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BPA-Free High-Performance Sustainable Polycarbonates Derived from Non-Estrogenic Bio-Based Phenols

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ABSTRACT

Bisphenol A (BPA) is a versatile petrochemical used in the preparation of high volume polymers including polycarbonates and epoxy resins. Unfortunately, BPA is also an endocrine disrupter and has been banned from use in various consumer products by several regulatory agencies. To address this issue, our group evaluated the estrogenic activity of nine bio-based tris/bisphenols derived from resveratrol (**1** and **2**), anethole (**3**, **4**), eugenol (**5**), carvacrol (**6**), and creosol (**7** – **9**). Compounds **5-9** were determined to be non-estrogenic, while compound **3** exhibited a response at a lower concentration than BPA, and compounds **1**,**2**, and **4** exhibited responses similar to BPA. Polycarbonates of the bio-based bisphenols (**PC3** – **PC9**) were then synthesized via interfacial polymerization and characterized by SEC, MALDI-MS, DSC, TGA, and UV-VIS spectroscopy. The bio-based polycarbonates exhibited M_n values up to 14,600 Da (SEC) and had a wide range of glass transition temperatures (T_g) with values up to 156 °C (~25 °C higher than BPA with a similar molecular weight) depending on the monomer structure. The bio-based polycarbonates had high thermal stabilities with $T_{d5\%}$ values up to 383 °C under a nitrogen atmosphere. The non-estrogenic properties of **5-9** coupled with the good thermal properties of the derivative polycarbonates suggests that these materials are sustainable, lower toxicity alternatives for BPA-based polycarbonates.

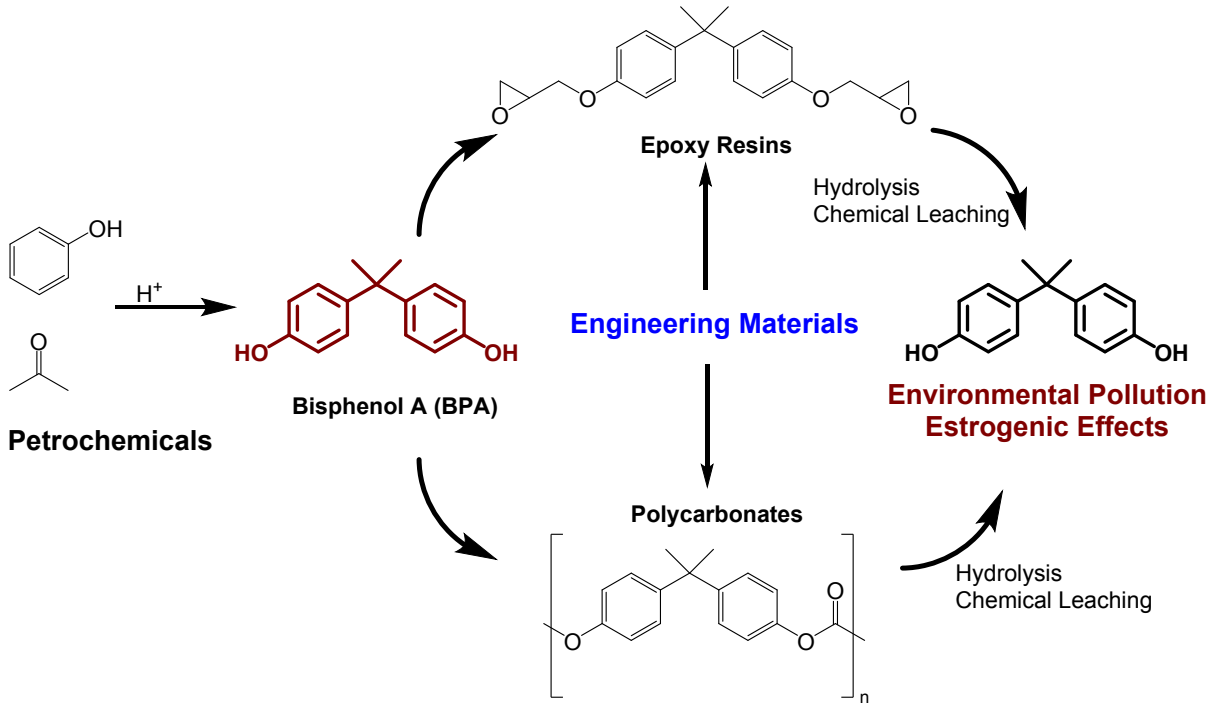
INTRODUCTION

Bisphenol A (BPA) is a ubiquitous commodity chemical, which serves as a monomer precursor to several commercial thermoplastics, thermoset resins, and additives. In 2015, global consumption of BPA was estimated at 7.7 million metric tons, with a projected consumption of 10.6 million metric tons by 2022.[1, 2] BPA-derived polymers are used in a multitude of applications including construction materials, optical lenses, household appliances, automotive parts, electronics devices, food and beverage containers, medical devices, dental materials, and thermal receipt paper.[2, 3] However, despite the chemical's prevalence in everyday life, the use of BPA in consumer products has raised concerns due to potential negative health effects. BPA is an endocrine disruptor that binds to human hormone receptors critical for the activity of estrogen, thyroid hormones, and androgens.[4 - 9] These interactions between BPA and biological receptors have been linked to several negative health effects in animal and epidemiological studies including cardiovascular disease,[2, 7, 10 – 13] behavioral changes,[3, 14 - 16] immunosuppression,[2, 17] and certain cancers.[2, 18 - 20] In addition to these adverse effects, the widespread use of BPA makes exposure nearly unavoidable. Recent studies have shown that free BPA is present nearly everywhere on earth (soil, air, water, etc.) including biological fluids (blood and urine) in nearly 90% of the human population.[3, 10, 21 - 25] Many humans are exposed via ingestion from food, beverage, and water storage sources after free BPA leaches out of packaging containers,[2, 26 - 32] but dermal exposure can also lead to uptake and retention of BPA in blood serum.[33] As a result, the FDA, EU, and Canada have banned the use of BPA in infant bottles and food packaging,[34 - 36] and more comprehensive bans are expected in the EU.[37] In response, plastic manufacturers began using BPA alternatives such as bisphenol F (BPF) and bisphenol S (BPS) to provide "BPA-free" products. Unfortunately, these replacement compounds have similar biological activity to BPA and are

known to be cytotoxic, genotoxic, and endocrine disruptors.[38 - 42] Therefore, low toxicity replacements for BPA are necessary to reduce the impact of bisphenol based products on human health, while affording alternative sustainable materials to meet industry demands.

In addition to the negative health effects of BPA, it is derived from limited petroleum resources and thus presents long-term sustainability concerns. BPA is synthesized from the condensation reaction of phenol and acetone (**Scheme 1**), which are derived from petrochemicals (benzene and propylene) via the cumene process. Although manufacturing, transportation, electricity generation and heating represent the bulk of petroleum consumption, the growing demand for bisphenol-derived materials still comprises an important target for sustainable development.[1] Phenolic compounds derived from widely available biomass sources represent a potential solution to these sustainability issues and may provide opportunities for less toxic monomer precursors with unique polymer properties.[43 – 45] Analogous to the petroleum refinery, the biorefinery concept has gained popularity over the last decade and focuses on the conversion of biomass feedstocks into fuels and valuable chemical precursors.[46, 47] Typical biological feedstocks include sugars, starches, and waste biomass (i.e., cellulose, lignin), which can be converted into novel chemicals through mechanical, chemical, thermochemical, or biochemical processing.[48] For example, resveratrol is a natural trisphenol that has shown promising health benefits and increased demand from the nutraceutical industry, but the process of isolating and purifying the trisphenol from natural resources is expensive due to low natural abundance.[49] However, recent studies have shown that resveratrol can be produced biosynthetically via fermentation of glucose or ethanol using metabolically engineered microorganisms.[49 - 51] The biorefinery concept can also be used to produce unique chemical precursors from waste biomass. Lignin is an abundant natural polymer typically found in the cell walls of plants and is considered

a waste byproduct isolated after extraction of cellulose fibers.[43] Further chemical processing of lignin can be performed to isolate useful chemical building blocks such as vanillin and creosol (2-methoxy-4-methylphenol), which have shown promise as precursors for thermoplastic and thermoset materials.[43, 52 – 62] The use of lignin and other forms of waste biomass is appealing due to the low cost of these materials and their abundant supply. The U.S. Department of Energy estimates that 1.3 billion tons of waste biomass feedstocks can be produced sustainably by 2030,[63] so these feedstocks provide promising sustainable alternatives to petroleum.



Scheme 1: The Life of Bisphenol A.

Polycarbonates are important commercial thermoplastics with exceptional impact resistance, ductility, creep resistance, dimensional stability, and optical transparency.[64, 65] As a result, polycarbonate materials have widespread use in construction, automotive, packaging, electronics, optics, and medical materials.[64 - 67] In 2018, polycarbonates had the second highest global production volume among engineering resins behind only nylon.[66] However, the majority

of polycarbonates are synthesized industrially from BPA, with polycarbonates representing 64% of BPA consumption.[1] Due to the concerns associated with BPA and the promise of sustainable precursors, polycarbonates derived from bio-based feedstocks have become a growing field of study. For example, aliphatic polycarbonates have been synthesized from renewable resources such as limonene oxide,[67 - 69] fatty acids,[70] citric acid,[71] glycerol,[72, 73] isosorbides,[74] and carbohydrates.[75] In addition, rigid, aromatic polycarbonates have been produced from vanillin,[57,] lignin,[76] eugenol,[77] turpentine,[78] ferulic acid,[79] and guaiacol.[80] These bio-based polycarbonates have shown a wide range of thermal and thermomechanical properties making them useful for applications ranging from elastomeric materials to high temperature thermoplastics. Although these bio-based polymers present opportunities for commercial applications, limited data exist regarding the bioactivity of the monomers and whether these precursors represent lower toxicity monomers compared to BPA. A recent study using qualitative structure-activity relationships (QSAR) and molecular docking (MD) predicted the estrogenic activity of a variety of bio-based phenolic precursors, but due to a limited database, the confidence levels of the predictions were low.[81] While computational studies provide an efficient screening method for potential BPA alternatives, biological assays on phenolic precursors are still critical for evaluating the suitability of bio-based BPA replacements for further exploitation.

In this work, nine bio-based tris/bisphenols derived from resveratrol, anethole, eugenol, carvacrol and creosol were selected based on their availability from abundant biomass sources, ease of synthesis, and structural diversity. The phenols were analyzed for endocrine disruption activity via *in vitro* assays and the experimental results were compared with previous results determined by *in silico* predictions to gain insight into the biological activity of potential BPA replacements. The sustainable BPA alternatives were then polymerized to form polycarbonate

thermoplastics and characterized to determine the resulting thermal and spectroscopic properties. Overall, this study provides insight into lower toxicity, bio-based BPA replacements for polycarbonate applications.

EXPERIMENTAL

General. The phenol precursors are shown in **Figure 1**. Compounds **2 - 9** were synthesized as described in previous work.[56, 77, 78, 82, 83] Biosynthetic resveratrol (compound **1**) was provided by Evolva and used as received. Triphosgene, triethylamine (TEA), deuterated chloroform ($CDCl_3$) and the reference standards used for in vitro assays [beta-estradiol (E2), diethylstilbestrol (DES), methoxychlor, BPA, dimethylsulfoxide (DMSO)] were purchased from Sigma-Aldrich. BPA for polycarbonate synthesis was acquired from Pfaltz and Bauer, NaOH from PolarChem, while dichloromethane (DCM) and methanol (MeOH) were acquired from Fisher Chemicals. All commercial chemicals were used as received. ^{1}H and ^{13}C NMR spectra were collected on a Bruker AVANCE II 500 MHz spectrometer. The NMR samples were analyzed in $CDCl_3$ using the solvent peaks as references [$CDCl_3$: δ 7.27 (^{1}H), 77.36 (^{13}C)]. Ultraviolet-visible (UV-VIS) absorbance spectroscopy was performed using a CRAIC Technologies UV-visible-NIR Microspectrometer with a 40x objective and 1 micron spot size. The microspectrometer was calibrated with NIST alumina and silver standards. The UV-VIS measurements were performed on films of the polycarbonates after pressing with a force of 50 kN at 160 °C for 0.5 h.

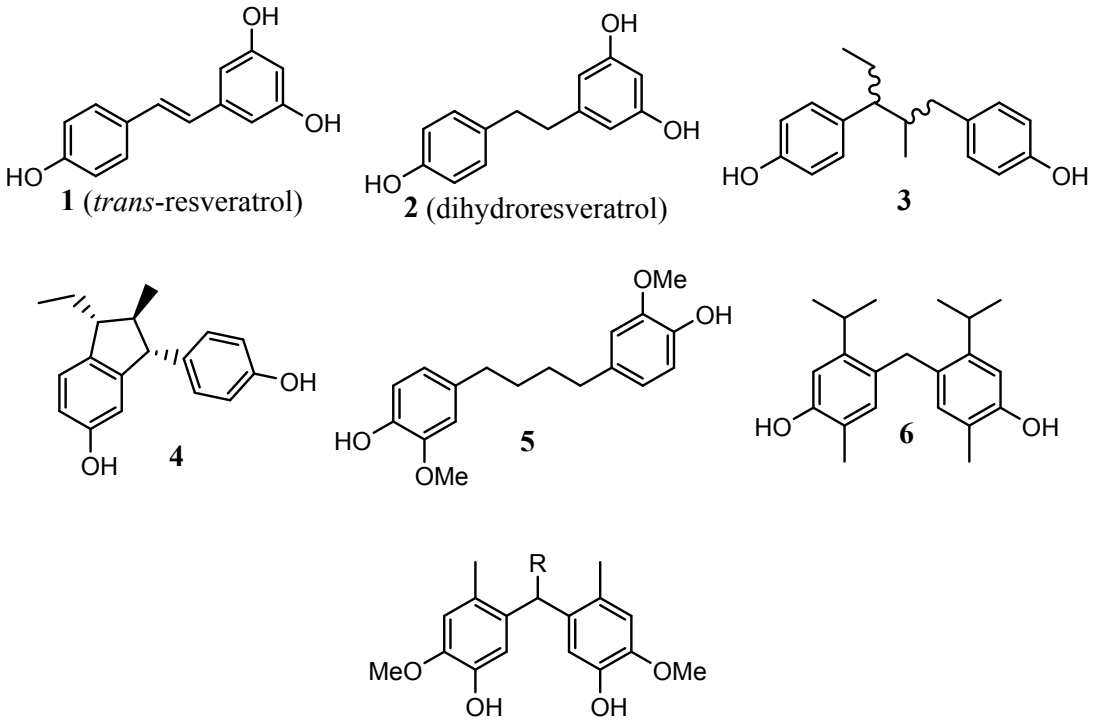


Figure 1: The bio-based phenols studied in this work.

***In Vitro* Studies of Endocrine Disruption.** *In vitro* endocrine disruption studies were performed on compounds **1** – **9** using the Organization for Economic Cooperation and Development (OECD) test guideline (TG 457).[84] E2, DES, and methoxychlor were used as reference standards, and BPA was used as a positive control. The assays were performed with BG1Luc4E2 cell lines (also known as VM7Luc4E2) obtained via material transfer agreement (UC Davis Case # 2011-003).[85, 86] The cell lines were genetically modified with a plasmid from Promega that produces luciferase upon estrogen receptor transcriptional activation. Luciferase is a bioluminescent protein, and the abundance of the protein can be determined spectrophotometrically, which correlates with estrogenic activity.[85] Detailed information regarding cell maintenance, testing, and analysis can be found in the Supporting Information.

Synthesis of Polycarbonates. Polycarbonates of bisphenolic compounds **3** – **9** were synthesized using a modified method described by Chen.[87] In a general procedure, the bisphenol (3.0 mmol) was dissolved in a 1.25 M NaOH solution (6 mL) followed by addition of TEA (0.05 mL, 0.3 mmol). Triphosgene (0.37 g, 1.25 mmol) was dissolved in dichloromethane (6 mL), and added to the aqueous solution dropwise to yield a biphasic reaction mixture. The mixture was stirred for 10 min at room temperature and then transferred to a separatory funnel. The organic layer was diluted with DCM (10 mL), and washed with distilled H_2O (4 x 20 mL). The solution was then poured into MeOH (200 mL) to precipitate the polycarbonate. The polycarbonate was isolated by centrifugation, followed by decantation of the supernatant, and was then dried in a vacuum oven (60 °C, ~50 torr) for 18h. All of the polycarbonates were isolated as either white or off-white powders. Alternatively, the precipitated polycarbonates were isolated by filtration on filter paper after precipitation in MeOH, and then washed with H_2O/MeOH and dried in a vacuum oven.

The polycarbonate of BPA (**PCBPA**) was synthesized as a reference for comparison. **PC5**, **PC6**, and **PC7** have been synthesized and reported in previous studies but were synthesized in this study for further analyses.[77, 78, 87] Polycarbonates of compounds **1** and **2** were synthesized, but not studied further due to the formation of intractable products. **PC3**, **PC4**, **PC8**, and **PC9** have not been reported previously and were characterized by ^{1}H NMR, ^{13}C NMR, and FTIR.

Polycarbonate 3 (PC3) from Racemic 3. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.22 – 7.06 (m, 8H, Ar), 2.84 (d, *J* = 13.2 Hz, CH), 2.69 (d, *J* = 13.2 Hz, CH), 2.48 (bs, CH), 2.39 (bs, CH), 2.20 (t, *J* = 10.4 Hz, CH), 2.10 (t, *J* = 11.5 Hz, CH), 2.03 – 1.88 (m, 3H, CH_2) 1.74 – 1.63 (m, 1H, CH_2), 0.87 (d, *J* = 6.1 Hz, CH_3), 0.82 – 0.74 (m, CH_3), 0.69 (d, *J* = 6.5 Hz, CH_3). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 152.7, 149.6, 149.4, 142.6, 141.5, 140.0, 139.8, 130.4, 130.3, 130.1, 129.8, 120.9, 120.6, 53.0, 52.5, 41.1, 40.7, 40.1, 26.3, 25.2, 17.1, 16.4, 12.8, 12.7.

Polycarbonate 4 (PC4) from Racemic 4. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 7.23 – 7.04 (m, 5H, Ar), 6.75 (d, *J* = 12.1 Hz, Ar), 6.69 (d, *J* = 11.2 Hz, Ar), 3.76 (m, 1H, CH), 2.75 (bs, 1H, CH), 2.09 (bs, 1H, CH), 1.87 (bs, 2H, CH_2), 1.18 – 1.13 (m, 3H, CH_3), 1.01 – 0.96 (m, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 152.2, 149.8, 147.7, 144.7, 141.5, 129.7, 123.8, 120.9, 119.3, 117.2, 58.1, 51.1, 24.1, 17.0, 10.7.

Polycarbonate 8 (PC8). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.92 (s, 2H, Ar), 6.75 (s, 2H, Ar), 4.20 (bs, 1H, CH), 3.80 (bs, 6H, Ar-O-CH_3), 2.19 (bs, 6H, Ar-CH_3), 1.49 (bs, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 151.4, 148.7, 138.3, 136.1, 134.5, 120.4, 114.8, 56.0, 36.6, 20.9, 19.2.

Polycarbonate 9 (PC9). ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 6.93 (bs, 2H, Ar), 6.74 (bs, 2H, Ar), 3.93 (bs, 1H, CH), 3.78 (bs, 6H, Ar-O-CH_3), 2.19 (bs, 6H, Ar-CH_3), 1.88 (bs, 2H, CH_2), 0.93 (bs, 3H, CH_3). ^{13}C NMR ($CDCl_3$, 500 MHz) δ: 151.4, 148.6, 138.3, 134.8, 120.8, 114.8, 55.9, 43.6, 28.7, 19.4, 12.7.

FTIR Spectroscopy. The samples were analyzed by Fourier transform infrared (FTIR) spectroscopy using a Thermo Fisher Nicolet 6700 spectrometer equipped with the "SMART iTR" Attenuated Total Reflection (ATR) accessory. The detector type was a liquid nitrogen cooled MCTA. The spectra are an average of 32 scans with 4 cm^{-1} resolution. Background subtraction (clean germanium crystal) and baseline corrections were used to decrease noise from the system.

Density. Density measurements were obtained on a Micrometrics Accupyc 1330 gas pycnometer using helium gas. The instrument was calibrated using a 0.718527 cm^3 metal ball bearing standard. The samples were pressed into pucks using a hydraulic Carver Press at 20,000 psi (0.5" die) and then weighed to ± 0.1 mg. The pycnometer provides five measurements per analysis and density is reported as the average of five runs.

Size Exclusion Chromatography (SEC). Size exclusion chromatography (SEC) to determine the molecular weight of the samples was performed on a Viscotec TriSEC Model 302 GPC with a refractive index (RI) detector. Separation was accomplished using two in-series Varian PLgel 5µm Mixed-D 300 X 7.5 mm GPC columns with a matching 50 X 7.5 mm guard column. A tetrahydrofuran (THF) mobile phase flowing at 1 mL/min was used. Prior to injection, the sample was dissolved in THF, with a small amount of toluene used as a flow rate marker, and passed through a 0.2 µm PTFE filter. A nine-point calibration curve using polystyrene standards ranging from approximately 1,000 to 480,000 Da was used for the analysis.

Matrix-Assisted Laser Desorption/Ionization Mass Spectroscopy (MALDI-MS). All MALDI-MS experiments were carried out on a Bruker Autoflex MAX MALDI-TOF-TOF mass spectrometer (MS) (Bruker Daltonics, Bremen, Germany), equipped with a Smartbeam II laser. Samples were prepared by co-depositing 1 µl of saturated polymer solution in 50/50 (v/v) acetonitrile (ACN):THF with 1 µl of a saturated 2,5-dihydroxybenzoic acid matrix in a 30:70 (v/v) ACN:trifluoroacetic acid (TFA) solution with 0.1% water onto an MTP 384 polished steel BC target plate. The MALDI-TOF-TOF MS was operated in positive reflection mode with the following conditions: ion source 1 = 19.0 kV, ion source 2 = 16.75 kV, lens voltage = 7.50 kV, reflector 1 = 21.00 kV, and reflector 2 = 9.65 kV. A mass range of *m*/*z* 800–15,000 was collected with a total of 500 laser shots fired per measurement at 2,000 Hz frequency and 90% laser power. Calibration was performed, prior to analysis of each polymer, by spotting the Bruker Protein 1 calibrant in the well directly to the left of each polymer. Data processing was performed using the Bruker Flex Analysis (version 3.4) software.

Differential Scanning Calorimetry (DSC). The polycarbonates were analyzed by DSC to determine glass transition temperatures (T_g). All DSC studies were performed on a TA Instruments

Q200 differential scanning calorimeter calibrated with indium under a nitrogen atmosphere (50 mL/min). The samples (5 – 10 mg) were heated from 0 °C to 200 °C at a heating rate of 10 °C/min. Two heating cycles were performed on each sample. The T_g was determined on the second scan of each run and is reported as the average determined by three runs.

Thermogravimetric analysis (TGA). All TGA studies were performed on a TA Instruments Q5000 thermogravimetric analyzer under nitrogen or air (50 mL/min). The samples (5- 10 mg) were heated to 600 °C at 10 °C/min. The decomposition temperature is reported as the temperature at which 5% mass loss occurs ($T_{d\ 5\%}$) or the peak mass loss temperature ($T_{d\ peak}$) and is an average of three runs.

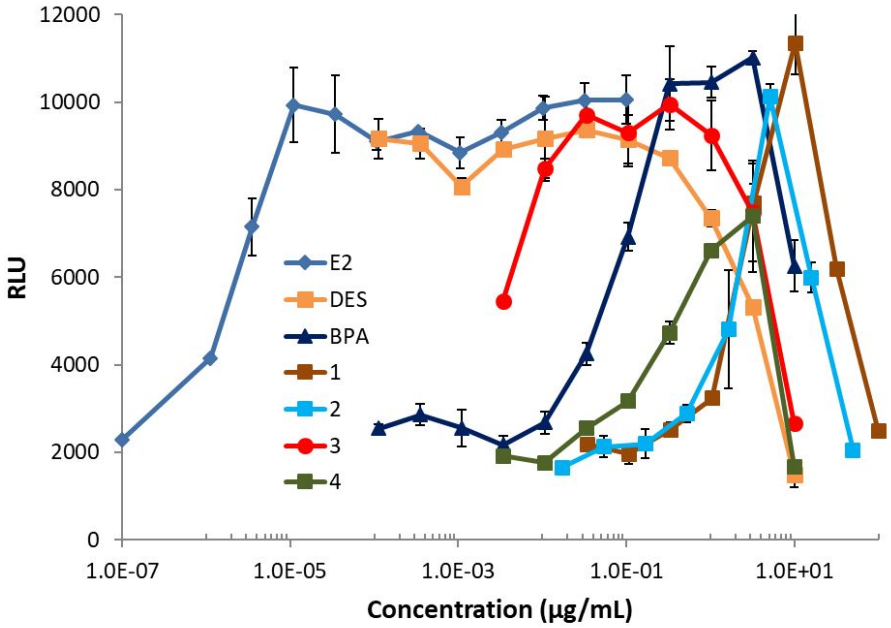
RESULTS AND DISCUSSION

***In Vitro* Assays for Estrogenic Activity of Phenols.** Compounds **1** – **9** were selected based on the derivation of the starting phenols from sustainable feedstocks, ease of synthesis, and unique structural characteristics, which deviate significantly from BPA. These characteristics are summarized in **Table 1**. **1-9** were analyzed via *in vitro* assays for estrogenic activity, and the results are shown in **Figure 2**. The graphs depict estrogenic activity in relative luminescence units (RLU) for the tested concentrations. The positive controls (BPA and DES) elicited maximal responses that were over 300% of the vehicle control response, and the threshold for a positive response was defined as 200% of the vehicle control response. Two *in vitro* assays were performed on different days, and compounds **1** – **4** elicited responses in both experiments, whereas compounds **5** – **9** elicited negative responses. The resveratrol-based trisphenols (compounds **1** and **2**) elicited maximal responses greater than BPA but these responses were at higher test concentrations (> 5 μg/mL) than the maximum BPA response. Interestingly, compound **3** elicited higher estrogenic responses than BPA at lower test concentrations (< 0.1 μg/mL), which indicates compound **3** is

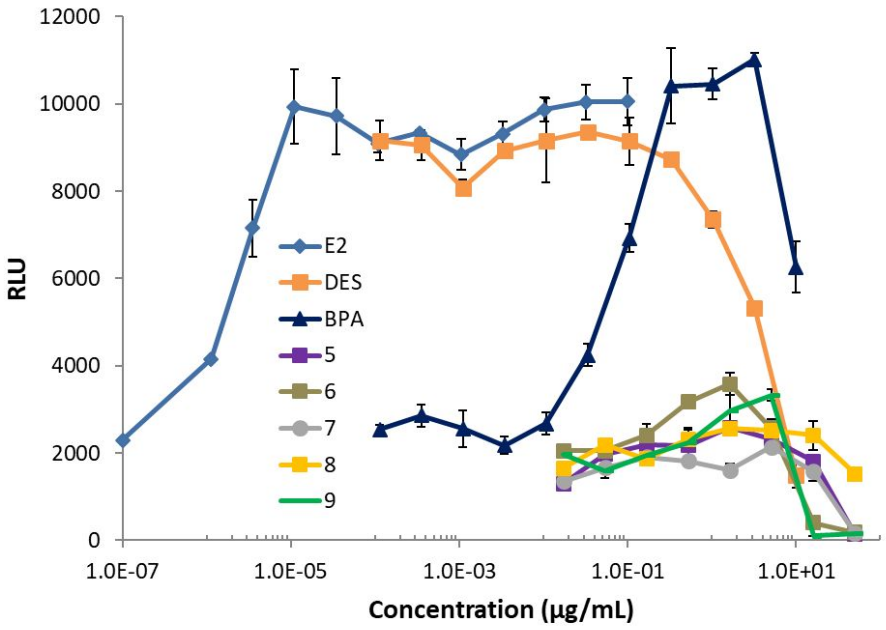
Table 1. Rationale for selecting bio-based tris/bisphenols

Phenol	Source	Synthetic Procedure	Structural Characteristics
1	Plant extract or produced via fermentation from biomass sugars	Biosynthetic (aqueous solution with metabolically engineered organisms	Trifunctional; two hydroxyl groups on a single ring
2	Same as **1**	Hydrogenation of **1** (near-quantitative)[82]	Similar to **1**, with greater flexibility (saturated bridge)
3	Anethole (star anise)	Acid-catalyzed dimerization followed by hydrogenation and demethylation[83]	Functionalized three carbon chain between aromatic groups
4	Same as **3**	Same as **3**	Rigid cyclic bridging group
5	Eugenol (clove oil, lignin)	Ru-catalyzed metathesis reaction followed by hydrogenation[88]	Methoxy groups ortho to the hydroxyl groups; 4-carbon chain between aromatic rings
6	Turpentine or plant extracts	Acid catalyzed coupling with formaldehyde[78]	methyl group ortho and isopropyl group meta to the hydroxyl groups
7-9	Lignin or biosynthetic vanillin	Acid catalyzed coupling with aldehydes[56]	Variable bridging groups meta to the hydroxyl group; methoxy groups ortho and methyl groups para to the hydroxyl groups

likely not a suitable BPA alternative. Compound **4** elicited a higher response than DES at high test concentrations (> 1 µg/mL) but had lower estrogenic responses than BPA over the entire test range. Based on the defined threshold response, compounds **5** – **9** were considered non-estrogenic in these assays and could be viable BPA replacements based on biological activity.



a)



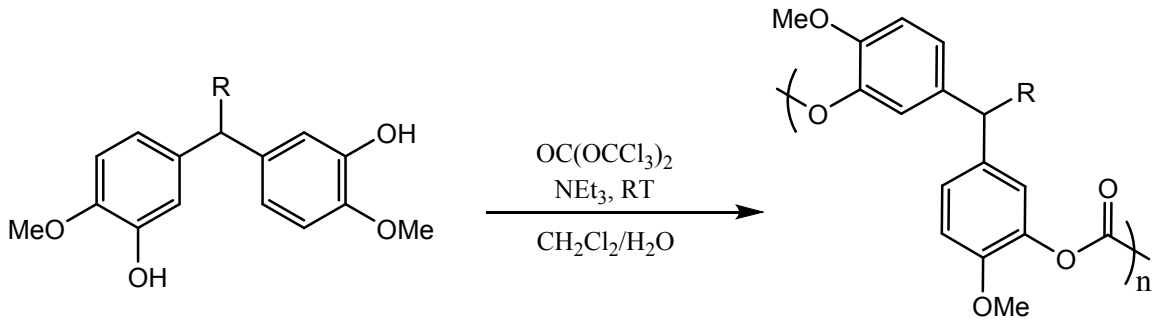
b)

Figure 2: Transactivation of BG1 Cell Lines for Estrogenic Activity for a) Compounds **1** – **4** and b) Compounds **5** – **9**. Each graph displays positive reference compounds (E2, DES, and BPA) for comparison purposes.

The low estrogenic activity of compounds **7** – **9** was predicted in previous computational work, which indicated the lignin-derived bisphenols would be nonbinders.[81] The most likely reason for the reduced estrogenic activity in these compounds is the methoxy substituents ortho to the hydroxy groups. Previous studies on lignin-based bisphenols showed significantly lower estrogenic activity for methoxy-substituted bisphenols compared to BPA through *in vitro* assays.[89, 90] Specifically, the presence of methoxy substituents that are *ortho* to the phenol –OH is believed to sterically inhibit the formation of effective hydrogen bonds in the estrogen binding pocket.[89] In addition, the –OH groups for compounds **7** – **9** are *meta* to the bridging carbon instead of *para* like in BPA, which may be another contributing factor to lower estrogenic activity. Like compounds **7** – **9**, compound **5** contains *ortho* methoxy substituents that are likely responsible for the lower estrogenic activity. Compounds **3** – **6** were predicted to have higher estrogenic activity than BPA

in the previous computational study,[81] but only compound **3** elicited the expected estrogenic response in the *in vitro* assay. The lower estrogenic activity of compound **4** compared to BPA was surprising considering the molecule has a rigid structure like BPA and unhindered –OH groups. However, the fused, substituted cyclopentane ring changes the distance and relative positions of the hydroxyl groups in compound **4**, which may contribute to the lower activity. In a similar fashion to the ortho-methoxy groups, the ortho-methyl group and meta-isopropyl group in compound **6** provide steric hindrance that likely contributes to the lower estrogenic activity of this bisphenol in the *in vitro* assays. Compounds with bulky alkyl substituents were not well-represented in the libraries used for the *in silico* predictions, which likely contributed to the discrepancy between the predicted and observed result. Considering the confidence levels for many of the *in silico* predictions were low, the results of the *in vitro* assays further highlight the importance of experimental studies when exploring BPA alternatives.

Synthesis and Characterization of Polycarbonates. Polycarbonates of compounds **3** – **9** (**PC3** – **PC9**) were synthesized via a biphasic reaction (**Scheme 2**) in which the sodium bisphenolate salts were formed in aqueous NaOH solution (1.25 M) followed by dropwise addition of triphosgene in DCM.[78,87] Triphosgene is safer to use and handle compared to phosgene, but from a green



R = H (**7**), Me (**8**), Et (**9**)

R = H (**PC7**), Me (**PC8**), Et (**PC9**)

Scheme 2. Synthesis of polycarbonates from creosol-derived bisphenols. Similar conditions were utilized for the BPA polycarbonate control samples as well as **PC3**-**PC6**

chemistry perspective is problematic due to its high toxicity. Several synthetic routes to polycarbonates are available in the literature, but interfacial polymerization was selected because this route is commonly used industrially to produce polycarbonate oligomers, which are precursors to high molecular weight polycarbonate plastics.[91] To reduce exposure to toxic chemicals, future studies should focus on the use of alternative reagents including diphenyl carbonate.

The synthetic results are summarized in **Table 2**. The yields for the bio-based polycarbonates were between 51 – 68% with the exception of **PC5** (30%). Comparatively, the yield of **PCBPA** was 68% under the same reaction conditions. **PC4** and **PC6** had the highest yields for the bio-based polycarbonates at 68%. The low yield for **PC5** was likely due to the insolubility of the bisphenol in basic solution, which resulted in a heterogeneous mixture even after rigorous stirring. Despite the low yield under these conditions, **PC5** has been synthesized previously in pyridine solution with a more acceptable yield of 57%.[77] To increase product yields, longer reaction times (60 min) were explored for **PCBPA** and **PC7**. The improvement was modest with the **PCBPA** yield increasing to 72% and that of **PC7** increasing to 66%. Due to the subtle

Table 2. Synthetic and characterization results for polycarbonates formed under biphasic polymerization conditions.

Polycarbonate	Reaction Time	% Yield	Density (g/cm^3)	M_n, SEC (Da)	PDI	T_g, °C (DSC)[b]
PCBPA-10	10	68.1	1.242 ± 0.001	6,600	2.2	130 ± 1
PCBPA-60	60	72.0	1.207 ± 0.001	8,600	2.4	132 ± 2
PC3	10	57.5	1.143 ± 0.001	14,600	2.4	94 ± 1
PC4	10	68.0	1.171 ± 0.002	7,100	2.0	156 ± 1
PC5	10	29.9	1.308 ± 0.001	3,600	2.1	51 ± 2
PC6	10	67.9	1.074 ± 0.002	8,200	1.6	107 ± 2
PC7-10[a]	10	63.9	1.281 ± 0.002	1,000	1.3	134 ± 1
PC7-60[a]	60	65.9	1.231 ± 0.001	3,800	1.2	137 ± 1
PC8	10	51.1	1.217 ± 0.002	2,300	1.3	151 ± 1
PC9	10	54.8	1.211 ± 0.003	1,400	1.4	131 ± 1

[a]**PC7** was not completely soluble in THF, so the SEC results may reflect the presence of low molecular weight oligomers after high molecular weight polymer was removed during sample preparation. [b]T_g was measured with a heating rate of 10 °C/min on the second heating cycle.

improvement in yield for these two systems, 60 min reactions were not attempted with the other bio-based phenols. For clarity, **PCBPA** and **PC7** samples prepared via the 10-minute protocol are denoted as **PCBPA-10** and **PC7-10**, respectively, while the samples prepared via the 60 minute protocol are denoted as **PCBPA-60** and **PC7-60**, respectively.

The generation of polycarbonates was confirmed via FTIR spectroscopy, which showed a carbonyl stretch for all of the synthesized polymers (Figures **S9** – **S16**). The carbonyl peak was observed at 1,776 cm^{-1} for alkyl-substituted aromatic polycarbonates (**PC3**, **PC4**, and **PC6**), 1,778 cm^{-1} for **PC5** and 1,784 cm^{-1} for **PC7**, **PC8**, and **PC9**. ^{13}C NMR spectroscopy also confirmed formation of polycarbonates with peaks above 150 ppm (Figures **S2**, **S4**, **S6**, and **S8**).

The molecular weights of the polycarbonates were measured by SEC. In general, the methoxy-substituted bisphenols produced lower molecular weight polycarbonates than **PCBPA**, and the bisphenols without methoxy-substituents produced polymers with higher molecular weights. **PCBPA-10** exhibited a M_n = 6,600 Da (PDI = 2.2), while **PCBPA-60** exhibited a M_n = 8,600 Da (PDI = 2.4). The anethole-derived **PC3** (M_n = 14,600 Da, PDI = 2.4) and **PC4** (M_n = 7,100 Da, PDI = 2.0) had higher molecular weights than **PCBPA-10**. **PC6** had M_n = 8,200 Da (PDI = 1.6), which was slightly lower than the polycarbonate synthesized in previous work (M_n = 10,200 Da, PDI = 1.6).[78] In contrast, the *ortho*-methoxy substituted polycarbonates exhibited much lower molecular weights (M_n < 5,000 Da) than **PCBPA**. Eugenol-derived **PC5** had M_n = 3,600 Da (PDI = 2.1), while the creosol-based **PC7**, **PC8**, and **PC9** had the lowest molecular weights (M_n < 2,500 Da) after 10 min reaction time. The lower molecular weight of **PC5** can partially be attributed to the insolubility of the phenol during the polymerization reaction. However, in previous work, low molecular weight (M_n = 4,300 Da) and high molecular weight (M_n = 8,400 Da) **PC5** were synthesized under the same conditions in pyridine solution, and the difference in

polymer size was attributed to minor impurities in the different monomer batches.[77] Therefore, the molecular weight of **PC5** may be more sensitive to synthetic conditions and monomer purity than the other polycarbonates. **PC7-10** exhibited the lowest molecular weight of all the polycarbonates [M_n = 1,000 Da (PDI = 1.3)], which increased to 3,800 Da (PDI = 1.2) for **PC7-60**. However, both **PC7** samples were difficult to analyze by SEC because the polymers were not fully soluble in either THF or DMF. The **PC7** solutions were cloudy but became clear after filtration through a 0.2μm PTFE filter prior to analysis, so the SEC results likely only show soluble, low molecular weight oligomers. Chen et al. also noted the solubility issue in previous work and analyzed the molecular weight via viscosity measurements, which showed M_w = 46,800 Da for **PC7**.[87] **PC8** and **PC9** were soluble in common organic solvents due to the increased aliphatic content, but these polycarbonates also had relatively low molecular weights at M_n = 2,300 Da (PDI = 1.3) and M_n = 1,400 Da (PDI = 1.4), respectively. Thus, the creosol-based monomers appear to be less reactive than BPA under interfacial polymerization conditions and form lower molecular weight oligomers based on the SEC results.

To supplement the SEC analysis, the polycarbonates were also analyzed using MALDI-MS (**Figures 3, 4**). Compared to SEC, MALDI-MS provides greater molecular weight resolution and more information regarding the species present. The MALDI-MS spectra for the **PCBPA** samples showed a repeat unit of 254 Da, which was consistent with the expected value and literature reports. Both samples exhibited peaks at molecular weights primarily below 5,000 Da, but the relative abundance of higher molecular weight species increased when the reaction time was increased to 60 min (**PCBPA-60**). The molecular weight distribution of **PC3** was similar to that of **PCBPA-10,** but exhibited a repeat unit of 296 Da and a higher relative abundance of polymers at higher molecular weights, which was consistent with the higher M_n measured by

SEC. The MALDI-MS spectrum of **PC4** was comparable to that of **PCBPA-60** and consistent with the SEC results. The repeat unit was 294 Da, which matched the calculated value for the cyclic structure of the precursor monomer **4**. The low M_n of **PC5** observed by SEC was confirmed by the MALDI-MS results. A repeat unit of 328 Da was observed with the majority of the peaks below 4000 Da. The spectrum for **PC6** showed a similar molecular weight distribution to that of PCBPA-60, which was consistent with the SEC results. In contrast to the results for **PCBPA** and **PC3**–**PC6**, the MALDI-MS experiments revealed that all of the creosol-derived polycarbonates (**PC7–PC9)** had higher molecular weights compared to the values estimated by the SEC experiments. The majority of the peaks for the **PC7-10** and **PC7-60** polymers were observed between 1,500 – 7,000 Da. There are at least two reasonable explanations for the different values obtained from the two techniques. First, the low SEC M_n values are likely due to low solubility of longer chain polymers of PC7 in the SEC solvent. Second, the presence of the polycarbonate linkage in a position meta to the bridging group results in a kinked structure that may respond differently than the polystyrene standards used to calibrate the GPC instrument. Increasing the reaction time of **7** from 10 to 60 min increased the molecular weight substantially (**Figure 3**). In addition, new peaks were visible in the **PC7-60** spectrum that represent polymer chains with a single creosol endcap. This result is likely due to the presence of traces of creosol remaining from the synthesis of the bisphenol. The MALDI-MS spectrum for **PC8** was quite similar to that of **PC7-10**, with peaks observed up to 7000 Da. The repeat units for PC7, PC8 and PC9 were 314, 328, and 342 Da, respectively, which were consistent with the expected values.

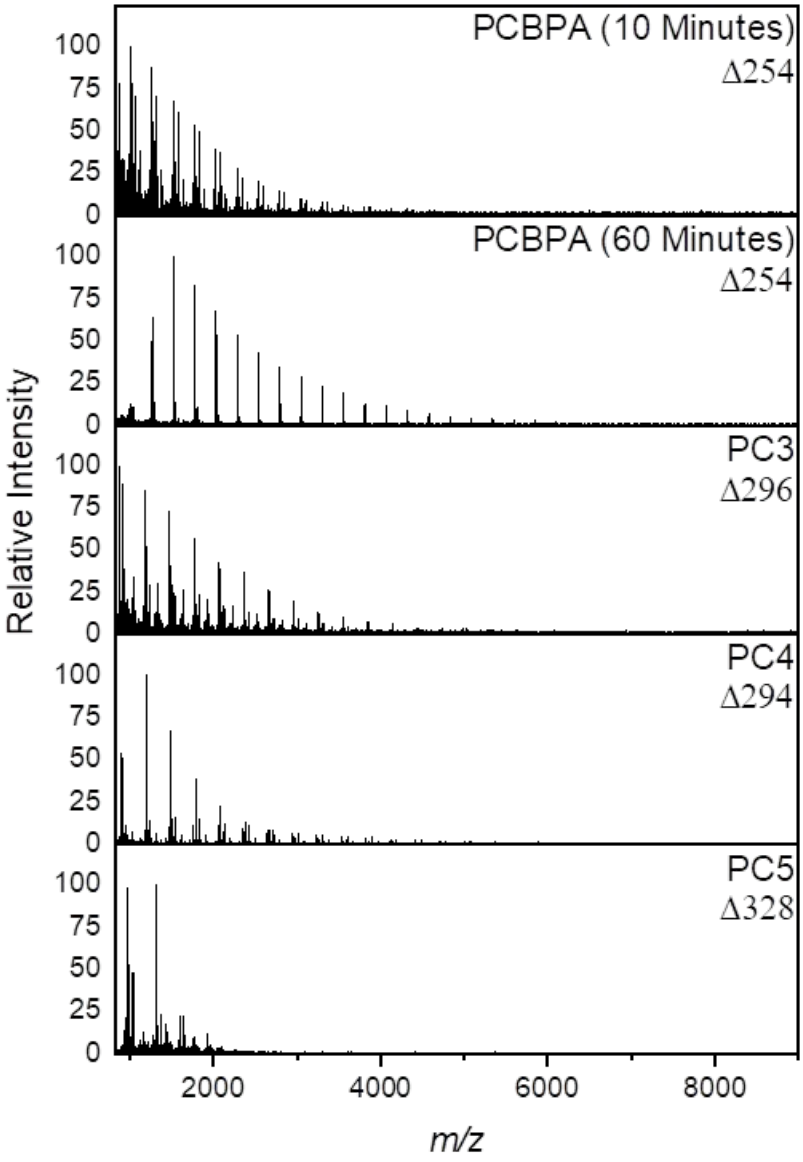


Figure 3. MALDI-MS spectra for **PCBA** and **PC3–PC5**

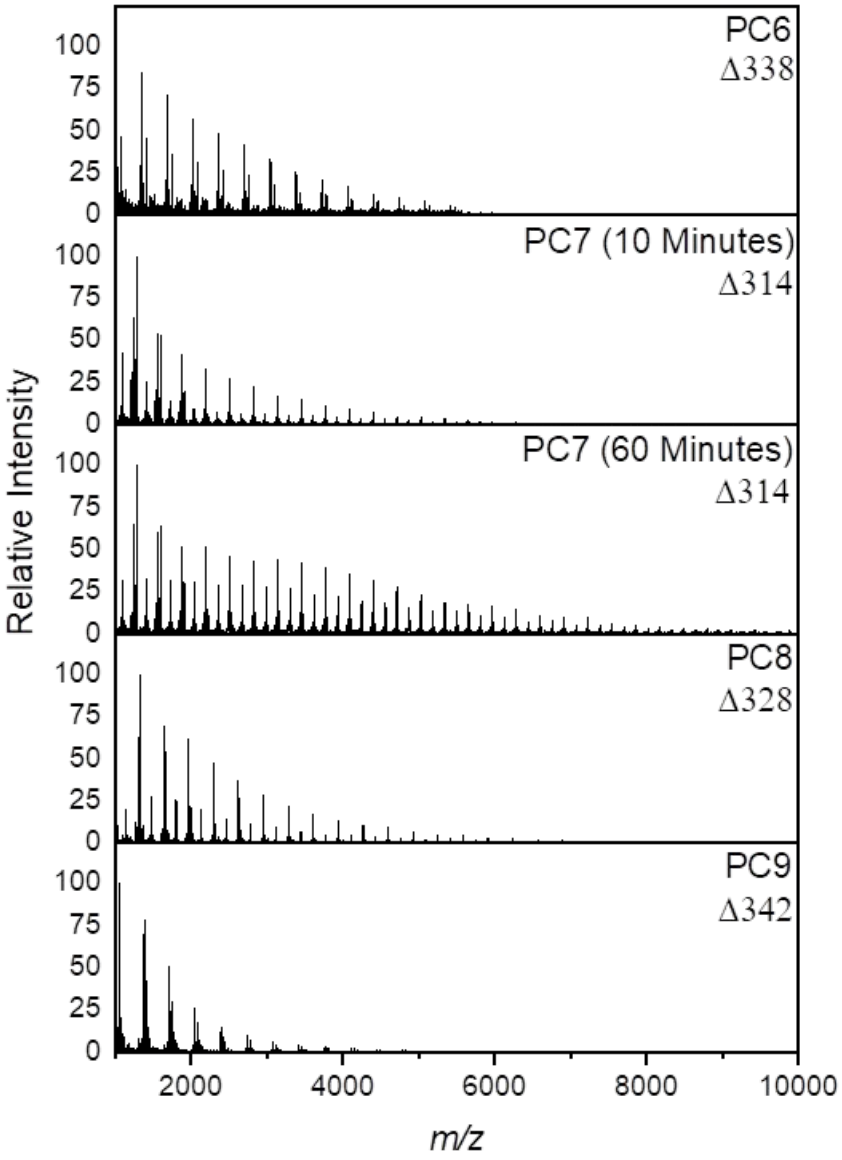
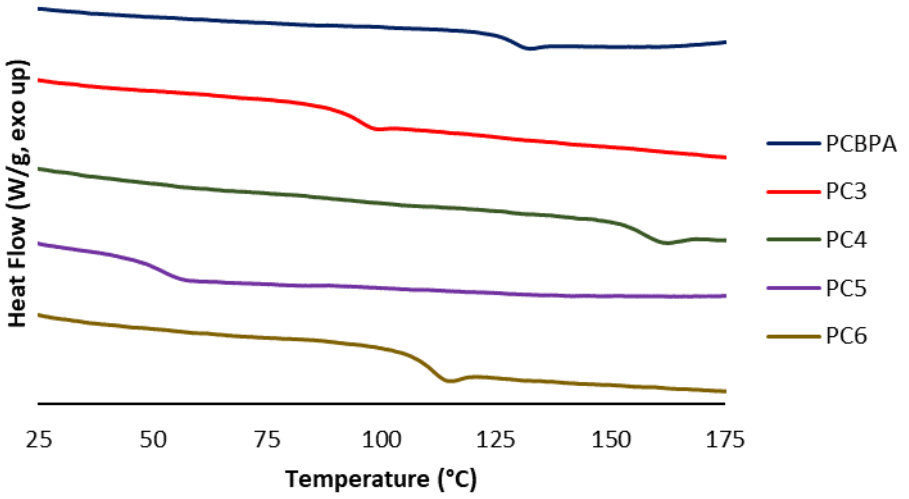


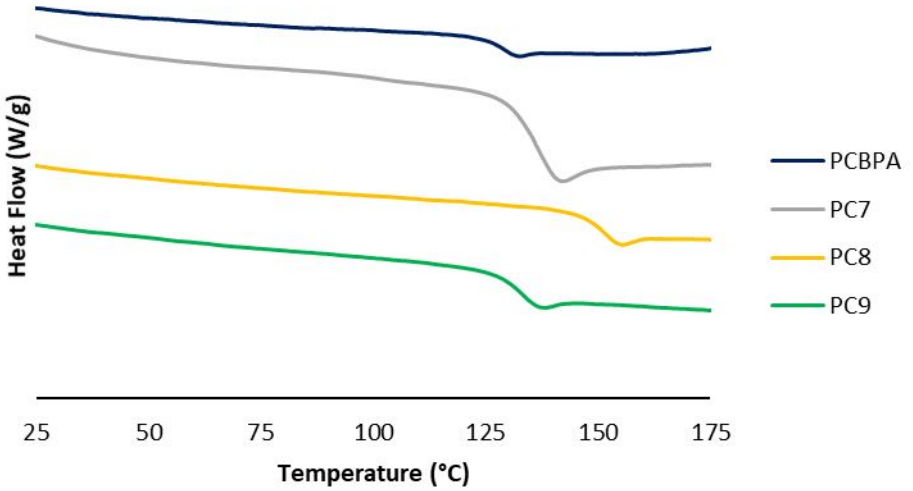
Figure 4. MALDI-MS Results for **PC6–PC9**

Differential Scanning Calorimetry (DSC) of Polycarbonates. The polycarbonates were also analyzed by DSC to measure glass transition temperatures (T_g), melting points (T_m), and crystallization temperatures (T_c) (**Figure 5)**. In general, the polycarbonates with large bridging

aliphatic groups between aromatic rings had the lowest T_gs whereas the polycarbonates with methylene bridges typically had T_gs that were similar to **PCBPA** or higher. The **PCBPA** samples exhibited T_gs of 130 and 132 °C for **PCBPA-10** and **PCBPA-60**, respectively, which are in good agreement with literature values (129.8 and 133.1 °C) for **PCBPA** with M_n between 6,000 – 8,000 Da.[92] **PC3** and **PC5** had the lowest T_gs (94 °C and 51 °C, respectively), primarily due to the flexible aliphatic bridges in each polycarbonate. The T_g of **PC3** was likely higher than that of **PC5** due to the greater M_n, shorter propylene bridge between aromatic rings, and the adjacent methyl- and ethyl-substituents on the bridging carbons, which can reduce conformational mobility of the bridge. The T_g of **PC5** was identical to the value obtained for the low molecular weight polymer in a previous study (T_g = 51 °C for M_n = 4,300),[77] with the modest value attributed to the flexible butylene bridge between aromatic rings. **PC4** had the highest T_g of the polycarbonates (156 °C), which is due to the rigid fused ring system between aromatic rings. Carvacrol-based **PC6** exhibited a T_g of 107 °C, which is roughly 23 °C lower than **PCBPA** despite having a similar M_n. The aliphatic isopropyl and methyl groups on the aromatic rings of carvacrol are responsible for the lower T_g compared to the BPA analogue, which has been demonstrated previously for a polycarbonate as well as epoxy-amine and cyanate ester thermoset networks.[78, 93]



a)



b)

Figure 5. DSC thermograms of polycarbonates based on a) anethole, eugenol, carvacrol (**PC3** – **PC6**) and b) creosol (**PC7** – **PC9**).

The creosol-based polycarbonates had higher T_gs than **PCBPA. PC7** was semicrystalline and showed cold crystallization peaks at 187 °C (ΔH_{cc} = 23 J/g) and 203 °C (ΔH_{cc} = 35 J/g) for **PC7-10** and **PC7-60**, respectively, with no discernible T_g on the first temperature scan. The crystallinity of **PC7** was also observed in previous work by Chen and confirmed further by XRD.[87] The low and high molecular weight **PC7** samples had T_ms (based on peak endotherms) at 292 °C (ΔH_m = 55 J/g) and 294 °C (ΔH_m = 45 J/g) for **PC7-10** and **PC7-60**, respectively. The lower ΔH_{cc}

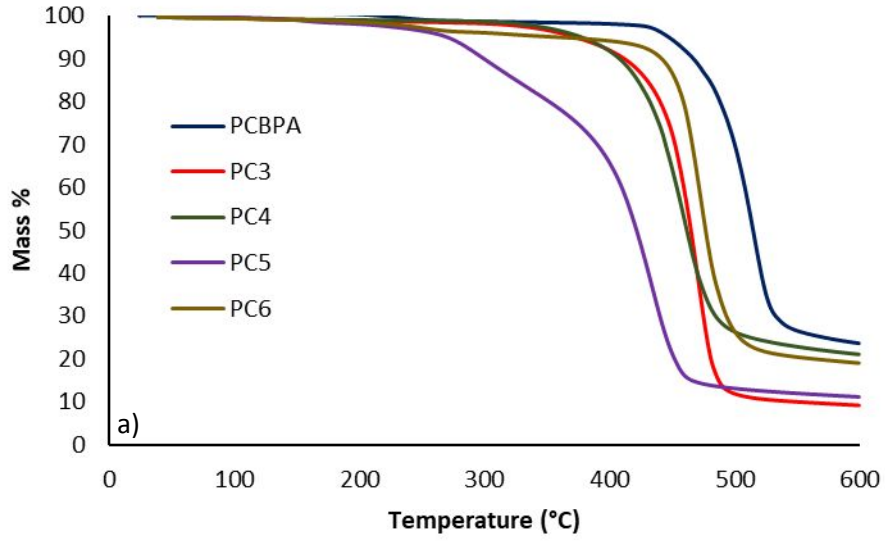
and higher ΔH_m values for **PC7-10** reflects the higher degree of crystallinity in the as-processed sample. On the second temperature scan, **PC7** had T_gs of 134 °C and 137 °C for **PC7-10** and **PC7-60**, respectively. The T_gs were higher for **PC7** than were previously reported (T_g = 122 °C).[87] As was noted in the previous work, the absence of crystallization events during cooling shows that **PC7** does not readily recrystallize after melting.[87] In contrast, **PC8** and **PC9** did not show crystalline behavior upon heating to 300°C. It seems likely that the ethylidene and propylidene bridges on **PC8** and **PC9** prevent the polymer chains from readily packing into crystalline domains. **PC8** and **PC9** had T_gs of 151 °C and 131 °C, respectively. The high T_g of **PC8** was unexpected considering the polycarbonate had a similar molecular weight distribution (MALDI-MS compared to **PCBPA** and **PC7**. In addition, a cyanate ester prepared from **8** exhibited a lower T_g in fully cured cyanurate networks than the corresponding cyanate ester analogue of **7**.[55] Thus, in polycarbonates, the ethylidene bridge of monomer **8** likely increases the rigidity of the polymer due to steric interactions with the adjacent methyl groups on the aromatic rings. Although the propylidene bridge in **9** would be expected to impart the same rigidity, **PC9** likely had a lower T_g than **PC8** because of its lower molecular weight and disruption of interactions between polymer chains by the larger propylidene groups.

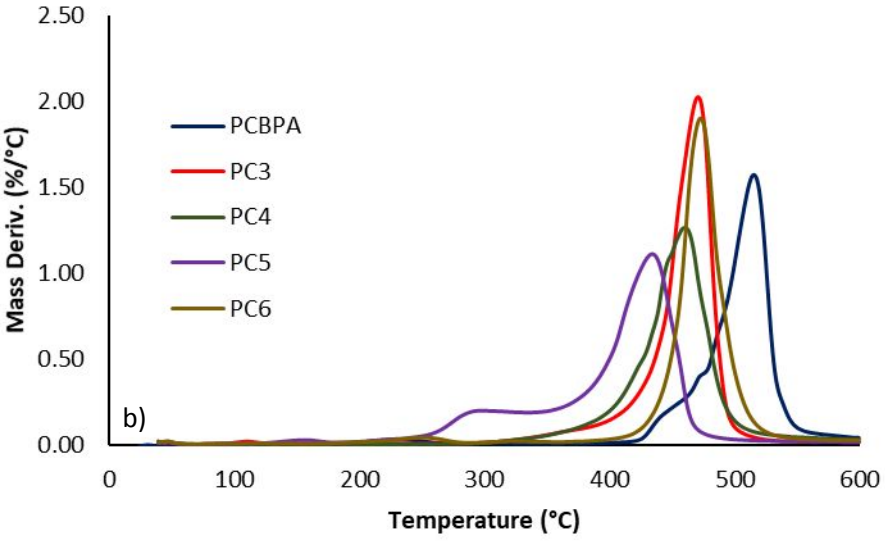
Thermogravimetric Analysis (TGA) of Polycarbonates. The thermal stabilities of the polycarbonates were analyzed using TGA under a nitrogen atmosphere. The results are summarized in **Table 3** and shown in **Figure 6**. In general, the bio-based polycarbonates had lower decomposition temperatures than **PCBPA** based on the temperature at 5% mass loss ($T_{d5\%}$) and the peak of the mass loss derivative curve (T_d^{peak}). **PCBPA-10** had the highest thermal stability with a $T_{d5\%}$ of 446 °C and peak mass loss at 515 °C (**Figure S21**). For **PCBPA-60**, the $T_{d5\%}$ was

Table 3. Decomposition temperatures of PCBPA and the bio-based polycarbonates

Polycarbonate	$T_{d5\%}$, °C (N_2)	T_d^{peak}, °C (N_2)	$T_{d5\%}$, °C (Air)	T_d^{peak}, °C (Air)*
PCBPA-10	446 ± 5	515 ± 3	390 ± 4	492 ± 12
PCBPA-60	412 ± 1	509 ± 1	374 ± 3	497 ± 2
PC3	375 ± 7	471 ± 1	315 ± 9	428 ± 6
PC4	378 ± 4	460 ± 1	374 ± 4	429 ± 9
PC5	269 ± 2	433 ± 2	281 ± 1	381 ± 24
PC6	382 ± 3	473 ± 1	298 ± 20	448 ± 4
PC7-10	358 ± 7	437 ± 3	356 ± 12	424 ± 1
PC7-60	383 ± 5	447 ± 1	405 ± 4	423 ± 13
PC8	365 ± 3	431 ± 7	360 ± 2	427 ± 1
PC9	340 ± 1	428 ± 6	338 ± 7	421 ± 8

*Multiple degradation peaks were observed due to the complex decomposition mechanisms in air. The reported peaks coincide with the maximum degradation peak after 5% weight loss.





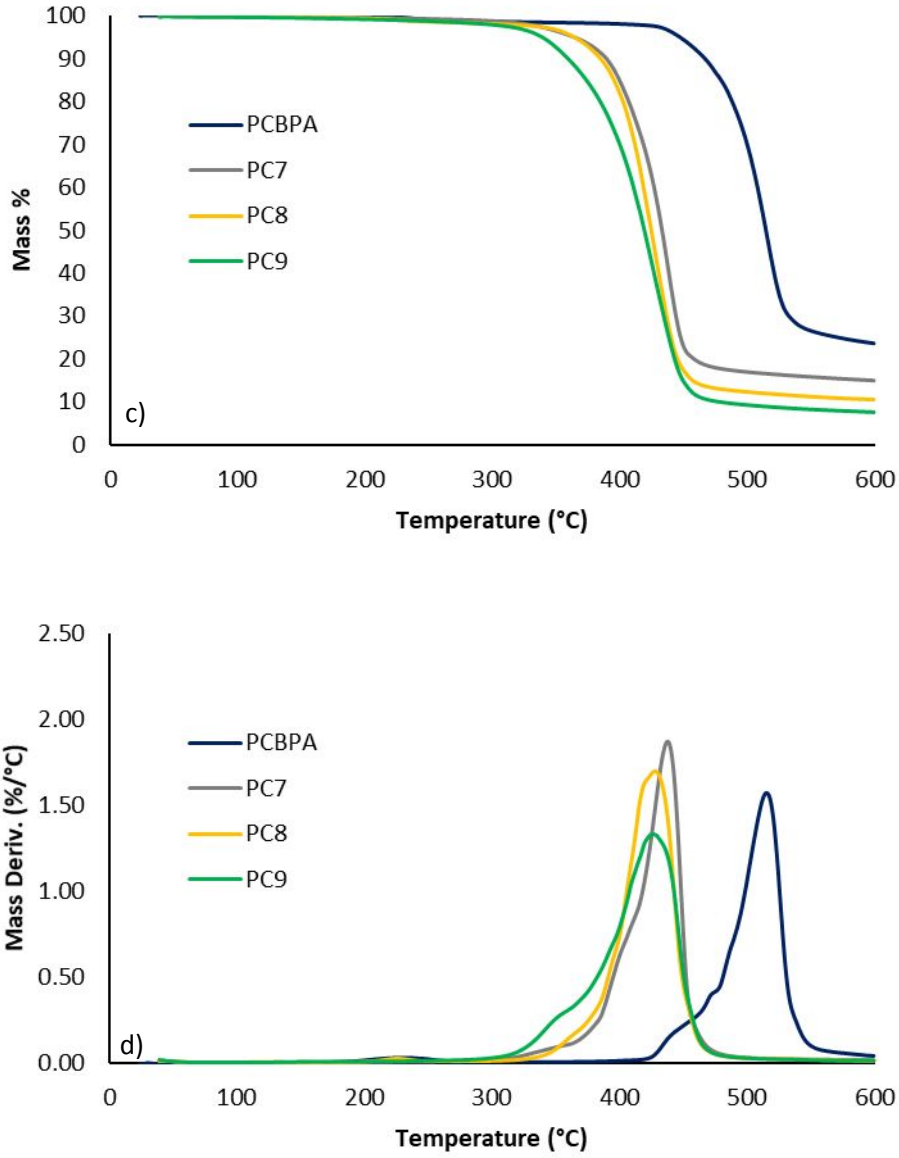


Figure 6. TGA thermograms of the polycarbonates (a, c) and the derivative curves (b, d).

significantly lower at 412 °C, but the T_d^{peak} was similar to **PCBPA-10** with a value of 509 °C. The discrepancy in the $T_{d5\%}$ values for the **PCBPA** samples is likely due to a difference in the amount

of small molecules (i.e. solvent or monomer) trapped in the samples from processing, but the similarity in T_d^{peak} confirms the similar decomposition behavior between samples. ^{1}H NMR analysis showed the presence of traces of residual BPA in the **PCBPA-60** sample, which explains the disparity in the TGA results. **PC6** had modest thermal stability with a $T_{d5\%}$ at 382 °C and T_d^{peak} at 473 °C. The $T_{d5\%}$ of **PC6** measured in a previous study by Harvey et al. was 353 °C for low molecular weight **PC6** (M_n = 5,519) and 421 °C for high molecular weight **PC6** (M_n = 10,200), so the intermediate value obtained in this study is consistent with past results.[78] Despite the relatively high $T_{d5\%}$ and T_d^{peak} values, the carvacrol-based polycarbonate showed a 4% mass loss by 300 °C likely representing partial decomposition of the alkyl substituents attached to the aromatic ring system or potential reactions of end-groups. This low temperature decomposition behavior was observed in previous work on **PC6** as well as for epoxy-amine networks derived from carvacrol and *p*-cymene. The small decrease in mass for the latter was attributed to unreacted functional groups.[78, 93] **PC3** and **PC4** had similar thermal stabilities as **PC6** with $T_{d5\%}$ values of 375 °C and 378 °C, respectively. Although the two anethole-derived polycarbonates had similar decomposition temperatures, **PC4** degrades less completely at temperatures up to 600 °C and had a char yield of 21% in nitrogen compared to **PC3** with a char yield of only 11%. The higher char yield of **PC4** compared to **PC3** demonstrates the greater stability imparted by the fused ring system of **PC4**.

The polycarbonates with methoxy-substituents had much lower thermal stability than their alkyl-substituted counterparts. This result was not surprising considering cyanurate networks derived from bisphenols **7**, **8**, and **9** exhibited lower thermal stability (typically 50 – 80 °C drops in $T_{d5\%}$) compared to the deoxygenated analogues.[94] **PC5** had the lowest thermal stability with a $T_{d5\%}$ at 269 °C, which was lower than the value reported previously for **PC5** with a slightly higher

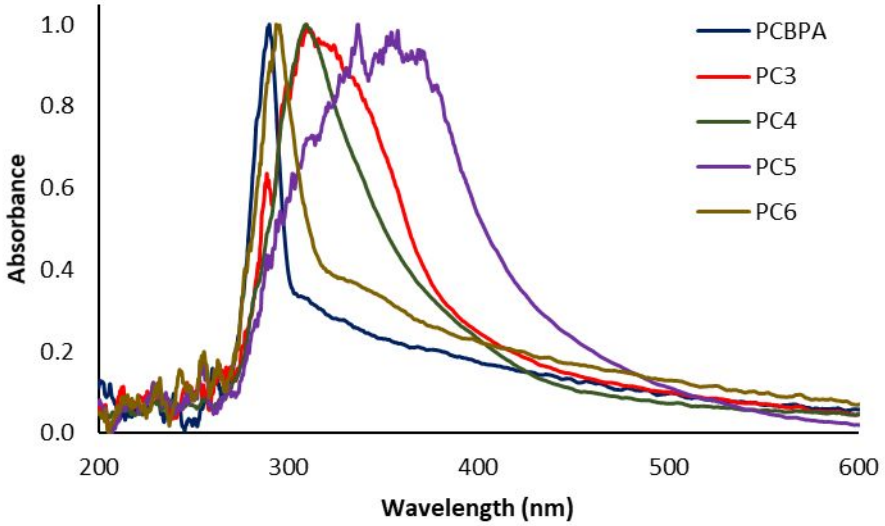
M_n ($T_{d5\%}$ = 310 °C).[77] Thus, the lower thermal stability of **PC5** in this work is likely due to the lower M_n obtained under interfacial polymerization conditions. The creosol-derived polycarbonates had much higher thermal stabilities than **PC5** due to the shorter methylidene, ethylidene, and propylidene bridges between the aromatic rings of **7**, **8**, and **9**, respectively, which result in more rigid polymers. **PC7** had the highest thermal stability of the bio-derived polycarbonates based on $T_{d5\%}$ (383 °C), which was similar to the value reported previously by Chen ($T_d^{5\%}$ = 382 °C).[87] **PC8** and **PC9** had $T_{d5\%}$ values of 365 °C and 340 °C, respectively, with the lower thermal stabilities, compared to **PC7**, attributed to the increasing aliphatic content arising from the bridging ethylidene and propylidene groups.

The thermo-oxidative stability of the polymers was analyzed via TGA in air. These TGA curves can be observed in **Figures S22 – S25**. All the polycarbonates decomposed fully before 600 °C and typically showed multiple derivative mass peaks due to the more complex decomposition mechanism in air compared to nitrogen. However, comparison of $T_{d5\%}$ values in nitrogen and air provided some insight regarding the initial decomposition mechanism of the polymers. For example, the $T_{d5\%}$ for **PCBPA** dropped to 390 °C (56 °C lower) in air compared to nitrogen, which showed that an oxidative step preceded the thermal degradation mechanism. Similar behavior was observed for the bio-based polycarbonates **PC3** and **PC6**, which exhibited $T_{d5\%}$ decreases of 60 °C and 83 °C, respectively. **PC3** and **PC6** each have two tertiary aliphatic carbons per monomer unit that can react with diradical oxygen molecules to form stable radicals and peroxides, which are likely responsible for the dramatically lower decomposition temperature in air for these polycarbonates. Also, both tertiary carbons on **PC6** are attached to aromatic ring systems that can stabilize the radicals through resonance. In contrast, **PC4**, **PC8**, and **PC9** exhibited minor decreases in $T_{d5\%}$ when analyzed in air, with values of 374 °C, 360 °C, and 338

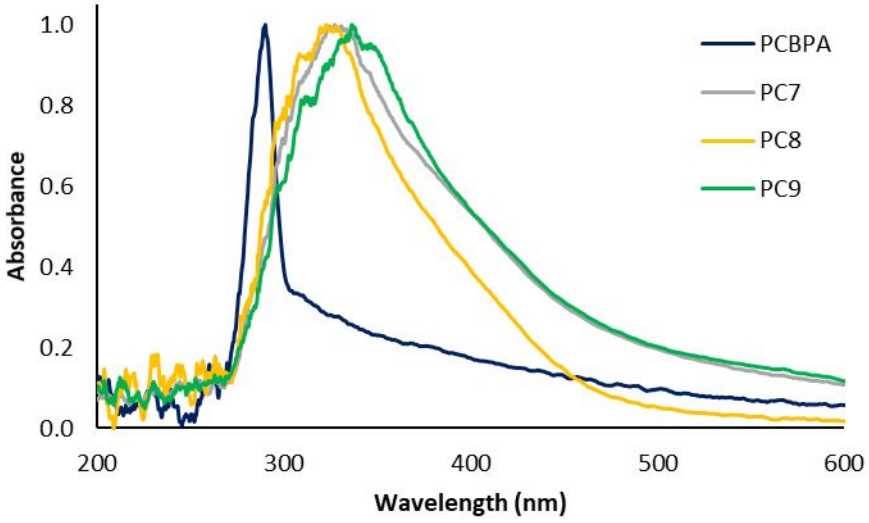
°C, respectively, which represented decreases of only 2 – 5 °C compared to decomposition in nitrogen. The higher thermo-oxidative stability of **PC8** and **PC9** is likely due to each polycarbonate only having one tertiary aliphatic carbon per monomer unit. The relatively high stability of **PC4** is surprising considering each monomer unit contains three tertiary aliphatic carbons with two being attached to aromatic ring systems. The enhanced stability of **PC4** is likely imparted by the fused ring system, which gives the monomer unit less conformational flexibility and could prevent the nearby aromatic groups from effectively stabilizing tertiary radicals. Another potential factor could be that the reaction with oxygen, which increases sample mass, had a comparable or faster rate than polymer decomposition and thus artificially inflated $T_{d5\%}$ to values comparable with nitrogen. This phenomena would explain the decomposition behavior of **PC5** and **PC7**, which had higher $T_d^{5\%}$ values in air than in nitrogen at 281 °C and 405 °C, respectively. To confirm this hypothesis, the samples were analyzed in air at a slower heating rate of 2 °C/min (**Figures S26** and **S27**). Although weight gain due to oxidation reactions was not observed at the slower heating rate, the results for **PC7-60** were similar with a higher $T_{d5\%}$ in air (366 °C) than in nitrogen (338 °C). Oppositely, for **PC5**, the $T_{d5\%}$ in nitrogen (248 °C) was slightly higher than in air (239 °C) when performed at a slower heating rate, which shows the decomposition behavior for **PC5** is heating rate dependent.

UV-VIS Studies of Polycarbonates. Considering commercial polycarbonates degrade when exposed to UV irradiation (especially sunlight),[95 – 97] the UV-VIS absorbance spectra (**Figure 7)** of the polycarbonates were analyzed for comparison with **PCBPA**. Both **PCBPA** and **PC6** showed sharp peaks at 290 and 293 nm, respectively, which reflects the similarity in electronic structure of the two polycarbonates. The absorbance peaks of the anethole-derived polycarbonates shifted to slightly longer wavelengths with peak maxima at 314 nm and 309 nm for **PC3** and **PC4**,

respectively. The peaks in the **PC3** and **PC4** spectra were also broader than the peaks observed in the spectra of **PCBPA** and **PC6**. **PC5**, **PC7**, **PC8**, and **PC9** all showed broader absorbance peaks at longer wavelengths (300-450 nm) compared to **PCBPA**. This effect is attributed to the electron-donating ability of the methoxy-substituents.



a)



b)

Figure 7. UV-VIS Absorbance Spectra of **PCBPA** and the Bio-Based Polycarbonates.

The exact photochemical decomposition mechanism of commercial polycarbonates is still uncertain, but previous studies suggest either a photo-Fries rearrangement (favored at wavelengths

< 300 nm), photo-oxidation (favored at wavelengths > 340 nm), or a combination of the two mechanisms acting simultaneously.[95 - 97] The similarity in absorbance spectra between **PCBPA** and **PC6** suggests that the photo-Fries rearrangement could occur for **PC6** under long-term irradiation at wavelengths < 300 nm. However, the additional aliphatic substituents on the aromatic rings in **PC6** may inhibit photo-Fries rearrangement. The broad absorbances in the methoxy-substituted polycarbonates were at wavelengths conducive to photo-oxidation, which suggests that photo-oxidation could be more favorable in these polycarbonates. Overall, the long-term photochemical decomposition behavior of the bio-based polycarbonates will need to be further explored to determine the suitability of the materials as BPA alternatives.

CONCLUSIONS

The estrogenic effects of a series of bisphenols derived from sustainable substrates including anethole, eugenol, carvacrol, and creosol were quantified through *in vitro* assays. The bisphenols derived from eugenol, carvacrol, and creosol exhibited no estrogenic effects, while the anethole derived bisphenols were less estrogenic than BPA. To evaluate these materials as potential BPA replacements, a series of polycarbonates were synthesized from the sustainable phenolic substrates. The bio-based polycarbonates exhibited T_gs ranging from 51-156 °C. All of the creosol-derived polycarbonates and one of the polycarbonates derived from anethole exhibited higher T_gs compared to BPA polycarbonate (PCBPA) prepared under similar laboratory conditions. TGA experiments in nitrogen and air showed that the thermal stabilities of the bio-based polycarbonates were lower than that obtained for PCBPA. However, considering the upper use temperature in most polycarbonate applications is below the T_g, the reduced thermal stabilities of the bio-based materials should not impact their potential as BPA replacements. UV-Vis studies of the bio-based polycarbonates showed a significant red shift in the absorbance for the more

electron-rich aromatic systems, which may allow these materials to be used in diverse applications (e.g. blue light blocking lenses).

This work has demonstrated that bio-based bisphenols are promising alternatives to BPA, which allow for the synthesis of high-performance materials while potentially reducing long-term health impacts. To build on the results described herein, further work on the green synthesis of high-molecular weight bio-based polycarbonates, and methods to recycle sustainable polycarbonates and related thermoset networks are currently underway in our laboratory. In vivo estrogenic studies of the bisphenols, particularly **5**-**9**, should also be conducted to provide further support for the use of these materials as BPA replacements.

SUPPORTING INFORMATION

Detailed procedures for cell cultures and *in vitro* assays; ^{1}H NMR, ^{13}C NMR, and FTIR spectra for **PC3**, **PC4**, **PC8**, and **PC9;** GPC chromatograms and TGA thermograms (in air) of all polycarbonates.

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