CHAPTER III

CONTROLLED MOLECULAR ALIGNMENT VIA MOLECULAR DESIGN ON AZA-METHYLENE PHENOL (2): POLYETHYLENE GLYCOL METHYL ETHER BASED AZA-METHYLENE PHENOL COMPOUNDS

Abstract

A series of aza methylene phenol compounds enhanced with hydrophilic group by conjugating polyethylene glycol chain is proposed. The structural characterization by FTIR, ^{1}H NMR clarifies the successful preparation. The molecular alignment observed by optical microscope exhibits the spherulite crystal similar to that of polyethylene glycol. The studies on the effect of temperature using DSC and WAXD clarify that the alignment of the aza-methylene phenol compounds is mainly controlled by polyethylene glycol chain.

Keywords: Molecular assembly, Aza-methylene phenol compounds, Molecular alignment, Wide-angle X-ray diffractometer, Differential scanning calorimeter, Optical microscope, Polyethylene glycol methyl ether

Introduction

Recently, nanomaterials[1] have received much attention in order to achieve the specific properties of the materials from molecular level. One of the guidelines for nanomaterials is to architect the molecule with an understanding of the molecular interactions. Supramolecules[2] is an asset of molecules where molecular interactions are generated under the molecular assembly[3]. For the past few years, with a progress in instrumentation technologies, many supramolecular structured compounds have been developed with information in nano-scale be nanomaterials. It is important to consider. For example, liquid crystal thermotropic materials[4] can be designed in nano-scale by having a rigid molecule of biphenyl, azobenzene, pyridine, cyanobenzene, etc., with a flexible chain of alkane, alkoxy, ether, etc. Chemomechanical materials[5] such as artificial muscle can be possible when the nano level allows the charges movement as seen in the case of polyacrylic acid (PAA), and polyvinyl alcohol (PVA).

For the past few years, our group has clarified the unique stability and specific properties of aza-methylene phenol compounds obtained from dimerization of benzoxazines. The structural characterization by single crystal[6] and solid state NMR[7] insists that the stability of the compounds arises from the intra- and intermolecular hydrogen bonding. As a result, the compounds perform the asymmetric reaction to give mono-oxazine compounds[8] as well as the termination at dimer level[9]. In another point of view, aza-methylene compounds and the derivatives exhibit the inclusion phenomena by entrapping metal ions as guest molecules via their assembly structure[9]. The functionalization of the molecules by cyclization was achieved by simple reaction. The compounds obtained give the metal entrapment[9] under the ratio of 1:1 or 2:1 depending on the type of the metals and the size of the ring.

The present work is, thus, aimed on the molecular design and synthesis of aza-methylene phenol with controlled hydrophobic and hydrophilic chains on the structure to challenge the controlled molecular assembly. It is expected that the hydrophilic or hydrophobic chain will play an important role to induce the molecular alignment, which is never achieved from the individual molecule of aza-methylene phenol.

Experimental

Materials. Paraformaldehyde was purchased from Sigma (U.S.A.). 4-Ethylphenol, potassium t-butoxide, and *p*-toluenesulfonyl chloride were obtained from Fluka Chemicals (Buchs, Switzerland). 1,4-Dioxane and sodium sulfate anhydrous were purchased from Ajax Chemicals (Australia). Cyclohexylamine was from Merck KgaA (Germany). Chloroform, ethanol, isopropanol, sodium hydroxide, and toluene were from Lab-Scan Ltd. (Ireland). n-Hexane was from J.T. Baker (USA). Polyethylene glycol methyl ether M_w 2,000 and 550 were purchased from Aldrich Chemical Company, Inc. (USA). All chemicals were AR grade and used without further purification.

Measurements. Fourier transform infrared (FTIR) spectra were taken at a resolution 4 cm^{-1} by using a Bruker Equinox55/S spectrophotometer equipped with deuterated triglycine (DTGS) detector. Proton nuclear magnetic resonance (^1H NMR) spectra were obtained from a 400 MHz JEOL GSX-400 spectrometer. Samples were dissolved in deuterated chloroform using 1% TMS as an internal standard. Thermogravimetric analyses were done by a Dupont TGA 2950 analyzer. Samples were heated to 600°C with a heating rate of 10°C under nitrogen flow rate of 20 ml min^{-1}. Thermal transitions were determined by using a Perkin-Elmer DSC 7 differential scanning calorimeter with a heating and cooling rate at 5°C min^{-1}. X-ray diffraction patterns were obtained from a RIGAKU RINT 2000 using CuK_α (λ = 0.145 nm) as an X-ray source and operating at 40 kV, 30 mA with Ni filter for 2θ of 5°-90°.

Synthesis of N,N'-bis(2-hydroxyl-5-ethyl)cyclohexylamine 1. Compound 1 was prepared from the reaction of 3-cyclohexyl-3,4-dihydro-6-ethyl-2H-1,3-benzoxazine (0.49 g, 2.00 mmol) and ethyl phenol (0.27 g, 2.20 mmol) as reported previously[9].

Synthesis of tosylated polyethylene glycol methyl ether M_{w550}, 2, and tosylated polyethylene glycol methyl ether M_{w2000}, 3. Polyethylene glycol

methyl ether M_w 550 ($mPEG_{550}$) (1.65 g, 3.00 mmol) and the solution of KOH (0.17 g, 3.00 mmol) in isopropanol were mixed in 50 ml of 1,4-dioxane. The mixture was added dropwisely to the solution of *p*-toluenesulfonyl chloride (0.60 g, 3.16 mmol) in dioxane (30 ml). After the addition was completed, the mixture was refluxed for 6 h, and cooled to room temperature. The solvent was evaporated to obtain the yellowish fluid. The product was further purified by vacuum distillation to obtain **2**. $mPEG_{2000}$ was used for preparing **3** with the same procedures.

Compound **2**: 75% yield; R_f = 0.09 (5% MeOH in $CHCl_3$); FTIR (ZnSe, cm^{-1}): 1351 (w, asym O=S=O), 1174 (s, sym O=S=O), 1104 (br s, C-O-C); ^1H NMR (400 MHz, $CDCl_3$, ppm): 2.33 (s, 3H, Ar-CH_3), 3.26 (s, 3H, O-CH_3), 3.47 (m, 44H, O-$(CH_2)_{11}$-O), 4.03 (t, 2H, SO_3-CH_2-CH_2), 5.20 (t, 2H, SO_3-CH_2-CH_2), 7.22 (d, 2H, Ar-*H*), 7.67 (d, 2H, Ar-*H*).

Compound **3**: 69% yield; R_f = 0.07 (5% MeOH in $CHCl_3$); FTIR (KBr, cm^{-1}): 1177 (m, sym O=S=O), 1114 (br s, C-O-C); ^1H NMR (400 MHz, $CDCl_3$, ppm): 2.42 (s, 3H, Ar-CH_3), 3.35 (s, 3H, O-CH_3), 3.61 (m, 176H, O-$(CH_2)_{44}$-O), 4.12 (t, 2H, SO_3-CH_2-CH_2), 5.20 (SO_3-CH_2-CH_2), 7.24 (d, 2H, Ar-*H*), 7.75 (d, 2H, Ar-*H*).

Synthesis of $mPEG_{550}$-N,N'-bis(2-hydroxyl-5-ethyl)cyclohexylamine, 4, and $mPEG_{2000}$-N,N'-bis(2-hydroxyl-5-ethyl)cyclohexylamine, 5. Compound **1** (1.00 mmol) and potassium t-butoxide (2.10 mmol) were refluxed in toluene (30 ml). Compound **2** or **3** (2.00 mmol) in 50 ml of toluene was then added dropwisely. After the addition was completed, the mixture was further refluxed for 12 h. The solvent was removed and dichloromethane (50ml) was added and extracted with water. The organic phase was collected and concentrated to obtain the yellowish fluid of compound **4** or yellowish flake of **5**. The product was dried at 30°C under vacuum for over night.

Compound **4**: 79% yield; R_f = 0.07 (5% MeOH in $CHCl_3$); FTIR (ZnSe, cm^{-1}): 1500 (w, C-N), 1103 (br s, C-O-C); ^1H NMR (400 MHz, $CDCl_3$, ppm): 1.10 (t, 6H, Ar-CH_2-CH_3), 1.54 (m, 6H, CH_2), 1.89 (q, 4H, Ar-CH_2-CH_3), 2.46 (m, 4H, CH_2), 2.75 (m, 1H, N-*CH*), 3.31 (s, 3H, O-CH_3), 3.57 (m, 44H, O-$(CH_2)_{11}$-O), 3.75 (s, 4H, CH_2-N-CH_2), 4.01 (t, 4H, Ar-O-CH_2-CH_2), 4.64 (t, 4H, Ar-O-CH_2-CH_2), 6.74 (d, 2H, Ar-*H*), 7.24 (s, 2H, Ar-*H*), 7.28 (d, 2H, Ar-*H*).

Compound **5**: 75% yield; R_f = 0.04 (5% MeOH in $CHCl_3$); FTIR (KBr, cm^{-1}): 1500 (w, C-N), 1114 (br s, C-O-C); ^1H NMR (400 MHz, $CDCl_3$, ppm): 1.17 (t, 6H, Ar-CH_2-*CH_3*), 1.52 (q, 4H, Ar-*CH_2*-CH_3), 1.56 (m, 6H, *CH_2*), 2.49 (m, 4H, *CH_2*), 2.81 (m, 1H, N-*CH*), 3.35 (s, 3H, O-*CH_3*), 3.61 (m, 44H, O-*$(CH_2)_{44}$*-O), 3.80 (s, 4H, *CH_2*-N-*CH_2*), 4.09 (t, 4H, Ar-O-CH_2-*CH_2*), 4.69 (t, 4H, Ar-O-*CH_2*-CH_2), 7.23 (d, 2H, Ar-*H*), 7.27 (s, 2H, Ar-*H*), 7.36 (d, 2H, Ar-*H*).

Results and Discussion

Synthesis of Compound 1. The preparation and characterization in details of N,N'-bis(2-hydroxyl-5-ethyl)cyclohexylamine, **1**, was reported elsewhere[9]. Figure 1 confirms the hydroxyl band at 3200-2800 cm^{-1} and C-N stretching of aza-methylene linkage at 1500 cm^{-1}. This implied the open ring structure of benzoxazine. The protons on the aza-methylene linkage exhibit at 4.19 ppm (Figure 2) supports the successful preparation.

Synthesis of Compound 2-3. In order to achieve a reaction as designed, an encapsulated polyethylene glycol methyl ether (mPEG) was applied (Scheme I). Here, tosylation of mPEG was used to prepare a reactive *p*-toluenesulfonate ester, FTIR spectra of 2-3 (Figure 3) show asymmetric and symmetric stretching of sulfonyl groups at 1353 and 1177 cm^{-1}, respectively and C-O-C stretching of ether linkage in mPEG chain. The completion of the reaction was confirmed from the elimination of hydroxyl groups belonging to mPEG. Figure 4 clarifies the methylene protons at 3.00-3.50 ppm referring to the ethylene glycol unit. The tosyl group is observed at 6.50-7.50 ppm for proton in benzene ring. The results implied that tosylated mPEG was accomplished.

Synthesis of Compound 4-5. It can be expected that the coupling reaction of aza-methylene phenol and *p*-toluenesulfonate ester of mPEG be proceeded via nucleophilic substitution. Thus, dilute potassium t-butoxide was added to enhance the nucleophilicity of phenoxide salt. The coupling reactions of **1** and **2** or **3** were confirmed from C-N stretching of aza-methylene linkage at 1500 cm^{-1}, C-O-C stretching of ether in mPEG chain at 1110 cm^{-1} and the absence of hydroxyl peak

around 3200-2800 cm^{-1} (Figure 5). ^1H NMR gives the multiple and singlet peaks around 3.00-3.50 ppm referring to protons on mPEG chain. The peaks of protons along with the benzene ring of aza-methylene phenol appear between 6.50-7.50 ppm. (Figure 6). The results insisted the structure of 4 obtained from the reaction.

Thermal Stability of 4 and 5. In order to study the self-assembly phenomenon responsive to thermal condition, the thermal stability of each compound was studied. Hemvichian et al. reported the thermal degradation of a series of aza-methylene phenol compounds to find two steps of degradation temperature (T_d) at around 200 and 370 °C referring to the cleavage at methylene linkage and destruction of the phenol ring[10], respectively. As shown in Table 1, the T_d of **1** is at 187 and 362°C while the melting temperature (T_m) is at 178 °C. By conjugating with mPEG of M_w 550, the T_d is increased for 30°C and becomes close to that of mPEG (350°C). In the case of **5** and mPEG, similar results were observed. This suggests that ethylene glycol chain stabilized the aza-methylene phenol compounds as a result of hydrophilicity.

Table 1 also indicates that by conjugating the mPEG, the melting temperature of **5** is drastically decreased for more than 120°C and becomes close to that of mPEG. In other words, the performance of aza-methylene phenol responded to the heat was changed significantly to give the phase transition of solid to molten stage at relatively low temperature (at only 46°C for **5**), when the ethylene glycol chain was introduced. It should be noted that since **4** was a viscous solution, the studies on crystallization using DSC have to be done in low temperature system. Thus, the present study is mainly focused on **5**.

Figure 7 shows the T_m as well as crystallization temperature (T_c) of **5**, which are found to be close to that of $mPEG_{2000}$. The T_c of **5** implies that the hydrophilicity of polyethylene glycol chain might induce the chain alignment to aza-methylene phenol. The T_c of **5** at 23 °C also indicates that there be some packing structure different from the pure $mPEG_{2000}$.

Packing Structure of 5. In order to clarify the packing structure responded to the heat, the wide angle X-ray diffraction (WAXD) patterns were observed. Since the T_m of **1** is close to that of T_d, the degradation of **1** soon after melting cannot be avoided. Thus, the comparative studies were done for the cases shown in Figure 9. XRD pattern of **5** shows the shoulder peak at 16°2θ, major peaks at 19°, 23°2θ, and a significant peak at 32.6°2θ. Comparing the result to that of mPEG, it can be concluded that the chain alignment at room temperature is mainly controlled by mPEG. However, when the samples (**5** and $mPEG_{2000}$) were recrystallized at 50 °C, the minor peaks of **5** are disappeared and changed to the pattern similar to that of mPEG. This also supports our expectation that the hydrophilic chain control the packing structure of aza-methylene phenol compounds.

Optical Microscope Observation. The optical microscope observation is another information to conclude the effect of polyethylene glycol on the chain packing. When **1** is heated and cooled down, the crystallization was not observed (Figure 10 (a)-(b)). However, **5** and mPEG show the recrystallization as a complete spherulite structure (Figure 10 (c)-(f)) after heating and cooling, which suggests that mPEG mainly induces the alignment of **5**.

Conclusions

The present work demonstrated the molecular design and syntheses of aza-methylene phenol compounds with a long hydrophilic chain of polyethylene glycol. The key of success in conjugating polyethylene glycol onto OH group of aza-methylene phenol was the use of methyl ether encapped polyethylene glycol compound. The thermal stability (degradation and melting temperatures) of the compounds obtained were changed drastically and become close to those of polyethylene glycol. WAXD and optical microscope clarified that the molecular alignment was mainly controlled by polyethylene glycol to be spherulite structure at the temperature below 40 °C.

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Figure Captions

Figure 1. FTIR spectrum of **1.**

Figure 2. ^{1}H NMR spectrum of **1.**

Figure 3. FTIR spectra of: (a) $mPEG_{550}$, (b) *p*-toluenesulfonyl chloride, and (c) **2.**

Figure 4. ^{1}H NMR spectrum of **2.**

Figure 5. FTIR spectra of: (a) **1**, (b) **2**, and (c) **3.**

Figure 6. ^{1}H NMR spectrum of **4.**

Figure 7. DSC thermograms of: (a) $mPEG_{2000}$, (b) **1**, and (c) **5**.

Figure 8. XRD patterns of: (a) **1** at 30°C, (b) **5** at 30°C, (c) **5** at 30°C after melt, (d) $mPEG_{2000}$ at 30°C **5**, and (e) $mPEG_{2000}$ at 30°C after melt.

Figure 9. Optical micrographs of: (a) **1** at 30°C, (b) **1** at 30°C after melt, (c) **5** at 30°C, (d) **5** at 30°C after melt, (e) $mPEG_{2000}$ at 30°C, and (f) $mPEG_{2000}$ at 30°C after melt.

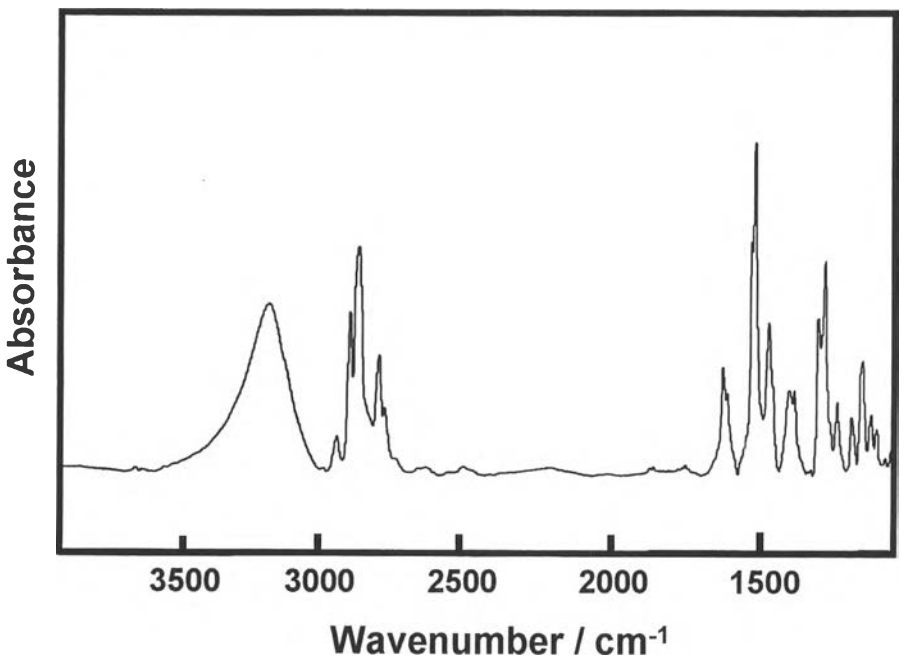
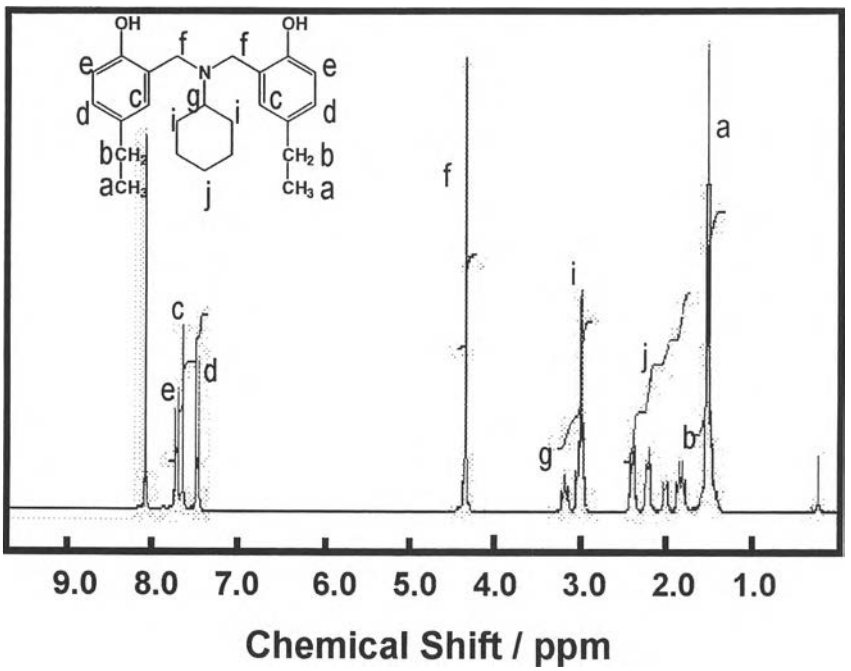


Figure 1. (Chanchai et al.)



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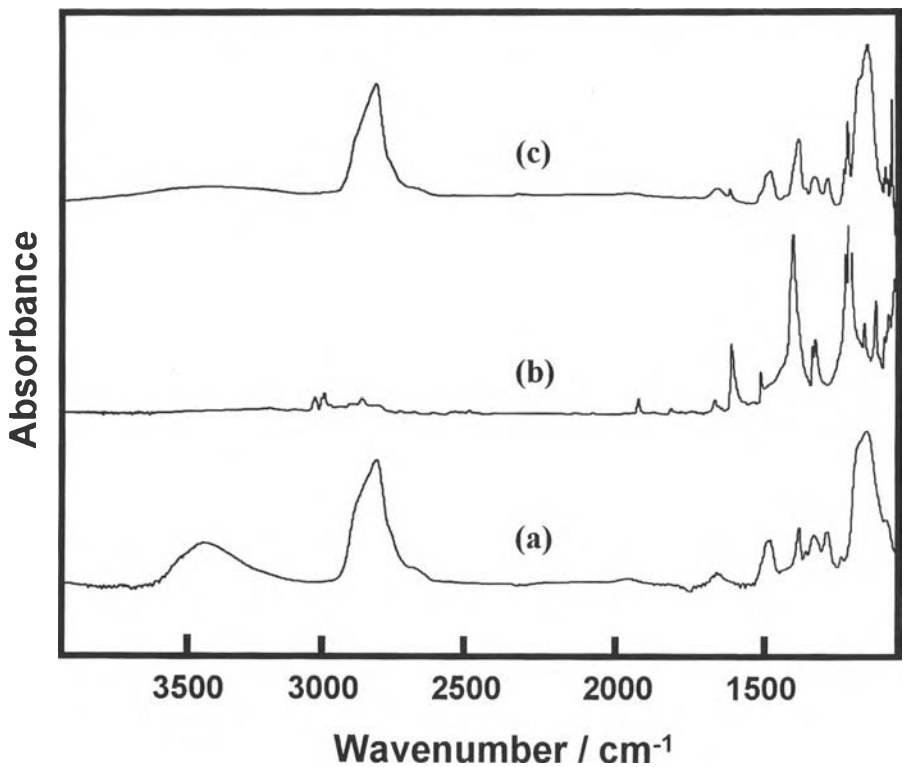

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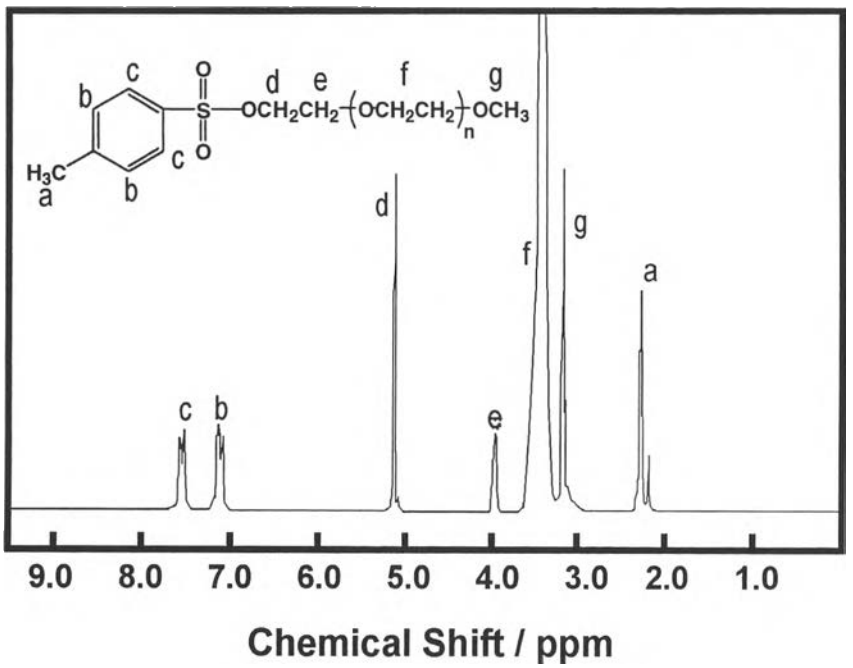

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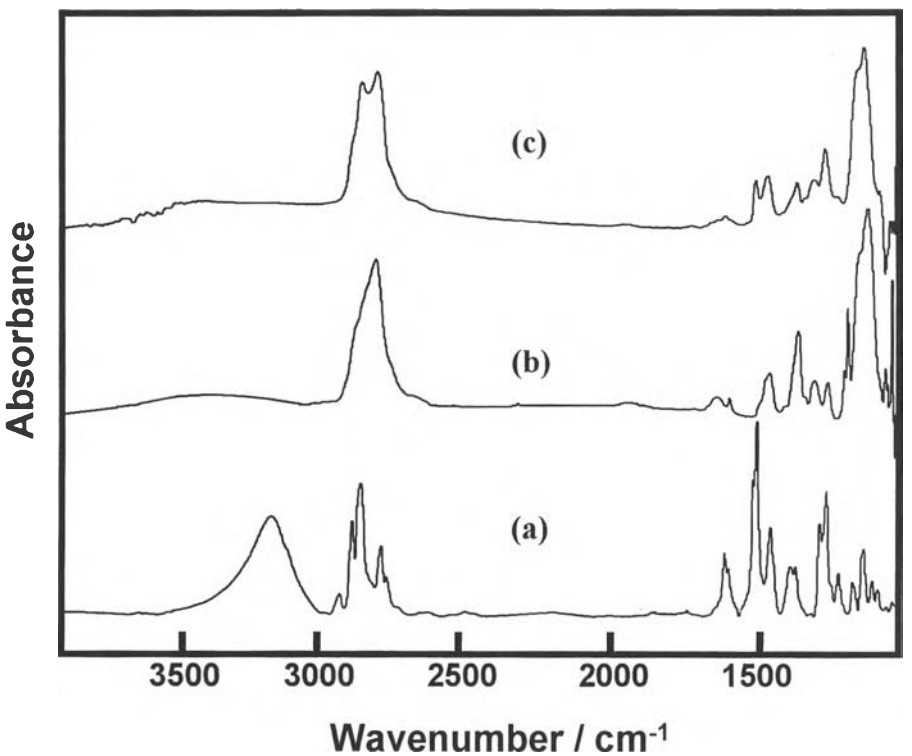


Figure 5. (Chanchai et al.)

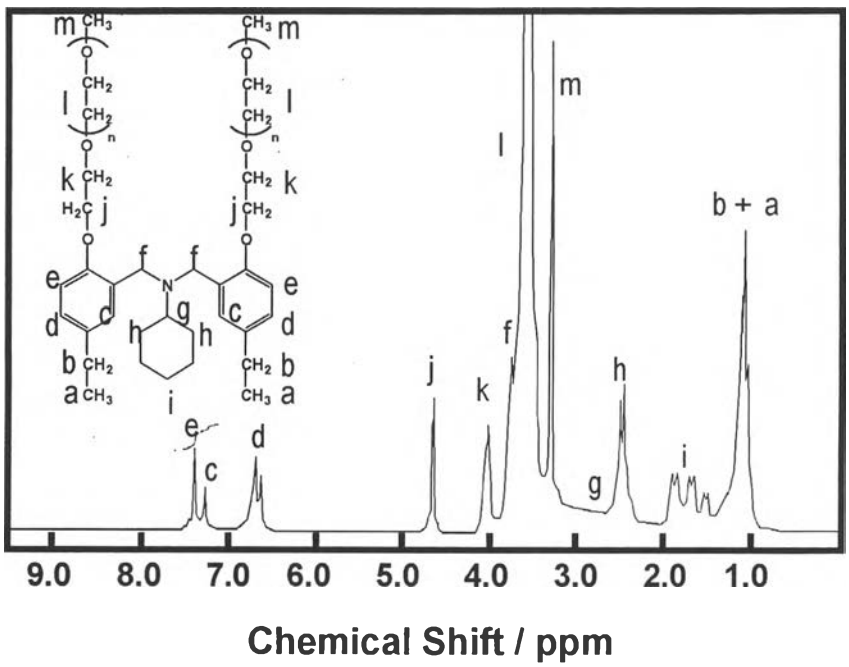


Figure 6. (Chanchai et al.)

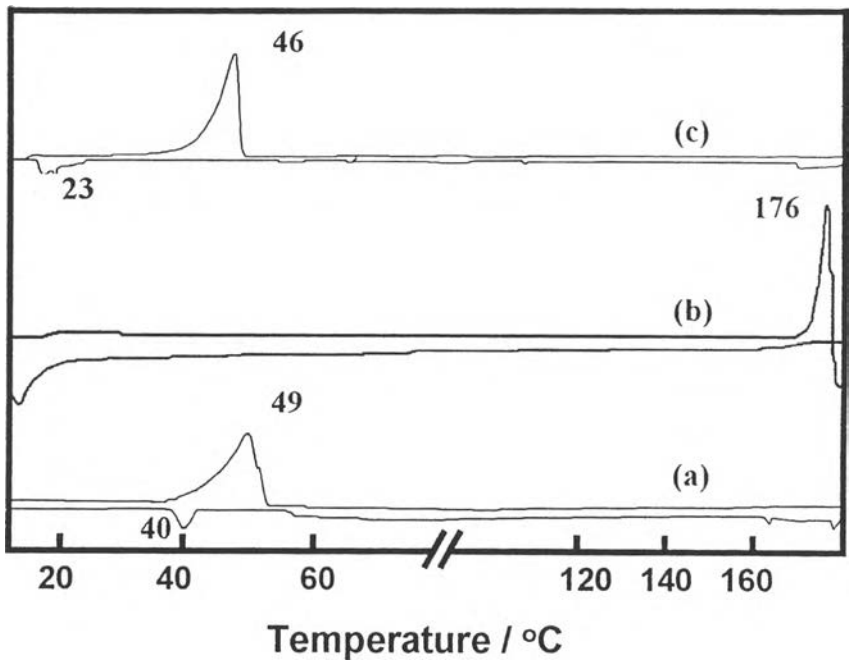


Figure 7. (Chanchai et al.)

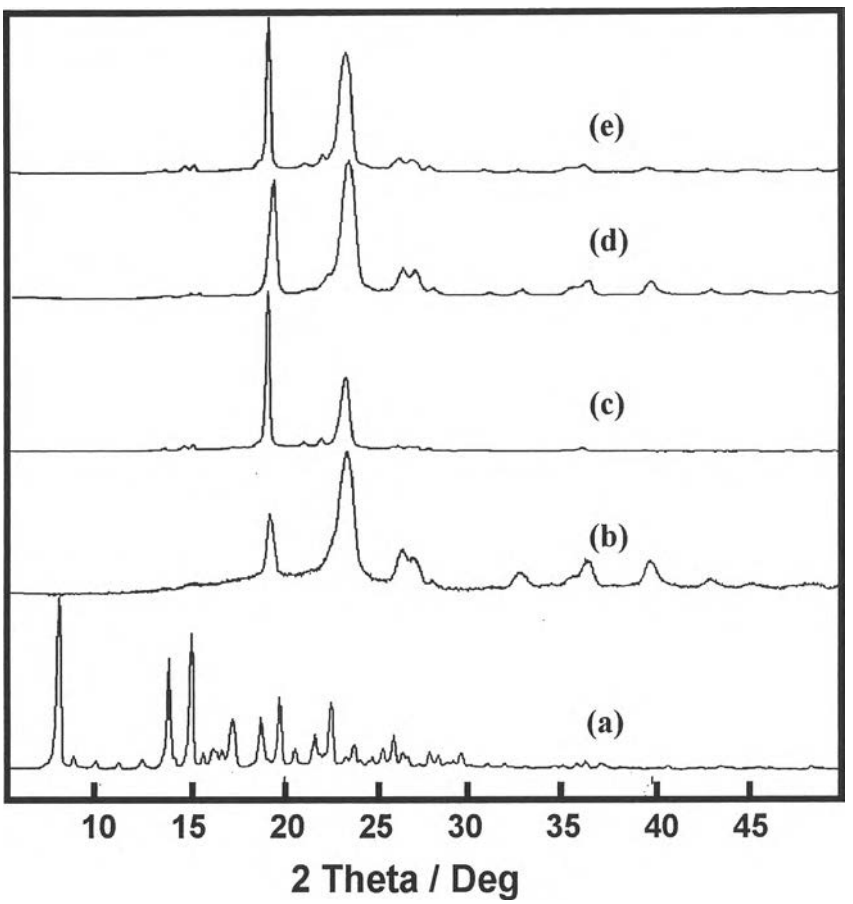


Figure 8. (Chanchai et al.)

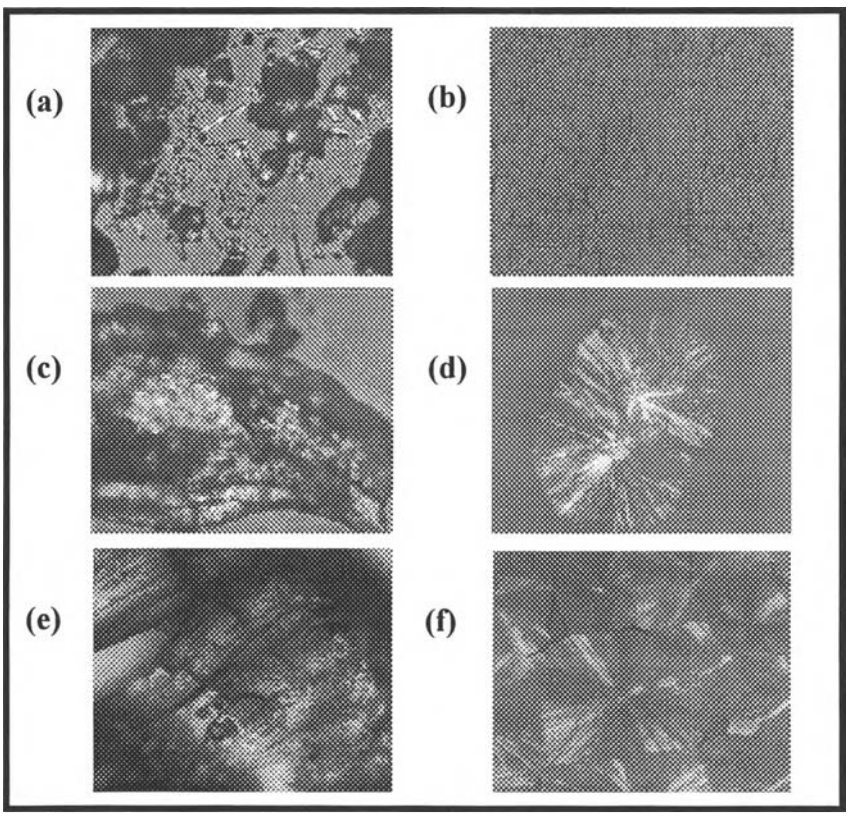


Figure 9. (Chanchai et al.)

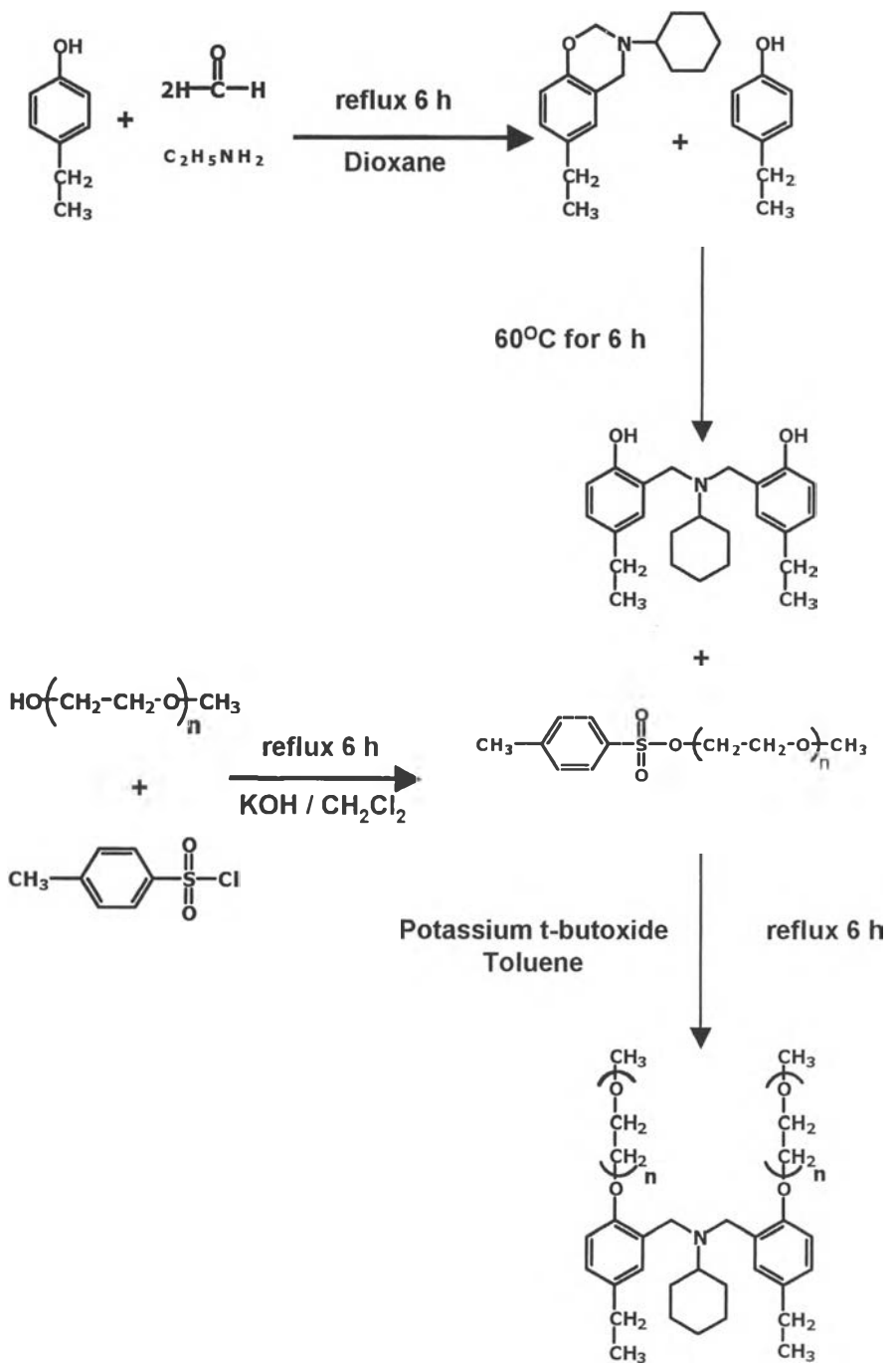
Table Caption

Table 1. Thermal stability of mPEG and compounds **1**, **4**, and **5**

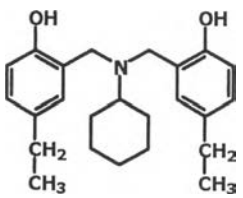
Compound	Degradation Temperature (T_d)/ °C	Melting Temperature (T_m) / °C
$mPEG_{550}$	349	20
$mPEG_{2000}$	382	49
1	187, 362	178
4	389	18
5	392	46

Table 1. (Chanchai et al.)

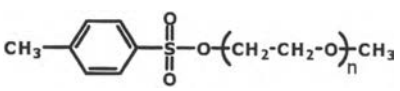
Scheme I


reflux 6 h
Dioxane
60°C for 6 h
reflux 6 h
KOH / CH2Cl2
Potassium t-butoxide
Toluene
reflux 6 h

Scheme II

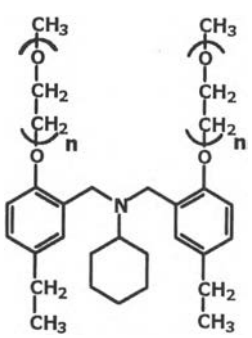


(1)



n = 12, (2)

= 44, (3)



n = 12, (4)

= 44, (5)