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Stability, Kinetic, and Mechanistic Investigation of 1,8-Self-Immolative Cinnamyl Ether Spacers for Controlled Release of Phenols and Generation of Resonance and Inductively Stabilized Methides

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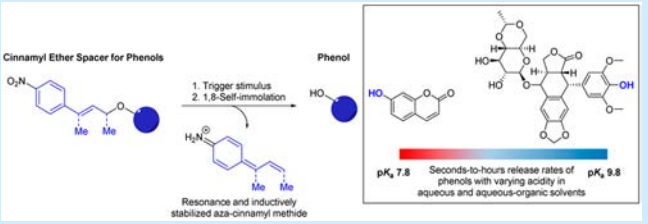
Supporting Information

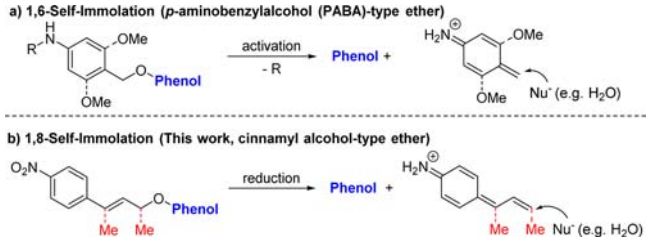
ABSTRACT: Three cinnamyl ether spacers (non-methyl, α-methyl, and γ-methyl) for caging of phenols have been synthesized and are physiologically stable. When triggered, the γ-methyl spacer releases phenols (pK_a 7.8 and 9.8) with a $t_{1/2}$ < 30 s and <2 min in aqueous and aqueous−organic solvent, respectively. The α-methyl spacer releases a phenol (pK_a 7.8) with a $t_{1/2}$ = 27 and 54 min. For the γ-methyl spacer, the results suggest the presence of a resonance and inductively stabilized aza-cinnamyl methide.



The phenolic moiety is a key component for many biologically active drugs, fluorescent probes, and responsive materials.[1] While strategies for protecting phenols in organic syntheses are vast, caging with a self-immolative spacer for prodrug therapy, diagnostics, and responsive materials is mostly limited to esters, carbonates, and benzyl ethers.[1a,2] The ester and carbonate linkers have limited biological application because they only form moderately stable conjugates with higher pK_a phenols or alcohols and can be subjected to nonspecific hydrolysis.[1a,3] On the other hand, benzyl ethers form stable conjugates, and in a strictly aqueous (aq) environment, they have been successfully utilized in the activation of prodrugs.[2b] However, when this translates to a less polar solvent (e.g., 1:1 MeCN/buffer), a requirement for many responsive material applications, the benzyl ether is only capable of slow release of acidic phenols (pK_a <9.2; $t_{1/2}$ < 3 h).[4] Therefore, the need for stable benzyl ether−phenol conjugates still capable of rapid release in prodrug/pro-probe science and the need to control depolymerization rates for responsive materials[2e,5] warrant the investigation of faster self-immolation mechanisms ($t_{1/2}$ = seconds) for use with a broad range of phenols (pK_a 7−10.5).

Since the first report of 1,6-self-immolative *p*-aminobenzyloxycarbonyl/benzyl alcohol (PABC/PABA) spacers,[6] variants have been used as protecting groups in synthesis or for prodrugs,[2b] pro-probes,[3b] and polymers.[7] PABC spacers are beneficial in caged drug/probe design as the amino (or hydroxyl) group can be converted to a trigger designed to stabilize the caged adduct (e.g., NO_2, N_3, *N*-/*O*-acyl) until an appropriate stimulus is introduced.[8] However, phenols (particularly acidic phenols, pK_a <8) and alcohols attached to the PABC spacer via a carbonate are rapidly hydrolyzed under aq and aq−organic conditions, making them poor caging groups for prodrugs/probes.[3b,d] To combat low stability (esters, carbonates) and slow release (from benzyl ethers) for less acidic phenols (pK_a >9.2) in nonpolar environments, benzyl ethers exhibiting reduced aromaticity[2e] and methoxy-substituted benzyl ethers (Scheme 1a)[4] have been reported. The methoxy-substituted benzyl ethers form stable conjugates of phenols and acidic benzyl alcohols and, once triggered, decage phenols with varying acidities (pK_a 7−12).[4] This enables release of phenols from ethers in organics; however, there is still a need to develop broadly applicable and synthetically accessible spacers able to rapidly release phenols of all acidities.

Scheme 1. Self-Immolative Ether Spacer Strategies



To overcome the shortcomings of PABC-linked phenols and increase the applications of ether-linked self-immolative spacers (e.g., in prodrugs and degradable materials), we designed a series of ether spacers based on the cinnamyl alcohol scaffold (Figure 1). 7-Hydroxycoumarin **3** and etoposide **4** were selected as model phenols as they represent examples of phenols that can be used in prodrug/pro-probe science and their leaving group ability in polar and nonpolar solvents can be extrapolated to the

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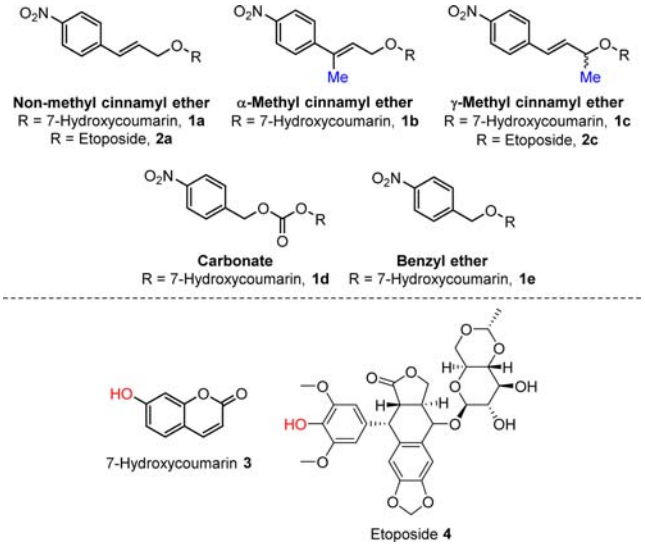

Figure 1. Structures of phenolic pro-probes **1a**−**1e** and prodrugs **2a** and **2c** used in this study.

majority of phenols encountered in the chemist's toolbox.[9] The cinnamyl ether spacers were designed such that they would undergo a 1,8-self-immolation (Scheme 1b) (cf. a 1,6-self-immolation; Scheme 1a). Previous reports by de Groot and co-workers utilizing an elongated self-immolative spacer[10] demonstrated that the increased conjugation resulted in an immolation that was expected to be faster than a PABC-type 1,6-self-immolation. In these examples, they described a *p*-amino-cinnamyloxycarbonyl paclitaxel prodrug (linked via a carbonate ester).[10] However, for phenols, this is expected to be hydrolytically unstable. We hypothesized that by replacing the carbonate ester with an ether, the majority of phenols (pK_a 7−10.5) would form physiologically stable cinnamyl ether-linked conjugates capable of a controlled and rapid 1,8-self-immolation under varying solvent polarities (Scheme 1b). We hypothesized that spacers functionalized with α- and γ-methyl groups (relative to the cinnamyl ether aromatic ring) would further stabilize the partial positive (δ^+) charge of the transition state[11] and therefore lead to accelerated rates of release over less conjugated PABC/PABA-type linkers and non-methylated cinnamyl ethers (Scheme 1 and Figure 1). Herein, we demonstrate that the cinnamyl ether spacer is a physiologically stable caging group with varying rates of decaging that can be programmed by the absence, presence, and location of a methyl group. In 1:1 aq−organic solvent, the rate of the self-immolation for the γ-methyl spacer is similar to that of the PABC spacer and the methoxy-substituted benzyl ether spacer.[4] The α-methyl-substituted linker resulted in a slower rate of release. These rate-differing spacers could have potential in chemotherapy, imaging, degradable polymers, and synthesis.[12]

In this study, 7-hydroxycoumarin **3** (pK_a 7.8)[13] and etoposide **4** (pK_a 9.8)[14] were selected as model phenols; **3** has a pK_a representative of other fluorescent/bioluminescent probes, and **4** has a pK_a representative of most phenols (pK_a 10) encountered in a chemist's toolbox.[9] The nitro group was selected as the trigger so that release could be initiated via complete reduction to the amine with zinc/acetic acid;[10a,15] however, the trigger could be modified to suit the desired stimulus for future applications. Due to the importance of caging strategies in imaging (e.g., fluorescence, near-IR, bioluminescence), we focused our initial efforts on the stability and rate of release of **3** from the cinnamyl ether spacers **1a**−**1c**, the related carbonate ester **1d** (PABC/PABA analogue), and benzyl ether (PABA analogue) **1e**, whose syntheses via cinnamyl bromides **6**, **9**, **13**, activated ester **15**, and benzyl bromide **16**, respectively, are described in section S2 and Scheme S1.

The instability of the carbonate in **1d**, compared to the cinnamyl ether spacers of **1a**−**1c** under aq conditions (PBS and 4.5:4.5:1 mouse serum/PBS/DMSO) was confirmed in our initial stability studies (Figure 2 and sections S3.1 and S3.3). In

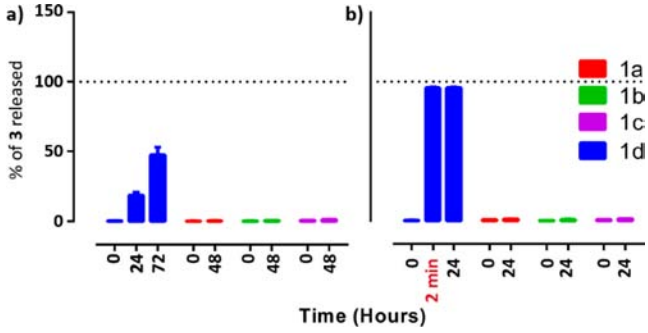

Figure 2. Release of **3** measured by fluorescence (ex. 360 nm, em. 455 nm), demonstrating the stability of **1a**−**1d** in (a) PBS and (b) 4.5:4.5:1 serum/PBS/DMSO (sections S3.1 and S3.3).

1:1 mouse serum/PBS (with 10% DMSO), cinnamyl ethers **1a**−**1c** did not release **3** over 24 h, whereas complete release of **3** from carbonate **1d** was observed in just 2 min. HPLC analysis confirmed that the spacers **1a**−**1c** remained intact and that there were no other degradation processes occurring (Table S1 and Figure S3).

The quantity of **3** released and its rate of release from **1a**−**1e** were then investigated using fluorescence (aq; PBS) and HPLC-UV (aq−organic solvent; 1:1 PBS/MeCN) (Figure 3 and section

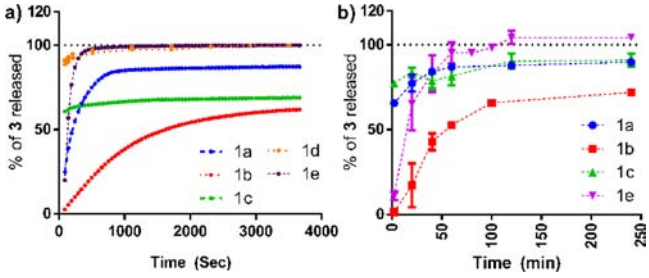

Figure 3. Release of 7-hydroxycoumarin **3** from pro-probes **1a**−**1e** following a reductive trigger measured by (a) fluorescence (PBS-only, 10 μM concn of **1a**−**1e**, pH ∼6) and (b) HPLC-UV (1:1 PBS/MeCN, 50 μM concn of **1a**−**1e**, pH ∼5). Results are an average of triplicate experiments (section S4).

S4). Reduction of the nitro trigger was initiated with zinc in MeCN/acetic acid,[15] releasing **3** via the relevant 1,8- or 1,6-self-immolation (Scheme 1 and section S4). Previous reports for the release of a fluorescent probe from a carbonate linker (triggered by reduced pH) had a reported half-life ($t_{1/2}$) of 16 s.[16] In our hands, reduction of the nitro group on **1d** and dilution into PBS supported these data (Figure 3a), with complete release of **3** occurring in <30 s (time for diluting in PBS and measurement of fluorescence = 30 s). The release kinetics for the 1,8-self-immolation of **3** from the cinnamyl ethers **1a**−**1c** demonstrated that the presence and location of a methyl group on the cinnamyl

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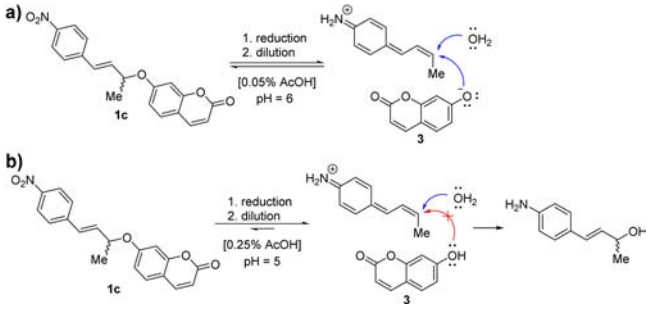
spacer in the α- or γ-position resulted in significantly different release kinetics (Figure 3). Non-methylated **1a** undergoes a relatively fast 1,8-self-immolation of **3** (50% release = 3.5 min), whereas the α-methyl analogue **1b** has a substantially slower release of **3** (50% release = 27 min) and the γ-methyl analogue **1c** is extremely fast in releasing **3** (50% release < 30 s) (Figure 3a). Benzyl ether **1e** demonstrated kinetics (50% release = 60 s) faster than that of non-methyl analogue **1a** but kinetics slower than that of γ-methyl analogue **1c**. However, based on a previous report,[4] under more organic-type conditions and with higher pK_a phenols, the rate of benzyl ether release would be expected to slow down, and this was the case for our benzyl ether **1e** (see below). Notably, even with complete reduction of **1a**−**1c** and **1e** under the reaction conditions (confirmed by HPLC; see Schemes S10−S13), cinnamyl ethers **1a**−**1c** deviated from the expected pseudo-first-order kinetics after the initial release period (i.e., <100% release observed at plateau). Ether **1a** showed a maximum release of ∼87%, and the methylated **1b** and **1c** plateaued at ∼50−60% release of **3**. Interestingly, when activation of **1a**−**1c** was performed in 1:1 aq−organic solvent (1:1 PBS/MeCN) and analyzed by HPLC-UV, release of **3** was significantly higher (∼91% for **1a** and **1c**) (Figure 3b).

The stability of **1a**−**1c**/**1e** and the rate of self-immolation in 1:1 aq−organic solvent were investigated (Figure 3b) to gauge the applicability of our spacers to other applications in materials science (e.g., triggered polymer degradation). Cinnamyl ether **1b** showed significantly slower release kinetics in a 1:1 mixture of aq−organic solvent (Figure 3b, ∼66% release after 100 min); however, **1a** and **1c** maintained rapid 1,8-self-immolation of **3**. For **1a** and **1c**, 66 and 77% release of **3** was confirmed in <2 min; the preparation time for the HPLC experiment (see section S4) includes dilution, mixing, and injection time. These rates compare favorably with those of the methoxy benzyl ethers reported by Phillips and co-workers.[4] In PBS-only (Figure 3a), **1e** demonstrated a faster release profile than the non-methyl analogue **1a** and a slower release than the γ-methyl analogue **1c** (see above). However, in 1:1 aq−organic solvent (Figure 3b), 1,6-self-immolation of **1e** was significantly slower than the cinnamyl ether analogues **1a** and **1c**. At 2 min, **1e** had only released 11% of **3** (66 and 77% for **1a** and **1c**). At 20 min, ∼65% of **3** had been released (77 and 84% for **1a** and **1c**). Comparison of the HPLC trace of **1a**/**1c** to **1e** (Figures S10 and S12 cf. S13) provided further evidence for the superior release rate of **3** from **1a**/**1c**. After 20 and 2 min, the 1,8-self-immolation of the reduced intermediate ($t_{R(1a)}$ = 6.3 min, $t_{R(1c)}$ = 7.3 min) was almost complete for **1a** and **1c**, respectively, and 1,6-self-immolation was incomplete (at 20 min) for the reduced intermediate of **1e** (t_R = 5.2 min).

Incomplete release for the cinnamyl ethers **1a**−**1c** in PBS (Figure 3a) and PBS-organic solution (Figure 3b) suggests that, upon 1,8-self-immolation, the electrophilic methide is sufficiently stabilized via resonance (for **1a**−**1c**) and hyperconjugation (for **1b** and **1c**), enabling a reversible addition with the nucleophilic phenolate of **3** (Scheme 2). As an alternate hypothesis, quenching of fluorescence via noncovalent interactions could occur in the PBS-only studies. However, the relatively low concentration of **3** generated (≤10 μM) and the fact that the observed release of **3** is only lower (<100%) for the cinnamyl ethers **1a**−**1c** (cf. **1d**,**e**) suggest that the aza-cinnamyl methide is significantly more stable than PABC-type methides (from **1d**,**e**) which react with the most abundant (and weaker) nucleophile, that is, the surrounding water molecules. Further support for our argument is the difference in nucleophilicity of **3** in the fluorescence versus HPLC-UV assay. Under purely aq conditions (fluorescence exp.), 0.05% acetic acid (AcOH) was present and the solution had pH ∼6. In 1:1 aq−organic solvent (HPLC-UV exp.), 0.25% AcOH was present and the solution was more acidic (pH ∼5). The 5-fold increase in AcOH was a result of dilution into the PBS-organic solution, which required a higher concentration of **1a**−**1c** and **1e** (50 μM), so that aliquots containing 2.5 nmol of analyte could be injected and quantified by HPLC-UV (section S4.2). However, the increased acidity results in the phenolic substituent on **3** (pK_a 7.8) being protonated to a greater extent in the PBS organic solvent assay (Scheme 2b). This prevents, or at least slows down, the nucleophilic attack of **3** on the methyl-stabilized spacers of **1b** and **1c**, supporting the greater extent of release observed in the PBS-organic (∼71% for **1b** (at 240 min) and ∼91% for **1c**) versus PBS-only assay (∼62% for **1b** and ∼69% for **1c**).

Scheme 2. Proposed Mechanism for Nucleophilic Attack of 3 on the Stabilized Methide Generated from 1c in (a) Fluorescence and (b) HPLC-UV Experiments



The proposed mechanism in Scheme 2 suggests the methide could have use in the design of prodrugs where additional cytotoxicity is required, similar to the PABA-methide approach reported by others.[17] The increased methide stability is expected to result in a greater residence time (compared to other aza- and quinone methides),[18] enabling it to react with stronger but less abundant cellular nucleophiles (e.g., DNA, lysine, glutathione).[17,19]

In regards to the release of **3** from α-methyl cinnamyl ether **1b** (Figure 3), we hypothesized that the slower rate of self-immolation [50% at 27 min (PBS-only) and 54 min (1:1 aq−organic)] was the result of steric clash of the methyl group with the adjacent hydrogen atoms of the aryl ring. This would result in distortion of the alkene, deviating from the 180° dihedral angle required for π-orbital overlap and hindering the 1,8-self-immolation. Examination of X-ray diffraction structures for α-methyl-substituted cinnamyl analogues in the Cambridge structural database confirmed disruption in planarity of the π-conjugated system (section S5).[20]

Finally, we investigated the release of a model phenolic drug, etoposide **4** (pK_a 9.8),[14] from two of our cinnamyl ethers. Etoposide is a potent, clinically used topoisomerase inhibitor, and prodrugs masking the phenol have been reported to reduce cytotoxicity of the parent drug;[2b,21] hence, two analogues, **2a** and **2c**, were synthesized via the intermediate cinnamyl bromides **6** and **13**, respectively (Scheme S2). The high stability of **2a** and **2c** in 1:1 mouse serum/PBS (with 10% DMSO) was demonstrated over 48 h (section S3.2 and Table S2), and the decaging rate of **4** from **2a** and **2c** was measured by HPLC in a 1:1 aq−organic solvent (section S4.2 and Figure S7). Release of **4** from **2c** was rapid ($t_{1/2}$ < 2 min), with 76% measured at 2 min. The decaging rate from **2a** was slower than that from **2c** (45% after 42 min),

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demonstrating that the γ-methyl spacer promotes rapid release of higher pK_a phenols (≥9.8) in aq−organic conditions.

In summary, we have developed cinnamyl ether spacers that are effective at caging phenols of high to moderate acidity (pK_a 7.8−9.8), making them broadly applicable to the majority of phenols (pK_a 7−10.5). The spacers are stable and, following a trigger, undergo a self-immolative release of the parent phenol. The strategic placement of a methyl group results in different rates of phenol release. The γ-methyl group helps stabilize the δ^+ charge of the transition state, resulting in extremely fast (almost spontaneous) decaging of phenols, a highly desirable property of prodrugs, pro-probes, and degradable polymers. When a methyl group is situated on the α-carbon of the alkene, the rate of decaging is significantly slower. The cinnamyl ether spacers could have applications in the fields of organic and medicinal chemistry, drug delivery, or materials science where rapid or sustained decaging is required. Due to the increased stability of the methide in **1c**, which we demonstrated in our release experiments, investigations are underway to see if the spacer could be used as a cytotoxic agent, capable of inhibiting cellular nucleophiles.[17]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b03695.

Full experimental details; NMR spectra of **1a**−**1e**, **2a**, **2c**, **13**, sections S1−S8, Figures S1−S17, Tables S1−S3 (PDF)

2D NMR spectra of **1c** and **2c** (PDF)

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Notes

The authors declare no competing financial interest.

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