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Single- and two-photon absorption induced photocleavage of dimeric coumarin linkers: Therapeutic versus passive photocleavage in ophthalmologic applications

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Abstract

Phototriggered chemical reactions are elegant and spatially selective. However, in application a general problem is that aside of the desired changes, e.g. induced by laser, undesired changes may occur, e.g. induced by daylight or sunlight. One such example which we are studying here is the phototriggered release of drugs from materials suitable for polymeric intraocular lenses (IOL). Through such an IOL sunlight needs to pass for several years without affecting the drug loading, but at the therapeutically required moment the drug release shall be triggered also by light. We studied this using a novel coumarin dimer (7,7′-[3-(*tert*-butyldimethylsilyloxy)propoxy]-dicoumarin) synthesized from the monomer in a photochemical [2π + 2π] cycloaddition reaction. The cleavage of the obtained photodimer by single-photon (SPA) and two-photon absorption (TPA) excitation was investigated in acetonitrile solution and in polymethylmethacrylate in order to exclude major matrix entrapment effects. The cleavage quantum yields and TPA cross-section were determined to be $\Phi \approx 0.13$ and $\delta_{TPA} \approx 2.7$ GM, respectively. It was found that 10% undesired drug release would require more than 16 years of continuous exposure to sunlight. Release of 90% of drug under therapeutic conditions would be completed within seconds. This shows that photochemically triggered drug release is capable to become a powerful tool for drug delivery in ophthalmology.

Keywords: Coumarin dimer; Two-photon absorption; Controlled drug delivery; Intraocular lenses

1. Introduction

Coumarin and its derivatives have received considerable attention in applied photochemistry, owing to their highly reversible photodimerization and photocleavage capabilities [1–4]. Dimeric coumarin derivates were employed in different applications, e.g. as photocontrolled molecules for opening and closing a silica pore [5] or in photodegradable polymers [3]. In all these cases single-photon absorption (SPA) excitation in the UV spectral range was employed. We recently reported two-photon absorption (TPA) controlled drug delivery materials utilizing coumarin dimers as photocleavable linker molecules using wavelengths in the visible range [6–8]. One advantage of TPA-induced processes is their excellent spatial selectivity in three-dimensions because of the quadratic dependence of TPA-dependent reactions on the incident-light intensity [9]. Another advantage is the use of longer wavelength for TPA excitation compared to SPA excitation. This is the key to a photochemical access to regions where the penetration depth of the UV light is heavily restricted by the linear absorption of the material. Furthermore it has been shown that even photolabile drugs may be successfully released by TPA but not SPA photocleavage [7]. With regard to ophthalmic applications, TPA opens the possibility of the photocleavage of coumarin dimers behind the UV light absorbing barrier formed by the cornea. This makes TPA a promising tool for photocontrolled drug release from suitably equipped polymeric intraocular lenses.

A suitable coumarin dimer linker requires at least two different functional groups. A first one for polymerization into the base polymer and a second one for drug attach-

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ment. One candidate would be a symmetrical photodimer of 7-hydroxycoumarin. However, the photochemical dimerization of 7-hydroxylcoumarin suffers from the phenolic groups tendency to form stable radicals during irradiation which leads to side products [3]. We introduced an alkyl spacer at the hydroxyl group, and protected it using *tert*-buthyldimethylsilyl-chloride (TBS). TBS is widely used for protecting a hydroxyl group [10–16] and in a previous work we have reported TBS-functionalized coumarin dimers with an improved solubility in organic solvents [17]. The presence of the alkyl spacer is very attractive because of the increased flexibility of the reactive side group an increased efficiency in the during drug attachment step is observed, in particular for sterically hindered larger drug molecules.

Here we present the isomer selective synthesis of the novel coumarin dimer, 7,7′-[3-(*tert*-butyldimethylsilyloxy)propoxy]-dicoumarin (TBS-p-C dimer) in anti-head-to-head configuration in 95% yield and its photochemical characterization.

The photocleavage quantum yield of the TBS-p-C dimer and its TPA cross-section were determined in solution as well as dispersed in a polymeric matrix (PMMA) in order to study matrix entrapment effects. The results are compared to the data reported earlier for other coumarin dimers [18].

Based on the experimental data obtained, undesired photocleavage due to sunlight exposure was compared to the time required for phototriggered drug release under therapeutic exposure conditions in order to study whether extended sunlight exposure might affect the drug depot and cause undesired slow drug release.

2. Experimental

2.1. Materials

Chemicals were used as received where not explicitly mentioned: 7-hydroxycoumarine (Acros Organics 99%), 3-bromo-1-propanol (Alfa Aesar 92%), *tert*-butyldimethylsilyl-chloride TBSCl (Fluorochem), imidazole (Fluka p.a.), benzophenone (Fluka p.a.), acetone (Merck), acetonitrile ACN (Fisher scientific HPLC grade), poly-methylmethacrylate PMMA pellets (Bayer), water (Millipore), silica gel 60 (Merck). Tetrahydrofuran (THF) was dried over sodium and distilled. Solvents for flash chromatography were distilled before use.

2.2. Instrumentation

MS measurements were done on a LCQduo (Thermo Electron) equipped with 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. ^{1}H (300 MHz) and 13C NMR (75 MHz) spectra were collected on a Bruker AC-300 spectrometer using $CDCl_3$ as a solvent. Analytical HPLC was performed on a Hewlett-Packard Model 1050 equipped with a Nucleosil RP18 column (250 mm × 4 mm, 3 μm particle size, Bischoff) using a mixture of acetonitrile/water as an eluent. Preparative HPLC was carried out using a Knauer HPLC Pump 64, a reversed-phase column (EnCaPharm 100 RP18 250 mm × 32 mm, 10 μm particle size), and a variable wavelength UV-detector set to 280 nm (Model 1050, Hewlett-Packard). The UV/vis absorption spectra were recorded on an UVIKON 922 spectrophotometer (Kontron). Elemental analysis was done on a CHN-rapid from Hereaus.

2.3. Synthesis of 7-(3-hydroxypropoxy)-coumarin (p-C)

Heating of 4.16 g (26 mmol) 7-hydroxycoumarin (HO–C) and 3.91 g (28 mmol) potassium carbonate in 70 mL acetone to 70 °C gave a clear solution. 3.56 g (26 mmol) 3-bromo-1-propanol was added and the mixture was stirred for 22 h at 70 °C. The resulting solution was concentrated under vacuum. The residue was dissolved in 100 mL of 10% hydrochloric acid and extracted three times with 100 mL $CHCl_3$. The organic extracts were combined and evaporated under vacuum. The crude product was purified by column chromatography on silica gel using a gradient of ethylacetate/*n*-pentan (1:2 → 10:1) as an eluent. Yield: 4.64 g (81%).

2.4. Synthesis of 7-[3-(tert-butyldimethylsilanyloxy)propoxy]-coumarin (TBS-p-C)

8.18 g (37 mmol) 7-(3-hydroxypropoxy)-coumarin and 6.43 g (94 mmol) imidazole were dissolved in 150 mL dry THF. After adding 6.85 g (45 mmol) *tert*-butyldimethylsilyl-chloride, the reaction mixture was stirred at 35 °C for 19 h. The solution was filtered and diluted with 200 mL of saturated sodium hydrogen carbonate solution. The solution was extracted three times with 150 mL $CHCl_3$. The organic extracts were combined, dried over $MgSO_4$ and evaporated under vacuum to give the crude product. The crude product was then purified by column chromatography using an eluent mixture of ethylacetate/*n*-pentan (1:4). Yield: 9.98 g (81%).

2.5. Synthesis of 7,7′-[3-(tert-butyldimethylsilyloxy)propoxy]-dicoumarin (TBS-p-C dimer)

The photosensitized dimerization of TBS-p-C was performed in five pyrex tubes. Each tube was filled with 5 mL solution of 7-[3-(*tert*-butyldimethylsilanyloxy)propoxy]-coumarin (0.2 g, 0.60 mmol) and benzophenone (0.025 g, 0.13 mmol) in chloroform. The mixtures were irradiated in a Rayonet reactor equipped with 12 UV-lamps with emission maximized at 350 nm (Eversun 40 W/79 K, Osram) for 20 h. The crude product was purified by preparative HPLC using an eluent mixture of acetonitrile/water (85:15). Yield 185 mg (38%).

2.6. Single- and two-photon absorption induced photocleavage of TBS-p-C dimer

For the single-photon absorption (SPA), a monochromatic light of 266 nm from a fluorescence spectrophotometer (RF-1502, Shimadzu) was used for excitation. The average irradiation intensity measured using a photodiode (S1337-1010BQ,

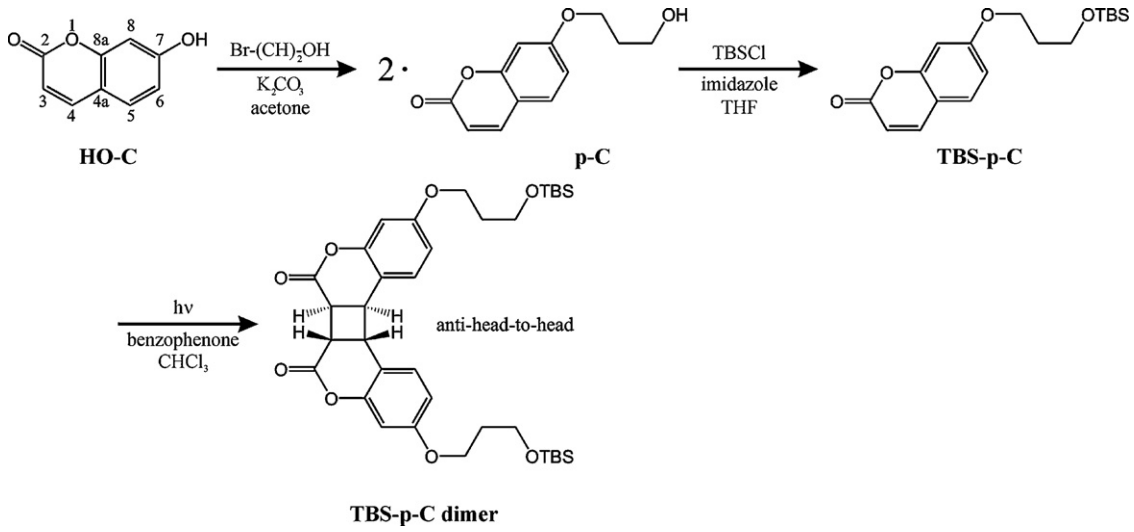

Fig. 1. Synthesis of 7,7′-[3-(*tert*-butyldimethylsilyloxy)propoxy]-dicoumarin (TBS-p-C dimer). The anti-head-to-head isomer of TBS-p-C dimer is obtained by photodimerization of 7-[3-(*tert*-butyldimethylsilyloxy)propoxy]-coumarin (TBS-p-C).

Hamamatsu) was 1.05 mW/cm^2. For the two-photon absorption (TPA) induced cleavage a Q-switched Nd:YAG laser operating at 532 nm was used (infinity 40–100, coherent). The pulse width and repetition rate were 3 ns and 20 Hz, respectively. The laser beam with a near flat-top profile was not focused and used as delivered (beam diameter: 5.5 mm). To investigate the photocleavage of TBS-p-C dimer in solution, a 0.30 mM solution of TBS-p-C dimer in acetonitril was used. SPA- and TPA-induced photocleavage was conducted in a quartz cuvette with 10 mm path length. The cuvette was filled with 2.5 mL of the sample solution and irradiated under continuous stirring at room temperature. To investigate the photocleavage of TBS-p-C dimer in polymeric matrix, 800 mg PMMA and 50 mg of TBS-p-C dimer were dissolved in 2.5 mL THF. The solution was cast on a glass substrate and dried over night under light exclusion in order to obtain a transparent film with a thickness of 200 μm.

3. Results and discussion

3.1. Assignment of the stereochemistry of the synthesized 7,7′-[3-(tert-butyldimethyl-silyloxy)-propoxy]-dicoumarin as anti-head-to-head

Starting from 7-hydroxylcoumarin (HO-C) 7,7′-[3-(*tert*-butyldimethyl-silyloxy)-propoxy]-dicoumarin (TBS-p-C dimer) was synthesized as shown in Fig. 1. Analytical HPLC of the purified product confirmed that the photodimerization of TBS-p-C at the conditions employed leads to only one of the four possible isomeric photodimers in 95% yield. The absolute configuration was determined using ^{1}H NMR and ^{13}C NMR analysis. According to Yu et al. [19], the patterns and chemical shifts of the cyclobutyl protons around 4 ppm assign its configuration to anti-head-to-head. The TBS-p-C dimer was furthered characterized by elemental analysis, mass spectroscopy and UV/vis spectroscopy (Fig. 2A).

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.05 (s, 12H), 0.89 (s, 18H), 1.99 (q, 4H, J = 6.05 Hz), 3.73 (d, 2H, J = 7.9 Hz), 3.80 (t,

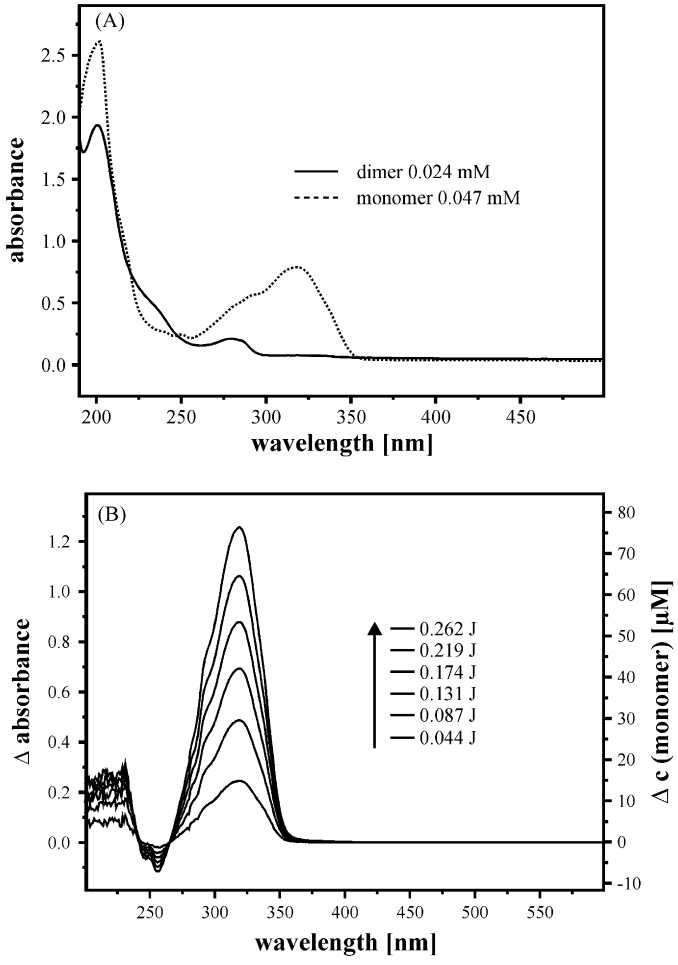

Fig. 2. Single-photon absorption (SPA) induced cycloreversion of TBS-p-C dimer. (A) The UV/vis spectra of TBS-p-C (0.047 mM, dashed line) and TBS-p-C dimer (0.024 mM, solid line) in acetonitrile are shown. (B) Spectral changes (difference spectra) of a 0.30 mM TBS-p-C dimer solution in acetonitrile during irradiation with monochromatic 266 nm light are shown. The absorption increase at 318 nm indicates the formation of TBS-p-C monomer.

4H, $J = 5.9$ Hz), 3.88 (d, 2H, $J = 6.0$ Hz), 4.06 (t, 4H, $J = 6.2$ Hz), 6.63 (d, 2H, $J = 2.5$ Hz), 6.71 (dd, 2H, $J = 8.5$ Hz, $J = 2.5$ Hz), 7.01 (d, 2H, $J = 8.3$ Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ [ppm] = −5.4, 18.3, 25.9, 32.2, 40.0, 43.6, 59.3, 65.0, 103.4, 112.1, 112.3, 128.4, 152.0, 160.0, 166.1.

CHN-analysis calculated C 64.67%, H 7.78% found C 59.31%, H 7.51%.

ESI-MS *m*/e 686.4 [$M^+ + H_2O$].

3.2. Single-photon absorption (SPA) induced photocleavage of TBS-p-C dimer in solution

The formation of a cyclobutane ring during photodimerization of TBS-p-C results in the loss of the conjugated π-system which in turn leads to a decrease in absorption at 318 nm. As the 318 nm absorption is characteristic for the monomer, the amount of cleaved dimer during photoinduced cycloreversion, i.e. cleavage of the cyclobutane ring, was monitored by UV/vis spectroscopy. Fig. 2A shows the UV/vis spectra of pure monomer (TBS-p-C) and pure dimer (TBS-p-C dimer). From the absorption at 318 nm and the molar extinction coefficient of the monomer $\varepsilon_{318} = 16375.2\ L\ mol^{-1}\ cm^{-1}$ the amount of cleaved dimer was determined and the cleavage rate was calculated. The excitation wavelength of 266 nm was chosen for the SPA-induced photocleavage in order to correspond to the two-photon excitation at 532 nm described below. In Fig. 2B the increase in absorption caused by SPA-induced photocleavage is shown. For the determination of the SPA quantum yield we assume that at the beginning of the reaction all photons from the excitation light source are absorbed by TBS-p-C dimer. This approximation holds as long as the initial absorption at 266 nm is high enough. In our experiments it was about OD (266 nm) = 2. This means that only about 1% of the photons were not absorbed. The quantum yield was determined by dividing the change in concentration per second by the absorbed (≈exposed) photons per second resulting in $\Phi_{SPA} \approx 0.16$, which is about 25% lower compared to the value found for the coumarin dimer [18].

3.3. Two-photon absorption (TPA) induced photocleavage of TBS-p-C dimer in solution

TPA-induced photocleavage of TBS-p-C dimer using a pulse energy of 70.0 mJ leads to the different spectra shown in Fig. 3A. The increase in 318 nm absorption indicates the formation of monomer. HPLC analysis proved that the monomer (TBS-p-C) is the only product obtained from the cycloreversion of TBS-p-C dimer. The TPA-induced cycloreversion was repeated at different pulse energies (52.0 mJ, 60.5 mJ, 70.0 mJ, 77.5 mJ, 85.0 mJ). In each case a linear increase of 318 nm absorption was observed, but with different slopes (Fig. 3B). The TPA cross-section of TBS-p-C dimer was determined be 1.36 GM ($1.36 \times 10^{-50}\ cm^4\ s\ photon^{-1}$). As a proof for a TPA-induced photo process the dependence of the initial cycloreversion rate on the square of the light intensity was checked using the double logarithmic plot of the incident intensity versus the initial cycloreversion rate [9]. The experimentally obtained slope of 1.64 (Fig. 3C) confirms that the photocleavage of the dimer is a TPA-process.

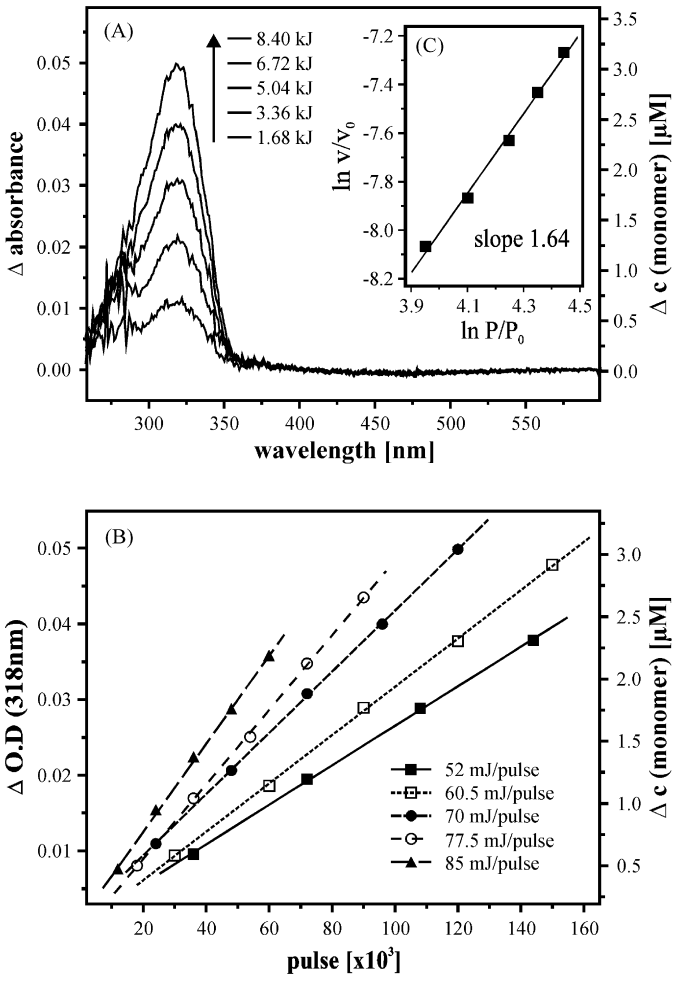

Fig. 3. Two-photon absorption (TPA) induced cycloreversion of TBS-p-C dimer. (A) Difference spectra obtained from a 0.30 mM dimer solution in acetonitrile upon exposure to 70.0 mJ pulses at 532 nm. The total energy exposed increases from bottom to top. (B) Linear dependences of the absorption increases at 318 nm (TBS-p-C) on the pulse intensities applied are observed. (C) A slope of 1.64 derived from the double logarithmic plot of incident intensities vs. the initial rates of photocleavage indicates the TPA nature of the process.

3.4. SPA- and TPA-induced cycloreversion of TBS-p-C dimer in PMMA matrix

For applications such as 3D optical data storage and drug release it is important to analyse whether the SPA- and TPA-induced photocleavage of TBS-p-C dimer is affected by matrix entrapment. PMMA films with a load of 5% (w/w) TBS-p-C dimer were prepared and analysed at 266 nm (SPA) and 532 nm (TPA) as described above. The SPA-induced cycloreversion shows a linear increase in absorption at 318 nm in dependence on the total exposure energy dose (Fig. 4A). TPA-induced cycloreversion of TBS-p-C dimer was analysed at different pulse energies (8.5 mJ, 11.0 mJ, 13.0 mJ, 16.5 mJ). In Fig. 4B the results obtained for 16.5 mJ/pulse are shown representatively.

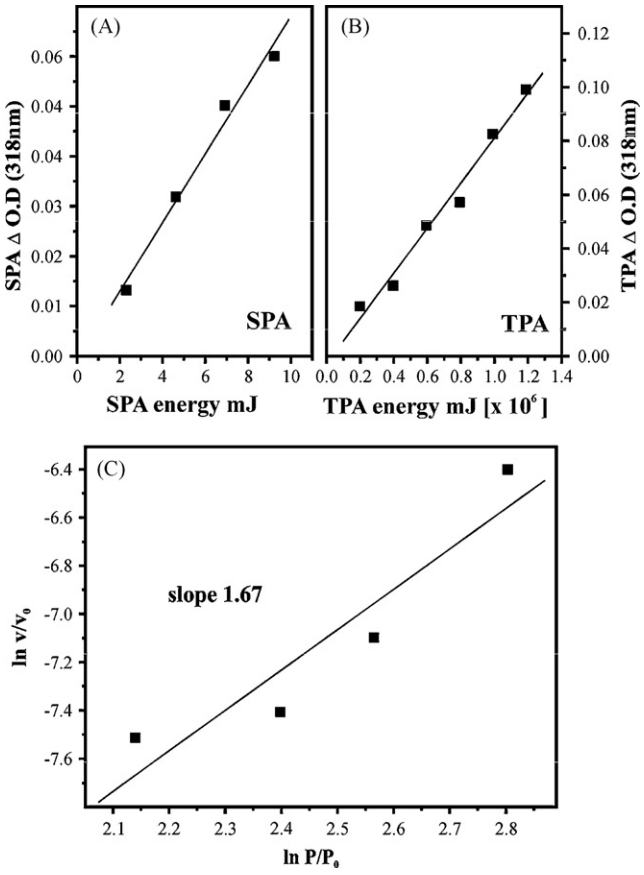

Fig. 4. Photocleavage of TBS-p-C dimer in PMMA films. (A) A linear dependence of the monomer formation (absorption at 318 nm) on the irradiated energy is observed. The quantum efficiency derived is similar to the value in solution and is $\Phi_{266} = 0.16$. (B) TPA-induced cycloreversion of dimer in PMMA matrix by 16.5 mJ pulses of 532 nm wavelength also reveals a linear dependence. The cross-section derived is about twice the value found in solution and 2.7 GM. (C) The slope of 1.67 derived from the double logarithmic plot of incident intensity vs. the initial rate of cycloreversion proves that the TPA-induced photocleavage of dimer has a similar efficiency like in solution.

The double logarithmic plot of the incident intensity versus the initial rate of cycloreversion results in a slope of 1.67 (Fig. 4C), indicating that the TPA reaction is more or less not affected by the matrix entrapment. The quantum yield for the photocleavage in polymer matrix is derived to be $\Phi \approx 0.13$. The calculated cross-section of 2.71 GM for the TPA-induced cycloreversion of TBS-p-C dimer in PMMA matrix is two times higher than in solution. (Table 1)

Table 1
Photochemical characteristics of TBS-p-C dimer measured in acetonitrile and PMMA matrix

	Quantum yield cycloreversion (SPA = TPA)	TPA cross-section [cm^4 s $photon^{-1}$] 532 nm
ACN solution	0.16	1.36×10^{-50}
PMMA matrix	0.13	2.71×10^{-50}

3.5. Probability of undesired photocleavage of TBS-p-C dimer by sunlight

The usage of coumarin dimers as photocleavable linkers to attach drug molecules to a transparent polymer backbone in IOLs is one of the potential applications. It is essential for light-controlled drug depots that undesired drug release caused in particular by sunlight is negligible over the time the IOL is implanted before the therapeutic treatment. Another important aspect is the time required to release the drug under therapeutic conditions. It should be as short as possible, because this is more convenient to the patient and one of the properties required to make ambulant treatment possible.

We assume a loading of the IOL material with the coumarin linker to be about 5% (w/w) as reported earlier [6]. The total mass of the IOL is about 50 mg. The molecular weight of the linker is 658 g/mol. The diameter of the IOL was taken to 5.5 mm. A uniform illumination of the IOL was assumed. A cumulated loss of 10% of the bound drug by photocleavage of the linker molecules over the years seems to be acceptable. For therapeutic applications higher release ratios were examined as such drug depots may be considered for several applications (multi-dose) we calculated the time required for 10%, 50% and 90% linker cleavage.

SPA-induced photocleavage requires wavelength shorter than 300 nm [20]. As irradiation in the UV-C range (100–290 nm) of the solar spectrum is almost completely absorbed by stratospheric ozone [21,22], we did the calculation for 290–300 nm of the total sunlight spectrum measured at ground level in Germany [22]. Integration over the mentioned range from 290 nm to 300 nm results in 50 mW/m^2. Two absorption barriers have

Table 2
Times required for the photocleavage of TBS-p-C dimer by single-photon and two-photon induced processes under exposure to sunlight and for therapeutical conditions

Linker cleavage	Therapeutic conditions (desired)		Sunlight exposure (undesired)	
	SPA[a]	TPA[b]	SPA[c]	TPA[d]
	266 nm	532 nm	290–300 nm	400–600 nm
10%	55 s	23 s	322 years	2.1×10^8 years
50%	277 s	114 s	–	–
90%	498 s	207 s	–	–

[a] Irradiance (SPA, therapeutic): 0.1 W/cm^2.
[b] Irradiance (TPA, therapeutic): 0.1 mJ/3 ns pulse, spot diameter 10 μm (42 GW/cm^2), 20 kHz pulse rate.
[c] Irradiance (SPA, sunlight): 50 mW/m^2 (290–300 nm).
[d] Irradiance (TPA, sunlight): 380 W/m^2 (400–600 nm).

to be considered, first the cornea with an absorption of 99% at these wavelength [23] and second the UV-absorber bound to the IOL material (>99%) [24].

For a therapeutic SPA-triggered release a light exposure at 266 nm of 0.1 W/cm^2 was assumed (about 20,000-times the solar value). Such an exposure could be realized by a glass fiber penetrating the capsular bag during exposure time.

For the undesired TPA process we integrated the global irradiation spectrum from 400 nm to 600 nm using an average spectral irradiation of 1900 mW/(m^2 nm) [25]. As a result 380 W/m^2 for the wavelength range mentioned were taken for the calculations.

For a therapeutic TPA process, we have employed, as a first approximation, the parameters in posterior Nd:YAG laser capsulotomy. Excitation laser pulses at 532 nm with 0.1 mJ pulse energy, a pulse duration of 3 ns and a repetition rate of 20 kHz were assumed. The focus diameter was assumed to be 10 μm.

Based on the obtained experimental data (see Table 1), we calculated the time of continuous exposure to sunlight until undesired photocleavage of 10% of the linker molecules through a SPA or TPA process will take place as well as the corresponding values for therapeutic photocleavage of 10%, 50% and 90% of the linker molecules (Table 2).

4. Summary and conclusion

A process is presented which leads to the stereoselective photochemical dimerization of 7-[3-(*tert*-butyldimethylsilyloxy)propoxy]-coumarin (TBS-p-C dimer) in anti-head-to-head configuration in high yield (95%). The employed spacer and the protecting group are stable during photodimerization as well as SPA- and TPA-induced photocleavage. The quantum yield for SPA-induced reversion of TBS-p-C dimer was determined for solution and PMMA films to be 0.16 and 0.13, respectively. The TPA cross-section of TBS-p-C dimer was derived to be 1.36 GM in solution and 2.71 GM in PMMA films (Table 1). The photochemical characteristics are not significantly affected by the entrapment of the dimer into a polymer matrix. Photochemically induced cleavage leads solely to TBS-p-C without any observable side products. From the experimental data derived, the times required for therapeutic drug release as well as undesired drug release by sunlight exposure were calculated. Sunlight exposure was clearly shown not to be relevant as a potential interference. Therapeutic drug release is a matter of seconds and very attractive for a potential ambulant application in ophthalmology.

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