NMR Oligomer Resolution by Intramolecular Complexation in a Poly(ethylene glycol) with an Electron-Acceptor End Group

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Poly(ethylene glycol) (PEG) has many interesting and useful properties, which make it attractive for multicomponent structures, especially for solvent-selective combination, due to its water solubility.[1] In the process of investigating an end-capped PEG sample, we have noticed novel intramolecular charge transfer (CT) interactions. We report here one very unusual consequence of such interactions: the possibility to separately identify the oligomers in concentrated aqueous solution NMR spectra. Thus, the CT complex behaves like a chemical shift reagent[2] for PEG of different molecular weights. To our knowledge, this is the first report of a molecular weight distribution curve obtained from a simple NMR spectrum.

The sample analyzed was of an oligo(ethylene glycol) (PEG) capped with a methyl ether at one end and 3,5-dinitrobenzoate (DNB) ester at the other (PEG−DNB). The ^{1}H NMR spectra of the chloroform solutions (Figure 1a) showed the expected signals for the molecular structure, similar to those in dilute aqueous solutions (Figure 1b,c). A different behavior is noticed in more concentrated aqueous solutions. At concentrations higher than about 4 wt %, some of the peaks show uncommon patterns (Figure 1d−g). For example, the methyl signal, which is expected to be a singlet, consists of 12 distinct peaks. A similar multiplicity can be observed for the aromatic protons, but there coupling complicates the picture. This splitting is less obvious for the rest of the signals (not shown) due to substantial overlapping.

PEG−DNB forms an intramolecular CT complex in water solutions. The ether oxygen atoms can act as good p-electron donors, while the DNB groups are π-electron acceptors.[3] The existence of the n−π CT complexes in concentrated solutions is confirmed by the red color and by an UV absorbance tail between 400 and 500 nm (Figure 2a−e). Furthermore, there is a significant upfield shift of the aromatic protons with increasing concentration (see Figure 1), suggesting an increase of the electron density at this acceptor site as a consequence of CT interactions. The DNB group is hydrophobic, while the PEG chain is hydrophilic; consequently, the PEG chain will tend to coil around the DNB group to diminish its contact with water, providing conformations that are favorable to CT interactions. The presence of a coil conformation of the PEG chain around DNB is supported by the 2D nuclear Overhauser effect spectroscopy (NOESY) spectra in D_2O, which showed cross-peaks between the H_m peaks (at about 3.7 ppm) and the aromatic multiplet.[4] These cross-peaks were not present in the NOESY spectra run in chloroform or at low concentrations in D_2O. The absence of the multiplet pattern in dilute aqueous solutions can be explained by the prevalence of hydrogen bonding, which may now overcome both the hydrophobic effect and the CT

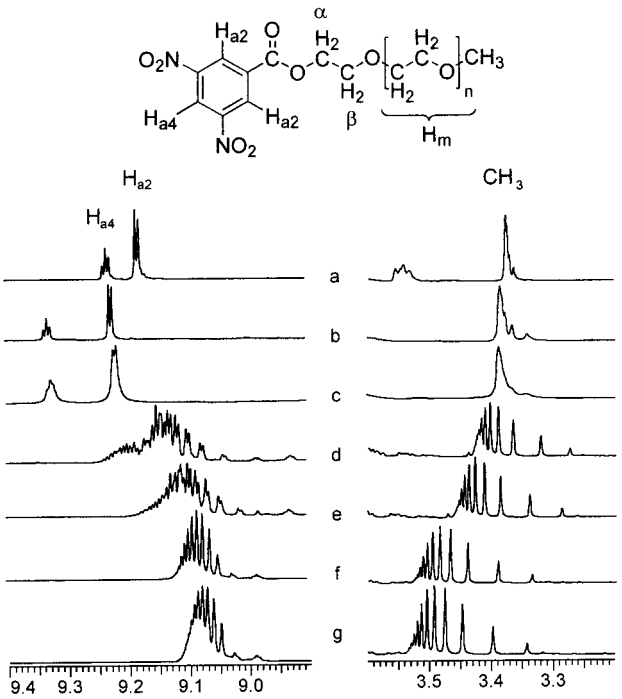

Figure 1. ^{1}H NMR of PEG−DNB solutions: (a) 15.0 wt % in $CDCl_3$, (b) 0.3, (c) 2.2, (d) 4.3, (e) 6.4, (f) 15.0, and (g) 17.6 wt % in D_2O.

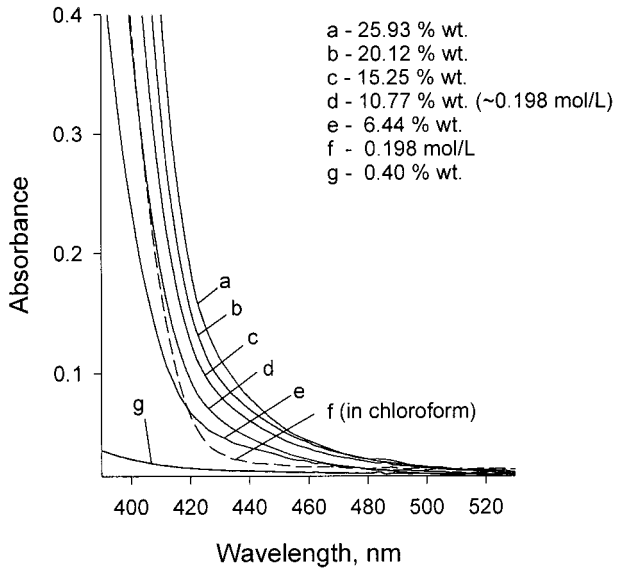

Figure 2. Electronic spectra of PEG−DNB in water (a−e, g) and chloroform solutions (f).

interactions. In fact, at concentrations between 0.5 and 4.0 wt % phase separation is observed, probably as a consequence of the complex being stretched by hydration and leaving the hydrophobic DNB exposed to water. Both PEG and DNB are soluble in chloroform; therefore, there is less driving force for CT interactions, as confirmed by the lower absorbance in chloroform solution (Figure 2f).

The first tentative interpretation of this multiplet pattern was to assign it to the possibility of multiple conformations of the intramolecular CT complex. It is also known that polyoxygenated ethers can contribute

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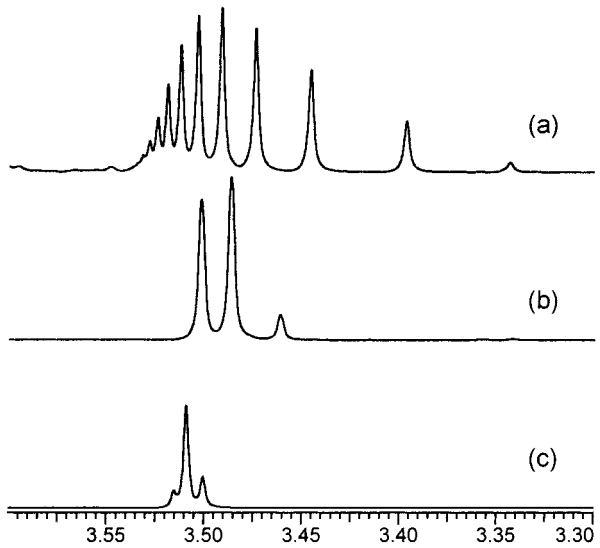

Figure 3. Methyl region of the ^{1}H NMR spectra of 15 wt % D2O solution: (a) PEG−DNB polydisperse sample, (b) fractions 4th to 6th, and (c) 6th to 8th from silica gel column fractionation.

with more than one oxygen atom in n−π complexes.[5] To test this assignment, 2D exchange spectroscopy (EXSY) experiments with varying mixing times (t_m = 0.1−2.5 s) were performed. Cross-peaks in these experiments would indicate conformational exchange; since these were absent, the unusual multiplet is not a consequence of conformational polydispersity. Furthermore, the chemical shift difference between the multiplet signals did not show any dependence on either temperature (5−40 °C) or magnetic field (4.7, 7.1, 9.4, and 11.7 T), again proof that the multiplet cannot be assigned to various exchanging conformations.

The multiplet pattern should then be assigned to different molecular structures that do not "communicate" with each other. In the PEG−DNB sample the polydispersity index is about 1.1 with molecular weights varying between 300 and 800 g/mol, as determined by GPC. This means that there should be about 12 detectable fractions with 2−13 ethylene oxide (EO) repeating units. The number of fractions is pretty much identical with the number of peaks seen in the methyl multiplet. The chemical shift should change more when an EO unit is added to a shorter chain. One can assign the peak at 3.34 ppm in Figure 1f to the methyl protons in a PEG oligomer with only two EO units and the subsequent downfield peaks to the methyl protons in PEGs with increasing degrees of polymerization by one.

To confirm this assignment, the PEG sample was fractionated on a silica gel column, and the ^{1}H NMR of some groups of fractions was run. The methyl spectra (Figure 3) clearly show that the peaks belong to various fractions of different molecular weight. Now, if we plot on the same graph (Figure 4) the molecular weight distribution obtained from GPC and from the methyl NMR signal, the two curves are very similar. It is reasonable to assume that the precision of molecular weight determination for the lower molecular weight side of the curve is better when using NMR than when using the refractive index detector of the GPC. Given the assignment above, we can even calculate molecular weight averages and compare them with those obtained from GPC. M_w from NMR and GPC are 563 and 542 g/mol, respectively.

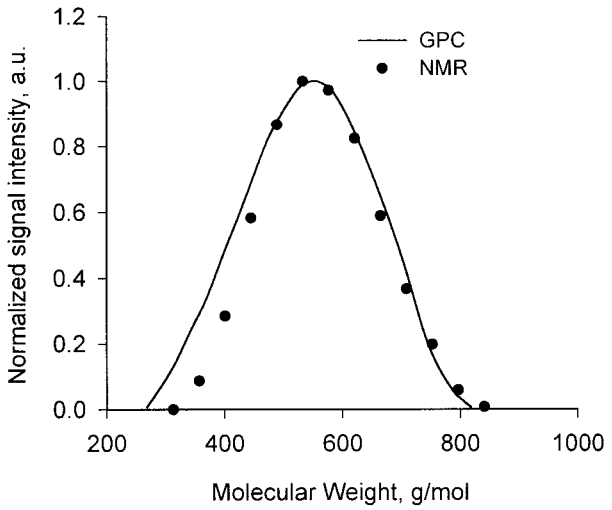

Figure 4. Comparison of MWD data obtained by NMR and GPC.

The NMR results presented here are definitely related to the dependence of the PEG−DNB conformation on the length of the PEG chain, the nature of the solvent, and the concentration in aqueous solutions. A detailed investigation of these factors will be presented elsewhere.[4]

In conclusion, in this specific instance, CT complexation allows the NMR resolution of the molecular weight distribution in aqueous solutions at high concentrations. The resolution and the correlation of the number of peaks with the number of fractions confirm the dominant intramolecular character of the CT complexes. From the peak integrals, a very precise calculation of the distribution and polydispersity index is possible. The resolution appears to increase with the solution concentration, the best separation being seen at about 15 wt %. The lower limit for the concentration range is imposed by phase separation, while the upper limit is based on the increased viscosity of the solution.

Experimental Section. a. Materials. Poly(ethylene glycol) monomethyl ether, PEG350 (M_n = 350 g/mol, Aldrich), was dried in a vacuum at 40 °C overnight. 3,5-Dinitrobenzoyl chloride (Aldrich) was recrystallized from petroleum ether (30−60 °C). THF and triethylamine (TEA) were dried over sodium/benzophenone and CaH_2, respectively.

b. Synthesis of PEG−DNB. PEG350 (7.15 mL, 0.022 mol) was dissolved together with TEA (6.26 mL, 0.045 mol) in THF (70 mL). A solution of 3,5-dinitrobenzoyl chloride (10.380 g, 0.045 mol) in 40 mL of THF was added dropwise under stirring, while the flask was kept in an ice bath. The solution was allowed to stir for about 20 h, under argon atmosphere, at room temperature. The reaction mixture was then filtered to remove the triethylamine chlorohydrate. The brown viscous liquid obtained after rota-evaporation was purified by flash chromatography on silica gel (chloroform/methanol 7/1 by volume) to afford pure PEG−DNB (8.9 g, 74% yield). ^{1}H NMR ($CDCl_3$, ppm): δ 3.37 (s, CH_3), 3.51−3.75 (b, $-(CH_2-CH_2-O)_n-$, 29 protons), 3.89 and 4.61 (m, $-CH_2-CH_2-O-$ next to DNB), 9.18 (d, 2 aromatic protons), and 9.23 (t, 1 aromatic proton). IR (KBr, cm^{-1}): 1731 ($\nu_{C=O}$, aromatic ester).

c. Techniques. ^{1}H NMR was recorded at 298.0 ± 0.1 K on a Bruker AVANCE-400 spectrometer using D_2O or $CDCl_3$ as solvents. 2,2,3,3-d(4)-3-(Trimethylsilyl)-

propionic acid sodium salt (concentration of about 50 ppm) was used as internal reference in aqueous solutions. 2D NOESY and EXSY experiments[6,7] were performed in the phase-sensitive mode (TPPI).[8] Electronic spectra were recorded on a Hewlett-Packard 8452A diode array ultraviolet−visible spectrophotometer, at room temperature, using the same deuterated solvents as for the NMR. GPC data were obtained using a Waters 2690 separations module equipped with a Waters 410 differential refractometer and Waters styragel columns. THF was used as solvent and narrow molecular weight poly(styrene) fractions were used as standards. The fractionation of the PEG−DNB was done on a silica gel column at atmospheric pressure using a mixture of acetonitrile/chloroform 7:1 (v:v).

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