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Intramolecular Transfer of Singlet Oxygen

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Supporting Information

ABSTRACT: The intramolecular transfer of energy (FRET) and electrons (Dexter) are of great interest for the scientific community and are well-understood. In contrast, the intramolecular transfer of singlet oxygen ($^1O_2$), a reactive and short-lived oxygen species, has until now been unknown. This process would be very interesting because $^1O_2$ plays an important role in photodynamic therapy (PDT). Herein, we present the first successful intramolecular transfer of $^1O_2$ from a donor to acceptor. Also, we found a dependence of conformation and temperature comparable with those of FRET. We provide several pieces of evidence for the intramolecular character of this transfer, including competition experiments. Our studies should be interesting not only from the theoretical and mechanistic point of view but also for the design of new $^1O_2$ donors and applications in PDT.

Singlet oxygen ($^1O_2$)[1] is the lowest excited state of oxygen[2] and can undergo different reactions such as [2 + 2]-cycloadditions,[3] [4 + 2]-cycloadditions,[4] and Schenck–Ene reactions.[5] It is not only a very convenient oxidant in chemistry but also of great interest for medicine[6] and highly important in the field of cancer treatment.[7] In the process of photodynamic therapy (PDT),[8] $^1O_2$ is generated by light and a sensitizer.[7b,9] Unfortunately, this is limited by the transparency of tissues for visible light.[10] There are two possible solutions: either the use of two photon sensitizers that absorb in the infrared region with more tissue permeability[11] or $^1O_2$ can be generated in the dark from naphthalene or anthracene endoperoxides (EPOs) via the reversible [4 + 2]-cycloaddition ($^1O_2$ carriers).[12] Here, the first in vitro tests have already been carried out,[10] and very recently, we were able to contribute to this field with the design of new $^1O_2$ donors.[13]

To apply such $^1O_2$ donors in chemistry, a large excess of up to 10 equiv over the acceptor and high concentrations are essential to achieve good yields. This is uneconomical and leads to difficulties in the separation of the products. The latter problem was solved by the use of water-soluble carriers,[14] but because of the predominant physical quenching, the donor is still used in excess.[14,15]

A transfer within one molecule (intramolecular), known as FRET,[16] Dexter electron,[17] and proton transfer[18] would, in contrast, overcome these problems (Figure 1). Also, stereoselective reactions might be possible.

Very recently, the intermolecular transfer of photochemically generated $^1O_2$ on DNA origami was studied, pointing toward a distance dependence.[19] Until now, only one unsuccessful intramolecular approach has been described in literature.[20] An

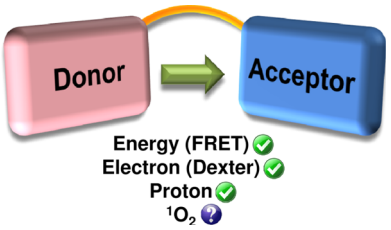

Figure 1. Intramolecular transfer reactions.

anthracene EPO that was substituted with a crown ether should transfer $^1O_2$ onto an oxazole ring bound over a long chain with an ammonium salt. However, no intramolecular transfer superior to the intermolecular transfer was observed.

During the course of our studies on applications of $^1O_2$ in material sciences,[21] we became interested in the intramolecular transfer of this reactive species. Indeed, we found a new sandwichlike structure with $^1O_2$ located in between two anthracenes.[22] However, a transfer was not possible because the thermolysis of anthracene EPOs requires rather harsh conditions in high-boiling solvents.[23] $^1O_2$ also has a shorter lifetime at increased temperatures.[24] Naphthalene EPOs should be more attractive donors because they require lower thermolysis temperatures.[14,15a]

Herein we present the first example of an intramolecular $^1O_2$ transfer between two acenes. We determined the conformation and temperature dependence as well as the independence from concentration and the presence of a second $^1O_2$ acceptor by detailed kinetic studies. Finally, our results from these model systems led to a deeper understanding of both intra-/intermolecular $^1O_2$ transfer. This topic should gain special attention because it could contribute to the use of $^1O_2$ carriers in dark oxygenations and PDT.

One main challenge for the synthesis of a $^1O_2$ donor/acceptor system is that it is not possible to synthesize this combination completely and react it with $^1O_2$ afterward. This would lead to the photooxygenation of the acceptor because it reacts faster with $^1O_2$ than the donor. A transfer would no longer be possible, so the donor has to be photooxygenated first and then coupled with the acceptor.

Hence, we decided to use naphthalene endoperoxides as donors because they exhibit excellent $^1O_2$ yields (η) in general (up to 80%), react reasonably fast with $^1O_2$, and are thermolyzed under rather mild conditions.[14,15,25]

The acceptors are represented by anthracene moieties that react very fast with $^1O_2$, and the resulting EPOs are more

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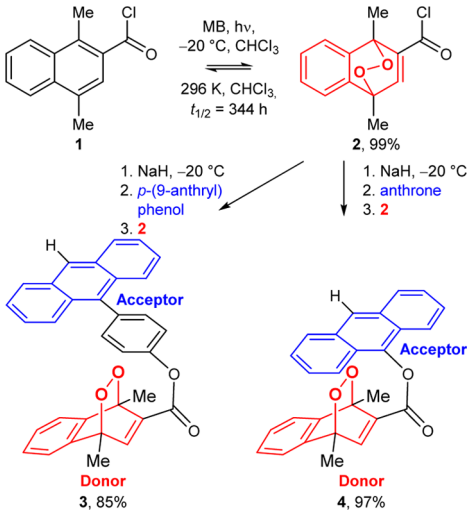
thermostable.[26] As mentioned above, naphthalene endoperoxides are temperature-sensitive, so the coupling of donor and acceptor must be done under careful cooling.

They are also highly reactive, can easily be reduced[27] or cleaved by acids such as hydrochloric and formic acids leading to side-chain-substituted naphthalenes,[28] and with ketones or aldehydes, 1,2,4-trioxanes are generated.[29] The scope of reactions is strongly restricted.

From earlier studies, we found 2-substituted 1,4-dimethyl naphthalenes **1** to be excellent $^1O_2$ carriers[13] because they exhibit very high $^1O_2$ yields and prolonged half-lives $t_{1/2}$ (up to 350 h at 296 K)[13] compared to the one of unsubstituted 1,4-dimethyl naphthalene (1,4-DMN) (5.3 h at 296 K).[30]

Of special interest was 2-carboxy-1,4-dimethyl naphthalene and its corresponding acid chloride **1**, which can be easily synthesized in only three steps.[14] Also, the acid chloride reacts in a completely reversible way with $^1O_2$ and exhibits a very long $t_{1/2}$ (344 h at 296 K), making it an ideal candidate for further transformations. Therefore, **1** was photooxygenated and coupled with two different acceptors (Scheme 1).

Scheme 1. Synthesis of the Donor/Acceptor Systems 3 and 4



We were able to prepare the corresponding esters of anthrone and *p*-(9-anthryl)phenol at low temperature in good to excellent yields after column chromatography at −20 °C. With these donor/acceptor systems in hand, we carried out the first transfer experiments on a 5×10^{-5} M scale in chloroform, which is ideal for UV/vis measurements. At low temperatures, both **3** and **4** are stable for weeks. Upon warming, **3** releases $^1O_2$ but shows nearly no intra-/intermolecular transfer under these conditions (Figure S11), which is important because we wanted to rule out an intermolecular process. We observed ~6% of transfer and expect this to be the background amount of intermolecularly transferred $^1O_2$, which can be explained by the $^1O_2$ travel distance from root-mean-square radial displacement[31] $d = (6t_{1/2}D)^{1/2}$. The radial travel distance d in chloroform ($D \approx 2.7 \times 10^{-5}$ cm^2/s)[32] after three lifetimes ($t_{1/2}$ = 120 μs)[33] amounts to ~2.5 μm. No dramatic effect was expected for shorter-bond **4**. Surprisingly, in **4** we were able to record a $^1O_2$ transfer (Figure 2). Indeed, this transfer has to proceed intramolecularly and would be the first example where an intramolecular transfer of $^1O_2$ between two acenes has been realized. During the reaction, only one isosbestic

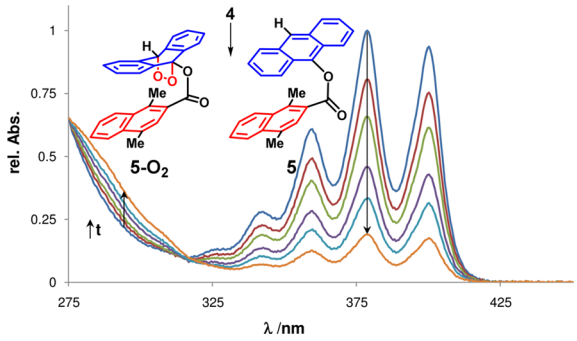


Figure 2. Intramolecular $^1O_2$ transfer experiments of donor/acceptor system **4** at 303.2 K.

point was obtained at 322 nm (Figure 2), which accounts for no consecutive reactions taking place.[34]

To explain the different behavior of **3** and **4** during thermolysis, we carried out conformational analysis by quantum chemical calculations because an effect resulting from a difference in the donor/acceptor distance (Å range) is unlikely by the larger $^1O_2$ random walk travel distance d (μm range). For both **3** and **4**, an anti conformation of the ester group is possible, in accordance to literature.[35] However, only in **4** is the anthracene acceptor close to the peroxide bridge, whereas in **3**, the phenyl ring covers this functional group (Scheme 1 and Figure S17). Therefore, the trajectory for the random walk is more suitable for an intramolecular transfer in **4** compared to that in **3**.[36] The success of an intramolecular $^1O_2$ transfer strongly depends on conformations and trajectories and is only possible because the anthracene in EPO **4** is in close proximity to the peroxide. The importance of conformations and distances are known for FRET as well.[37]

To prove the preferred orientation of the ester group, we measured UV/vis spectra for **3**−**5** at low temperature. Indeed, only **4** shows charge transfer bands[38] at 420 and 510 nm (Figure S16), indicating an n−π interaction of the peroxide bridge with the anthracene and a close contact of both. We found similar effects in an anthracene sandwich complex previously.[22] A direct transfer of oxygen from the peroxide onto the anthracene without release of free $^1O_2$ might be possible.[39]

To elucidate this hypothesis, we carried out quenching and trapping experiments (Supporting Information). **4** was thermolyzed in the presence of 1,4-diazabicyclo[2.2.2]octane (dabco), a strong physical quencher of $^1O_2$,[40] and in another experiment with 10 equiv of tetramethylethylene (TME), which exclusively reacts with $^1O_2$.[41] Indeed, the transfer of $^1O_2$ was suppressed (Figure S13) with dabco, and we detected the corresponding hydroperoxide with TME by NMR (Figure S15). These results are in favor of the release of free $^1O_2$, which is transferred intramolecularly when no quencher is present.

To confirm this first evidence for an intramolecular transfer, we decided to use NMR spectroscopy as method of choice because all involved substances can be easily detected (Figure 3). Although the system with the longer distance (**3**) was ruled out for these studies, we went on with directly bound **4**. We investigated the reaction at different temperatures (Table 1) to gain information on the kinetics (k) and to find optimal conditions for the intramolecular transfer of $^1O_2$ (η). The thermolyses were carried out on NMR and preparative scales (c_0 = 0.1 M) and showed no products other than **5-O$_2$** and O-free **5**. Also, both experimental setups led to the same results. As expected from the literature, the reaction rate as well as the

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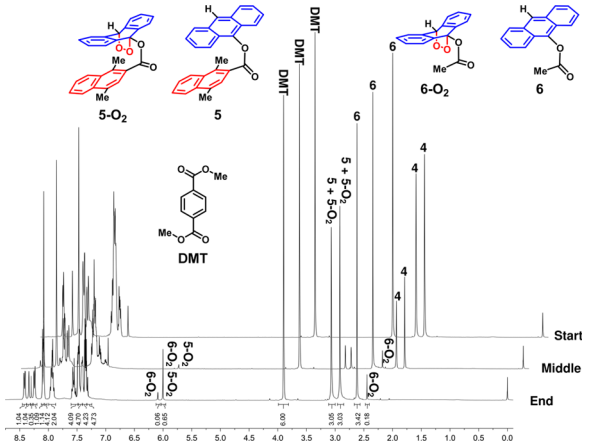

Figure 3. NMR spectra of a competition experiment for the intramolecular $^1O_2$ transfer of donor/acceptor system **4** with 9-acetoxyanthracene (**6**) at 303.2 K. **4**, donor/acceptor system; **5**, donor/acceptor system without O after release; **5-O$_2$**, donor/acceptor system with O after transfer; **6**, 9-acetoxyanthracene; **6-O$_2$**, 9-acetoxyanthracene-9,10-endoperoxide; DMT, dimethyl terephthalate (NMR reference).

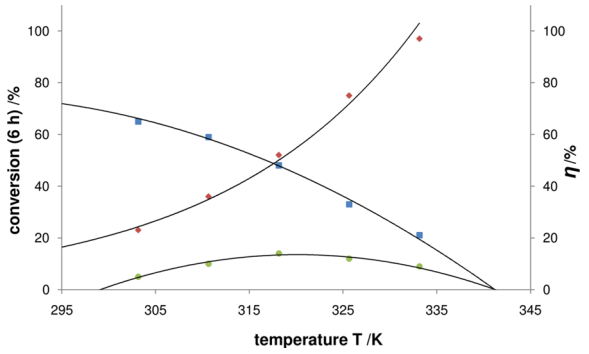

Figure 4. Conversion (6 h, red diamonds, left axis) and yield (η, right axis) for the intra- (blue squares) and intermolecular (green circles) singlet-O transfer of donor/acceptor system **4** with intermolecular acceptor **6** at different temperatures.

conversion increases with rising temperature.[42] However, the amount of transferred $^1O_2$ decreases under these conditions, which is a completely new result for the transfer of molecule fragments but is comparable with FRET where the transfer quantum yield also drops with increasing temperature.[16]

We found an important temperature range (~315 K) for an optimal intramolecular $^1O_2$ transfer, where the conversion and $^1O_2$ yield are equal. Also, this fits well with increased body temperature, which could be interesting for the release of $^1O_2$ in cancer therapy. A possible explanation for this remarkable temperature dependence might be that the EPO is cleaved too rapidly at higher temperature and the acceptor cannot be oxidized fast enough under these conditions. (For details, see the Supporting Information.)[43] Another explanation could be the faster $^1O_2$-quenching rate at increased temperatures.[24]

Finally, the solvent cage, which is the solvating shell around molecules that has to be reordered during a reaction, must be taken into account; it is stronger at lower temperature.[33] Thus, the degree of freedom for the random walk of $^1O_2$ into the solution is reduced, leading to a better direction toward the acceptor at lower temperature.[44]

To further prove the intramolecular character of the transfer, we repeated all experiments under identical conditions in the presence of 9-acetoxyanthracene (**6**), a second acceptor for $^1O_2$ of similar reactivity (Figures 3 and S14). We compared the intra- (η_{intra}) and intermolecular (η_{inter}) $^1O_2$ transfer at different temperatures (Table 1, columns 8 and 9). It is obvious that not only the intra- but also the intermolecular transfer is temperature-dependent (Figure 4, green circles), which can be explained by the above-mentioned reasons. To the best of our knowledge, there is not yet any study available emphasizing a reduced $^1O_2$ yield for increased temperature, either inter- or intramolecularly.

Interestingly, the maximum yield of the oxidized intermolecular acceptor (**6-O$_2$**) is only 14% (Table 1, column 9). This process can only compete to a small extent with the intramolecular transfer (Figure 4, blue squares). More important is the amount of intramolecularly transferred $^1O_2$; it is almost independent from the presence of **6** (Table 1, columns 7 and 8). This is more clear evidence for the intramolecular character of this transfer.

We synthesized donor/acceptor systems for the first successful intramolecular transfer of $^1O_2$. A combination of UV/vis measurements, NMR experiments, competition reactions, and quenching experiments clearly show the migration of this reactive species within the molecule. We found a strong dependence of the transfer on the orientation, comparable with that of FRET. Another interesting aspect is the influence of the temperature on the reaction because this is always a crucial point using $^1O_2$ donors. We found an optimal balance of transfer rates (k) and $^1O_2$ yield (η) at around 315 K, which fits well with increased body temperature. Therefore, our new $^1O_2$ donors might be of great interest for the treatment of cancer by the release of $^1O_2$ in the dark. Finally, our results should be important for physical and preparative chemists as well as medical applications.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07848.

Experimental procedures and compound characterization data. (PDF)

Table 1. Intra- vs Intermolecular $^1O_2$ Transfer at Different Temperatures for 4 with or without 9-Acetoxyanthracene (6)

		conversion after 6 h (%)		yield **5-O$_2$** at 6 h (%)		yield **5-O$_2$** (η_{intra}) at full conversion (%)		yield **6-O$_2$** (η_{inter}) at full conversion (%)
entry	T (K)	without **6**	with **6**	without **6**	with **6**	without **6**	with **6**	with **5**
1	303.2 ± 0.1	23.2 ± 0.3	23.1 ± 0.2	16.2 ± 0.4	15.1 ± 0.3	70 ± 1.1	65 ± 1.0	5 ± 0.2
2	310.7 ± 0.1	36.1 ± 0.2	36.4 ± 0.2	22.8 ± 0.5	22.7 ± 0.4	63 ± 0.8	59 ± 0.8	10 ± 0.3
3	318.2 ± 0.1	51.9 ± 0.4	51.6 ± 0.3	24.4 ± 0.5	24.2 ± 0.4	49 ± 0.9	48 ± 0.8	14 ± 0.3
4	325.7 ± 0.1	75.2 ± 0.3	75.4 ± 0.5	28.1 ± 0.4	27.1 ± 0.3	39 ± 0.8	33 ± 0.7	12 ± 0.4
5	333.2 ± 0.1	96.7 ± 0.5	96.5 ± 0.4	22.9 ± 0.3	20.2 ± 0.2	24 ± 0.5	21 ± 0.4	9 ± 0.2

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Notes

The authors declare no competing financial interest.

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