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Introduction

Ever since its commercial debut in 1926, polyvinyl chloride (PVC) has continued to benefit modern civilization in a myriad of aspects. In recent years, global market demand for PVC materials has witnessed continuous growth, from 38.3 million tons in 2013 to 41.3 million tons in 2016.¹ PVC comes in two basic forms: rigid (unplasticized) and flexible (plasticized). Despite versatility and cost-efficiency, the safety of flexible PVC is now being questioned, partially due to allegations that di-(2-ethylhexyl) phthalate (DEHP), the most widely used PVC plasticizer, is bio-accumulative, and recognized as a human endocrine disruptor and a probable carcinogen.^{2–4} Over the past

A potentially general approach to aliphatic ester-derived PVC plasticizers with suppressed migration as sustainable alternatives to DEHP†

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The safety of flexible polyvinyl chloride (PVC) materials is now being questioned, partially due to allegations that di-(2-ethylhexyl) phthalate (DEHP), the dominant PVC plasticizer, is an endocrine disruptor and a probable carcinogen. As sustainable alternatives, aliphatic ester-derived plasticizers feature low cytotoxicity, biodegradability, and renewability, but they can only partially replace DEHP in PVC formulations because they have a strong tendency to migrate. Here, using epoxidized fatty acid methyl esters and aliphatic diesters as representatives, we demonstrate that covalently attaching one short ester at each α -position of aliphatic esters *via* Claisen condensation with judiciously selected dialkyl carbonate significantly suppresses their migration from the PVC matrix. In certain scenarios, the engineered plasticizers even migrate at a rate comparable to, or improved beyond that of DEHP. This approach harnesses the α -proton, a structural feature shared by all aliphatic esters, and dialkyl carbonate, an established "green chemical", thus providing a potentially general and green route towards DEHP alternatives with unprecedented performance that may contribute to sustainability of the old and oft-maligned PVC industry.

decade, multiple regulations have been enacted in both the European Union and Unite States that restrict the use of DEHP in processing particular PVC products. Accordingly, *ortho*-phthalates accounted for 65% of global plasticizer consumption in 2017, down from approximately 88% in 2005, and are projected to decline sharply to 60% in 2022.⁵ In this context, burgeoning academic and industrial interest emerged for alternatives with performance equal to DEHP but good toxicological profiles.

Promising alternatives include those derived from aliphatic esters, as exemplified by epoxidized fatty acid methyl esters (EFAMEs) and aliphatic diesters (ADEs). EFAMEs are obtained from unsaturated, single-chain fatty acid methyl esters by epoxidation. In addition to renewability and biodegradability, EFAMEs exhibit higher plasticizing efficiency and lower cost than high-molecular-weight epoxidized triglycerides (e.g., epoxidized soybean oil), and are thus now industrially established as an important coplasticizer.⁶⁻⁸ ADEs are synthesized from linear dibasic acids and alcohols, also known as a biodegradable plasticizer with the degradation products being generally non-toxic. When combined with DEHP, ADEs are particularly effective in improving the low temperature flexibility of the PVC products.^{5,9} Despite their good toxicological profiles, neither EFAMEs nor ADEs can be used in PVC formulations alone, because they have a strong tendency to migrate. For example, even with a high epoxy value of 5.8%, EFAMEs

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still migrate tenfold faster than DEHP, burdening the environment and shortening the lifespan of the end-products.^{10,11} Thus, the performance of these aliphatic ester-derived plasticizers is far from comparable to that of DEHP; an urgent task is to engineer their structure in a manner that efficiently counteracts migration.

To this end, previous researchers have reported several promising strategies, including increasing the molecular weight of EFAMEs by transesterification,¹² hyperbranched polymerization from specific feedstocks,⁴ and covalently linking the plasticizers to PVC by click chemistry.¹³ Despite their efficiency, these strategies require unique chemistry to be developed for each feedstock of interest, and thus are only useful for a single feedstock composition, ultimately limiting their applicability in industry where a large number of varieties of aliphatic ester-derived plasticizers are available. Therefore, a key challenge in this field is the development of a molecular engineering approach with general applicability that may decelerate migration of any aliphatic ester-derived PVC plasticizer, regardless of its composition.

Previously, we demonstrated that an engineered short ester protruding from a linear epoxidized methyl ricinoleate chain was more competent in trapping the plasticizers in the PVC matrix than the traditional strategy that underscored a high epoxy value.¹⁴ The branched plasticizer, in certain scenarios, even migrated as slowly as DEHP, pointing a way to address the leaching problem long haunting EFAME plasticizers. However, covalently attaching such ester was achieved by esterification using acetic anhydride that entailed a unique midchain hydroxyl in the feedstock. Unfortunately, apart from methyl ricinoleate, almost all feedstocks for EFAME synthesis, as well as other sub-classes of aliphatic ester-derived plasticizers, bear no hydroxyls. Thus, this approach, similar to any previously reported strategy mentioned above, could not be extended to other systems to have a general significance.

Claisen condensation is a carbon-carbon bond forming reaction that occurs between two esters in a strong base, yielding a β-keto ester. A Claisen condensation proceeds on the premise that at least one of the reactants must have an α -proton, and thus can be enolized. By combining different ester partners, this fundamental reaction allows chemists to strategically synthesize a multitude of structurally diverse, complex organic compounds.^{15,16} Here, we notice that although lacking hydroxyl handles, all aliphatic ester-derived PVC plasticizers contain α -protons, and thus theoretically, they may be enolized to undergo a mixed Claisen condensation with another non-enolizable ester, enabling a specific ester to be covalently attached at the α -position. In this way, we envision that all aliphatic ester-derived plasticizers, regardless of their composition, can be branched with one short ester that has been proved efficient in suppressing migration from the PVC matrix.

To demonstrate the feasibility of the proposed strategy, proof-of-concept experiments were conducted herein by using (1) methyl oleate, the main component of the feedstocks for synthesizing EFAMEs, (2) methyl stearate, a fast-migrating, undesirable component existing in almost all commercial EFAME plasticizers, and (3) another two industrially established aliphatic ester-derived plasticizers, diethyl sebacate and dimethyl sebacate, as the feedstocks. They were allowed to react with dimethyl carbonate or diethyl carbonate via Claisen condensation, yielding four structurally new plasticizers with one or two short ester branches. The migration behavior of the engineered plasticizers was investigated by combining experiments with theoretical prediction from molecular dynamics simulation. In particular, the green and sustainable advance of the present strategy with respect to our previous report that utilized an esterification reaction¹⁴ was discussed. The rationale underlying the present effort utilizes dialkyl carbonate, an established "green chemical", as a raw material, and is in principle amenable to any aliphatic ester-derived plasticizer, thus providing access to DEHP alternatives with unprecedented performance in a potentially general and green manner that may address the challenge of sustainability now confronting the PVC industry.

Experimental

Materials

Methyl oleate (MO, 85%, iodine value = 73 g I_2 per 100 g), methyl stearate (MS, >96%), dimethyl sebacate (DMS, 99%), diethyl sebacate (DES, 98%), dimethyl carbonate (DMC, anhydrous, >99%), diethyl carbonate (DEC, anhydrous, >99%), sodium hydride (NaH, a 60% dispersion in mineral oil, washed three times with n-hexane before use), N,N-dimethylformamide (DMF, anhydrous, 99.8%), and DEHP (99%) were purchased from Aladdin reagent Co., Ltd (Shanghai, China). Phosphoric acid (85%), formic acid (88%), and hydrogen peroxide (H₂O₂, 50%) were provided by Chron Chemicals Co., Ltd (Chengdu, China). The PVC resin employed herein was an SG-5 suspension-grade homopolymer powder with a K-value of 68-66, kindly donated by Jinlu Resin Co., Ltd (Chengdu, China). The thermal stabilizer composition included a calcium/zinc system (5096, Goldstab Organics Pvt. Ltd, India) and a β-diketone compound (Rhodiastab®, Solvay Chemicals, China) in a weight ratio of 10:1.

Synthesis of ester-branched plasticizers *via* Claisen condensation

Four plasticizers branched with one or two short esters were synthesized *via* Claisen condensation between MO, MS, DMS or DES, and an excessive amount of DMC or DEC. Here, a detailed synthesis procedure for ester-branched epoxidized methyl oleate (EB-EMO) was typically introduced. In brief, into a 500 mL flask were added NaH (12 g, 0.5 mol), DMC (360 g, 4.0 mol), DMF (29 g, 0.4 mol), and MO (60 g, 0.2 mol), which was heated up to 55 °C under a nitrogen atmosphere. After 26 h, the paste was neutralized by being poured into excess 1 M aqueous solution of hydrochloric acid, followed by washing with ultrapure water three times. The organic phase was finally subjected to vacuum distillation at 50 °C to recycle excess DMC, affording ester-branched methyl oleate (EB-MO) in 95% yield.

EB-MO was then epoxidized to obtain the plasticizer, employing cheap and environmentally benign hydrogen peroxide as an oxidant that gave water as the only byproduct. First, EB-MO (50 g), formic acid (0.2 g), and phosphoric acid (0.15 g) were mixed homogeneously at 50 °C, into which hydrogen peroxide (40 g) was added dropwise at a constant rate over a period of 3.0 h by using an automatic dripping kit. The mixture was continuously stirred at 50 °C for another 4 h, followed by washing the organic layer successively with 3% (w/w) aqueous solution of sodium bicarbonate and ultrapure water. Once distilled under vacuum, EB-EMO with a yield of 96% was obtained. For comparison, MO was also epoxidized directly under the same epoxidation conditions, yielding an ordinary, linear EFAME plasticizer (EMO).

Ester-branched methyl stearate (EB-MS), dimethyl sebacate (EB-DMS), and diethyl sebacate (EB-DES) were synthesized in a similar way except that they required no epoxidation procedure. The Claisen condensation conditions for all plasticizers reported herein are tabulated in Table 1, with their synthesis procedure and chemical structure illustrated in Scheme 1.

 Table 1
 Synthesis conditions for ester-branched aliphatic ester-derived plasticizers via Claisen condensation

	[Feedstock]/[NaH]/	Temperature	Time	Yield
	[DMC or DEC]/[DMF] ^a	(°C)	(h)	(%)
EB-EMO ^b	1/2.5/20/2	55	26	96
EB-MS ^b	1/2.5/20/2	55	26	93
EB-DMS ^b	1/5.0/40/4	50	36	95
EB-DES ^c	1/5.0/40/4	50	36	92

^a Molar ratio. ^b React with DMC. ^c React with DEC.



Scheme 1 Synthesis procedure and chemical structure of (a) EB-EMO; (b) EB-MS; (c) EB-DMS; and (d) EB-DES.

Preparation of flexible PVC membranes

To obtain flexible PVC membranes with fully compatible compositions that prevented putative artifactual migration of plasticizers, a two-pot dry blending technique suggested by B.I. Chaudhary et al. was adopted.¹⁷ In brief, PVC powder (100 g) and the thermal stabilizer (2.0 g) were first mixed in a container using a spatula, followed by stirring at 90 °C and 40 rpm for 2 min. The plasticizer (50 g), preheated at 90 °C, was then poured into the mixture, which was stirred at 90 °C and 40 rpm until complete plasticizer absorption by visual observation. Thereafter, the blend was heated to 150 °C and meltmixed at 40 rpm using HTK-200 cam rotors (Haer Machinery Co., Ltd, China) for 5 min, followed by being pressed using a CH-0201 two-roll mill (Chuanghong Instrument Equipment Co., Ltd, China) with a rotation speed of 12 rpm at 150 °C for 5 min. Finally, a transparent and flexible PVC membrane with an average thickness of 0.3 mm was obtained, and conditioned in a desiccator at ambient temperature for five days before any characterization.

Characterization

Physicochemical parameters including the acid value, iodine value, epoxy value, and flash point of the as-synthesized plasticizers were measured according to Chinese Standards GB/T 1668-2008,¹⁸ GB/T 1676-2008,¹⁹ GB/T 1677-2008,²⁰ and GB/T 1671-2008,²¹ respectively, with the experimental results tabulated in Table 2. Fourier transform infrared (FT-IR) spectra were recorded on a Nicolet iS10 FT-IR spectrometer (Thermo Scientific, USA) at a resolution of 2 cm⁻¹ after 32 scans. Nuclear magnetic resonance (NMR) spectra were collected on an AV11-600MH NMR spectrometer (Bruker, Swiss) in deuterated chloroform (CDCl₃-d₆, 99.9 atom% D) containing 0.03% (v/v) tetramethylsilane (TMS). Gas chromatography-mass spectrometry (GC-MS) analysis was carried out on an Agilent 7890A/5975C series GC-MS system (Santa Clara, USA) equipped with a Rxi-5 ms capillary column (30 m, 0.25 mm I.D., 0.25 µm) containing 5% diphenyl-95% dimethyl polysiloxane as the stationary phase. Helium (99.999% pure) with a flow

Table 2Physicochemical parameters of ester-branched plasticizerssynthesized from different aliphatic ester feedstocks viaClaisencondensation

	Acid value (mg KOH per g)	Iodine value (g I ₂ per 100 g)	Epoxy value (%)	Flash point (°C)
мо	<0.1	73 ± 2	n/a	n/a
EMO	<0.1	0.5 ± 0.1	4.2 ± 0.2	180 ± 1
EB-MO	<0.1	62 ± 2	n/a	n/a
EB-EMO	<0.1	0.5 ± 0.1	$\textbf{3.6} \pm \textbf{0.1}$	210 ± 2
MS	<0.1	n/a	n/a	173 ± 1
EB-MS	<0.1	n/a	n/a	184 ± 1
DMS	<0.1	n/a	n/a	158 ± 2
EB-DMS	<0.1	n/a	n/a	180 ± 1
DES	<0.1	n/a	n/a	162 + 2
EB-DES	<0.1	n/a	n/a	186 ± 2

rate of 3.0 mL min⁻¹ was adopted as the carrier gas. The column temperature was initially programmed at 100 °C for 5 min, increased to 250 °C at 10 °C min⁻¹, and finally up to 290 °C at 2 °C min⁻¹. The injection temperature was 290 °C. The ionization energy was 70 eV with a scan time of 0.5 s. Identification of the components was performed by matching their recorded mass spectra with the NIST08 Mass Spectral Library. Differential scanning calorimetry (DSC) analysis was carried out on a 204 F1 DSC analyzer (NETZSCH, Germany) that scanned the sample at a heating rate of 10 °C min⁻¹ under a nitrogen atmosphere. Cell proliferation assay was conducted according to ISO 10993-5²² to evaluate the *in vitro* cytotoxicity of the engineered plasticizers. Stress-strain curves of the PVC membranes were obtained using a GT-A1-7000S universal testing machine (Chengdu GT Test Machine Co. Ltd, China) according to ASTM D-638.²³

A HAAKE Phoenix II fogging tester (Thermo Fisher Scientific, USA) was employed to evaluate plasticizer migration from PVC membranes by volatilization at 100 \pm 0.5 °C for 16 h according to ISO 6452:2007²⁴ and DIN 75201-2011-11.²⁵ To determine the resistance of the plasticizers to extraction, the PVC membranes (30 mm \times 30 mm \times 0.3 mm) were soaked in 50 mL *n*-hexane or alcohol and thermostated at 25 \pm 1 °C with a constant stirring speed of 150 rpm. At a fixed time interval, 0.1 mL solvent was withdrawn and analyzed by the GC technique. The accumulative amount of plasticizer extracted with increasing time was calculated by using calibration curves, expressed as the percentage of the initial weight of the PVC membrane. The reported data were mean \pm standard deviation of triplicate samples for each measurement.

Simulation details

All-atom molecular dynamics simulations were conducted using a commercial software package, Materials Studio 8.0, provided by Accelry Inc. (San Diego, USA). The interatomic interactions were described by the COMPASS force field. The van der Waals term was summed by an atom-based approach that truncated atom pairs with a distance greater than 11.5 Å. The truncation was implemented using a quantic switching function with a spline width of 1.0 Å. A buffer width of 0.5 Å was specified to generate the neighbor list. The coulombic interaction was calculated using the Ewald summation method with an Ewald accuracy of 0.01 kcal mol⁻¹ and an update width of 1.0. Andersen and Berendsen algorithms were adopted to maintain a constant temperature and pressure (1 bar), respectively. The time step was 1 fs for all dynamics runs.

To calculate the mobility of the plasticizers within the PVC matrix, a series of PVC-plasticizer binary systems were constructed using the amorphous cell module in Materials Studio 8.0. In brief, one atactic PVC chain with 100 repeat units that were aligned in a head-to-tail orientation with random torsion was first constructed using a literature procedure.²⁶ It was then enclosed, together with ten plasticizers, in a cubic simulation cell at 300 K *via* the "self-avoiding" random-walk method. Finite-size effects were prevented by periodic boundary conditions in all three dimensions. After construction, the cell was

energy-minimized until complete convergence, and subjected to three annealing cycles in which the temperature was escalated stepwise to 500 K and then back to 300 K at intervals of 10 K. At each temperature interval, an NPT dynamic simulation was run until full equilibration. Subsequently, the assembly was equilibrated at 450 K for 10 ns using an NPT ensemble, from which self-diffusion coefficients, D_{α} , of the plasticizers were calculated according to the Einstein relation:

$$D_{\alpha} = \frac{1}{6N_{\alpha}} \lim_{t \to \infty} \frac{d}{dt} \sum_{i=1}^{N_{\alpha}} |R_i(t) - R_i(0)|^2$$
(1)

where N_{α} stands for the number of plasticizers of species α , $R_i(t) - R_i(0)$ is the vector distance travelled by plasticizer *i* over the time interval *t*, and $\langle |R_i(t) - R_i(0)|^2 \rangle$ represents the averaged mean-square displacement (MSD) of plasticizer *i*. The angular brackets indicate averaging over all time origins.

Results and discussion

Chemical structure of ester-branched plasticizers

As a proof-of-concept, MO, the main component of the feedstocks for synthesizing EFAMEs, was first selected as a representative to be ester-branched via Claisen condensation. In the first step, MO was deprotonated in the α -position by a strong base, yielding a resonance-stabilized enolate. The strong base of choice herein was sodium hydride, given that it not only promoted a full conversion unachievable by sodium methoxide, but also precluded transesterification that altered the backbone structure of the feedstock as sodium ethoxide did. Designing low-migrating plasticizers from aliphatic esters should not substantially alter their original structure; otherwise their intrinsic performances were compromised. Next, the carbonyl carbon in DMC was nucleophilically attacked by the enolate, followed by elimination of one methoxy group, yielding an alkoxide, where the doubly α-proton generated was further removed to form a new, highly resonance-stabilized enolate. Note that non-enolizable DMC was present 20 times per MO chain to suppress self-condensation (Table 1). Of course, DEC or other dialkyl carbonates might work as well under elegantly designed conditions, but in that case, transesterification problem arose again that impaired the backbone structure, and hence, intrinsic performances of MO. Finally, aqueous acid, hydrochloric acid herein, was employed to neutralize the enolate and any base still present, resulting in an ester-branched methyl oleate that could be further epoxidized by hydrogen peroxide.

Successful attachment of an extra methyl ester in the epoxidized product could be validated by a combination of the following experimental results. First, from the FT-IR spectra in Fig. 1, we calculated the absorption intensity ratios of carbonyl (1739 cm⁻¹) and C–O (1196 cm⁻¹) stretching to that of methylene (2854 cm⁻¹). Methylene remained stoichiometrically consistent throughout consecutive reactions of Claisen condensation and epoxidation, thus serving as an internal standard



Fig. 1 FT-IR spectra of (a) MO; (b) EB-MO; and (c) EB-EMO. The rationale behind the selection of methylene as the internal standard for quantitative comparison was based on the fact that they remained stoichiometrically consistent throughout Claisen condensation and subsequent epoxidation.

for quantitative analysis. Compared with MO (Fig. 1(a)), EB-MO (Fig. 1(b)) showed a noticeable increase in these two ratios, from 1.15 to 1.45 for carbonyl, and 0.36 to 0.70 for C–O, indicating that extra esters were generated after condensation with DMC. Upon epoxidation, the double bond-derived absorption (3003 cm⁻¹) disappeared completely (Fig. 1(c)), accompanied by a notable decrease of the iodine value from 62 to 0.5 g I₂ per 100 g (Table 2), yielding a methyl esterbranched EFAME plasticizer.

Analyzing the ¹H NMR spectrum (Fig. 2) of the epoxidized plasticizer at each step of the functionalization procedure confirmed its engineered structure. Relative to the signal corres-

ponding to methyl protons (1) whose position and integral remained constant throughout the functionalization procedure, the integral under the methoxy resonance signal (7) doubled in EB-MO and EB-EMO, suggesting that those extra methyl esters were in stoichiometric quantities. One could surmise that the ester branch was covalently attached at the α -position, given the integral under the α -proton signal (6) was halved after Claisen condensation. Meanwhile, the attached ester thinned the electron clouds on adjacent protons, and thus the resonance position of the α - (6) and β -protons (5) shifted downfield from 2.2 and 1.5 to 3.3 and 1.8 ppm, respectively. The intermediate EB-MO could be further epoxidized as ordinary, unsaturated fatty acid methyl esters, as evidenced by the appearance of a new resonance signal (4) at 2.9 ppm in EB-EMO assignable to oxirane protons, at the expense of the double bond-associated multiplets (4) ranging from 5.2 to 5.3 ppm in EB-MO.

FT-IR and NMR analysis provided a rough structural snapshot of the engineered plasticizer, but the GC-MS technique unequivocally showed generation of the α -ester, as well as the conversion ratio at each step of the functionalization procedure. According to the GC-MS data presented in Fig. 3(a) and Table 3, the feedstock was primarily composed of methyl oleate (1) with a small amount of methyl stearate (2), in good agreement with specification of the feedstock supplier. These components disappeared completely after Claisen condensation, whereas two new components (3 and 4) with a retention time between 23.1 and 23.8 min were detected (Fig. 3(b)). They were identified respectively as methyl oleate and methyl stearate, both bearing a methyl ester at the α -position



Fig. 2 ¹H NMR spectra of (a) MO; (b) EB-MO; and (c) EB-EMO. The signal corresponding to methyl protons (1) was qualified as an internal standard for quantitative comparison in that it was undisturbed with respect to the position and integral throughout the two-step functionalization procedure.



Fig. 3 Gas chromatograms of (a) MO; (b) EB-MO; and (c) EB-EMO. By matching the recorded mass spectra against the NIST08 Mass Spectral Library, the chemical composition of each component was inferred and is tabulated in Table 3.

Table 3 Composition of each component in Fig. 3 as identified by comparing their recorded mass spectra against the NIST08 Mass Spectral Library

				Area (%)			24.11
Peak	(min)	Composition	formula	Feedstock	Intermediate	Product	degree (%)
1	20.2	Methyl oleate	C ₁₉ H ₃₆ O ₂	83.8			95
2	20.4	Methyl stearate	$C_{19}H_{38}O_2$	16.2			94
3	23.3	Ester-branched methyl oleate	$C_{21}H_{38}O_4$		84.1		n/a ^a
4	23.6	Ester-branched methyl stearate	$C_{21}H_{40}O_4$		15.9	14.3	85
5	26.0-26.3	Ester-branched epoxidized methyl oleate	$C_{21}H_{38}O_5$			85.7	n/a ^a

^{*a*} Indeed, components 3 and 5 could not be explicitly identified by the NIST08 Mass Spectral Library. However, their chemical structures could be inferred from their retention time and peak area in Fig. 3, characteristic fragment ions in the recorded mass spectra (ESI, Fig. S10,† m/z 132 and 145, corresponding to dimethyl malonate and dimethyl methylmalonate anionics, respectively), and composition of the feedstock.

(Table 3). This observation indicated that the condensation condition designed herein was rational such that a full conversion to the anticipated intermediate was achieved. Since saturated fatty acid methyl ester was not epoxidizable, the gas chromatogram peak (4) corresponding to ester-branched methyl stearate in the final product remained unchanged with respect to retention time and area (Fig. 3(c) and Table 3). Instead, multiple new chromatogram peaks (5) associated with esterbranched epoxidized methyl oleate were discerned in the retention time range of 25.8–26.5 min, accompanied by a complete consumption of the unsaturated intermediate (3).

EFAME plasticizers of industrial grade are indeed a mixture that also contains varying concentrations of saturated fatty acid methyl esters (e.g., methyl stearate).^{27,28} These saturated components cannot be epoxidized, and hence, barely interact with PVC chains. As such, no matter how leaching-resistant the epoxidized components in an EFAME plasticizer become, the migration problem persists as long as the saturated components remain. The results from foregoing experiments revealed that a small amount of methyl stearate in the methyl oleate feedstock was also engineered with an extra methyl ester over the Claisen condensation procedure. We believed that this branch, although unlikely to qualify methyl stearate as a primary plasticizer, might at least assist interaction with the PVC matrix, contributing to suppressed migration of the EFAME plasticizers as a whole. Thus, the fundamental properties of such ester-branched methyl stearate deserve our particular attention. In addition to EFAMEs, ADEs are another industrially established sub-class of aliphatic ester-derived plasticizers. They are efficient in endowing the PVC products with low temperature flexibility, but their application as primary plasticizers is problematic since they are confronted with the same leaching problem as EFAMEs. In this context, following the preparation of EB-EMO, we decided to synthesize another three branched plasticizers via Claisen condensation using MS, DMS or DES as the feedstock, and an excessive amount of DMC or DEC as the non-enolizable ester, to assess general applicability of the strategy proposed herein. Again, the design concept was to ester-branch the feedstocks without altering their original backbone structures. Accordingly, the non-enolizable ester of choice for DES was DEC instead of DMC. In addition, since DMS and DES possess two α-positions

with equal reactivity, their reaction with dialkyl carbonate yields two ester branches attaching at one feedstock molecule. For the same reason, it is likely that DMS and DES can react not only through intermolecular Claisen condensation, but also intramolecularly to give cyclic β -keto esters. Thus, the dosage of dialkyl carbonates in these two cases was enhanced to 40 times per feedstock chain so as to provide enough reactants and suppress self-condensation (Table 1). Likewise, the chemical structures of the as-synthesized plasticizers were systematically characterized by FT-IR, ¹H NMR, and GC-MS techniques. Similar results (ESI, Fig. S1–S12 and Tables S1–S3†) were obtained as in EB-EMO, demonstrating that the feedstocks were successfully engineered with one short ester at each α -position.

Suppressed migration of ester-branched plasticizers

The design rule that had been established in our previous study based on ester-branched epoxidized methyl ricinoleate provided access to an EFAME plasticizer whose migration was impeded to a level comparable to DEHP.14 To demonstrate that this rule was also applicable to the engineered plasticizers herein, their migration behavior from the PVC matrix was determined by a standardized fogging test and an extraction procedure, respectively. In a PVC-decorated car parked under direct sunlight whose interior temperature can quickly climb up to 78 °C,²⁹ or in a plasticizing oven where the temperature is typically between 130 and 170 °C,³⁰ plasticizer migration by volatilization expedites, fogging the car window, leading to a substantial waste of plasticizers, and finally, burdening the environment. Thus, a fogging tester was first employed to evaluate how the short esters generated from Claisen condensation influenced plasticizer volatilization from PVC membranes at high temperature. In all cases, the engineered plasticizers displayed remarkably enhanced resistance to fogging relative to the parent ones (Fig. 4(a)). In particular, 20.79 \pm 1.56 mg of EMO evaporated from the PVC membrane upon heating at 100 °C for 16 h, approximately 16 times as high as DEHP that exhibited a fogging value of 1.32 ± 0.05 mg. Compared with EMO, EB-EMO turned resistant to volatilization, with its fogging value decreasing more than tenfold to 2.01 ± 0.08 mg, a level quite close to that of DEHP. A similar trend occurred for the other two ADE plasticizers; the presence



Fig. 4 (a) Fogging values of PVC membranes containing ester-branched and the parent plasticizers. (b) and (c) illustrated accumulative percentage leaching of different plasticizers from the PVC membranes as a function of time in *n*-hexane and alcohol, respectively. The solid lines in (b) and (c) represented the fitting results of the experimental data using the simplified version of Crank's migration model (eqn (2)) by linear regression. For comparison, experimental data of DEHP-plasticized PVC membranes were also included in (a), (b), and (c). Error bars show standard deviations calculated from measurements in triplicate.

of one short ester at each α -position resulted in a sharp drop of their fogging values from 121.61 ± 2.18 mg (DMS) and 93.53 ± 2.66 mg (DES) to 27.02 ± 1.89 mg (EB-DMS) and 9.16 ± 1.33 mg (EB-DES), respectively. These results indicated that even though the short esters were attached at the α -position, rather than the midchain of the feedstock as in our previous report,¹⁴ they were still implicated in additional polar interaction and physical interdigitation with PVC at the molecular level, leading to restrained plasticizer migration.

Not only at elevated temperature but also in solvents can plasticizers leach out of the PVC membrane. To evaluate whether the engineered plasticizers also became resistant to extraction, the PVC membranes were soaked in nonpolar *n*-hexane or alcohol with high polarity, where the accumulative percentage leaching of different plasticizers was measured by the GC technique as a function of time. According to the profiles in Fig. 4(b) and (c), all ester-branched plasticizers decelerated in migration relative to the parent ones, regardless of the solvents. In some cases, the engineered plasticizers even migrated at a rate compared to, or much slower than DEHP. For example, the leaching rates of EB-DMS and EB-DES remained quite low in n-hexane, with only 1.9% of EB-DMS and less than 0.3% of EB-DES leached out at the end of the experiment, as against 18.4% of DMS, 6.9% of DES, and more than 20.5% in the case of DEHP. Over the initial phase of the migration or when only a small percentage of plasticizers was extracted throughout the experiment, the migrant in the solvent remained far lower than that in the polymer. Under both circumstances, the migration should follow the simplified version of Crank's migration model:³¹

$$\frac{M_t}{C_{\rm P0}} = 2 \cdot \sqrt{D} \cdot \sqrt{\frac{t}{\pi}} \tag{2}$$

where M_t is defined as the amount of plasticizer leached out at time t, C_{P0} stands for the initial plasticizer concentration in the polymer, while D denotes the diffusion coefficient. Using the least-squares procedure, diffusion coefficients of different plasticizers were estimated from the slope of the linear regression lines fitted to the experimental data in Fig. 4(b) and (c). In terms of high coefficients of determination approaching unity (Table 4), eqn (2) provided fairly good fit to the accumulative leaching data. Moreover, the diffusion coefficients of all ester-branched plasticizers were significantly lower than those of the parent ones; the extent of decline was a complex function of the plasticizer type, the number of α -esters covalently attached, and the solvent where the extraction experiment was carried out. Particularly in the case of

Table 4 Measured diffusion coefficients (*D*) and simulated selfdiffusion coefficients (D_{α}) of different plasticizers from the PVC matrix, obtained by linear-fitting the experimental data in Fig. 4(b) and (c) using eqn (2), and from the slope of the MSD vs. time plots shown in Fig. 5, respectively

	$D \times 10^{-11} (\mathrm{cm}^2 \mathrm{s}^{-1})$		Coefficient of determination		
	<i>n</i> -Hexane	Alcohol	<i>n</i> -Hexane	Alcohol	$\begin{array}{c} D_{\alpha} \times 10^{-3} \\ (\mathrm{cm}^2 \mathrm{s}^{-1}) \end{array}$
DEHP	4346.6	43.2	0.9825	0.9921	15.9
EMO	3988.3	896.9	0.9463	0.9970	45.4
EB-EMO	1347.8	213.4	0.9990	0.9884	9.4
DMS	1493.1	1874.3	0.9993	0.9996	32.7
EB-DMS	5.8	30.1	0.9647	0.9689	5.3
DES	43.5	$1018.4\\107.4$	0.9816	0.9923	16.3
EB-DES	0.08		0.9850	0.9605	11.1

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EB-DMS and EB-DES, the presence of two ester branches in each plasticizer reduced their diffusion coefficients in *n*-hexane to 5.8×10^{-11} and 0.08×10^{-11} cm² s⁻¹, respectively, not only several hundred times lower than that of DMS and DES, but also incomparably lower than that of DEHP. In alcohol, similar results were visible, demonstrating that the α -esters generated from Claisen condensation had appreciable effects on migration behavior of both EFAME and ADES. Typically, DMS, in its pristine form, was otherwise susceptible to extraction by alcohol, displaying a high diffusion coefficient of 1874.3 $\times 10^{-11}$ cm² s⁻¹, but Claisen condensation with DMC yielded a significantly decreased diffusion coefficient (30.1 \times 10^{-11} cm² s⁻¹), which was quite close to that of DEHP (43.2 \times 10^{-11} cm² s⁻¹) under the same experimental conditions.

Here, we believed that EB-EMO became migration-resistant partially because the small amount of methyl stearate in the feedstock was also engineered with an α-ester branch. To confirm this assertion, we used methyl stearate of reagent grade to synthesize another ester-branch fatty acid methyl ester, EB-MS. Unfortunately, even with an extra ester displaying strong and permanent polarity, the product was not qualified as a primary plasticizer such that EB-MS alone failed to plasticize the PVC powder by the two-pot dry blending technique employed herein. Then, we turned to investigate the compatibility of the engineered methyl stearate with PVC by measuring the temperature at which 2 g of PVC powder dissolved completely in 100 mL EB-MS. As expected, the PVC powder was insoluble in MS even when heated above 200 °C, but the polymer dissolved completely in EB-MS at 160 °C, suggesting notably enhanced compatibility.

According to the aforementioned results, to ester-branch aliphatic ester-derived plasticizers for suppressing migration, Claisen condensation presents the following advance over our previous effort¹⁴ that utilizes acetic anhydride-involved esterification. First, esterification requires specific feedstock that bears unique midchain hydroxyls, whereas Claisen condensation centers around the α -proton, a structural feature shared by all aliphatic esters, thus being applicable to a variety of feedstocks. Second, in the case of EFAMEs that are typically a mixture, esterification only engineers the hydroxy-bearing component, while Claisen condensation affects all components, saturated and unsaturated, contributing to suppressed migration of the plasticizer as a whole. Third, compared with acetic anhydride that has been listed as a U.S. DEA List II precursor,³² short-chain dialkyl carbonates, particularly DMC and DEC herein, are well-established environmentally benign reagents. Currently, the large-scale production of dialkyl carbonates is carried out through a clean (phosgenefree) process, which includes direct insertion of CO₂ into epoxides, allowing possibility and opportunity to alleviate global climate changes and to reduce the dependence of the chemical industry on petroleum-based carbon resources.33 Furthermore, unlike acetic anhydride that is highly corrosive and irritant, DMC and DEC themselves are important organic compounds and chemical intermediates with the label of "green chemicals" by virtue of their biodegradability, low toxicity, and low

bioaccumulation; in particular, they have negligible irritating and mutagenic effects either by contact or inhalation.³⁴ It is equally important that Claisen condensation with DMC or DEC yields relatively safe and recyclable methanol or ethanol as the only by-products, rather than hazardous acetic acid, recovery of which from the wastewater remains a challenge.^{35,36} Since DMC and DEC display reasonably low boiling temperature (90 °C for DMC; 126 °C for DEC), and are immiscible with water, excess DMC and DEC can be recycled from the reactants by simple vacuum distillation, which is also in line with the concept of green chemistry.

The measured phenomenology was further verified by a full-atomic molecular dynamics simulation that reproduced a series of PVC amorphous cells containing a fixed number of different plasticizers. Accurate simulation of the PVC material was validated by comparing specific properties estimated from calculation with experimental values (ESI, Table S4†). Following annealing, the binary cells were equilibrated for 10 ns using an NPT (T = 450 K; P = 1 bar) ensemble, from which the MSD *vs.* time plots of the plasticizers were obtained (Fig. 5) for self-diffusion coefficient calculation. From the results tabulated in Table 4, we found that the ester branches, from a com-



Fig. 5 MSD of different plasticizers within a well-equilibrated PVC amorphous cell over a 10 ns NPT (P = 1 bar; T = 450 K) dynamics run. To exclude the initial anomalous diffusion regime as well as quality decline of statistics over a long time, only the parts with simulation time in the range of 1–5 ns, where the slope of the double logarithmic plots of MSD vs. time approached unity, were chosen for self-diffusion coefficient calculation.

putational perspective, were particularly effective in counteracting migration of EMO and DMS. In their pristine form, EMO and DMS migrated much faster than DEHP over the NPT dynamics run, manifested by their self-diffusion coefficients being 2–3 times higher than that of DEHP. Once engineered with one ester branch at each α -position, their self-diffusion coefficients decreased sharply to 9.4×10^{-8} and 5.3×10^{-8} cm² s⁻¹, respectively, indicating that the engineered plasticizers migrated within the PVC model now at a rate much slower than DEHP (15.9×10^{-8} cm² s⁻¹).

Other performances of ester-branched plasticizers

In general, one unique advantage discriminating aliphatic ester-derived plasticizers from other alternatives is that they display much higher plasticizing efficiency than DEHP.³⁷ Since the α -esters attached on EFAMEs and ADEs in this study were only three or four atoms long, we envisioned that those short esters might not substantially influence the intrinsic performances of the parent plasticizers. To evaluate this assertion, we measured the glass transition temperature of the PVC membranes using the DSC technique (Fig. 6). We observed no significant difference in glass transition temperatures of the PVC membranes containing the same amount of EB-EMO and EMO. Even in the case of EB-DMS and EB-DES that were engineered with two α -esters, the glass transition temperatures of the PVC membranes were only 4-5 °C higher than those containing DMS and DES, indicating hardly effected plasticizing efficiency. This conclusion was also confirmed by molecular simulation, from which we found an almost identical frac-



Fig. 6 DSC curves of PVC membranes containing ester-branched and the parent plasticizers. The glass transition temperature was determined as the midpoint of the endothermal displacement.



Fig. 7 (a) Atomistic simulation of binary PVC-plasticizer cells showing the free volume enclosed by Connolly surfaces that were generated with a Connolly radius of 1.5 Å. The atoms and bonds constituting the polymer and plasticizers were rendered as lines. The Connolly surfaces facing the free volume side were in blue while the opposite side in gray. (b) Fractional free volume of the binary PVC-plasticizer cells, calculated as the ratio of free volume to the total volume of the simulation cell. Error bars show standard deviations calculated from the last 100 ps of the dynamics simulation.

tional free volume of the PVC-plasticizer binary cells before and after the plasticizers were ester-branched (Fig. 7). In addition, the stress–strain curves of the PVC membranes were also experimentally obtained. It was found that the mechanical properties of the membranes were not compromised by the ester-branched plasticizer relative to the corresponding control (ESI, Fig. S13[†]).

Finally, we evaluated the *in vitro* cytotoxicity of the engineered plasticizers using MTT assay. As shown in Fig. 8, incubation with EB-EMO, EB-DMS or EB-DES did not cause a sig-



Fig. 8 Cytotoxicity of ester-branched and the parent plasticizers. L929 cells were seeded at 10^4 cells per well, and cultured with each plasticizer with a fixed concentration of 0.1 mg mL⁻¹ for three days. Then, cell viability was evaluated by using MTT assay. Polystyrene wells and latex were used as negative and positive controls, respectively. The MTT absorbance was normalized with that of the negative control. Statistical analysis was performed with Student's *t* test compared with the negative control. NS, not significant; * *P* < 0.05.

nificant decrease of cell viability relative to the negative control, in sharp contrast to latex and DEHP that displayed evident cytotoxicity. Also, we observed no significant discrepancy in cell viability between the ester-branched and the parent plasticizers, indicating that Claisen condensation with DMC or DEC had no detrimental effect on cytotoxicity of aliphatic ester-derived PVC plasticizers.

Conclusions

In summary, we have demonstrated a potentially general and green approach for functionalizing aliphatic ester-derived plasticizers with short ester branches that suppress their migration from the PVC matrix. This approach exploits Claisen condensation with judiciously selected dialkyl carbonate, an established "green chemical", and is, in principle, amenable to any aliphatic ester regardless of its composition. Indeed, a simple literature search for aliphatic ester-derived plasticizers, either industrially established or still at a laboratory scale, unearths a large number of varieties. By combining this set of plasticizers with the approach reported herein, the scientific community can create many new DEHP alternatives with unprecedented performance, helping the PVC industry find its way out of the sustainability plight it is now confronted with.

Conflicts of interest

There are no conflicts to declare.

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