



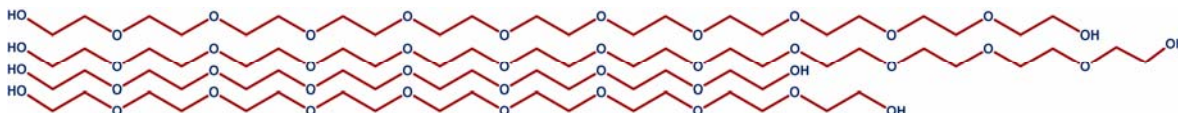
Oxidative Degradation of Polyethyleneglycol (PEG) studied by LC-IR

Summary

We subjected a sample of PEG 1000 (Polyethyleneglycol of average molecular weight 1000) to vigorous air oxidation, and then analyzed it by reverse-phase LC-IR to learn about the identity and distribution of the oxidation products within the bulk polymer. The bulk material showed very weak IR bands at 1720 and 1640 cm^{-1} which were absent from the original PEG 1000. On examination by LC-IR, we found two series of oxidative cleavage products, one series containing aldehyde functionality, and the other a series of carboxylic acid salts, which account for the extra IR bands. This information gives insight towards preservation strategies for extending the shelf life of formulations containing PEG.

Background

Polyethyleneglycol (PEG) is a water-soluble polymer with low toxicity, used in many consumer products such as toothpastes, laxatives, and cosmetics. Other commonly used names are Polyoxyethylene (POE), Polyethylene oxide (PEO), and the trade name Carbowax. It is a polyether terminated with hydroxyl groups, of formula and structure as follows:



PEG is used in medicinal formulations, and has even been attached to protein medications through its hydroxyl end groups, referred to as PEGylation of proteins, as a way to modify the biological uptake of the protein. In formulations, PEG is used to modify the absorption of ingested medications. In these applications, any degradation of the PEG can have an adverse effect on the shelf life or potency of the medication. This study was proposed to gain insight into the identity of oxidative degradation products, and to locate where, within the normal LC profile of the PEG, the degradation products fall.

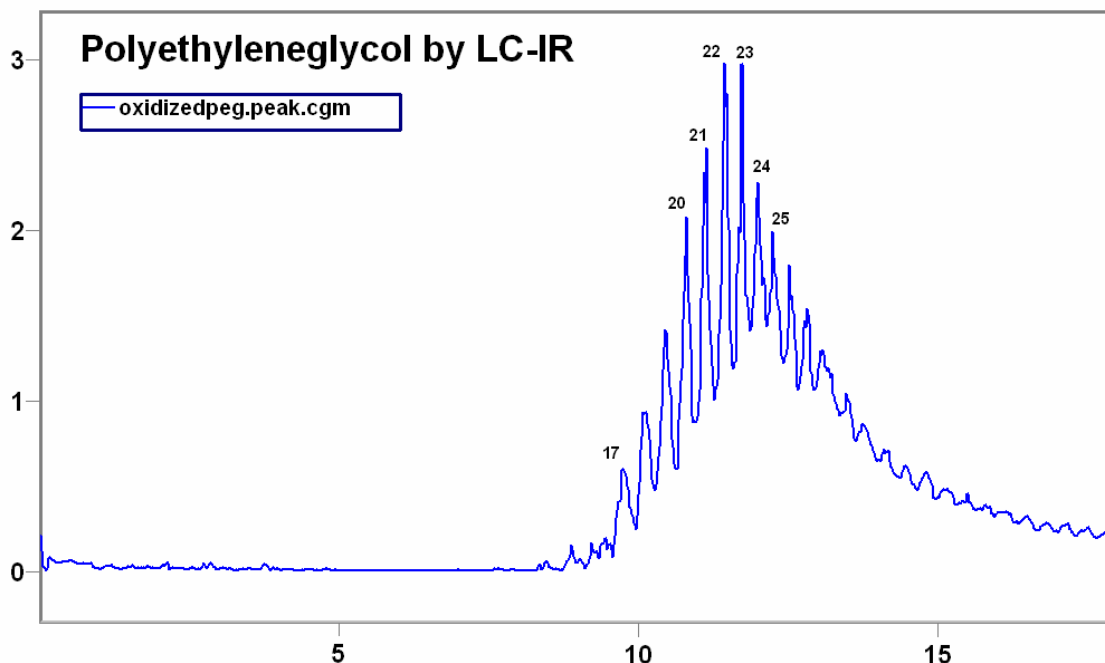


Experimental

Instrument: DiscovIR-LC
Sample: PEG air oxidized, 4.5 mg/mL in 15% acetonitrile / water
Column: Eclipse C-18, 4.6 x 50 mm
Flow: 1.0 mL/min
Program: Ramp from 10 to 90% Acetonitrile over 30 minutes.

Results and Discussion

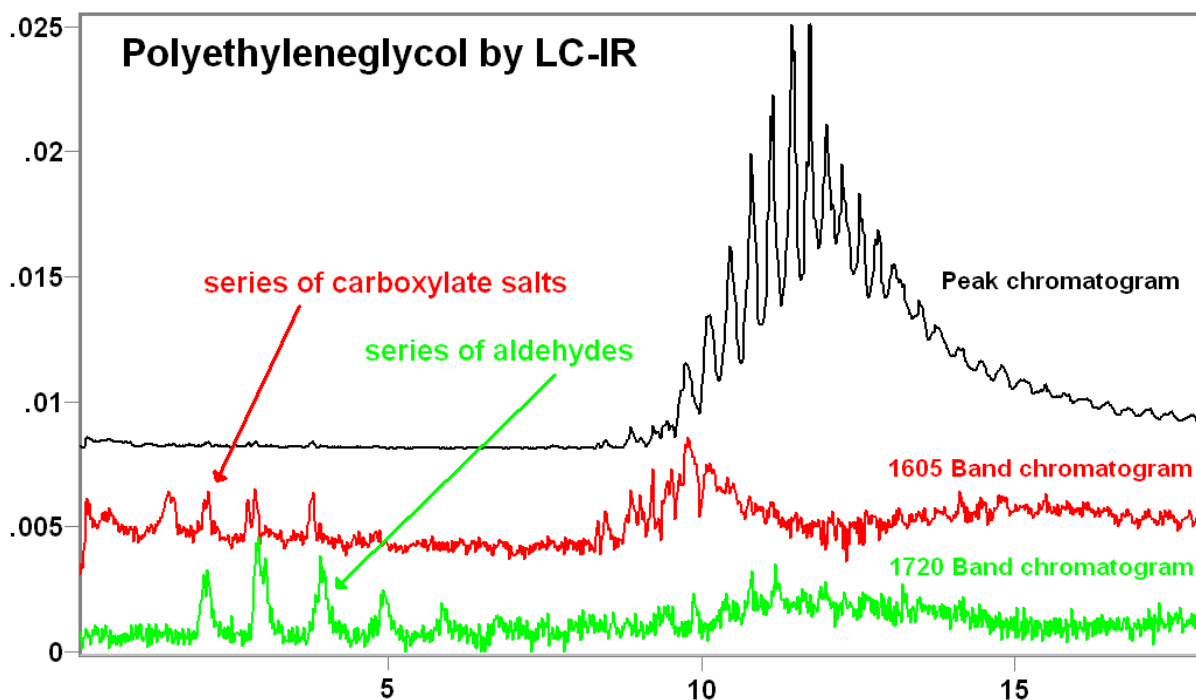
Under the reverse-phase conditions, the bulk of the PEG eluted in a series of peaks centered near 12 minutes. The individual oligomers were clearly separated. Although no molecular weight calibration was used, the PEG was known to have an average MW of 1000, which calculates to about 20 to 25 monomer units in the center of the peak. The approximate number of monomer units is shown on the chromatogram below.





Since we had particular interest in the oxidation products which expressed themselves in the bulk IR bands at 1720 and 1640, we focused on them using chromatograms based specifically on these bands. The 1720 band showed a distinct series of aldehydes, while the 1640 showed only noise. However, a series of chromatographic peaks appeared in the 1605 band chromatogram, which we attribute to carboxylate salts. We hypothesize that the shift from 1640 wavenumbers in the bulk material to 1605 in the separated peaks is due to exchange of the cation during the chromatography.

Note that oxidation products appear not only in the first five minutes of the chromatogram, but buried under the front edge of the main polymer elution around 10 minutes.



The two early series interfered with each other. However, they are clearly distinct, since the carboxylate series elutes earlier than the aldehydes, and has a slightly narrower spacing between oligomers. We were able to obtain clean spectra from the first and fourth carboxylate peaks having no aldehyde interference. However, all of the aldehydes showed carboxylate interference.



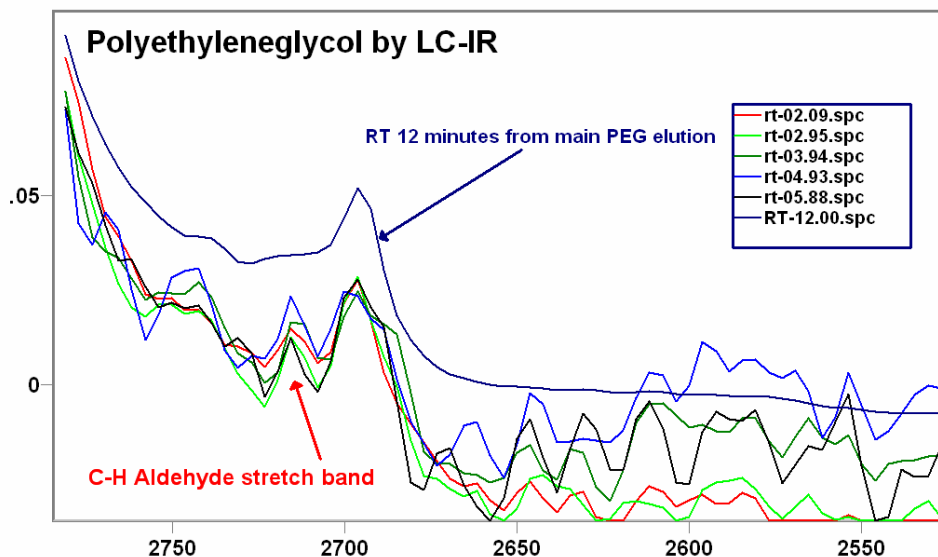
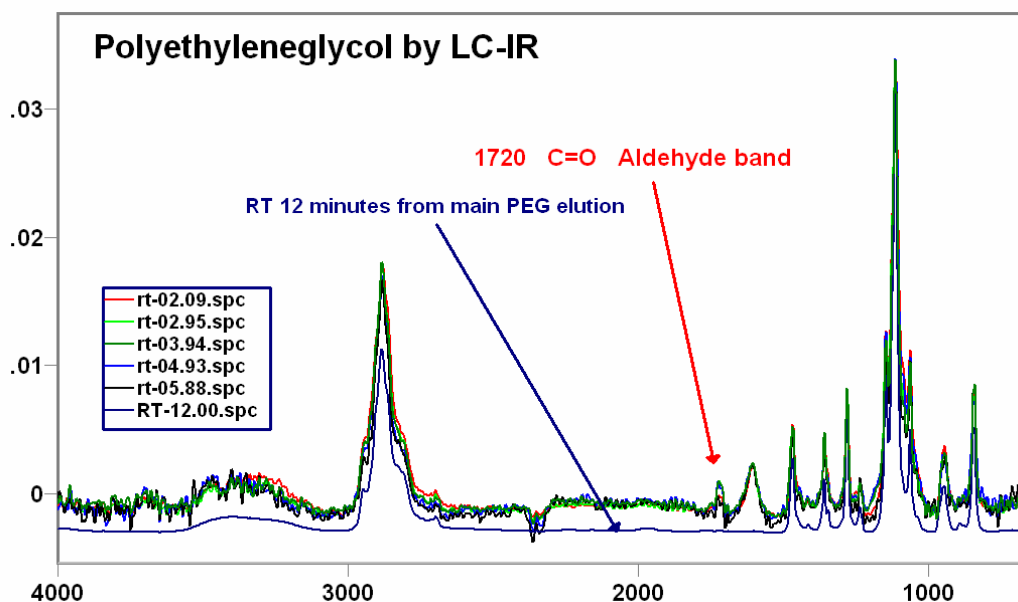
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The spectra below show the early series of aldehydes. Spectra from each of the five distinct LC peaks are overlaid, and compared to the spectrum of the main PEG at 12 minutes. The spectra are consistent with a PEG chain containing an aldehyde end group. Since these aldehydes elute very early, that indicates that they are more polar and more soluble in water than the bulk material, and thus are probably short chain length oligomers.

The spectra show the aldehyde carbonyl band at 1720, and also the confirming aldehyde C-H stretch band at 2715, as shown in the expanded spectra. This 2715 band is almost buried in the noise, but the fact that all five of the spectra show it, and it is absent from the main spectrum, gives us confidence that it is real.



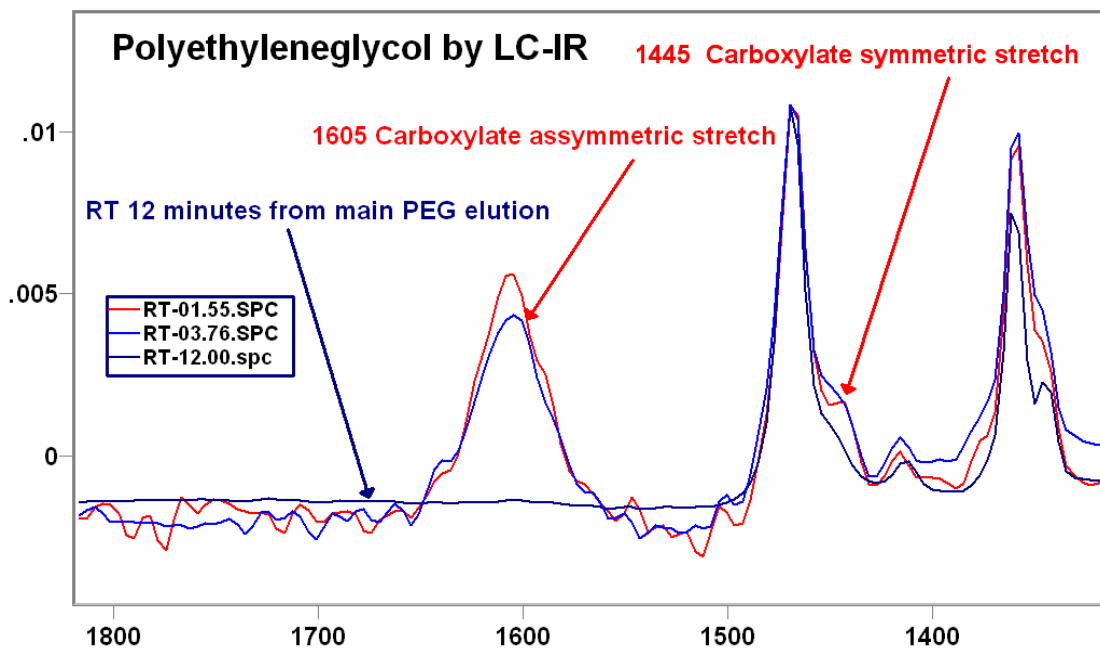
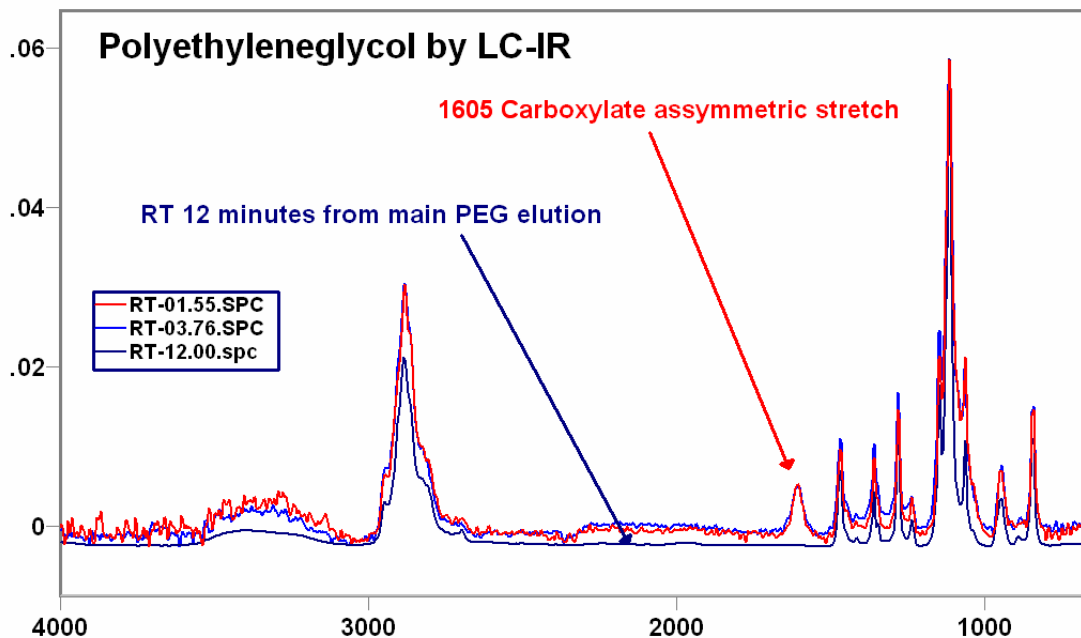


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Spectra from the two clean carboxylate peaks likewise tell a consistent story. Both the 1605 strong asymmetric stretch band, and the weaker 1445 symmetric stretch band are seen, above and beyond the backbone bands from the PEG polymer.





Conclusions

From these data, we can draw some tentative conclusions, and provide a tool for monitoring the quality of PEG batches.

1. Air oxidation of PEG generates unstable peroxides, typical of the autooxidation of ethers. The peroxides then react further, leading to cleavage of the PEG chain between oxygen and carbon atoms.
2. The resulting aldehydes and carboxylate salts that we see are PEG oligomers with oxidized end groups, as shown below.
3. Both series elute early in the reverse-phase chromatogram, and thus they would be cleavage products of the bulk PEG chains, of shorter length than the bulk.
4. Longer-chain cleavage products appear under the front edge of the main PEG mass.
5. The bulk material shows the carboxylate IR band at 1640, consistent with a tightly-bound cation such as a transition metal. This perhaps is residue from the catalyst used in the polymerization. The spectra from the chromatographic analysis are more typical of sodium or potassium salts. Cation exchange might have occurred during the chromatography, from residues in the solvents and column.
6. Most of the oxidized degradation products are more polar than the bulk PEG. This property provides a handle for cleanup or preservation of the bulk material to improve the shelf life of products containing PEG.

