Photochemical & Photobiological Sciences (2021) 20:773–780
https://doi.org/10.1007/s43630-021-00058-2

ORIGINAL PAPERS

Oxidative formation of bis-*N*-methylquinolinone from *anti*-head-to-head *N*-methylquinolinone cyclodimer

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Received: 1 March 2021 / Accepted: 17 May 2021 / Published online: 12 June 2021

Abstract
The light-driven formation and cleavage of cyclobutane structural motifs resulting from [2 + 2]-pericyclic reactions, as found in thymine and coumarin-type systems, is an important and intensively studied photochemical reaction. Various applications are reported utilizing these systems, among others, in cross-linked polymers, light-triggered drug release, or other technical applications. Herein coumarin is most frequently used as the photoactive group. Quite often, a poor quantum yield for dimerization and cyclobutane-cleavage and a lack of reversibility are described. In this work, we present the identification of a heterogeneous pathway of dimer cleavage found in a rarely studied coumarin analog molecule, the N-methyl-quinolinone (NMQ). The monomer was irradiated in a tube flow-reactor and the reaction process was monitored using online HPLC measurements. We found the formation of a pseudo-equilibrium between monomeric and dimeric NMQ and a continuous rise of a side product via oxidative dimer splitting and proton elimination which was identified as 3,3'-*bis*-NMQ. Oxidative conversion by singlet oxygen was identified to be the cause of this non-conventional cyclobutane cleavage. The addition of antioxidants suppressing singlet oxygen enables achieving a 100% photochemical conversion from NMQ to the *anti*-head-to-head-NMQ-dimer. Using dissolved oxygen upon light activation to singlet oxygen limits the reversibility of the photochemical [2 + 2]-cycloaddition and cycloreversion of NMQ and most likely comparable systems. Based on these findings, the development of highly efficient cycloaddition–cycloreversion systems should be enabled.

Keywords 1-Methyl-quinolinone · *Bis-N*-methylquinolinone · Quinolinone dimer · [2 + 2]-Cycloaddition · Oxidative dimer cleavage

1 Introduction

UV light excitation of organic matter normally enables more chemical reaction passes than thermal ground state chemistry. After the first report of a photo-triggered bond formation, the [4 + 4] dimerization of anthracene [1], further studies focused on the interaction between light and organic matter, starting with cinnamic acid [2], stilbene, and coumarin [3]. The discovery of DNA photodamage under UV irradiation [4] further stimulated research on [2 + 2] and [4 + 4] cycloaddition. Upon UV excitation, two adjacent thymine nucleobases form a dimeric species, which can be cleaved enzymatically, leading to DNA repair [5, 6]. The concept of reversible photochromic switches found a wide range of medical applications, important examples being the controlled release of small molecules from coumarin-modified porous media [7], drug release from polymeric materials [8–10], crosslinking of biomedical coatings [11], as well as in vivo reactions in biopolymers [12]. Also, several applications can be found in technical disciplines [13–16]. Although these examples provide a wide range of applications based on [2 + 2]-cycloaddition of coumarin-containing systems, several works indicate lower yields of dimerization and cleavage than expected, especially after several dimerization/cleavage cycles [17–19]. The quantum yield for coumarin dimerization from an excited singlet state was determined as $\Phi_{dim} \approx 0.001$ (in 0.3 M in acetonitrile) and $\Phi_{dim} \approx 0.1$ from an excited triplet state with benzophenone sensitization [20]. The lack of reversibility and inefficient dimerization yields are limiting factors for all the above-mentioned applications. To improve the performance of the photochromic system, we decided to investigate the structure–function relationship behind the [2 + 2]-cycloaddition

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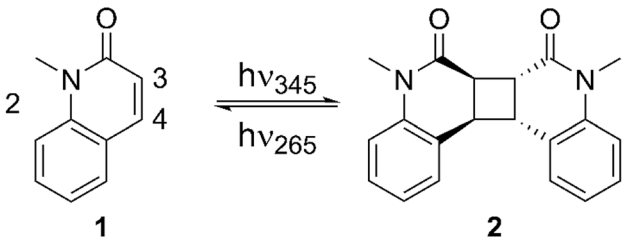
and -reversion by substituting coumarin for its lactam analog quinolinone [21]. Heterocoumarins were found to show cytotoxic effects against cancer cells [22], and the class of quinolinones itself finds several applications in medical applied research [23–25].

2 Results and discussion

Despite the possible applications, only a few publications focus on the photochemistry of quinolinones. Upon $\pi \rightarrow \pi^*$ excitation by irradiation with UV-A light of appropriate wavelength, i.e., > 300 nm, and intersystem crossing to a more stable triplet state, [2 + 2] cycloaddition is observed following the Woodward–Hofmann rules [26]. In this study, we perform the photochemical dimerization of 1-methyl quinoline-2(1*H*)-one (NMQ, (**1**)) in acetonitrile (ACN) under irradiation with 345 nm UV light (Scheme 1) using a Fluorinated Ethylene Propylene (FEP)-tube flow-reactor (for details, see Supplementary Information). The reaction was monitored by directly coupled two-dimensional high-performance liquid chromatography (HPLC). With the chosen conditions selectively, *anti*-head-to-head dimer (NMQ-dimer, (**2**)) is received (Scheme 1).



Scheme 1 Irradiation of NMQ (**1**) dissolved in acetonitrile with UV-A 345 nm light leads to selective formation of NMQ-dimer (**2**) Photochemical cycloreversion requires UV-B light, e.g., 265 nm

2.1 NMQ (1) dimerization followed by UV/Vis spectroscopy

The UV/Vis spectra of NMQ (**1**) and NMQ-dimer (**2**) differ due to the absence of the double bond in α,β-position resulting in a decreased extension of the π-system in NMQ-dimer (**2**)**.** Only negligible absorption above 310 nm is observed (Fig. 1a). Excitation of NMQ-dimer (**2**) with wavelengths λ < 300 nm induces the photochemically triggered cycloreversion to the NMQ (**1**). Irradiating a solution containing NMQ (**1**) at 345 nm, which has its maximal absorbance at 328 nm, resulting from the double bond between carbons 3 and 4, the NMQ-dimer (**2**) is formed (Fig. 1b). Three isosbestic points are observed, indicating a stoichiometric reaction leaving the chromophoric system fully intact. The plot of NMQ (**1**)-concentration in dependence on the applied photon energy is given in Fig. 2. At low conversion ratios, the reaction follows pseudo-first-order kinetics as expected. Extended irradiation of NMQ (**1**) with 345 nm light leads to deviations from the idealized model. This behavior is accompanied by the formation of an absorption shoulder around 370 nm, which could be assigned neither to NMQ (**1**) nor NMQ-dimer (**2**).

2.2 NMQ (1) flow-dimerization followed by online HPLC analytics

The spectral analysis did not give any hints on the nature of the postulated side reaction or the number of dimeric isomers formed. We used time-resolved chromatography

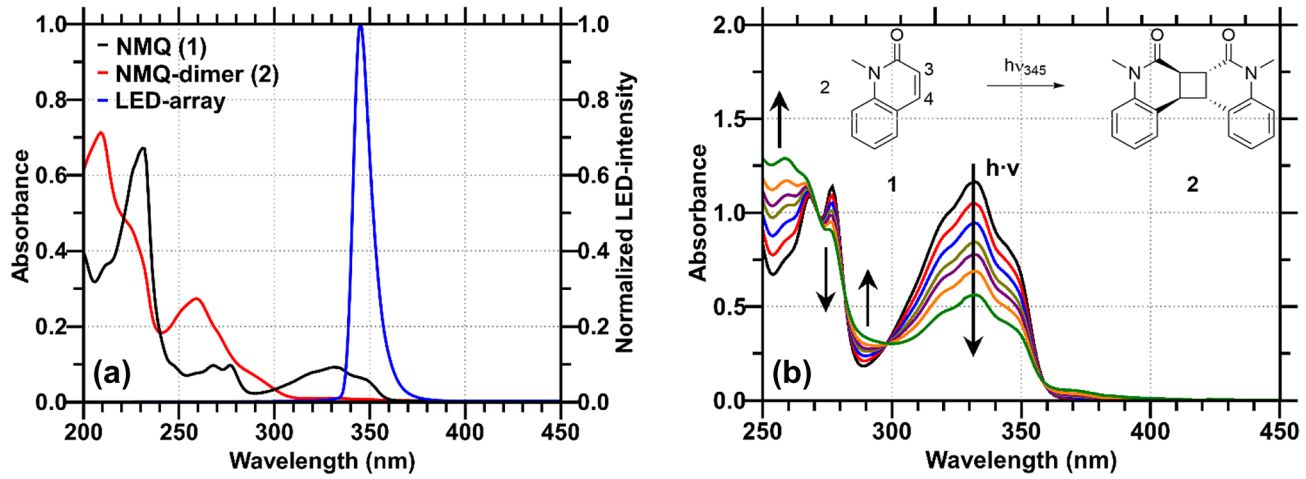


Fig. 1 **a** Absorption spectra of NMQ (**1**) and NMQ-dimer (**2**). The concentration of both compounds was 0.015 mM. The LED light source emits the spectrum shown which is centered at 345 nm. **b** UV/Vis difference spectra tracing the [2 + 2]-cycloaddition of NMQ (**1**)

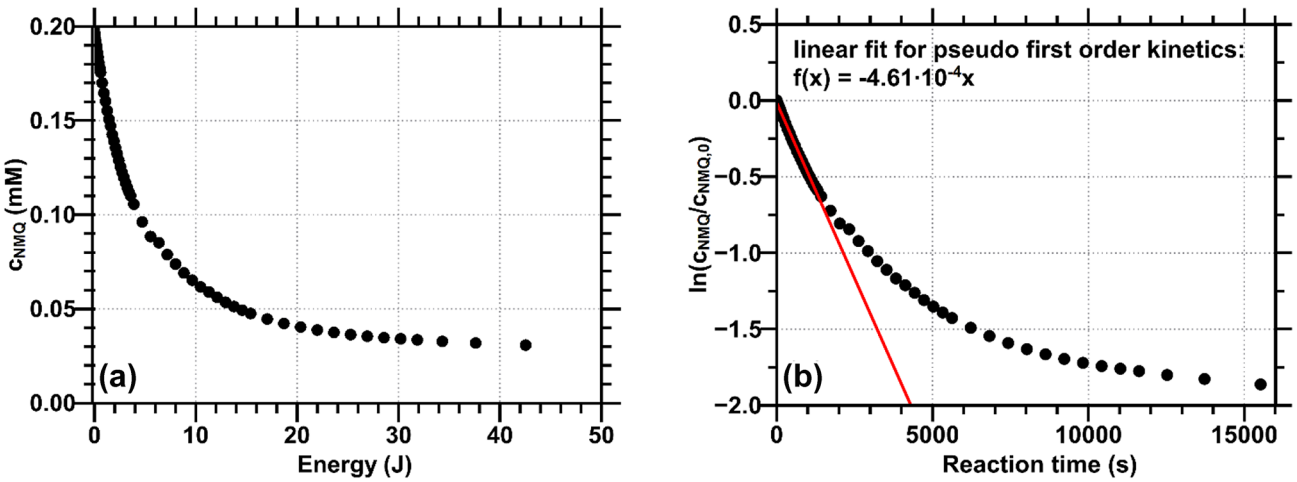
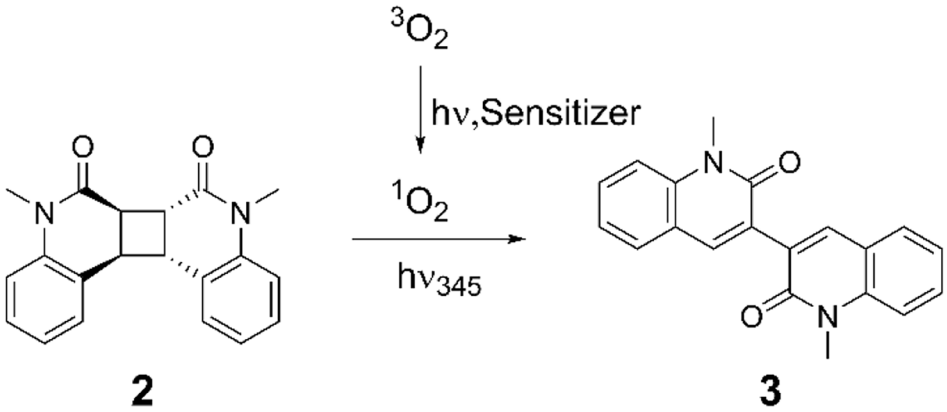


Fig. 2 **a** Decreasing NMQ (**1**) concentration in dependence on the applied total light energy. **b** Pseudo-first-order kinetics plot for the NMQ (**1**) consumption. The initial rate constant was determined as $k_2 = 2.9 \cdot 10^{-3} \frac{L}{\text{mol·s}}$

Scheme 2 Excitation of dissolved oxygen by 345 nm light in the presence of an appropriate sensitizer produces singlet oxygen $^1O_2$ which facilitates the cleavage of the 4,4'-bond and the formation of *bis*-NMQ (**3**).



consisting of a photo flow-reactor (see Supplementary Information) coupled to an HPLC. This setup allows performing high throughput experiments with an increased rate of data recording compared to the experiments described above. The quantum yield for the initial photoreaction was determined as 0.13, which is higher by two orders of magnitude compared to coumarin [20]. The photon count was investigated via chemical actinometry utilizing the *cis/trans*-isomerization of azobenzene. Experiments on the dimerization efficiency as well as an actinometric protocol are given in the supporting information. Within our studies on dimer-formation, we observed the unusual dimer cleavage while exciting with 345 nm light and identified a pseudo-equilibrium between NMQ (**1**) and NMQ-dimer (**2**). This behavior is rather unexpected as the latter merely shows no absorption at 345 nm. Furthermore, we found that the equilibrium shifts towards NMQ (**1**) with increasing photon count, and the formation of the yet unknown side-product *bis*-NMQ (**3**) is detected. At the beginning of the reaction, up to 500 s, a selective conversion from NMQ (**1**) to NMQ-dimer (**2**) is observed. After about 3 min of reaction ($E_{\text{Photo}} \sim 70$ J), almost 90% conversion is reached. However, with further illumination, the peak of NMQ-dimer (**2**) decreases, and in parallel, the peak of NMQ (**1**) increases in height again (Fig. 3a). The new arising product compound was isolated and identified as the yet unknown *bis*-NMQ (**3**). Within this structure, two NMQ-moieties are linked together across the 3,3′-bond. Its absorption spectrum is presented in Fig. 3b. NMR spectra are found in Supporting Information Fig. S10–S14. Due to torsion of approximately 20° between the two NMQ units, electronic conjugation throughout the molecule is limited (Fig. 4), which explains the rather weak bathochromic absorption shift compared to NMQ (**1**).

Taking the decreasing concentration of NMQ-dimer (**2**) and the formation of *bis*-NMQ (**3**) into account, a second light-induced process in parallel to the [2 + 2]-cycloaddition is postulated, which causes the formation of *bis*-NMQ (**3**). This side product is somewhat a dead-end for the photochemical reaction. It does not only influence the equilibrium between NMQ (**1**) and NMQ-dimer (**2**), but it also

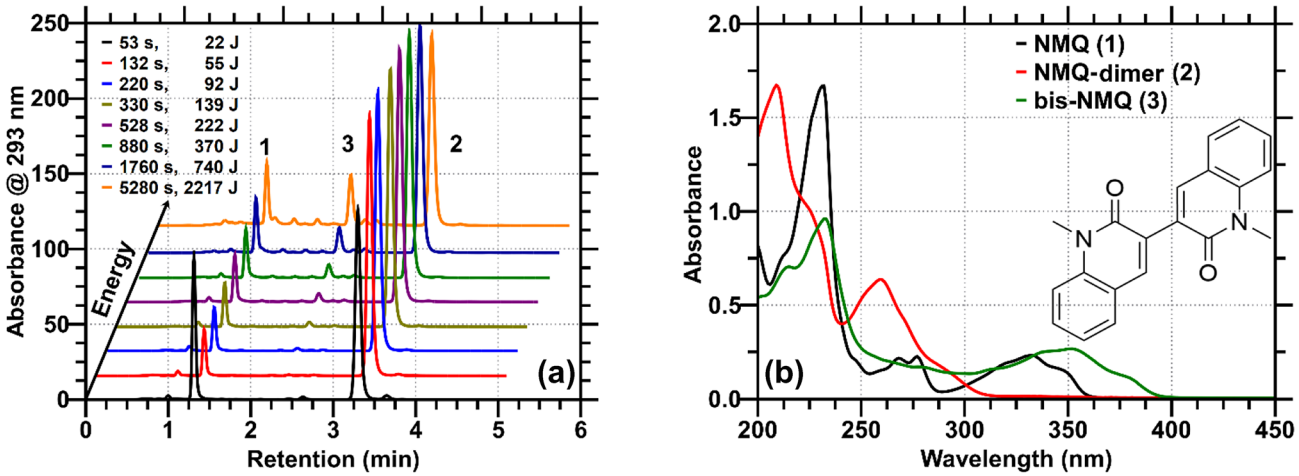


Fig. 3 **a** Reaction progress followed by HPLC of the light-induced NMQ dimerization. NMQ (**1**), NMQ-dimer (**2**), the side product was identified as *bis*-NMQ (**3**). **b** Absorption spectra of 0.035 mM *bis*-NMQ (**3**) in comparison to NMQ (**1**) and NMQ-dimer (**2**), both 0.035 mM in acetonitrile

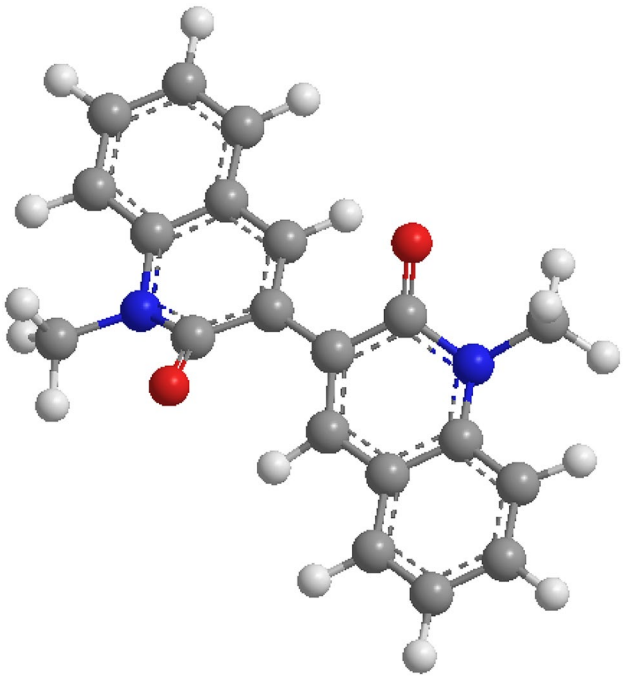


Fig. 4 Structure of *bis*-NMQ (**3**) derived from NMR and molecular simulation. The two NMQ-moieties are about 20° distorted

hinders the dimerization reaction, as it shows about 80% higher absorption at 345 nm than NMQ (**1**) $\left(\varepsilon_{345\ nm}^{bis\ -\ NMQ;\ ACN}\right) = 7346.1\ \frac{L}{mol \cdot cm}$; $\left(\varepsilon_{345\ nm}^{NMQ;\ ACN}\right) = 3932.4\ \frac{L}{mol \cdot cm}$. The occurrence of this species is an inhibiting factor of this and similar reaction systems in applied chemistry as the assumed excellent reversibility of the [2 + 2]-cycloaddition, which is the key feature in several systems, does not hold anymore.

2.3 Influences on *bis*-NMQ (3) formation

A more in-depth analysis revealed that the formation of *bis*-NMQ (**3**) from NMQ-dimer (**2**) is initiated by oxygen diffusing through the permeable FEP tubing of the flow reactor. In a previous study, we described a high intersystem crossing yield for a quinolinone similar to the here investigated NMQ (**1**). The excited states upon irradiation with 320 nm were efficiently quenched in an aerobic environment, and thus, we expect energy transfer between NMQ (**1**) and dissolved oxygen to form the reactive species singlet oxygen [27]. A more in-depth analysis revealed the validity of this theory, the results being presented in the supporting information. We found NMQ (**1**) to be a highly efficient singlet oxygen sensitizer, which can initiate the side reaction to form *bis*-NMQ (**3**) (Scheme 2). To demonstrate the responsibility of singlet oxygen on the occurrence of the undesired side reaction, we added a series of oxygen scavengers and quenchers to suppress its influence on the reaction (Table 1).

NaN_3 acts as an efficient singlet oxygen quencher, ascorbic acid as a scavenger [28, 29]. The addition of both agents to the reaction solution inhibits the formation of NMQ (**1**) as well as *bis*-NMQ (**3**). This proves that singlet oxygen is the responsible chemical species that causes the light-induced formation of *bis*-NMQ (**3**) in standard solvents and also points the way to achieve 100% photoconversion to NMQ-dimer (**2**). As the presence of singlet oxygen is an important issue on the formation of NMQ (**1**) and *bis*-NMQ (**3**) from NMQ-dimer (**2**), the electrochemical properties of the three species were investigated. The cyclic voltammograms

Table 1 Influence of singlet oxygen in experiments on the photo-triggered formation of NMQ (**1**) and *bis*-NMQ (**3**) from NMQ-dimer (**2**)

	NMQ-dimer (**2**) (educt)	NMQ (**1**) (product)	*bis*-NMQ (**3**) (product)
ACN[a]	84	16	0
ACN degassed	95	5	0
NaN_3	100	0	0
Ascorbic acid[b]	100	0	0

Solutions containing 0.02 M of NMQ-dimer (**2**) were irradiated at 345 nm for 30 min in solutions containing equimolar amounts of oxygen scavengers or quenchers, respectively. Relative peak areas at 280 nm were evaluated

[a]Standard conditions, HPLC grade ACN

[b]Due to low solubility in ACN ascorbic acid was added in water (ACN/water 1:1)

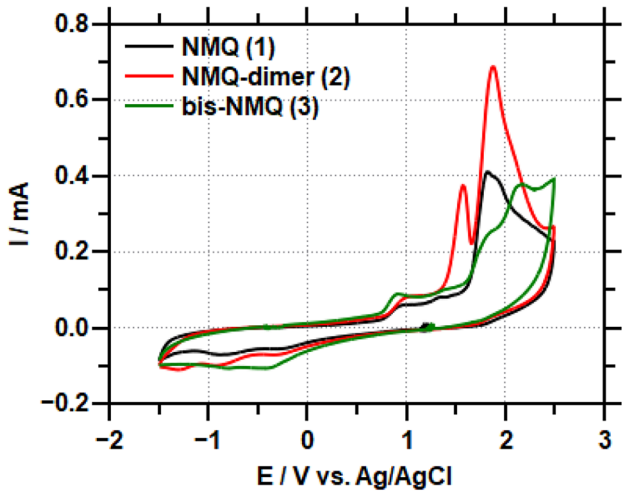


Fig. 5 Cyclic voltammograms of NMQ (**1**) (black), NMQ-dimer (**2**) (red), and bis-NMQ (**3**) (green)

(CVs) presented in Fig. 5 of NMQ (**1**), NMQ-dimer (**2**), and *bis*-NMQ (**3**) show significant differences. The most important difference between the obtained CVs is the irreversible oxidation peak around 1.6 V vs. Ag/AgCl of NMQ-dimer (**2**) which explains its sensitivity towards oxidizing agents. Experimental details on the electrochemical setup are given in the supporting information.

We tested a set of oxidizing agents whether a chemical pathway from NMQ-dimer (**2**) to NMQ (**1**) exists and whether *bis*-NMQ (**3**) occurs as a side product. The results are summarized in Table 2.

Cerium ammonium nitrate (CAN) nearly quantitatively and selectively reacts with NMQ-dimer (**2**) to form NMQ (**1**), splitting the cyclobutane ring symmetrically like in a photoinduced cycloreversion. [30] Silver nitrate in the dark does not cause any reaction with NMQ-dimer (**2**); however, as soon as irradiation with 345 nm is switched on a high amount of 39% *bis*-NMQ (**3**) is received. As NMQ-dimer (**2**) more or less does not absorb light at 345 nm, the light-induced formation of nitrate radicals from silver nitrate, which have an even higher potential than CAN, induces the reaction [31]. The high amount of *bis*-NMQ (**3**) formed within this experiment could be explained by a coordination of the Ag^+ by NMQ-dimer (**2**), making the protons in position 4 and 4' easier to access for elimination.

2.4 Mechanism of *bis*-NMQ (3) formation

From the results reported, we postulate the reaction pathways summarized in Scheme 3. NMQ-dimer (**2**) is oxidized by a suitable oxidizing agent, e.g., singlet oxygen, to form the distonic radical cation ($\mathbf{2}^{+}\bullet$) located at positions 4 and 4' of the dimer. The reactive species ($\mathbf{2}^{+}\bullet$) can follow one of two possible pathways, indicated by red and blue arrows. Cyclobutane cleavage is achieved via bond splitting between carbons 3 and 3', forming NMQ (**1**) and its radical cationic form ($\mathbf{1}^{+}\bullet$), which in turn may act as an oxidizing agent and upon reaction with NMQ-dimer (**2**) initiates the formation of ($\mathbf{2}^{+}\bullet$) after electron transfer**,** itself being reduced to form also NMQ (**1**). In total, two molecules NMQ (**1**) from one NMQ-dimer (**2**) are obtained by symmetric cleavage of the cyclobutane ring. Depending on the radical lifetime of ($\mathbf{1}^{+\bullet}$) and the concentration of NMQ-dimer (**2**), this pathway requires only a small amount of added oxidizing agent. The

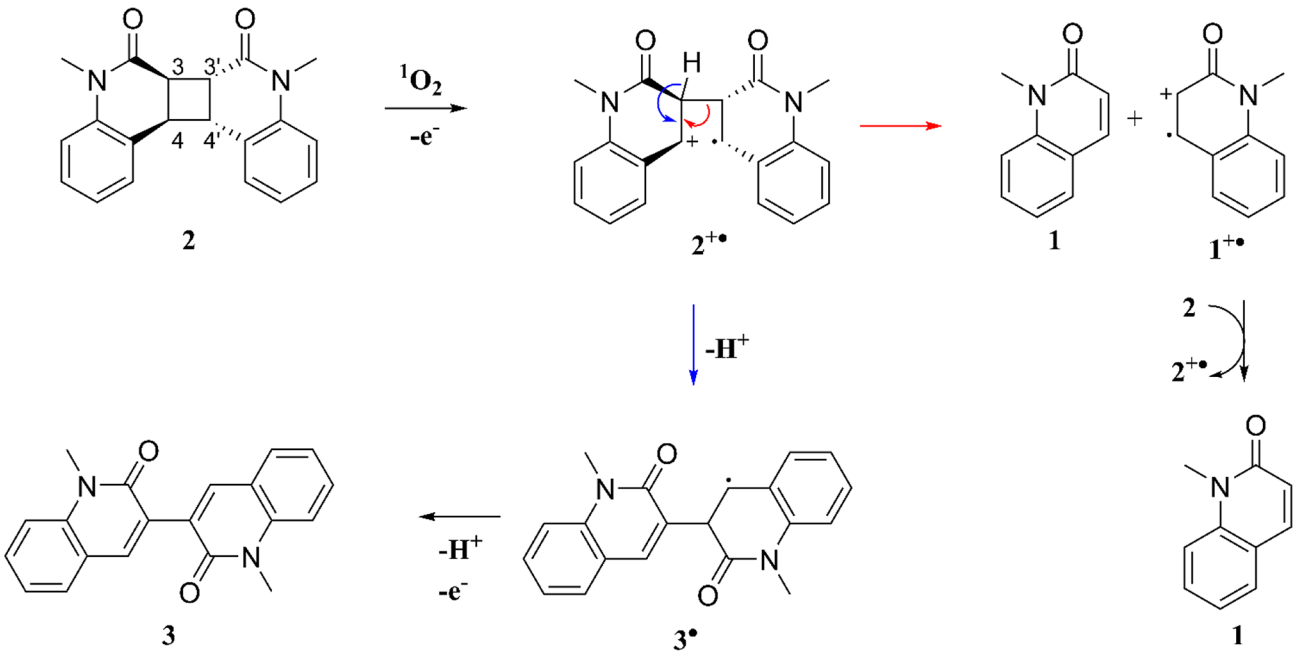
Table 2 Chemical oxidation of NMQ-dimer (**2**) to form NMQ (**1**) and bis-NMQ (**3**)

	Ratio	345 nm	ACN/water	NMQ-dimer (**2**)	NMQ (**1**)	*bis*-NMQ (**3**)
KPS[a]	Onefold	+ (30 min)	1:1	80	19	1
CAN[b]	Onefold	–	ACN	0	97	3
Silver nitrate	Tenfold	–	ACN	100	0	0
Silver nitrate	Tenfold	+ (2 h)	ACN	50	11	39

Oxidizing agents in the ratio given were added to solutions containing 0.02 M of NMQ-dimer (**2**). Relative peak areas at 280 nm were evaluated

[a]Potassium peroxo disulfate (KPS)

[b]Cerium ammonium nitrate (CAN)



Scheme 3 Proposed mechanism for oxidative cyclobutane cleavage and the formation of *bis*-NMQ (**3**) as well as NMQ (**1**).

formed NMQ (**1**) upon [2 + 2]-cycloaddition will form NMQ-dimer (**2**) again, and a fully reversible equilibrium between these two species should be observed.

However, our data show a shift of this equilibrium towards NMQ (**1**). This shift results from a second pathway indicated by the blue arrow in Scheme 3 where the distonic radical cation (**2**$^+$●) after two consecutive proton elimination steps and a second electron transfer finally forms *bis*-NMQ (**3**). This species shows a very similar absorption spectrum to NMQ (**1**), but is photochemically inactive. This product has not been reported in the literature before. It limits the reversibility of the NMQ (**1**)—NMQ-dimer (**2**) system significantly, because *bis*-NMQ (**3**) does not further participate in the photochemical conversions, in particular not in the formation of NMQ-dimer (**2**). Additionally, *bis*-NMQ (**3**) shows enhanced efficiency towards singlet oxygen sensitizing, and thus, its formation leads to an even increased shift of the equilibrium towards NMQ (**1**). This unexpected finding may be of relevance to many other cyclobutane derivatives.

A chemical cyclobutane-cleavage process is also known from biology and the formation and splitting of *bis*-pyrimidine in DNA repair [30]. In this case, the splitting is enzymatically catalyzed in an aqueous environment [6, 32]. The active center of the enzyme resembles the hydrophobic environment we find in our experiments in ACN.

3 Conclusions

Studying the photochemical dimerization by [2 + 2]-cycloaddition of NMQ (**1**) in an FEP tube flow reactor illuminated by 345 nm LEDs revealed the singlet oxygen-dependent formation of an unknown compound which was identified as *bis*-NMQ (**3**). Given the total number of photons irradiating the reactor, the quantum yield of the NMQ-dimer (**2**) formation was determined to be 0.13, which is two orders of magnitude higher than that of the structurally related coumarin dimerization [33]. The addition of oxygen scavengers and quenchers suppress the here presented formation of *bis*-NMQ (**3**) from the NMQ-dimer (**2**), presenting an efficient way to obtain an ideal and reversible photoreaction. Also, a chemical cleavage of the cyclobutane moiety by cerium ammonium nitrate is observed, fully reversing the photochemical [2 + 2]-cyclobutane formation chemically. Using NO_3● radical, generated from the potentially coordinating oxidizing agent silver nitrate ($AgNO_3$) under light exposure, enables to obtain significant amounts of the interesting structure *bis*-NMQ (**3**).

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s43630-021-00058-2.

Acknowledgements We thank Sebastian Inacker for his help in the experiments during his internship.

Author contributions Authors contributed equally to the manuscript.

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval Authors followed all ethical standards.

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