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Photodimerized 7-hydroxycoumarin with improved solubility in PMMA: Single-photon and two-photon-induced photocleavage in solution and PMMA films

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Abstract

tert-Butyldimethylsilyl-chloride (TBS) revealed to be a photostable protecting group for the photodimerization of 7-hydroxycoumarin in a [2 + 2]-cycloaddition. TBS-functionalized coumarin dimers show an about 100-fold increased solubility in organic solvents enabling them to be easily incorporated into polymeric films, e.g., PMMA. In the described photochemical dimerization reaction almost pure anti-head-to-head isomer is obtained. The single- and two-photon absorption-induced cycloreversion reactions in acetonitrile as well as in PMMA matrix were investigated and the two-photon absorption cross sections and quantum yields were determined to be around 1 GM and about 0.36, respectively. The only product obtained upon photocleavage of the dimer is the TBS-protected 7-hydroxycoumarin monomer. The TBS-protecting group withstands the high light intensities required for two-photon absorption-induced photocleavage without any noticeable degradation. The mild deprotection conditions for *tert*-butyldimethylsilyl-ethers (TBS-ethers), the chemical stability of the compound as well as its significantly improved solubility in organic solvents and its miscibility with acrylic polymers, make this a very useful compound for potential applications in 3D volumetric optical data storage and photocontrolled drug delivery.

Keywords: 7-Hydroxycoumarin; Coumarin dimer; Photodimerization; Two-photon absorption; Solubility; *tert*-Butyldimethylsilyl-ether

1. Introduction

Dimerization of coumarin and its derivates has been intensively investigated in view of fundamental as well as applied aspects. The basics of the dimer formation are reviewed, e.g., in [1–3]. Coumarin dimers recently were employed, e.g., as photocontrolled molecules opening and closing a silica pore, wherefrom guest molecules are released, or in photodegradable polymers [3,4]. In our research efforts coumarin dimers play an important role as photocleavable linker molecules for two-photon absorption controlled drug delivery [5]. The refractive index changes accompanying the photocleavage of the cyclobutane structure may be of use in optical and holographic recording [6]. The main advantage of two-photon absorption-induced photochemistry in both applications is the precise 3D spatial control of the photoreactions. In the case of our main application, the photocontrolled drug delivery from polymeric intraocular lenses, an additional advantage of the two-photon absorption photochemistry is, that a photochemical reaction can be triggered behind a barrier absorbing photons required for the single-photon excitation.

The coumarin dimer is a photocleavable linker between a polymer backbone and a drug molecule. In order to attach coumarin dimers to polymers, reactive side groups are required. A first choice would be 7-hydroxycoumarin, but due to the properties of the phenolic group it cannot be photochemically dimerized easily [3] because upon light irradiation, the phenolic group forms rather stable radicals which lead to undesired side products. As a protecting group for the phenolic group acetylation has been employed, but this group is only cleavable at rather harsh conditions [3], what is undesired for the further steps. A further requirement to the dimer is that it should have a good solubility in organic solvents and polymers. The coumarin dimer itself is very poorly soluble in common

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Table 1
Overview of determined photochemical characteristics of TBS-C dimer in acetonitrile solution and PMMA matrix

	Cycloreversion quantum yield (SPA = TPA)	SPA cross section (cm^2)		TPA cross section (cm^4 s $photon^{-1}$)
		266 nm	532 nm	532 nm
ACN solution	0.36	In both cases		1.1×10^{-50}
PMMA matrix	0.37	7.85×10^{-18}	1.70×10^{-20}	1.9×10^{-50}

organic solvents, what is a problem for the further coupling steps.

In summary, a photostable hydroxyl group protection group for the photodimerization, a significantly improved solubility of the dimer for the further processing, and comparably mild deprotection chemistry for the linkage step with other molecules, e.g., drugs is required.

We studied *tert*-butyldimethylsilyl-chloride (TBS^+Cl^-) [7] as a protecting group for the coumarin's hydroxyl group, because a wide choice for the deprotection conditions is reported in the literature [7–11]. In particular the mild deprotection with potassium hydrogensulfate in aqueous methanol or lithium hydroxide in dimethylformamide [8,12] is very attractive for our applications. We present an efficient route for the photochemical dimerization of 7-hydroxycoumarin after protection with TBS^+Cl^-, leading to 7,7′-(*tert*-butyldimethylsilyloxy)-dicoumarin (TBS-C dimer). In addition to the required photochemical stability, the employed protection group increases the solubility of TBS-C dimer compared to 7,7′-hydroxydicoumarin about 100-times. This enables the preparation of highly loaded polymer films.

We characterized the photochemical properties of the TBS-C dimer in acetonitrile solution as well as in PMMA films. Absorption cross section and the quantum yield for photocycloreversion were experimentally determined for both, single-photon absorption (SPA) as well as two-photon absorption (TPA) (Table 1). The TBS-protection group was stable in both photochemical processes investigated, as checked by HPLC analysis. Highly loaded polymer films containing TBS-C-dimer in combination with TPA-induced photocleavage are required for photocontrolled drug delivery from polymeric intraocular lenses [13].

2. Experimental

7-Hydroxycoumarin 99% (Acros Organics), *tert*-butyldimethylsilyl-chloride (Fluorochem), imidazole p.a. (Fluka), benzophenone p.a. (Fluka), acetonitrile HPLC grade (Fisher Scientific), polymethylmethacrylate (PMMA) pellets (Plexiglas®, Degussa), silica gel 60 (Merck) were used as received. Tetrahydrofuran (THF) was dried over sodium. THF, ethylacetate and *n*-pentane were distilled before use. Water was prepared using a Milli-Q gradient system (Millipore).

HPLC analysis was done using a Hewlett-Packard Model 1050. The isomers were separated on a 250 mm × 4 mm RP18 column (Nucleosil, 3 μm, Bischoff) using acetonitrile and water as an eluent.

UV–vis absorption spectra were recorded on an UVIKON 922 (Kontron) spectrophotometer.

Elemental analysis was done on a CHN-Rapid (Hereaus).

EI-MS measurements were done on a CH7A (Finnigan). ESI-MS measurements were done on a LCQ-duo (Thermoquest Finnigan) equipped with an ESI ionization (positive mode). A spray voltage of 4.50 kV, a capillary temperature of 200 °C and a capillary voltage of 10.00 V were used.

^1H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were collected on a Bruker AC-300 spectrometer using $CDCl_3$ as solvent.

3. Synthesis

3.1. 7-(tert-butyldimethylsilyloxy)-coumarin

For the synthesis of 7-(*tert*-butyldimethylsilyloxy)-coumarin (TBS-C) (see Fig. 1) 3.36 g (21 mmol) 7-hydroxycoumarin (I) and 3.53 g (53 mmol) imidazole were dissolved in 75 mL dry THF in a Schlenk flask under argon atmosphere. After a clear solution was obtained, 3.75 g (25 mmol) *tert*-butyldimethylsilylchloride were added. The mixture was heated to 50 °C for 3.5 h and then cooled down to room temperature and stirred for another 22 h. The ammonium salts were filtered off and the solution was reduced under vacuum and then washed with 5% aqueous sodium hydrogen carbonate ($NaHCO_3$) solution. Then it was extracted three times with 50 mL chloroform ($CHCl_3$)

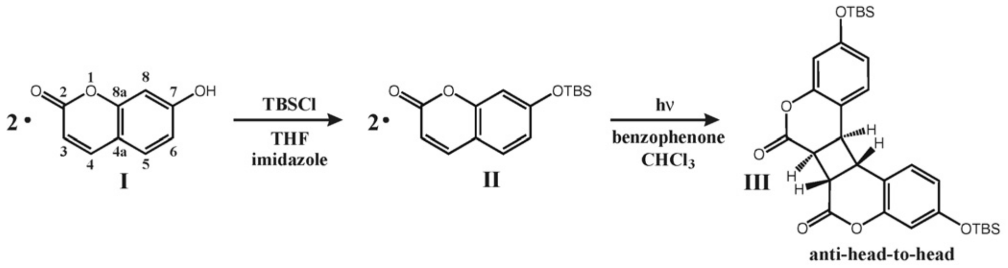

Fig. 1. Synthesis of 7,7′-(*tert*-butyldimethylsilyloxy)-dicoumarin (TBS-C dimer). Anti-head-to-head TBS-C dimer (III) is obtained by photodimerization of 7-(*tert*-butyldimethylsilyloxy)-coumarin (II, TBS-C) which is prepared from 7-hydroxycoumarin (I, 7HC).