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Polymeric Phthalates: Potential Non-migratory Macromolecular Plasticizers

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(Additional Supporting Information may be found in the online version of this article.)

ABSTRACT

The synthesis of 4-vinyl-1,2-phthalate esters via Suzuki coupling is described, followed by nitroxide-mediated polymerization to prepare short homopolymers (Degree of Polymerization DP = 10-40, Polydispersity Index PDI = 1.1-1.3). Random copolymers with *n*-butyl acrylate were prepared. Copolymers rich in phthalate ester residues of medium lengths (DP = 16-48, PDI = 1.2-1.8), and of shorter lengths (DP = 8-17, PDI = 1.2-1.3) were prepared. Copolymers rich in n-butyl acrylate residues were also prepared (DP = 13-19, PDI = 1.2-1.3). All polymers were oily liquids, with glass transitions temperatures undetected between 75 to -40 °C, indicating these polymeric phthalates hold promise as potential non-migratory phthalate plasticizers.

KEYWORDS (phthalate, plasticizer, radical polymerization, copolymerization, synthesis)

INTRODUCTION

The use of poly(vinyl) chloride (PVC) in consumer goods is widespread, ranging from applications in construction materials, floor coverings, toys, food packaging, medical devices, and blood storage bags. In 2005, phthalates made up 87% of the 10.4 billion pounds/year (5.2 million tons/year) of the world-wide plasticizer market.[1] PVC is inherently an inert, durable material, with good resistance to heat and cold and physical abrasion. However, PVC is brittle, requiring large amounts of plasticizers to impart flexibility[2] and the ability to be processed using molds. The plasticizing effect is postulated to increase the free volume, which a concomitant decrease in the glass transition temperature. The macroscopic effect of the addition of plasticizers is increased flexibility and workability, a reduced melt viscosity and lower elastic modulus.[3] Small phthalate

plasticizers, most commonly di(2-ethylhexyl) phthalate **1** (DEHP, Figure 1, also known as dioctyl phthalate, DOP) are absorbed into PVC to obtain the desired mechanical properties. However, low molecular weight alkyl phthalate esters can leach out of flexible PVC, changing the physical properties with age, and contaminating the environment. Studies on the migration of low molecular plasticizers and their decomposition products into food and biological fluids like saliva or blood and the resulting health risk have raised serious concerns.[4-9] For mammals, rodent studies indicate DEHP is toxic to the liver, kidney and testes,[10] raising significant concerns about safety for use in toys and medical applications. Oral and intravenous introduction of phthalate plasticizers into humans is the most common source of contamination, although the highly hydrophobic sidechains of DEHP allow this plasticizer to transverse the skin. Metabolism of DEHP forms Endocrine Disrupting Chemicals (EDC).[11-13] Although the influence of plasticizers and their metabolism products on human health is not completely understood, toxicological data indicates that phthalates may lead to a variety of medical problems, including endocrine disruption resulting in decreased sperm count, developmental abnormalities, and breast cancer. The use of the phthalate esters DEHP, DBP (dibutyl phthalate) and BBP (butylbenzyl phthalate) in toys and other child care articles was forbidden by the European Union in 2005, and was banned by the Consumer Safety Commission in 2009 in the United States for toys marketed to children younger than 12 years old, and child care articles for children up to age 3. The use of three additional phthalate esters: diisononyl phthalate (DINP), diisodecyl phthalate (DIDP) and di-*n*-octyl phthalate (DnOP) in toys and childcare products are now strongly restricted.[14-15] For the particular application of blood bags, red blood cells have been found to survive for longer time intervals in the presence of DEHP

than without this phthalate ester plasticizer.[16-17] Thus the use of DEHP is both advantageous and deleterious, in enhancing the storage stability of blood samples, while resulting in the leaching of the plasticizer into the contents, which is then introduced intravenously to patients. Plasticizers are widely used in medical devices, food packaging, cosmetics and personal care products, furnishings, garden hoses, construction materials, toys, athletic shoes, and car interiors. Thus there is an ongoing need for effective "general purpose"**Error! Bookmark not defined.** plasticizers that cannot leach out of consumer products, yet still provide the desired plasticizing properties.

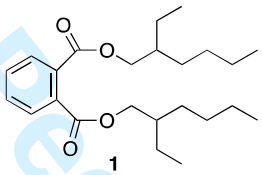


FIGURE 1 DEHP is a widely utilized traditional small molecule plasticizer.

Cross-linking PVC using a diamine has been probed to slow plasticizer migration:[18] a decrease in leaching of phthalate esters was observed, but thermal degradation (most likely due to enhanced elimination of HCl) was also accelerated.[19] Covalent attachment of phthalate esters to PVC is a promising approach: Reinecke has demonstrated S_N2 displacement of chloride from PVC using the very nucleophilic thiol group appended to the benzene ring of DEHP to provide non-leachable phthalate plasticization.[20] Development of this strategy to achieve solvent-free derivatization would be very attractive to industrial applications.

Polymeric plasticizers have been investigated, and do show decreased migratory aptitude[9] in comparison to small molecule phthalate plasticizers. Polymeric plasticizers are

characterized as low, medium or high molecular weight plasticizers, with average molecular weights ranging from 1 000 – 10 000. While the migration resistance improves with increasing molecular weight, the processability decreases. Polyesters, such as poly(ε-caprolactone) (PCL) **2** and poly(butylene adipate) (PBA) **3** (Figure 2), have been investigated as polymeric plasticizers since 1947.[21] In 1977, Hubbel[22] reported that poly(ε-caprolactone) is compatible with PVC in a concentration range of 10% - 90%, and demonstrated efficient plasticizing properties. In considering the miscibility of polyester plasticizers with PVC, molecular dynamics simulations by Lee[23] indicate that a ratio of 3–4 methylene units per ester is a lower limit for miscibility, while the upper limit is 10–12 methylene units per ester. An optimal ratio of 6 methylene units per ester was determined, which was corroborated by experimental data: the melting point depression method gave an optimal length of 7, whereas thermodynamic measurements gave an optimal length of 5, corresponding to PVC/poly(caprolactone) blends. The plasticizing behavior of polycaprolactone-polycarbonate,[24] and commercial elastomers such as poly(ethylene-*co*-vinyl acetate-*co*-carbon monoxide) terpolymers (Elvaloy 741 and Elvaloy 742 developed by DuPont),[25-26] poly(1,3-butylene adipate) (Reoplex® developed by Ciba-Geigy)[27] and poly(1,2-propylene glycol adipate) with nano-$CaCO_3$[28] have been investigated. These polymeric plasticizers are miscible with PVC, and display reduced migration in comparison to low molecular plasticizers, while their plasticizing effects are useful for specific applications.[29] The influence of molecular weight and branching of poly(butylene adipate)s on the plasticizer efficiency and migration aptitude was recently studied by Hakkarainen.[30-33] A diblock copolymer made of PEG and polycaprolactone has been developed for manufacturing flexible biomedical supplies.[34] The major disadvantage

of these polyester plasticizers is their susceptibility towards hydrolysis, which changes their physical properties with aging and exposure to moisture.

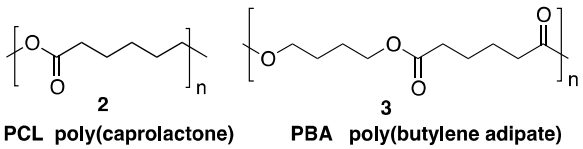


FIGURE 2 Hydrolyzable polyester plasticizers PCL **2** and PBA **3**.

Terpolymers prepared by uncontrolled, AIBN-initiated radical polymerization with various ratios of maleic anhydride, styrene and vinyl acetate (and derivatives obtained by opening the anhydride with alcohols) have been investigated as polymeric plasticizers.[35-36] The plasticizing results were not optimal: blending with additional additives has been investigated.[37] A terpolymer plasticizer made of ethylene, vinyl acetate and carbon monoxide, named "EVACO" has been developed for food products.[25]

The inherent degradability of polyesters, leading to lower molecular weight hydrolysis products, makes polyester plasticizers of limited utility. Thus a non-hydrolyzable polymeric plasticizer with widespread applicability is desirable. Phthalate esters are benzene rings bearing *ortho* alkyl ester substitution. As polystryene consists of a robust hydrocarbon chain bearing pendant benzene rings on every other carbon, the concept of polymeric phthalates, in which the benzene groups of polystryene bear *ortho* alkyl ester substituents suggested the development of polymeric phthalates. Thus 4-vinyl phthalate esters **4** (VPE, Figure 3) were envisioned as monomers to prepare polymeric phthalates, which would be expected to show decreased migratory aptitude out of PVC, while hopefully imparting plasticization to the bulk material.

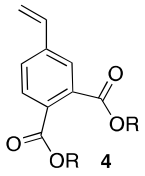
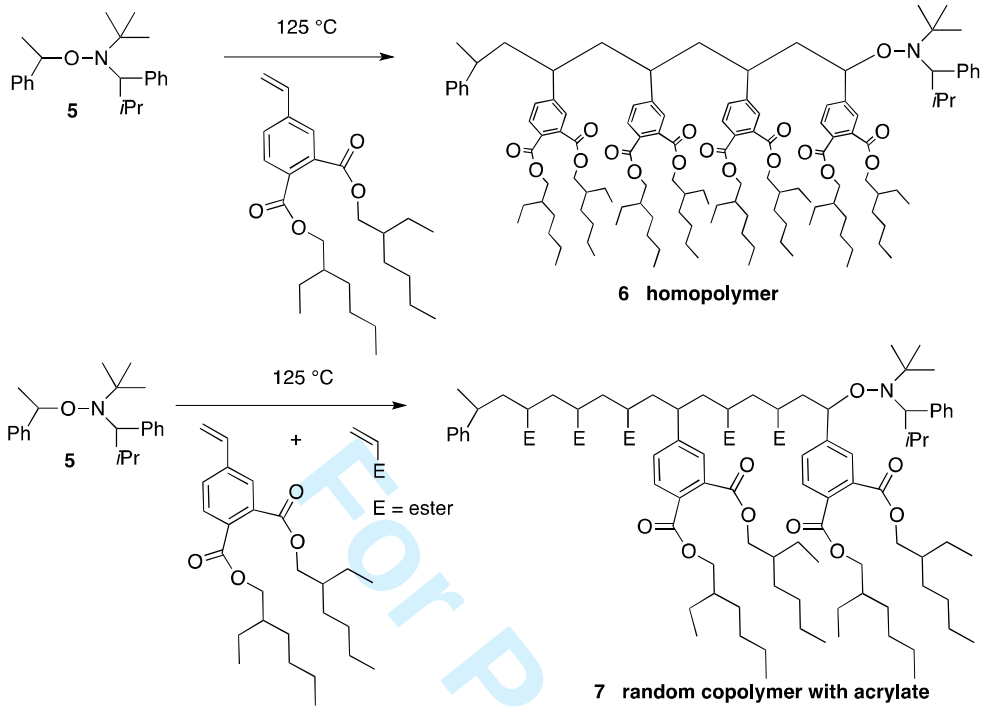


FIGURE 3 A 4-vinyl phthalate ester (VPE), a monomer to prepare poly(vinyl phthalates).

The alkyl group of the phthalate esters can be easily manipulated to mimic various phthalate esters used in PVC plasticization. Since moderate molecular weight polyester plasticizers have been found to be optimal, the use of nitroxide-mediated radical polymerization[38-39] (NMRP) was chosen to control the approximate size of the polymeric phthalates. Use of the alkoxyamine initiator **5** based on TIPNO[38] enables the facile preparation of either homopolymers **6**, or random copolymers **7** between 4-vinyl phthalate esters and acrylates, to "dilute" the phthalate ester density in these polymeric phthalates (Scheme 1). As opposed to the current polyester plasticizers, these poly(vinylphthalates) are linked together by an all-carbon polymer backbone: hydrolysis will release only alcohols, rather than phthalates. Thus degradation products should pose no danger of being metabolized to form Endocrine Disruptor Chemicals.



SCHEME 1 Homo and random copolymers of vinyl phthalate esters.

EXPERIMENTAL

Materials

Phthalic anhydride, bromine, ethanol, *iso*propanol, *iso*butanol, 3,3,5-trimethyl-1-hexanol, 2-ethyl-1-hexanol, palladium(II)acetate, thionylchloride, triphenyl phosphine, trimethyl borate, vinylmagnesium bromide and calcium carbonate were used as received. *n*-Butyl acrylate (NBA) (99+%, Acros Organics) was distilled under vacuum before use. Water was deionized.

Characterization

NMR spectra were recorded at ambient temperature on a Varian 500 MHz spectrometer, in $CDCl_3$ as solvent, unless otherwise noted. Gel permeation chromatography (GPC) was performed using a Waters apparatus equipped with two PLgel 5 µm MIXED-D columns (Agilent) and a guard column (Agilent). Tetrahydrofuran (THF) was used as the eluent at a flow rate of 0.35 mL/min at ambient temperature. A refractive index detector was used and the molecular weights

were calibrated against eight linear polystyrene standards ranging from 370 to 371100 (M_n [*g/mol*]). IR spectra were recorded neat on a Perkin-Elmer spectrometer. Each sample was prepared by casting a film on a KBr cell. Glass transition temperatures were measured using a Mettler Toledo DSC822e differential scanning calorimeter.

Preparation of 4-bromo-phthalic acid monosodium salt 8.

Following the general procedure of Sabourin,[40] sodium hydroxide (27.03 g, 675.9 mmol) was dissolved in 224 mL of deionized H_2O; phthalic anhydride (50.00 g, 337.6 mmol) was added and stirred until all solids had dissolved. Ice-cooled bromine (18.2 mL, 356 mmol) was added dropwise while stirring. The reaction mixture was heated at 90 °C for 7 h. After cooling, the mixture was allowed to sit at room temperature overnight: the resulting precipitate was isolated by filtration and recrystallized[41] twice from hot water. The resulting solid was dissolved in hot water, and the solution was adjusted to approximately pH = 1.5 by addition of concentrated hydrochloric acid, cooled to room temperature, and extracted with ethyl acetate, dried over $MgSO_4$, and the solvent removed *in vacuo* to give 20.2 g (22% yield) of the monosodium salt of 4-vinyl phthalic acid as a solid.

mp > 260 °C.

^{1}H NMR (500 MHz, DMSO-d_6, δ): 8.06 (br s, 1H), 7.88 (br s, 1H), 7.74 (*m*, 1H).

Preparation of 4-bromo-phthalic diacid.[42]

In order to characterize the above material, a sample of the monosodium salt **8** was dissolved in hot water, and a large excess of concentrated HCl was added. The volatiles were reduced *in vacuo*, and the residue extracted with acetone. Removal of the acetone *in vacuo* provided the diacid.

mp 175 °C (lit.[43] mp 176-178 °C).

^{1}H NMR (500 MHz, acetone-d_6, δ): 11.6 (br s, 2H), 7.91 (*d*, *J* = 2.0 Hz, 1H), 7.84 (*dd*, *J* = 2.0, 8.0 Hz, 1H), 7.76 (*d*, *J* = 8.0 Hz, 1H).

Esterification to form 4-bromo-dialkyl-phthalate esters (Et, *i*Pr, *i*Bu and 2-ethyl-1-hexyl): The following procedure is representative.

Preparation of 4-bromo-diethyl-phthalate ester[44] 9a.

Following the general procedure of Hosangadi[45] and modified from that of Norman,[41] thionyl chloride (7.3 mL, 101 mmol) was added dropwise to a suspension of 4-bromo-phthalic acid monosodium salt (6.00 g, 22.5 mmol) in 47 mL of ethanol while cooling the flask in an ice bath. The reaction mixture was heated to reflux (85 °C) for two hours. Upon cooling, volatiles were evaporated, 90 ml of H_2O were added, and the reaction mixture was extracted three times with ethyl acetate. The combined organic phase was washed with aqueous $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil was purified by silica gel column chromatography with 20:1 hexanes/ethyl acetate, to give 4.82 g (86% yield) of a the title compound as a slightly yellow oil.

TLC: 10:1 hexanes/ethyl acetate, UV, R_f : 0.72.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.84 (*d*, *J* = 1.5 Hz, 1H), 7.69–7.62 (*m*, 2H), 4.40–4.35 (*m*, 4H), 1.40–1.36 (*m*, 6H).

4-bromo-di(*iso*propyl)-phthalate ester 9b. 7.10 g (96% yield) of the product as a slightly yellow oil.

TLC: 5:1 hexanes/ethyl acetate, UV, R_f: 0.42.

IR (neat): 2982, 2937, 2878, 1736, 1589, 1566, 1467, 1375, 1291, 1135, 1108, 918, 845, 829, 768 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.92 (*d*, *J* = 1.5 Hz, 1H), 7.65 – 7.58 (*m*, 2H), 5.28 – 5.21 (*m*, 2H), 1.38 – 1.36 (*m*, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.2, 166.0, 134.9, 133.8, 131.8, 131.2, 130.6, 125.4, 69.8, 69.6, 21.8.

DEPT (125 MHz, $CDCl_3$, δ): 134 (CH), 132 (CH), 130 (CH), 70 (CH), 22 (CH_3).

4-bromo-*di*(*iso*butyl)-phthalate[46] **9c.** 3.30 g (84% yield) of the product as a slightly yellow oil.

TLC: 20:1 hexanes/ethyl acetate, UV, R_f: 0.67.

IR (neat): 2962, 1729, 1589, 1566, 1470, 1367, 1287, 1126, 1089, 1069, 981, 946, 840, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.829 (*d*, 1H, *J* = 2), 7.682 – 7.624 (*m*, 2H), 4.105 – 4.078 (*m*, 4H), 2.09 – 1.998 (*m*, 4H), 1.003 – 0.982 (*m*, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.83, 166.63, 134.6, 133.9, 131.9, 130.9, 130.68, 125.7, 72.26, 72.07, 27.74, 19.17.

DEPT (125 MHz, $CDCl_3$, δ): 134 (CH), 132 (CH), 130 (CH), 72 (CH_2) 28 (CH), 19 (CH_3).

4-bromo-di(2-ethyl-1-hexyl)-phthalate ester[47] **9d.** 12.3 g (79% yield) of the product as a slightly yellow oil.

TLC: 40:1 hexanes/ethyl acetate, UV, R_f: 0.74.

IR (neat): 2960, 2861, 1732, 1589, 1566, 1463, 1381, 1288, 1125, 1089, 1068, 957, 766 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.81 (*d*, *J* = 2 Hz, 1H), 7.68 – 7.60 (*m*, 2H), 4.27 – 4.18 (*m*, 4H), 1.74 – 1.65 (*m*, 2H), 1.44 – 1.31 (*m*, 16H), 0.95 – 0.89 (*m*, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.9, 166.7, 134.7, 134.0, 131.9, 130.9, 130.6, 125.7, 68.7, 68.4, 38.8, 30.4, 29.0, 23.7, 23.0, 14.1, 11.0.

DEPT (125 MHz, $CDCl_3$, δ): 134 (CH), 132 (CH), 130 (CH), 68 (CH_2) 39 (CH), 30,5 (CH_2), 29 (CH_2), 23.9 (CH_2), 23 (CH_2), 14 (CH_3), 11 (CH_3).

4-bromo-di(3,5,5-trimethyl-1-hexyl)-phthalate ester 9e.

4-Bromo-phthalic acid monosodium salt (2:1 mixture with phthalic acid monosodium salt, 12.0 g, 33 mmol) was dissolved in 3,5,5-trimethyl-1-hexanol (77 mL, 147 mmol). The reaction mixture was heated to 175 °C for 5 hours. The residual 3,5,5-trimethyl-1-hexanol was removed by distillation with heating up to 160 °C under mild vacuum, and the resulting oil was purified by silica gel column chromatography with 98:2 hexanes/ethyl acetate as the eluent, followed by a second flash column using 40:1 hexanes/ethyl acetate as the eluent, to give 14.8 g (90% yield) of the product as a slightly yellow oil, free from contamination from the non-brominated material.

TLC: 10:1 hexanes/ethyl acetate, UV, R_f: 0.51.

IR (neat): 2956, 1732, 1589, 1567, 1469, 1393, 1365, 1288, 1129, 1089, 1070, 960, 840, 767 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.82 (*d*, *J* = 1.5 Hz, 1H), 7.68 – 7.60 (*m*, 2H), 4.36 – 4.43 (*m*, 4H), 1.79 – 1.70 (*m*, 2H), 1.70 – 1.63 (*m*, 2H), 1.62 – 1.54 (*m*, 2H), 1.30 – 1.25 (*m*, 2H), 1.15 – 1.10 (*m*, 2H), 1.00 – 0.09 (*dd*; *J* = 3 Hz, *J* = 3.5 Hz, 6H), 0.91 – 0.90 (*m*, 18 H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 166.8, 166.6, 134.6, 134.0, 131.9, 130.8, 130.6, 125.7, 64.8, 64.6, 51.1, 37.7, 31.2, 30.0, 27.3, 26.4, 22.6.

DEPT (125 MHz, $CDCl_3$, δ): 134 (CH), 132 (CH), 130 (CH), 65 (CH_2), 51 (CH_2), 38 (CH_2), 30 (CH_3), 26 (CH), 23 (CH_3) .

Suzuki vinylation of 4-bromo-dialkyl phthalate esters: the following procedure is representative.

Preparation of 4-vinyl-diethyl-phthalate ester 10a.

Following the procedure of Grosjean,[48] vinylboronic acid was prepared *in situ*: vinylmagnesium bromide (36 mL, 0.7 M solution in THF, 25.2 mmol) was added to trimethylborate (2.84 mL, 25.2 mmol) in anhydrous toluene (88 mL) at -78 °C under a nitrogen atmosphere. The mixture was allowed to warm to room temperature, and 4-bromo-diethyl-phthalate (2.53 g, 8.40 mmol), K_2CO_3 (2.32 g, 16.8 mmol) and H_2O (22 mL) were added. The resulting suspension was degassed by bubbling the solution with N_2 for 30 minutes. Catalytic palladium(II) acetate (38 mg, 0.17 mmol, 2 mole %) and triphenylphosphine (110 mg, 0.42 mmol, 5 mole %) were added. The reaction mixture was heated at 85 °C for 12 h, and then the temperature was increased to 90 °C for 18 h. Upon cooling, the organic and aqueous phase were separated, and the organic phase was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resulting oil is purified by silica gel column chromatography with 3:1 hexanes/ethyl acetate and by silica gel column chromatography with 4:1 hexanes/ethyl acetate, to give 1.01 g (49% yield) of the title vinyl phthalate ester as a slightly yellow oil.

TLC: 5:1 hexanes/ethyl acetate, UV, R_f: 0.53.

IR (neat): 2984, 1732, 1605, 1446, 1390, 1367, 1287, 1197, 1130, 1070, 1020, 921, 849, 789 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.74 – 7.69 (m, 2H), 7.54 – 7.28 (*m*, 1H), 6.76 – 6.71 (*dd*, 1H, *J* = 11 Hz, *J* = 6.5 Hz), 5.89 – 5.85 (*d*, 1H, *J* = 17.5 Hz), 5.42 – 5.39 (*d*, 1H, *J* = 11 Hz), 4.40 – 4.33 (*m*, 4H), 1.39 – 1.35 (*m*, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 168.0, 167.0, 140.7, 135.3, 134.0, 133.5, 131.9, 131.1, 130.6, 129.7, 129, 128.35, 126.5, 117.5, 61.6, 61.8, 14.15.

DEPT (125 MHz, $CDCl_3$, δ): 136 (CH), 130 (CH), 128 (CH), 126,5 (CH) 117,5 (CH_2), 62 (CH_2), 14 (CH_3).

4-vinyl-di(*iso*propyl)-phthalate ester 10b. 0.901 g (78% yield) as a slightly yellow oil.

TLC: 5:1 hexanes/ethyl acetate, UV, R_f: 0.72

IR (neat): 2982, 1723, 1605, 1468, 1374, 1351, 1288, 1199, 1135, 1108, 1068, 989, 918, 849 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.71 – 7.65 (*m*, 2H), 7.52 – 7.50 (*m*, 1H), 6.77 – 6.71 (*dd*, *J* = 11 Hz, *J* = 6.5 Hz, 1H), 5.88 – 5.85 (*d*, *J* = 17.5 Hz, 1H), 5.42 – 5.40 (*d*, *J* = 11 Hz, 1H), 5.30 – 5.21 (*m*, 2H), 1.39 – 1.36 (*m*, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 167.5, 166.7, 140.5, 135.4, 133.9, 131.1, 130.9, 129.6, 128.9, 128.1, 126.4, 117.1, 69.4, 69.2, 21.8.

DEPT (125 MHz, $CDCl_3$, δ): 135.5 (CH), 129.8 (CH), 128 (CH), 126 (CH) 117 (CH_2), 69 (CH), 22 (CH_3).

4-vinyl-di(*iso*-butyl)-phthalate ester 10c. 2.00 g (78% yield) as a slightly yellow oil.

TLC: 20:1 hexanes/ethyl acetate, UV, R_f: 0.82

IR (neat): 2963, 1726, 1605, 1471, 1377, 1285, 1196, 1127, 1070, 986, 919, 851, 783 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.75 – 7.69 (*m*, 2H), 7.55 – 7.53 (m, 1H), 6.78 – 6.72 (*dd*, *J* = 11 Hz, *J* = 6.5 Hz, 1H), 5.90 – 5.86 (*d*, *J* = 18 Hz, 1H), 5.43 – 5.41 (*d*, *J* = 11 Hz, 1H), 4.11 – 4.08 (*m*, 4H), 2.07 – 2.03 (*m*, 2H), 1.00 – 0.99 (*m*, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 168.2, 167.3, 140.7, 135.3, 133.6, 130.8, 129.6, 129, 128.3, 126.5, 117.2, 72, 71.8, 27.80, 27.75, 19.2.

DEPT (125 MHz, $CDCl_3$, δ): 135.5 (CH), 130 (CH), 128.1 (CH), 126.5 (CH), 137.3 (CH_2), 72 (CH_2), 28 (CH), 19.3 (CH_3).

4-vinyl-di(2-ethyl-1-hexyl)-phthalate ester 10d. 1.78 g (26% yield) as a yellow oil.

TLC: 20:1 hexanes/ethyl acetate, UV, R_f : 0.4

IR (neat): 2960, 2931, 2874, 2861, 1732, 1605, 1464, 1381, 1283, 1195, 1127, 1070, 987, 961, 915, 851, 791, 772 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.73 – 7.68 (*m*, 2H), 7.55 – 7.53 (*m*, 1H), 6.78 – 6.72 (*dd*, *J* = 11 Hz, *J* = 6.5 Hz, 1H), 5.89 – 5.86 (*d*, *J* = 17.5 Hz, 1H), 5.43 – 5.41 (*d*, *J* = 10.5 Hz, 1H), 4.27 – 4.18 (*m*, 4H), 1.70 – 1.70 (*m*, 2H), 1.45 – 1.32 (*m*, 16H), 0.95 – 0.90 (*m*, 12H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 168.3, 167.3, 140.6, 135.4, 133.7, 131.0, 130.8, 129.6, 128.9, 128.2, 126.5, 117.2, 68.4, 68.2, 38.8, 30.4, 29.0, 23.8, 23.0, 14.1, 11.0.

DEPT (125 MHz, $CDCl_3$, δ): 135.4 (CH), 129.6 (CH), 128.2 (CH), 126.5 (CH), 117.2 (CH_2), 68.4 (CH_2), 68.2 (CH_2), 38.8 (CH), 30.4 (CH_2), 29.0 (CH_2), 23.8 (CH_2), 23.0 (CH_2), 14.1 (CH_3) 11.0 (CH_3).

4-vinyl-di(3,5,5-trimethyl-1-hexyl)-phthalate ester 10e. 1.37 g (49% yield) as a yellow oil.

TLC: 20:1 hexanes/ethyl acetate, UV, R_f: 0.71.

IR (neat): 2956, 2869, 1728, 1605, 1469, 1365, 1286, 1195, 1129, 1071, 987, 963, 915, 851, 790 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.73 – 7.69 (*m*, 2H), 7.54 – 7.52 (*m*, 1H), 6.77 – 6.71 (*dd*, *J* = 11 Hz, *J* = 6.5 Hz, 1H), 5.89 – 5.86 (*d*, *J* = 17.5 Hz, 1H), 5.43 – 5.41 (*d*, *J* = 11 Hz, 1H), 4.37 – 4.28 (*m*, 4H), 1.80 – 1.72 (*m*, 2H), 1.72 – 1.64 (m, 2H), 1.63 – 1.55 (*m*, 2H), 1.31 – 1.26 (*m*, 2H), 1.15 – 1.11 (*m*, 2H), 1.01 – 0.99 (*dd*, *J* = 2.5 Hz, *J* = 4.0 Hz, 6H), 0.92 – 0.91 (*m*, 18H).

^{13}C NMR (125 MHz, $CDCl_3$, δ): 168.2, 167.3, 140.6, 135.3, 133.5, 131, 130.7, 129.6, 128.3, 126.5, 117.2, 64.5, 64.3, 51.1, 37.8, 31.2, 30.4, 30, 29, 27.3, 26.4, 22.7.

DEPT (125 MHz, $CDCl_3$, δ): 135.3 (CH), 129.6 (CH), 128.3 (CH), 126.5 (CH), 117.2 (CH_2), 64.5 (CH_2), 51.1 (CH_2), 38 (CH_2), 30 (CH_3), 26.4 (CH), 22.7 (CH_3).

Homopolymerization of *4*-vinyl-*di*-alkyl-phthalate esters 10a-10d.

The following procedure using the di-*iso*butyl vinyl phthalate is representative of the general procedure: a mixture of *2,2,5*-trimethyl-*3*-phenyl-ethoxy-*4*-phenyl-*3*-azahexane **5** (12.7 mg, 0.039 mmol), *4*-vinyl-*di-iso*butyl-phthalate **10c** (347 mg, 1.14 mmol) was degassed in an ampoule by three consecutive freeze-pump-thaw cycles, and sealed under nitrogen. The ampoule was immersed in an oil bath at 125 °C for 19 hours, then cooled to room temperature.

A crude ^{1}H NMR spectrum was taken to provide data to allow calculation of % $yield_{NMR}$ and molecular weight (Mn_{NMR}, *g/mol*). For samples containing residual unpolymerized *4*-vinyl-*di*-alkyl-phthalate ester, the copolymer was transferred using a minimum amount of dichloromethane to a

Thermo Scientific SnakeSkin Dialysis Tubing (3.5 K MWCO) and dialysed for 24 hours using ethanol as solvent. The homopolymer was concentrated *in vacuo* and the sample weighed to determine the gravimetric yield ($yield_{gr}$); a molecular weight (Mn_{gr}, [*g/mol*]) was calculated. Analysis by GPC using THF as the eluent (calibrated against eight polystyrene samples) gave a third value of molecular weight (Mn_{GPC}).

Copolymerization of *4*-vinyl-*di*-alkyl-phthalate esters 10a – 10e with *n*-butyl acrylate.

The following procedure is representative of the general procedure: a mixture of *2,2,5*-trimethyl-*4*-phenyl-*3*-azahexane-*3*-nitroxide (0.2 mg, 0.0009 mmol, 2.3% with respect to the alkoxyamine initiator), *2,2,5*-trimethyl-*3*-phenyl-ethoxy-*4*-phenyl-*3*-azahexane **5** (12.7 mg, 0.039 mmol), *4*-vinyl-*di*-ethyl-phthalate **10a** (270 mg, 1.09 mmol), and *n*-butyl acrylate (125 mg, 0.974 mmol) was degassed in an ampoule by three consecutive freeze-pump-thaw cycles, and sealed under nitrogen. The ampoule was immersed in an oil bath at 125 °C for 19 hours, then cooled to room temperature.

A crude ^{1}H NMR spectrum was taken to provide data to allow calculation of % $yield_{NMR}$, and the ratio of vinyl phthalate ester vs. *n*-butyl acrylate incorporated into the polymer, from which a molecular weight (Mn_{NMR}, *g/mol*) was calculated (see Tables 3-5). For samples containing only unpolymerized *n*-butyl acrylate as the remaining monomer, the copolymer sample was transferred to a flask using dichloromethane and all volatiles (including *n*-butyl acrylate) were removed *in vacuo*. For samples containing residual unpolymerized *4*-vinyl-*di*-alkyl-phthalate esters, the copolymer was transferred using a minimum amount of dichloromethane to a Thermo Scientific SnakeSkin Dialysis Tubing (3.5 K MWCO) and dialysed for 24 hours using ethanol as solvent. The copolymer was concentrated *in vacuo* and the sample weighed to determine the gravimetric yield ($yield_{gr}$); a molecular weight (Mn_{gr}, [*g/mol*]) was

calculated. Analysis by GPC using THF as the eluent (calibrated against eight polystyrene samples) gave a third value of molecular weight (Mn_{GPC}).

Three different series of copolymerizations were carried out:

Series 1: with respect to 1.0 equivalent of alkoxyamine initiator: 2.5 mol% free nitroxide, 25 equivalents of acrylate, 29.4 equivalents of vinyl phthalate monomer

Series 2: with respect to 1.0 equivalent of alkoxyamine initiator: 1 mol% free nitroxide, 10 equivalents of acrylate, 11.7 equivalents of vinyl phthalate monomer (2.5 times more initiator than in series 1)

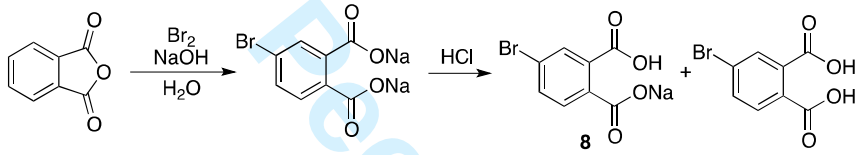
Series 3: with respect to 1.0 equivalent of alkoxyamine initiator: 1 mol% free nitroxide, 20 equivalents of acrylate, 1.7 equivalents of vinyl phthalate monomer (similar to series 2, but a large excess of acrylate monomer: ratio of acrylate : vinyl phthalate monomer approximately 12:1)

Results and Discussion

Synthesis of 4-vinyl phthalate esters

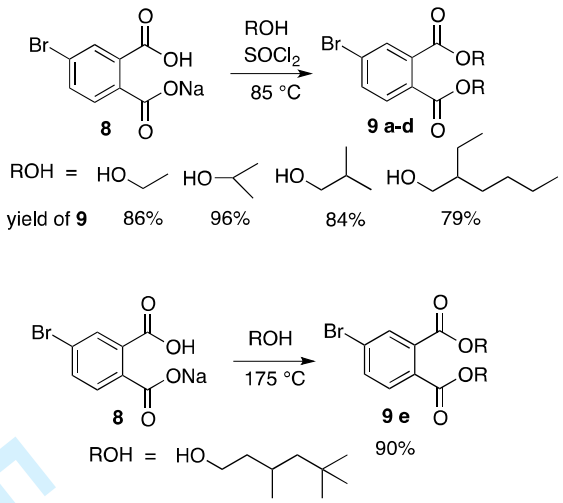
The only literature method for the preparation of 4-vinylphthalic acid derivatives is the 1994 work of Stadler[49] (preparing 4-vinyl phthalic anhydride), utilizing a Heck reaction in an autoclave with 40 bars of ethylene gas. The German patent literature describes the formation of copolymers of 4-vinylphthalic acid, 4-vinylphthalic anhydride, and 4-vinylphthalic esters with styrene using uncontrolled AIBN-initiated radical polymerization, with the aim of making heat resistant polystyrenes[50] and polymer blends with enhanced impact strength.[51]

Our synthesis of 4-vinyl phthalate esters started with the large-scale electrophilic bromination of phthalic anhydride[40-41] (Scheme 2), which resulted in mixtures of the dicarboxylic acid, the monosodium salt, or the disodium salt, depending on the work-up. Acidification with concentrated HCl to approximately pH = 1.5 (as judged by pH paper) and extraction with ethyl acetate gave the monosodium salt **8**. If acidification was carried out with a large excess of concentrated HCl, followed by removal of volatiles *in vacuo*, extraction with acetone delivered the diacid.[52] Attempts to accomplish 4-bromination using sodium bromate and sulfuric acid as an alternative route were unsuccessful.



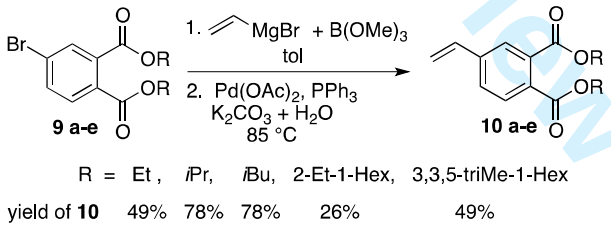
SCHEME 2 Bromination of phthalic anhydride.

Esterification (Scheme 3) was carried out with five different alcohols: ethanol, *iso*propanol, *iso*butanol, 3,5,5-trimethyl-1-hexanol, and 2-ethyl-1-hexanol, with the later forming a direct analogue of the branched alkyl phthalate plasticizer DEHP. In all cases except for 3,5,5-trimethyl-1-hexanol, an excess of thionyl chloride was added to an alcoholic solution of 4-bromo-phthalic acid monosodium salt following the method of Hosangadi.**Error! Bookmark not defined.** Use of thionyl chloride with 3,5,5-trimethyl-1-hexanol led to the formation of a side-product, thus esterification with this alcohol was carried out at 175 °C without thionyl chloride.



SCHEME 3 Esterification of 4-bromo phthalic acid monosodium salt.

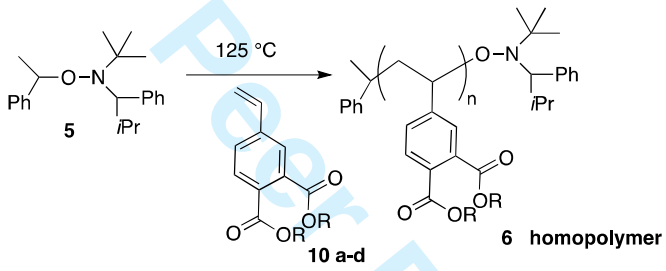
With five different 4-bromo phthalate esters in hand, the vinyl group was introduced in a straightforward manner employing a Suzuki coupling reaction. Vinylboronic acid is prone to polymerization, thus an *in situ* generation of vinylboronic acid from vinyl Grignard and trimethylborate developed by Grosjean[48] was adopted, resulting in low to good yields of the desired 4-vinyl phthalate esters **10 a-e** (VPE) (Scheme 4).



SCHEME 4 Suzuki vinylation of 4-bromo phthalic esters.

Polymerizations. Conversion of the 4-vinyl phthalate esters into short polymers was then pursued. Short homopolymers were prepared by nitroxide-mediated radical polymerization (Scheme 5, Table 1), forming polymers with an estimated Degree of

Polymerization ranging from 10-40 monomers, with excellent control of polydispersities (Table 2). As expected, use of larger ratios of vinyl phthalate monomer compared to alkoxyamine initiator resulted in longer polymers given the same polymerization time (19 h). Unreacted vinyl phthalate ester monomer was removed by dialysis: the isolated polymers were all viscous liquids. In order to calculate a rough Degree of Polymerization (DP), the average of the gravimetric and GPC Mn values was taken, as the NMR derived yields and Mn_{NMR} values were less reliable. It should be noted that the Mn_{GPC} values cannot be considered highly accurate, as polystryene samples are utilized to calibrate the GPC.

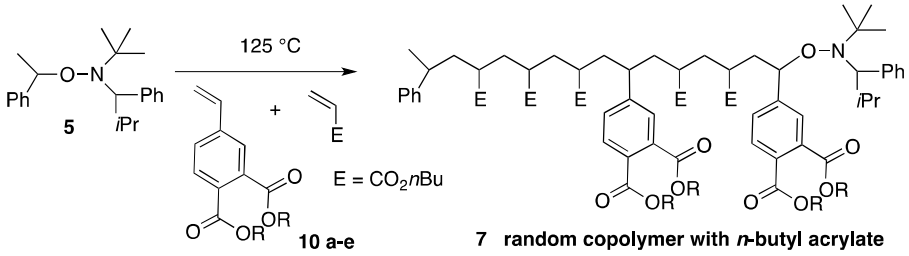


SCHEME 5 Polymerization of 4-vinyl phthalate esters.

Insert TABLE 1 Here

Potential plasticizers must be miscible with PVC. One of the advantages of using NMRP is that a variety of random copolymers can be produced, in which the density of the phthalate residues can be easily varied. *n*-Butyl acrylate was chosen as the comonomer, as earlier studies involving *in situ* polymerization of *n*-butyl acrylate in PVC[53] and of vinyl chloride in poly(n-butyl acrylate)[54] indicate that these should form homogenous mixtures. Thus three different series (Table 2) of copolymerizations of 4-vinyl-phthalate esters with NBA (Scheme 6) were carried out: the first used a close to 1:1 ratio of the two monomers, the second used 2.5 times more alkoxyamine initiator than the first (to provide shorter

polymers), and the third utilized ten times more NBA, with the aim of preparing copolymers rich in NBA residues, with a small amount of VPE incorporated.



SCHEME 6 Random copolymerization of 4-vinyl phthalate esters with NBA.

Insert TABLE 2 Here

In the first series of VPE-*r*-NBA copolymerizations, a 1.2:1.0 ratio of VPE:NBA was utilized (Table 3). The resulting copolymers incorporated much larger amounts of VPE than the ratio of starting monomers, indicating that polymers terminated with a VPE residue preferentially add to another VPE monomer, compared to NBA. This phenomenon has been observed in a somewhat related NMRP copolymerization using substituted styrenes and methacrylates.[55] In some cases, only VPE residues were incorporated into the polymer, as assessed by ^{1}H NMR. These medium-sized copolymers had estimated Degrees of Polymerization values varying between 16-48, largely governed as a function of polymerization time.

Insert TABLE 3 Here

In the second series of VPE-*r*-NBA copolymerizations, the same ratio of VPE:NBA was utilized, but the amount of alkoxyamine initiator was increased by a factor of 2.5, producing shorter random copolymers (Table 4). Incorporation of NBA was higher than in series 1, with the exception of the 2-ethyl-1-hexyl VPE, which did not show any NBA

incorporation. In this series, these shorter random copolymers gave estimated Degrees of Polymerization values of 7-16 monomer units, with good control of polydispersity. All polymerization times were standardized in Series 2 to 19 hours. It is interesting to note that the long branched alkyl chain phthalate esters resulted in substantially shorter polymers than the short-chained phthalate esters.

Insert TABLE 4 Here

In the third series of VPE-*r*-NBA copolymerizations, an almost twelve-fold excess of NBA compared to VPE monomer was utilized, with the aim of producing poly(*n*-butyl acrylate) with small amounts of incorporated phthalate esters (Table 5). This was successful, producing moderate length random copolymers with Degree of Polymerization values estimated at 13-19 residues. These copolymers consist largely of NBA residues containing approximately 2-3 phthalate ester moieties. Again, the long branched alkyl chain phthalate esters resulted in shorter polymers than the short-chained phthalate esters, all with good control over polydispersity.

Insert TABLE 5 Here

All of the homo and random copolymers were obtained as viscous, slightly yellow liquids. DSC analysis starting at 25 °C with cooling to -40 °C, followed by heating to 75 °C did not show evidence of a glass transition temperature for any of the samples. Thus it is assumed that all of the samples have T_g values below -40 °C. As low glass transition temperatures are indicative of good plasticizing properties, these polymerized phthalates hold promise as possible plasticizers in PVC blends. These polymeric materials would not be expected to migrate easily out of the PVC products, and even if they did, ingestion or

absorption into mammalian systems would not give the same metabolic products as small molecule phthalate esters. Thus this approach towards polymeric phthalate plasticizers could mitigate the health concerns stemming from the current widespread use of phthalate esters in PVC consumer products. Work towards determining the miscibility of these polyphthalate esters with PVC, and the plasticization efficacy of these materials is now being pursued.

CONCLUSIONS

Five different 4-vinyl dialkyl phthalate esters were prepared from phthalic anhydride by electrophilic bromination, esterification, and Suzuki coupling. Nitroxide mediated radical polymerization using TIPNO alkoxyamine gave homopolymers, in which each residue mimics a small molecule plasticizer, but these phthalate esters are stitched together by a robust all-carbon chain. Similarly, random copolymerization by NMRP using *n*-butyl acrylate produced three series of copolymers, in which the polymer lengths and density of plasticizer mimics were varied. All of the polymers were viscous yellow liquids, with T_g values apparently below -40 °C, indicating promise as possible plasticizers. The possibility that these polymers can be used to replace DEHP and other phthalate plasticizers in PVC is intriguing. Polymeric phthalates used in PVC blends are expected to resist migration, and are unlikely to be metabolized into small Endocrine Disrupting Chemicals.

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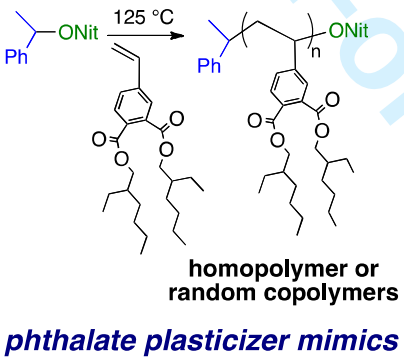
GRAPHICAL ABSTRACT

REBECCA BRASLAU,* FRIEDERIKE SCHÄFFNER, AND ARUNA EARLA

POLYMERIC PHTHALATES: POTENTIAL NON-MIGRATORY MACROMOLECULAR PLASTICIZERS

Several 4-vinyl phthalate esters are synthesized using Suzuki coupling. Nitroxide mediated-polymerization is utilized to form short homopolymers, and random copolymers with *n*-butyl acrylate. These polymeric phthalates have the potential to act as non-migratory plasticizers for PVC. Use in consumer products could address the health issues associated with monomeric phthalate plasticizers, which are implicated as endocrine disrupting compounds.

GRAPHICAL ABSTRACT FIGURE



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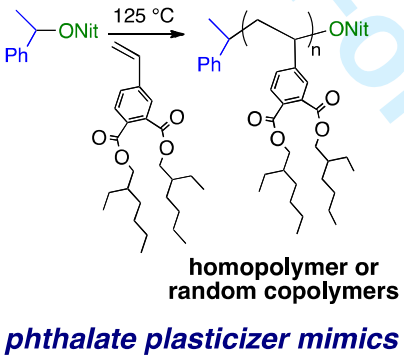
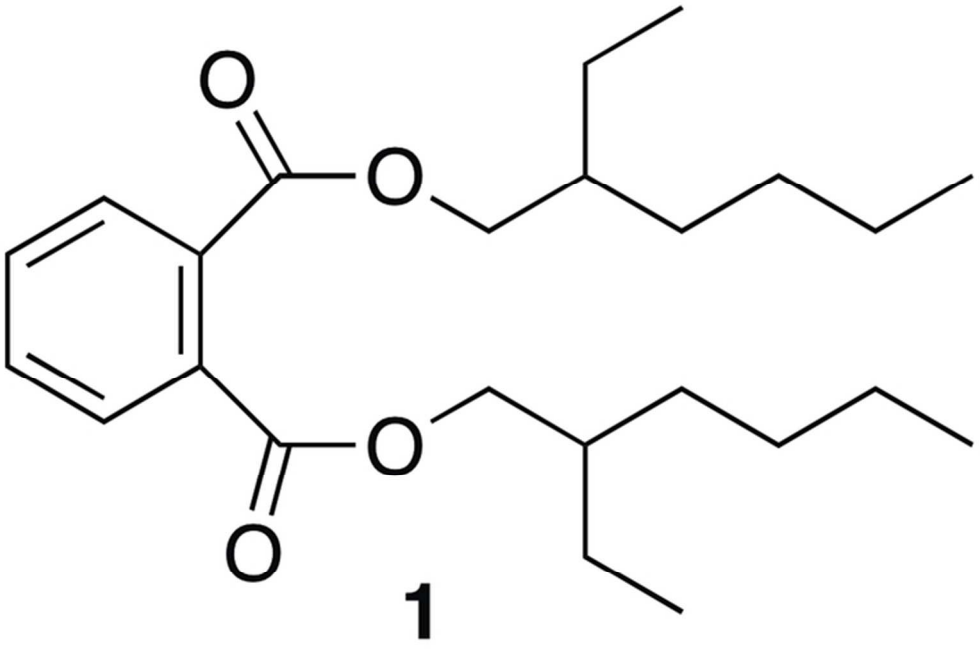
GRAPHICAL ABSTRACT FIGURE





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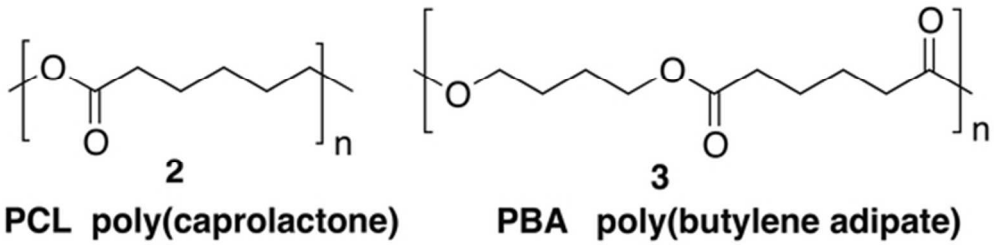

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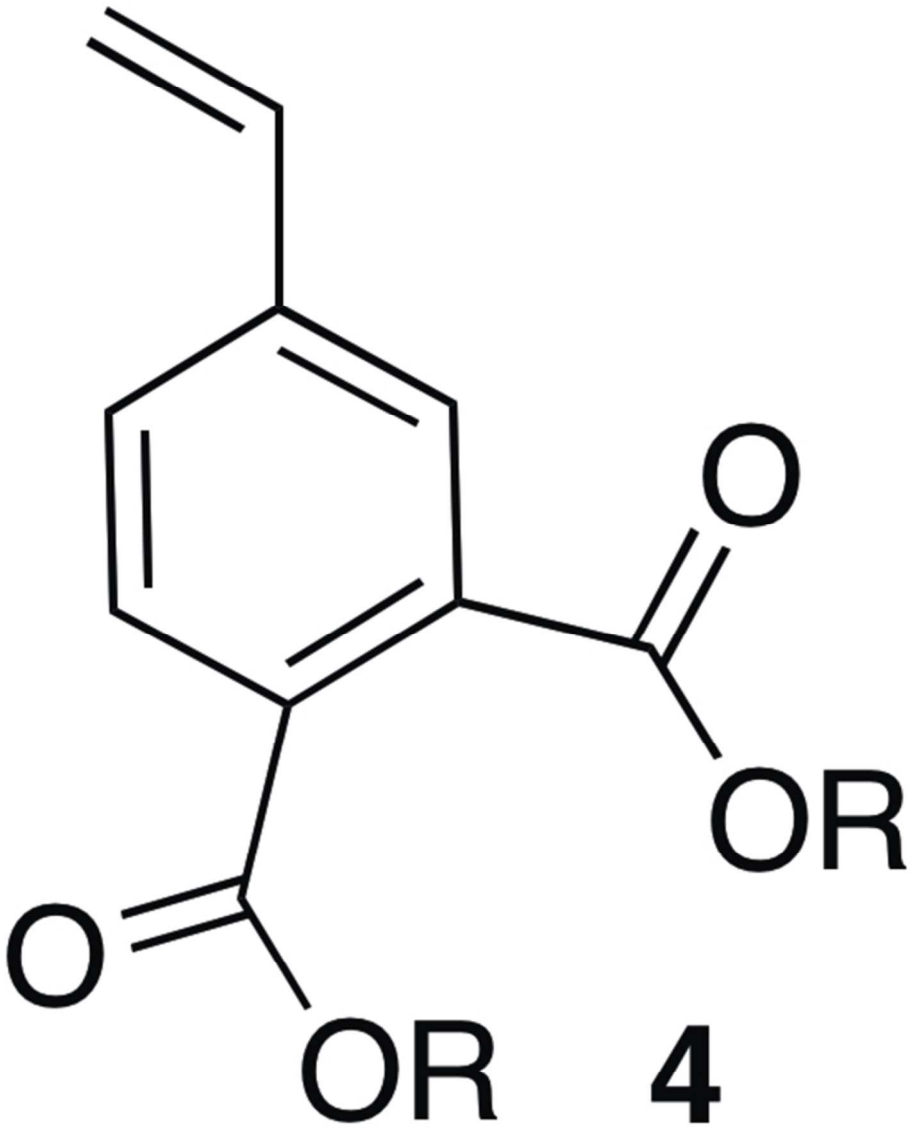

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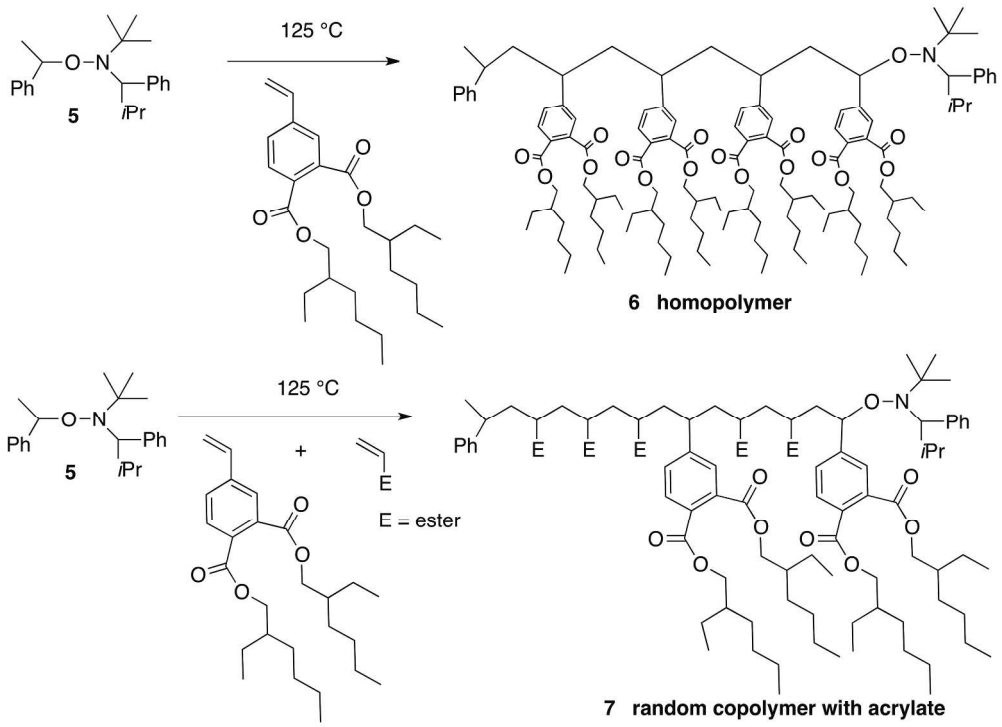

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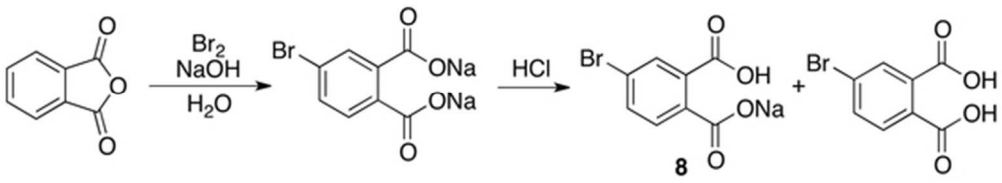

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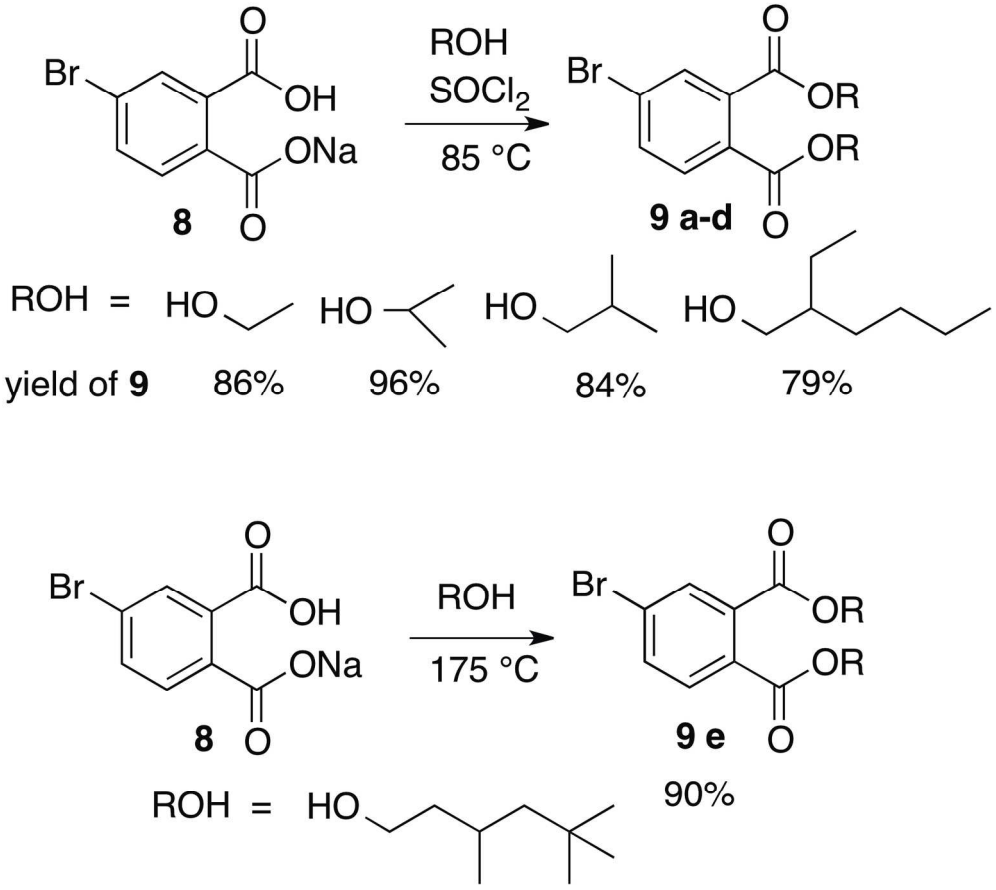
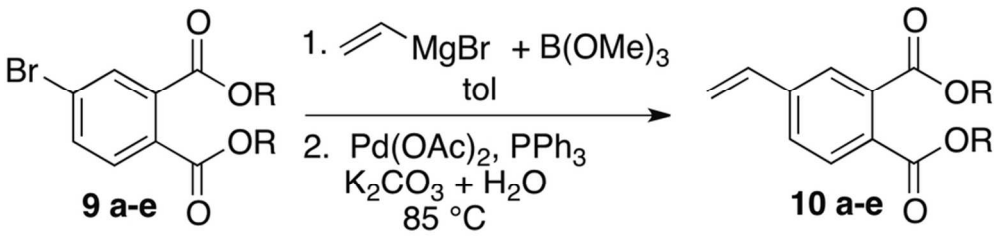
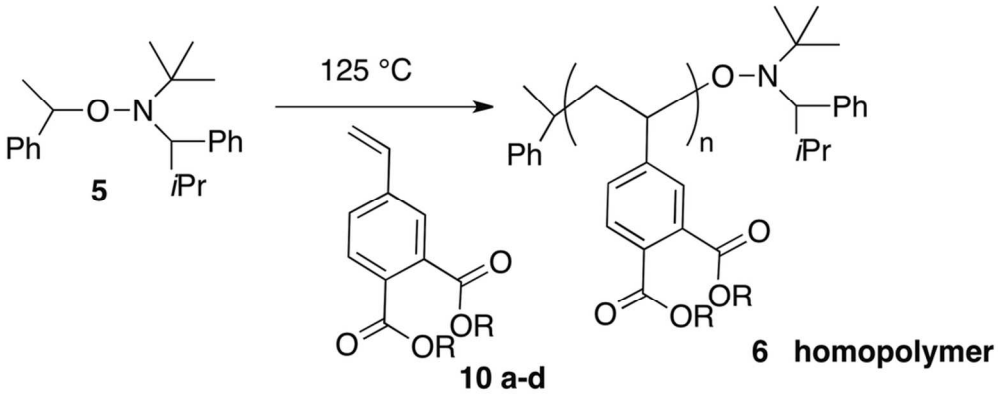


88x79mm (600 x 600 DPI)



R =	Et ,	*i*Pr,	*i*Bu,	2-Et-1-Hex,	3,3,5-triMe-1-Hex
yield of **10**	49%	78%	78%	26%	49%

39x14mm (600 x 600 DPI)



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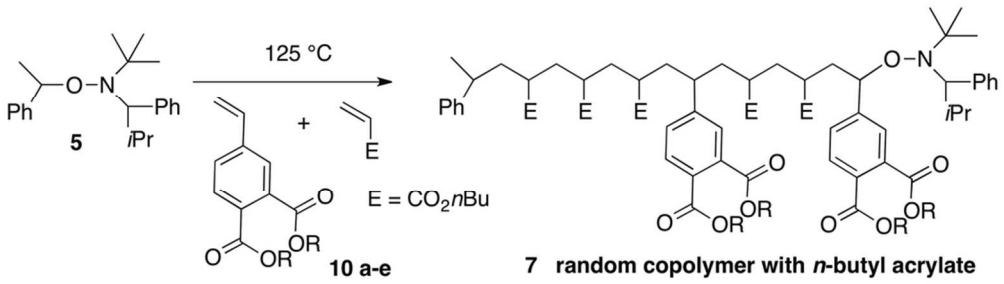

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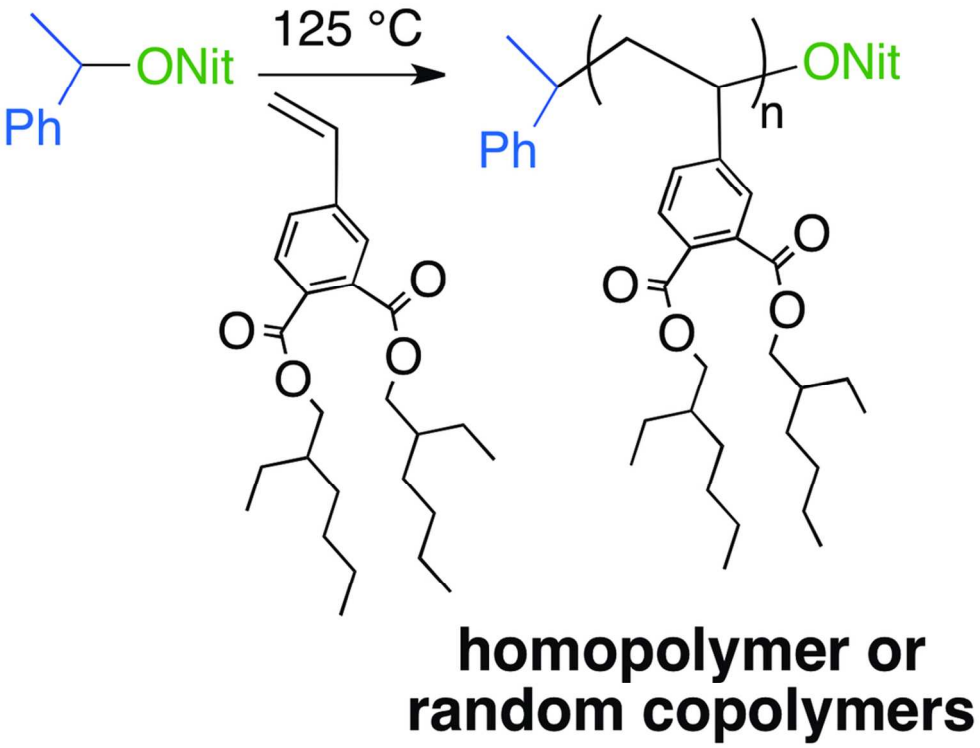


47x42mm (600 x 600 DPI)

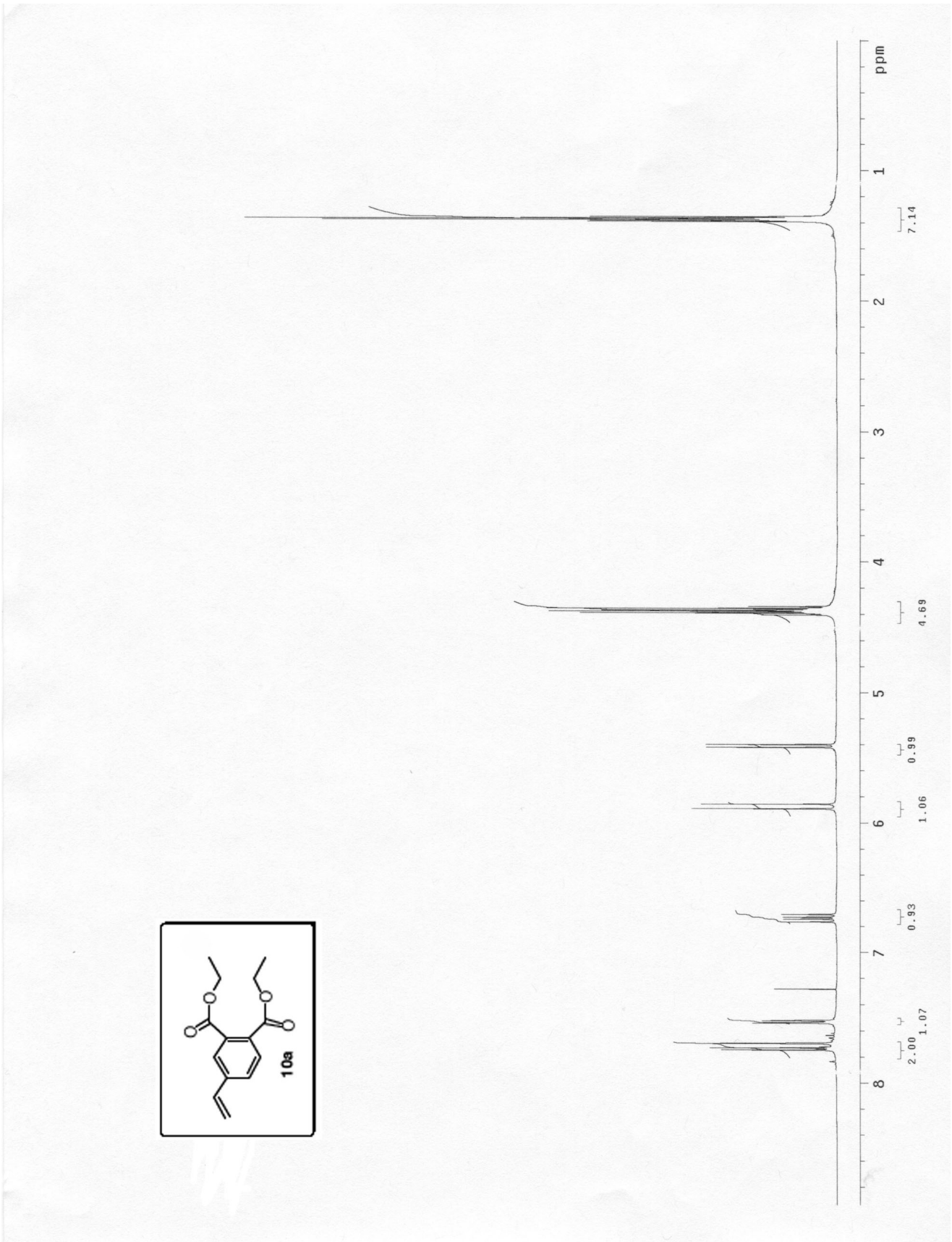
Supporting Information:

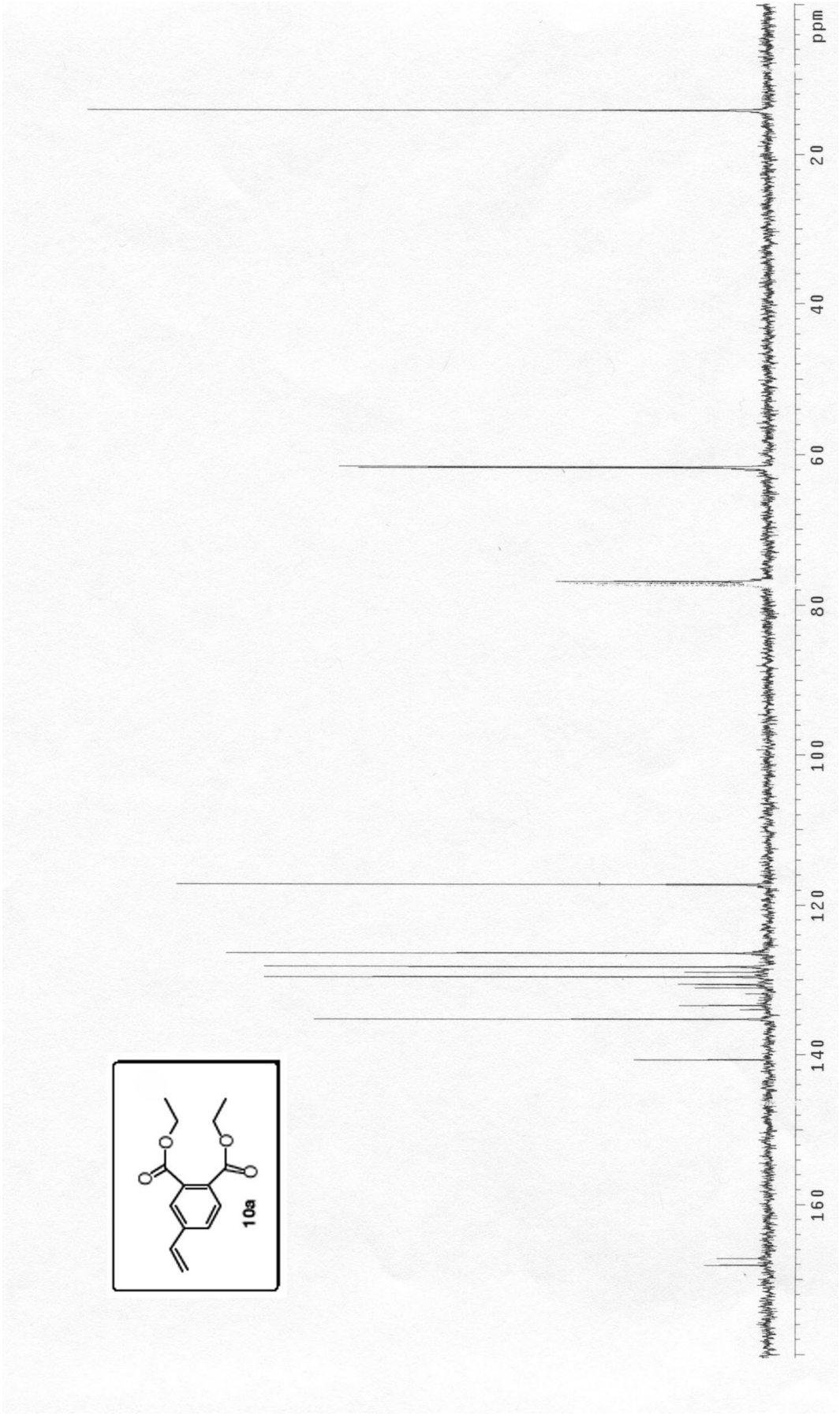
Polymeric Phthalates: Potential Non-migratory Macromolecular Plasticizers

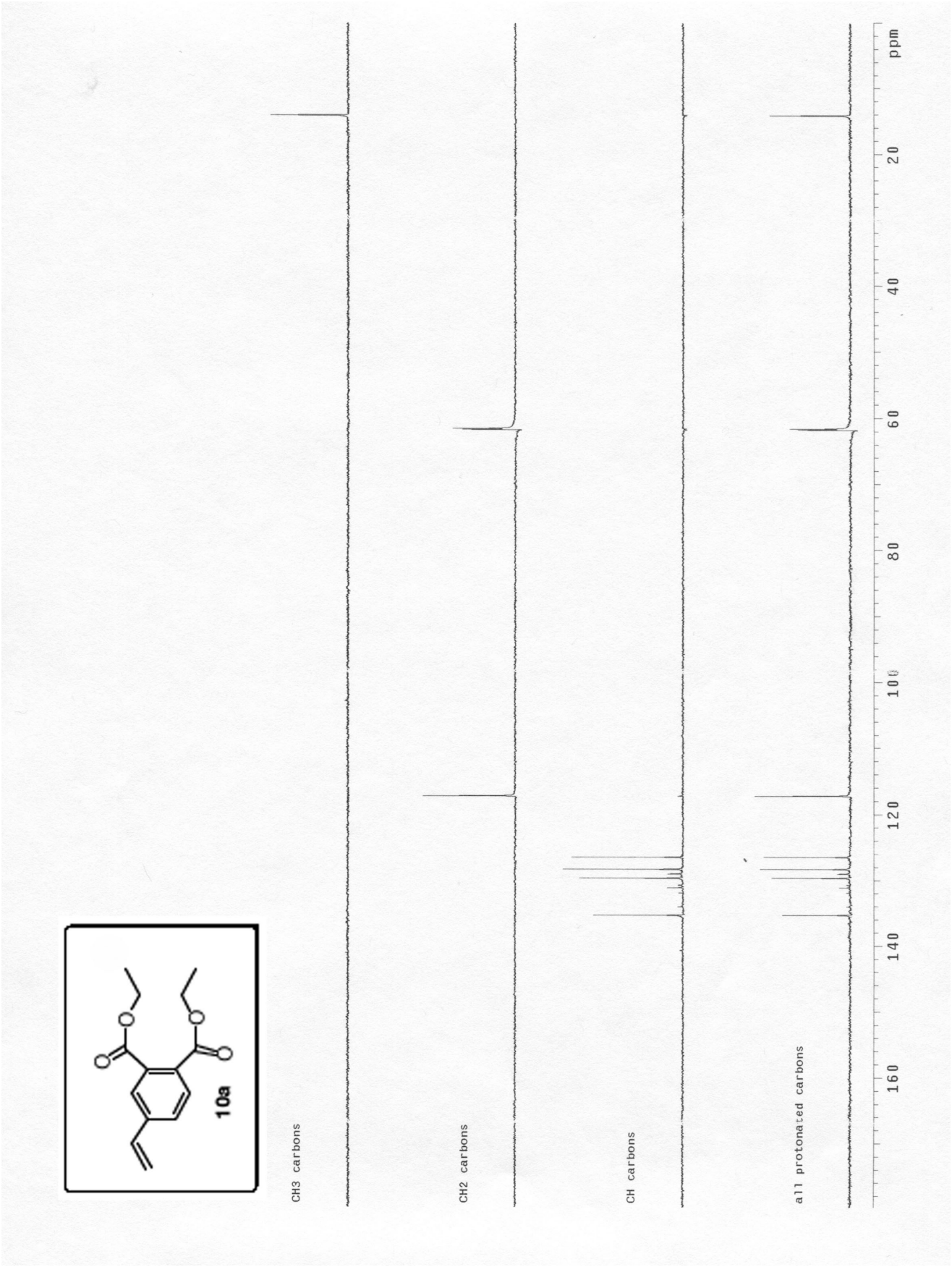
Rebecca Braslau,* Friederike Schäffner, and Aruna Earla

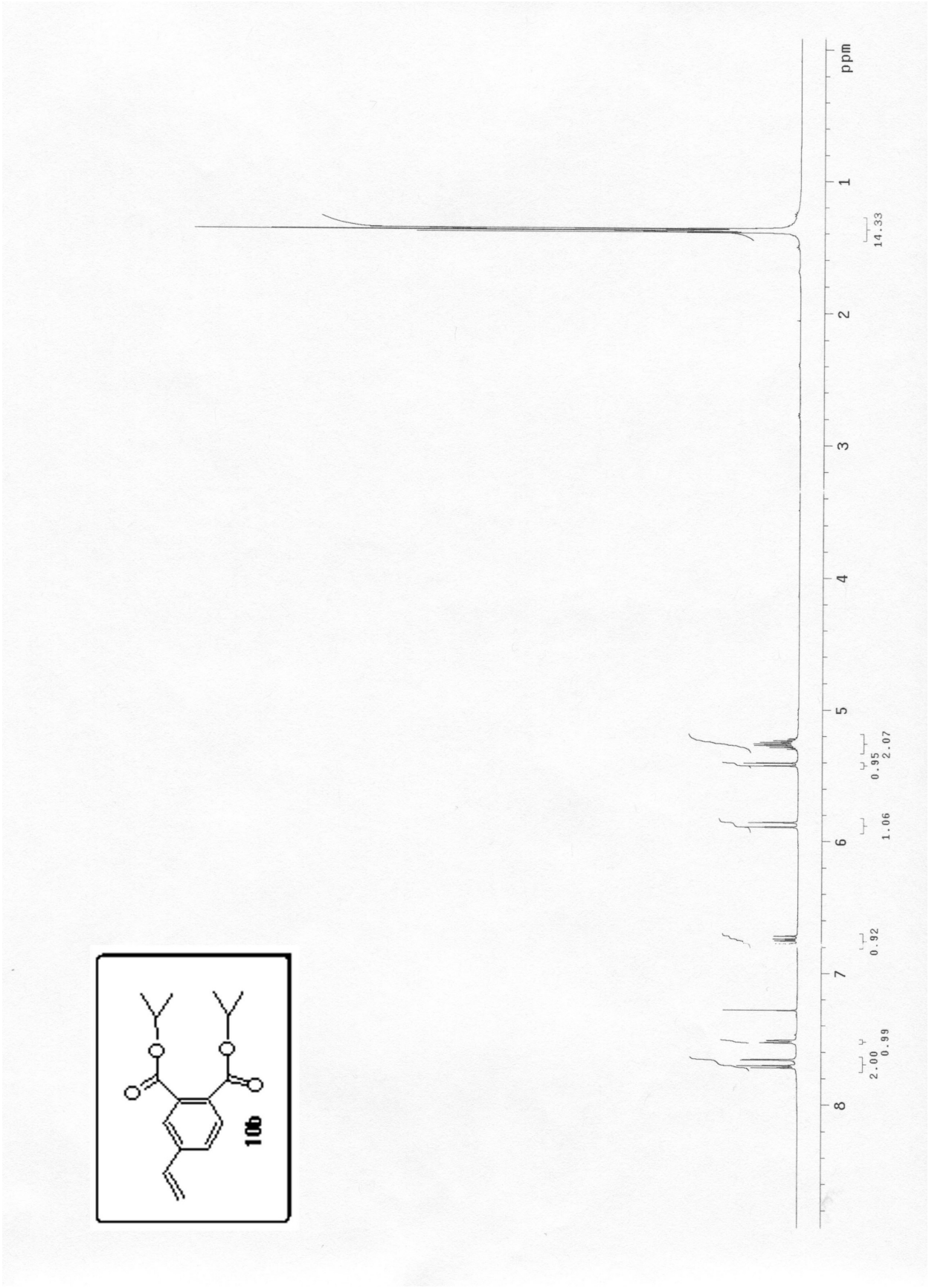
Department of Chemistry and Biochemistry, University of California, Santa Cruz, CA, 95064, USA

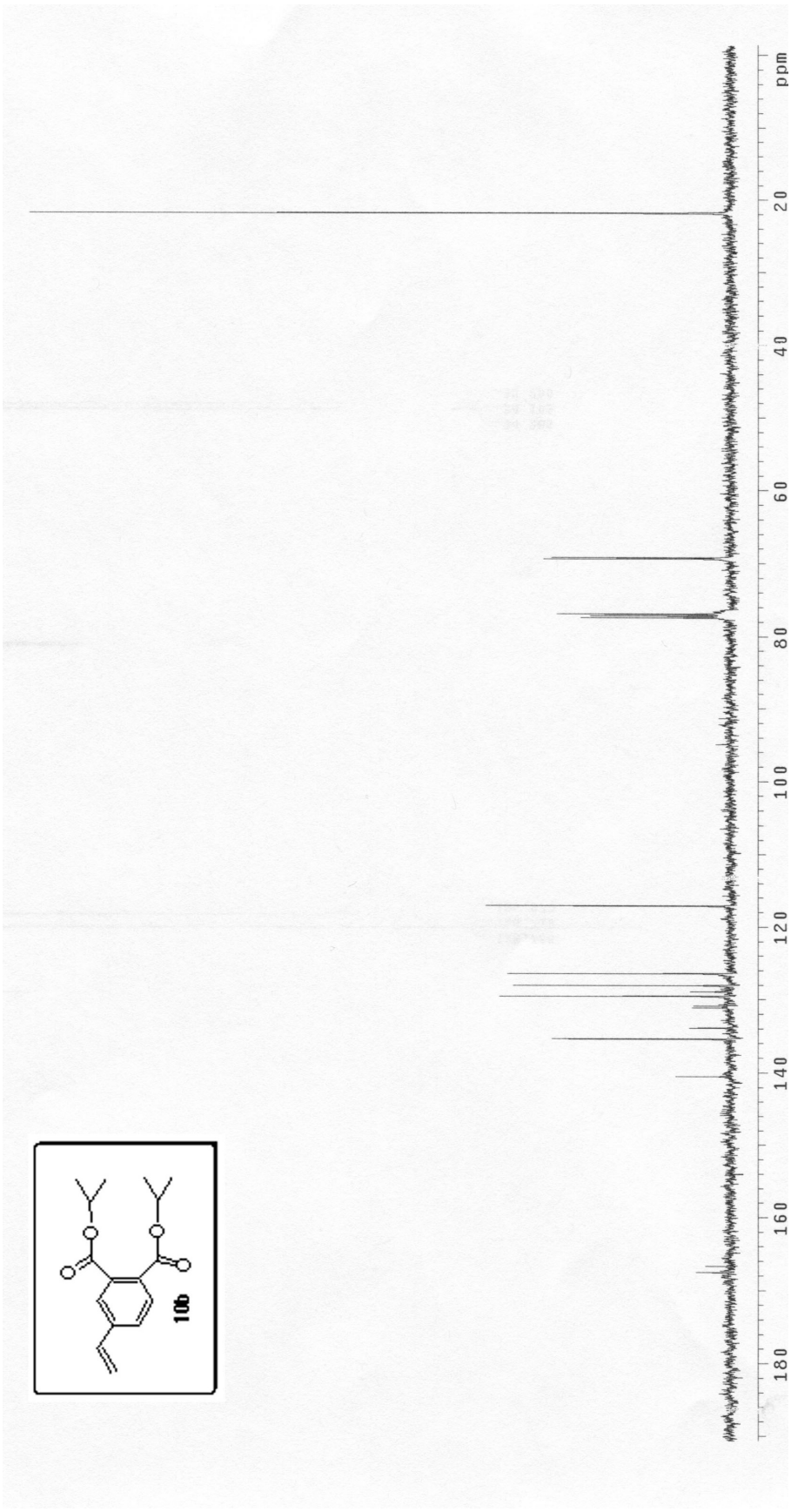
NMR Spectra of Vinyl Phthalate Esters **Page**

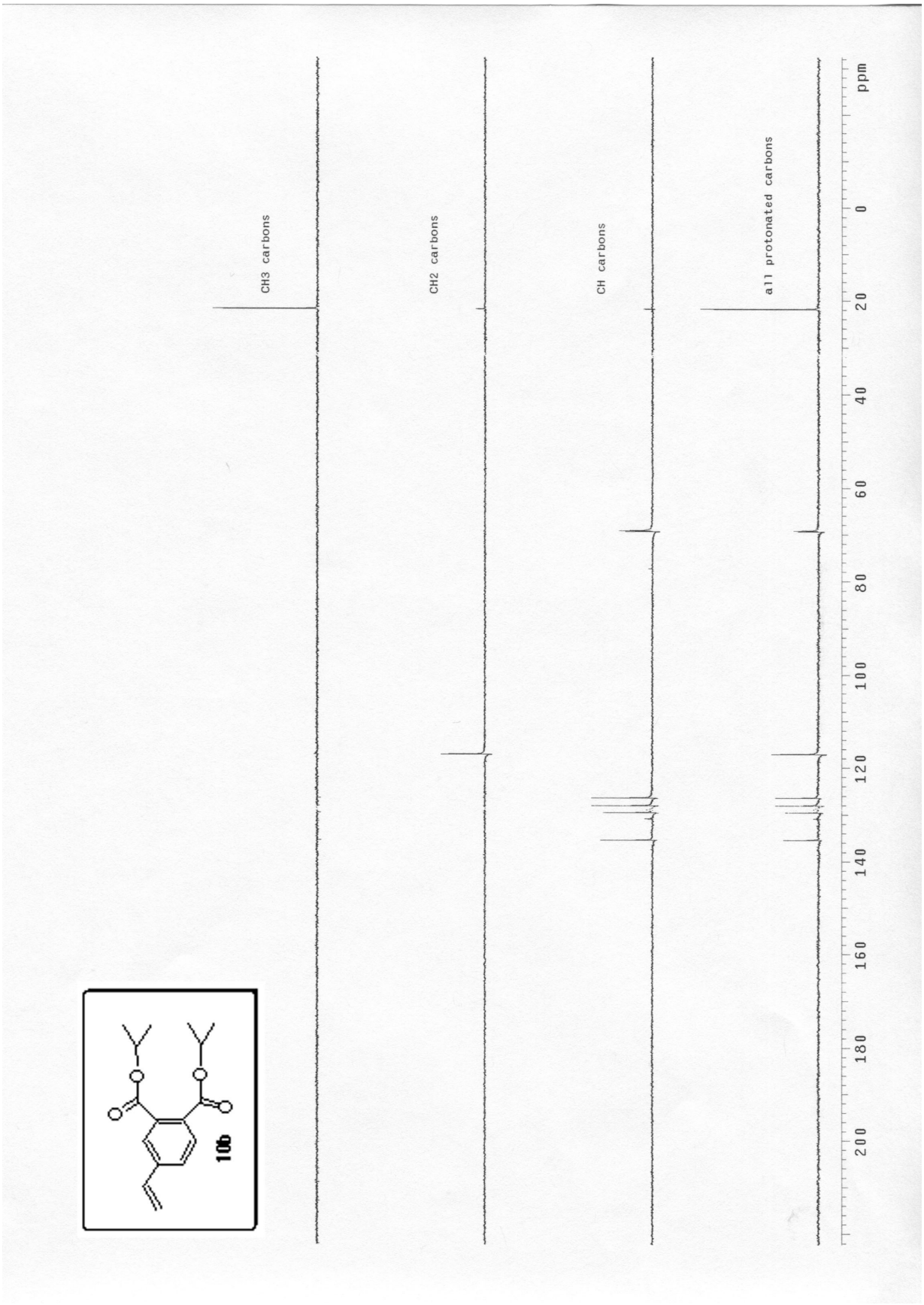


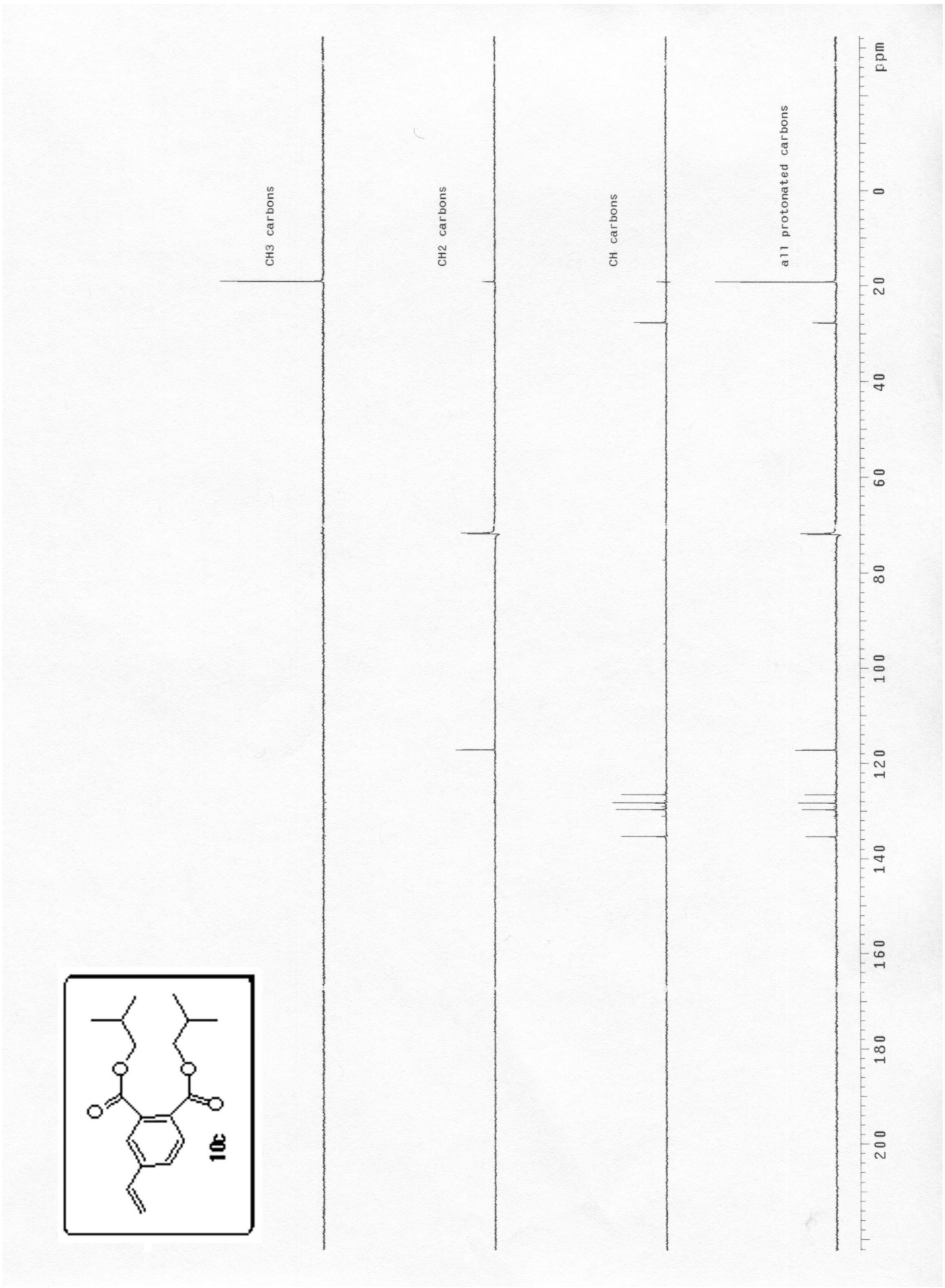


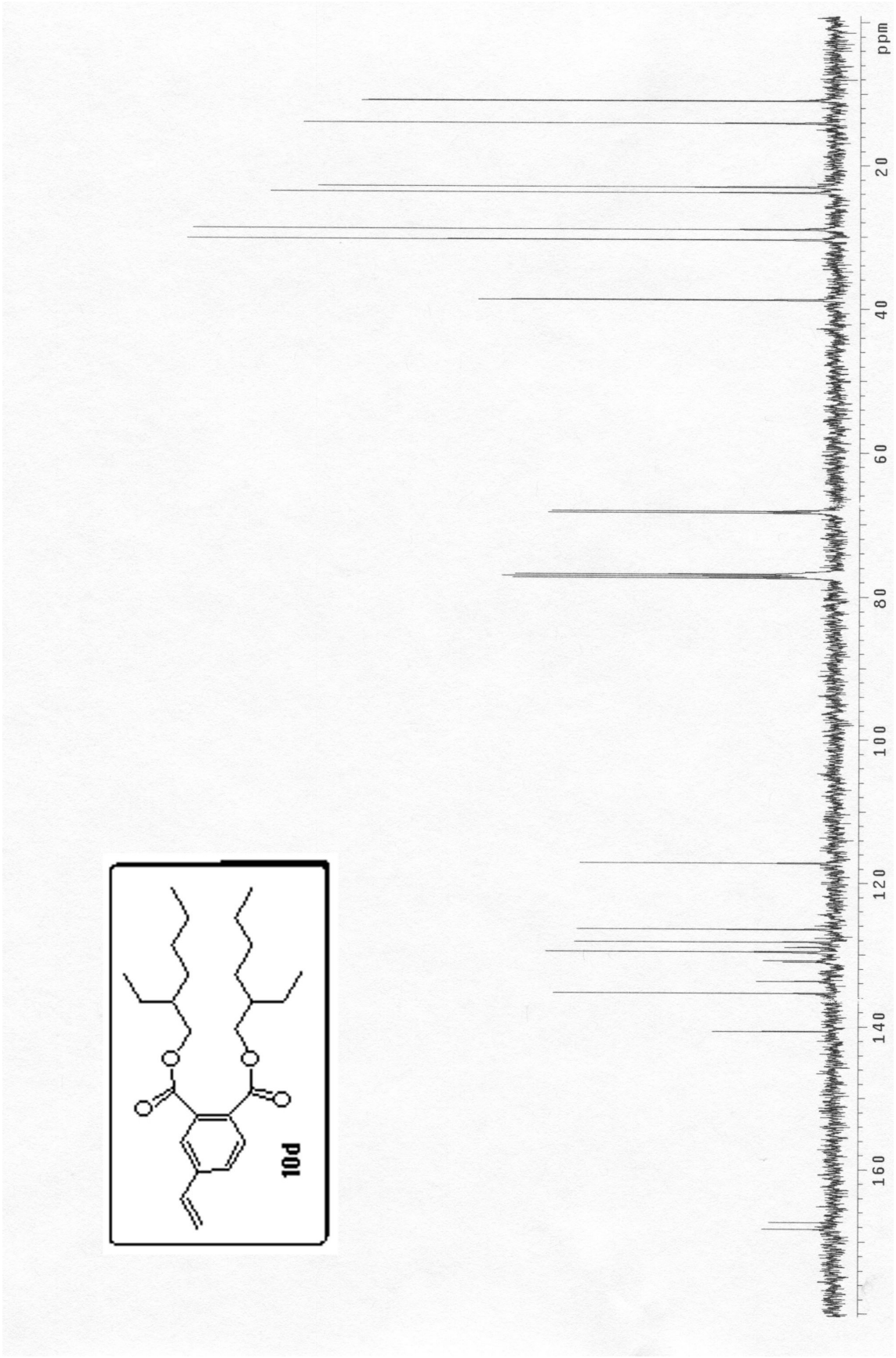


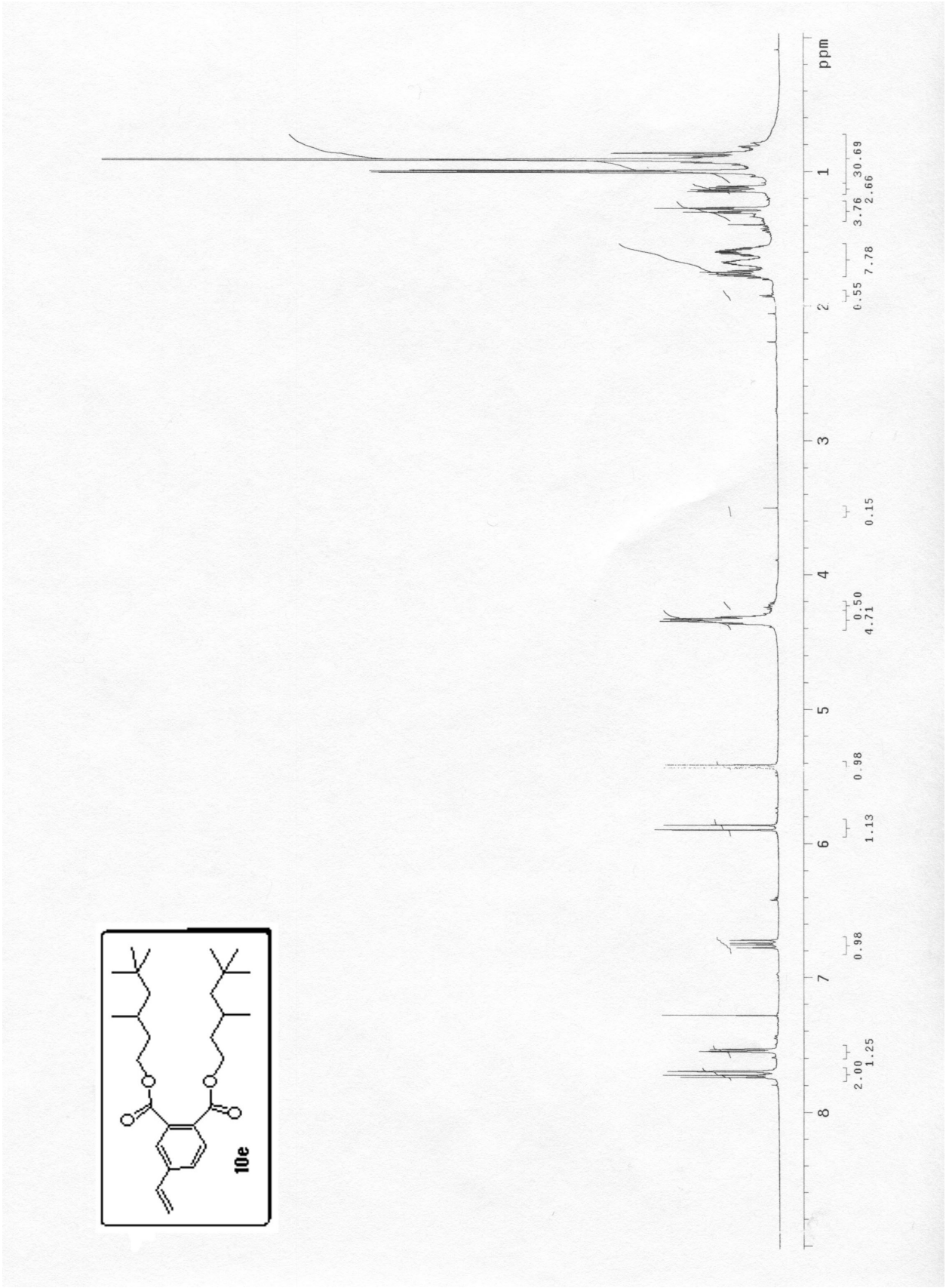












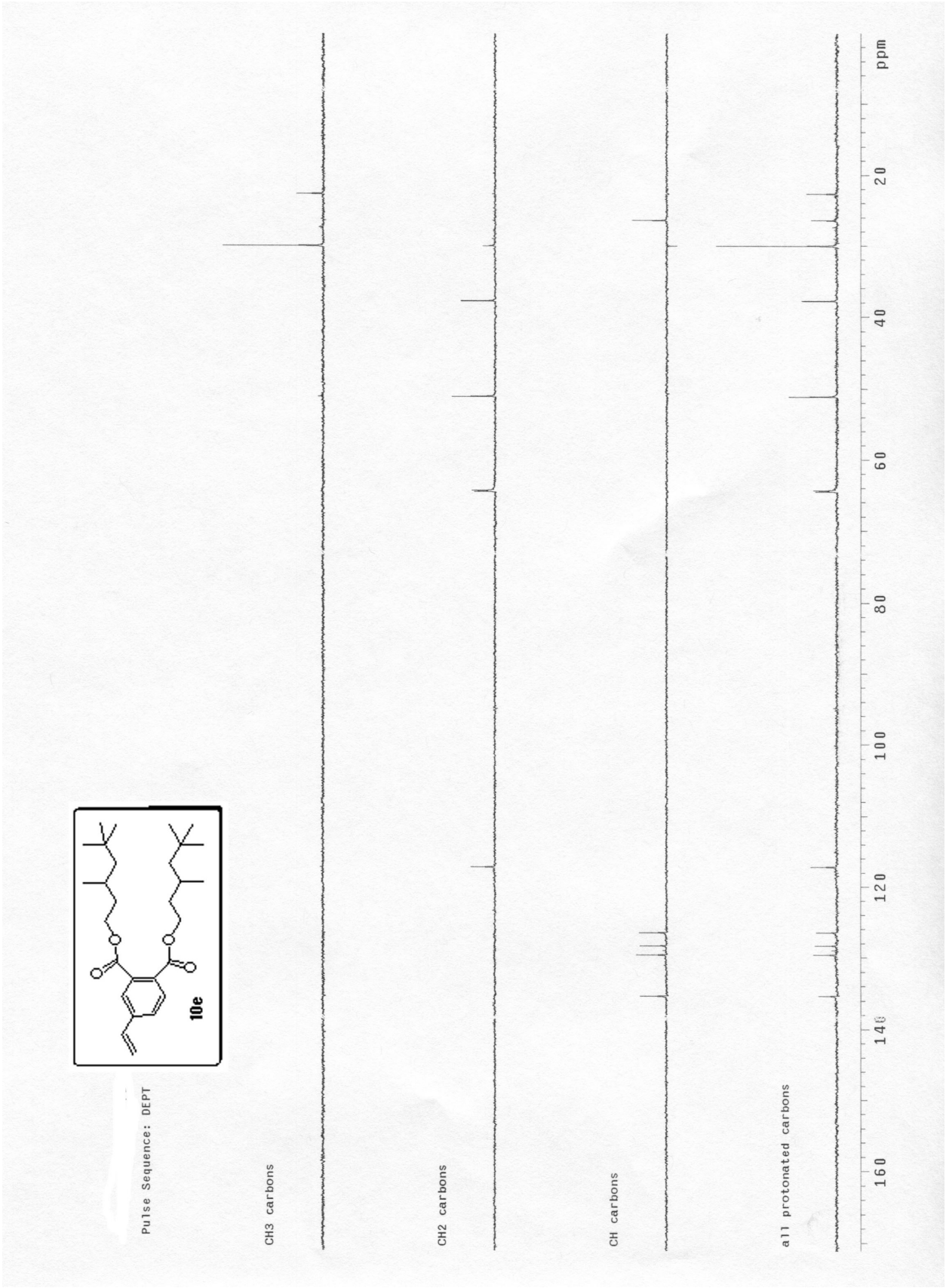


TABLE 1 Homopolymerization of 4-vinyl phthalate esters at 125 °C

R	equiv. monomer[a]	$time_{polym}$	$Yield_{gr.}$ [%]	$Yield_{NMR}$ [%]	Mn_{gr} [g/mol]	Mn_{NMR} *[g/mol]*	Mn_{GPC} *[g/mol]*	PDI	Mn_{ave}[b] *[g/mol]*	DP
Et	30	19 h	43	100	3323	7248	4825	1.20	4074	16
	20		50	100	2644	4940	3389	1.20	2692	12
i-Pr	30	19 h	46	100	3891	8129	4623	1.25	4257	15
	20		41	98	2463	5426	3463	1.27	2963	10
i-Bu	60	4 h	46	84	8492	5070	11275	1.20	9884	31
	60	19 h	75	92	13822	5580	11303	1.20	12562	40
	30		72	95	6758	8763	3424	1.20	5091	16
	20		72	99	4637	6197	3835	1.30	4236	13
2-Et-1-Hex	20	19 h	100	100	8751	8751	1633	1.10	5192	12

[a] Compared to 1 equiv. of alkoxyamine initiator 5. [b] Average of Mn_{gr} and Mn_{GPC}.

TABLE 2 Copolymerizations of vinyl phthalate ester (VPE) with *n*-butyl acrylate **(**NBA) at 125 °C

Series	equiv. alkoxyamine initiator **5**	equiv. nitroxide	equiv. NBA	equiv. VPE
1	1.0	0.025	25	29
2	1.0	0.01	10	12
3	1.0	0.01	20	2

TABLE 3 Copolymerizations of 4-vinyl phthalic esters (VPE) with *n*-butyl acrylate (NBA)
Series 1: 29.4 equiv. VPE + 25.0 equiv. NBA + 1.0 equiv. alkoxyamine **5** + 2.5 mol% NitO• at 125 °C

R	$time_{polym}$	$Yield_{gr.}$ [%]	$Yield_{NMR}$ [%]	Mn_{gr} [g/mol]	Mn_{NMR} *[g/mol]*	Mn_{GPC} *[g/mol]*	PDI	Ratio VPE:NBA by NMR	Mn_{ave}[a] *[g/mol]*	DP[b]
Et	4 h	29	44	3279	4781	6759	1.2	4.3:1	5019	23
	19 h	60	83	6353	8650	13506	1.5	2.6:1	9929	48
i-Pr	4 h	26	40	3223	4720	5206	1.3	VPE only	4214	16
	19 h	62	58	7200	6739	11920	1.4	VPE only	9560	36
i-Bu	19 h	54	84	6910	10538	14027	1.5	1.3:1	10468	46
3,3,5-triMe-1-Hex	19 h	58	82	9752	13642	18341	1.5	2.9:1	4046	39
	43 h	/	92	/	15220	8289	1.8	0.8:1	8289	17
2-Et-1-Hex	19 h	28	80	4828	13316	8303	1.2	VPE only	6566	16
	43 h	54	68	9132	11399	6565	1.5	VPE only	7848	19

a Average of Mn_{gr} and Mn_{GPC}.. b Degree of Polymerization calculated from the Mn_{ave} and the ratio of VPE:NBA incorporation as determined by 1H NMR.

TABLE 4 Copolymerizations of 4-vinyl phthalic esters (VPE) with *n*-butyl acrylate (NBA)
Series 2: 11.8 equiv. VPE + 10.0 equiv. NBA + 1.0 equiv. alkoxyamine **5** + 1 mol% NitO• at 125 °C

R	$time_{polym}$	$Yield_{gr.}$ [%]	$Yield_{NMR}$ [%]	Mn_{gr} [g/mol]	Mn_{NMR} *[g/mol]*	Mn_{GPC} *[g/mol]*	PDI	Ratio VPE:NBA by NMR	Mn_{ave}[a] *[g/mol]*	DP[b]
Et	19 h	50	67	2377	3059	3316	1.2	1.5:1	2846	15
i-Pr	19 h	74	94	3655	4562	3264	1.2	1.3:1	3460	17
i-Bu	19 h	63	96	3413	5021	3640	1.2	1.3:1	3526	16
3,3,5-triMe-1-Hex	19 h	59	89	2235	3211	3478	1.3	2.3:1	2856	8
2-Et-1-Hex	19 h	42	78	2915	5189	2640	1.3	VPE only	2778	7

[a] Average of Mn_{gr} and Mn_{GPC}.. [b] Degree of Polymerization calculated from the Mn_{ave} and the ratio of VPE:NBA incorporation as determined by ^{1}H NMR.

TABLE 5 Copolymerizations of 4-vinyl phthalic esters (VPE) with *n*-butyl acrylate (NBA)
Series 3: 1.7 equiv. VPE + 19.7 equiv. NBA + 1.0 equiv. alkoxyamine **5** + 1 mol% NitO• at 125 °C

R	$time_{polym}$	$Yield_{gr.}$ [%]	$Yield_{NMR}$ [%]	Mn_{gr} [g/mol]	Mn_{NMR} *[g/mol]*	Mn_{GPC} *[g/mol]*	PDI	Ratio VPE:NBA by NMR	Mn_{ave}[a] *[g/mol]*	DP[b]
Et	19 h	89	66	2963	2291	2275	1.2	0.1:1	2619	19
i-Pr	19 h	81	70	2757	2440	2115	1.2	0.1:1	2436	17
i-Bu	19 h	85	69	2944	2447	2265	1.2	0.1:1	2604	18
3,3,5-triMe-1-Hex	19 h	80	54	2975	2127	1979	1.3	0.2:1	2477	14
2-Et-1-Hex	19 h	73	59	2711	2254	2001	1.2	0.2:1	2356	13

[a] Average of Mn_{gr} and $Mn_{GPC.}$ [b] Degree of Polymerization calculated from the Mn_{ave} and the ratio of VPE:NBA incorporation as determined by ^{1}H NMR.