Polymeric Phthalates: Potential Nonmigratory Macromolecular Plasticizers

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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 (NBA) 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 NBA residues were also prepared (DP = 13–19, PDI = 1.2–1.3). All polymers were oily liquids, with glass transitions temperatures undetected between 75 and −40 °C, indicating these polymeric phthalates hold promise as potential nonmigratory phthalate plasticizers. © 2012 Wiley Periodicals, Inc. J. Polym. Sci., Part A: Polym. Chem. **2013**, *51*, 1175–1184

KEYWORDS: copolymerization; phthalate; plasticizer; radical polymerization; 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 worldwide 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 result from an increase in the free volume, with 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, Fig. 1, also known as dioctyl phthalate), 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 indicate 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, dibutyl phthalate, and 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, 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"[3] plasticizers that cannot leach out of consumer products, yet still provide the desired plasticizing properties.

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

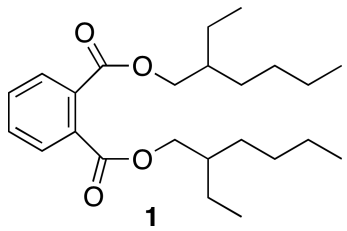


FIGURE 1 DEHP is a widely used traditional small molecule plasticizer.

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 nonleachable 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 1000 to 10,000. Although 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** (Fig. 2), have been investigated as polymeric plasticizers since 1947.[21] In 1977, Hubbell and Cooper[22] reported that PCL 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 et al.[23] indicate that a ratio of three to four 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 six 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 PBAs on the plasticizer efficiency and migration aptitude was recently studied by Hakkarainen and coworker.[30–33] A diblock copolymer made of polyethylene glycol and polycaprolactone has been developed for manufacturing flexible biomedical supplies.[34] The major disadvantage of these polyester plasticizers is their susceptibility toward hydrolysis, which changes their physical properties with aging and exposure to moisture.

Terpolymers prepared by uncontrolled, azobisisobutyronitrile (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 nonhydrolyzable 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, Fig. 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.

The alkyl group of the phthalate esters can be easily manipulated to mimic various phthalate esters used in PVC plasticization. As 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 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO)[38] enables the facile preparation of either homopolymers **6**, or random copolymers **7** between VPE and acrylates, to "dilute" the phthalate ester

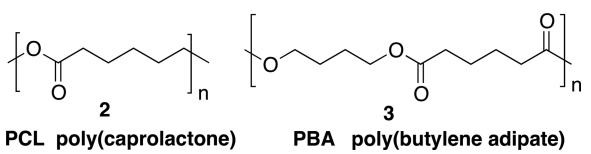


FIGURE 2 Hydrolyzable polyester plasticizers PCL **2** and PBA **3**.

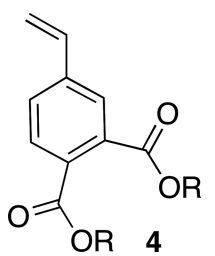
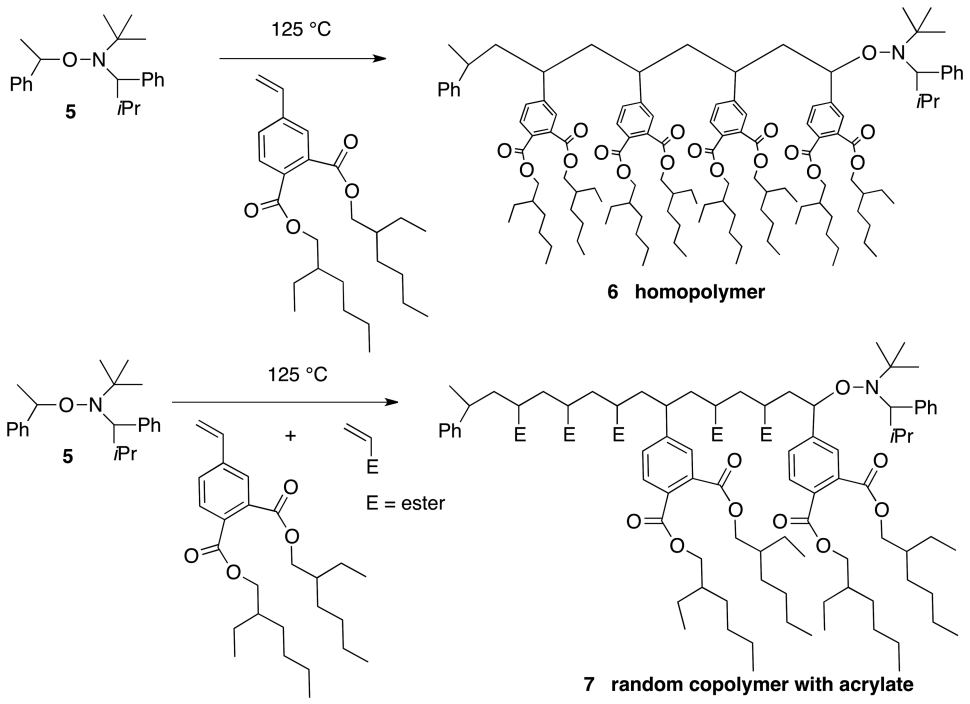


FIGURE 3 A VPE, a monomer to prepare poly(vinyl phthalates).



SCHEME 1 Homo and random copolymers of vinyl phthalate esters.

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.

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 371,100 (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. ^{1}H, ^{13}C and DEPT NMR spectra of vinyl phthalate ester monomers **10a-e** are available in the Supporting Information.

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 the 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]

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 was 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 and Dave[45] and modified from that of Norman et al.,[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 2 h. Upon cooling, volatiles were evaporated, 90 mL of H_2O was 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 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).

Preparation of 4-Bromo-di(isopropyl)-phthalate Ester 9b
7.10 g (96% yield) of the product was obtained 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).

Preparation of 4-Bromo-di(isobutyl)-phthalate[46] 9c
3.30 g (84% yield) of the product was obtained 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).

Preparation of 4-Bromo-di(2-ethyl-1-hexyl)-phthalate Ester[47] 9d
12.3 g (79% yield) of the product was obtained 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).

Preparation of 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 h. 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 nonbrominated 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}.

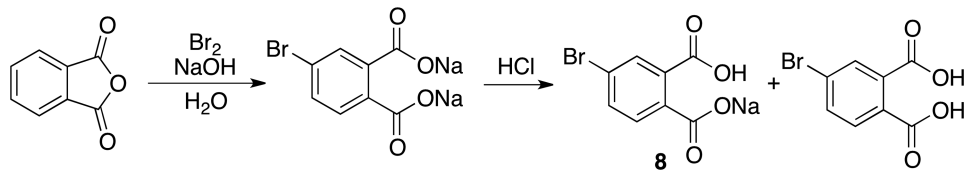
^{1}H NMR (500 MHz, $CDCl_3$, δ): 7.82 (d, J = 1.5 Hz, 1H), 7.68–7.60 (m, 2H), 4.36–4.43 (m, 4H), 1.79–1.70 (m, 2H), 1.70–1.63 (m, 2H), 1.62–1.54 (m, 2H), 1.30–1.25 (m, 2H), 1.15–1.10 (m, 2H), 1.00–0.09 (dd; J = 3 Hz, J = 3.5 Hz, 6H), 0.91–0.90 (m, 18 H).

^{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 et al.,[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-



SCHEME 2 Bromination of phthalic anhydride.

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 min. Catalytic palladium(II) acetate (38 mg, 0.17 mmol, 2 mol %) and triphenylphosphine (110 mg, 0.42 mmol, 5 mol %) 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 phases 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}.

^1H 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).

Preparation of 4-Vinyl-di(isopropyl)-phthalate Ester 10b

0.901 g (78% yield) was obtained 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}.

^1H 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).

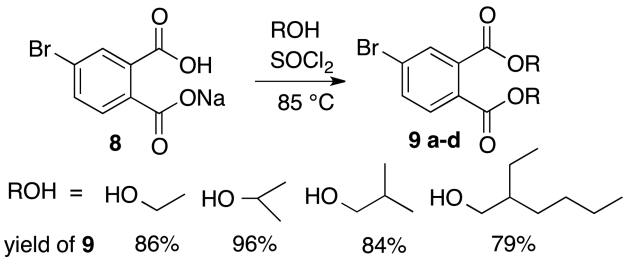
Preparation of 4-Vinyl-di(iso-butyl)-phthalate Ester 10c

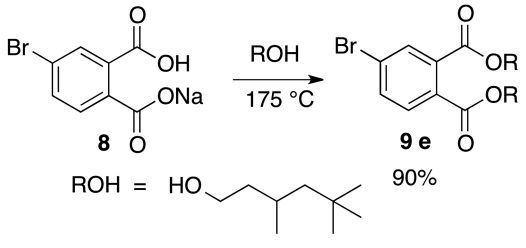
2.00 g (78% yield) was obtained as a slightly yellow oil.

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

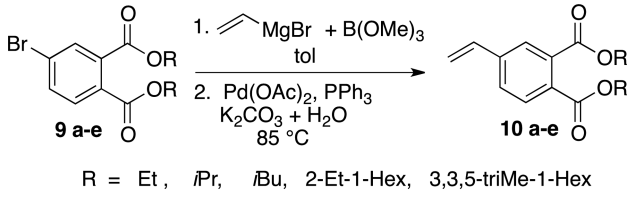
IR (neat): 2963, 1726, 1605, 1471, 1377, 1285, 1196, 1127, 1070, 986, 919, 851, 783 cm^{-1}.

^1H 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

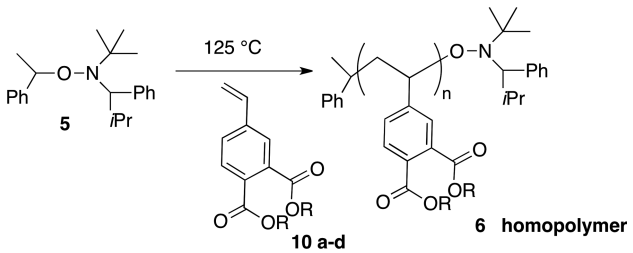




SCHEME 3 Esterification of 4-bromo-phthalic acid monosodium salt.



SCHEME 4 Suzuki vinylation of 4-bromo-phthalic esters.



SCHEME 5 Polymerization of VPE.

TABLE 1 Homopolymerization of VPE at 125 °C

R	Equiv. monomer[a]	$Time_{polym}$	$Yield_{gr}$. (%)	$Yield_{NMR}$ (%)	$M_{n\ gr}$ (g/mol)	M_{nNMR} (g/mol)	$M_{n\ GPC}$ (g/mol)	PDI	$M_{n\ ave}$[b] (g/mol)	DP
Et	30	19 h	43	100	3,323	7,248	4,825	1.20	4,074	16
	20		50	100	2,644	4,940	3,389	1.20	2,692	12
i-Pr	30	19 h	46	100	3,891	8,129	4,623	1.25	4,257	15
	20		41	98	2,463	5,426	3,463	1.27	2,963	10
i-Bu	60	4 h	46	84	8,492	5,070	11,275	1.20	9,884	31
	60	19 h	75	92	13,822	5,580	11,303	1.20	12,562	40
	30		72	95	6,758	8,763	3,424	1.20	5,091	16
	20		72	99	4,637	6,197	3,835	1.30	4,236	13
2-Et-1-Hex	20	19 h	100	100	8,751	8,751	1,633	1.10	5,192	12

[a] Compared to 1 equiv. of alkoxyamine initiator 5.
[b] Average of $M_{n\ gr}$ and $M_{n\ GPC}$.

(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).

Preparation of 4-Vinyl-di(2-ethyl-1-hexyl)-phthalate Ester 10d

1.78 g (26% yield) was obtained 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).

Preparation of 4-Vinyl-di(3,5,5-trimethyl-1-hexyl)-phthalate Ester 10e

1.37 g (49% yield) was obtained 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) and 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 h and 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 (M_{nNMR}, 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 h using ethanol as solvent. The homopolymer was concentrated *in vacuo* and the sample weighed to determine the gravimetric yield ($yield_{gr}$); a molecular weight ($M_{n\ gp}$, g/mol) was calculated. Analysis by GPC using THF as the eluent (calibrated against eight polystyrene samples) gave a third value of molecular weight ($M_{n\ GPC}$).

*Copolymerization of 4-Vinyl-*di*-alkyl-phthalate Esters 10a–10e with NBA*

The following procedure is representative of the general procedure: a mixture of 2,2,5-trimethyl-4-phenyl-3-azahexane-3-nitroxide (TIPNO) (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

TABLE 2 Copolymerizations of VPE with 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

NBA (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 h and 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 versus NBA incorporated into the polymer, from which a molecular weight (M_{nNMR}, g/mol) was calculated (see Tables 3–5). For samples containing only unpolymerized NBA as the remaining monomer, the copolymer sample was transferred to a flask using dichloromethane and all volatiles (including NBA) 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 h using ethanol as solvent. The copolymer was concentrated *in vacuo* and the sample weighed to determine the gravimetric yield (yield$_{gr}$); a molecular weight ($M_{n\ gp}$, g/mol) was calculated. Analysis by GPC using THF as the eluent (calibrated against eight polystyrene samples) gave a third value of molecular weight ($M_{n\ GPC}$).

Three different series of copolymerizations were performed:

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 VPE

The only literature method for the preparation of 4-vinylphthalic acid derivatives is the 1994 work of Rectanus and Stadler[49] (preparing 4-vinyl phthalic anhydride), using 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 VPE 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 performed 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.

Esterification (Scheme 3) was performed 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 and Dave.[45] Use of thionyl chloride

TABLE 3 Copolymerizations of VPE with NBA

R	Time$_{polym}$	Yield$_{gr}$ (%)	Yield$_{NMR}$ (%)	$M_{n\ gr}$ (g/mol)	M_{nNMR} (g/mol)	$M_{n\ GPC}$ (g/mol)	PDI	Ratio VPE:NBA by NMR	$M_{n\ ave}$[a] (g/mol)	DP[b]
Et	4 h	29	44	3,279	4,781	6,759	1.2	4.3:1	5,019	23
	19 h	60	83	6,353	8,650	13,506	1.5	2.6:1	9,929	48
i-Pr	4 h	26	40	3,223	4,720	5,206	1.3	VPE only	4,214	16
	19 h	62	58	7,200	6,739	11,920	1.4	VPE only	9,560	36
i-Bu	19 h	54	84	6,910	10,538	14,027	1.5	1.3:1	10,468	46
3,3,5-triMe-1-Hex	19 h	58	82	9,752	13,642	18,341	1.5	2.9:1	4,046	39
	43 h	/	92	/	15,220	8,289	1.8	0.8:1	8,289	17
2-Et-1-Hex	19 h	28	80	4,828	13,316	8,303	1.2	VPE only	6,566	16
	43 h	54	68	9,132	11,399	6,565	1.5	VPE only	7,848	19

[a] Average of $M_{n\ gr}$ and $M_{n\ GPC}$.
[b] DP calculated from the $M_{n\ ave}$ and the ratio of VPE:NBA incorporation as determined by ^{1}H NMR.Series 1: 29.4 equiv. VPE + 25.0 equiv. NBA + 1.0 equiv. alkoxyamine **5** + 2.5 mol % NitO• at 125 °C

TABLE 4 Copolymerizations of VPE with NBA

R	$Time_{polym}$	$Yield_{gr}$ (%)	$Yield_{NMR}$ (%)	$M_{n\ gr}$ (g/mol)	M_{nNMR} (g/mol)	$M_{n\ GPC}$ (g/mol)	PDI	Ratio VPE: NBA by NMR	$M_{n\ ave}$[a] (g/mol)	DP[b]
Et	19 h	50	67	2,377	3,059	3,316	1.2	1.5:1	2,846	15
i-Pr	19 h	74	94	3,655	4,562	3,264	1.2	1.3:1	3,460	17
i-Bu	19 h	63	96	3,413	5,021	3,640	1.2	1.3:1	3,526	16
3,3,5-triMe-1-Hex	19 h	59	89	2,235	3,211	3,478	1.3	2.3:1	2,856	8
2-Et-1-Hex	19 h	42	78	2,915	5,189	2,640	1.3	VPE only	2,778	7

[a] Average of $M_{n\ gr}$ and $M_{n\ GPC}$.
[b] DP calculated from the $M_{n\ ave}$ and the ratio of VPE:NBA incorporation as determined by ^{1}H NMR.Series 2: 11.8 equiv. VPE + 10.0 equiv. NBA + 1.0 equiv. alkoxyamine 5 + 1 mol % NitO• at 125 °C

with 3,5,5-trimethyl-1-hexanol led to the formation of a side-product, thus esterification with this alcohol was performed at 175 °C without thionyl chloride.

With five different 4-bromo-phthalate esters in hand, the vinyl group was introduced in a straightforward manner using 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 et al.[48] was adopted, resulting in low to good yields of the desired VPE **10a–10e** (VPE) (Scheme 4).

Polymerizations

Conversion of the VPE into short polymers was then pursued. Short homopolymers were prepared by NMRP (Scheme 5, Table 1), forming polymers with an estimated degree of polymerization (DP) ranging from 10 to 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. To calculate a rough DP, the average of the gravimetric and GPC M_n values was taken, as the NMR derived yields and M_{nNMR} values were less reliable. It should be noted that the $M_{n\ GPC}$ values cannot be considered highly accurate, as polystyrene samples are used to calibrate the GPC.

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. NBA was chosen as the comonomer, as earlier studies involving *in situ* polymerization of NBA in PVC[53] and of vinyl chloride in poly(NBA)[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 performed: 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 used 10 times more NBA, with the aim of preparing copolymers rich in NBA residues, with a small amount of VPE incorporated.

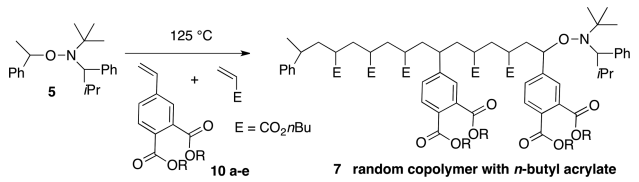
In the first series of VPE-*r*-NBA copolymerizations, a 1.2:1.0 ratio of VPE:NBA was used (Table 3). The resulting copolymers incorporated much larger amounts of VPE than the ratio of starting monomers, indicating that polymers terminated with a VPE residue preferentially add to another VPE monomer, 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 DP values varying between 16 and 48, largely governed as a function of polymerization time.

In the second series of VPE-*r*-NBA copolymerizations, the same ratio of VPE:NBA was used, 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-

TABLE 5 Copolymerizations of VPE with NBA

R	$Time_{polym}$	$Yield_{gr}$. (%)	$Yield_{NMR}$ (%)	$M_{n\ gr}$ (g/mol)	M_{nNMR} (g/mol)	$M_{n\ GPC}$ (g/mol)	PDI	Ratio VPE: NBA by NMR	$M_{n\ ave}$[a] (g/mol)	DP[b]
Et	19 h	89	66	2,963	2,291	2,275	1.2	0.1:1	2,619	19
i-Pr	19 h	81	70	2,757	2,440	2,115	1.2	0.1:1	2,436	17
i-Bu	19 h	85	69	2,944	2,447	2,265	1.2	0.1:1	2,604	18
3,3,5-triMe-1-Hex	19 h	80	54	2,975	2,127	1,979	1.3	0.2:1	2,477	14
2-Et-1-Hex	19 h	73	59	2,711	2,254	2,001	1.2	0.2:1	2,356	13

[a] Average of $M_{n\ gr}$ and $M_{n\ GPC}$.
[b] DP calculated from the $M_{n\ ave}$ and the ratio of VPE:NBA incorporation as determined by ^{1}H NMR.Series 3: 1.7 equiv. VPE + 19.7 equiv. NBA + 1.0 equiv. alkoxyamine 5 + 1 mol % NitO• at 125 °C.



SCHEME 6 Random copolymerization of VPE with NBA.

ethyl-1-hexyl VPE, which did not show any NBA incorporation. In this series, these shorter random copolymers gave estimated DP values of 7–16 monomer units, with good control of polydispersity. All polymerization times were standardized in Series 2 to 19 h. It is interesting to note that the long-branched alkyl chain phthalate esters resulted in substantially shorter polymers than the short-chained phthalate esters.

In the third series of VPE-*r*-NBA copolymerizations, an almost 12-fold excess of NBA compared to VPE monomer was used, with the aim of producing poly(NBA) with small amounts of incorporated phthalate esters (Table 5). This was successful, producing moderate length random copolymers with DP values estimated at 13–19 residues. These copolymers consist largely of NBA residues containing approximately two to three 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.

All of the homo and random copolymers were obtained as viscous, slightly yellow liquids. Differential scanning calorimetry (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 toward polymeric phthalate plasticizers could mitigate the health concerns stemming from the current widespread use of phthalate esters in PVC consumer products. Work toward 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. NMRP 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 NBA produced three series of copolymers, in which the polymer lengths and density of plasticizer mimics were varied. All 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 EDC.

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