Photochemistry with Visible Light

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Molecular Oxygen as a Redox Catalyst in Intramolecular Photocycloadditions of Coumarins**

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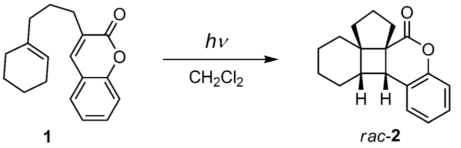
Nature uses sunlight as a source of energy for various chemical transformations by exploiting suitable chromophores or light-absorbing photocatalysts. Taking natural processes as a role model, various new photochemical transformations are currently being developed especially targeting applications in photovoltaics, solar energy storage, and water splitting.[1] Moreover, photocatalysis enjoys increasing use in organic synthesis,[2] most prominently in [2+2] cycloadditions of enones,[3] in photoredox-mediated enantioselective organocatalysis,[4] and in the photoreductive generation of radicals from alkyl bromides and chlorides.[5] Most common are metal-based visible-light photocatalysts such as the readily accessible complex [Ru(bpy)$_3$Cl$_2$] (bpy = 2,2′-bipyridyl).[6]

Photochemical [2+2] cycloadditions are of importance because cyclobutanes represent valuable synthetic intermediates and are also found as substructures in many bioactive natural products.[7] The intramolecular [2+2] cycloaddition of 4-substituted coumarins was extensively studied by Bach and co-workers, who even succeeded in performing such reactions in an enantioselective fashion using chiral templates or Lewis acids.[8]

Recently, we became interested in the intramolecular [2+2] cycloaddition of coumarins bearing an unsaturated alkyl substituent in the 3-position (such as **1**), and we realized that virtually no examples for this type of transformation have been reported in the literature.[9] Herein we describe the results of a study which has led to the discovery that such transformations can be performed efficiently using visible light in the presence of oxygen as a redox catalyst. Moreover, the unique role of molecular oxygen as a promoter of these (nonoxidative) photochemical transformations was proven by spectroscopic and electrochemical methods.

Our study started with an attempt to synthesize the cyclobutane *rac*-**2** by irradiating a degassed dichloromethane solution of the coumarin **1**[10] using a 150 W HQI lamp. However, after a full day of irradiation only very little conversion of **1** to a new (isomeric) product (*rac*-**2**) could be detected by GC–MS analysis (Table 1, entry 1). By chance, we found that the formation of *rac*-**2** was significantly faster when a non-degassed solution of **1** (in the same solvent) was employed (Table 1, entry 2). To probe whether oxygen might promote the photocycloaddition, a third experiment (Table 1, entry 3) was conducted using a solution of **1** flushed with air. And indeed, after 4 days 90% conversion of **1** to *rac*-**2** was observed, which could even be improved by using pure oxygen gas (Table 1, entry 4). The very clean reaction afforded the product *rac*-**2** as a single diastereomer (NMR analysis) the structure of which was unambiguously proven by X-ray crystal structure analysis (Figure 1). Two additional experiments (Table 1, entries 5 and 6) showed that the addition of 1 mol% of Rose Bengal (as a common singlet-oxygen sensitizer) had at best very little effect on the reaction outcome both in the presence and absence of oxygen gas.

Table 1: Intramolecular [2+2] photocycloaddition of the 3-substituted coumarin derivative **1** under different conditions demonstrating an accelerating effect of oxygen.



Entry	Conditions[a]	*t* [days]	**1**/*rac*-**2**[b]
1	degassed under Ar	1	95:5
2	under Ar	4	59:41
3	under air	4	10:90
4	under O_2	4	5:95
5	under O_2 + Rose B[c]	4	5:95
6	under Ar + Rose B[c]	4	55:45

[a] A solution of **1** was irradiated with a 150 W HQI lamp (white light) at room temperature. [b] The ratio **1**/*rac*-**2** (conversion) was determined by ^{1}H NMR spectroscopy. [c] Reaction performed in the presence of 1 mol% of Rose Bengal (Rose B.).

In a second series of experiments the irradiation of **1** with white light was investigated in the presence of oxygen and different additives using a standard irradiation time of 24 h. The results shown in Table 2 indicated that the presence of Rose Bengal or other common sensitizers such as TPP (tetraphenylporphyrin), or electron acceptors such as DCA (9,10-dicyanoanthracene), DNB (1,4-dinitrobenzene), or *para*-benzoquinone (p-BQ) did not result in any increase of product formation. However, the addition of 5 mol% of the

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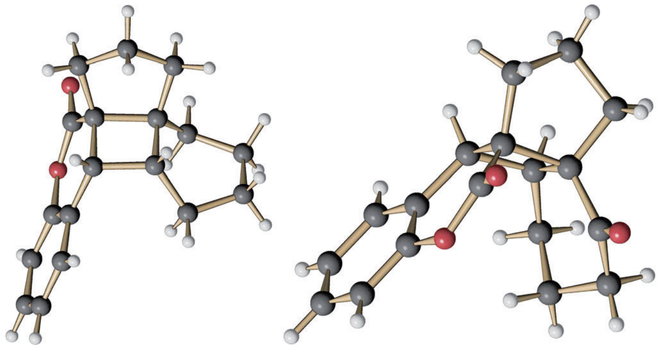


Figure 1. Structures of the [2+2] cycloadducts *rac*-**2** (left) and *rac*-**10** (right) in the crystalline state. C gray, H white, O red.

Table 2: Outcome of the irradiation of **1** under various conditions (for the reaction shown in Table 1).

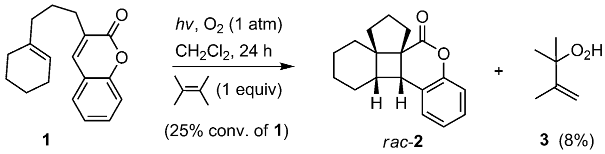
Entry	Conditions[a]	Additive[b]	**1**/*rac*-**2**[c]
1	O_2	–	21:79
2	O_2	Rose B	20:80
3	Ar	TPP	91:9
4	Ar	TPP/acetone	83:17
5	Ar	DCA	90:10
6	O_2	DCA	66:34
7	Ar	p-BQ	91:9
8	O_2	p-BQ	66:34
9	Ar	1,4-DNB	83:17
10	Ar	DABCO[d]	87:13
11	O_2	DABCO[d]	66:34
12	**O_2**	**BHT[d]**	**14:86**
13	O_2	BHT + DABCO[d]	54:46

[a] A solution of **1** in CH_2Cl_2 was irradiated for 24 h with a 150 W HQI lamp at room temperature either in the presence of oxygen (1 atm) or under argon (after ultrasound-assisted deoxygenation of the solvent). [b] Unless otherwise indicated 1 mol% of additive was used. [c] Ratios were determined by ^1H NMR spectroscopy and represent average values of several independent experiments. [d] 5 mol% of additive was used. DABCO = 1, 4-diazabicyclo[2.2.2]octane.

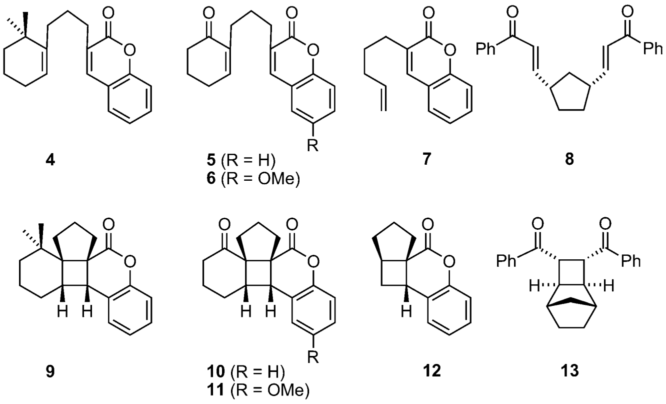
“antioxidant” BHT (3,5-di-*tert*-butyl-4-hydroxytoluene) to the oxygen-saturated reaction mixture resulted in a significantly improved (86 ± 10 %) conversion (Table 2, entry 12). Noteworthy, BHT did not lead to any increase in product formation in the absence of oxygen. We also performed an experiment using DABCO as a $^1O_2$-quenching additive,[11] which markedly inhibited product formation in the presence of oxygen, also after addition of BHT (Table 2, entries 11 and 13).

The existence of $^1O_2$ in the reaction system was also supported by the outcome of an experiment performed in the presence of 2,3-dimethylbut-2-ene (Scheme 1). In this case, the conversion of **1** after 24 h was only 25 % while significant amounts of the peroxide **3** were formed, probably as a result of the Schenck–Alder ene reaction of 2,3-dimethylbut-2-ene with $^1O_2$.[12]

We next tested the effect of oxygen (alone or in combination with BHT) on the outcome of [2+2] cycloadditions employing a set of additional substrates (Scheme 2).



Scheme 1. Irradiation of **1** in the presence of oxygen and 2,3-dimethylbut-2-ene. The formation of **3** indicates the presence of $^1O_2$.



Scheme 2. Various substrates (upper row) used in this study and the expected photocycloaddition products (lower row).

Besides the 3-substituted coumarins **1**, **4**–**7**, the symmetric diolefin **8** was employed (for comparison purposes as this compound had been studied before by Yoon et al. in a $[Ru(bpy)_3Cl_2]$-catalyzed photocycloaddition).[3c] All substrates were irradiated in CH_2Cl_2 under three different standard conditions, that is, (A) under an atmosphere of argon, (B) in the presence of oxygen, and (C) in the presence of oxygen and 5 mol % of BHT. The resulting solutions were analyzed by GC–MS and NMR spectroscopy. The outcomes of the various experiments are summarized in Table 3.

In contrast to **1**, which smoothly afforded the photoadduct *rac*-**2** under the preoptimized conditions (C) in 81 % yield, the related substrate **4** bearing two geminal methyl substituents at the cyclohexene ring did not react at all, probably as a consequence of steric crowding. The cyclohexenone **5**, however, provided the photoproduct *rac*-**10** in a clean transformation. Again, the rate was strongly accelerated by oxygen (especially in the presence of BHT). After prolonged irradiation (to achieve full conversion) *rac*-**10** could be isolated in 90 % yield as a pure diastereomer, the structure of which was confirmed by X-ray crystallography (Figure 1).[13] Irradiation of the methoxy-substituted coumarin **6** resulted in complete conversion after 12 h to give the cycloadduct *rac*-**11** in 85 % yield. However, the presence of oxygen (and BHT) did not have much effect in this case. This was demonstrated by determining the conversion under the different conditions after 4 h.

In contrast to **1**, **5**, and **6**, the coumarin **7** with a simple pent-4-en-1-yl side chain reacted only very slowly. Nevertheless, the product *rac*-**12** was obtained in good yield after several days of irradiation under the proven conditions (C). The photocycloaddition of substrate **8** proceeded slowly (but

Table 3: Results of the irradiation of various substrates under three different sets of standard conditions.

Entry	Substr.	Cond.[a]	*t* [h]	Conv. [%][b]	Product (isolated)
1	**1**	A	24	5	*rac*-**2**
2	**1**	B	24	79	*rac*-**2**
3	**1**	C	24	86	*rac*-**2** (81 %)
4	**4**	A, B, C	24	0	--
5	**5**	A	24	15	*rac*-**10**
6	**5**	B	24	31	*rac*-**10**
7	**5**	C	24	61	*rac*-**10** (90 %)[c]
8	**6**	A	4	44	*rac*-**11** (85 %)[c]
9	**6**	B	4	34	*rac*-**11**
10	**6**	C	4	36	*rac*-**11**
11	**7**	A	96	22	*rac*-**12**
12	**7**	B	96	59	*rac*-**12**
13	**7**	C	96	84	*rac*-**12** (69 %)
14	**8**	A	24	21	**13**
15	**8**	B	24	32	**13**
16	**8**	C	24	37	**13** (36 %)

[a] The substrate (0.2 mmol in 1 mL of CH_2Cl_2) was irradiated (150 W HQI lamp) at room temperature either in the presence of O_2 (1 atm) or under Ar after ultrasound-assisted deoxygenation of the solvent.
[b] Determined by ^1H NMR spectroscopy. [c] Yield obtained after prolonged irradiation to achieve full conversion of the substrate.

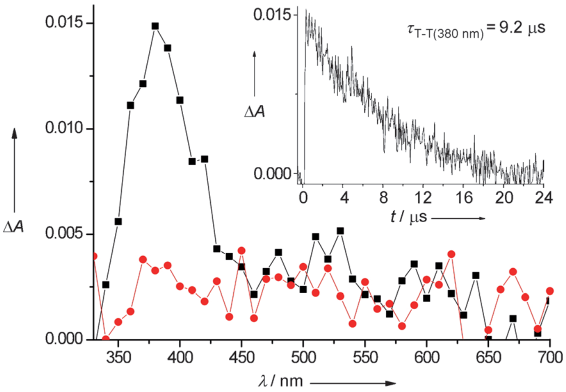


Figure 2. Laser flash photolysis of **1** (10^{-3} M) at 355 nm in acetonitrile under nitrogen (■) and under air (●) recorded 0.4 µs after the laser pulse. Inset: decay trace at 380 nm under nitrogen.

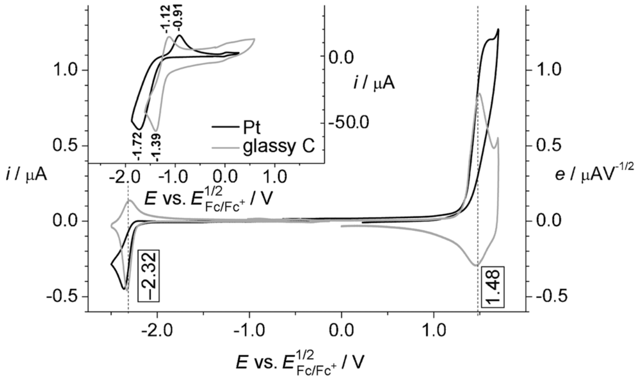


Figure 3. Cyclic voltammogram (black, left scale) and its semiderivative (gray, right scale) of **1** in MeCN with 0.1 M $TBAPF_6$ using a platinum disk electrode (r = 0.25 mm). Inset: pure MeCN/$TBAPF_6$ in equilibrium with ambient air at a glassy carbon (gray, r = 1 mm) or a platinum electrode (black, r = 1.5 mm). T = 293 K; ν = 0.1 Vs^{-1}.

cleanly) under argon to afford the product **13** (21 % conversion after 24 h). Again, the conversion rate was significantly higher in the presence of oxygen but associated with the formation of several by-products, unless BHT was added. Using conditions (C) the expected product **13** could be isolated in 36 % yield after 24 h. A control experiment performed parallel using [$Ru(bpy)_3Cl_2$] (5 mol %) as a photocatalyst (as described by Yoon et al.)[3c] afforded **13** in a comparable yield of 41 %.

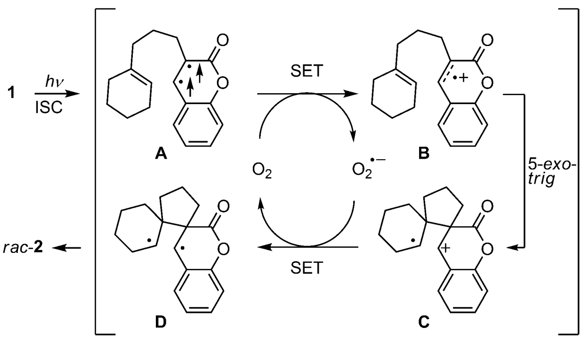
Having thus demonstrated the rate-accelerating effect of oxygen in the photocycloaddition of different substrates, we next turned our attention to the mechanistic rationalization of this unique phenomenon. To gain insight into the behavior of the primary species formed by photoexcitation of the coumarin substrates, we first investigated compounds **1** and **5** by means of time-resolved transient absorption spectroscopy (laser flash photolysis).[14] The triplet of the parent coumarin generated by triplet–triplet (TT) energy transfer from benzophenone showed a TT absorption at 400 nm and a lifetime of 0.9 µs in acetonitrile under nitrogen. The direct excitation of **1** and **5** led to triplets (TT absorption at 380 nm) with a lifetime of 9 and 4 µs, respectively, both showing monoexponential decay (the data for **1** are displayed in Figure 2).

Thus, the transients observed for **1** and **5** lived even longer than that of the parent coumarin and too long to act as "reactive" triplets. Under air, however, no transients were observed 0.4 µs after the laser pulse for the parent coumarin as well as for **1** (Figure 2) and **5**. From the TT sensitization experiments and literature data[15] the triplet energy of the coumarins **1** and **5** was estimated as 2.6–2.7 eV.

The cyclic voltammogram of **1** in acetonitrile with tetrabutylammonium hexafluorophosphate ($TBAPF_6$) as the supporting electrolyte (0.1 M) at room temperature under argon shows an anodic wave at 1.48 V (oxidation of **1**) and a cathodic one at −2.32 V (reduction of **1**) both indicating irreversible processes (Figure 3). Under the same conditions (without argon) half-wave potentials of −1.26 V and −1.32 V (depending on the material of the electrode) were determined for the reduction of O_2. These values for $E(O_2^{-}/O_2)$ are in accordance with the results reported by Vasudevan and Wendt.[16]

The free energy change for a photoinduced electron transfer from the phototransient derived from **1** to oxygen can now be estimated using the equation $\Delta G^0 = E_{ox}(\mathbf{1}) - E(O_2^{-}/O_2) - E_T(\mathbf{1})$.[17] As a result, triplet-state quenching of the coumarin substrates by oxygen (with formation of the superoxide radical anion) should be slightly exergonic (or at least isoenergetic) and therefore possible. A clearly exergonic electron transfer could also occur from the corresponding singlet states ($\Delta G^0 > -1$ eV with $E_S(\mathbf{1}) = 3.8$ eV; as calculated from the redox potential differences of **1**).

Based on these data and considerations, we propose an overall mechanism for the oxygen-promoted photocycloaddition of these coumarin derivatives, in which oxygen plays



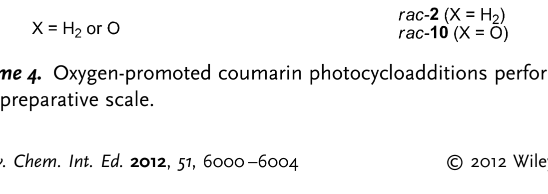
Scheme 3. Proposed mechanism for the oxygen-mediated coumarin photocycloaddition.

a key role as a redox catalyst (Scheme 3). This mechanism consists of the following five steps:

1) The triplet transient **A** is formed from **1** through light absorption and intersystem crossing (ISC).
2) Intermediate **A** reacts with oxygen ($^3O_2$) under single-electron transfer (SET).
3) The resulting radical cation **B** then undergoes a *5-exo-trig* radical cyclization to form the distal radical cation **C**.
4) **C** is reduced by the superoxide radical anion (formed in step 2) to give the biradical **D**.
5) The isolated cycloaddition product *rac*-**2** finally arises from radical combination under formation of the four-membered ring.

This mechanism is in accordance with all the experimental facts. The different behavior of the methoxy-substituted coumarin **6**, the reaction of which is not accelerated by oxygen, is probably due to a more favorable intramolecular electron transfer. Similar to **1** and **5**, the triplet of **6** has a lifetime of 5 μs, but the oxidation potential is shifted by 0.5 V to lower potentials (see the Supporting Information). The formation of singlet oxygen under the reaction conditions may result from the (nonproductive) reaction of **A** with $^3O_2$ (to give **1** and $^1O_2$) or, possibly, from the oxidation of the superoxide radical anion by intermediate **C**.[18] The beneficial effect of the antioxidant BHT in the reaction mixture remains unclear; it may be attributed to the prevention of radical side reactions.

In summary, we have discovered a rather unique effect of oxygen on a nonoxidative photochemical transformation.[19] The proposed mechanism, in which oxygen serves as a redox catalyst, was supported by transient absorption spectroscopy and electrochemical measurements. As light and oxygen are both abundant, the results presented here suggest the possibility that related effects may also play a role in aerobic photochemical reactions in nature. In any case, the developed (metal-free) oxygen-mediated photocycloaddition of 3-substituted coumarins represents a useful method for organic synthesis. We demonstrated this by performing the synthesis of *rac*-**2** and *rac*-**10** on a gram scale using a standard 150 W HQI lamp (Scheme 4).



Scheme 4. Oxygen-promoted coumarin photocycloadditions performed on a preparative scale.

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