# Single Step Room Temperature Oxidation of Poly(ethylene glycol) to Poly(oxyethylene)-Dicarboxylic Acid

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**ABSTRACT:** Poly(oxyethylene)-dicarboxylic acids were obtained in high yields by room temperature oxidation of poly(ethylene glycol)s of molecular weights in the 4000–100,000 range using Jone's reagent ($CrO_3$ and $H_2SO_4$) as the oxidizing agent. Oxidation by-products from the reaction mixture were eliminated by adsorbing chromium salts onto activated charcoal. The acid values of poly(oxyethylene)-dicarboxylic acids so synthesized were in agreement with the theoretical values. Poly(oxyethylene)-dicarboxylic acids were characterized by $^1$H-NMR, IR spectroscopy. Spectral data were in agreement with the proposed structures of products. In summary, a convenient, one pot method for the synthesis of a wide range of poly(oxyethylene)-dicarboxylic acids was developed. © 1998 John Wiley & Sons, Inc. J Appl Polym Sci 70: 883–890, 1998

**Key words:** poly(ethylene glycol); poly(oxyethylene)-dicarboxylic acids; Jone's reagent; oxidation

## INTRODUCTION

Poly(ethylene glycol)s (PEGs) and their derivatives have diverse applications. Poly(oxyethylene)-dicarboxylic acids (POE-dicarboxylic acids) in particular are used in a wide range of applications such as water soluble polymer support for Merrifield type peptide syntheses,[1,2] polymeric drug carriers (prodrugs),[3–7] antistatic agents in polyamides,[8] enzyme–metal ion conjugates for improved stability and activity of enzymes,[9–11] hemoglobin conjugates for oxygen carrying blood substitute,[12] lipid conjugates for enhanced longevity in blood circulation,[13] surface modifying agents for transition metal alluminides,[14] two phase aqueous separation of enzymes,[15] stabilizers for water based epoxy formulations,[16] and so on.

To meet these growing demands for POE-dicarboxylic acids, various methods for their synthesis have been developed. These methods could be broadly classified into two types: carboxymethylation or succinylation of terminal hydroxymethyl groups of PEGs[1,3,6,7,17–19] and oxidation of terminal hydroxymethyl groups of PEGs.[8,20–25] The first approach involves multistep reactions that require expensive reagents such as potassium *t*-butoxide and bromoethyl acetate. Therefore, these methods are less attractive for industrial applications. The latter involves oxidation of terminal hydroxymethyl groups by various oxidizing agents at high temperatures, pressure followed by removal of oxidation by-products by cumbersome methods such as neutralization of oxidizing agents, concentration, and isolation. Also, the reaction conditions need to be modified according to the choice of the oxidizing agent and the molecular weights (mol. wts.) of the PEGs chosen.[21–23]

Thus, there is a need for a simpler method for oxidation of PEGs to POE-dicarboxylic acids, which will obviate drastic reaction conditions and tedious

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recovery techniques. It is also desirable that such a method be applicable to PEGs having a wide range of molecular weights. In this communication, we report a novel method for synthesis of POE-dicarboxylic acid. The method is essentially a one pot synthesis wherein room temperature oxidation of PEGs by Jone's reagent and charcoal treatment of the reaction mixture for removing oxidation by-products is demonstrated.[26]

## EXPERIMENTAL

### Materials

PEG 4000, PEG 6000, chromium trioxide ($CrO_3$), sulfuric acid ($H_2SO_4$), potassium hydroxide (KOH), and phenolphthalein indicator were from local suppliers. Monomethoxy-PEG 5000 (Ome-PEG 5000) and PEG 20,000 were from Fluka. PEG 100,000 was from Aldrich. Commercial grade acetone was distilled and used as the solvent for the reactions.

### Instrumentation and Analysis

$^1$H-NMR spectra were recorded on a Bruker 90-MHz or Varian 200-MHz spectrometer. IR spectra were recorded on a Perkin–Elmer 1600 FTIR spectrophotometer. Melting points were recorded on a Mettler melting point apparatus. The acid values of the POE-dicarboxylic acids synthesized in this study were determined.

#### *Estimation of Acid Values of POE-Dicarboxylic Acids*

In a typical estimation, 1 g of POE-dicarboxylic acid dissolved in 10 mL distilled water was placed in a conical flask. Two drops of phenolphthalein indicator was added to this, and the solution was titrated against 0.01680*N* KOH solution (normality determined by titration with potassium hydrogen phthalate) until the colorless to faint pink colored end point was obtained. The amount of KOH required for titration of POE-dicarboxylic acid was noted and the acid value was calculated using the following formula:

$$\text{acid value (mg KOH/g)} = 56.1 * (\text{mL KOH required}) * \text{normality of KOH/weight POE-dicarboxylic acid (g)}$$

The acid value so calculated is in terms of mg of KOH required to neutralize 1 g of POE-dicarboxylic acid. The acid value in terms of millimoles of the carboxyl groups (—COOH groups) per g was calculated as

$$\text{acid value (mmol carboxyl groups/g)} = \text{acid value (mg KOH)}/56.1$$

Theoretical acid values were calculated from the nominal molecular weights of the PEGs used, assuming PEG chains have uniform mol wts. For example, the mol wt of PEG 4000 was assumed to be 4000, although in reality it exhibits a mol wt distribution in the range of 3500–4500.

### Syntheses

#### *Preparation of Oxidizing Agent (Jone's Reagent)*

Jone's reagent was synthesized according to the following procedure.[27] Seventy grams of $CrO_3$ was dissolved in 500 mL distilled water and the solution was stirred with magnetic needle at 10–15°C (ice-water bath). To this solution, 61 mL concentrated $H_2SO_4$ was added in small portions. After the addition was over, the solution was stirred for additional 10 min and allowed to reach room temperature. Jone's reagent so prepared was stored at room temperature and used in syntheses of all POE-dicarboxylic acids.

#### *Synthesis of POE 4000-Dicarboxylic Acid*

Forty grams PEG 4000 (0.01*M*) was placed in a 1-L round bottom flask and 400 mL acetone was added to it. The contents of the flask were heated in a heating mantle to obtain a clear, homogeneous solution. The solution was allowed to attain room temperature. To this solution, 17 mL Jone's reagent (containing 0.02*M* $CrO_3$) was added in a single portion and the reaction mixture was stirred at room temperature ($\sim$ 25°C) with a magnetic needle. Within a few minutes after the addition, blue-green colored chromium salts (oxidation by-products) precipitated out in the form of a fine suspension in the acetone solution. Stirring of the reaction mixture was continued overnight (16 h). Then the reaction was quenched by adding 5 mL isopropyl alcohol (free radical scavenger).

#### *Removal of Chromium Salts from Reaction Mixture*

The above suspension of chromium salts cannot be readily filtered. Four grams of finely powdered

activated charcoal (10% of the wt. of PEG) was added and stirred with a magnetic needle for 2 h. This was then filtered in a Buckner funnel to obtain a colorless, clear acetone solution.

The clear acetone solution was concentrated *in vacuo* to a viscous liquid. This was poured into a petri dish and allowed to cool to room temperature which solidified it. Residual moisture from the product so obtained was removed by drying it in a vacuum desiccator for 48 h. The product was a white powder. **Yield:** 33 g (82%). **Acid value: found,** 0.53 mmol carboxyl groups/g; **theoretical,** 0.49 mmol carboxyl groups/g. **Melting point: 53–54°C. IR (nujol):** 1700 $cm^{-1}$ (carbonyl of acid), 3400 $cm^{-1}$ (—OH stretching). **$^1$H-NMR (DMSO $d_6$):** 4.44 δ broad singlet $(—CH_2—CH_2—O—)_n$ of PEG chain, 4.77 δ singlet ($—CH_2—$ vicinal to $—O—CH_2—COOH$), 6.0 δ ($—O—CH_2—$ vicinal to —COOH), 10.0 δ singlet (—COOH).

### *Synthesis of Ome-POE 5000-Monocarboxylic Acid*

Fifty grams Ome-PEG 5000 (0.01*M*) was dissolved in 400 mL acetone as mentioned in the synthesis procedure of POE 4000-dicarboxylic acid. To this solution, 8.5 mL Jone's reagent (containing 0.01*M* $CrO_3$) was added in a single portion and the reaction mixture was stirred with a magnetic needle overnight at room temperature. Then the reaction was quenched by adding 5 mL isopropyl alcohol. The chromium salts that formed were removed from the reaction mixture by adding 5 g finely powdered activated charcoal (10 wt % of the PEG taken), stirring for 2 h, and filtering it to obtain a colorless acetone solution. The solution was concentrated *in vacuo,* and a white powdered product was isolated as mentioned earlier. **Yield:** 44 g (88%). **Acid value: found,** 0.16 mmol carboxyl groups/g, **theoretical,** 0.19 mmol carboxyl groups/g. **Melting point: 66–67°C. IR (nujol);** 1690 $cm^{-1}$ (carbonyl of acid), 3480 $cm^{-1}$ (—OH stretching). **$^1$H-NMR (DMSO) $d_6$):** 2.44 δ singlet ($—O—CH_3$), 3.00 δ singlet ($—CH_2$ vicinal to $—O—CH_2—COOH$), 3.33 δ broad singlet $(—CH_2—CH_2—O—)_n$ of PEG chain, 3.82 δ singlet ($—O—CH_2—$ vicinal to —COOH), 8.2 δ singlet (—COOH).

### Synthesis of POE 6000-Dicarboxylic Acid

Sixty grams PEG 6000 (0.01*M*) was dissolved in 400 mL acetone. To this solution, 17 mL Jone's reagent (containing 0.02*M* $CrO_3$) was added in a single portion and the reaction mixture was stirred with a magnetic needle overnight at room temperature. Then the reaction was quenched by adding 5 mL isopropyl alcohol. The chromium salts that formed were removed from the reaction mixture by adding 6 g finely powdered activated charcoal (10 wt % of the PEG taken), stirring for 2 h, and filtering it to obtain a colorless acetone solution. The solution was concentrated *in vacuo,* and a white powdered product was isolated. **Yield:** 53 g (88%). **Acid value: found,** 0.42 mmol carboxyl groups/g, **theoretical,** 0.33 mmol carboxyl groups/g. **Melting point: 52–53°C. IR (nujol):** 1710 $cm^{-1}$ (carbonyl of acid), 3340 $cm^{-1}$ (—OH stretching). **$^1$H-NMR (DMSO $d_6$):** 3.4 δ broad singlet $(—CH_2—CH_2—O—)_n$ of PEG chain, 3.71 δ singlet ($—CH_2$ vicinal to $—O—CH_2—COOH$), 4.00 δ singlet ($—O—CH_2—$ vicinal to —COOH), 9.82 δ singlet (—COOH).

### Synthesis of POE 20,000-Dicarboxylic Acid

Two hundred grams of PEG 20,000 (0.01*M*) was dissolved in 800 mL acetone. To this solution, 17 mL Jone's reagent (containing 0.02*M* $CrO_3$) was added in a single portion and the reaction mixture was stirred with a magnetic needle overnight at room temperature. Then the reaction was quenched by adding 5 mL isopropyl alcohol. The chromium salts that formed were removed from the reaction mixture by adding 20 g finely powdered activated charcoal (10 wt % of the PEG taken), stirring for 2 h, and filtering it to obtain a colorless acetone solution. The solution was concentrated *in vacuo,* and a white powdered product was isolated. **Yield:** 123 g (61%). **Acid value: found,** 0.24 mmol carboxyl groups/g; **theoretical,** 0.10 mmol carboxyl groups/g. **Melting point: 64–65°C. IR (nujol):** 1710 $cm^{-1}$ (carbonyl of acid), 3400 $cm^{-1}$ (—OH stretching). **$^1$H-NMR (DMSO $d_6$):** 3.04 δ broad singlet $(—CH_2—CH_2—O—)_n$ of PEG chain, 3.35 δ singlet ($—CH_2—$ vicinal to $—O—CH_2—COOH$), 3.75 δ singlet ($—O—CH_2—$ vicinal to —COOH), 8.37 δ singlet (—COOH).

### Synthesis of POE 100,000-Dicarboxylic Acid

Fifty grams of PEG 100,000 (0.5 mmol) was dissolved in 1000 mL acetone. To this solution, 1 mL Jone's reagent (containing 1.0 mmol $CrO_3$) was added in a single portion and the reaction mixture was stirred with a magnetic needle overnight at room temperature. Then the reaction was quenched by adding 5 mL isopropyl alcohol. The chromium salts that formed were removed from

the reaction mixture by adding 5 g finely powdered activated charcoal (10 wt % of the PEG taken), stirring for 2 h, and filtering it to obtain a colorless acetone solution. The solution was concentrated *in vacuo,* and white powdered product was isolated. **Yield:** 37 g (74%). **Acid value: found,** 0.05 mmol carboxyl groups/g; **theoretical,** 0.02 mmol carboxyl groups/g. **IR (nujol):** 1620 $cm^{-1}$ (carbonyl of acid), 3400 $cm^{-1}$ (—OH stretching). **$^1$H-NMR (DMSO $d_6$):** 3.0 δ broad singlet (—$CH_2$—$CH_2$—O—)$_n$ of PEG chain, 3.2 δ singlet (—$CH_2$— vicinal to —O—$CH_2$—COOH), 3.5 δ singlet (—O—$CH_2$— vicinal to —COOH), 8.0 δ (—COOH).

## RESULTS AND DISCUSSION

As mentioned in the Introduction section, there are two types of methods for the synthesis of POE-dicarboxylic acids.

### Carboxymethylation or Succinylation of Terminal Hydroxymethyl Groups of PEGs

Garfield and Ananthramaiah[1] synthesized POE-dicarboxylic acid by carboxymethylation involving activation of terminal hydroxymethyl groups by reacting PEG with strong bases such as potassium *tert*-butoxide, reaction of PEG alcoholate with bromoethyl acetate, saponification of ethyl ester, and isolation of PEG-dicarboxylic acid from the reaction mixture by conventional work ups (i.e., filtration of by-product salts, concentration of solvent, and extraction of product in organic solvents). This method with some modifications was used by Ulbrich et al.,[3] Pechar et al.,[7] Buckmann et al.,[17] Keiji et al.,[18] and Martinez and Greenwald.[19] Zalipsky et al.[6] reacted PEG with succinic anhydride to derivatize hydroxyl groups with —CO—$CH_2$—$CH_2$—COOH groups.

Because this method involves multiple steps, as well as specialty reagents, it is not attractive for large-scale production of POE-dicarboxylic acid.

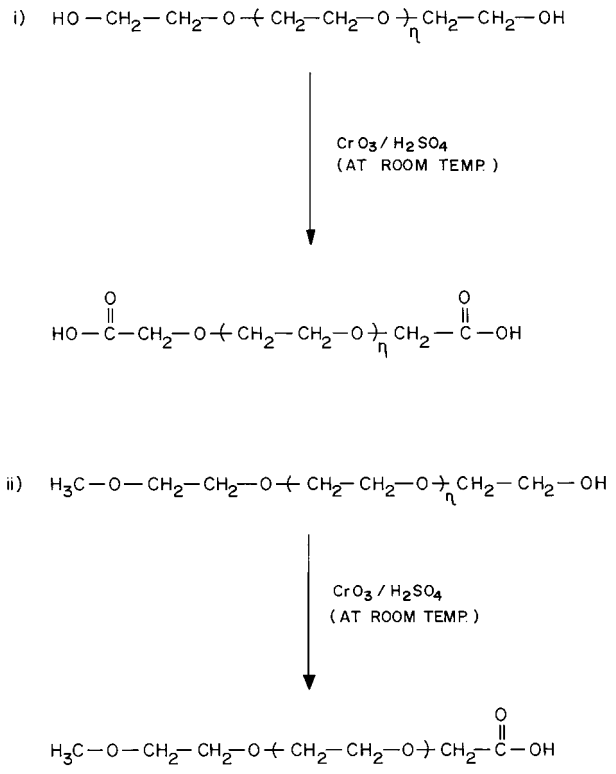
### Oxidation of Terminal Hydroxymethyl Groups of PEGs

A number of patents that are based on this technique have been filed. Yonemitsue et al.[20] oxidized low mol wt PEGs to POE-dicarboxylic acids using oxygen and concentrated nitric acid ($HNO_3$) as the oxidizing reagent in an autoclave at 80°C at 3 $kg/cm^2$ pressure. Low mol wt PEGs have been oxidized using platinum/charcoal (Pt.C) catalysts and oxygen under pressure at 50°C in a column reactor.[21] Synthesis of POE-dicarboxylic acids by oxidation of PEGs in the presence of $Co(OAc)_2 \cdot 4H_2O$ using oxygen under pressure at 140°C and using a mixture of catalysts [$Cu(OAc)_2 \cdot H_2O$, $NH_4VO_3$, $HNO_3$, and HCHO] at 50–90°C was also reported.[22,23] Jan and Frantisek[8] synthesized low mol wt POE-dicarboxylic acids (1000–3000) by oxidation of respective PEG using $K_2Cr_2O_7$ and $H_2SO_4$ at 70°C using water as the solvent. Microbial oxidation of PEGs (mol wt 200–2000) by *Rhinocladiella actrovirens* was reported by Shuichi et al.[24] This oxidation required up to 2 weeks. Fried[25] reported oxidation of various PEGs to POE-dicarboxylic acids at 35°C using oxygen, $HNO_3$, and 2,2,6,6-tetramethylpiperidine-1-oxyl as the oxidizing agent.

Most of the above oxidation processes required drastic reaction conditions such as high temperature and pressure or specialty oxidizing agents. Also, in most of the cases low mol wt PEGs were used.[21–23] Besides, the recovery of products involved multiple steps such as concentration of solvents, removal of oxidation by-products, and extraction of products in suitable solvents.

**Table I Effect of $CrO_3$ Concentration on Extent of PEG Oxidation**

| | Amount of | | | Acid Value: Carboxyl Groups/g | |
|---|---|---|---|---|---|
| No. | PEG 4000 | Jone's Reagent | $CrO_3$ in Jone's Reagent | Found | Theoretical |
| 1 | 4 g (0.002*M* hydroxyl group) | 0.85 mL | 0.001*M* | 0.22 | 0.49 |
| 2 | 4 g (0.002*M* hydroxyl group) | 1.7 mL | 0.002*M* | 0.51 | 0.49 |




**Scheme 1** Reaction scheme.

### Jone's Reagent as Oxidizing Agent

As compared to the aforementioned oxidizing agents, a mixture of $CrO_3$ and $H_2SO_4$ (Jone's reagent) is a stronger oxidizing agent that brings about oxidation of hydroxymethyl groups to carboxyl groups at room temperature.[27] Thus, Loeffler et al.[27] used Jone's reagent for oxidation of 1-acetamidomethyl-4-hydoxymethyl bicyclo [2.2.2] oct-2-ene to 4-acetamidomethylbicyclo [2.2.2] oct-2-ene-1-carboxylic acid. Despite the strong oxidizing power of Jone's reagent, its use in oxidation of PEGs has not yet been reported. In this study we used Jone's reagent for room temperature oxidation of PEGs of various mol wts (4000–100,000) to corresponding POE-dicarboxylic acids.

We first optimized the amount of Jone's reagent to be used for oxidations. It was found that to oxidize 1*M* of hydroxymethyl groups, Jone's reagent containing 1*M* of $CrO_3$ was required. Data listed in Table I show the effect of the amount of $CrO_3$ on the extent of oxidation. The data show that nearly stoichiometric amounts of PEG-hydoxyl groups and $CrO_3$ are required.

Thus, oxidation of PEG 4000, PEG 6000, Ome-PEG 5000, PEG 20,000, and PEG 100,000 was carried out at room temperature ($\sim$ 25°C) using Jone's reagent containing stoichiometric amounts of $CrO_3$ with respect to the hydroxyl groups. The reaction scheme is shown in Scheme 1. Acetone was used as a suitable solvent for the reactions because the chromium salts formed after oxidation precipitate out in acetone. The oxidation proceeded smoothly with the appearance of blue-green colored chromium salts that formed a fine suspension in the acetone solution. After overnight stirring, the reaction was quenched by adding isopropyl alcohol as a free radical scavenger.

### Removal of Chromium Salts from Reaction Mixture

It was observed that chromium salts were not easily separated from the reaction mixture by filtration. This was especially so for high mol wt POE-dicarboxylic acids. Under these conditions, the oxidation product is conventionally isolated by concentration of the reaction mixture and extraction of product in organic solvents.[27] Because products formed in our case are strongly polar POE-dicarboxylic acids of various mol wts, such extractions in organic solvents would be ineffi-

**Table II Acid Values and Percentage Yield Data for Various POE-Dicarboxylic Acids**

| No. | POE-Dicarboxylic Acid | Acid Value: mmol Carboxyl Groups/g | | Percentage Yield |
|---|---|---|---|---|
| | | Found | Theoretical | |
| 1 | POE 4000-dicarboxylic acid | 0.53 | 0.49 | 82 |
| 2 | Ome-POE 5000-monocarboxylic acid | 0.16 | 0.19 | 88 |
| 3 | POE 6000-dicarboxylic acid | 0.42 | 0.33 | 88 |
| 4 | POE 20,000-dicarboxylic acid | 0.24 | 0.1 | 61 |
| 5 | POE 100,000-dicarboxylic acid | 0.05 | 0.02 | 74 |

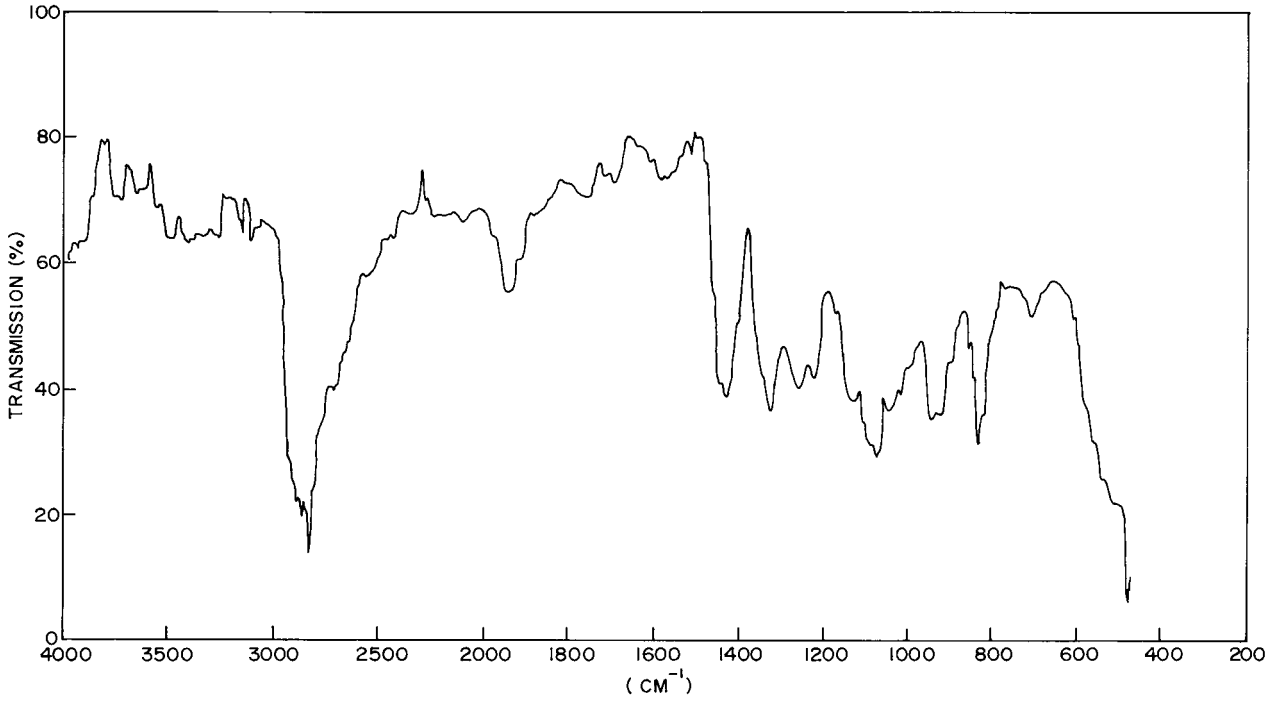



**Figure 1** FTIR spectrum of PEG 4000.

cient because of poor solubility characteristics. Also, our aim was to develop a method that will obviate a multistep isolation procedure. Therefore, we chose to remove chromium salts from reaction mixtures by adsorption of these salts on activated charcoal. Activated charcoal is routinely

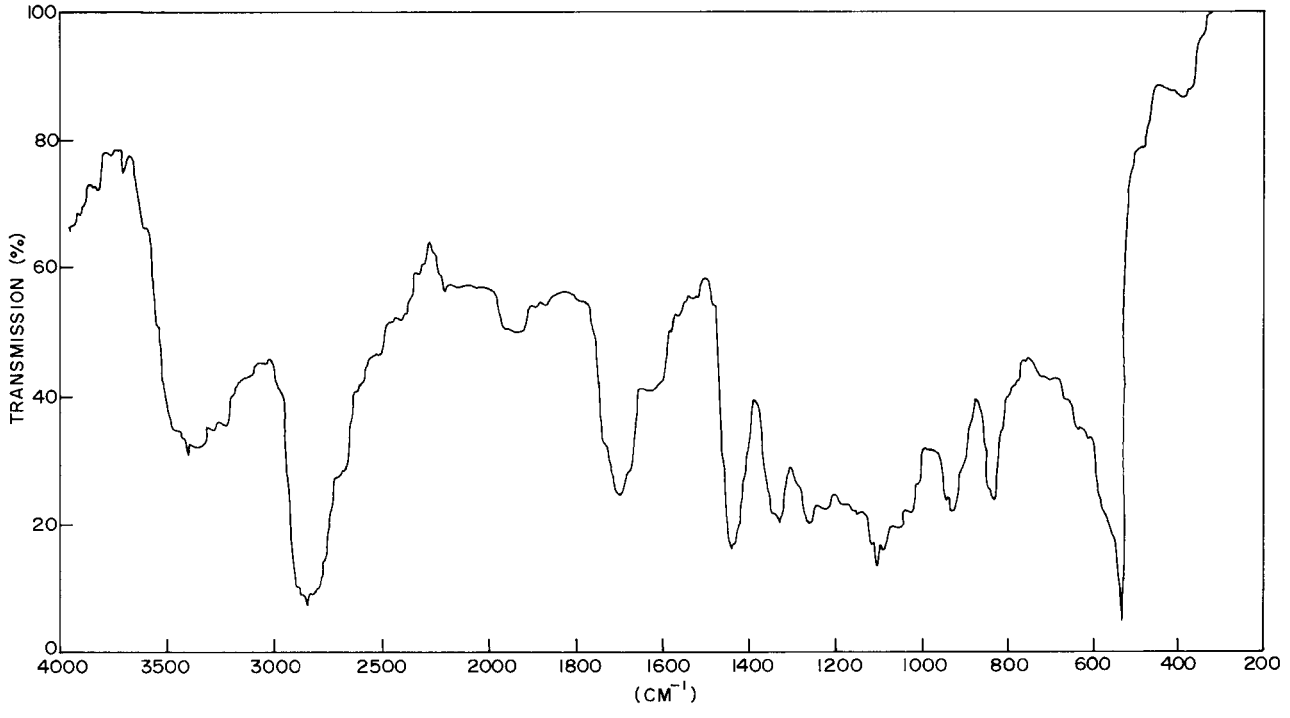



**Figure 2** FTIR spectrum of POE 4000-dicarboxylic acid.

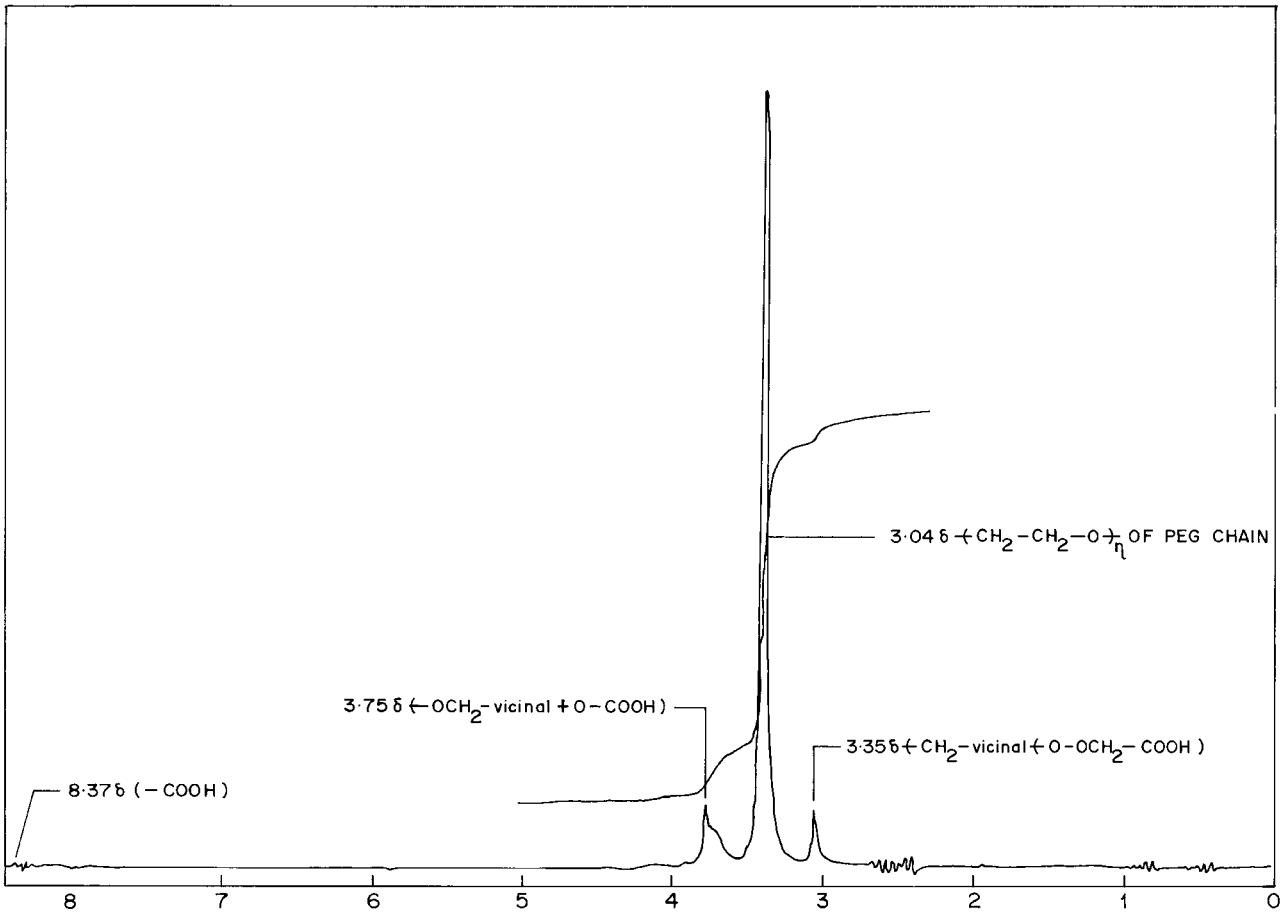



**Figure 3** $^1$H-NMR spectrum of POE 20,000-dicarboxylic acid.

used to adsorb colored impurities from various compounds in organic syntheses. Thus, charcoal treatment was given to all the reaction mixtures of POE-dicarboxylic acids according to the procedure described in the Experimental section. As expected, activated charcoal adsorbed all chromium salts from the reaction mixtures, affording clear, colorless acetone solutions upon filtration. Subsequently, acetone solutions were concentrated and products were isolated as disclosed earlier.

### Characterization of POE-Dicarboxylic or -Monocarboxylic Acids

Data listed in Table II show that this procedure produced all five products in high yields (60–88%). Table II also shows that for PEGs in the mol wt range of 4000–6000, the acid values of resulting POE-monocarboxylic or -dicarboxylic acids are in good agreement with the theoretical values calculated assuming oxidation of terminal hydroxyl groups. But for POE-dicarboxylic acids prepared from the oxidation of high mol wt PEGs (PEG 20,000, PEG 100,000), the acid values deviate significantly from theoretical values. This could be due to a wider mol wt distribution of the PEGs used and/or chain cleavage. This is being investigated further.

The POE-dicarboxylic acids synthesized in this study were characterized by IR and $^1$H-NMR spectroscopy. As an example, FTIR spectra of PEG 4000 and POE 4000-dicarboxylic acid are shown in Figures 1 and 2, respectively. It can be seen that the sharp peak at 1700 cm$^{-1}$ corresponding to the carbonyl frequency of —COOH groups is present in the IR spectrum of POE 4000-dicarboxylic acid, which is absent in the case of PEG 4000. Also, it was observed that $^1$H-NMR spectra of all compounds exhibited a peak for carboxyl protons (8–10 δ). As an example, the $^1$H-NMR spectrum of POE 20,000-dicarboxylic

acid is shown in Figure 3. It shows that well-resolved peaks that correspond to the methylene protons of the PEG chain, methylene protons vicinal to —O—$CH_2$—COOH group, and —$OCH_2$— protons vicinal to —COOH groups are present at 3.04, 3.35, and 3.75 δ, respectively. A small peak at 8.37 δ for the carboxyl proton is also seen in the spectrum.

It may be noted that during oxidation of Ome-PEG 5000, selective oxidation of hydroxymethyl groups and not methoxy groups took place, as indicated by the presence of a signal at 2.44 δ in the $^1$H-NMR spectrum for Ome-POE 5000-monocarboxylic acid. Also, due to oxidation of the terminal hydroxymethyl groups to carboxyl groups, downfield signals ranging from 2.8 to 6.0 δ, corresponding to —O—$CH_2$— protons vicinal to —COOH groups, are observed in all $^1$H-NMR spectra (see characterization data listed in the Experimental section). These characterization data indicate that oxidation of PEGs by Jone's reagent and adsorption of chromium salts on activated charcoal provides a simple and cleaner method for the synthesis of POE-dicarboxylic acids.

## CONCLUSION

Various POE-dicarboxylic acids ranging from low mol wt (4000) to very high mol wt (100,000) were synthesized by room temperature oxidation of PEGs using Jone's reagent. The process afforded nearly complete oxidation of the hydroxymethyl groups at a stoichiometric ratio of hydroxymethyl groups to $CrO_3$. For Ome-PEG 5000, selective oxidation of hydroxymethyl groups occurred. Multiple recovery procedures for product isolation were obviated by adsorbing oxidation by-products on activated charcoal. Thus, a simple one pot method for synthesis of POE-dicarboxylic acids was developed.

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