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Effect of aromaticity on the rate of azaquinone methide-mediated release of benzylic phenols

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Herein we use small molecule models of stimuli-induced degradable/depolymerizable polymers to demonstrate that less aromatic releasing units provide faster rates of azaquinone methide-mediated release of benzylic phenols (a surrogate for a group released in a polymer) than highly aromatic releasing units. Copyright © 2013 John Wiley & Sons, Ltd.

Supporting information may be found in the online version of this paper.

Keywords: aromaticity; azaquinone methide; controlled release; solvent effects

INTRODUCTION

Polymers that degrade or depolymerize in response to specific applied stimuli have the potential to transform the magnitude, selectivity, and rate of response of stimuli-responsive materials composed of these polymers. Such polymers ultimately may impact diverse fields such as diagnostics, controlled drug release, and self-healing materials.[1–6] To realize many of these applications, however, depolymerizable and degradable polymers must be capable of responding to an applied stimulus quickly in environments that are less polar than water (e.g., in the shells of responsive microscale and nanoscale capsules,[3,5] films,[7] plastics,[8] or other solid state materials). A common strategy for enabling controlled degradation and/or depolymerization in responsive polymers involves the use of moieties that release a benzylic phenol or carbamic acid via formation of azaquinone methide when a specific stimulus is applied to the polymer (Fig. 1).[1,2] In small molecule model studies, we demonstrated that the rate of this type of azaquinone methide elimination reaction is directly proportional to the polarity of the chemical environment: the more polar the environment, the faster the rate of elimination,[9,10] whereas in low polarity environments, azaquinone methide-mediated release may not proceed at all.

Ideally, the structure of the releasing group that forms azaquinone methide could be modified in a logical way that enables predictable and tunable rates of azaquinone methide-mediated release in nearly any environment. However, the design principles to enable these types of structural modifications have yet to be fully established. In this work we test one new strategy for increasing azaquinone methide-mediated release (i.e., we alter the aromaticity of the releasing unit) and demonstrate its potential for increasing the rate of release of benzylic phenols. The results of this study move us one step closer to a set of predictable design rules that can be applied in the context of azaquinone methide-mediated degradable and depolymerizable polymers.

Specifically, we use small molecule model systems to demonstrate that the level of aromaticity of the aromatic unit (which could be a repeating unit in a polymer) has a substantial effect on the rate of stimuli-initiated release of a pendant phenol. X-ray crystal structures of these model compounds reveal a direct relationship between the lengths of the carbon-carbon bonds within the aromatic ring and the rate of release – that is, the longer the carbon–carbon bonds, the faster the rate of azaquinone methide-mediated release.

RESULTS AND DISCUSSION

Our design strategy is based on the hypothesis that the rate of release in systems such as those depicted in Fig. 1 is slow, because the releasing moiety must proceed through a less aromatic transition state (i.e., azaquinone methide) than that of the ground state. This less aromatic transition state presumably results in a large energy penalty for depolymerization/degradation. We reasoned that by decreasing the aromatic character of the releasing moiety we could raise the ground state energy of the unit and decrease the activation energy barrier associated with the azaquinone methide-mediated release reaction, thus increasing the rate of release.

To test this hypothesis, we developed three small molecule model compounds (Fig. 2) to evaluate the effect of aromaticity on the rate of azaquinone methide-based elimination reactions under controlled circumstances without the added complexities associated with studying responses in polymers. The compounds each contain an allyl carbamate (Alloc) reaction-based detection unit (bold), which is cleaved by the stimulus Pd(0), and a pendant phenol (gray), which serves as a surrogate for a phenol that may be released in a degradable[5] or depolymerizable polymer.[1,2] Phenol also provides a convenient spectroscopic probe for following the kinetics of the release reaction by using a liquid chromatograph coupled to a mass spectrometer (LCMS).

Model compounds **2** and **3** were prepared through relatively short syntheses (Schemes 1 and 2) whereas compound **1** was

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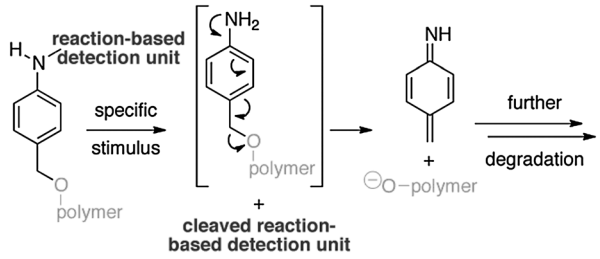


Figure 1. General mechanism of a stimulus-induced depolymerization and/or degradation reaction of a polymer functionalized with a reaction-based detection unit (often referred to as an endcap or trigger). Once the reaction-based detection unit is cleaved by a specific stimulus, the next portion of the polymer is released via an azaquinone methide elimination reaction

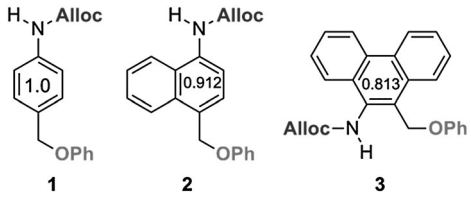
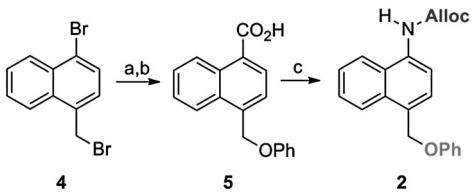
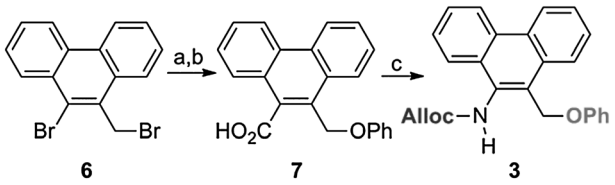


Figure 2. Three model compounds used to measure whether ground state aromaticity of the releasing group affects the rate of azaquinone methide-mediated release of a pendant phenol. The numbers written on each compound correspond to the calculated relative aromaticity values for each ring (the values correspond to rings without substituents)[11]



Scheme 1. Synthesis of model compound **2**. Reagents and conditions: (a) phenol, K_2CO_3, dimethylformamide, 50°C; (b) *n*-BuLi, CO_2, tetrahydrofuran, −78°C; and (c) diphenylphosphoryl azide, triethylamine, allyl alcohol, 85°C (40% over three steps)



Scheme 2. Synthesis of model compound **3**. Reagents and conditions: (a) phenol, K_2CO_3, dimethylformamide, 50°C; (b) *n*-BuLi, CO_2, tetrahydrofuran, −78°C; and (c) diphenylphosphoryl azide, triethylamine, allyl alcohol, 90°C (19% over three steps)

prepared previously.[9] In all cases, a Curtius rearrangement was used as the last step to introduce the reaction-based detection unit to the test compounds, which proved to be a convenient strategy for introducing the orthogonal functionality required in these compounds.

The rates of release of phenol from compounds **1**, **2**, and **3** were determined by treating each compound with $Pd(PPh_3)_4$, Bu_3SnH, and acetic acid in tetrahydrofuran (THF) (to cleave the Alloc group), then diluting a 10 μL aliquot of the solution in a 1:1 mixture of MeCN and pH 7.1 buffered water (to enable azaquinone methide-mediated release of phenol) (Fig. 3). The rate of disappearance of the aniline intermediate was monitored by repetitive injections at 20-min intervals into an LCMS.[12] The aniline intermediate is stable (i.e., will not proceed through azaquinone methide on the time-scale of the experiments) when dissolved in THF, but once the aniline is dissolved in the MeCN : water mixture (a more polar solvent mixture than THF), the azaquinone methide elimination reaction becomes favorable. Thus, our assay measures the release reaction independent of the kinetics of cleavage of the reaction-based detection unit (Alloc).

Based on the relative aromaticity values depicted in Fig. 2, we expected the phenanthrene derivative **3** to release phenol faster than the naphthalene or benzene model systems (**2** and **1**,

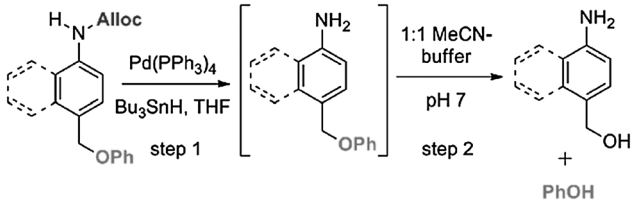


Figure 3. Reaction conditions used for the cleavage of the Alloc group and monitoring the kinetics for release of phenol from the three model compounds in Fig. 2

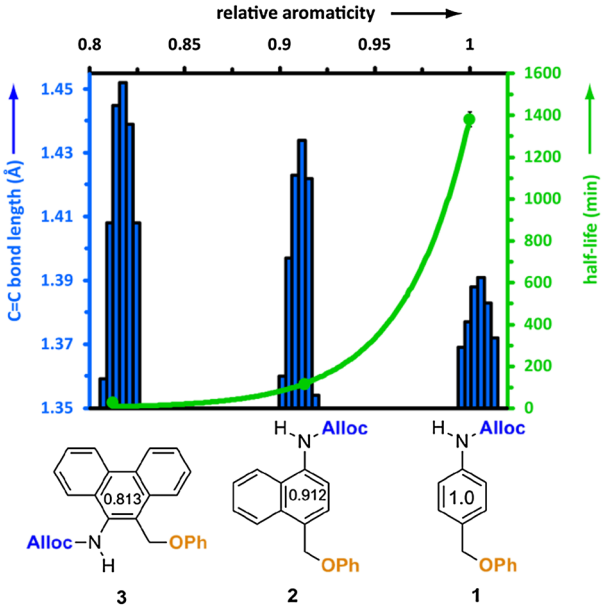


Figure 4. Comparison of the relative aromaticity values for compounds **1**, **2**, and **3** with: (i) the distribution of carbon–carbon bond lengths within the aromatic ring where azaquinone methide is generated during the release reaction; and (ii) the half-life for release of phenol after the Alloc group is removed using Pd(0). The blue bars represent the lengths for the five carbon–carbon bonds within the central aromatic ring for each structure indicated at the bottom of the graph.[13] The green data points represent the relationship between relative aromaticity value[11] and the half-life for release of phenol. These data points correspond to the structures depicted below the graph and are the average of three measurements. The error bars are smaller than the data points

respectively). Indeed, when the half-lives for the release reactions were compared with the calculated relative aromaticity values, we observed a direct relationship between relative aromaticity value[11] and half-life for release (Fig. 4). For example, the phenanthrene derivative **3** (relative aromaticity value = 0.813)[11] releases phenol with a half-life of 27 min, which is ~51× faster than the benzene derivative **1** (half-life = 23 h; relative aromaticity value = 1.0).[11]

X-ray crystallographic analysis of the lengths of the carbon–carbon double bonds within the central rings in **1**–**3** reveal an inverse relationship between the distributions of bond lengths and the calculated relative aromaticity value for the ring.[13] In other words, aromatic releasing moieties with lower relative aromaticity values have longer carbon–carbon bonds than derivatives with higher relative aromaticity values and correspondingly faster rates of release of phenol (Fig. 4).

CONCLUSION

In conclusion, we have established a new strategy for increasing the rate of azaquinone methide-mediated release of benzylic phenols. This strategy involves increasing the ground state energy of the aromatic releasing unit by decreasing the aromaticity of this group. Until now, the available strategies for increasing the rate of analyte-triggered azaquinone methide-mediated release of a benzylic leaving group have involved adding electron density to the aromatic ring of the releasing unit,[9,10,14] introducing substituents at the benzylic position,[15] and increasing the polarity of the medium in which the release reaction occurs.[9,10] In the context of stimuli-responsive solid-state polymeric materials, only the former two strategies are generalizable. Thus, these results add to the short but growing list of design principles that are available to guide the creation of polymers that efficiently degrade or depolymerize via azaquinone methide pathways in nonpolar environments when exposed to a specific stimulus.

EXPERIMENTAL

General Conditions for Measuring the Release Kinetics of 1, 2 and 3. An Alloc-protected compound (**1**, **2**, or **3**) (0.01 mmol) and tetrakis(triphenylphosphine)palladium(0) (1.1 mg) were dissolved in 0.1 mL of tetrahydrofuran in a 2-mL vial. Acetic acid (1.5 μL) and tributyltin hydride (5 μL) were added to the reaction mixture, and the solution was shaken for 3 min. An aliquot (10 μL) of the solution was added to an high-performance liquid chromatography vial and was diluted with acetonitrile (0.5 mL) and phosphate buffer (0.1 M, pH 7.1, 0.5 mL). The solution was shaken for 10 s and then was filtered through a syringe filter (polytetrafluoroethylene, 0.22 μm). The rate of release of phenol was inferred[12] by monitoring the disappearance of the aniline intermediate by LCMS by using an ultraviolet detector set at 254 (for compounds **1** and **2**) or 330 nm (compound **3**).

SUPPORTING INFORMATION

Detailed synthetic procedures, compound characterization data, crystal structure data, tables of primary data, and figures of NMR spectra.

Acknowledgements

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[12] Alternatively, we could have monitored the release of phenol, but the aniline intermediate absorbed more strongly in the HPLC spectra than phenol, and therefore the peak for the aniline intermediate was easier to integrate and quantify than the peak for phenol.
[13] The crystal structure data for **1** is available in reference.[9]
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