Bioorganic Chemistry

**ortho-Quinones and Analogues Thereof: Highly Reactive Intermediates for Fast and Selective Biofunctionalization**

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Abstract: Fast, selective and facile functionalization of biologically relevant molecules is a pursuit of ever-growing importance. A promising approach in this regard employs the high reactivity of quinone and quinolone analogues for fast conjugation chemistry by nucleophilic addition or cycloadditions. Combined with in situ generation of these compounds, selective conjugation on proteins and surfaces can be uniquely induced in a time and spatially resolved manner: generation of a quinone can often be achieved by simple addition of an enzyme or stoichiometric amounts of chemoselective oxidant, or by exposure to light. In this Minireview, we discuss the generation and subsequent functionalization of quinones, iminoquinones, and quinone methides. We also discuss practical applications regarding these conjugation strategies.

Introduction

Bioconjugate chemistry, the science to chemically modify a biomolecule with a functionality of interest, finds purpose in various fields such as chemical biology (e.g. trafficking of fluorescent proteins),[1] healthcare (e.g. genetic profiling with microarrays or antibody−drug conjugates),[2] and industrial biocatalysis (e.g. immobilization of enzymes).[3] A number of reviews have summarized bioconjugation strategies based on either native reactive amino acids,[4−6] introduction of unnatural amino acid tags for selective coupling,[6,7] chemical ligation strategies[8] or chemoenzymatic conversions.[9] However, novel approaches to functionalize natural amino acid residues continue to be discovered,[8] including strategies regarding labeling inside living cells[10] and strategies entailing a selective pre-activation step.[10a]

One class of compounds of particular reactivity are ortho-quinones: central feature of these molecules is a cyclic 3,5-dien-1-one system that is conjugated in an exocyclic manner to either an additional ketone (ortho-quinone), an imine (ortho-iminoquinone) or an alkene (ortho-quinone methide) functionality (Figure 1). Either of these structures enable highly selective and/or rapid conjugation, specifically utilizing their susceptibility towards Michael addition and Diels−Alder-like reactions (vide infra). Of particular convenience in this regard is the option to generate the quinone intermediate directly from a canonical amino acid (tyrosine) that is readily engineered into a protein by conventional molecular biology techniques. In this review, we comprehensively discuss the application of quinones in biomolecular functionalization, including polymerization chemistry, fluorescent labeling, and surface immobilization.

Ortho-quinones

Nucleophilic addition

Ortho-quinones (from now on referred to as quinones) are formed by stepwise oxidation of phenols to 1,2-catechols to quinones by for example, mushroom tyrosinase (mTyr), as shown in Scheme 1A for the oxidation of tyrosine (1) to its quinone derivative (2).[11] Alternatively, quinones can be directly generated from catechols by chemical or by enzymatic means.[3,12] The resulting quinones are highly electrophilic compounds that readily undergo attack by nucleophilic species like a thiol or an amine to afford a stable aromatic conjugate (3). Within the context of a protein, this means that quinones will react with the sidechains of cysteine, lysine, or histidine residues by Michael addition reactions.[3,13]

Utilizing this concept, Kodadke et al. showed that nucleophilic amino acids are able to undergo pseudo-intramolecular cross-coupling when brought in close proximity by two short complementary peptide nucleic acid (PNA) strands.[14] Thus, an in situ generated quinone from 3,4-dihydroxypheynylalanine (DOPA) using sodium periodate (Scheme 1B) underwent Michael addition with specific amino acid residues attached to the complementary PNA strand. Clearly, the hybridized PNA strands ensure close proximity of the intermediate quinone and the nucleophilic amino group on the complementary strand. First, it was found that the α-amino group of alanine was capable of performing this reaction (not depicted), but not when the amine was protected with an acetyl group. Similarly, Kodadke et al. detected products resulting from the cross-coupling by the side-chains of lysine, histidine and cysteine (Scheme 1B), with the thiol of cysteine being the most reactive partner. Finally, lack of reactivity of the side-chains of Arg, Glu, Met, Ser, Thr, Trp, Tyr, Phe and Gln residues corroborated the ability of a free amine, imidazole, or thiol group for Michael addition to quinones, but not of alcohol, guanidine, thioether, indole, carboxylic acid, and amide.
Polymerization and cross-coupling of proteins

The tendency of tyrosine to polymerize upon exposure to oxidizing conditions finds a prominent role in nature in the form of melanin formation, either through copolymerization with cysteine to form pemelamin,[16] or self-polymerization to eumelanin.[18] This phenomenon has been widely studied and applied to for example, grafting of chitosan,[17] and immobilization of proteins to amino-modified polystyrene beads.[18] Despite the fact that phenolic side-chains of tyrosine residues are themselves incapable of nucleophilic attack on quinone residues,[14] Hedstrom et al. were able to show that proteins bearing a tyrosine-rich tag (i.e. hemagglutinin-tag, abbreviated as HA-tag) can be used for protein crosslinking upon addition of free tyrosine.[19] Interestingly, when the HA-tag (YPYDVPDYA) was expressed at the C-terminus of Escherichia coli dihydrofolate (eDHFR), oxidation of the tyrosine-rich tag by mushroom tyrosinase (mTyr) led to the formation of quinones, which combined with the addition of free tyrosine to the mixture led to cross-coupled HA-labelled eDHFR (Scheme 2). This was due to polymerization of tyrosine, with incorporation of the tyrosine-rich HA-tag. This effect was intensified in case of introduction of a more tyrosine-rich tag (GGYGYYGGY). Not surprisingly, in the presence of excess nucleophilic amino acids other than tyrosine, functionalization was observed instead of polymerization, whereas fragmentation of the HA-tag was observed in the absence of any additional amino acid.

The use of tyrosine-bearing tags as employed by Hedstrom et al. allows for modifications on proteins by selective oxidation of tyrosine residues and subsequent functionalization. However, a more selectively addressable coupling strategy is required to prevent non-selective cross-coupling between nucleophilic amino acid residue sidechains and the formed quinones.

Cycloaddition reaction (SPOCQ)

We recently developed an inducible click chemistry-type alternative for the widely applied [3+2] cycloaddition between an organic azide and BCN (SPAAC).[20] Instead of using an artificially incorporated azido group, we utilized the unique propensity of a tyrosine residue for oxidation into a quinone. Incubation of the latter quinone with a strained alkyne was found to lead to rapid cycloaddition in a process conveniently abbreviated as SPOCQ: strain-promoted oxidation-controlled cyclooctyne-1,2-quinone cycloaddition (Scheme 3A).[21] SPOCQ entails in situ oxidation of a phenol or catechol into a quinone, followed by rapid Diels–Alder cycloaddition with the triple bond of a strained alkynyl. In a model reaction between 4-tert-butyl-1,2-quinone 4 and BCN-alcohol 5, a reaction rate of 495 ± 70 M⁻¹ s⁻¹ was determined, leading to cycloaddition product 6. SPOCQ is 2–3 orders of magnitude faster than the strain-promoted cycloaddition of azides and cyclooctynes, but falls somewhat short with respect to tetracene–TCO ligation, the fastest bioorthogonal ligation strategy currently known.[22] However, an important advantage of SPOCQ is that it does not require the introduction of a non-canonical amino acid, for example, by genetic encoding, unlike the aforementioned SPAAC and tetracene-TCO ligation. A noteworthy observation is that SPOCQ proceeds via an inverse-electron-demand Diels–Alder cycloaddition of the LUMO of the quinone with the HOMO of BCN. As a logical consequence, the strained alkyne DBCA[23] also known as DBCO (dibenzocyclooctyne), reacts over 1000× slower (0.19 M⁻¹ s⁻¹) than BCN, due to its much lower-lying HOMO orbital. This difference in reactivity between strained alkyne and quinone parallels that of the relative reaction rate with 1,2,4,5-tetrazine or electron-poor azide.[24]

In order to optimally benefit from the ability to conjugate to a naturally occurring amino acid residue, our lab used the enzyme mushroom tyrosinase (mTyr) to generate quinones on

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proteins by selective oxidation of a tetra-glycyltyrosine tag (G₄Y-tag), which allowed for in situ SPOCQ with a variety of functionalized BCN probes. It was demonstrated that efficient conjugation could be induced within 30 minutes for a C-terminally modified model protein, laminarinase A, and within 6 hours for antibodies with a G₄Y-tag on the C-terminus of each light chain (Scheme 3B). Importantly, no conjugation was observed when the G₄Y-tag was absent, indicating that the approach is selective for artificially incorporated exposed tyrosine residues. The versatility of the method was demonstrated by preparation of an antibody–drug conjugate (ADC), a class of promising chemotherapeutics used for targeted treatment of tumors by combining a highly cytotoxic drug with an antibody specific for an upregulated tumor antigen. The same chemistry was also applied in a variety of different circumstances, revealing its general applicability.

Iminoquinones

Similar to regular quinones, ortho-iminoquinones (7) (from now on referred to as iminoquinones) can be generated from aminophenols (8) upon oxidation with NaIO₄ or K₃Fe(CN)₆, or by photoactivation of azidophenols (9) (Scheme 4). Based on their ability to selectively react with nucleophilic nitrogen atoms like the N-terminus of a protein or the amine functionality of anilines, iminoquinone derivatives have found useful applications in bioconjugation chemistry. After Michael addition of an N-terminal amino acid or aniline residue, tautomerization to 11 occurs and a second oxidation takes place to yield 12 in presence of oxidant (Scheme 4) or 13 if N-
terminal proline was the used as the nucleophile.\textsuperscript{29} It was observed that proline was most reactive and yielded the highest conversion among all amino acid residues.\textsuperscript{29} Francis et al. also observed that NaIO\textsubscript{4} was a more potent oxidant than K\textsubscript{3}Fe(CN)\textsubscript{6} but also gave rise to multiple products, whereas K\textsubscript{3}Fe(CN)\textsubscript{6} only yielded a single product.\textsuperscript{27b} Furthermore, when photoactivation of azido phenols was performed to obtain iminoquinones, coupling with the N-terminus of proteins was not observed due a much higher reaction rate of aniline addition and a general lack of N-terminal coupling at pH 6.0.\textsuperscript{29}

Besides nucleophilic addition, iminoquinones are also able to undergo \((4+2)\) cycloaddition with acrylamides, leading to morpholine-type structures.\textsuperscript{10} Due to the electron-poor character of the acrylamide double bond, cycloaddition in this case proceeds via the regular hetero-Diels–Alder HOMO–LUMO interaction of an alkene with the oxygen and nitrogen atom.

Iminoquinone conjugation in biomolecules has been realized by introducing \(p\)-aminophenylalanine on the external surface of genome-free MS2 capsids using amber stop codon suppression (not depicted).\textsuperscript{27a} The incorporated aniline moieties could be modified by various \(o\)-aminophenol compounds after oxidation with NaIO\textsubscript{4}, including a cyclic penta-amino acid variant of RGD peptide. Comparable results were obtained when the iminoquinone was generated from \(o\)-azido phenols upon irradiation with 302 nm light.\textsuperscript{28} The applicability of this chemistry was not limited to bioconjugation strategies in solution, but was also applicable on surfaces (Scheme 5, top). For example, glass modification with aniline-bearing trimethoxysilane group coupled followed by selective surface patterning with in situ generated iminoquinone (by light irradiation of \(o\)-azidophenol) attached to a single stranded DNA. Subsequent binding of \textit{Saccharomyces cerevisiae}, modified with the complementary DNA strand, allowed visualization of the photolithographic pattern.

Bioconjugation with iminoquinones was also employed to label high-molecular weight polyethylene glycol (PEG) chains to the N-terminus of various proteins (not depicted).\textsuperscript{29} Using K\textsubscript{3}Fe(CN)\textsubscript{6}, a milder oxidant with less side-reactions than NaIO\textsubscript{4},\textsuperscript{27c} oxidation of \(o\)-aminophenols allowed for quick and selective modification of N-terminal residues, with proline having the highest degree of conjugation. This was applied to modify aniline-bearing glass surfaces with enzymes.\textsuperscript{29} Analogously to the light-induced patterning modification of glass, single stranded DNA was introduced by in situ generated iminoquinone via K\textsubscript{3}Fe(CN)\textsubscript{6} oxidation. Next, a complementary strand of DNA was introduced (Scheme 5, bottom), which was linked in an identical fashion to the N-terminal proline residue of fructose–bisphosphate aldolase (ALD). The enzyme was shown to retain its activity after immobilization and could be removed by adding a complementary DNA-strand, regenerating the DNA-bearing glass surface. Finally, fresh enzyme-bearing DNA could be added, and catalytic activity was achieved once more.

**Quinone methides**

Ortho-quinone methides (from now on referred to as quinone methides) are carbon analogues of a regular quinones, with one of the oxygen atoms replaced by a carbon atom (most typically a methylene group). Quinone methide derivatives are widely reported in synthesis and catalysis,\textsuperscript{33} and, by virtue of their DNA alkylation properties,\textsuperscript{34} are known as potent anticancer drugs. Like quinones, quinone methides have both an electrophilic character and a propensity to undergo \((4+2)\) cycloaddition.\textsuperscript{33d,e} In this regard, it is clear that protein modification based on quinone methides requires careful modulation of stability and reactivity. To this end, Rokita et al. explored the ef-

\begin{scheme}
\centering
\begin{tikzpicture}[scale=0.8]
\node at (0,0) {A: NaIO\textsubscript{4}};
\node at (1,0) {B: K\textsubscript{3}Fe(CN)\textsubscript{6}};
\node at (2,0) {C: \text{hv} (302 nm)};
\node at (4,0) {A-C};
\node at (6,0) {A};

\node[draw,rectangle,minimum width=2cm,minimum height=2cm] at (0,0) (A) {
\begin{tikzpicture}[scale=0.5]
\node at (0,0) {R\textsubscript{1}};
\node at (0,1) {O\textsubscript{2}};
\node at (0,2) {NH\textsubscript{2}};
\node at (1,0) {R\textsubscript{2}};
\end{tikzpicture}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] at (1,0) (B) {
\begin{tikzpicture}[scale=0.5]
\node at (0,0) {R\textsubscript{1}};
\node at (0,1) {O\textsubscript{2}};
\node at (0,2) {NH\textsubscript{2}};
\node at (1,0) {R\textsubscript{2}};
\end{tikzpicture}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] at (2,0) (C) {
\begin{tikzpicture}[scale=0.5]
\node at (0,0) {R\textsubscript{1}};
\node at (0,1) {O\textsubscript{2}};
\node at (0,2) {NH\textsubscript{2}};
\node at (1,0) {R\textsubscript{2}};
\end{tikzpicture}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] at (4,0) (D) {
\begin{tikzpicture}[scale=0.5]
\node at (0,0) {R\textsubscript{1}};
\node at (0,1) {O\textsubscript{2}};
\node at (0,2) {NH\textsubscript{2}};
\node at (1,0) {R\textsubscript{2}};
\end{tikzpicture}};
\node[draw,rectangle,minimum width=2cm,minimum height=2cm] at (6,0) (E) {
\begin{tikzpicture}[scale=0.5]
\node at (0,0) {R\textsubscript{1}};
\node at (0,1) {O\textsubscript{2}};
\node at (0,2) {NH\textsubscript{2}};
\node at (1,0) {R\textsubscript{2}};
\end{tikzpicture}};

\draw[->] (A) -- (B);
\draw[->] (B) -- (C);
\draw[->] (C) -- (D);
\draw[->] (D) -- (E);
\draw[->] (E) -- (A-C);
\draw[->] (A-C) -- (A);
\end{tikzpicture}
\end{scheme}
fecteds of substituents on the formation and stability of quinone methide derivatives and their adducts based on nucleophilic addition.\cite{35} Recently, Bieniarz et al. reported covalent labeling of tissue in close proximity of cancer epitopes with in situ generated quinone methides.\cite{36} To this end, a primary antibody was utilized to recognize and bind to a specific cancer antigen, followed by binding of a secondary antibody conjugated to alkaline phosphatase (Scheme 6). Next, incubation with phosphorylated quinone methide precursor 14 led to enzymatic hydrolysis of the phosphate group by alkaline phosphatase to form 15, and subsequent 1,4-elimination of the fluoride group yielded the desired quinone methide 16. The quinone methide reacted with any proximate immobilized nucleophile, or was quenched by any nucleophile in the reaction media (e.g. Tris or water). Despite the high reactivity of the quinone methide, Bieniarz et al. were able to visualize B-cell lymphoma marker BCL6 on tonsil tissue with both biotin and fluorophore markers. This method of proximity-based generation of a quinone methide is similar to a method developed by Li et al.,\cite{37} in which conjugation was achieved by using an affinity tag and subsequently generation of quinone methide by activation with UV light.

Another quinone methide bioconjugation method was developed by Lei et al., who reported that a [4+2] cycloaddition reaction of a vinyl thioether with ortho-quinolinone could be used for cellular organelle imaging (Scheme 7).\cite{38} After incubating quinolinone 17 at 37°C, quinone methide derivatives 18 were formed that were found to undergo cycloaddition with a vinyl thioether. Michael addition of free thiols to the formed quinone methide was also observed, but due to reversibility of this reaction, the [4+2] cycloaddition product 19 was obtained as the main product. When biotin or fluorescein (FITC) were attached to the quinone methide precursor (20 and 21, respectively), labeling and imaging of vinyl thioether-bearing BSA and vinyl thioether-bearing taxol inside live cells was achieved.\cite{38a} A 2nd generation ortho-quinolinone (22) was developed with around 20-fold higher reaction rate (2.8 × 10⁻² M⁻¹ s⁻¹ versus 1.5 × 10⁻³ M⁻¹ s⁻¹) and its bioorthogonality to SPAAC was demonstrated.\cite{38c} While this method is chemoselective and bioorthogonal to the broadly applied SPAAC conjugation approach, the ortho-quinolinone quinone methide requires introduction of the vinyl thioether by a non-selective

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Scheme 5. Glass surfaces bearing aniline residues and their subsequent modification for DNA-directed immobilization. ALD = fructose-bisphosphate aldolase.

Scheme 6. Selective tissue modification by in situ dephosphorylation and generation of quinone methides.
lysine–NHS conjugation strategy. Furthermore, with a reported rate of $2.8 \times 10^{-5}$ M$^{-1}$s$^{-1}$ for the second generation, the reaction is considerably slower ($\approx 10^3$-fold) than SPOCQ$^{[25]}$ or the iminoquinone conjugation methods.$^{[25]}$ Similar to the reaction of acrylamides with iminoquinones, cycloaddition takes place by normal electron-demand Diels–Alder cycloaddition on the oxygen and methylene group.

Summary and Outlook

In this Minireview, we comprehensively discussed the use of quinone and quinone analogues in bioconjugation chemistry. In the last few years, significant progress has been made to utilize these highly reactive compounds through in situ formation and subsequent conjugation via Michael addition or Diels–Alder reaction. The ability to have a trigger-dependent activation of one of the reaction partners, that is, by addition of specific reactants, enzymes or light, enables fast and selective coupling strategies of (large) biomolecules. In principle, such approaches can be applied in cases where one of the two reaction partners remains dormant until the appropriate trigger is added or generated in situ. In a sense, these quinone-based ligation approaches are biomimetic since their occurrence depends on the application of a trigger. In the case of regular quinones, an additional benefit is their accessibility using naturally occurring tyrosine, which can conveniently be incorporated in a protein sequence. Iminoquinones can generated from genetically encoded p-aminophenylalanine, or by appending a aminophenol onto a proteins N-terminus first. Finally, quinone methides have not yet been developed to selectively conjugate to natural amino acids, but quick random conjugation and labelling was achieved by enzymatic means, and two-step conjugation by introduction of vinyl thioethers on lysine residues and subsequent Diels–Alder reaction was realized. Moreover, it has been amply shown that intramolecular nucleophilic reactions of endogenous amino acid side chains is negligible if the competing intermolecular conjugation chemistry is sufficiently fast. Therefore, we expect that future work in bioconjugation with quinone, and its analogues, will find its way in the field of fast and selective protein functionalization strategies.

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Conflict of interest

F.L.V.D. declares that he is also an employee and share-holder of Synaffix BV.

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