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1,1-Dimethylnaphthalenon-dimers as photocleavable linkers with improved two-photon-absorption efficiency and hydrolytic stability

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ABSTRACT

Coumarins are well known for reversible dimer formation with wavelengths greater than 300 nm and dimer cleavage below 300 nm. In a photochemical [2+2]-cycloaddition a cyclobutane ring is formed. Formation as well as cleavage of the cyclobutane ring may be accomplished by a single-photon-absorption as well as by a two-photon-absorption triggered reaction. The coumarin system is of interest for various kinds of applications, ranging from drug delivery for ophthalmic implants to optical data storage. However, the two-photon-absorption coefficient of coumarin dimers is rather low falling in the range of 1 GM in the visible range. We present here a substitute for the coumarin dimer system which not only has an about one order of magnitude higher two-photon-absorption coefficient, but also overcomes several other problems of the coumarin dimer system. Coumarines and in particular coumarine dimers have a very limited solubility in common solvents and are susceptible to hydrolysis of the lactone ring, which leads to an undesired complexity in the photochemical cleavage reaction. The 1,1-dimethylnaphtalenone dimers introduced here show excellent stability, lead only to a single cleavage product, and have a two-photon-absorption coefficient of about 10 GM at 532 nm. These properties make the 1,1-dimethylnaphtalenone dimers a superior substitute over the well-known coumarin dimers in particular in applications where two-photon-absorption induced photocleavage is required.

1. Introduction

The photochemistry of coumarins has been extensively studied throughout the last century [1–4], due to its wide range of applications, i.e., laser dyes [5], fluorescent markers [6], therapeutic properties [7], and data storage [8]. Coumarins are able to form dimers upon irradiation with wavelengths above 300 nm, which was first discovered by Ciamician and Silber in 1902 [9]. The dimers formed may occur in one out of four different isomeric configurations, *syn* and *anti* head-to-head and *syn* and *anti* head-to-tail [10]. This reaction is reversible at wavelengths below 300 nm and was already employed in the photopolymerisation of functionalized coumarin monomers [11]. Recently, dicoumarin has been evaluated as a functional building block for drug delivery devices to treat posterior capsule opacification [12,13]. The coumarin dimer forms the functional unit for the two-photon-absorption photocontrolled separation of polymer backbone and the cytostatic drug in the intraocular lens (IOL).

Of particular relevance for the process is the molecular stability in aqueous surroundings, as they are given in modern hydrophilic IOL materials, and a high and efficient two-photon-absorption (TPA) cross-section of the dimer. However, this is difficult if not impossible with coumarine dimers. The lactone ring motives in the dimers are easily hydrolyzed by nucleophilic attack in water, which leads to an unsymmetric cleavage in the applied head-to-head dimer, not yielding the desired release of the cytotoxic compound. In this study, we present 7-methoxy-1,1-dimethylnaphthalenone dimer as a replacement for coumarin dimer which is based on the same principle, but shows better stability, better solubility, well separated absorption bands of monomer and dimer, and a significantly improved two-photon-absorption coefficient.

2. Materials and methods

All chemicals were bought from commercial suppliers and used without further purification. Organic solvents were received in technical quality and purified by filtration and distillation. The coumarin dimers were prepared according to Härtner [14] and 2-iodoxybenzoic acid was prepared according to Frigerio [15]. As aqueous eluent for HPLC, ultra pure water (0.05 μS/cm) was acidified with 300 μL H_3PO_4 per liter. Buffers were prepared with ultra

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pure water and the desired pH values were adjusted with a HI 9017 pH-meter (Hanna Instruments).

Analytical RP-HPLC measurements were done on an UltiMate 3000 System (Dionex) equipped with a Nucleosil column (RP18, 5.0 μm, 250 mm × 4 mm, Bischoff Chromatography) using acetonitrile and acidified water as eluents. For preparative RP-HPLC a YMC-Pack ODS-A column (C18, 5.0 μm, 250 mm × 4 mm, YMC) was used, an AD 25 absorbance detector and a P680 HPLC pump (both Dionex). All NMR spectra were recorded on a Bruker Avance 300B spectrometer (300 MHz). For UV/VIS spectroscopy a sample was dissolved in acetonitrile and measured against the solvent in 1 cm quartz cuvettes. All UV/VIS spectra were recorded on an Uvikon 922 (Kontron Instruments). GC–MS measurements were done on a GC-MS-QP5050 (Shimadzu) on a SE-54-cb column (Chromatography Service).

Monomers were dimerized in an UV-reactor equipped with 12 fluorescent tubes Eversun 40W/79, 25X (Osram). Photocleavage of dimers in acetonitrile was either done at 266 nm in a fluorescence spectrophotometer type RF 1502 (Shimadzu) or at 512 nm using a frequency-doubled Nd:YAG pulse-laser (Infinity 40-100, Coherent). Photon densities at 266 nm were determined using a photodiode 1337-1010 BQ (Hamamatsu).

2.1. Hydrolysis of the lactone ring in coumarin dimers

The coumarin dimers were dispersed in MeOH and stirred over night at 80 °C. The solvent was removed *in vacuo* and the dimer was extracted with chloroform, dried and analyzed by NMR.

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.82 (d, 2H, J = 8.5 Hz), 6.22 (d, 2H, J = 2.3 Hz), 6.16 (d, 1H, J = 2.3 Hz), 6.14 (d, 1H, J = 2.3 Hz), 4.78 (d, 2H, J = 8.9 Hz), 3.86 (d, 2H, J = 9.0 Hz), 3.26 (s, 6H), 0.80 (s, 18H), and 0.00 (s, 12H).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 173.3, 155.2, 154.5, 127.4, 117.9, 111.9, 107.2, 51.3, 43.3, 37.7, 25.2, 17.8, and −4.9.

2.2. Photocleavage of coumarin dimers

2.5 mL of a solution of dimer in acetonitrile (1 mol L^{-1}) was irradiated with 266 nm. Three different products were obtained and were purified using preparative HPLC. The products were identified as dimethyl fumarate and (E) and (Z)-6,6′-(ethene-1,2-diyl)bis(3-(tert-butyldimethyl-silyloxy)phenol).

E-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.17 (d, 2H, J = 8.3 Hz), 6.97 (s, 2H), 6.20–6.16 (m, 6H), 0.77 (s, 18H), and 0.00 (s, 12H).

Z-isomer: ^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 6.88 (d, 2H, J = 8.4 Hz), 6.53 (s, 2H), 6.18 (dd, 2H, J = 8.4 Hz, J = 2.0 Hz), 0.95 (s, 18H), and 0.18 (s, 12H)

GC–MS (EI, m/z): retention times of the isomers = 29.4 min, 35.4 min, fragmentation pattern: 470 (M+), 413, 385, 207, 178, and 73.

2.3. Synthesis of 7-methoxy-1,1-dimethyltetralone

7-Methoxy-2-tetralone (250 mg, 1.42 mmol) was dissolved in 10 mL THF under argon and stirred at −78 °C. Butyllithium (1.42 mL, 2.84 mmol) was added slowly followed by methyl iodide (0.18 mL, 2.84 mmol) after 30 min. The solution was stirred for another 30 min at −78 °C and then warmed to room temperature over night. The solvent was removed *in vacuo.* The oily residue was dissolved in chloroform and washed with brine four times. The organic phase was dried with Na_2SO_4, filtered and the solvent was removed. 270 mg (1.32 mmol, 93%) of a deeply red colored oil were obtained.

^{1}H NMR (300 MHz, CDCl3): δ/ppm = 7.09 (d, 1H, J = 8.3 Hz), 6.88 (d, 1H, J = 2.6 Hz), 6.73 (dd, 1H, J = 2.6 Hz, J = 8.3 Hz,), 3.81 (s, 3H), 3.03 (t, 2H, J = 6.5 Hz, J = 7.1 Hz), 2.65 (t, 2H, J = 6.5 Hz, J = 7.1 Hz), and 1.42 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ/ppm = 213.5, 157.8, 143.9, 128.0, 126.4, 111.2, 110.4, 54.3, 46.9, 36.4, 26.7, and 25.8.

2.4. Synthesis of 7-methoxy-1,1-dimethylnaphthalenone

7-Methoxy-1,1-dimethyltetralone (475 mg, 2.33 mmol) was dissolved in 23 mL of a mixture of DMSO:toluene (1:2) and 829 mg 2-iodoxybenzoic acid (2.69 mmol, 1.3 equiv.) were added. The reaction was heated to 70 °C and stirred for 5 days. The solution was diluted with diethyl ether and washed with 5% $NaHCO_3$ (2×), H_2O (1×) and brine (1×). The solvents were removed and the crude product was purified using preparative RP-HPLC with acetonitrile and acidified water (35:65) as the eluent. A yellowish solid was obtained (355 mg, 1.76 mmol, 76%).

^{1}H NMR (300 MHz, $CDCl_3$): δ/ppm = 7.39 (d, 1H, J = 9.8 Hz), 7.26 (d, 1H, J = 8.4 Hz), 7.09 (d, 1H, J = 8.2 Hz), 6.98 (d, 1H, J = 2.4 Hz), 6.04 (d, 1H, J = 9.8 Hz), 3.86 (s, 3H), 3.04 (t, 2H, J = 6.4 Hz, 7.3 Hz), 2.66 (t, 2H, J = 6.5 Hz, 7.3 Hz), and 1.46 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ ppm = 144.6, 131.0, 130.0, 127.0, 122.0, 115.2, 115.0, 113.0, 111.3, 55.4, 55.2, and 28.1

2.5. Dimerization of 7-methoxy-1,1-dimethylnaphthalenone

7-Methoxy-1,1-dimethyl-naphthalenone (100 mg, 0.50 mmol) and benzophenone (18 mg, 0.10 mmol) were dissolved in 2 mL chloroform and degassed with argon. The solution was irradiated with UV light for 8 days and the dimerization was monitored by HPLC. The solvent was removed, the crude product was dissolved in acetonitrile and purified via isocratic preparative RP-HPLC with acetonitrile and acidified water (50:50) as the eluent. The main product, the *anti*-head-to-head dimer, was obtained as a white solid (71 mg, 0.18 mmol, 72%).

^{1}H NMR (300 MHz, $CDCl_3$): δ ppm = 7.40 (d, 2H, J = 8.5 Hz), 6.91 (dd, 2H, J = 2.6 Hz, 8.5 Hz), 6.87 (d, 2H, J = 2.6 Hz), 4.05 (d, 2H, J = 8.7 Hz), 3.81 (s, 6H), 3.64 (d, 2H, J = 8.7 Hz), 1.48 (s, 6H), and 1.33 (s, 6H).

^{13}C NMR (75 MHz, $CDCl_3$): δ ppm = 214.0, 160.2, 146.0, 130.2, 129.6, 118.2, 113.8, 111.4, 55.9, 48.5, 42.9, 28.5, and 21.4.

3. Results

3.1. Cycloreversion of dicoumarin derivatives with hydrolyzed lactone rings

Nucleophilic agents, e.g. methanol, water, mixtures thereof, cause ester cleavage of the lactone rings of coumarin dimers only. Coumarin monomers do not show any lactone ring opening at the same conditions [16]. This reaction may be easily monitored by UV/VIS spectroscopy. For our experiments we used the tert-butyldimethylsilyl (TBS) protected 7-hydroxy-dicoumarin. The TBS-protected 7-hydroxy-coumarin dimer (CD) and the resulting dimethyl-3,4-bis(4-(tert-butyldimethylsilyloxy)-2-hydroxyphenyl)cyclobutane-1,2-dicarboxylate (DBCD) show significant spectral differences between 200 and 300 nm (Fig. 1).

The hydrolysis of the lactone ring in TBS-protected dicoumarin was accomplished by MeOH and analyzed via NMR. The results show opening of the lactone rings on both sides in the dimer, probably due to steric restrains of the cyclobutane ring.

The various isomers, i.e. head-to-head and head-to-tail, in combination with either closed or opened lactone rings, cause that upon dimer photocleavage a number of different products might be obtained (Table 1). An intact lactone ring structure leads for head-to-head as well as for head-to-tail isomers exclusively to symmetric

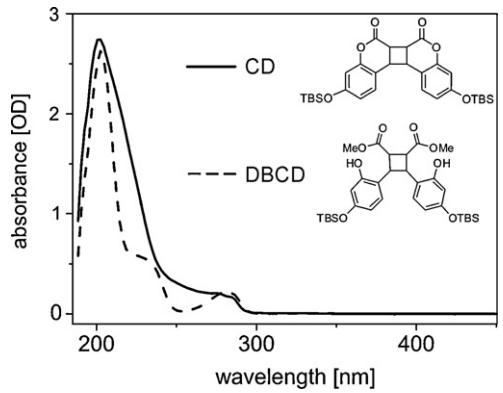


Fig. 1. Absorption spectra of the TBS-protected coumarin dimer (CD, solid line) and of dimethyl-3,4-bis(4-(tert-butyldimethylsilyloxy)-2-hydroxyphenyl)cyclobutane-1,2-dicarboxylate (DBCD, dashed line) which is obtained after dissolving CD in methanol.

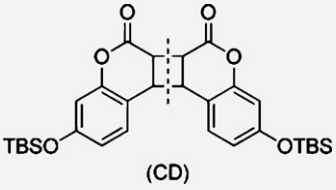
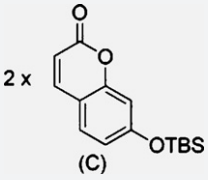
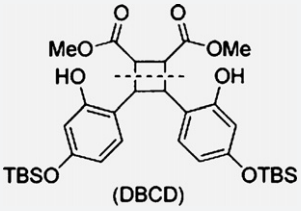
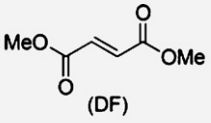
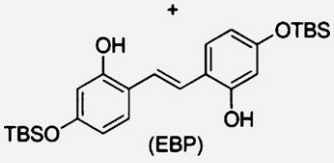
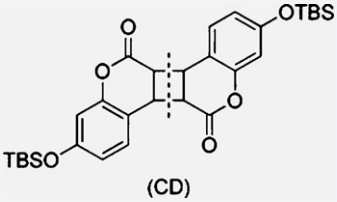
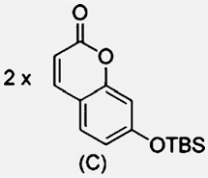
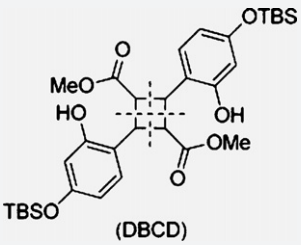
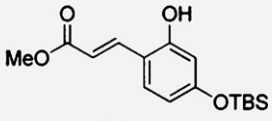
dimer cleavage. With hydrolyzed lactone rings the cleavage pattern differs between head-to-head and head-to-tail isomers. The head-to-head isomer can cleave both, symmetric and asymmetric, yielding different products [15]. In these lactone opened coumarin dimers the bonds along the C_1–C_4 and C_2–C_3 axes are more strained than those along the C_1–C_2 and C_3–C_4 bonds. An asymmetric cleavage reduces this strain and therefore represents the main reaction path [17].

Obviously the lactone ring cleavage is a problem in cases where the coumarin dimers are used as photocleavable linker molecules because up to four different products might be obtained.

3.2. Photocleavage of TBS-protected dicoumarin by single-photon-absorption

DBCD was irradiated at 266 nm and the resulting products were analyzed via NMR and GC/MS. Two products were obtained which were identified as dimethyl fumarate (DF) and (*Z*)-6,6′-(ethene-1,2-diyl)bis(3-(*tert*-butyldimethylsilyloxy)phenol) (EBP). In daylight the *E*-product is formed from the *Z*-product by photo-induced *cis-trans* isomerization, which does not occur when kept in the dark. The photocleavage of DBCD was found to be exclusively asymmetric and the aromatic part of the linker molecule remains intact. In cases where the aromatic positions are used to attach, e.g., a linker to a polymer backbone or a drug, the material would loose its function as a photocleavable linker.

Table 1
Photocleavage products of head-to-head and head-to-tail coumarin dimers in dependance of lactone ring opening.

	Cleavage	Products
Head-to-head dimers		
 (CD)	Symmetric	2 x  (C)
 (DBCD)	Asymmetric	 (DF) +  (EBP)
Head-to-tail dimers		
 (CD)	Symmetric	2 x  (C)
 (DBCD)	Symmetric	2 x  (EBA)

Modified from [17].

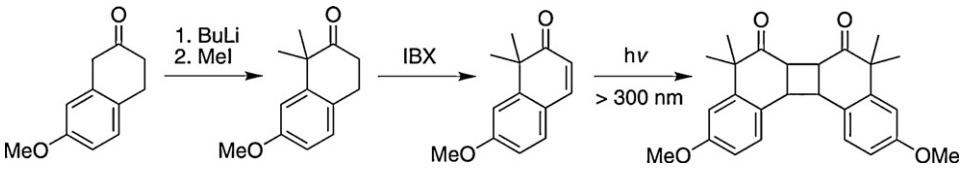


Fig. 2. Synthetic route to 7-methoxy-1,1-dimethylnaphthalenone-dimer (MND).

An option seems to be to use solely head-to-tail dicoumarin to overcome this problem. The products of both cleavage directions would be identical. However, to the authors knowledge, no investigations regarding the cycloreversion of lactone-hydrolyzed head-to-tail dimers have been reported so far. Maybe the reason is the very low yield of the head-to-tail coumarin dimerization [18–20].

Thus we decided to synthesize a new linker molecule basically using the well established reversible [2+2]-cycloaddition, but including the required stability and having a single cleavage product, and most of all, having a higher two-photon-absorption coefficient. In order to achieve the higher stability against nucleophilic attack the removal of the lactone ring is required. After considering several possible alternatives, we have chosen 7-methoxy-1,1-dimethyl-2(*1H*)-naphthalenone as a promising candidate meeting the discussed requirements. Photo-induced dimerization similar to coumarin has been reported earlier [20,21]. A synthetic route for 1,1-dimethyl-2(*1H*)-naphthalenone has been developed by Wenkert [22], but did not include any functional group in the molecule, which is required for using it as a photocleavable linker.

3.3. Synthesis

To synthesize a molecule like 7-methoxy-1,1-dimethyl-2(*1H*)naphthalenone (7-MN) the commercially available 7-methoxy-2-tetralon is a suitable precursor. Having no oxygen in the ring system and preventing the target molecule from rearrangement into an aromatic system, the introduction of two methyl-groups at the C_1-atom is required (see Fig. 2).

This was carried out in a first step, using two equivalents of butyl lithium, followed by two equivalents of methyl iodide. In the next step the molecule was oxidized with 2-iodoxybenzoic acid (IBX) in toluene/dimethylsulfoxide [23] to introduce a double bond in the 3,4-position. Finally, the molecule was dimerized according to the procedure described for coumarins with benzophenone as a photosensibilisator [24]. Two photo-products were detected in a ratio of 10:1 and the dominating product was isolated and identified as the *anti*-head-to-head dimer.

3.4. Hydrolytic stability of the monomer and the dimer

Several tests were run to verify the stability of 7-methoxy-1,1-dimethylnaphthalenone and 7-methoxy-1,1-dimethylnaphthalenone dimer (MND) in aqueous solutions, at different pH values and against various nucleophiles. Monomer and dimer were dispersed in pure methanol, pure water, and a 50:50 mixture of water and methanol and stored at room temperature for 17 days. The samples were monitored by analytical HPLC. For the pH tests, three different buffer systems were used, an acetate buffer for pH 4.0–5.5, NaH_2PO_4/NaOH for pH 5.5–8.0 and glycine/NaOH for pH 8.5–10.0. A series of measurements from pH 4 to pH 10 in half pH steps at room temperature were done and monitored by analytical HPLC for four days. In all samples the MN and MND did not undergo any decomposition (Table 2).

Table 2
Comparison of the stabilities of coumarin (TBS-C) and MN monomer and TBS-CD and MND dimer.

Stabilities	TBS-C	7-MN	TBS-CD	7-MND
Distilled water	+	+	–	+
Methanol	+	+	–	+
H_2O:MeOH (1:1)	+	+	–	+
pH 4–10	+	+	–	+

3.5. Measurement of photophysical properties

Linker cleavage via two-photon-absorption processes requires high photon densities, which require use of a pulse-laser system. The quadratic power dependence of the TPA process provides precise spatial control since the cyclobutane cleavage is only induced in the very confined focal area.

For the determination of the two-photon cross-section an extinction coefficient of a characteristic band for monomer formation and the single-photon-absorption quantum yield were employed.

3.5.1. Extinction coefficient of the monomer

Cycloreversion of MND causes an absorption band with a maximum at $\lambda = 331$ nm, which results from the conjugated π-system in MN between the carbonyl group and the double bond formed by the cycloreversion of the cyclobutane ring. The MND dimer possesses no absorption in this region. Thus, it is possible to use the 331 nm band for monitoring and quantization of the reaction (Fig. 3).

The mean value of the extinction coefficient of this band was determined to be 10,250 L mol^{-1} cm^{-1}, which lies in the same region as coumarins do (11,347 L mol^{-1} cm^{-1}) [25].

3.5.2. Quantum yield of single-photon-absorption induced cleavage of 7-methoxy-1,1-dimethylnaphthalenone-dimer

For single-photon-absorption (SPA), a dimer sample dissolved in acetonitrile was irradiated at 266 nm. Absorption spectra of MND as a function of irradiation time are shown in Fig. 4. The light energy of the lamp was measured to be 1.172×10^{15} photons s^{-1}.

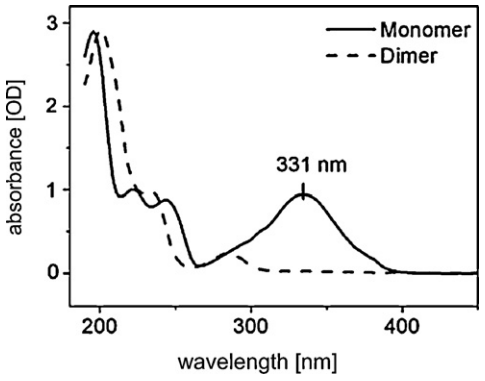


Fig. 3. UV/VIS spectra of 7-methoxy-1,1-dimethylnaphthalenone monomer (MN) and dimer (MND).

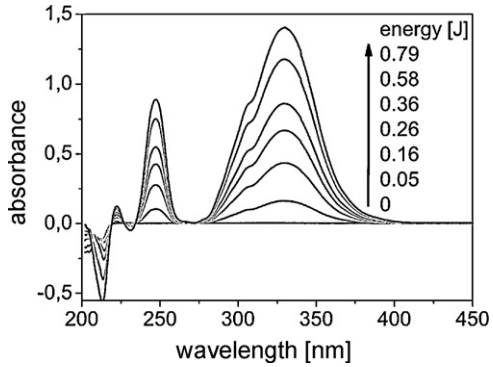


Fig. 4. UV/Vis difference spectra during the course of SPA cleavage of MND.

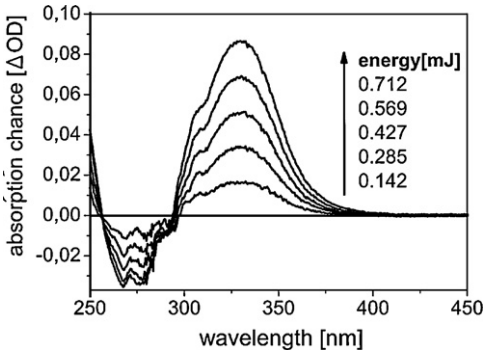


Fig. 6. Difference spectra at 331 nm of the TPA cleavage of 7-MND with Nd:YAG laser pulses at 532 nm (59.3 mJ, 20 Hz, 3 ns).

The efficiency of the SPA-induced photocleavage is characterized by the quantum yield Φ_{SPA} which is defined as the ratio of the number of molecules n_{Mol} cleaved by the number of photons n_{Phot} [25]:

$$\Phi_{SPA} = \frac{n_{Mol}}{n_{Pho}} \quad (1)$$

The number of cleaved molecules is calculated from the initial reaction rate v_0 ($t \rightarrow 0$) according to Lambert–Beers law.

The initial reaction rate was measured to be $v_0 = 1.454 \times 10^{14}$ molecules s^{-1} as shown in Fig. 5 and a SPA quantum yield of $\Phi_{SPA} = 0.12$, i.e. 12%, was calculated. For coumarin dimers this value is three times higher, i.e. $\Phi_{SPA} = 0.36$.

The absorption at 512 nm, which is of interest for excitation of the TPA process, is for both compounds practically zero.

3.5.3. Two-photon-absorption cross-section of the of 7-methoxy-1,1-dimethylnaphthalenone-dimer

Irradiation of the MND in acetonitrile with intense 532 nm pulses (20 Hz, 3 ns) causes TPA-induced cleavage of the dimer similar to CD. The formation of monomer is monitored at $\lambda = 331$ nm in the UV spectrum (Fig. 6) and a constant increase in the absorption indicates the cleavage of the linker.

The change in the absorption should be linearly proportional to the applied irradiation energy. To verify this, the TPA cross-section was measured at four different energies (28.9 mJ, 38.8 mJ, 50.0 mJ and 59.3 mJ). The results are shown in Fig. 7.

The TPA cross-section σ_{TPA} was calculated according to the procedure reported earlier [13]. The change in monomer concentrations is plotted against the irradiation times for the different pulse energies in order to obtain the initial reaction rates v_0. The initial reaction rates give the number n of cleaved cyclobutane rings in the irradiated solution. This number together with the diameter of the laser beam allows to calculate the number of the effectively cleaved dimers n_{eff} in the beam volume. The two-photon-absorption cross-section is derived from Eq. (2), where n_{eff} represents the cleaved cyclobutane rings, Φ_{SPA} the cleavage efficiency following single-photon excitation, F the laser photon density, and c_0^{Dimer} the initial number of cyclobutane rings in the solution.

$$\sigma_{TPA} = \frac{n_{eff}}{\phi_{SPA} F^2 c_0^{Dimer}} \quad (2)$$

To verify the TPA characteristic of the cycloreversion, the relation between the initial reaction rate and the square of the photon density F, which is dependant on the square of the irradiation power, is considered. The following equation (3) gives a mathematical representation [26,27]:

$$v_0^{Monomer} = 2 c_0^{Dimer} \Phi_{TPA} \sigma_{TPA} F^2 \quad (3)$$

The initial reaction rate v_0 increases twice as fast as the dimer concentration c_0^{Dimer} decreases. Φ_{TPA} is the quantum yield of the two-photon induced photocleavage and σ_{TPA} the TPA cross-section of the dimer. In most cases reported in the literature the quantum yield of the TPA has been assumed to be the same as for SPA [28].

From Eq. (3) follows that in a double logarithmic plot of the initial reaction rate versus the light intensities a linear relation with a slope of 2 should result. The measured rates v_0 were plotted versus the laser intensities P in Fig. 8 for MND.

The slope of the double logarithmic plot of the pulse intensities against the initial reaction rate is found to be closely to 2 which indicates the two-photon nature of the process. The calculated TPA cross-section is ~9.8 GM (10^{-50} cm^4 s photon^{-1}) for all energies. This value is one order of magnitude higher than the TPA cross-section of coumarin dimers, which is in the range of ~1 GM for CD [13]. To ensure that exclusively monomer is formed during cycloreversion, we analyzed the solution for exposure to 59.3 mJ pulses after each irradiation period via HPLC (Fig. 9). Only a rising

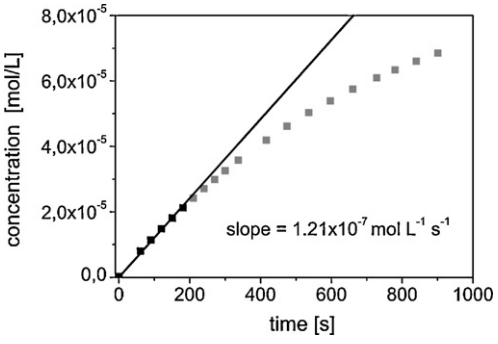


Fig. 5. Plot of the absorption at 331 nm versus time for the rising monomer concentrations.

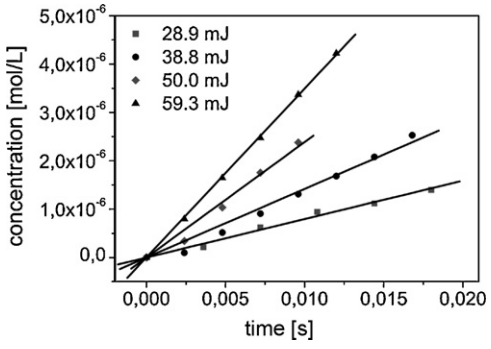


Fig. 7. TPA-induced cleavage of the 7-MND at different energies. Monomer formation measured as the increase of the absorption at 331 nm in dependence on the incident laser power.

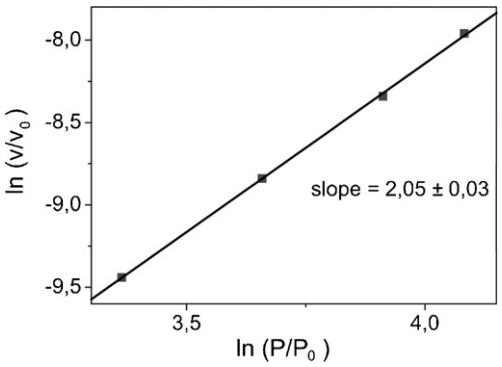


Fig. 8. Double logarithmic plot of the applied laser intensities P versus the initial rates v_0 of the linker cleavage. The TPA-induced nature of the photocleavage corresponds with the slope of 2 when ln v is plotted versus ln P.

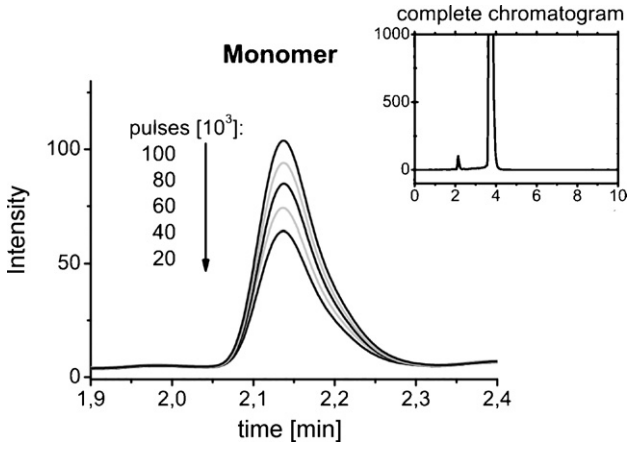


Fig. 9. HPLC analysis of the photoinduced cycloreversion via Nd:YAG laser (λ = 532 nm, 60 mJ/pulse, pulse length 3 ns, repetition rate 20 Hz) of 7-methoxy-1,1-dimethylnaphthalenone-dimer (MND) in acetonitrile. Only dimer (large peak, insert) and a rising monomer peak (small peak) are detectable.

monomer peak and no other photo-products are observed.

4. Discussion

The difficulties faced with coumarin dimers in the application as a drug delivery device have been investigated. We analyzed the lactone hydrolysis of the coumarin dimer, which occurs easily under nucleophilic attack and leads to asymmetric cleavage of the dimer upon irradiation. In cases where the 7-positions would be used to link the polymer backbone as well as the drug compound, no drug release would be observed and the material would loose its function completely. We present the synthesis and the characterisation of a new photo-cleavable linker which overcomes these difficulties. The 7-methoxy-1,1-dimethylnaphthalenone dimer (MND) was characterized with respect to its stability as well as its SPA and TPA properties. The monomer and the dimer proved to be stable under physicochemical conditions which cause severe problems with coumarins. The SPA quantum yield was measured to be Φ_{SPA} = 0.12, which is one-third of the quantum yield of dicoumarin. The TPA cross-section, however, is significantly greater, yielding 9.8 GM compared to ~1 GM with coumarins for an excitation wavelength of 532 nm. The newly developed monomer MN and its dimer MND are suitable substitutes for coumarin and coumarin dimer with significantly improved parameters (Table 3).

Table 3
Comparison of the photochemical properties of 7,7-(tert-butyldimethylsilyloxy)-coumarin and 7-methoxy-1,1-dimethylnaphthalenone monomer and dimer [26].

	Coumarin dimer (CD)	Methylnaphtalenone dimer (MND)
Hydrolysis	In nucleophilic solvents	None
Φ_{SPA}	0.36	0.12
σ_{TPA} (532 nm)	0.87 GM	9.8 GM
Melting point		
Monomer	228–234 °C*	94.5 °C
Dimer	179–181 °C*	54 °C**
Spectral separation		
Monomer	λ_{max} = 316 nm, ε = 11,347 L mol^{-1} cm^{-1}	λ_{max} = 331 nm, ε = 10,250 L mol^{-1} cm^{-1}
Dimer	λ_{max} = 266 nm, ε = 4729 L mol^{-1} cm^{-1}	λ_{max} = 266 nm, ε = 1,507 L mol^{-1} cm^{-1}

The σ_{TPA} is given for 532 nm excitation wavelength.
* Taken from Krauch et al., Photo-C4-cyclodimerisation von Cumarin, Chem. Ber. 99 (1966) 625–633.
** Anti head-to-tail.

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