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Effect of aliphatic chain length on the chemical structures of low molecular weight hyperbranched polyesters

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Abstract: Low molecular weight hyperbranched (HB) polyesters were synthesized via melt polymerization from tri-methylolpropane and three aliphatic dicarboxylic acids, namely, succinic acid (SA), adipic acid (AA) and dodecanedioic acid (DA). The degrees of branching (DBs) ranged between 30% and 75% depending on the monomer ratio. Their DB, cyclic index and terminal index were all determined, indicating that the shorter chain HB polyesters PE-SA and PE-AA showed a greater degree of intramolecular cyclization, compared to the longer aliphatic chains within PE-DA. The HB polyesters form stable colloidal suspensions in buffered aqueous media and were found to be pH responsive. The stability of the colloidal suspensions is enhanced by two factors: (1) increasing the aliphatic chain length and (2) increasing the pH of the solution for the same HB polyester.

Keywords: aliphatic polyesters; hyperbranched polyesters; low molecular weight; pH-responsive particles; TMP.

1 Introduction

Hyperbranched (HB) polymers have witnessed a huge upsurge in interest in the last 20 years as novel materials for a wide variety of domains and applications. Interest in their synthesis and physicochemical properties has been driven by the ability to combine the ease

of synthesis, while keeping the intricate structures and physicochemical properties of dendritic polymers. Numerous reviews have since been published on HB polymers that wonderfully exhibit the vast range of possibilities that exist in terms of their structures and applications (1–5). Hence, the properties of a step-growth polymer vary with molar mass and molar mass distribution but also intramolecular cyclization and topologies (3, 6–8). HB polyesters synthesized via the combination of A_2 and B_3 monomers (usually a dicarboxylic acid and a poly-alcohol) are an important class of HB polymers as they can be synthesized under mild conditions, with the resulting HB polyesters showing a multitude of dendritic structures, good solubility in organic solvents and low melt viscosities (3). Furthermore, the terminal carboxylic acid groups provide excellent interactive sites with their external environment, allowing for potentially numerous applications, particularly molecular encapsulation for drug delivery in which the pH-responsive nature of HB polyesters allows for a controlled release of encapsulated molecules via a change in aggregate structure upon application of an external stimuli (9).

HB polyesters synthesized from poly-alcohols (B_3), such as glycerol or trimethylolpropane (TMP) (10–12), and aliphatic dicarboxylic acids (A_2), such as succinic, adipic (13, 14) or azelaic acid have already been reported, which display good degrees of branching (DB) and high average molecular weights (15–17). HB polyesters with a high content of polar group functionalities along the branched polyester chains, mainly hydroxyl and/or acidic, have also been reported (18). Despite these studies, there remains as yet no direct evaluation as to the effect of the amphiphilic nature of one of the monomers used on the subsequent HB polyester structure and its physicochemical properties. Our laboratory has had a long-standing interest in amphiphilic molecules (19, 20) and polymeric materials (21); thus, we have chosen to study the effect of changing the aliphatic chain length of the dicarboxylic acid monomer (A_2) used upon the chemical properties of the resulting HB polyester, while retaining in all cases the same poly-alcohol monomer (B_3). The three dicarboxylic acids chosen were succinic acid (SA), adipic acid (AA) and dodecanedioic acid (DA). The B_3 monomer chosen

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was TMP as it provides good characterization by nuclear magnetic resonance (NMR) spectroscopy in order to determine conversions and DB. Specifically, we targeted low molecular weight HB polyesters as their synthesis and characterization remain less well studied than their larger molecular weight analogs. Finally, we wished to elucidate the pH-responsive nature of the HB polyesters in differing acid-base aqueous media, in relation to the length of the aliphatic branches within the polyester.

2 Materials and methods

2.1 Materials and instrumentation

All reagents and solvents were purchased from Sigma-Aldrich (St Quentin Fallavier, France) and used without further purification. ^1H and ^{13}C NMR spectra were recorded on a Bruker Advance[®] 300 MHz instrument (Bruker, Wissembourg, France) using tetramethylsilane as an internal standard.

2.2 Synthesis of hyperbranched polyesters

The polyesters were synthesized *via* melt polymerizations of TMP (1 eq.) and the dicarboxylic acid (1 or 2 eq.) in the presence of the catalyst $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ (1 wt.% vs. total weight). For example, 50 g of TMP, 44 g of SA and 0.94 g of $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ are loaded into a 250-ml three neck round bottom flask equipped with a thermometer and two drying tubes filled with SiO_2 to ensure trapping removal of H_2O . The reaction mixture was heated at 140°C in an oil bath for 4 h. After this time, the reaction mixture was poured hot into a separate vial and analyzed without further purification.

Purified samples were achieved by dissolving the polyester in a THF/ CHCl_3 mixture (1:2) and washing the organic phase three times with equal volumes of water. Evaporation of the organic solvents gave a clear gel of the desired polyester for further analysis.

2.3 Characterization of hyperbranched polyesters

The M_n , M_w and polydispersity index (PDI) of the polyesters were estimated on a GPC-SEC system (Shimadzu, Marne La Vallée, France) consisting of two Oligopore columns (Agilent Technologies, Les Ulis, France) in series, held in an oven at 40°C , and connected to a Varian Prostar

350 refractive index detector. THF was used as the solvent carrier at a flow rate of 0.7 ml/min. The system was calibrated with a number of polystyrene standards of known molar mass and low polydispersity. Theoretical molecular weights were estimated using a literature procedure involving ^1H NMR spectroscopy (22).

The degree of branching (DB) in the hyperbranched polyesters can be determined by ^{13}C NMR spectroscopy (23, 24). It was here determined using inverse-gated ^{13}C NMR spectroscopy in accordance with the procedure described by Frey et al. (25). Fifty milligrams of the sample were dissolved in 0.6 ml of deuterated methanol. The spectra was acquired with 1024 scans and the solvent signal was used as reference. The DB is given by equation 1:

$$\text{DB}(\times 100) = \frac{2D}{2D + L} \quad [1]$$

where (D) is the dendritic unit and (L) is the linear unit that refer to the substitution pattern of the TMP units in the polyester chain. The values of each are given by the integration of the corresponding peaks in the inverse-gated ^{13}C NMR spectra.

Similarly, the terminal index (TI) and cyclic index (CI) for the purified HB polyesters were determined by a method already reported in the literature (3), by the integration of the same TMP units in the inverse-gated ^{13}C NMR spectra and calculated using equations 2 and 3 (cf. supplementary material):

$$\text{TI} = \frac{T}{D + L} \quad [2]$$

$$\text{CI} = (N_{\text{TMP}} + N_{\text{ACID}}) / D_{\text{TMP}} \quad [3]$$

where (T) is the terminal unit, $N_{\text{(TMP)}}$ is the total number of terminal TMP units, $N_{\text{(ACID)}}$ is the total number of terminal acid units and $D_{\text{(TMP)}}$ is the total number of dendritic units for an individual HB polyester.

Acid numbers (ANs) and hydroxyl values (HVs) were determined by the American Oil Chemists' Society protocols. ANs were determined by the standard AOCS Cd 3d-63, and HVs were determined by AOCS Cd 13-60. Each measurement was repeated at least three times and the average reported.

2.4 Granulometry and ζ potential

Granulometric studies and ζ potential measurements were performed on a Malvern Granulometry Zetasizer – Nano ZS Laser (Malvern, Orsay, France). Both granulometry and ζ potential studies were performed on dispersions

of 1 wt.% polyester in buffered solutions of pH 4 and 9. Each measurement was repeated at least six times upon calculation of the averages and standard deviations.

3 Results and discussion

3.1 Polyester conversion, molecular weights and DB

The synthesis of the HB polyesters was achieved by melt polymerization of the combined monomers and produced exclusively low molecular weight HB polyesters in good to high conversions (up to 95%). All initial experiments were performed on TMP and SA initially without the use of a catalyst in order to determine if the polymerization was autocatalytic, a phenomenon that we have previously observed for esterification reactions (Table 1 entries 1, 2 and 4) (26). The optimal reaction conditions appear to be 140°C for 4 h, even without the use of catalyst as the reaction temperature drives off the water produced by the esterification reaction. Addition of 1 weight% $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ as catalyst increased the conversion of polyester by approximately 10% compared to using no catalyst at all (entries 3, 5 and 6). At 0.5 weight% catalyst loading, a 5% increase in conversion is observed compared to using no catalyst (entry 8). Zinc stearate was also tested with the intention of it being a more soluble catalyst in the reaction mixture and would give a higher conversion to polyester (entry 7). The zinc stearate, however, was effectively inactive under the melt polymerization conditions, giving the same conversion to HB polyesters as that of the reaction where no catalyst was used. Similar HB polyesters have been reported in the literature using similar synthetic protocols using organic solvents and either acidic or tin based catalysts (13, 15, 17, 18). The major advantage of our system is the avoidance for the

need of an organic solvent and the use of a non-toxic, inexpensive metal catalyst. Another advantage of our system is that the $\text{ZnSO}_4 \cdot \text{H}_2\text{O}$ catalyst is insoluble in the reaction mixture, presumably acting in a heterogeneous manner, which at the end of the reaction can be easily separated from the polyester product by decantation. Inverse-gated ^{13}C NMR spectroscopy was very effective in determining the conversion to polyester, the quantity of residual monomers and the DB, by the integration of the differing substituted TMP signals using the method described by Frey et al. (25). Interestingly, the DB remained fairly constant (around 37%) regardless of the reaction conditions used, catalyst used or polyester conversion.

Based on these initial experiments, we fixed the reaction conditions at 140°C and a reaction time of 4 h and extended our investigations to evaluate the effect of the carbon chain length upon the chemical properties of the resulting HB polyesters. The dicarboxylic acid was changed from SA to AA and DA, thus increasing the aliphatic carbon chain length from 4 to 6 or 12 carbons, respectively. For the same ratio of the SA and AA monomers, the difference in length of the aliphatic chain had little effect upon the resulting DB nor Mn. Only in the case of the DA monomer was a 50% increase observed in the Mn, due to the doubling of the carbon chain in the aliphatic backbone of the HB polyester. Regardless of the increase in the Mn, no significant difference in the DB was observed (Table 2). These results suggest that regardless of the diacid used, the degree of polymerization remains around 5, suggesting that pentamers are the predominant HB products, all with similar DBs. HB polyesters, however, are notorious for giving inaccurate readings by GPC-SEC chromatography because they form aggregates that result in an overestimation of the molecular weight. Therefore, in addition to using an Oligopore column and low molecular polystyrene standards, we calculated the theoretical M_n for each HB polyester. Based on the application of a

Table 1: Preliminary experiments to determine optimal catalyst and conditions.

| Entry ^a | Catalyst (1 wt.%) ^b | Time (h) | Temp. (°C) | Residual TMP (%) ^d | Residual SA (%) ^d | Polyesters (%) ^d | DB (%) ^d |
|--------------------|--------------------------------|----------|------------|-------------------------------|------------------------------|-----------------------------|---------------------|
| 1 | – | 4 | 80 | 50.0 | 50.0 | Trace | 0 |
| 2 | – | 4 | 100 | 29.2 | 26.3 | 44.5 | 0 |
| 3 | ZnSO_4 | 4 | 100 | 29.2 | 18.4 | 52.6 | 0 |
| 4 | – | 4 | 140 | 8.2 | 3.0 | 88.8 | 31.4 |
| 5 | ZnSO_4 | 3 | 140 | 5.3 | 2.3 | 92.4 | 36.4 |
| 6 | ZnSO_4 | 4 | 140 | 5.1 | 0.7 | 94.2 | 37.3 |
| 7 | $\text{Zn}(\text{Stearate})_2$ | 4 | 140 | 5.4 | 3.7 | 90.9 | 36.4 |
| 8 | ZnSO_4^c | 4 | 140 | 5.8 | 2.4 | 91.7 | 38.1 |

^aMelt polymerization of TMP and SA, ratio = 1:1. ^bTotal weight of reagents. ^c0.5 wt.% catalyst loading. ^dDetermined by inverse-gated ^{13}C NMR spectroscopy.

Table 2: HB polyester conversions and characteristics.

| | Diacid | Ratio OH:CO ₂ H ^a | Residual TMP (%) ^b | Residual diacid (%) ^b | HB polyesters (%) ^b | DB (%) ^b | M _n ^c | M _n (Theor.) |
|----------|----------|---|-------------------------------|----------------------------------|--------------------------------|---------------------|-----------------------------|-------------------------|
| PE-1(SA) | SA (C4) | 3:2 | 3.5 | 1.8 | 94.7 | 37.3 | 1377 | 1159 |
| PE-1(AA) | AA (C6) | 3:2 | 6.1 | 10.6 | 83.3 | 40.3 | 1353 | 1288 |
| PE-1(DA) | DA (C12) | 3:2 | 6 | 7.6 | 86.4 | 39.1 | 1790 | 1792 |
| PE-2(SA) | SA (C4) | 3:4 | 0 | 32 | 68 | 74.6 | 1282 | 1411 |
| PE-2(AA) | AA (C6) | 3:4 | 0 | 37.7 | 62.3 | 75.1 | 1423 | 1338 |

^aReaction conditions: 140°C, 4 h. ^bDetermined by inverse-gated ¹³C NMR spectroscopy. ^cDetermined by GPC-SEC (all weights are in g · mol⁻¹).

literature procedure using the number of repeating units in the polyester chain, estimated by the ¹³C NMR spectra, we obtained theoretical molecular weights for the HB polyesters similar to those estimated by the GPC-SEC. This provided us with a higher confidence that the values estimated experimentally were in good correlation with those calculated theoretically, and that aggregation in the column was not imparting a significant error.

Compared to the long chain of DA (12), it is interesting to double the number of shorter chains of SA and AA (4 and 6). From 3:2 to 3:4, the ratio of carboxylic acid groups to hydroxyl groups was doubled for PE-AA and PE-SA. This had the effect of increasing the DB from 40% to 75% for PE-AA and PE-SA. Even though the DB is largely increased, there was little change in the average M_n of each polyester. As expected, large quantities of the acid monomers remain unreacted at the end of the polymerization, suggesting that the TMP units are substituted to form dendritic (branched) units, leading to little or no increase in the linear degree of polymerization.

PE-1(SA), PE-1(AA) and PE-1(DA), with lower residual diacid than PE-2(SA) and PE-2(AA), could be purified further by taking them up in a mixture of THF and chloroform, and upon washing with water, we were able to remove all unreacted monomers. This allowed us to obtain pure HB polyester mixtures with which we could analyze further and more precisely (Table 3). The GPC-SEC spectra did not vary significantly upon purification of the polyesters, and our analysis confirms that we have produced significantly lower molecular weight polyesters than those previously reported for similar HB polyesters (13, 17, 18). A large difference between M_n and M_w for each type of polyester is observed along with relatively

high PDIs. This, however, was expected given that the polyesters were synthesized under melt conditions, and thus no control over polymer dispersity is possible. Infra-red spectroscopy was not sensitive enough to distinguish the carboxylic acid bands from the carboxylic ester bands as the stretching bands overlapped. We therefore used acid number (AN) and hydroxyl value (HV) indices as more quantitative methods of determining the number of carboxylic acid and hydroxyl functionalities upon the HB polyesters, respectively. Both AN and HV values for our three HB polyesters show a good degree of functionality throughout the polymer backbones regardless of the dicarboxylic acid used in their synthesis. Despite the presence of polar functional groups such as carboxylate and hydroxyl units, our HB polyesters remain insoluble in water but are highly soluble in polar solvents or water-alcohol mixtures.

A recent review in the scientific literature has revealed that the topological structure of HB polymers can be determined more precisely by calculation of the terminal (TI) and cyclic (CI) indexes (3). The CI gives a quantitative determination of the degree of intramolecular cyclization of the polymer chains (CI ≥ 1 suggests negligible cyclization, whereas CI < 1 suggests cyclization is prevalent). We determined PE-SA and PE-AA to have similar CIs of 3.72 and 3.81, whereas PE-DA gave a CI of 6.97. It is interesting to note that the CI of PE-DA is nearly double that of PE-AA, especially considering that PE-DA contains aliphatic chains twice the length of those in PE-AA. In a similar manner, the TI is another method to determine the structural features of a HB polymer, by defining the amount of cyclization vs. branching (0 being complete cyclization and 1 indicating perfectly branched).

Table 3: Purified HB polyester chemical characteristics (see experimental for determination methods).

| Polyester | DB | CI | TI | M _n (g/mol) | M _w (g/mol) | PDI | AN (mg KOH/g) | HV (mg KOH/g) |
|-----------|------|------|------|------------------------|------------------------|------|---------------|---------------|
| PE-SA | 40.4 | 3.72 | 0.43 | 1379 | 4929 | 3.57 | 71 | 178 |
| PE-AA | 37.5 | 3.81 | 0.49 | 1356 | 3214 | 2.37 | 56 | 161 |
| PE-DA | 37.2 | 6.97 | 0.67 | 1722 | 3547 | 2.06 | 73 | 113 |

Table 4: Granulometric measurements and ζ potentials of HB polyesters at 1 wt.% in buffered solutions.

| Polyester | pH 4 | | pH 9 | |
|-----------|-------------------|----------------------|-------------------|----------------------|
| | Vol. ^a | ζ ^b | Vol. ^a | ζ ^b |
| PE-SA | 572 (\pm 191) | -18.1 | 170 (\pm 5) | -68.8 |
| PE-AA | 889 (\pm 85) | -25.2 | 29.2 (\pm 2) | -75.0 |
| PE-DA | 747 (\pm 166) | -28.1 | 18.8 (\pm 2) | -90.8 |

^aVolume average particle radius (nm). ^b ζ potential (mV).

PE-SA and PE-AA exhibit very similar TIs of 0.43 and 0.49, whereas PE-DA shows a much higher TI of 0.67. Combining the DB, CI and TI allows for a more complete understanding of the fine structure of each HB polyester depending upon the carbon chain length present within. The data for PE-SA and PE-AA suggest a polymeric structure with a good degree of intermolecular branching, but also a significant amount of intramolecular cyclization of their polyester chains. The data for PE-DA, on the other hand, suggest a polymeric structure with a high DB and negligible cyclization. It can therefore be suggested that an increase in the aliphatic carbon chain lengths of low molecular weight HB polyesters results in more branched units and less internally cyclized units within the polymeric structure.

3.2 pH-responsive HB polyesters

The self-assembly of HB polyesters into vesicles or aggregates in aqueous solutions has led to a growing interest into the nature of their aggregation, especially their ability to change shape or size upon application of an external stimulus (2, 27–29). pH-responsive aggregates are of particular interest as potential drug delivery agents as a change in pH environment is a common pathological occurrence in biological systems (4, 30–32). Reports on the pH-responsive nature of HB polyester self-assembly and their encapsulation of organic compounds as drug delivery systems are already known (29). In these systems, carboxylate and hydroxyl functionalities are vital in order to display pH-responsive behavior; thus, given that our HB polyesters are highly functionalized and are water insoluble, we suspected that their self-assembly would be determined by their interaction with the external pH of an aqueous media.

Aqueous solutions of the three HB polyesters gave colloidal suspensions at 1 wt.% in aqueous buffered solutions of pH 4 and pH 9. Granulometric analysis showed that the volume average radius of the colloidal particles formed by

the HB polyesters changes depending upon the pH of the aqueous solution (Table 4). At pH 4, the three types of HB polyesters display volume average radii that are approximately similar, and the radii appear to be independent of the three aliphatic chain lengths within each branched structure. Under basic conditions of pH 9, all three HB polyesters show a significant decrease in average radii compared to at pH 4. The average radius of PE-SA aggregates decreases by 402 to 170 nm, whereas the average radii of PE-AA and PE-DA aggregates show an even greater decrease from 889 and 747 nm to 29.2 and 18.8 nm, respectively. This suggests that upon deprotonation of the terminal carboxylic acids to carboxylate groups, anionic charge is able to induce greater electrostatic repulsion between the HB polyesters chains causing them to organize into smaller aggregate particles compared to their protonated forms in acidic aqueous media. More strikingly, under basic conditions exclusively is the decrease in aggregate radii upon an increase in the aliphatic branches of the polyester structure. An increase of just two carbon atoms in the aliphatic chain results in a decrease in average radius from 170 nm in PE-SA to 29 nm in PE-AA. This appears to be a critical limit as doubling from 6 carbons to 12 carbons in the aliphatic chain only results in a decrease of 10 nm between PE-AA and PE-DA. PE-SA shows a loss of 402 nm, whereas PE-AA and PE-DA exhibit losses of nearly double this of around 800 nm each. Our data suggest that longer aliphatic carbon chain in the HB polyester structures allows for the polyester chains to organize themselves more tightly, thus forming colloids with smaller average radii.

The length of the aliphatic chain within the polyester backbone appears to also play a significant role in the stability of the colloidal particles as demonstrated by the ζ potential data. To remain consistent, the ζ potentials were also measured at 1 wt.% HB polyester in the same acid/base buffered solutions. Two very clear trends can be seen with the ζ potentials: (1) the ζ potentials decrease with increasing aliphatic carbon chain length within the HB polyester chains and (2) the ζ potentials decrease with an increase in the pH of the aqueous solutions. The second trend suggests that upon deprotonation of the carboxylic acid groups in basic solutions, anionic charge is sufficiently expressed at the surface of the particles to create a greater degree of potential difference at the interface of the aggregated particles and their external solution, resulting in lower ζ potentials and thus more stable polyester-aqueous colloids. The first trend suggests that lengthening the aliphatic chain in the branched polyester backbone provides for a greater degree of flexibility to which the polyester molecules can organize themselves

into more compact aggregates, producing lower ζ potentials due to a greater degree of stability of the resulting colloidal suspensions.

4 Conclusion

Our study here reveals that by judicious choice of the length of the aliphatic carbon chain, it is possible to control the degree of cyclization versus terminal end groups within the HB polyester structure, while keeping the DB and molecular weights relatively constant. The HB polyesters aggregate in aqueous media and in their protonated form have similar aggregate sizes regardless of aliphatic chain length. Upon deprotonation of the terminal carboxylic acid groups, the HB polyester aggregates reorder dramatically to much smaller particles sizes. This responsiveness is a critical property of HB polyesters and could lead to the development of tailored applications. Further investigations are currently underway to discover the host-guest nature of these HB polyesters with respect to the encapsulation of molecules and the coordination of substrates.

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ePolymers - Supplementary Material

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2 **Effect of Aliphatic Chain Length on the Physio-Chemical Properties of Low** 3 **Molecular Weight Hyperbranched Polyesters**

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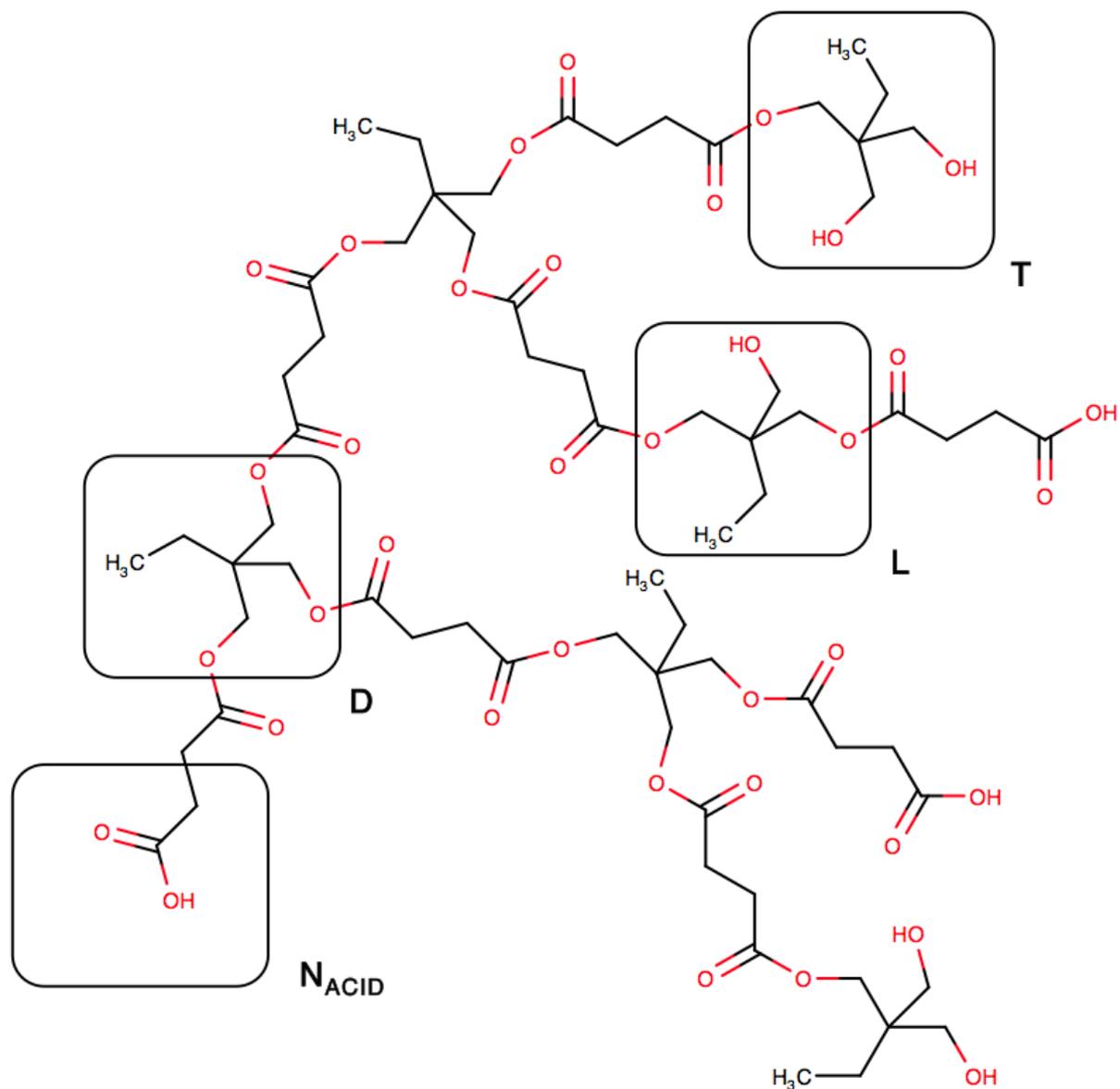
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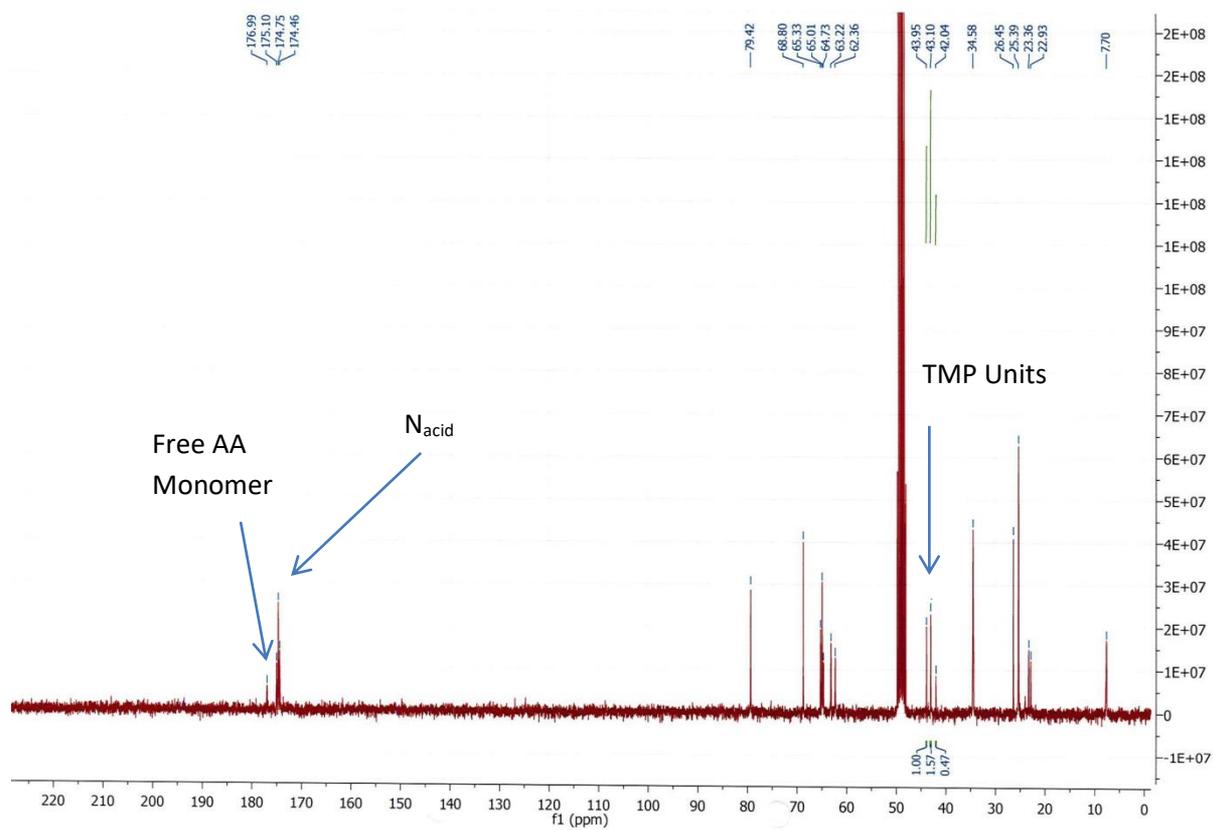
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15 **Figure 1. Diagrammatic Representation of PE_1(SA) with examples of T, L and D**
16 **polyester TMP units highlighted.**



17
18

19 **Figure 2. Inverse-Gated ^{13}C NMR Spectrum of PE_1(AA).**



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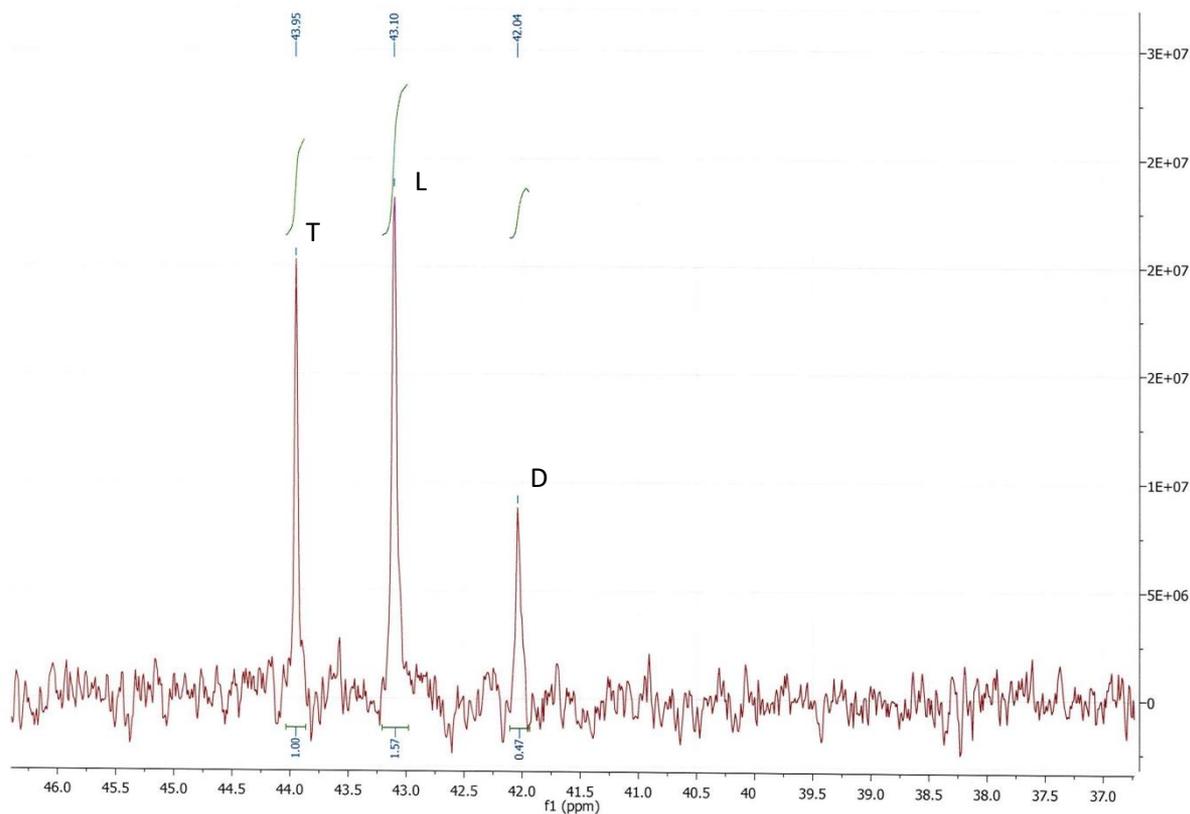
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24 **Figure 3. Expansion of Inverse-Gated ^{13}C NMR spectrum region of TMP Units.**

25



26

27

28 **Example of Calculations for PE_1AA. (Taken from spectrum above).**

| Unit | Integration |
|--------------------------|-------------|
| N_{ACID} | 0.79 |
| T Unit | 1 |
| L Unit | 1.57 |
| D Unit | 0.47 |

29

30 Degree of Branching (DB), Cyclic Indexes (CI) and Terminal Indexes (TI) Calculations for
 31 PE_1(AA):

32 $\text{DB} (\%) = 2\text{D}/2\text{D}+\text{L}$ $[(2 \times 0.47) / (2 \times 0.47) + 1.57] \times 100 = 37.5 \%$

33

34 $\text{TI} = \text{T} / \text{D} + \text{L}$ $[1 / (1.57 + 0.47)] = 0.49$

35

36 $\text{CI} = (\text{T} + \text{N}_{\text{ACID}}) / \text{D}$ $[(1+0.79) / 0.47] = 3.81$