Click Chemistry in Functional Aliphatic Polycarbonates

Yu Dai, Xiaojin Zhang,* and Fan Xia*

Click chemistry, one of the most important methods in conjugation, plays an extremely significant role in the synthesis of functional aliphatic polycarbonates, which are a group of biodegradable polymers containing carbonate bonds in their main chains. To date, more than 75 articles have been reported on the topic of click chemistry in functional aliphatic polycarbonates. However, these efforts have not yet been highlighted. Six categories of click reactions (alkyne-azide reaction, thiol-ene reaction, Michael addition, epoxy-amine/thiol reaction, Diels-Alder reaction, and imine formation) that have been afforded for further post-polymerization modification of polycarbonates are reviewed. Through this review, a comprehensive understanding of functional aliphatic polycarbonates aims to afford insight on the design of polycarbonates for further post-polymerization modification via click chemistry and the expectation of the practical application.

1. Introduction

Polycarbonates containing carbonate bonds in their chemical constitutions are divided into two major categories: aromatic polycarbonates and aliphatic polycarbonates.[1] The main role of aromatic polycarbonates is in CDs, DVDs, strong window panes and shields, etc. Aromatic polycarbonates are strong, tough, and highly transparent materials sold under the trade name “Makrolon”. Compared to aromatic polycarbonates, aliphatic polycarbonates have broad biomedical application prospects in scaffolds for tissue regeneration, drug delivery, and antimicrobial due to good biodegradability and biocompatibility.[2] Aliphatic polycarbonates are typically prepared by ester exchange, phosgene condensation, CO₂-epoxy addition polymerization and ring-opening polymerization. The traditional aliphatic polycarbonates, for instance, poly(trimethylene carbonate) (PTMC) and poly(dimethyl trimethylene carbonate) (PDTC), usually go through poor hydrophilicity and slow degradation rate. To alter mechanical properties, control biodegradation, and extend chemical/biological properties of aliphatic polycarbonates, some strategies including crosslinking, copolymerization, and post-polymerization modifications are employed.[3–7] Post-polymerization modifications, for example, the addition of biologically active molecules, will advance their use in biomedical applications, such as controllable drug release. Generally, the methods of post-polymerization modifications have been divided through functional groups such as aryl, alkyl, alkyne, azide, halogen, and carbamate.[8] In particular, post-polymerization modifications of alkene-functional polycarbonates have attracted wide attention in developing advanced biomaterials in recent years.[9] However, the techniques and methodologies that greatly promote the development of functional aliphatic polycarbonates are not yet well highlighted so far. The most outstanding one should be a class of specific and controllable bioorthogonal reactions that are commonly called click chemistry.

Click chemistry that was first fully proposed by Sharpless et al. in 2001 is a method for joining some units together through heteroatom links (C-X-C) to generate new substances.[10] Cu(I)-catalyzed alkyne-azide cycloaddition that was first developed by Sharpless et al.[11] and Meldal et al.[12] is one of the most useful click reactions because azides and alkynes could be incorporated into a molecule at most organic and biological conditions. In most cases, azides and alkynes remain relatively stable and afford 1,2,3-triazoles with Cu(I) as the catalyst under mild reaction conditions.[13] The metal-catalyzed alkyne-azide cycloadditions have been expanded to other metals (Ru, Ag, Au, Ir, Ni, Zn, Ln).[14] It is important to note that copper as well as other metals are toxic to living cells. The metal-catalyzed azide-alkyne cycloadditions are greatly limited for applications in vivo. Cu-free click reactions, particularly strain-promoted azide-alkyne cycloaddition that was developed by Bertozz’s group to overcome the cytotoxicity of copper, could be used in biology, in some cases, living organisms.[15] In addition, the thiol-based addition[16,17] and Diels-Alder reaction that could avoid any copper salt during the reaction[18–21] are also a powerful and widely used tool in click chemistry. The applications of click chemistry have been extended in almost all fields of chemical conjugations from chemistry to materials science.[22] For instance, click chemistry as one of the most powerful tools has been employed in pharmaceutical science, receptor-ligand binding, and biological systems[23] as well as peptide-conjugates[24] and functional soft materials.[25] As claimed by Lahann et al., click chemistry has become a versatile toolbox in the hands of materials scientists to prepare multifunctional materials with unique properties.[26]

In a review published in 2008, Jérôme et al. discussed macromolecular architecture and functionality of biodegradable aliphatic polyesters that are synthesized by ring-opening polymerization of lactones and click chemistry, in particular,
Cu(I)-catalyzed azide-alkyne cycloaddition. They focused their attention on the derivations of poly(ε-caprolactone), poly-lactide, and polyglycolide. This is understandable because functional carbonate monomers or polycarbonates containing azide or alkyn group were only a handful before 2008. In the past 10 years, click chemistry in the synthesis of biodegradable aliphatic polycarbonates has flourished. Using “click” plus “poly-carbonate” as keywords for the topic search in Web of Science, more than 75 articles could be obtained but have not yet been well summarized so far. In this review, we focus on click chemistry that has been used to synthesize functional aliphatic polycarbonates. According to the type of click reactions in synthesizing functional aliphatic polycarbonates, the main part of this review is divided into six categories: (1) alkyn-azole reaction, (2) thiol-ene reaction, (3) Michael addition, (4) epoxy-amine/thiol reaction, (5) Diels-Alder reaction, and (6) imine formation. We also discuss the achieved results of functional aliphatic polycarbonates prepared by click chemistry and the expectation of promising application in the fields of biological and biomedical sciences as well.

2. Click Chemistry in the Synthesis of Functional Aliphatic Polycarbonates

2.1. Alkyne-Azide Reaction

Alkyne-azole reaction, the premier example of click chemistry, is a 1,3-dipolar cycloaddition of alkyne and azide to generate a 1,2,3-triazole. A notable case of alkyn-azole reaction is Cu(I)-catalyzed alkyn-azole cycloaddition that was first reported by Sharpless et al. in 2002. After that, alkyn-azole reaction was developed using other metals as the catalyst. The metal-mediated alkyn-azole cycloaddition has received widespread applications in chemistry and materials science, including polymer science. In the field of functional aliphatic polycarbonates, Jing et al. reported a cyclic carbonate monomer 5-methyl-5-propargyloxycarbonyl-1,3-dioxan-2-one (MPC) that was used to prepare biodegradable aliphatic poly(ε-lactide-co-carbonate) by ring-opening copolymerization with ε-lactide, as shown in Scheme 1. Poly(ε-lactide-co-carbonate) containing pendant acetylene groups was prepared by 2-azidoethyl β-d-glucopyranoside and 2-azidoethyl β-lactoside via Cu(I)-catalyzed alkyn-azole cycloaddition. The functional copolymers showed specific recognition and binding affinity with lectin molecules. MPC, owing to its facile synthesis and good stability, has become a valuable monomer in the synthesis of functional aliphatic polycarbonates. To date, trifluoromethoxy-azobenzene, spiropyran, 2,4-dinitrobenzensulfonyl disulfide, dimethylamine, benzylbenzeneboronic acid pinacol ester, and 4-trifluoromethoxy-azobenzene have been decorated via alkyn-azole click chemistry to develop functional aliphatic polycarbonates such as stimuli-responsive micelles as biosensors or for the controlled release of hydrophobic drugs. Amphiphilic block copolymer PEG-b-PMPC could be used to construct redox-responsive, core-crosslinked micelles via click reaction with the addition of bis-(azidoethyl) disulfide. Other alkyn-containing cyclic carbonate monomers such as 5-methyl-5-propargyl-1,3-dioxan-2-one, 5,5-di(propargy)l-1,3-dioxan-2-one, and methyl-2-O-ethylxoycarbonyl-3-O-propargyloxycarbonyl-4,6-O-carbonylα-o-glucopyranoside were also reported for the preparation of reduction-sensitive polymeric prodrug, tumor-targeting polymeric nanocarriers, and functional sugar-based polymers, respectively. These alkyn-containing cyclic carbonate monomers are capable of improving the property...
of aliphatic polycarbonates such as on-demand drug release, high intracellular doxorubicin accumulation at cancer cells, and low cytotoxicity. It should be mentioned that glycidyl propargyl ether is an alkyne-contained monomer that could be used in the synthesis of alkyne-functionalized aliphatic polycarbonates via CO₂/epoxide copolymerization.\[44–46\]

On the other side, azide groups could be introduced into cyclic carbonate monomer \[47\] or polycarbonate \[48,49\] for further click reaction with alkyne-decorated compounds. We reported six-membered cyclic carbonate monomer with azide groups, 2,2-bis(azidomethyl)trimethylene carbonate (ADTC), which was used to prepare azide polycarbonates via ring-opening polymerization, as shown in Scheme 2.\[50\] Various alkyne compounds (e.g., alkyne-terminated poly(ethylene glycol), propargyl alcohol, dimethylpropargylamine, and propargyl methacrylate) could be conjugated to polycarbonates via Cu(I)-catalyzed alkyne-azide cycloaddition. This provides a facile platform for the synthesis of functional aliphatic polycarbonates. According this useful approach, palmitate,\[51\] poly(methyl acrylate), polystyrene, and poly(t-butyl acrylate)-block-polystyrene\[52\] were successfully grafted to the polycarbonate backbone to generate amphiphilic block-graft copolymers or degradable molecular brushes. Using monomethoxy poly(ethylene glycol) as an initiator, amphiphilic block copolymer PEG-b-P(DTC-ADTC) bearing the pendant azide groups could be synthesized for preparing core-shell redox-responsive polymeric micelles in which the cores are crosslinked via click chemistry with the disulfide-containing dicyne as the crosslinker to enhance the stability of the micelles and improve the drug-loading property.\[53\] To avoid the toxicity of copper and improve biomedical applications such as

Scheme 1. Functional aliphatic polycarbonates bearing pendant alkyne groups for alkyne-azide reaction. Poly(l-lactide-co-carbonate) was synthesized via ring-opening polymerization of l-lactide and 5-methyl-5-propargyloxycarbonyl-1,3-dioxan-2-one and used for grafting glucose and lactose moieties by alkyne-azide reaction. Reproduced with permission.\[31\] Copyright 2007, Wiley Periodicals, Inc.

Scheme 2. Functional aliphatic polycarbonates bearing pendant azide groups for alkyne-azide reaction. Azido polycarbonates were synthesized via ring-opening polymerization of ADTC and DTC. Various alkyne compounds could be connected to azido polycarbonates via alkyne-azide reaction to afford functional aliphatic polycarbonates. Reproduced with permission.\[50\] Copyright 2011, American Chemical Society.
cytocompatible hydrogels for tissue engineering and regenerative medicine, azide polycarbonates were functionalized with dibenzocyclooctyne via copper-free, strain-promoted alkyne-azole cycloaddition.\[54–56\]

Compared to linear counterparts, cyclic polymers have unique physical and chemistry properties.\[57\] Alkyne-azide reaction was introduced to the synthesis of polystyrene macrocycles by Grayson et al. in 2006.\[58\] Scheme 3 presents an example of cyclic polycarbonates that were synthesized via alkyne-azole reaction.\[59\] The terminal hydroxyl groups of linear polycarbonates were transformed to alkyne groups via esterification. A disulfide-containing diazide linker was added to result in bimolecular ring closure via Cu(I)-catalyzed alkyne-azide cycloaddition. The grafted RAFT chain transfer agent could initiate RAFT polymerization of acrylamide derivatives such as N-acryloylmorpholine (NAM) to afford polycarbonate-g-PNAM copolymers that could form unimolecular micelles in water.

### 2.2. Thiol-Ene Reaction

Thiol-ene reaction is an organic reaction that generates alkyl sulfide between thiol and alkene.\[60\] It was first reported in 1905 and has gained prominence for a wide range of applications during the recent twenty years.\[61,62\] Owing to high yield, high reaction rate, stereoselectivity, and thermodynamic driving force, thiol-ene reaction is considered as a click reaction. In the synthesis of functional aliphatic polycarbonates, thiol-ene reaction plays a vital role. In 2008, Parzuchowski et al. described an AB$_2$-type cyclic carbonate monomer containing a primary hydroxyl group, 5-{3-[(2-hydroxyethyl)thio]propoxy}-1,3-dioxan-2-one, which was synthesized by thiol-ene reaction between mercaptoethanol and allyl-containing carbonate monomer. Ring-opening polymerization of \(\text{AB}_2\)-type monomer yielded hyperbranched polycarbonates, as shown in Scheme 4.\[63\] Allyl-containing carbonate monomer could be employed to generate polycarbonates for post-polymerization modification such as the transformation of pendent carboxyl groups using thioglycolic acid\[64\] or hydrophobic chains using 1-dodecanethiol\[65\] by thiol-ene reaction.

It is noteworthy to mention that the most frequently used carbonate monomer for thiol-ene reaction is 5-methyl-5-allyloxycarbonyl-1,3-dioxan-2-one (MAC) that was reported by Jing et al. in 2008.\[66\] Ring-opening copolymerization of \(\ell\)-lactide and MAC and subsequent thiol-ene reaction generated folic acid-grafted block copolymer that had good adhesion and proliferation behavior to cells. They then developed this approach by incorporating allyl groups in the hydrophobic block or the terminal of the hydrophilic segment of amphiphilic block copolymer, as shown in Figure 1.\[67\] This amphiphilic block copolymer could be further modified by thiol-ene reaction with 3-mercaptopropionic acid, 2-(Boc-amino)ethanethiol, and 3-mercapto-1,2-propanediol. After that, functional aliphatic polycarbonates grafted with small molecules\[36,37,68–71\] and drug\[72\] were reported by the combination of ring-opening polymerization of MAC and post-polymerization modification through thiol-ene reaction. Using dithiol-PEG as the crosslinker, allyl-functionalized polycarbonates could form microsized networks.\[73\] Norbornene-functional aliphatic polycarbonates were shown to react with thiols via thiol-ene reaction in a wide range of post-polymerization modification.\[74\]

Besides ring-opening polymerization of cyclic carbonate monomers, CO$_2$-epoxy addition polymerization also plays an important role in the synthesis of functional
aliphatic polycarbonates. 

For example, the copolymerization of limonene oxide and CO$_2$ gave a polycarbonate platform in which the double bond was used for thiol-ene reaction to produce rubber, antibacterial polymer, heat processing grade material, and sea water soluble polymer, as shown in Figure 2. 

In the presence of dithiols, double-bond-containing polycarbonates were able to yield crosslinked polymers with improved thermal properties. Propylene oxide/CO$_2$ polymerization and subsequent allyl glycidyl ether/CO$_2$ coupling reaction as well as further modification with various thiols including mercaptoacetic acid, 2-(Boc-amino)ethanethiol and Boc-cysteine by thiol-ene reaction constructed amphiphilic block polycarbonates. Allyl-functional polycarbonates were modified with 3-mercaptopropionic acid via thiol-ene reaction, followed by reacting with lithium hydroxide, to generate single-ion-conducting polycarbonate electrolyte that showed high ionic conductivity and high lithium ion transference number. The ene-containing monomers such as 1,2-epoxy-4-cyclohexene, 1,2-epoxy-5-hexene, 4-vinyl-cyclohexene-1,2-epoxide, 2-vinylloxirane, allyl glycidyl ether are employed to generate functional polycarbonates via CO$_2$/epoxides copolymerization and the postpolymerization functionalization via thiol-ene reaction provides suitable moieties for further application.

2.3. Michael Addition

Michael addition that belongs to a class of conjugate additions is the nucleophilic addition of a nucleophile to an $\alpha,\beta$-unsaturated carbonyl compound. In the synthesis of functional aliphatic polycarbonates, the $\alpha,\beta$-unsaturated carbonyl groups mainly include (methyl) acrylate and the nucleophiles typically have thiol/amine-containing compounds. In 2010, Zhong et al. reported acryloyl carbonate (AC) and
prepared various functional aliphatic polycarbonates by combining ring-opening polymerization of AC and Michael addition with thiol-ligand such as 2-mercaptoethanol, 2-mercaptoethylamine hydrochloride, 3-mercaptopropanoic acid or l-cysteine, as shown in Scheme 5.[86] Based on this strategy, hydroxyl groups could be introduced into side chain to improve the hydrophilicity of the polycarbonates.[69] Moreover, ethylenediamine and polyethyleneimine could be grafted onto the methacrylamino pendant groups of the polycarbonates to give cationic polycarbonates as potential biomaterials for use as gene vectors.[87] Using 1,6-hexanedithiol as the crosslinker, the pendant acrylate groups in the hydrophobic block of PEG-b-PAC were crosslinked via Michael addition to obtain core crosslinked micelles.[88] It is important to note that vinyl sulphone[89] and maleimide[90,91] containing polycarbonates have also been reported to prepare functional aliphatic polycarbonates by post-polymerization modification via Michael addition. If introducing thiol groups in the polycarbonates, maleimide-decorated compounds could be conjugated to the polycarbonates via Michael addition.[72,92]

Figure 2. Functional aliphatic polycarbonates via the combination of CO₂-epoxy addition polymerization and thiol-ene reaction. These post-polymerization modifications provided a versatile approach to tune the properties of aliphatic polycarbonates. Reproduced with permission.[76] Copyright 2016, Macmillan Publishers Limited, part of Springer Nature.

Scheme 5. Functional aliphatic polycarbonates prepared by combining ring-opening polymerization and Michael addition. Various thiol-containing ligands were conjugated to aliphatic polycarbonates via Michael addition to prepare biodegradable polymers with different functionalities and properties. Reproduced with permission.[86] Copyright 2010, American Chemical Society.
2.4. Epoxy-Amide/Thiol Reaction

Epoxy may be reacted or crosslinked with a wide range of reactants such as amines, anhydrides, phenols, and thiols. A syringe of epoxy glue is one of the most important applications of epoxy resins normally containing at least two epoxide groups that react with a hardener such as triamine. In 2009, He et al. synthesized the allyl epoxidation product of PMAC that was further modified by low molecular weight polyethyleneimine via epoxy-amide reaction to gain polyethyleneimine-grafted polycarbonates as non-viral vectors for gene delivery. Dove et al. present epoxide-functionalized polycarbonates by ring-opening polymerization of trimethylene carbonate monomer. Subsequently, post-polymerization modification of epoxide-functionalized polycarbonates was investigated using a set of amines (e.g., aniline and diisopropylamine) through epoxy-amine reaction and thiols (e.g., dodecanethiol, benzylmercaptan, and thiophenol) through epoxy-thiol reaction, as shown in Scheme 6. Another case afforded by Hedrick et al. is the polycarbonates containing pendant thioether groups that allow for post-polymerization modification of functional epoxides, giving a wide range of sulfonium-functionalized block polycarbonates.

2.5. Diels-Alder Reaction

The Diels-Alder reaction, in particular [4+2] cycloaddition, is a powerful chemical reaction between a conjugated diene and a substituted alkene to afford six-membered systems. Shoichet et al. reported furan-grafted functional aliphatic polycarbonates, poly(2-methylene-2-carboxytrimethylene carbonate-co-D,L-lactide)-g-poly(ethylene glycol)-furan, which self-assembled to form polymeric micelles in aqueous solution and afforded further modification with antibodies through Diels-Alder reaction. Other examples of furan-functionalized aliphatic polycarbonates for Diels-Alder reaction were reported by Wang et al. and Nelson et al. In addition, CO$_2$-epoxy addition polymerization of CO$_2$ and the epoxides such as furfuryl glycidyl ether and glycidyl methyl ether could produce furfuryl-containing polycarbonates that were crosslinked by a variety of maleimide derivatives through Diels-Alder reaction to result in reversible network formation, as shown in Scheme 7. Aside from the furan group, anthracene is also used in Diels-Alder reaction for the preparation of functional aliphatic polycarbonates. Tunca et al. synthesized anthracene-functionalized cyclic carbonate monomer, anthracen-9-ylmethyl 5-methyl-2-oxo-1,3-dioxane-5-carboxylate, for the preparation of anthracene-functionalized polycarbonates that were further clicked with α-furan protected-maleimide terminated-polymers through Diels-Alder reaction.

2.6. Imine Formation

Imine formation including hydrazone, Schiff base, and oxime linkages is an organic reaction that is usually generated by the reaction of amine (e.g., hydrazine, primary amine, hydroxylamine) and aldehydes or ketones. In 2009, Ji et al. developed a pH-sensitive polymeric prodrug in which DOX was connected to the polycarbonate backbone by hydrazone bonds. The other example of amphiphilic polycarbonate conjugates of doxorubicin with pH-sensitive hydrazone linker was reported by He et al. Recently, Shunmugam et al. reported a pH-responsive nanocarrier in which DOX was conjugated to the polycarbonate backbone by oxime bonds. Wooley et al. provided aldehyde-functionalized polycarbonates that were a potential platform for transformation into various active materials via oxime bonds. Yang et al. synthesized amphiphilic block copolymers with aldehyde groups by ring-opening polymerization of a functionalized cyclic carbonate monomer using PEG as the initiator and the copolymers were covalently conjugated with DOX via a pH-sensitive Schiff-base linkage, as shown in Scheme 8.

3. Conclusion

This review has highlighted several click reactions that have been successfully applied in the synthesis of functional
aliphatic polycarbonates, for example, alkyne-azide reaction, thiol-ene reaction, Michael addition, epoxy-amine/thiol reaction, Diels-Alder reaction, and imine formation, summarized in Table 1. Both aliphatic polycarbonates and click chemistry have attracted lots of attention in recent years. No doubt, the emergence of functional cyclic carbonate monomers greatly promotes the development of aliphatic polycarbonates. The past two decades have been the golden age of the design and synthesis of functional cyclic carbonate monomers and aliphatic polycarbonates. It is noteworthy to realize that a novel and facile functional cyclic carbonate monomer may be of the essence in future publications. Similarly, click chemistry has made significant progress in synthetic methodology to date. It is extremely difficult to discover a new click reaction due to a series of stringent criteria of click chemistry. Therefore, it may be time to avert our research focus from synthetic methodology to potential application, particularly in the fields of biological and biomedical sciences. It is well-known that aliphatic polycarbonates are biodegradable and biocompatible materials. In addition, click chemistry has been successfully employed at physiological conditions. Although the materials based on functional aliphatic polycarbonates prepared by click chemistry have been reported to form polymeric micelles, polymeric prodrug, hydrogels, and tissue scaffolds for applications in the fields of drug delivery and tissue engineering, almost all research still remains at the bench and the clinical trial has not yet been carried out as far as we know. We hope to see that the commercial products based on functional aliphatic polycarbonates prepared...
Table 1. Summary of click chemistry strategies employed to synthesize functional aliphatic polycarbonates.

<table>
<thead>
<tr>
<th>Reaction type</th>
<th>Polycarbonate</th>
<th>Reagent</th>
<th>Product</th>
<th>Feature</th>
<th>Limitation</th>
<th>References</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Nearly quantitative yields; a wide range of solvent tolerance</td>
<td>Toxic catalyst</td>
<td>[33–46]</td>
</tr>
<tr>
<td>Alkyne-azide reaction</td>
<td></td>
<td></td>
<td></td>
<td>No toxic catalyst; high yields at ambient temperature</td>
<td>Difficult synthesis of cyclooctynes</td>
<td>[54–56]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No toxic catalyst; the capability of spatial and temporal control of functionality</td>
<td>Side reactions, such as the polymerization of alkene and oxidation of thiol</td>
<td>[36,37,64–74,76–84]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No toxic catalyst; fast reaction kinetics and almost quantitative conversion</td>
<td>Side reactions, such as the polymerization of alkene and oxidation of thiol</td>
<td>[69,86,88]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No toxic catalyst; high selectivity; tunable reaction kinetics</td>
<td>Heat required</td>
<td>[98–103]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No toxic catalyst; highly selective; reversible and sensitive bond</td>
<td>Cross-reactivity with carbonate and amine</td>
<td>[108,109]</td>
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</table>

by click chemistry emerge in the market after clinical evaluation in the future.

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Conflict of Interest

The authors declare no conflict of interest.

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click chemistry, CO2-epoxy addition polymerization, modification ring-opening polymerization, polycarbonates, post-polymerization

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