Reversible Binding of Oxygen to Aromatic Compounds

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ABSTRACT

Many polycyclic aromatic hydrocarbons are able to trap singlet oxygen $^1O_2$. Some of the endoperoxides, thus obtained, exhibit the exceptional feature of releasing oxygen, frequently in the excited singlet state, under heating or UV irradiation. In this Account, we provide a short summary of the present knowledge on these endoperoxides: preparation and thermal and photolytic decomposition, with a special emphasis on the structural requirements to favor cycloreversion. The profitable use of this property in the development of highly reversible photochromic systems and of specific sources or traps of $^1O_2$ in aqueous media is also described.

Among the properties of endoperoxides (EPOs),[1] the ability of some members of this class of compounds to release oxygen on warming has appeared, since the very beginning, to be utterly exceptional. After the initial observation in 1926 that such a dissociation occurs with the photooxide of the still unknown rubrene,[2] Dufraisse devoted many studies to this phenomenon, which he called "the labile bonding of oxygen to carbon". Before recalling the major discoveries in the field, let us say that it took around 10 years to extend this behavior to 9,10-diphenylanthracene. Later on, investigations of the behavior of many other anthracenes resulted in a significant observation: the peculiar dissociation of the EPO of 1,4-dimethoxy-9,10-diphenylanthracene, which starts occurring already at room temperature.[3] This anomaly was explained much later by the exceptional 1,4 position of the dioxygen bridge,[4] but at the time, it was noted that this peroxide, wrapped in black paper and deposited on a photographic plate, was able to give rise to a print. Dufraisse concluded that there had occurred "the emission and the diffusion of some sort of activated oxygen with a long lifetime",[3] a premonitory assertion.

Following Foote's finding in 1964 that singlet oxygen ($^1O_2$) was the active species in photooxidations,[5] Wasserman demonstrated that a part of the evolved oxygen during thermolysis of 9,10-diphenylanthracene EPO is in its singlet state by the ability of transferring it to other photooxidizable substrates.[6] Subsequently, it has been shown that this is also the case during photodissociation of aromatic EPOs.[7,28] The activating effect of electron-donating groups on transannular addition of $^1O_2$ to aromatics allowed Rigaudy[8,9] to obtain EPOs of 1,4-dimethoxy- and 1,4-dimethyl-substituted naphthalenes which dissociate at lower temperatures than the 9,10-anthracenic analogues. Taking advantage of this property, several teams have prepared water-soluble naphthalenic EPOs, which are currently used as unequivocal sources of $^1O_2$ in biological media.[10,11]

We plan, in the present review, to deal with the recent developments of this reversible binding of oxygen to aromatic compounds, with a special emphasis on the design of highly reversible photochromic systems and of specific sources or traps of $^1O_2$.

Binding of Oxygen to Aromatic Compounds

Preparation of Endoperoxides. More than 400 EPOs derived from hydrocarbons with 1−9 fused benzenic cores have been described in the literature.[1b] Most of them were prepared by photosensitized oxygenation involving a [4+2] cycloaddition of $^1O_2$ on the electron-rich carbons of the aromatic substrate. However, in contrast to anthracene and higher members of the acene series, unsubstituted benzene and naphthalene fail to react with $^1O_2$, and the corresponding EPOs were indirectly synthesized by Yang[12] and Vogel[13], respectively. Another noticeable exception to the current access to EPOs via $^1O_2$ is the case of helianthrene **1** (HEL). This compound is one of the most reactive $^1O_2$ acceptors known since it reacts with $^1O_2$ at a nearly diffusion-controlled rate ($k_r = 5 \times 10^9$ $M^{-1}s^{-1}$). Surprisingly, Brauer observed that HEL also reacts with ground-state oxygen ($^3O_2$) in the dark, leading to the formation of the EPO $HELO_2$.[14] A detailed study of the mechanism indicates that the thermal formation of $HELO_2$ occurs via a polar transition state. The collision of HEL with $^3O_2$ yields a loosely bound complex. This triplet intermediate collapses through a spin-forbidden step to

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Jean Rigaudy, born in 1921, Emeritus professor, taught organic chemistry and photochemistry at Pierre et Marie Curie University and ESPCI in Paris. His research was mainly focused on auto-oxidations and on the chemical transformations of acenic endoperoxides. He was also an active member and chairman of the IUPAC Commission on organic nomenclature.

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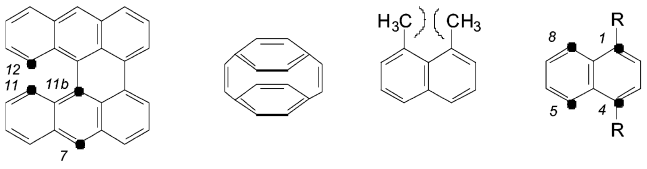
a singlet statezwitterion, $^{+}HEL-OO^{-}$, which undergoes ring closure to form $HELO_2$ (eq 1).

$$HEL + {}^3O_2 \rightleftharpoons {}^3[HEL\cdots O_2] \rightleftharpoons {}^1[{}^{+}HEL-OO^{-}] \rightleftharpoons HELO_2 \quad (1)$$

Structural Effects. The reactivity of aromatic hydrocarbons toward $^1O_2$ increases with the electron density of the substrate, reflecting the electrophilic nature of $^1O_2$.[1a] A first structural effect is the number of fused rings of the substrate. The comparison of anthracene, tetracene, and pentacene shows that the reactivity increases by about 2 orders of magnitude for each supplementary fused ring. For bent polycyclic aromatic hydrocarbons, the evolution of the reactivity according to the molecular structure is more complex, but Stevens has shown that the rate constants correlate nicely with the π-relocalization energy of each hydrocarbon.[15]

However, this method fails to describe quantitatively the relative reactivity of $^1O_2$ toward substituted aromatic molecules. The grafting of electron-releasing groups on the site of $^1O_2$ addition increases the rate constants in the order $H < C_6H_5 < CH_3 \leq OCH_3$. For instance, 1-methylnaphthalene reacts slowly with $^1O_2$, whereas naphthalene itself is completely unreactive. In the same way, neither benzene, toluene, xylene, nor tri- and tetramethyl benzene react with $^1O_2$, whereas penta- and hexamethyl-benzene provide the corresponding EPOs as primary oxidation products.[16] By applying the frontier molecular orbital theory, de Boer was able to find a good linear correlation between the logarithm of the experimental rate constants and the second-order perturbation energy for attack of $^1O_2$ on different positions of various substituted aromatic compounds.[17]

Steric Effects. Steric strain is also an important parameter which can modify both the reactivity of the substrate and the regioselectivity of the cycloaddition of $^1O_2$. Thus, in the [2.2] paracyclophane diene **2**, the benzene rings are sufficiently deformed to permit the reaction with $^1O_2$, affording the mono- and di-EPO.[18] Peri-interactions between two neighboring methyl groups bound to a polycyclic aromatic hydrocarbon enhance its reactivity toward $^1O_2$ because the steric strain is somewhat relieved in the transition state. This phenomenon explains why 1,8-dimethylnaphthalene **3** is 4 times more reactive than the 1,5-isomer.[17]



1 (HEL) **2** **3** **4**

Steric effects may also account for the exceptional reactivity of **1**. This hydrocarbon cannot be planar because the hydrogens at carbon atoms 11 and 12 cause steric hindrance, which forces the two benzo rings to twist out of the plane of the aromatic system. The twist induces a severe strain in the double bonds at carbons 7 and 11b, which is absent in EPO. The extra energy released accounts not only for the ability of **1** to accept $^3O_2$ but also for its very high reactivity toward $^1O_2$.[14]

Solvent Effects. In the early history of $^1O_2$ chemistry, the rate constants of the reaction between $^1O_2$ and organic substrates were inaccurate, and the first experiments performed to study a possible solvent effect on [4+2] cycloaddition of $^1O_2$ led to the conclusion that it seemed to be practically solvent independent in agreement with a mechanism analogous to the "normal" Diels–Alder reaction.[19] However, later studies comprising a wide range of solvents have revealed that the widely accepted dogma of solvent independency was completely wrong when the reaction was conducted in highly polar solvents such as *N*-methylformamide, formamide, or water.[20] Thus, the cycloaddition of $^1O_2$ to 1,4-dimethylnaphthalene **4** ($R = CH_3$) and derivatives has been studied in 28 solvents. It was found that the rate constant of $^1O_2$ addition increases by more than 2 orders of magnitude from cyclohexane to formamide and it was even much higher in water when using water-soluble derivatives of **4**. This huge solvent effect on kinetics was rationalized in terms of solvatochromic parameters, including dipolarity, polarizability (π^*), and Hildebrand solubility (δ_H) parameters.[20]

Mechanism of [4+2] Cycloaddition to Aromatics. The mechanism of [4+2] cycloaddition of $^1O_2$ to conjugated systems has received little attention probably because a concerted mechanism similar to the Diels–Alder reaction has been more or less assumed. A recent theoretical study of $^1O_2$ addition to benzene offers some clues to explain differences between [4+2] cycloaddition to aromatic compounds and normal Diels–Alder reaction.[21] It suggests that $^1O_2$ addition occurs through a single-step concerted mechanism with a symmetric transition structure exhibiting significant charge transfer from the organic donor to oxygen.

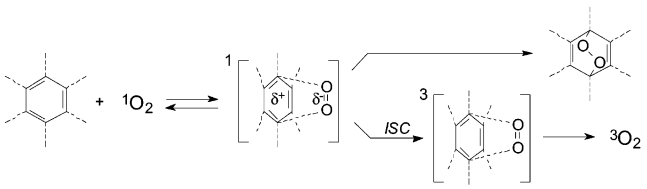


FIGURE 1. Mechanism of [4+2] cycloaddition of $^1O_2$ on aromatic hydrocarbons.

A mechanism that satisfactorily explains all the experimental data is outlined in Figure 1.[20–23] The first step of the reaction involves the reversible formation of an exciplex in the singlet state. This exciplex exhibits a charge-transfer character due to the strong electron attraction by $^1O_2$. Subsequently, the solvated exciplex either collapses through a concerted mechanism into EPO (chemical quenching) or suffers a spin-forbidden intersystem crossing (ISC), giving a triplet state complex which dissociates into $^3O_2$ and the starting substrate (physical quenching).[23]

Increasing the solvent polarity will shift the equilibrium toward the formation of the polar intermediate, whereas increasing the Hildebrand parameter will favor the closeness of reactants through the so-called hydrophobic effect.

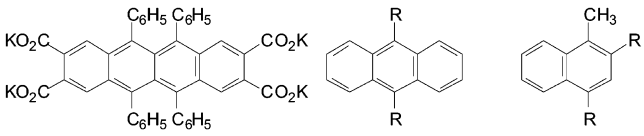
Quantification of $^1O_2$ Production in Aqueous Media by Chemical Trapping. Many important processes involving $^1O_2$ occur in aqueous media: (i) degradation of natural organic compounds in the sea under sunlight, (ii) generation of $^1O_2$ by enzymes in vivo, (iii) phototherapy of cancer, (iv) photoinactivation of viruses in blood products, and (v) disproportionation of H_2O_2 by metal ions. To distinguish $^1O_2$ from a variety of other ROS (reactive oxygen species), a technique with extreme selectivity is required.

Monitoring of the faint $^1O_2$ phosphorescence at 1275 nm is a very specific and noninvasive method (eq 2). However, the quantification of $^1O_2$ in aqueous systems generating a low stationary concentration of $^1O_2$ is troublesome because of the small emission quantum yield of 6.5 $\times$ 10^{-7} in H_2O.[23] Moreover, it may be inapplicable when the medium is either opaque or contains efficient physical quenchers such as amines or phenols.

$$^1O_2 \xrightarrow[media]{aqueous} {}^3O_2 + h\nu\ (1275\ nm) \qquad (2)$$

Chemical trapping by water-soluble aromatic hydrocarbons is also specific for $^1O_2$ and can be much more sensitive than the luminescence technique. Actually, under suitable conditions, appropriate substrates can trap most of the $^1O_2$ available even when the rate of $^1O_2$ generation is very low because the concentration of EPO formed is proportional to the cumulative amount of $^1O_2$ generated.

Compounds **5**−**7** are typical examples of this type of traps.[24] Each of them has its own advantages and drawbacks. The rubrene derivative **5** reacts rapidly with $^1O_2$ through a pure chemical process, and the fading of its red color allows its monitoring by visible spectroscopy; however, its synthesis is tricky, and it is light-sensitive. Anthracenic traps **6a** and **6b** are easier to prepare, but they are less reactive than **5**. The cationic trap **6c** is compatible with positively charged sensitizers and catalysts (such as methylene blue and calcium ions). The naphthalenic compound **7a** is only moderately reactive toward $^1O_2$, but it has two specific features: (i) it does not absorb in the visible range and can be used to quantitate $^1O_2$ photogenerated from a colored sensitizer; (ii) the formation of the EPO characteristic of $^1O_2$ can be proved unambiguously by a simple warming which regenerates **7a**.



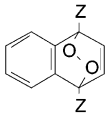
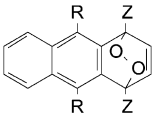
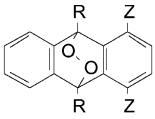
5 **6** **7**

a : R = CH_2-CH_2-CO_2Na
b : R = CH_2-CH_2-OSO_3Na
c : R=C_6H_4-$N(CH_3)_3Cl$

Dissociation of Endoperoxides

Two primary pathways of transformation may compete during thermolysis or photolysis of aromatic EPOs (Figure 2): cycloreversion, leading to parent substrate and to oxygen, in a singlet or a triplet state; and homolytic cleavage of the peroxidic bond, followed by rearrangement to more or less stable diepoxides or by decomposition, leading to hydroxy-ketones or quinones. The relative importance of both processes depends on structures and experimental conditions.

Table 1. Activation Parameters for the Thermolysis of Arenes Endoperoxides[12,13,25] [a]

EndoPerOxide		$\Delta H^{\neq}$ (kJmol^{-1})	$\Delta S^{\neq}$ (JK^{-1}mol^{-1})	$^1O_2$ (%)
	**8**	74.4±2	-1.7±8	90±3
	**9a**	97.0±4	0.8±5	≈100
	9b	101.1±1	8.4±4	76±1
	**10d**	124.6±1	-7.5±3	92±1
	10e	101.1±1	-1.3±3	95±5
	**11c**	135.8±1	40.1±2	32±1
	11d	132.9±1	30.9±3	52±4

[a] **a**: Z = H. **b**: Z = CH_3. **c**: R = C_6H_5, Z = H. **d**: R = C_6H_5, Z = CH_3. **e**: R = C_6H_5, Z = OCH_3. **f**: R = Z = C_6H_5.

Thermolysis of Endoperoxides. The ratio between cycloreversion and cleavage may be rationalized from the values of the relative activation energies reported in the literature[25] (Table 1). It appears that the activation enthalpy $\Delta H^{\ddagger}$ for cycloreversion increases from benzenic **8**[12] to naphthalenic **9**[13] and 1,4-anthracenic **10** EPOs, and then to the meso ones **11**. Consequently, one understands why cleavage starts to compete with cycloreversion in **11** and in more condensed analogues. Cycloreversion is greatly favored over cleavage by the presence of aromatic substituents at the bridgehead meso positions (for example, **11c**/**12a** and **22c/22e** in Table 2).

A mechanistic hypothesis for thermal cycloreversion has been suggested by Turro,[25] who found that the yields of generated $^1O_2$ were much higher for EPOs of the 1,4-type, **9** and **10**, than for the 9,10-type, **11** (Table 1). This hypothesis was based on the observation that $\Delta S^{\ddagger}$ for **8**, **9a**, and **10** was 0 or slightly negative while substantially positive values (+30 to +40 JK^{-1}mol^{-1}) were found for **11**. This hypothesis invokes the two basic and potentially competing pathways shown in Figure 3: (i) a concerted mechanism, producing $^1O_2$ quantitatively, which would be operative with **8**, **9a**, and **10**, and (ii) a sequence leading successively to diradicals, at first singlet ^1D and then triplet ^3D able to fragment to $^1O_2$ and $^3O_2$, respectively, operative with **11**, which would not allow a quantitative prediction of the yield of evolved $^1O_2$.

When homolysis of the peroxidic bond competes with cycloreversion, rearrangement and decomposition occur (Figure 2, Table 2).

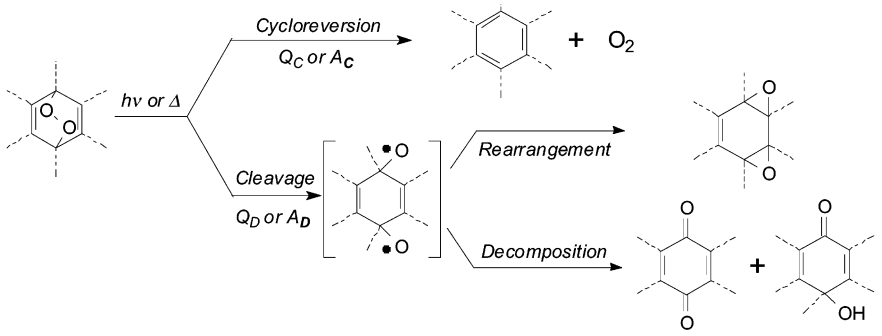
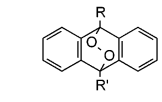
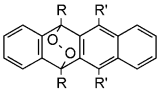
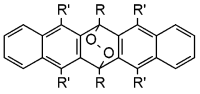


FIGURE 2. Transformation of EPOs during thermolysis or photolysis.

Table 2. Yields of Various Processes (Isolated Products) after Thermolysis of Endoperoxides in Refluxing Chlorobenzene (see Figures 2 and 4)[1b,26] [a]

EndoPerOxide		Cyclorever. (%)	Rearrang. a (%)	Rearrang. b (%)	Decomp. (%)
	**12a**	0	80	-	6
	12b	0	5	26	17
	11c	100	-	-	-
	12d	22	46	2	19
	12f	41	33	-	3
	**22a**	0	10	13	40
	22c	87	-	-	-
	22d	30	50	-	-
	22e	0	22	60	-
	**23a**	0	-	23	41
	23d	14	35	19	-
	23e	0	55	43	-

[a] **a**: R = R′ = H. **b**: R = R′ = CH_3. **c**: R = R′ = C_6H_5. **d**″ R = C_6H_5, R′ = H. **e**: R = H, R′ = C_6H_5. **f**: R= C_6H_5, R′ = CH_3.

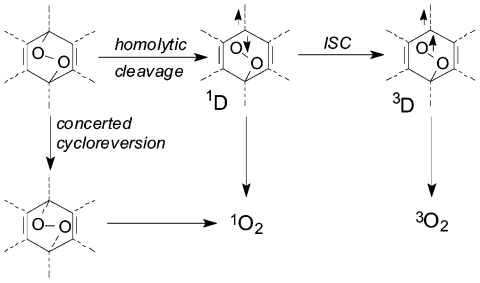


FIGURE 3. Competing pathways for the thermal cycloreversion of endoperoxides.

Considering the rearrangement pathway shown in Figure 4, its first step, an isomerization to a *vic*-diepoxide, is analogous to what happens with alicyclic EPOs under thermolysis or photolysis. In the present anthracenic series, photolysis is the only way to obtain effectively all the diepoxides **13** or **14**[27] since thermally **10** undergo cycloreversion whereas diepoxide **14** rearranges. In fact, the latter undergoes essentially a valence isomerization, brought about by the rearomatization of the lateral nucleus, leading through **17** to a stable benzocyclobutenic diether **20** (path a). Diepoxide **14** and intermediate **17** can be trapped as adducts **16** and **19**, respectively, when thermolysis is run in the presence of dienophiles such as *N*-methylmaleimide.[26,27] It can be inferred from Table 2 that isomerizations of diepoxides to benzocyclobutenic diethers are favored when phenyl substituents are present at bridgeheads, for instance, with acenic EPOs such as **12d**, **22d**, and **23d**. A competitive isomerization of di-

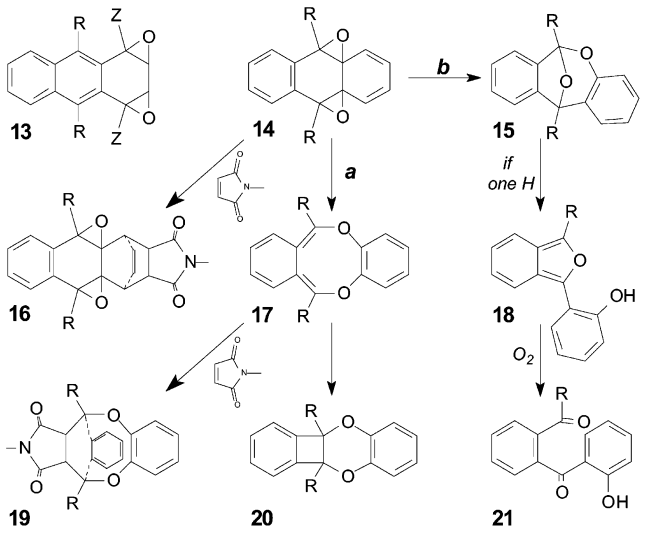


FIGURE 4. Rearrangements of diepoxide **14**.

epoxide **14** to a bicyclic acetal **15**, converted eventually into **18** (path b), is also observed and may predominate when alkyl groups or hydrogen atoms occupy these positions (for **22a** and **23a**, for example).

Photolysis of Endoperoxides. The same primary reactions as in thermolysis (Figure 2) compete in photolysis of EPOs. Irradiation of the EPO of 9,10-diphenylanthracene **11c** with wavelengths $\lambda > 250$ nm initiates cycloreversion, yielding the parent aromatic compound (PAC) and O_2, whereas $\lambda > 400$ nm excitation produces after O−O bond cleavage a diepoxide **14**, which undergoes irreversible subsequent reactions.[28] The detailed study of many EPOs showed that decomposition occurs from the lowest excited singlet state $S_1(\pi^*\sigma^*)$, corresponding to the locally excited peroxide chromophore, with quantum yield Q_D^{S1} (Figure 5).[29]

Q_D^{S1} values of 0.95 determined for the EPOs of tetracene and anthracene indicate that O−O bond cleavage is much faster than internal conversion of $S_1(\pi^*\sigma^*)$ into S_0.[29] Thermal and photoinduced O−O bond cleavage produce the same diepoxide **14** via a biradical. If steric hindrance influences diepoxide formation, a correlation between Q_D^{S1} and the yield of thermal decomposition $A_D = 1 - A_C$ could be expected, where A_C is the yield of thermal cycloreversion. This was actually found, see solid symbols of Figure 6.[29]

Nonsubstituted aromatic EPOs have maximum values of A_D and Q_D^{S1}. These values are smaller if the atoms next

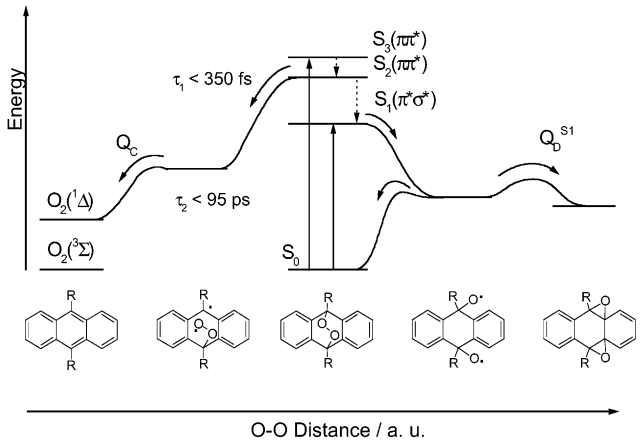


FIGURE 5. Photolysis of EPOs. Left, C−O bond cleavage inducing cycloreversion via singlet diradical ^{1}D (Figure 3); right, O−O bond rupture followed by back reaction or decomposition.

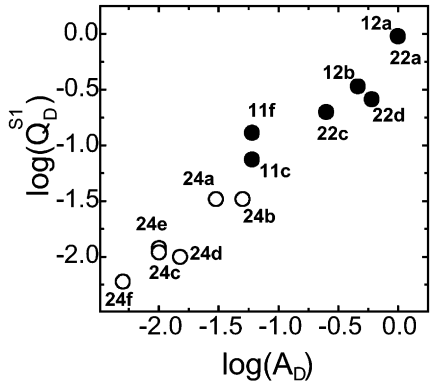
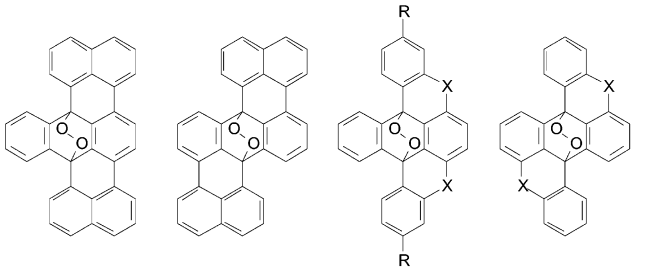


FIGURE 6. log−log correlation of Q_D^{S1} (quantum yield of decomposition from $S_1(\pi^*\sigma^*)$ state) vs A_D (thermal yield of decomposition, boiling *m*-xylene); open circles correspond to photochromic EPOs.[29]

to the O−O bridge are bound to methyl or phenyl groups and even smaller if the phenyl substituents are additionally bound to the anthracene frame, as in the compounds **24**.

The increase of substituent size and molecular rigidity hinders the formation of the strongly stressed diepoxide **14**, the key intermediate of decomposition. Thus, the principal reaction of the biradicals produced by O−O bond cleavage of EPOs **24** is reformation of the O−O bond.[29]



Generally, organic photoreactions in solution do not occur efficiently from upper excited singlet or triplet states S_n or T_n ($n \geq 2$) due to the very rapid relaxation to S_1 or T_1. Furthermore, adiabatic photoreactions leading to electronically excited products are rare. However, the photocycloreversion of EPOs is an exception in both respects. It was first shown with **24f** that cycloreversion originates from an upper excited $\pi\pi^*$ singlet state, and that O_2 is produced in its excited singlet state.[7] Further investigations revealed that cycloreversion of EPOs generally leads to formation of $^1O_2$ and ground-state PAC in 1:1 ratio and occurs from upper excited $S_n(\pi\pi^*)$ ($n \geq 2$), but not from $S_1(\pi^*\sigma^*)$ (Figure 5).[30,31] The latter assignment was recently claimed to be wrong based on theoretical calculations, which gave no indication of a low energy $\pi^*\sigma^*$ singlet state.[32] However, as explained in detail,[33] this theoretical result is completely inconsistent with the experimental findings of different groups.[28,30,31]

Cycloreversion quantum yield Q_C increases for many nonsymmetrical EPOs stepwise with decreasing λ, indicating that cycloreversion occurs from several excited $S_n(\pi\pi^*)$ ($n = 2, 3...$) states.[30,31] Cycloreversion must be very fast to compete efficiently with internal conversion. Several groups, however, measured surprisingly long PAC rise times τ_2 ranging for eight EPOs from 40 (**24f**) to 95 ps (**11c**).[34−36] These results indicate a two-step reaction with a much faster first step. Experiments with **24f** demonstrated that τ_2 does not depend on solvent polarity and viscosity, indicating a fast homolytic cleavage of a C−O bond of the peroxide bridge as first step.[34] The breakage of the second C−O bond initiating the loss of O_2 requires the same activation enthalpy of 22 kJ mol^{-1} for the four EPOs **24c** to **24f**,[36] but only **24d** to **24f** have similar rise times ($55 \geq \tau_2 \geq 40$ ps). The fastest reaction ($\tau_2 = 1.6$ ps) was observed with **24c**.[35] The striking difference is probably caused by the time required for the intramolecular flow of excitation energy from the site of the first C−O bond rupture to the site of the second. It was assumed that this time is much shorter for **24c**, since only **24c** has the extended conjugated $\pi\pi^*$-chromophore connected with both carbon atoms bound to the EPO bridge.[36] An upper time limit of 350 fs was obtained for the breakage of the first C−O bond, demonstrating that the first step is actually fast enough to compete with internal conversion.[35]

Aromatic Endoperoxides as Oxygen Carriers

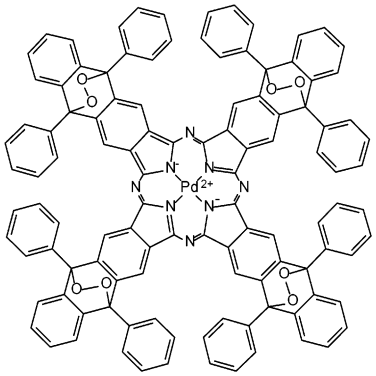
Highly Reversible Photochromic Systems. EPOs **24** exhibit structures derived from **11c**. The phenyl substituents are bound via fused rings or bridges X (=O, S, CO) to the anthracene frame. The corresponding PACs are planar with extended π-electron systems, causing strong absorption, fluorescence and color. They react fast with $^1O_2$ forming nonfluorescent, colorless and remarkably stable EPOs. In particular, X = CO yields compounds with extraordinary properties (Table 3).

EPOs **24** are components of photochromic systems which can be switched via vis/UV irradiation. Only small conversions are required for clearly detectable differences because of the PAC fluorescence. About 1000 and 3000 photochromic cycles result for **24f** and **24c** respectively. Thus, these systems have excellent photochromic proper-

Table 3. Main Features of Heterocoerdianthrone and p,p′-Dimethylhomeocoerdianthrone and Their EPOs 24f and 24c at 20 °C[7,37]

	Parent **A**romatic **C**ompound		**E**ndo**P**er**O**xide		
	color	k_r (M^{-1} s^{-1})	$t_{1/2}$ (years)	Q_C	Q_D (313 nm)
24f	red	7×10^7	880	0.26	0.0045
24c	blue	36×10^7	240	0.58	0.0036

ties. Aromatic compounds with reversible or irreversible binding of O_2 find applications in chemical actinometry, because of the corresponding large spectral shifts.[38] Up to four oxygen molecules are bound in the self-sensitized photoreaction of octaphenyltetraanthraporphyrazinato palladium **25**.[39] This fascinating complex with four endoperoxide bridges releases step-by-step all O_2 when excited by consecutive two-photon absorption at 662 nm.



25

When dissolved in aromatic solvents, EPOs could also be used to detect γ-radiations very effectively.[40] In this case each γ-photon induces excitation of several solvent molecules, which excite, in turn, EPOs.

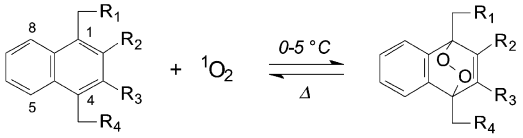
Hydrophobic Carriers of $^1O_2$. Nowadays **9b** is the sole EPO used to generate $^1O_2$ in organic solvent since its precursor, 1,4-dimethylnaphthalene, meets fully all requirements: commercial availability, fair reactivity toward $^1O_2$, chemical stability of the EPO, and ability to release $^1O_2$ under mild conditions ($t_{1/2} \approx 5$ h at 25 °C).[41] It is prepared through dye-sensitized photooxygenation of **4** (R = CH_3) at low temperature (0−5 °C) and is storable for months at −80 °C. At room temperature or on gentle warming, it releases a definite amount of $^1O_2$ free of other reactive oxygen species. Therefore, it can be used as a standard source $^1O_2$ to confirm the involvement of $^1O_2$ in complex photochemical processes[41] or as a dark source of $^1O_2$ to determine the quenching rate constants of organic substrates[42] or to calibrate detectors of the characteristic emission of $^1O_2$ at 1275 nm.[43]

Water-Soluble Carriers of $^1O_2$. In biological media, $^1O_2$ is endogeneously generated by the enzymes lactoperoxidase and chloroperoxidase, but it is more often exogeneously produced alongside other intermediates by the photodynamic effect. It can oxidize many biological targets, including unsaturated fatty acids, proteins, RNA, and DNA. However, considering the complexity of biological systems and the great variety of active species

Table 4. Overall Quenching Rate Constants of Carriers with $^1O_2$ and Half-Life of the Corresponding EPOs at 37 °C in Water[11,20,46,47]

Endo**P**er**O**xide	**26**	**27**	**28**	**29**	**30**	**31**	**32**
$10^{-6}(k_r+k_q)$ (M^{-1} s^{-1})	7.0	2.8	1.4	1.0	0.4	13.0	22.0
$t_{1/2}$ at 37°C (min)	23	23	22	23	7	319	>3000

generated by photochemistry, efforts have been devoted to develop suitable $^1O_2$ generators based on the thermolysis of water-soluble naphthalene endoperoxides (eq 3).[11]



(3)

26: R_1 = CH_2-CO_2Na; R_2 = R_3 = R_4 = H — **MNP**
27: R_1 = R_4 = CH_2-CO_2Na; R_2 = R_3 = H — **NDP**
28: R_1 = CH_2-$N(CH_3)_3Cl$; R_2 = R_3 = R_4 = H — **MNEA**
29: R_1 = R_4 = CH_2-CONH-CH_2-CHOH-CH_2OH; R_2 = R_3 = H — **DHPN**
30: R_1 = R_4 = CH-(CONH-CH_2-CHOH-CH_2OH)$_2$; R_2 = R_3 = H
31: R_1 = CH_2-CO_2Na, R_2 = R_4 = H; R_3 = CH_2-CH_2-CO_2Na
32: R_1 = R_4 = CH_2-CO_2Na; R_2 = R_3 = CH_3

As naphthalene itself does not trap $^1O_2$, at least one and preferably two electron-donating groups are required on the 1,4-positions to allow [4+2] cycloaddition of $^1O_2$. The simplest derivatives **26** and **27** bear sodium propanoate substituents grafted on the 1,4-positions of the naphthalene core.[10,11] To generate $^1O_2$ close to various biological targets, an acridine moiety, a quaternary ammonium group **28** or nonionic hydrophilic groups **29** have been attached to confer on carriers an enhanced affinity for polynucleotides, negatively charged sites, or intracellular targets, respectively.[11,44]

The preparation of EPOs is currently achieved by sensitized photooxygenation.[23] Alternatively, the chemical source of $^1O_2$, hydrogen peroxide/sodium molybdate, may be used for large scale synthesis.[45] In both cases, the oxidation proceeds more rapidly in deuterated solvents (D_2O and CD_3OD) since the $^1O_2$ lifetime is more than 15 times as long in these solvents as in protonated ones.[23]

The interaction of $^1O_2$ with a naphthalenic compound N can be described by reactions 4 and 5. The overall reactivity of N toward $^1O_2$ can be expressed by the sum ($k_r + k_q$), which is readily determined by flash photolysis (Table 4).

$$^1O_2 + N \xrightarrow{k_q} {}^3O_2 + N \qquad (4)$$

$$^1O_2 + N \xrightarrow{k_r} NO_2 \qquad (5)$$

To explain the difference in reactivity of 1,4-substituted carriers toward $^1O_2$, two phenomena have to be considered: the electron density of the naphthalene core and the steric hindrance induced by the substituents. Longer alkyl spacers increase the electron density of the aromatic ring, but the resulting steric hindrance lowers the rate of reaction with $^1O_2$ significantly. For instance, the overall rate constant of **27** is three times as high as the value found for the more crowded **29** and is lower than the value for **26**. For very crowded and poorly reactive compounds

such as **30,** 5,8-cycloaddition of $^1O_2$ competes with the usual reaction on the 1,4-positions.[48] The reactivity of naphthalene compounds can be considerably increased by grafting supplementary methyl groups on the same ring, as exemplified with **31** and **32**. However, the time necessary to decompose 50% of these EPOs (Table 4) becomes prohibitive; thus, these compounds are used as $^1O_2$ traps rather than as $^1O_2$ carriers.[24,46]

Thermolysis of naphthalenic EPOs (eq 6) gives back oxygen quantitatively according to first-order kinetics characterized by the half-life of decomposition reported in Table 4. The ratio α of singlet oxygen was measured by trapping with **5**[11] or **6b**.[49] It was shown that all the known water-soluble naphthalenic carriers release about 50% of $^1O_2$ in water at 37 °C.[11]

$$NO_2 \xrightarrow[water]{37^\circ C} N + \alpha\,{}^1O_2 + (1-\alpha)\,{}^3O_2 \quad (6)$$

Since the thermolysis of EPOs generates cleanly $^1O_2$ in known quantity, they are invaluable as reference sources of $^1O_2$ in aqueous solutions.[11] They can be used to determine physical (k_q) and chemical (k_r) $^1O_2$-quenching rate constants by measuring the rate of disappearance of water-soluble substrates[50] or by luminescence experiments.[51]

A special emphasis must be placed on the nonionic carrier **29**, which was shown to penetrate into cells and to inactivate all types of viruses (enveloped, nonenveloped, extracellular, intracellular), whereas the ionic carrier **27** inactivates only extracellular enveloped viruses.[52] Recently, a further improvement has been brought to this carrier by preparing a labeled EP^{18}O in order to convey $^{18}[^1O_2]$ up to specific biochemical targets.[53] Interestingly, the combined use of isotopically labeled EPO and the high-resolution HPLC-MS technique has allowed new light to be shed on the mechanistic features of the reaction of $^1O_2$ with cellular target such as DNA.[54]

Polymeric Carriers of Singlet Oxygen. Polymer-immobilized naphthalenes have been obtained by grafting the sodium salt of MNP **26** on a chloromethylated styrene-divinyl benzene beads or by polymerization of methyl-substituted vinylnaphthalene.[44,55,56] After photosensitized oxygenation, both systems give EPOs storable at low temperature which can provide a clean and rapid source of $^1O_2$ usable in synthetic reactions or chemical iodine laser. Oxidation of hydrophobic substrates can be performed on warming with the peroxidized polymer and the separation of the product from the polymer is readily achieved by simple filtration. Unfortunately, these hydrophobic polymers are unsuitable for aqueous media since (i) they cannot be peroxidized by the chemical source of $^1O_2$ based on the aqueous system H_2O_2/MoO_4^{2-} and (ii) the corresponding EPOs, prepared by photooxygenation, do not release a significant amount of $^1O_2$ in water. Despite considerable efforts devoted to this problem, the design of a polymeric carriers of $^1O_2$ suitable for aqueous media remains an open challenge.[57]

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