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Photolabile Protection of 1,2- and 1,3-Diols with Salicylaldehyde Derivatives

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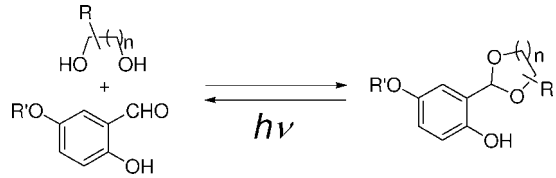
ABSTRACT



1,2- and 1,3-diols, including carbohydrates, can be readily caged as acetals of 5-methoxy- or 5-hydroxysalicylaldehydes. Irradiation of these acetals with 300 nm light results in their efficient ($\Phi = 0.2-0.3$) cleavage, regenerating an aldehyde and a glycol in excellent chemical yield. Photoreactive 5-hydroxysalicylaldehyde acetals can be produced by mild in situ reduction of photostable *p*-quinone precursors.

Photolabile protecting groups (PPGs), known as "cages" in biochemistry, allow for the spatial and temporal control of substrate release, as well as "reagentless" deprotection.[1−3] PPGs have found numerous applications in biochemistry,[3] organic synthesis,[1,2] fabrication of high density probe arrays (aka biochips),[4] and time-resolved X-ray crystallography.[5] While a large selection of photo cages is available for carboxylic acids,[6] phosphates,[7] amines,[8] and alcohols,[9] the choice of photolabile protecting groups for glycols is very limited.[10,11] Photolysis of *o*-nitrobenziledene acetal derivatives of 1,2- and 1,3-diols results in the acetal ring opening and the formation of two regioisomers of glycol mono-*o*-nitrobenzoate.[10] Acetals produced from 6-bromo-7-hydroxycoumarin-4-carbaldehyde and 1,2- and 1,4-diols liberate

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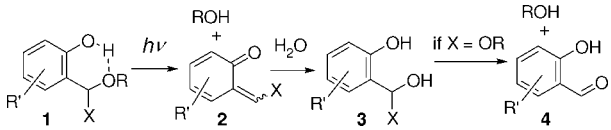
starting glycols under irradiation albeit with low quantum efficiency ($\Phi = 0.005-0.028$).[11a] Corresponding derivatives of 1,3-diols, on the other hand, are inert to photolysis. Monoethers of glycerol were liberated under single and two-photon photolyses from acetals of (8-bromo-7-hydroxyquinolin-2-yl)formaldehyde.[11b] Since glycol protection is a common procedure in natural product synthesis,[1] especially in carbohydrate chemistry,[12] the search for general, reliable, and efficient PPG for diols continues.

We have recently reported that alcohols caged with *o*-hydroxybenzyl-based PPGs are efficiently liberated under 300 nm irradiation.[13] This reaction proceeds via excited-state intramolecular proton transfer (ESIPT) from the phenolic hydroxyl to the ether oxygen, followed by the formation of an *o*-quinone methide intermediate (**2**, Scheme 1). In the presence of water, the latter undergoes rapid hydration to diol **3** (Scheme 1). We reasoned that similar ESIPT in salicylaldehyde acetals (**1**, X = OR′) would generate an unstable hemiacetal, which should undergo rapid dehydration to liberate a second molecule of an alcohol. Cyclic acetals in the same manner can serve as photolabile protecting groups for glycols.

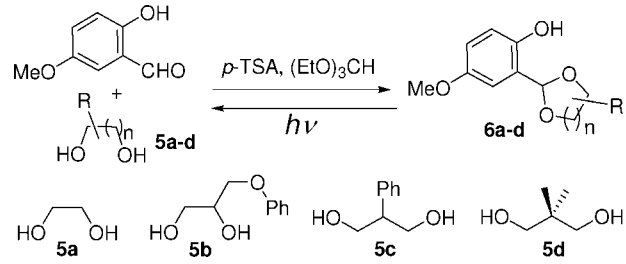
Scheme 1. Proposed Mechanism of the Photodecomposition



We have explored the utility of several 2-hydroxybenzaldehydes for the photolabile protection of glycols. While both the parent salicylaldehyde (**4**, R′ = H) and *o*-vanillin (**4**, R′ = 3-MeO) readily produce cyclic acetals with 1,2- and 1,3-diols, the latter have very weak absorbance at or above 300 nm. The use of 254 nm irradiation for the deprotection is impractical since aldehyde byproduct **4** is itself photoreactive and has a stronger absorbance at this wavelength. UV spectra of cyclic acetals produced from 5-methoxysalicylaldehyde, however, have a strong band at 295 nm (log $\varepsilon = 3.6$, Figure 1). The aldehyde itself (**4**, R′ = 5-MeO), on the other hand, is practically transparent at this wavelength.

Caged glycols **6a**−**d** were prepared by the direct reaction of 5-methoxysalicylaldehyde with diols **5a**−**d** in the presence of triethyl orthoformate and a catalytic amount of either *p*-toluenesulfonic acid or tetra-*n*-butylammonium tribromide[14] (Scheme 2, Table 1).[15]

Scheme 2. Formation and Photodecomposition of the Acetals of 5-Methoxysalicylaldehyde



Irradiation of solutions of acetals **6a**−**d** in 20% aqueous methanol with 300 nm light results in rapid decomposition of the starting material as evidenced by the bleaching of absorbance at 295 nm. This decay is accompanied by the formation of a characteristic 358 nm band of 5-methoxysalicylaldehyde (Figure 1). The yields of glycol release were determined by HPLC (**6b**,**c**) or NMR spectroscopy (**6a**,**d**); the quantum efficiencies of the uncaging reaction were measured using chemical actinometry (Table 1).[16]

1,2-Glycols are liberated upon irradiation of dioxolanes **5a**,**b** in excellent chemical (>90%) and high quantum yields ($\Phi_{300\ nm} \sim 0.3$). Efficiency of the photorelease of 1,3-diols from the corresponding dioxanes **6c**,**d** is notably lower ($\Phi_{300} = 0.03-0.1$). We believe that intermolecular nucleophilic attack by the hydroxy group on the intermediate *o*-quinone methide **2c**,**d**, resulting in the ring closure and the regeneration of starting material, efficiently competes with the hydration of **2c**,**d** to form hemiacetal **3c**,**d**. At low conversion of acetal **6c**, 2-phenyl-1,3-propanediol (**5c**) is the only photolysis product observed by HPLC. Further irradiation, however, results in the formation of several secondary photoproducts and the yield of **5c** at complete consumption of acetal **6c** drops to ca. 60%.

Acetals **6a**−**d** are not very stable neat or in chloroform or dichloromethane solutions and slowly decompose in the dark. We believe that an intramolecular hydrogen bond (**1**, Scheme

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(15) For details, see the Supporting Information.

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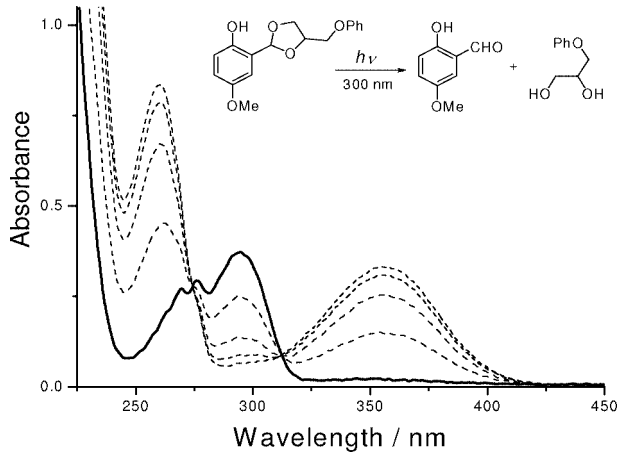


Figure 1. UV spectra of **6b** (solid line, ca. 1×10^{-4} M in 20% aqueous methanol) and its 300 nm photolysis (dashed lines, every 4 min).

Table 1. Yields of the Formation and the Hydrolytic Stability of Acetals **6a**−**d**; Quantum and Chemical Efficiencies of Photochemical Release of Glycols **5a**−**d**

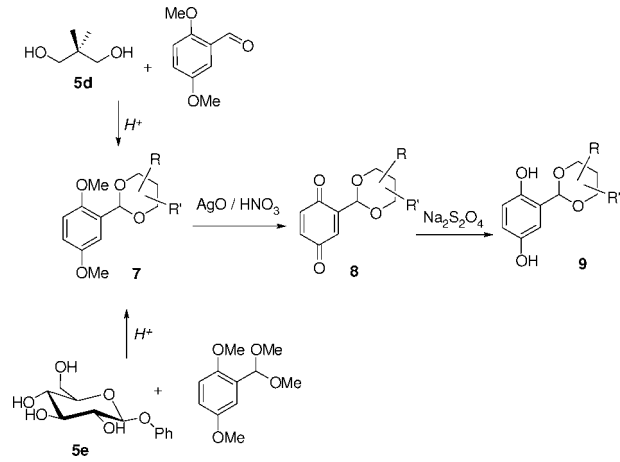
	yield of **6**, %	yield of uncaging, %	Φ_{300nm}	hydrolytic stability (τ, h)[c]
5a	89	100[a]	0.36	50
5b	75	96[b]	0.27	45
5c	74	59[b]	0.03	≫500
5d	74	100[a]	0.1	500

[a] NMR. [b] HPLC. [c] 20% aqueous methanol at ambient temperature.

1) facilitates slow proton transfer, even in the ground state. In fact, in hydrogen-bond-accepting solvents, such as methanol or ethers, these compounds are stable for weeks at ambient temperatures. In 20% aqueous methanol, which was used for the uncaging experiments, 1,3-dioxanes **6c**,**d** are stable toward hydrolysis, whereas the stability of dioxolanes **6a**,**b** is somewhat lower (Table 1). To increase the lifetime of caged glycols we decided to explore the release of diols from cyclic acetals of 5-hydroxysalicylaldehyde. This system is an analogue of a recently developed "safety catch" caging group for alcohols, which can be stored in a thermally and photochemically stable *p*-quinone form and quantitatively reduced in situ to the photoreactive hydroquinone.[13a] Acetals of 2-formyl-1,4-benzoquinone (**8d**,**e**) were prepared by the oxidative demethylation of 2,5-dimethoxybenzylidene acetals **7d**,**e** using silver(II) oxide in nitric acid (Scheme 3).[15] These 1,3-dioxanes are stable in the dark and under 300 nm irradiation. Mild heterogeneous reduction of **8d**,**e** in chloroform with aqueous sodium dithionite yielded reactive acetals **9d**,**e**.

The release of neopentylglycol in the photolysis of acetal **9d** was monitored by both UV (Figure 2) and NMR

Scheme 3. Preparation of 2,5-Dihydroxybenziledene-Caged 1,3-Glycols



spectroscopy. Irradiation of **9d** with 300 nm light resulted in efficient decomposition ($\Phi_{300} = 0.18$) of the starting acetal. The reduction of intensity of the acetal **9d** absorption band at 294 nm is concomitant with the formation of a 357 nm band corresponding to 2,5-dihydroxybenzaldehyde. NMR analysis of the photolysate confirmed clean and quantitative uncaging of neopentylglycol (**5d**) and the formation of 2,5-dihydroxybenzaldehyde as the only detectable byproduct.

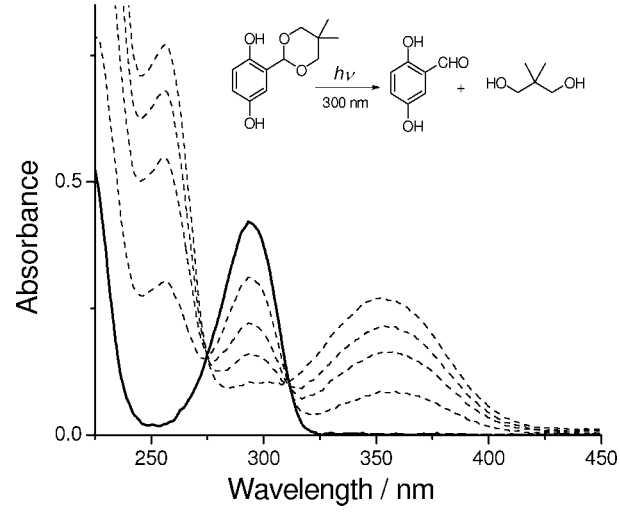
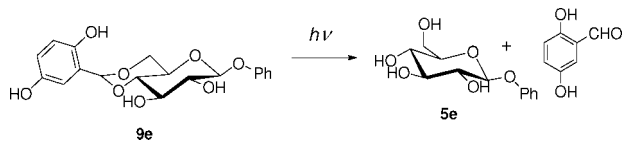


Figure 2. UV spectra of **9e** (solid line, ca. 1×10^{-4} M in 20% aqueous methanol) and its 300 nm photolysis (dashed lines, every 5 min).

The utility of the 2,5-dihydroxybenzylidene group as a photoremovable benzylidene protecting group for carbohydrates was tested on the glucose derivative **5e** (Scheme 3). Phenyl 4,6-*O*-(2,5-dimethoxybenzylidene)-β-D-glucoside (**7e**) was prepared by the treatment of **5e** with α,α-2,5-tetramethoxytoluene in the presence of a catalytic amount of

Scheme 4. Photochemical Deprotection of a Glucose Derivative



p-toluenesulfonic acid. Conversion of **7e** into 4,6-*O*-2,5-dihydroxybenzylidene derivative **9e** is discussed above (Scheme 3).[15] Irradiation of **9e** with 300 nm light in 20% aqueous methanol results in efficient ($\Phi_{300} = 0.21$) release of the phenyl glucoside **5e** in 97% chemical yield (Scheme 4).

In conclusion, two novel photolabile protecting groups, 2-hydroxy-5-methoxybenzylidene and 2,5-dihydroxybenzylidene, were developed for the protection of glycols. We have shown that 1,2- and 1,3-glycols can be readily converted into acetals of 5-methoxysalicylaldehyde and formylhydroquinone. These acetals efficiently release substrates upon 300 nm irradiation in a good to excellent yield. Photodeprotection is accompanied by the bleaching of the acetal band at ca. 295 nm and the rise of the aldehyde absorption at ca. 360 nm. Efficient bleaching at the irradiation wavelength allows for the use of a high substrate concentration. The quinone precursor of the 2,5-dihydroxybenzylidene cage is photochemically inert but can be quantitatively converted in situ into a photoreactive form using mild reducing agents.

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Supporting Information Available: Synthesis and characterization of the compounds **6a**−**d**, **7d**,**e**, **8d**,**e**, and **9d**,**e** and photolysis protocols. This material is available free of charge via the Internet at http://pubs.acs.org.

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