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Norbornadienes: Robust and Scalable Building Blocks for Cascade “Click” Coupling of High Molecular Weight Polymers

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Supporting Information Placeholder

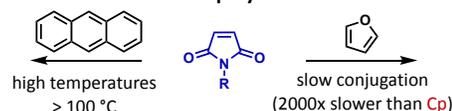
ABSTRACT: Herein we report the development of a scalable and synthetically robust building block based on norbornadiene (NBD) that can be broadly incorporated into a variety of macromolecular architectures using traditional living polymerization techniques. By taking advantage of a selective and rapid deprotection with tetrazine, highly reactive “masked” cyclopentadiene (Cp) functionalities can be introduced into synthetic polymers as chain-end groups in a quantitative and efficient manner. The orthogonality of this platform further enables a cascade click process where the “unmasked” Cp can rapidly react with dienophiles, such as maleimides, through a conventional Diels–Alder reaction. Coupling proceeds with quantitative conversions allowing high molecular weight star and dendritic block copolymers to be prepared in a single step under ambient conditions.

Introduction

The concept of “click” chemistry, first introduced by Sharpless and coworkers in 2001, is based on the philosophy that chemical reactions should be modular, simple, high yielding and orthogonal.¹ These essential characteristics have had a profound impact across the broader chemical sciences, transforming scientific disciplines ranging from bioconjugation to functional polymer synthesis.^{2,3} A range of post-polymerization modification strategies have emerged from the concept of “click” chemistry, enabling the synthesis of polymers with a diverse array of functionalities and architectures.^{4,5} Among these strategies, the copper catalyzed azide–alkyne click (CuACC) represents one of the most highly utilized “click” platforms in polymer synthesis, driven by the synthetic availability of alkyne and azide building blocks.⁶ However, a longstanding drawback for traditional CuAAC-based systems is the presence of metal catalysts. This challenge was mitigated by the development of copper-free or strain-promoted azide–alkyne click (SPAAC) chemistry; based on cyclooctyne derivatives,⁷ the inherent strain in the cyclooctyne ring dramatically increases the rate of the uncatalyzed reaction,⁸ enabling rapid room temperature coupling to azides. However the long-term instability of dibenzozacyclooctyne systems (DIBAC) (storage at $-20\text{ }^{\circ}\text{C}$),⁹ the difficulties in scalability and prohibitively high cost^{10,11} renders general use in functional polymer synthesis challenging. As such,

SPAAC has been mostly limited to small-scale systems such as dendritic¹² or biological applications.¹³

(a) Conventional Diels–Alder for polymer functionalization



(b) Next generation NBD “click” for polymer functionalization

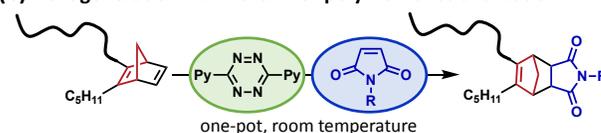


Figure 1. (a) Current methods for maleimide–polymer conjugation using anthracene or furan (b) Strategy reported herein introducing masked Cp into polymers, highlighted by red bonds.

A more cost-effective and scalable metal-free “click” platform for polymer synthesis is the Diels–Alder (DA) cycloaddition reaction. DA systems have been utilized across numerous applications ranging from polymer crosslinking,^{14,15} nanoparticle,¹⁶ surface functionalization,¹⁷ and the preparation of antibody–drug conjugates.¹⁸ Furan or anthracene-based dienes, in combination with maleimide dienophiles, are arguably the most commonly utilized building blocks for DA cycloaddition couplings in polymer synthesis (**Figure 1a**).¹⁹ However, despite their orthogonality, scalability, and wide spread availability, polymeric materials prepared by DA cycloadditions are plagued with certain fundamental limitations. For example, the propensity for furan–maleimide DA adducts to undergo retro Diels–Alder (rDA) reactions renders them unsuitable for applications requiring elevated temperatures.²⁰ Furthermore, the DA cycloaddition of anthracene–maleimide suffers from the necessity for high temperatures and long reaction times to achieve high coupling efficiency.²¹

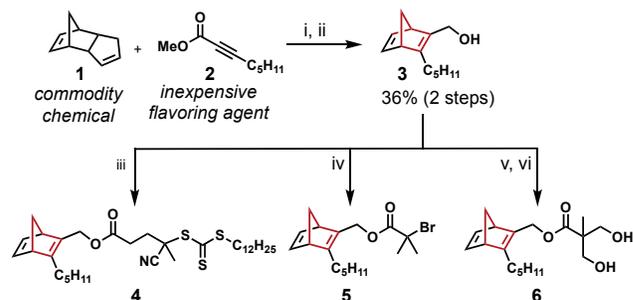
To overcome these challenges, an attractive alternative is to significantly increase the reactivity of the diene or dienophile. Du Prez and co-workers have reported the use of triazolinedione (TAD) compounds as ‘spring-loaded’ dienophiles which react with dienes at room temperature within minutes.²² The high reactivity of TAD compounds offers an elegant method for functionalizing polymers when less reactive dienes are required. In contrast, the reactivity of the diene can be increased through the use of

cyclopentadiene (Cp) derivatives.^{23,24} Recognizing the potential of Cp as a polymer “click” platform, Barner-Kowollik and coworkers have developed synthetic routes to access Cp-functionalized polymers for conjugation with maleimides,²⁵ electron-deficient dithioesters,²⁶⁻²⁸ and carbon nanoparticles.^{29,30} For stable backbones such as polystyrene or poly(ethylene glycol), nucleophilic substitution using ionic cyclopentadienyl salts (NaCp,²⁶ LiCp,³¹ or Me₂AlCp³²) allows for the efficient synthesis of Cp functionalized chain end derivatives. In the case of reactive backbones, such as polyesters, an alternative substitution strategy using nickelocene (NiCp₂) has been developed.^{27,33,34} Despite the success of these strategies, the ability to incorporate Cp has been limited to chain-ends via post-polymerization strategies due to the general instability²⁴ of Cp and its high reactivity towards electron-deficient vinyl monomers.³⁵

Identifying the limitations of general click strategies and the associated promise of cyclopentadiene (Cp) derivatives as a highly efficient coupling platform, we report the development of norbornadiene (NBD) building block as a “masked” Cp unit that can be used for the synthesis of high molecular weight tri-block and star copolymers. Our interest in NBD derivatives is driven by their scalability (derived from inexpensive starting materials such as dicyclopentadiene) and compatibility with a wide variety of polymerization techniques such as reversible addition–fragmentation chain-transfer (RAFT), atom transfer radical polymerization (ATRP) and ring-opening polymerization (ROP). A key insight in this study is the use of a cascade sequence of DA reactions to quantitatively couple the NBD units with dienophiles such as functional maleimides.³⁶ This “unmasking” of the NBD group is mediated by small molecule tetrazine derivatives through an initial inverse-DA reaction leading to the in situ generation of Cp functionalities that can then undergo efficient conjugation with maleimide-functionalized materials (**Figure 1b**). This novel cascade platform is metal-free, air tolerant, and quantitative for even demanding systems such as the coupling of high molecular weight, chain end functionalized linear polymers. This allows well-defined block copolymers to be prepared on multi-gram scale that are difficult to synthesize using traditional polymerization strategies.

Results and Discussion

Initial studies on the scalable synthesis of an NBD derivative employed the commodity chemical dicyclopentadiene (**1**) and methyl 2-octynoate (**2**), an inexpensive and innocuous flavoring agent (\$30 per kg). When **1** and **2** are heated neat in a pressure vessel at 200 °C, the resulting methyl ester can be isolated via distillation and subsequently reduced with DIBAL to furnish the NBD alcohol **3**³⁷ on a 50 g scale in a typical laboratory setting (**Scheme 1**). The simplicity of this process coupled with the availability of alkyne derivatives allows a range of other NBD derivatives to be prepared. A notable example includes the reaction of **1** with propargyl alcohol which affords the unsubstituted NBD alcohol directly.³⁸ Significantly it was observed that the NBD derivatives were stable and could be stored at room temperature under ambient conditions with no observable degradation or instability over 6+ months. In addition, a variety of functionalization reactions can be performed on the NBD building block to give functional initiator units for subsequent polymerization reactions (**Figure S23–S30**). For example, the alcohol **3** can be esterified to give the RAFT chain transfer agent, **4**, the ATRP initiator, **5**, or the difunctional bis(MPA) ROP initiator, **6**, in high yields.



Scheme 1. Synthesis of norbornadiene polymer building blocks. i) neat, pressure vessel, 200 °C, 5 h, 50% ii) DIBAL, THF, 0 °C, 30 min, 71% iii) CDTA, EDC·HCl, DMAP, DCM, rt, 16 h, 92% iv) α -Bromoisobutyl bromide, pyridine, THF, 0 °C, 2 h, 72% v) 2,2-Bis(*tert*-butyldimethylsilyloxymethyl)propionic acid, EDC·HCl, DMAP, DCM, rt, 2 days, 86% vi) TBAF, THF, rt, 2 h, 73%.

Drawing inspiration from small molecule reports^{39,40} and the pioneering development of additive-free polymer functionalization based on norbornene-tetrazine coupling chemistry by Dove, Du Prez, and O'Reilly,⁴¹ we identified norbornadiene (NBD), as a “masked” Cp precursor. Together with the synthetic accessibility demonstrated above, we envisaged that the high ring strain (32.2 kcal/mol)⁴²⁻⁴⁵ would allow for a cascade of selective cycloaddition reactions when used in conjunction with tetrazine.⁴³⁻⁴⁵ This highly efficient process proceeds through an initial inverse electron-demand DA (IEDDA) reaction that releases N₂, followed by a retro-DA (rDA), to yield pyridazine⁴⁶ and Cp as products.^{39,40} This strategy therefore permits the facile incorporation of Cp into a range of materials through the initial introduction of NBD units.

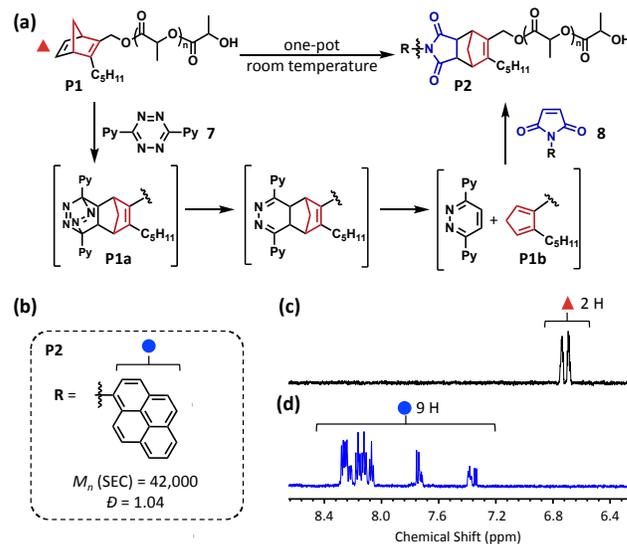


Figure 2. (a) One-pot deprotection of NBD and conjugation with maleimide. Note: quenched with norbornene after 4 h. (b) Pyrene chain end functionality introduced to PLA. ¹H NMR of (c) NBD-functionalized PLA, **P1** and (d) PyrM-functionalized PLA, **P2** in dichloromethane-d₂.

To demonstrate the versatility of **3** as a stable, “masked” Cp unit, end-functionalized polylactide (PLA) **P1** (**Figure 2a**) was prepared using the base-catalyzed ROP of D,L-lactide and **3** as an initiator. Significantly, the resulting polymer was determined to have a degree of polymerization of ~500 ($M_n = 42,000$ g/mol and $D = 1.04$), which compares favorably with the theoretical DP of 440 and illustrates the compatibility of the NBD unit under basic conditions. Additionally, ¹H NMR spectroscopy shows the unique signals for

the alkene present in the NBD units and confirms the efficient introduction of NBD at the end of the high molecular weight PLA chain.

The ability to liberate reactive Cp units was then demonstrated through sequential “demasking” of the NBD group followed by rapid, DA cycloaddition with readily available maleimide dienophiles containing a range of functionality (e.g., dye, biomolecule and photoswitch). From a practical point of view, one advantage of this approach is that the maleimide group lies dormant until the Cp group is revealed leading to a metal-free and room temperature “cascade click” functionalization process.³⁶ The orthogonality of these cycloaddition processes combined with the user-friendly nature of the reaction set-up addresses a number of challenges that exist in the synthesis of complex macromolecular architectures by coupling of polymeric building blocks. To validate the efficient conjugation via a “cascade click” sequence, a solution of **P1** in CDCl₃ was treated with the commercially available tetrazine (DpTz, 2.4 equiv) and *N*-(1-pyrenyl)maleimide (PyrM, 1.2 equiv) at room temperature with no precaution to exclude water or oxygen. As highlighted by **Figure 2a**, the cascade process proceeds through an initial inverse electron-demand DA (IEDDA) reaction with DpTz (**7**) at the unsubstituted olefin of NBD (**P1** to **P1a**). Upon release of N₂ from **P1a** a subsequent retro-DA occurs to yield an in situ generated terminal Cp unit (**P1b**) which undergoes a DA reaction with the functionalized maleimide (**8**) to give the desired pyrene-functionalized **P2**. Following purification

by precipitation, **P2** was obtained in quantitative yield with SEC characterization before and after functionalization confirming no change in molar mass distribution. Significantly, incorporation of pyrene was determined to be >95% by both ¹H NMR and UV-Vis spectroscopy calibrating against known concentrations of PyrM (**Figure 2d**, **S31–34**). Similar reactivity was observed for a range of PLA molecular weights and for maleimides bearing more complex biotin or azobenzene functionalities (**Figure S35–36**, **S39–40**). The ability to employ a wide range of functional starting materials and high (>40,000 kDa) molecular weight polymers highlights the efficiency of NBD as a building block with this “cascade click” strategy representing a viable alternative to both CuAAC and SPAAC.⁴⁷

The facile introduction of reactive Cp units to the chain ends of polymeric systems now opens up the intriguing possibility of coupling stable, end functionalized polymers to give high molecular weight block copolymers and other complex macromolecular architectures. To showcase the potential of this new strategy, a PLA-*b*-PEO-*b*-[G-4 dendron] triblock copolymer (**P5**) was prepared in a single step by coupling of a chain end functionalized PLA-NBD (**P3**, *M_n* = 21,800) derivative with a maleimide-terminated PEO-*b*-[G-4 dendron] (**P4**). Significantly, only a minor excess of **P4** (1.5 equivalents) was required to drive the reaction to completion with SEC showing the expected increase in molecular weight for the desired triblock copolymer and no detectable **P3** (**Figure S48**).

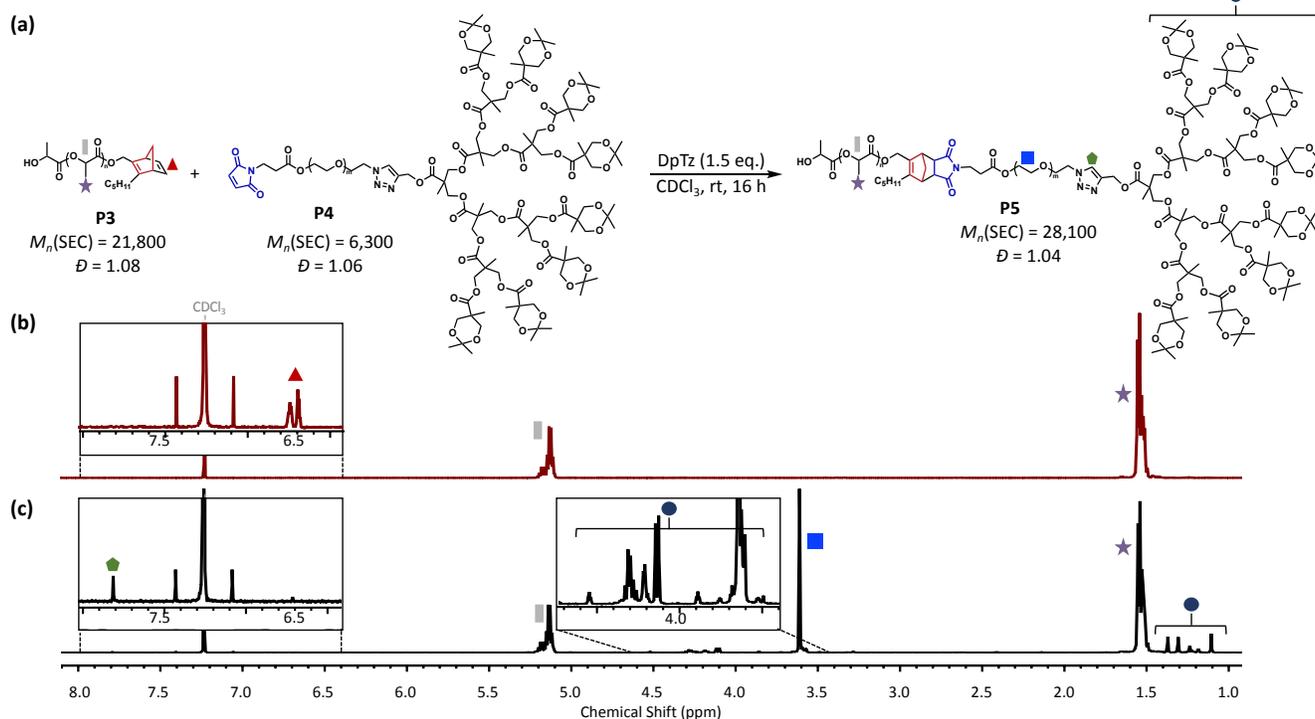


Figure 3. (a) Chemical schematic for synthesis of triblock copolymer, **P5**, using a sequential deprotection-conjugation strategy between NBD-functionalized PLA (**P3**) and maleimide-terminated PEO-*b*-[G-4 dendron] (**P4**); ¹H NMR of (b) NBD-functionalized PLA, **P3** and (c) triblock **P5** in chloroform-*d*.

To further illustrate the power of this cascade click approach for the synthesis of complex macromolecular architectures, we took inspiration from dendrimer and star copolymer targets. The NBD-containing diol **6** was subjected to standard lactide ROP conditions to obtain a two-armed B₂ precursor (**P6**, **Figure 4a**) where a “masked” Cp unit is located at the mid-point of the PLA chain. This allows access to high molar mass AB₂ miktoarm star polymers when coupled with linear maleimide-terminated polymers. Maleimide-terminated poly(*n*-butyl methacrylate) (PnBMA) **P7**⁴⁸

synthesized using metal-free ATRP⁴⁹ serves as the conjugation partner (*M_n*(SEC) 9,600 g/mol, *D* = 1.26) with the corresponding AB₂ PnBMA-*b*-(PLA)₂ miktoarm star copolymer **P8** obtained after room temperature reaction under ambient conditions (**Figure 4a**). It is important to note that excess **P7** was removed by simple precipitation of the crude reaction mixture into a 1:1 v/v/ methanol:isopropanol solution. SEC-RI analysis confirmed the efficient coupling and successful formation of a high molecular weight AB₂ miktoarm block copolymer (**Figure 4b**). ¹H NMR

analysis of **P8** corroborated a quantitative incorporation of *Pn*BMA and PLA blocks (**Figure S53**) based on the stoichiometric reaction between chain-ends and the estimated molecular weight of each precursor. Small-angle x-ray scattering (SAXS) provided additional evidence for efficient conjugation and the absence of unreacted homopolymer. After annealing **P8** at 120 °C for 4 h, multiple Bragg reflections corresponding to well-ordered lamellae were observed with a characteristic length-scale ($q^* = 0.25 \text{ nm}^{-1}$, $d = 25 \text{ nm}$) defined by the self-assembly of the neat and symmetric AB_2 block polymer ($f_{\text{PLA}} \approx 0.5$). As an additional demonstration of the modularity of this platform, a second AB_2 miktoarm star (**S-**

P12) was prepared using polymer precursors of different molar masses, targeting a $f_{\text{PLA}} \approx 0.7$ AB_2 miktoarm (**Figure S55–56**). Upon annealing, the miktoarm block copolymer also exhibited microphase separation, forming hexagonally packed cylinders as evidenced by SAXS (**Figure S57**). The ability to quickly and efficiently link polymer precursors promotes a more facile avenue to tune chemical composition and volume fraction of blocks through this “mix and match” approach. We envision that this strategy will enable easy access to a range of polymeric architectures or potentially afford new opportunities in reactive compatibilization of polymer blends.

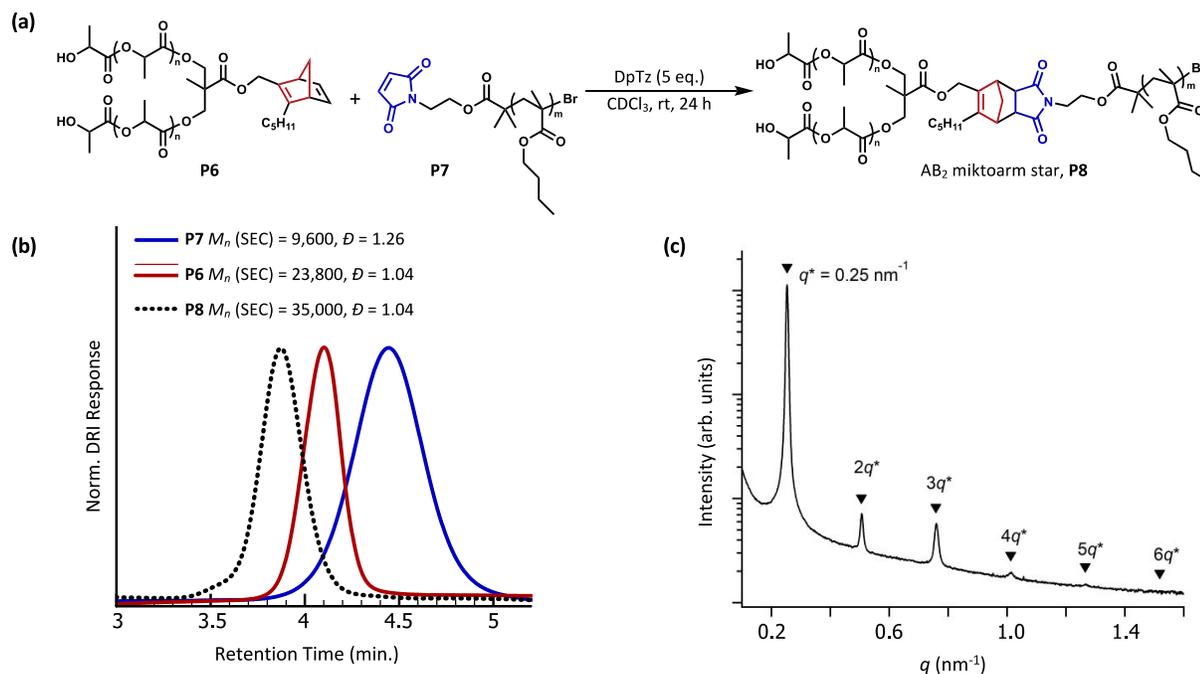


Figure 4. (a) Chemical schematic for one-pot AB_2 miktoarm star formation using a sequential deprotection-conjugation strategy between two-arm NBD-functionalized PLA (**P6**) and maleimide-terminated *Pn*BMA (**P7**) to yield **P8**. Note: quenched with norbornene after 5 h (b) SEC-RI overlay of polymer precursors and purified AB_2 miktoarm star (**P8**) (c) SAXS data confirming self-assembly of **P8** to a well-ordered lamellar structure.

Conclusion

In conclusion, we have developed a cascade click strategy for the facile preparation of high molecular weight macromolecular architectures. Based on synthetically accessible and chemically robust norbornadiene (NBD) building blocks, “masked” Cp units can be introduced into a range of polymeric systems. The general compatibility of the NBD building block with common polymerization techniques (i.e. RAFT, ATRP, ROP) is demonstrated, highlighting the versatility and orthogonality of NBD. Importantly, upon addition of DpTz, quantitative deprotection of NBD to form Cp is observed via a rapid cascade of DA reactions, and in the presence of a variety of functional maleimide derivatives, in situ coupling then occurs via a traditional DA cycloaddition. This metal-free process is highly efficient and requires no heating or precaution for an air- or moisture-free environment. Importantly, it is amenable across an array of functional maleimides, making this strategy accessible to the broader scientific community.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: XX.

Experimental details and characterization data, including Figures S1–S38 (PDF)

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Notes

The authors declare no competing financial interests.

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