the glycol be used since, if the latter were present in appreciable quantities, a chain condensation reaction could take place yielding polyoxyethylene glycols of indefinite length. For this reason, the sodium salt of diethylene glycol formed during the synthesis of hexaoxyethylene glycol was isolated in the crystalline state and, by conversion to its trityl derivative, was shown to be the mono-sodium salt.

The potassium salts of the 6- and the 18-membered polyoxyethylene glycols were not isolated. No formation of hydrogen chloride was detectable during the condensation reaction and in each case the potassium chloride formed was isolated in the theoretical amounts.

For the synthesis of the hexaoxyethylene glycol

(1) Paper presented at the Baltimore meeting of the American Chemical Society, April, 1939.

(2) Holder of a Bursary and Studentship under the National Research Council of Canada, 1937-1939.

(3) Holder of a Scholarship donated by Spruce Falls Power and Paper Company, Ltd., 1937-1938.

(4) (a) Staudinger, "Der Aufbau der hochmolekulären organischen Verbindungen—Kautschuk und Cellulose," Verlag von Julius Springer, Berlin, 1932; (b) recent review by Staudinger, *Papier Fabr.*, **36**, 373, 381, 473 (1938).

(5) Fischer, *Ber.*, **40**, 1754-1767 (1907).

(6) Abderhalden and Fodor, *ibid.*, **49**, 561-578 (1916).

(7) (a) Perry and Hibbert, *Can. J. Research*, **B14**, 77-83 (1936); (b) Barnes and Ross, *THIS JOURNAL*, **58**, 1129 (1936); (c) Perry, Ph.D. Thesis, McGill University, 1938.

(8) Lourenco, *Compt. rend.*, **49**, 619 (1859).

(9) Wurtz, *ibid.*, **49**, 813 (1859); *Ann. chim.*, [3] **69**, 331 (1863).

2 moles of the monosodium salt of diethylene glycol was condensed with 1 mole of β,β' -dichloroethyl ether. In the preparation of the 18- and 42-membered glycols, 2 moles of the monopotassium salt of hexaoxyethylene glycol and 2 moles of the potassium salt of 18-membered oxyethylene glycol, respectively, was condensed with one mole of hexaoxyethylene glycol dichloride.

In addition to the evidence for structure provided in the actual synthesis various other supporting data were obtained. Hydrogen was evolved in every case by interaction with metallic potassium and the presence of hydroxyl confirmed by the Grignard reagent. The molecular weights of the individual glycols were proved by chlorine analysis of their dichlorides and by cryoscopic molecular weights. The polyoxyethylene glycols synthesized were found free from halogen.

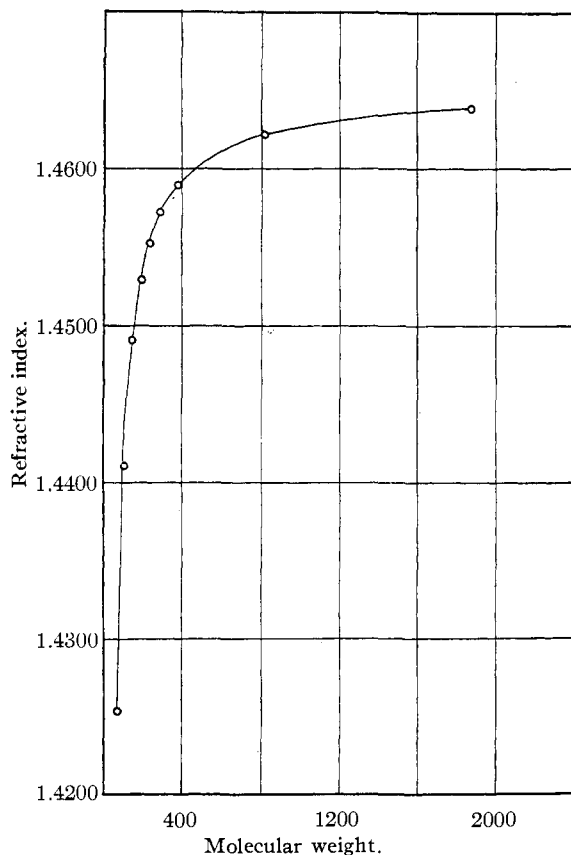


Fig. 1.—Refractive indices of the polyoxyethylene glycols at 40°.

As Fig. 1 shows, refractive index measurements of the synthetic polyoxyethylene glycols were found in agreement with their respective positions in the polyoxyethylene glycol series, although it

is evident that this property does not differentiate sharply between the higher glycols.

The agreement of the calculated molecular refractive indices with the observed values is interesting but it is not significant in establishing the identity of each glycol since the controlling factor in determining both values is the molecular weight itself.

The polyoxyethylene glycols show a uniform solubility behavior. They are readily soluble in water and the usual organic solvents, with the exception of ether and petroleum ether. Hexaoxyethylene glycol dichloride is soluble in ether and insoluble in water; while the 18-membered and the 42-membered polyoxyethylene glycol dichlorides are completely soluble in water and rather less soluble in ether, although to a greater extent than the corresponding glycol. Otherwise the solubilities of the dichlorides are quite similar to those of the glycols.

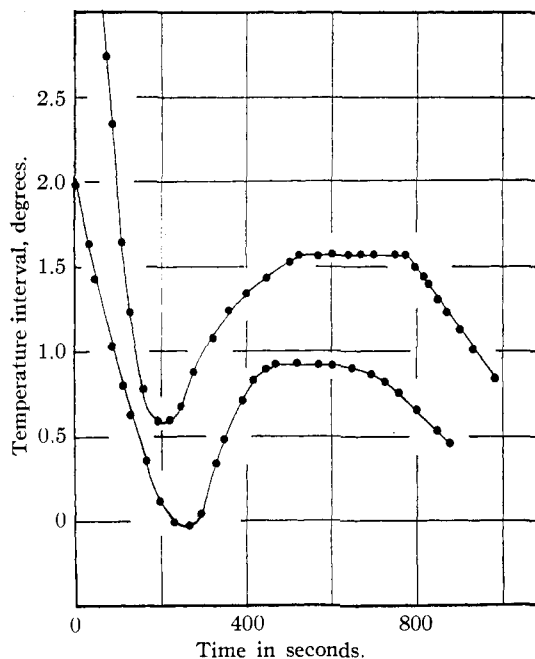


Fig. 2.—Time-temperature cooling curves of (a) hexaoxyethylene glycol (upper); and (b) hexaoxyethylene glycol containing 2.5 mole per cent. 42-membered oxyethylene glycol (lower).

The glycols crystallize in the form of characteristic, radiating clusters of thread-like crystals, which, under the polarizing microscope, show complete extinction of plane-polarized light.

It is obviously of great importance to establish, with certainty, the purity of these polyoxyethylene glycols. The shape of the time-temperature cool-

ing curve is perhaps the most significant, non-comparative, criterion of purity of a chemical compound¹⁰ and was therefore applied in the present research. A sharp break in the cooling curve when freezing is complete is perhaps one of the most sensitive effects observable with a very pure substance, as well as the actual length of the flat portion. From Figs. 2, 3, 4 and 5 it is evident that the polyoxyethylene glycols show both these effects and also that the addition of a small amount of a second component gives rise to a definite "rounding-out" of the break at the end of the flat portion. The cooling curve obtained from a polymeric mixture of glycols prepared and fractionated according to Staudinger⁴ shows no flat portion (compare Fig. 3), as is to be expected from such polymeric mixtures in contrast to chemically pure, homogeneous substances.

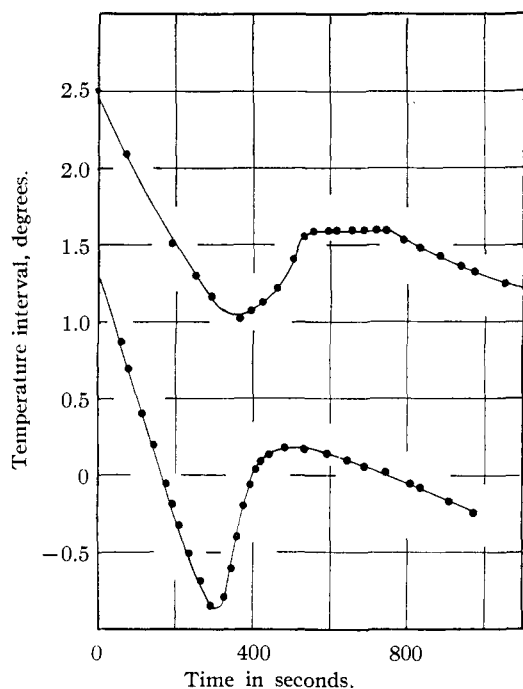


Fig. 3.—Time-temperature cooling curves of (a) 18-membered oxyethylene glycol (upper); and (b) the polymeric mixture of glycols (lower).

Experimental Part

Materials.—Commercial diethylene glycol and β,β' -dichloroethyl ether were prepared by careful fractionation. Since the glycols are hygroscopic, all reagents, solvents and apparatus were thoroughly dried prior to use and an atmosphere of dry, oxygen-free nitrogen maintained in the reaction flask during the formation of the mono-metallic salts of the glycols and their condensation with the dihalides.

(10) Skau, *Proc. Am. Acad. Arts Sci.*, **67**, 551 (1932).

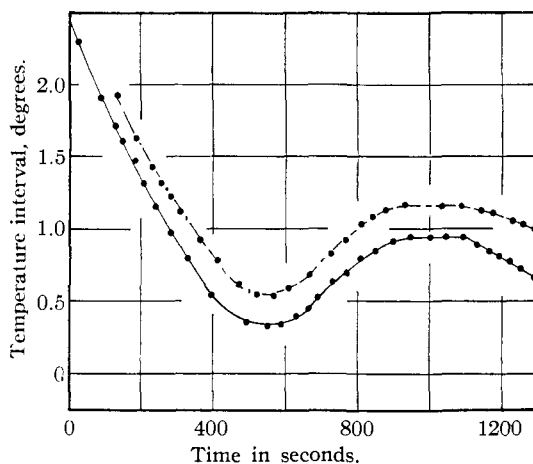


Fig. 4.—Time-temperature cooling curves of (a) 42-membered oxyethylene glycol (lower); and (b) 42-membered oxyethylene glycol containing 6.12 mole per cent. 18-membered oxyethylene glycol (upper).

Synthesis of Hexaoxyethylene Glycol, $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_6\text{H}$.—Ninety-two grams (4.0 moles) of sodium was dissolved in 700 cc. of methanol in a 2-liter Claisen flask, 900 g. (8.5 moles) of diethylene glycol added and the solution stirred at 40° for fifteen minutes. The methanol was then removed from the reaction mixture at 100° (20 mm.). Pure β,β' -dichloroethyl ether (314.6 g., 2.2 moles, 10% excess) was then added slowly and continuously through a dropping funnel during a three-hour period, the mixture being maintained at 95° and stirred vigorously throughout the addition, and then for a further three days at the same temperature. The neutral reaction mixture (phenolphthalein) was filtered from sodium

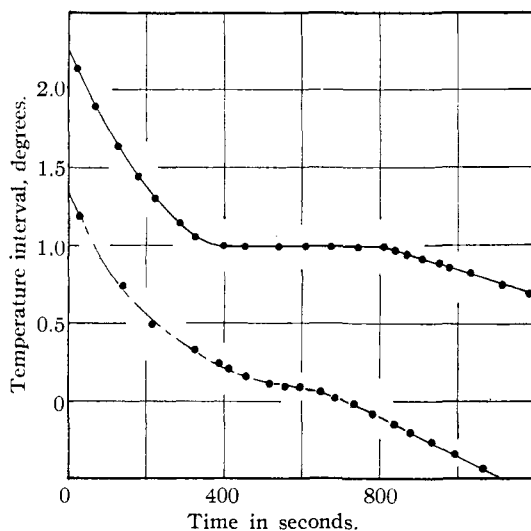


Fig. 5.—Time-temperature cooling curves (without supercooling) of (a) 42-membered oxyethylene glycol (upper); and (b) 42-membered oxyethylene glycol containing 24 mole per cent. 18-membered oxyethylene glycol (lower).

chloride and the filtrate distilled at 2 mm. pressure until everything boiling up to 200° had been removed. Repeated high vacuum distillation of the residual liquid yielded 260 g. (48% of theoretical) of hexaoxyethylene glycol as a colorless oil; b. p. 185–185.7° (0.015 mm.). The refractive index remained constant throughout the distillation.

Isolation of the Sodium Salt of Diethylene Glycol and Conversion into Trityl Derivative

If, during the previous synthesis of hexaoxyethylene glycol, the solution containing the sodium salt of diethylene glycol left after removal of the methanol is allowed to cool, large, hygroscopic, transparent crystals of the monosodium salt containing 1 mole of diethylene glycol of crystallization separate out. These crystals were separated by filtration, washed repeatedly with dioxane, then ether and dried.

Anal. Calcd. for $C_8H_{16}O_6Na$: Na, 9.83. Found: Na, 9.65, 9.44.

Trityl Derivative.—To a solution of 8.0 g. (0.0287 mole) of trityl chloride in 80 cc. of dioxane heated to 70° was added with stirring 6.7 g. (0.0287 mole) of the sodium salt and the reaction product kept at this temperature for two hours. It was then poured into twenty volumes of ice water. The resulting trityl derivative was recrystallized from a mixture of benzene–petroleum ether (30–50°): yield 9.0 g. (90%); m. p. 116–116.5°.

Anal. Calcd. for $C_{23}H_{24}O_3$ (monotrityl derivative): C, 79.3; H, 6.9. Found: C, 79.1, 79.2; H, 6.87, 6.97.

Preparation of Hexaoxyethylene Glycol Dichloride.—To 350 g. (1.24 moles) of hexaoxyethylene glycol dissolved in 205.8 g. of anhydrous pyridine was added slowly and with vigorous stirring at 45°, over a period of twenty minutes, 310.8 g. (2.67 moles, 10% excess) of thionyl chloride. The temperature of the reaction mixture rose to 80° during the addition and stirring was continued at this temperature for a further ten minutes. After cooling to room temperature the reaction mixture was extracted three times using 500, 400 and 300 cc. of ether, respectively. The extract was neutralized with sodium carbonate, and filtered, and the pyridine, ether and excess thionyl chloride removed at 100° (10 mm.). The residual oil on vacuum distillation yielded 245 g. (77%) of hexaoxyethylene glycol dichloride as a colorless liquid; b. p. 168–169° (0.100 mm.); f. p. –12.4°.

Anal. Calcd. for $Cl(CH_2CH_2O)_6CH_2CH_2Cl$: Cl, 22.26; mol. wt., 319. Found: Cl, 22.20, 22.34; mol. wt. (cryoscopic), 310.

Synthesis of Octadecaoxyethylene Glycol, $HO(CH_2CH_2O)_{18}H$.—Hexaoxyethylene glycol (230 g., 0.817 mole) was placed in a flask and covered with a layer of petroleum ether (b. p. 100–110°) and then, at room temperature, potassium metal (21.8 g., 0.56 mole) added in the form of small pieces. After stirring for fifteen hours at room temperature, this gradually was raised to 65° to complete the potassium salt formation. Hexaoxyethylene glycol dichloride (97.6 g., 0.306 mole, 10% excess) was then added, with stirring, at 135° over a two-hour period. After stirring at 175° for a further five hours, the reaction mixture was neutral to phenolphthalein. The precipi-

tated potassium chloride was removed by filtration and the filtrate distilled at a bath temperature of 265° (0.010 mm.) using a Claisen flask immersed to the side-arm.

The residual oil was then continuously extracted with ether (500 cc.) for three to four days. Methanol was added at room temperature to the ether extract until the glycol which had separated during extraction just dissolved. This solution was now decolorized by stirring for two hours with charcoal, filtered, the clear solution cooled to –11° and allowed to stand overnight at this temperature. The crude crystalline product was filtered, washed with anhydrous ether, then transferred to a flask and warmed gently with about 750 cc. of anhydrous ether. Most of the glycol remained undissolved and just sufficient anhydrous methanol was added (approx. 165 cc.) to effect its complete solution. Crystallization again was brought about by cooling at –11°. This recrystallization process was repeated six or seven times under the same conditions and with the same volumes of solvents until the freezing point of the final product remained constant: yield 113 g. (50.3%); f. p. 23.8°.

Preparation of Octadecaoxyethylene Glycol Dichloride.—Octadecaoxyethylene glycol (5.04 g., 0.00623 mole) was dissolved in pyridine (3.96 g.); to this was added, dropwise, thionyl chloride (1.92 g., 0.0161 mole, 30% excess) and the mixture stirred at 65° for three hours. The reaction mixture was then extracted with four 25-cc. portions of ether, solid sodium bicarbonate added to the combined extracts and the mixture allowed to stand until neutral. After filtration, the filtrate was distilled at 0.0025 mm. to a temperature of 175° to remove lower boiling constituents. The residual oil was dissolved in ether, decolorized with charcoal and then recrystallized three times at –80° from pure ether: yield 2.02 g. (38.5%), white crystalline solid; f. p. 22.9°.

Anal. Calcd. for $Cl(CH_2CH_2O)_{17}CH_2CH_2Cl$: Cl, 8.38. Found: Cl, 8.51, 8.50.

Synthesis of the Dotetracontaoxyethylene Glycol, $HO(CH_2CH_2)_{42}H$.—Octadecaoxyethylene glycol (141.2 g., 0.1745 mole) was placed in a three-necked flask, fitted with mercury seal stirrer and nitrogen inlet tube and covered with a layer of petroleum ether (b. p. 100–110°). Potassium metal (6.83 g., 0.1745 mole) previously weighed and cut into small pieces under anhydrous petroleum ether (b. p. 50°) was introduced in one addition to the stirred mixture at room temperature and the stirring maintained for about seventeen hours. The temperature was now gradually raised, over the following three-hour period to 135°, and the mixture stirred at this temperature for a further two hours to complete the potassium salt formation. Hexaoxyethylene glycol dichloride (30.6 g., 0.0958 mole, 10% excess) was now added at 135° with stirring during some fifteen minutes and after a further period of stirring for seventeen hours at the same temperature the reaction mixture reacted neutral to phenolphthalein. Filtration while still warm removed the precipitated potassium chloride and the filtrate was then continuously extracted with ether (250 cc.) for three days. Anhydrous methanol, about 40 cc., was then added at room temperature to the ether extract until the oily glycol, which had separated out during the extraction process, just dissolved. The mixture was cooled in a

TABLE I
 PHYSICAL CONSTANTS OF POLYOXYETHYLENE GLYCOLS AND THEIR DICHLORIDES

Substance	Appearance	Refr. index, n_{D}^{20}	Density, d_4^{20}	F. p., °C.	Mol. wt.		Mol. refr. index	
					Calcd.	Obsd.	Calcd. ^a	Obsd.
Hexaoxyethylene glycol	Colorless liquid	1.4500	1.0948	2.1	282	289	68.881	69.22
Hexaoxyethylene glycol dichloride	Colorless liquid	1.4510	1.1307	-12.4	319	311	75.565	75.97
18-Membered oxyethylene glycol	White crystalline solid	1.4550	1.0949	23.8	810	803	199.431	200.7
18-Membered oxyethylene glycol dichloride	White crystalline solid	1.4560	1.1060	22.9			206.115	208.2
42-Membered oxyethylene glycol	White crystalline solid	1.4563	1.0951	33.8	1866	1748	460.526	463.7
42-Membered oxyethylene glycol dichloride	White crystalline solid	1.4564	1.1001	33.4			467.209	461.4

^a Calculations are based on the atomic values suggested by Auwers and Eisenlohr, *Ber.*, **43**, 806 (1910).

brine-bath (-11°) and the crude glycol crystallized out. It was filtered, washed with anhydrous ether, then recrystallized from a mixture of 600 cc. of ether and just enough anhydrous methanol (*ca.* 155 cc.) to effect a solution of the glycol, and again recrystallized by cooling. After six or seven such crystallizations to constant freezing point, the pure 42-membered oxyethylene glycol was obtained: yield 113 g. (47% of theoretical); mol. wt. calcd. 1866, found (cryoscopic) 1748; f. p. 33.8°.

Preparation of the Dotetracontaoxyethylene Glycol Dichloride, $\text{Cl}(\text{CH}_2\text{CH}_2)_{41}\text{CH}_2\text{CH}_2\text{Cl}$.—The 42-membered oxyethylene glycol (4.35 g., 0.00233 mole) was dissolved in 5 cc. of pyridine and to this was added, dropwise, thionyl chloride (0.722 g., 0.00607 mole, 30% excess). The mixture was stirred for two and one-half hours at 65° and the reaction mixture then extracted with six 400-cc. portions of ether. Any acid present was removed by adding solid sodium bicarbonate to the combined ether extracts and allowing to stand for one and one-half hours. After filtration, the ether, thionyl chloride and pyridine were removed at 100° (10 mm.). The residual oil was recrystallized three times from about 50 cc. of ether and gave 1.25 g. (28.1% of theoretical) of a white crystalline solid; f. p. 33.4°.

Anal. Calcd. for $\text{Cl}(\text{CH}_2\text{CH}_2)_{41}\text{CH}_2\text{CH}_2\text{Cl}$: Cl, 3.72. Found: Cl, 3.69, 3.71.

Physical Properties and Constants of the Polyoxyethylene Glycols and their Dihalides.—Refractive indices were measured by means of an Abbe refractometer fitted with compensating prisms. Birefringence was observed with this instrument with the 18- and 42-membered oxyethylene glycols at a temperature 1° below their freezing points.

The freezing points ("setting" points) have been reported for these compounds rather than melting points because the former are known in general to be much more reproducible than the latter.¹¹ With the glycols investigated they were found to be reproducible to $\pm 0.1^\circ$.

The molecular weight values were determined cryoscopically in a standard Beckmann freezing-point apparatus, access of moisture to the solutions being prevented by a slow stream of dry air directed into the side-arm of the cryoscopic tube. For the 6-membered glycol and

its dichloride, as well as for the 18-membered glycol, carbon tetrachloride (cryoscopic constant, 29) was used as solvent; for the 42-membered glycol, pure, dry dioxane¹² ($K = 4.8$) in which the polyglycols are not associated,⁴ was employed. The results given are the average in each case of several determinations at concentrations in the range 0.07 to 1 mole per cent.

Density measurements were carried out by using a small specific gravity bottle (volume 1.8 cc.), having a removable ground-in capillary and cap. The temperature of the bath used in these measurements was maintained constant to within $\pm 0.02^\circ$.

The reproducible time-temperature cooling curves were obtained by using an alcohol thermometer of low heat capacity and reading to $\pm 0.01^\circ$. This was immersed in 5 cc. of the sample contained in a suitably lagged test-tube surrounded by a cooling bath maintained about 8° below the freezing point of the sample. In Fig. 2 cooling curves for both pure hexaoxyethylene glycol and for a mixture of this with 2.5 moles of diethylene glycol are shown. Figure 3 shows the cooling curve for the 18-membered oxyethylene glycol and also that of a polymeric mixture of glycols, freezing point 26.0°, which had been obtained by the fractionation procedure outlined by Staudinger. The effect of a 6.12 mole per cent. addition of the 18-membered ethylene glycol to the 42-membered glycol upon the cooling curve is shown in Fig. 4, while Fig. 5 shows the complete distortion produced when 24 mole per cent. impurity is added.

In conclusion, the authors wish to express their indebtedness to Dr. J. C. Pullman for preliminary experimental work in connection with this method of synthesis.

Summary

1. The syntheses and properties of pure straight chain polyoxyethylene glycols of the general formula $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_n\text{H}$, where $n = 6, 18$ and 42, are described.

2. The purity of these compounds was established by the time-temperature cooling

(11) Frances and Collins, *J. Chem. Soc.*, 137 (1936).

(12) Eigenberger, *J. prakt. Chem.*, [2] **130**, 75 (1931).

curve method and supported by cryoscopic molecular weight determinations and analysis of the dichlorides.

MONTREAL, CANADA

RECEIVED MAY 1, 1939

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Reactions Relating to Carbohydrates and Polysaccharides. LVII. The Synthesis of 90-Membered Oxyethylene and 186-Membered Oxyethylene Glycols¹

BY REID FORDYCE² AND HAROLD HIBBERT

The Williamson ether synthesis described previously³ has been used to synthesize further higher members of the polyoxyethylene glycol series, namely, the 90-membered and the 186-membered polyoxyethylene glycols $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_{90}\text{H}$ and $\text{HO}(\text{CH}_2\text{CH}_2\text{O})_{186}\text{H}$, respectively.

These were synthesized by reaction of 2 moles of the respective monosodium salts of 42- and 90-membered oxyethylene glycols with one mole each of the 6-membered oxyethylene glycol dichloride.

the freezing point following several recrystallizations. A further series of recrystallizations was carried out on the pure glycols and, while the final product represented only about 60% of the starting material, it was found that the freezing point of initial and final products was the same. Additional evidence of the purity of the 90- and 186-membered oxyethylene glycols was found in their time-temperature cooling curves (Fig. 1).

The preparation of derivatives of the two glycols suitable for end-group molecular weight determinations proved impracticable because the solubility and other physical characteristics of such derivatives were found to parallel those of the corresponding glycols so closely, even when large groups were attached, that their isolation in the pure state was rendered almost impossible.

Cryoscopic molecular weights, also, could not be employed as they had no significance due to the difficulty in measuring accurately the small freezing-point depression in question.⁴

The method of synthesis of the glycols together with the evidence of their purity, as shown by their physical properties, is strong evidence for the establishment of their molecular weights. Furthermore, the freezing points are shown to vary in a regular manner with the molecular weight and in ascendancy with a relationship developed by Lovell and Hibbert.⁵

The solubility characteristics of 90- and 186-membered glycols are the same as those of the lower members of the series. One of the most outstanding properties of these long chain compounds is their ready solubility in common solvents.

The birefringence observed³ with the lower members of this series is shown in the photomicrograph

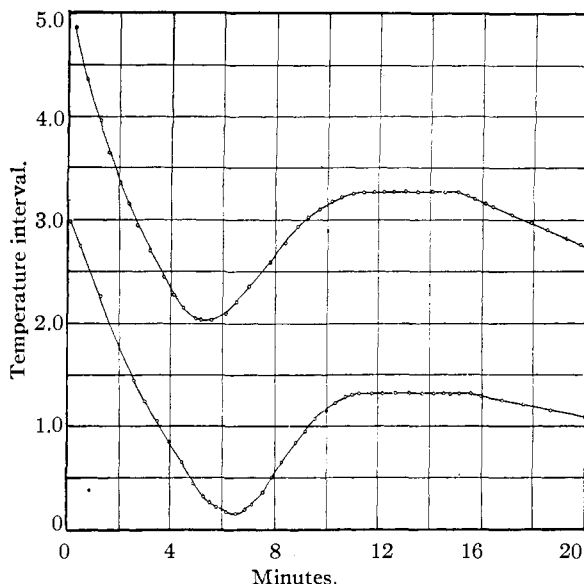


Fig. 1.—Time-temperature cooling curves of (a) 186-membered oxyethylene glycol (upper); (b) 90-membered oxyethylene glycol (lower).

Chlorine could not be detected in either of the isolated reaction products and their refractive indices gave the values to be expected for such higher members of this series.

Their purity was shown by the constancy of

(1) Paper presented at the Baltimore meeting of the American Chemical Society, April, 1939.

(2) Holder of a Bursary and Studentship from the National Research Council of Canada, 1937-1939.

(3) Fordyce, Lovell and Hibbert, *THIS JOURNAL*, **61**, 1905 (1939).

(4) An investigation of the determination of the molecular weights of the polyoxyethylene glycols by the "spinning top" method is being carried out by Professor McBain, Stanford University, and it is our intention to obtain supporting evidence from osmotic pressure measurements.

(5) Lovell and Hibbert, *THIS JOURNAL*, **61**, 1916 (1939).