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Covalently Linked Plasticizers: Triazole Analogues of Phthalate Plasticizers Prepared by mild Copper-free “Click” Reactions with Azide-functionalized PVC

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Copper-free azide-alkyne click chemistry is utilized to covalently modify polyvinyl chloride (PVC). Phthalate plasticizer mimics di(2-ethylhexyl)-1H-triazole-4,5 dicarboxylate (DEHT), di(n-butyl)-1H-1,2,3-triazole-4,5-dicarboxylate (DBT), and di(methyl)-1H-triazole-4,5-dicarboxylate (DMT) are covalently attached to PVC. DEHT, DBT, and DMT have similar chemical structures to traditional plasticizers di(2-ethylhexyl) phthalate (DEHP), di(n-butyl) phthalate (DBP), and dimethyl phthalate (DMP), but pose no danger of leaching from the polymer matrix and forming small endocrine disrupting chemicals. The synthesis of these

1 Supporting Information is available online from the Wiley Online Library or from the author.
covalent plasticizers is expected to be scalable, providing a viable alternative to the use of phthalates, thus mitigating dangers to human health and the environment.

1. Introduction

Polyvinyl chloride (PVC) is one of the most widely utilized plastics. It is found in a wide range of consumer products such as packaging, cling films, bottles, credit cards, CDs and DVDs, and imitation leathers as well as in construction materials such as window frames, cables, pipes, flooring, wallpaper and window blinds. PVC is also used in blood storage bags as well as in many other medical devices. Pure PVC is brittle; in order to obtain the desired durability and flexibility, and to allow for extrusion molding of consumer products, PVC is mixed with large amounts of plasticizers.\(^1,2\) The most common plasticizers are low molecular weight esters of phthalic acid such as di(2-ethylhexyl) phthalate (DEHP) 1 (also known as dioctyl phthalate, DOP), di(isodecyl) phthalate (DIDP), di(isononyl) phthalate (DINP), di(n-butyl) phthalate (DBP) 2, and di(methyl) phthalate (DMP) 3, as well as esters of adipic acid such as di(2-ethylhexyl) adipate (DEHA).\(^3\) These low molecular weight plasticizers have a tendency to migrate to the surface of the PVC matrix when it comes into contact with air, liquid, and some absorbent solid materials.\(^3-7\) The loss of plasticizer causes changes in the physical properties of PVC, contributing to loss of flexibility with aging and contamination of the environment.\(^8,9\) Leaching of DEHP out of blood bags and food packaging is a major route into the human body. Many of these plasticizers are suspected to be carcinogens. The metabolic products of DEHP and other phthalates are believed to behave as endocrine disruptors,\(^10\) particularly in young males.
DEHP is under strong scrutiny because of its reprotoxic properties in rats. It is commonly accepted that exposure to high levels of DEHP should be avoided by newborns, trauma patients, and pregnant women. Recently, mono(2-ethyl-hexyl) phthalate (MEHP), the main active metabolite of DEHP, has been demonstrated to increase the production of reactive oxygen species (ROS), resulting in oxidative damage, apoptosis, and differential expression of redox-sensitive genes. The lipophilicity of DEHP enables it to enter the body in many different ways, passing through the skin and pulmonary tissues in addition to oral and intravenous routes of exposure. However, blood bags made of PVC with DEHP enhance the survival rate of red blood cells used in transfusion.

Multiple alternatives to phthalate plasticizers have been investigated, including the use of adipates, succinates, glutarates, terphthalates, trimellitates, sebaccates, and citrates. Plasticizer migration can also be suppressed by blending PVC with polymeric plasticizers such as poly(caprolactone) and poly(butyleneadipate). Although many of these plasticizers have less tendency to migrate compared to DEHP, they reduce the chain mobility and flexibility of the PVC. Another approach to minimizing plasticizer migration from PVC is to chemically crosslink PVC with diamines. For example, use of isophoron diamine (IPDA) as a PVC crosslinking agent resulted in reduced DEHP migration, but thermal degradation of the PVC was enhanced. Recently, our group has investigated polymerized 4-vinyl-phthalates as an alternative to traditional phthahlate plasticizers. These polymeric phthalates in PVC blends are expected to minimize plasticizer migration and are unlikely to be metabolized into endocrine disrupting chemicals. However a significant drawback to this approach is the multistep synthesis required to prepare the vinyl phthalate monomers. New generation plasticizers di(2-ethylhexyl) terphthalate (DEHTP) and di(isononyl) 1,2-cyclohexanedicarboxylic acid (DINCH) (Figure
show lower migration rates than DEHP,\textsuperscript{[14]} yet are still able to leach out to contaminate the human population, and the environment.

![Chemical structures of phthalate plasticizers](image)

\textbf{Figure 1:} Chemical structures of common phthalate plasticizers 1-3, several current substitutes 4-6, and new triazole mimics 7-9.

The most effective approach to avoid migration of plasticizer from the PVC matrix is to covalently attach the plasticizer to the polymer. The covalent modification of PVC by displacing chlorine with the thiol derivatized plasticizer di(2-ethylhexyl) 4-mercaptophthalate (DOP-SH) 4, and di(2-ethylhexyl) 5-mercapto isophthalate (isoDOP-SH) was recently demonstrated by Reinecke et al.\textsuperscript{[22]} The resulting materials showed good plasticization and zero migration, however the viability of using this elegant approach is restricted by the cost of preparing the thiol phthalate esters. Historically, PVC has been modified by simple nucleophilic substitution of the chlorine atoms; the most common nucleophiles have been azide, thiolates, thiocyanate,
There are a number of reports of PVC being converted into PVC-N$_3$ in which some of the chlorides have been replaced by azide groups. The degree of substitution depends on the polarity of the solvent, temperature, and the duration of the reaction. Up to 66% displacement of chlorine atoms by azide groups can be achieved in DMF at 100° C.

The Huigsen 1,3-dipolar cycloaddition, colloquially known as a “click” reaction, has become a powerful tool for the transformation of azide groups into triazoles. Triazoles are flat aromatic rings, similar in size and shape to benzene rings. Treatment of alkyl azides with acetylenedicarboxylate esters result in the formation of 1,2,3-triazoles bearing esters at the 4 and 5 positions. Bakker et al. deployed the popular azide/alkyne copper catalyzed “click” reaction to append a ferrocene group pendant to a PVC membrane as an electron transducer to formulate an electrochemical ion sensor. Recently, Bakker’s group has also demonstrated functionalization of plasticized PVC membranes bearing partial azide substitution to attach fluorophores to the surface. Kébir et al. have attached cationic copolymers to PVC bearing partially azidized surfaces by copper catalyzed click reaction to impart bactericidal properties. To install a phthalate plasticizer analogue, Huisgen cycloaddition of PVC-N$_3$ with di(2-ethylhexyl) acetylenedicarboxylate would form compound 7, in which R is the PVC chain. This triazole is expected to mimic phthalate ester 1. Alkynes bearing ester groups on both termini are extremely electrophilic, thus enhancing the thermal 1,3-dipolar cycloaddition reaction by lowering the LUMO of the alkyne. Huisgen thermal cycloadditions with very electron-poor alkynes proceed near or at room temperature in the absence of a metal catalyst, providing materials free of metal (particularly copper) contamination. There are a few reports of such copper-free Huisgen cycloadditions with electron poor alkynes under thermal conditions. Thus triazoles formed
from acetylenedicarboxylate esters should be easily prepared from PVC-N$_3$; these phthalate mimics will be covalently linked to the PVC chains. Herein is a preliminary investigation into the synthesis of these covalently-bound phthalate mimics.

2. Results and Discussion

Synthetic modification of polymers results in polydisperse products, which are not amenable to facile characterization by $^1$H and $^{13}$C NMR or mass spectrometry. Thus two small molecule models were investigated to confirm the viability of the key Huisgen cycloaddition with dialkyl acetylene dicarboxylates using well-defined secondary alkyl azides.

2.1. Small Molecule Models

Azide substitution on PVC can take place either by the S$_{N}$2 mechanism at secondary alkyl chlorides or by the S$_{N}$2' mechanism at secondary allylic chlorides, generated by thermal, photo, or chemical dehydrochlorination of PVC.$^{[29,44-47]}$ Two low molecular weight compounds: 3(chloroheptyl)benzene 11 and (1-chloroethyl) benzene 13 were selected as small molecule models for secondary alkyl and secondary allylic chlorides of PVC (Scheme 1). The benzylic substrate 13 was obtained commercially whereas the secondary alkyl substrate 11 was synthesized by converting hydrocinnamaldehyde into 1-phenylhept-3-ol 14 by addition of $n$-BuLi, and subsequently transforming the alcohol into chloride 11 using thionyl chloride.
Scheme 1: Synthesis of secondary alkyl chloride 11; azidation of small molecule models 13 and 11, and partial azidation of PVC 10

The benzylic chloride 13 underwent straight-forward azidation using Amberlite 400/N₃ resin (Scheme 1). The azidation of (3-chloroheptyl) benzene 11 was carried out in dimethylformamide with NaN₃ at 60°C to yield secondary alkyl azide 16. The distinctive peak at 2100-2000 cm⁻¹ in the FTIR spectra of 15 and 16 is characteristic of the azide functional group. The initial thermal Huisgen cycloaddition of benzylic azide 15, following the general procedure of Brimble et al.[32] used 50 equivalents of commercially available dimethyl acetylenedicarboxylate (DMAD) 18a at 100°C for 40 minutes to form 19a (Table 1 in supporting information). This reaction was repeated with fewer equivalents of DMAD and at lower temperatures. The reaction went to
completion in 40 minutes at 50° C using only 1.5 equivalents of DMAD. Under ambient temperature, the reaction was complete within 22 hours with 1.5 equivalents of DMAD, both as a neat reaction, as well as in deuterchloroform solution as an NMR tube experiment. Subsequent cycloaddition reactions on model substrates 15 and 16 were carried out in chloroform at 0.3 M for 22 hours. Di(n-butyl) acetylenedicarboxylate (DBD) 18b and di(2-ethyl-hexyl) acetylenedicarboxylate (DEHAD) 18c were prepared by Fischer esterification of the diacid, as shown in Scheme 2.

Scheme 2: Fischer esterification to form dialkyl acetylenedicarboxylates 18b,c; thermal “click” reactions to prepare triazoles 19a-c and 20a-c, and triazoles attached to PVC 21a-c
Treatment of small model alkyl azides 15 and 16 with 1.5 equivalents of acetylene-dicarboxylates (18a-c) at room temperature resulted in 1,3-dipolar cycloaddition to give derivatives 19a-c, and 20a-c (Scheme 2). Triazoles 19a-c and 20a-c were fully characterized by $^1$H NMR, $^{13}$C NMR, IR, and high resolution mass spectrometry (HRMS). The disappearance of the azide peak at 2100-2000 cm$^{-1}$ accompanied by the appearance of peaks at 1725-1635 cm$^{-1}$ attributed to carbonyl (C=O), and 1550-1500 cm$^{-1}$ attributed to the triazole (C=N) in the FTIR spectra of 19a-c and 20a-c provide a convenient method to monitor the formation of the triazoles (Figure 2, spectra A and B).

Figure 2: FTIR spectra of A: 1-chloroethyl benzene 13, 1-azidoethyl benzene 15, and bis(2-ethylhexyl)-1-(1-phenylethyl)-1H-1,2,3-triazole-4,5-dicarboxylate 19c; B: (3-chloroheptyl) benzene 11, (3- azidoheptyl) benzene 16, and bis(2-ethylhexyl)-1-(1-phenyl-heptan-3-yl)-1H-
1,2,3-triazole-4,5-dicarboxylate 20c; C: PVC, PVC-N₃ 17, and PVC-DEHT 21c; D: ¹H NMR and ¹³C NMR of PVC-DEHT 21c in DMF-d₇.

2.1. Modification of PVC

Following the procedure of Rusen et al.,[³¹] PVC 10 was partially converted into PVC-N₃ 17 with the use of NaN₃ in dimethylformamide at 62° C (Scheme 1). The degree of azidation was determined by elemental analysis (38.17% C, 4.70% H, 9.81% N), indicating 14.7% displacement of Cl by N₃. In the ¹H NMR spectrum of PVC-N₃, the N₃-CH-CH₂ methine is observed as a collection of peaks between δ 3.85-4.22 ppm, the Cl-CH-CH₂- methine protons are observed as a family of peaks between δ 4.31-4.39 ppm, and the N₃-CH-CH₂- and Cl-CH-CH₂- methylene protons are found at δ 2.11-2.50 ppm. From the ¹³C NMR spectrum, N₃-CH-CH₂- and Cl-CH-CH₂- methine carbons are observed as a family of peaks between δ 53.8-55.9 ppm, N₃-CH-CH₂- methylene carbons appear as a family of peaks between δ 42.5-43.2 ppm, and the Cl-CH-CH₂- methylene carbons are found between δ 39.1-39.9 ppm. The characteristic peak of azide functional group at 2112 cm⁻¹ in the FTIR spectrum confirmed the partial azidation of PVC (Figure 2C). PVC-N₃ was then subjected to the key Huisgen thermal cycloaddition at room temperature for 22 h to form triazoles PVC-DHT 21a, PVC-DBT 21b, and PVC-DEHT 21c by copper-free “click” reaction using 1.5 equivalents of DMAD 18a, DBD 18b, and DEHAD 18c (Scheme 2). This cycloaddition reaction was carried out in THF rather than CHCl₃ due to the lack of solubility of PVC in CHCl₃. The conversion of azide to triazole diester groups pendant to the PVC is conveniently monitored by FTIR spectroscopy (Figure 2C): specifically the shrinking of the diagnostic azide band at 2100-2000 cm⁻¹, with concomitant appearance of
the ester C=O band at 1725-1635 cm\(^{-1}\), and C=N band at 1550-1500 cm\(^{-1}\). It is noteworthy that FTIR indicates that a small amount of azide remains in the PVC substrate, whereas the small alkyl azides were converted entirely to triazole under the same conditions, presumably due to steric inaccessibility of some azide groups in the polymeric substrate. Subjecting the “click” reaction of PVC-N\(_3\) to sonication did not improve the conversion. Elemental analysis for PVC-DEHT 21c (49.08% C, 6.62% H, 6.54% N) further supports the transformation of the azide groups to triazole phthalate mimics. \(^1\)H NMR in DMF-\(d_7\) shows a characteristic peak at \(\delta\) 3.29 for the methylene –OCH\(_2\)-CH doublets of the esters, and \(^{13}\)C NMR (and DEPT) peaks at \(\delta\) 156.1 and 157.3 for C=O, \(\delta\) 131.8 and 136.2 for aromatic C=C, and \(\delta\) 64.8 and 66.4 ppm for the –OCH\(_2\)-CH methylene carbons provide further evidence for the formation of PVC-DEHT (Figure 2D). Thus, the attachment to PVC of an aromatic triazole bearing ortho ester substituents occurs under extremely mild conditions. Whether these triazoles function effectively as phthalate-like plasticizers is now under investigation.

3. Conclusion and Future Directions

PVC has been modified to carry pendant triazoles bearing ortho ester groups, as a covalently bonded mimic of phthalate plasticizers. Three different triazoles: PVC-DEHT, PVC-DBT, and PVC-DMT have been prepared using a copper-free “click” reaction, as analogues of traditional phthalate ester plasticizers DEHP, DBP, and DMP. As the triazole diesters are covalently bound to the PVC chain, no migration of these plasticizer mimics is expected. The hydrolysis of these modified PVC materials are expected to be alcohols, avoiding the release of small compounds that can mimic endocrine signaling molecules. These PVC-triazoles mimics are easily
synthesized, and the degree of azidation of PVC can be varied to optimize material properties. The photo- and biodegradation products of these triazole diesters are of importance; these experiments are a current focus. The testing of the physical properties of these plasticizer mimics is now underway. It is hoped that this approach may contribute to solving the worldwide problem of phthalate ester contamination in an affordable manner and on a commercially viable scale.

**Supporting Information**

Table 1, experimental details, $^1$H NMR, $^{13}$C NMR, DEPT and FTIR spectra of small molecules 11, 14-16, 18a,b, 19a-c, and 20a-c, and PVC-derivatives 17 and 21a-c. Supporting Information is available from the Wiley Online Library or from the author.

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triazoles bearing *ortho* esters resembling phthalate diesters. This copper-free cyclization is demonstrated at room temperature: first on small molecule models, then on PVC.

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![Chemical Structure](image)
Supporting Information