The photochemistry of photodynamic (anti-cancer) therapy

Asst. Prof. Dr. René M. Williams
University of Amsterdam
Saturday 22 May 2021

10:30 (Miami)
16:30 (Amsterdam)
20:00 (New Delhi)

The photochemistry of photodynamic (anti-cancer) therapy

- porphyrins
- triplet excited states
- singlet oxygen
- reactive oxygen species

2


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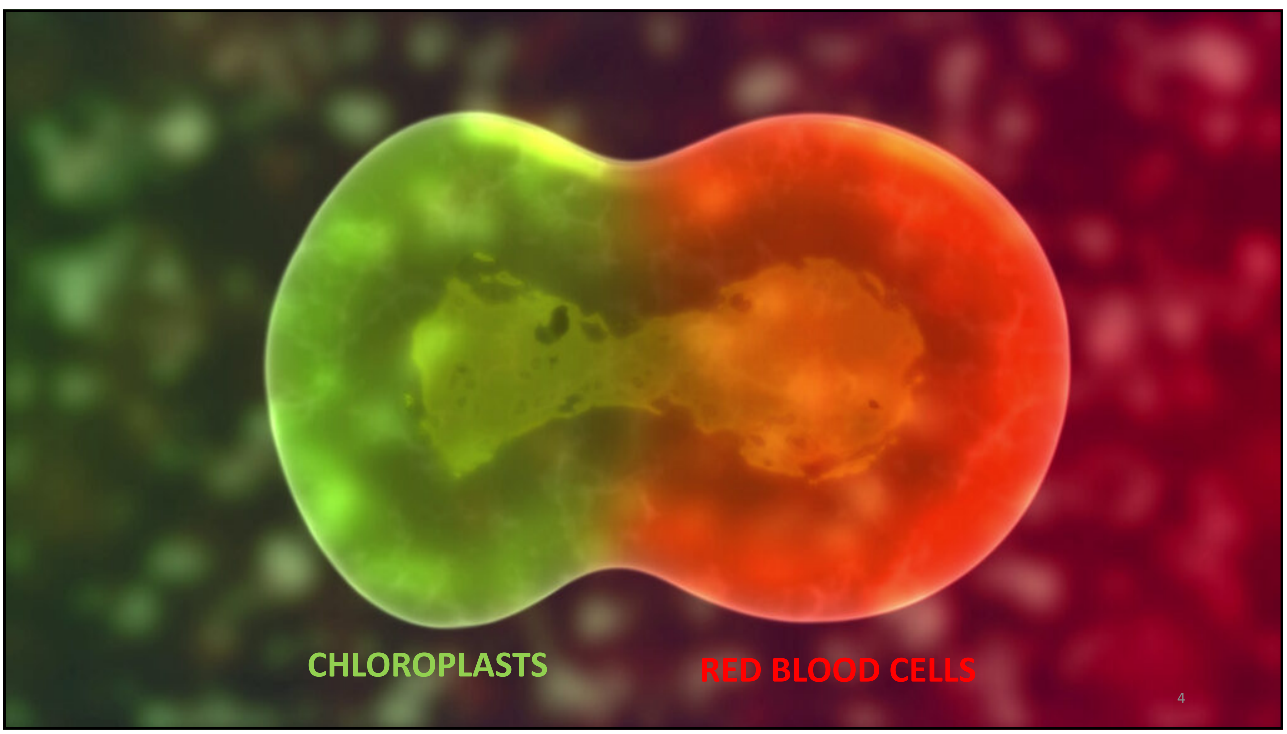
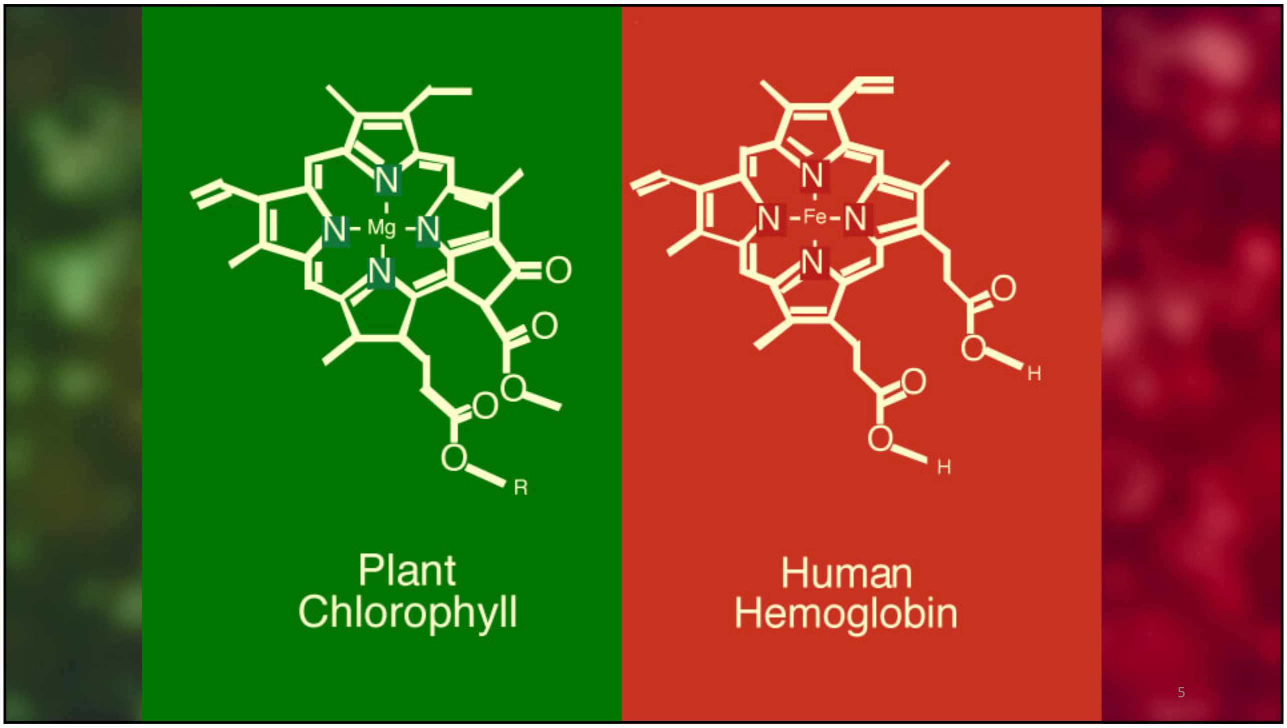

CHLOROPLASTS
RED BLOOD CELLS
4


N
N
Mg
N
N
O
O
O
O
O
R
Plant
Chlorophyll
N
N
Fe
N
N
O
O
H
O
O
H
Human
Hemoglobin
5

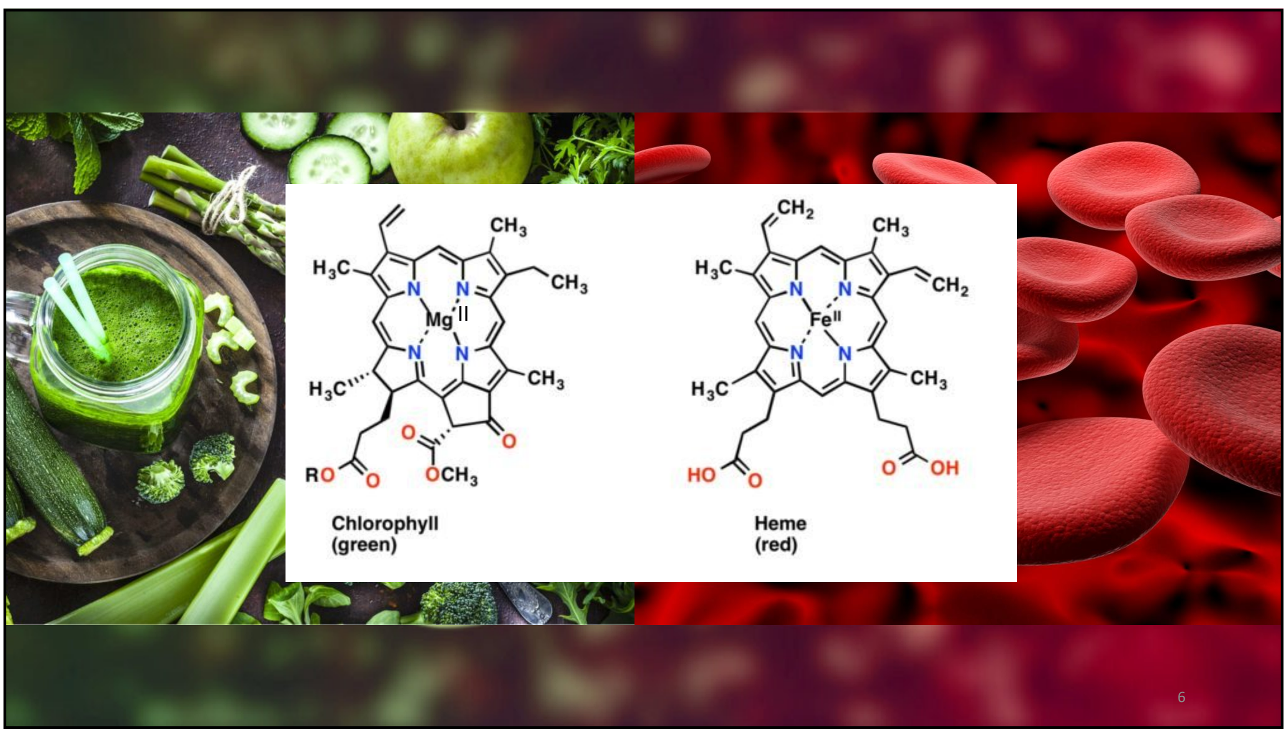
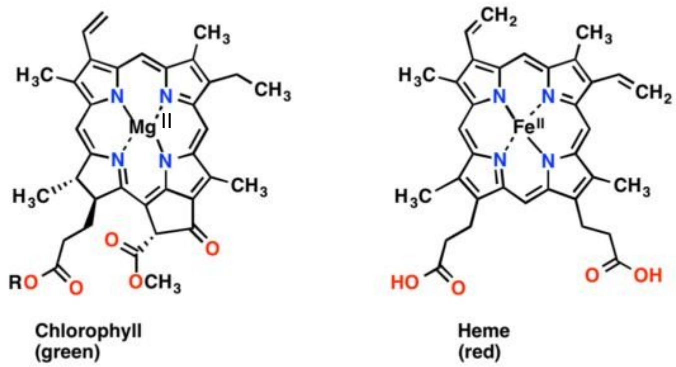

CH3
H3C
CH3
Mg II
H3C
CH3
O
O
RO
O
OCH3
Chlorophyll
(green)
CH2
CH3
H3C
CH2
Fe II
H3C
CH3
HO
O
O
OH
Heme
(red)
6

Photo-medicin??



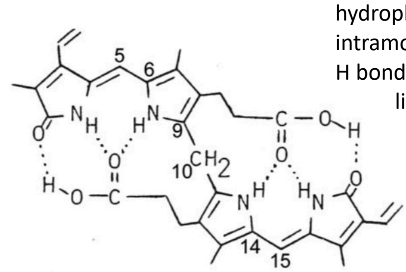
~0.1 g of daily oral intake

~750 g hemoglobin protein in 5 Liter of blood

7

Photo-medicin??

Photo-therapy!!



hydrophobic:
intramolecular
H bonds:
lipophilic

degradation product of hemoglobin

Neonatal Jaundice

2.7 million infants are treated word-wide annually

cis-trans isomerization

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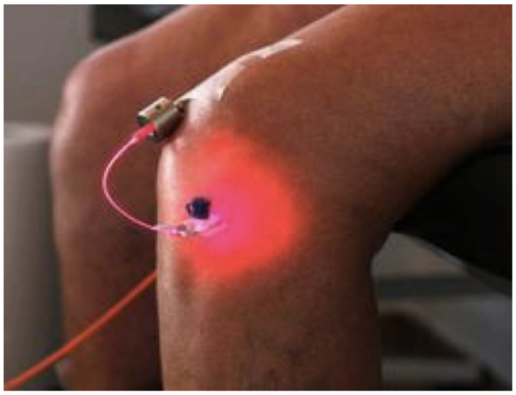
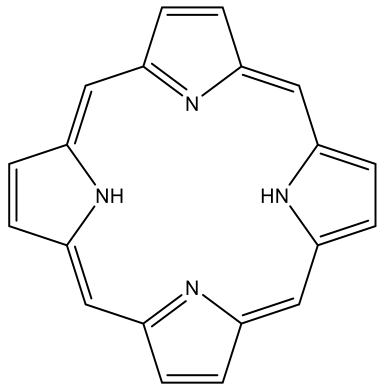
Photomedicin with porhyrin structures??



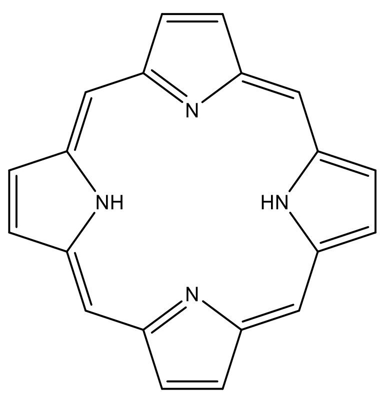


porphyrin

Photodynamic (anti-cancer) therapy

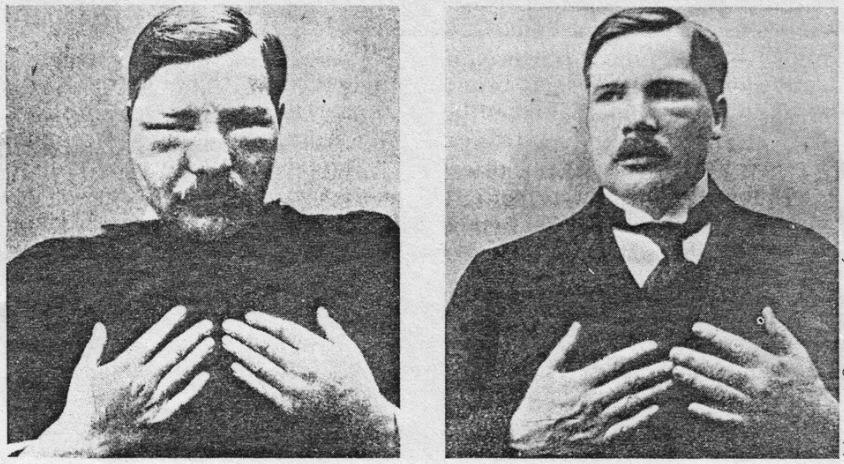
PhotoSensitizer + light
+ Molecular oxygen →
Reactive Oxygen
Species

Chlorins
Bacteriochlorins
Phthalocyanins



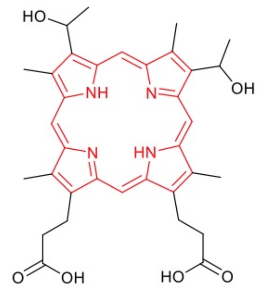
porphyrin

Friedrich Meyer-Betz, a German physician, injected himself with porphyrin in 1912 to test whether it made humans sensitive to light. The first photograph shows him four days later, after he took a walk on a sunny day. Most of the swelling subsided by the sixth day, second photograph, but he remained light-sensitive for several months.



courtesy A. M. McDonagh, UCSF (2)

SCIENCE 82



Hematoporphyrin

200 mg
intravenous

1912

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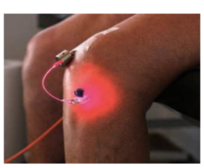
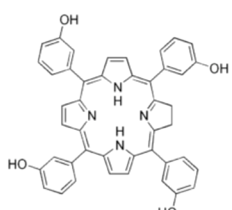
Porphyrin **L**ibra**ry** for **The**rapeutic **A**pplications

POLYTHEA
HOW LIGHT CAN SAVE LIVES

PDT

Photo-Dynamic Therapy
Photo-Catalysis for Health





mTHPC: TEMOPORFIN
meta-tetra-hydroxy-phenyl-chlorin

www.polythea.eu

liposomal solutions

This project has received funding from the European Union's Horizon 2020 research and innovation programme under the Marie Sklodowska-Curie grant agreement n°764837

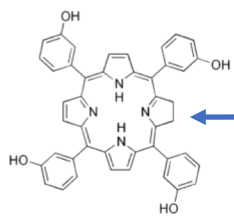
POLYTHEA
HOW LIGHT CAN SAVE LIVES

PDT: room for improvement…

There is a **delay of 4 days** between injection of Foscan® into the bloodstream and activation with laser light. This allows time for accumulation of Foscan® in the cancer cells.
As with other photosensitizing agents, administration of **Foscan®** results in patients becoming **highly sensitive to light**. This lasts **7 to 15 days** and, therefore, appropriate light exposure precautions should be followed during this period.

In October 2001, **Foscan®** was approved in the European Union, Norway & Iceland as a local therapy for the palliative treatment of patients with **advanced head and neck squamous cell cancer** who have failed prior therapies and are unsuitable for radiotherapy, surgery or systemic chemotherapy

650 nm excitation

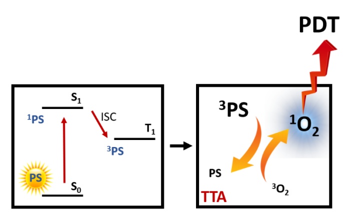


Chlorin

Chewing betel nut
India
Indonesia

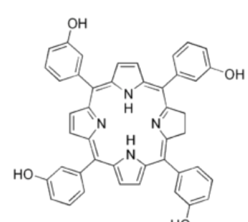
also used by Maurice Aalders

Photodynamic therapy



T_1 very long lived
without oxygen

Cell death



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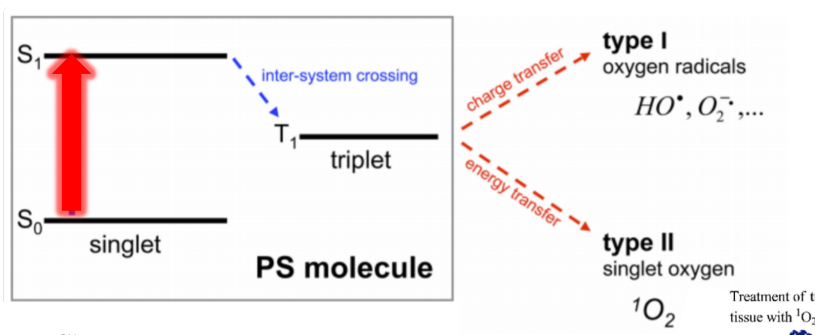
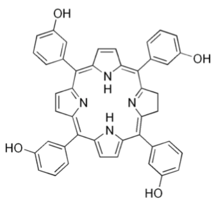
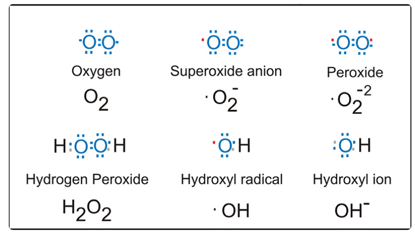
Photodynamic therapy

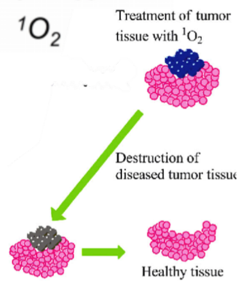




Foscan / Temoporfin



Reactive oxygen species **ROS**



peroxy acids
peroxy lipids
peroxy peptides
peroxy nucleotides

radical polymerization *in vivo*

Biochem. J. (2016) **473**, 805–825 doi:10.1042/BJ20151227

REVIEW ARTICLE

Protein oxidation and peroxidation

Michael J. Davies*[1]
*Department of Biomedical Sciences, Panum Institute, University of Copenhagen, Blegdamsvej 3, Copenhagen 2200, Denmark

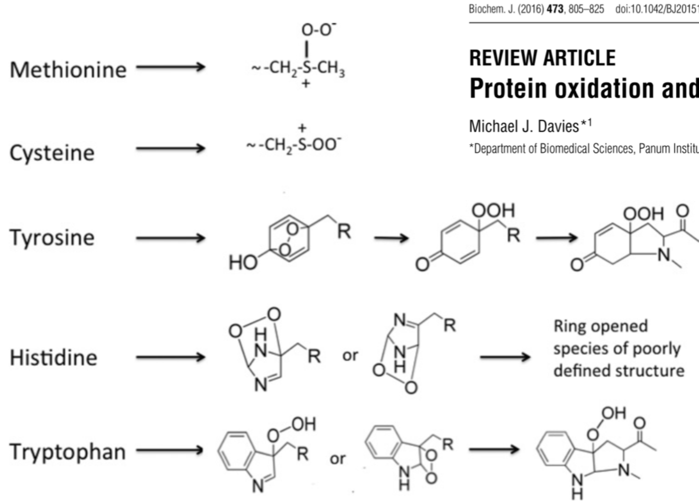


Figure 6 Peroxidic species identified on reaction of singlet oxygen ($^1O_2$) with reactive methionine, cysteine, tyrosine, histidine and tryptophan side chains

Other species may also be formed, particularly with histidine (see text).

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How can tumor cells die??

- necrosis
- apoptosis
- phagocytosis
- immunogenic cell death

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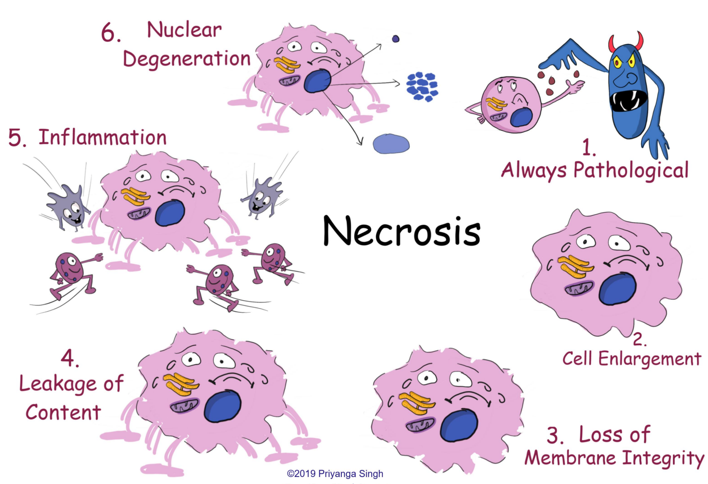
How can cells die??

- **necrosis**

cell explodes



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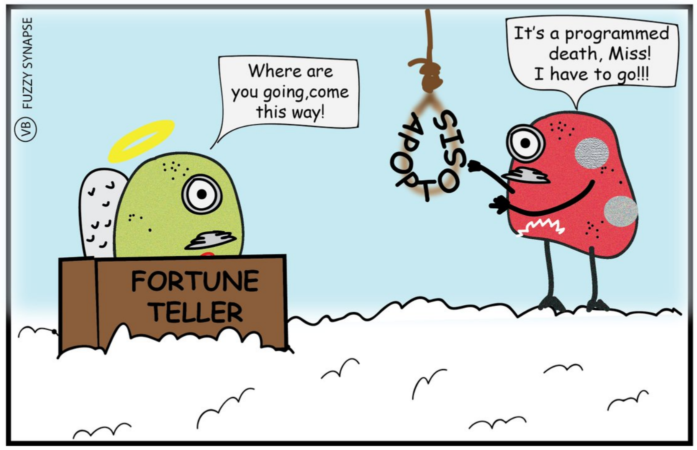
How can cells die??

- **apoptosis**

programmed cell death: cell shrinks and starfs itself



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How can cells die??

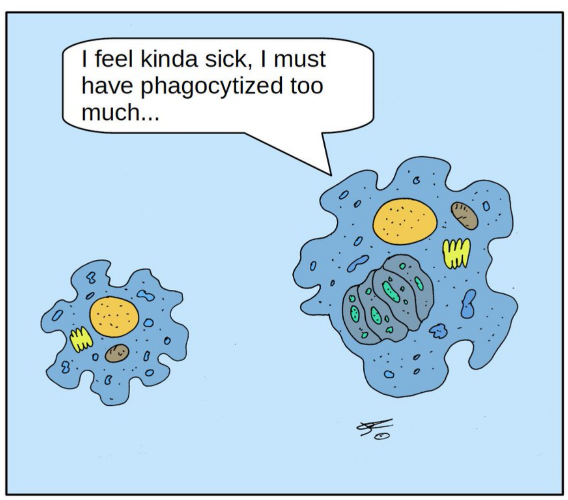
- **phagocytosis**

cells "eat" each other.

fuse

cell recycling

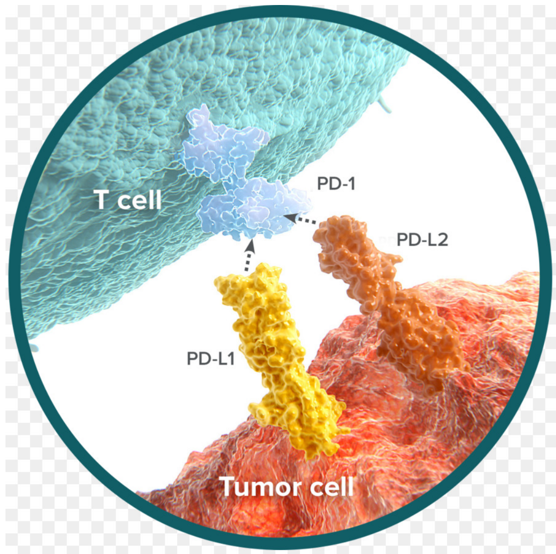
dieting & fasting stimulates phagocytosis



20

How can cells die??

- **immunogenic cell death**
death by T-cell attack



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ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Regulatory approval of photoimmunotherapy: photodynamic therapy that induces immunogenic cell death

Lígia C. Gomes-da-Silva[a], Oliver Kepp[b,c], and Guido Kroemer[b,c,d,e,f]

[a]CQC, Coimbra Chemistry Center, University of Coimbra, Coimbra, Portugal; [b]Metabolomics and Cell Biology Platforms, Gustave Roussy Comprehensive Cancer Institute, Villejuif, France; [c]Equipe 11 labellisée Ligue Contre le Cancer, Université de Paris, Sorbonne Université, Inserm U1138, Centre de Recherche des Cordeliers, Paris, France; [d]Pôle de Biologie, Hôpital Européen Georges Pompidou, AP-HP, Paris, France; [e]Suzhou Institute for Systems Medicine, Chinese Academy of Sciences, Suzhou, Jiangsu, China; [f]Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden

ABSTRACT
In September 2020, the Japanese government approved cetuximab saratolacan (previously known as RM-1929, commercial name: Akalux) for the treatment of unresectable locally advanced or recurrent head and neck cancer. Cetuximab saratolacan is a chemical conjugate of the photosensitizer IR700 with cetuximab, which targets EGFR. The treatment consists in the intravenous injection of cetuximab saratolacan, which binds to head and neck cancer cells expressing high levels of EGFR, followed by illumination of the tumor with red light (690 nm) for photodynamic therapy. This approach causes immunogenic cell death in malignant tissues, thus triggering a potent anticancer immune response.

ARTICLE HISTORY
Received 12 October 2020
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KEYWORDS
Cetuximab saratolacan; photosensitizer IR700; EGFR; immunogenic cell death; head and neck cancer

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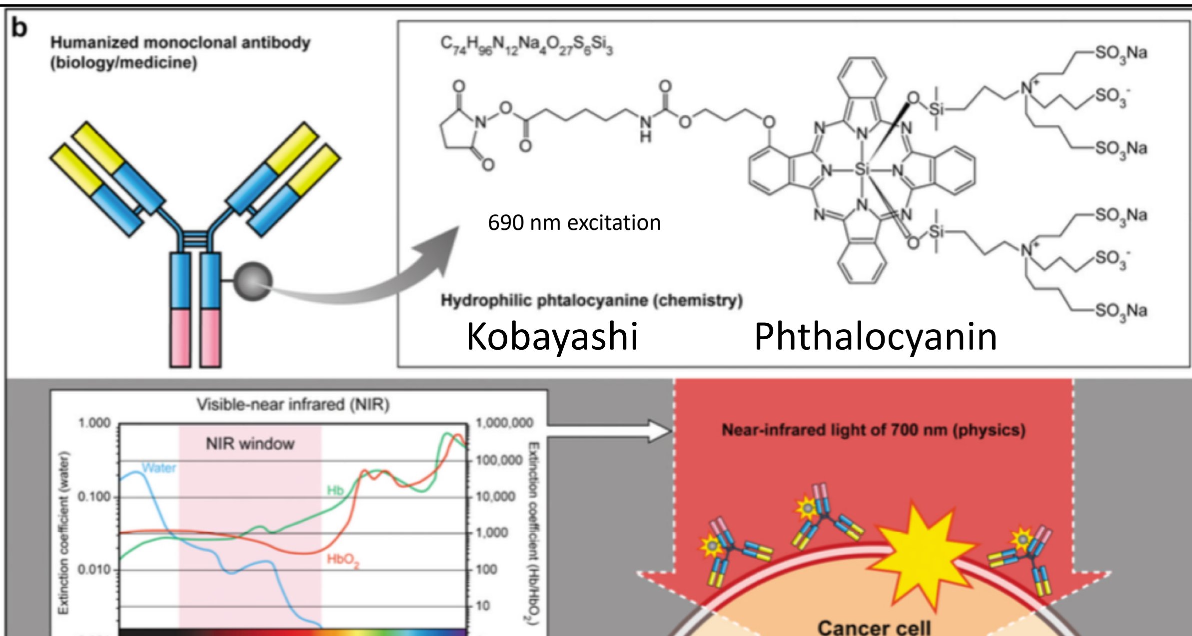

Cancer Cell-Selective *In Vivo* Near Infrared Photoimmunotherapy Targeting Specific Membrane Molecules

Makoto Mitsunaga, Mikako Ogawa, Nobuyuki Kosaka, Lauren T. Rosenblum, Peter L Choyke, and Hisataka Kobayashi

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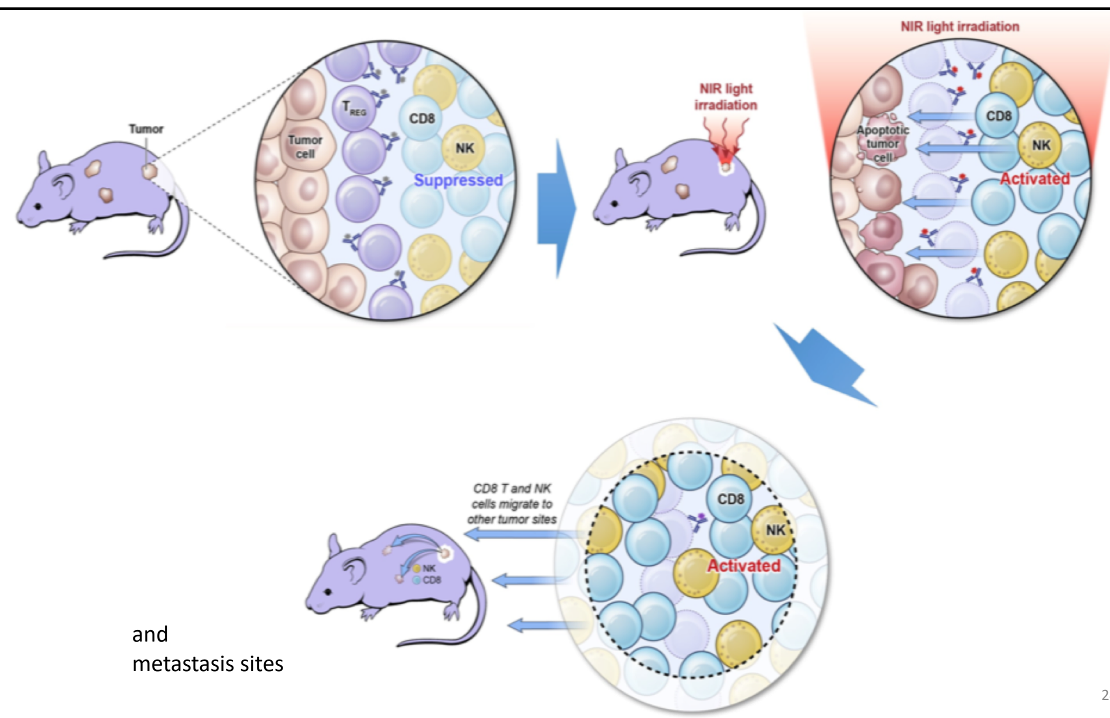
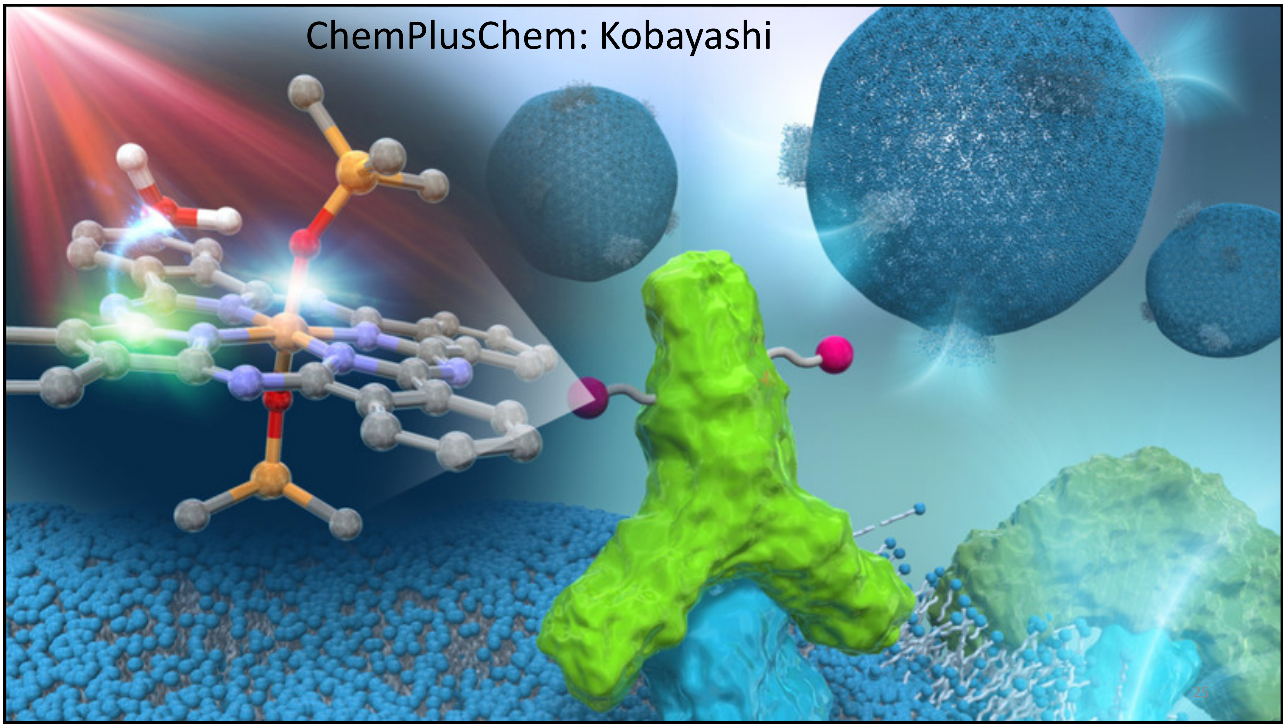
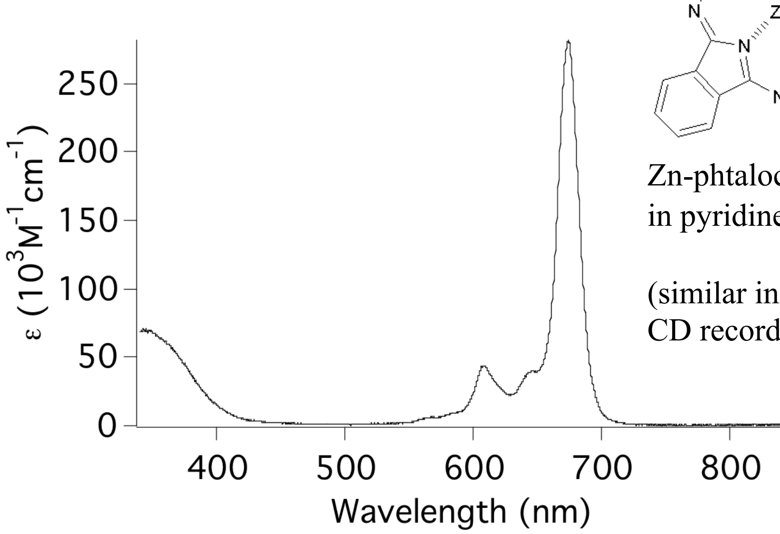


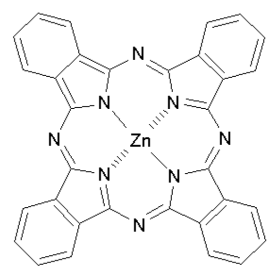
and
metastasis sites

24



λ_{max}= 674 nm
ε = 282 000 $M^{-1}cm^{-1}$



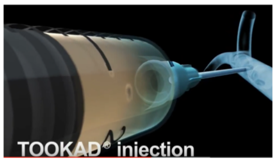


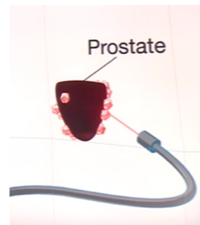
Zn-phtalocyanine
in pyridine

(similar in green
CD recordable: SONY cyanine)

Benchmark – Tookad soluble

- Recently approved (2019) on European Market for early stage prostate cancer





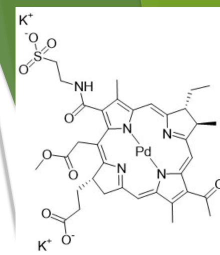
- Tookad injection

Irradiation

Distribution

- Our Goal = fight Cancer and Microbial infections
  - Develop new photosensitizers with better optimized properties

similar to
Rhodobacter Sphaeroides



Tookad soluble

Tookad Soluble was first synthesized in Prof. Scherz's lab from bacteriochlorophyll, the photosynthetic pigment of certain aquatic bacteria that draw their energy supply from sunlight.

Rhodovolum Sulfidophilum

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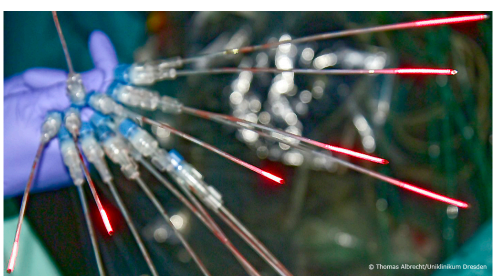
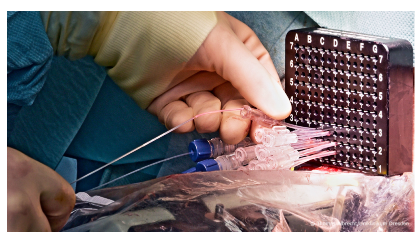
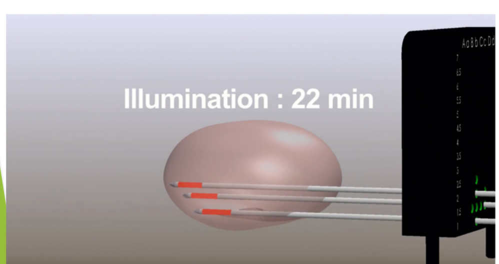
Tookad Soluble

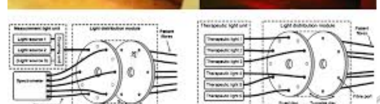
TYPE I photochemistry: $O_2{\bullet}^-$ + $\bullet OH$

induces the release of nitric oxide (•NO) radicals









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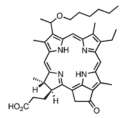
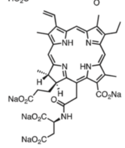
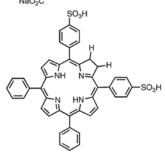
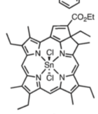
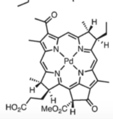
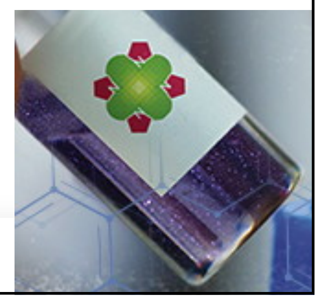
	3-(1-Hexyloxyethyl)-3-divinylpyropheophorbide *a* (HPPH) Trademark: Photochlor Class: Chlorin-based photosensitizers	Clinical trials for esophageal cancer (phase I/II), non-small cell lung cancer (phase II), basal cell skin cancer (phase I), treating dysplasia, carcinoma of the oral cavity, carcinoma of the oropharynx (phase I) and Barrett's esophagus (phase I/II)	Roswell Park Cancer Institute
	Mono-L-aspartylchlorin-e_6 (Npe_6) Trademark: Laserphyrin Class: Chlorin-based photosensitizers	Approved in Japan in 2003 to treat lung cancer Clinical trials for hepatocellular carcinoma (phase III), metastatic colorectal cancer (phase III) and benign prostatic hyperplasia or enlargement of the prostate (phase I/II)	Light Science Oncology
	Disulfonated tetraphenyl chlorin Trademark: Fimaporfin/Amphinex Class: Chlorin-based photosensitizers	Clinical trials for cholangiocarcinomas (phase I/II)	PCI Biotech
	Tin ethyl etiopurpurin Trademark: Purlytin Class: Chlorin-based photosensitizers	Clinical trials for breast adenocarcinoma, basal cell carcinoma and Kaposi's sarcoma (phase I/II)	Pharmacia
	Palladium bacteriopheophorbide *a* (WST-09) Trademark: Tookad Class: Bacteriochlorin-based photosensitizers	Approved for clinical use in the European Union, Norway and Iceland (approved for low-risk prostate cancer)	Steba Biotech

PorphyChem
Porphyrin Chemicals & Engineering

Some activities of PorphyChem illustrated by the applications of porphyrinoids in PDT, PIT and PDI

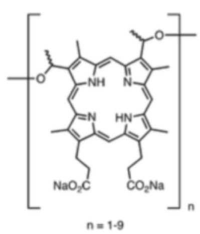
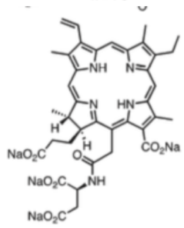
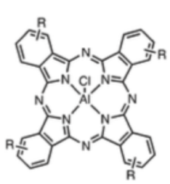
B. Habermeyer *a and R. Guilard b

14 compounds



Development:
~10 year
~10 million dollars

DOI: 10.1039/c8pp00222c

	Porfimer sodium Trademark: Photofrin Class: Porphyrin-based photosensitizers	Approved for clinical use in Canada, Japan and USA Approved for clinical use in Russia and Brazil under the trademark Photogem Approved for clinical use in Europe under the trademark Photosan-3 Approved for bronchial cancer and esophageal cancer	Pinnacle Biologics, Inc.
	Mono-L-aspartylchlorin-e_6 (Npe_6) Trademark: Laserphyrin Class: Chlorin-based photosensitizers	Approved in Japan in 2003 to treat lung cancer Clinical trials for hepatocellular carcinoma (phase III), metastatic colorectal cancer (phase III) and benign prostatic hyperplasia or enlargement of the prostate (phase I/II)	Light Science Oncology
 R = H or SO_3H	Aluminum phthalocyanine tetrasulfonate Trademark: Photosens Class: Phthalocyanine-based photosensitizers	Approved for clinical use in Russia (stomach, skin, lip, oral cavity, tongue, breast cancer)	NIOPIK

Next to Foscan, IR700/cetuximab, Tookad soluble

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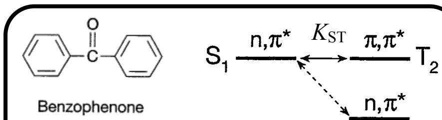
The photochemistry of photodynamic (anti-cancer) therapy

- porphyrins, chlorins, bacterio-chlorins, phthalocyanins
- triplet excited states
- reactive oxygen species
- triplet excited state formation and decay
- singlet oxygen

Triplet Formation: Spin Orbit Coupling

1. Allowed ISC in El-Sayed's Rule (selection rules for triplet formation)

$S_1(n,\pi^*) \rightarrow T_1(n,\pi^*)$	Forbidden
$S_1(n,\pi^*) \rightarrow T_1(\pi,\pi^*)$	$\boxed{\text{Allowed}}$
$S_1(\pi,\pi^*) \rightarrow T_1(n,\pi^*)$	Allowed
$S_1(\pi,\pi^*) \rightarrow T_1(\pi,\pi^*)$	Forbidden

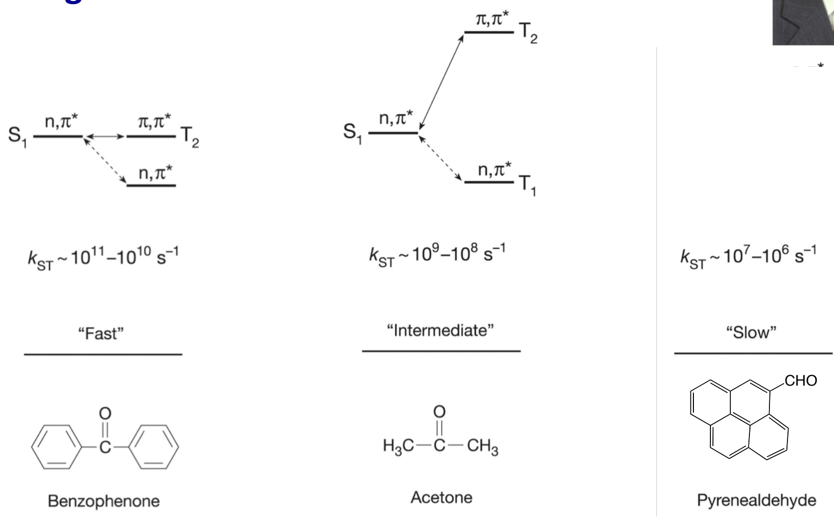


$K_{ST} \sim 10^{11} - 10^{10}\ s^{-1}$

Heavy atom effect:
SOC scales with Z^4 (Z is atomic number)
But also reduces triplet state lifetime!!

El-Sayed's Rule

Intersystem crossing is likely to be very slow unless it involves a change of orbital configuration.



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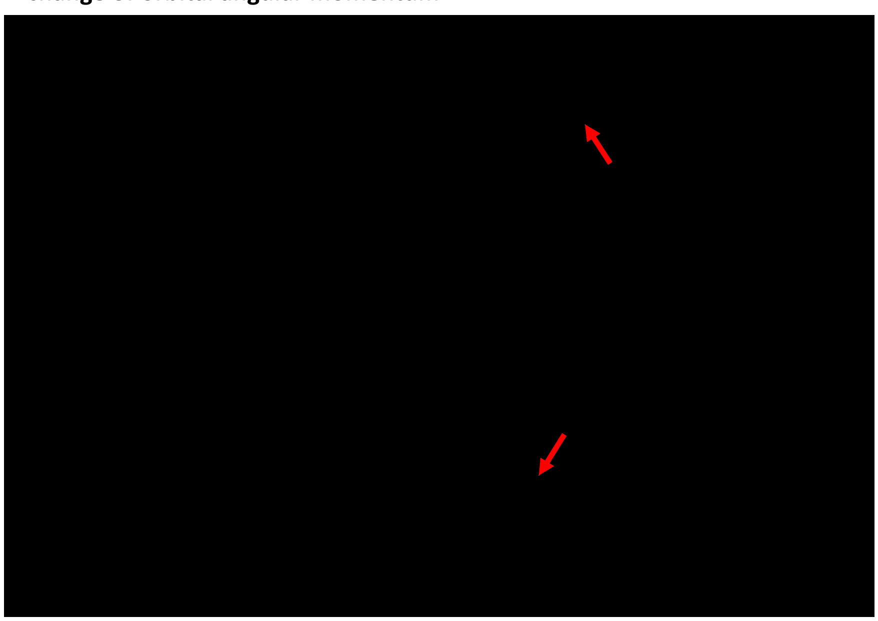
El-Sayed's Rule

(acetone)

change of electron spin angular momentum compensated by change of orbital angular momentum



(T.)

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observed triplet excited state decay

- NOT an exponential decay! (gives lower limit of τ_0^T)
- Second order decay kinetics involving

triplet-triplet annihilation (k_{TT}) in absence of oxygen!

- $\boldsymbol{\tau_0^T}$ of Tetraphenylporphyrin is **1.5 ms** in benzene.
- $\tau^T_{observed}$: f([*PS]$_{t=0}$, [O_2], k_{TT}, k_0 *(intrinsic decay* τ_0^T *))*

- τ^T_{phos} (PS) can be used to probe [O_2], and monitor oxygen consumption in cells, also in D_2O

TPP: Montalti et al. Handbook of photochemistry, 2006

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Second order decay kinetics

$$\Delta A(t) = \frac{C_0 k_0}{k_0 e^{(k_0 t)} + k_{TT} C_0 (e^{(k_0 t)} - 1)}$$

$$\Delta A(t) = \frac{C_0 e^{-(k_0 t)}}{1 + C_0 (k_{TT}/k_0)(1 - e^{(k_0 t)})}$$

$$\Delta A(t) = \frac{C_0 k_0}{e^{(k_0 t)}(C_0 k_{TT} + k_0) - C_0 k_{TT}}$$

triplet-triplet annihilation ($\boldsymbol{k_{TT}}$) and the intrinsic triplet decay ($\boldsymbol{k_0}$). Within triplet-triplet annihilation, the diffusion rate of the molecules in the triplet excited state as well as their concentration at time zero ($\boldsymbol{C_0}$) influenced by laser-power plays an important role due to bimolecular collisional quenching.

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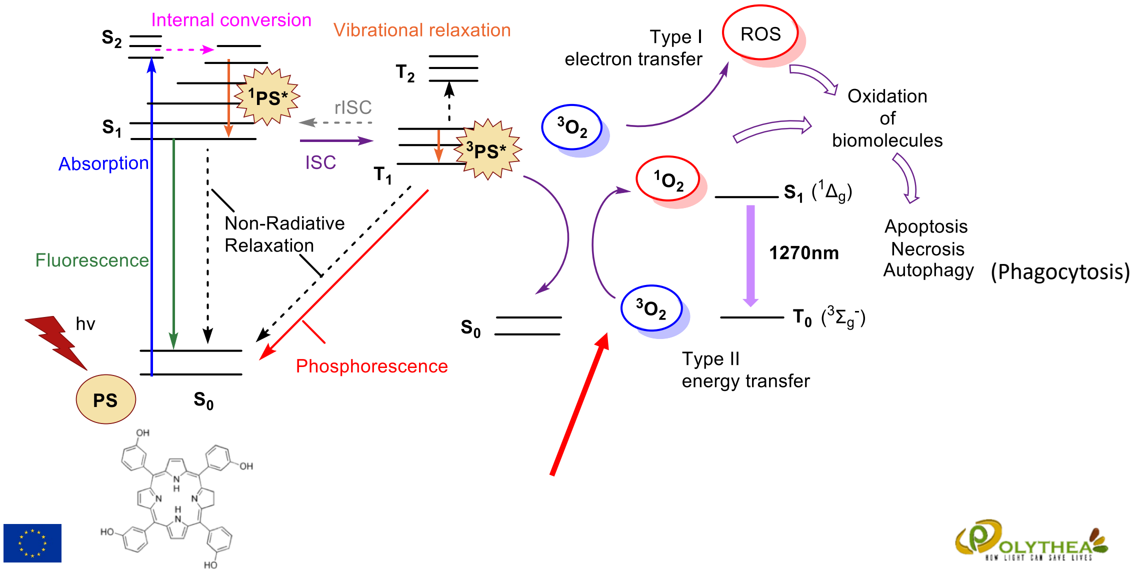
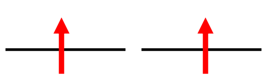
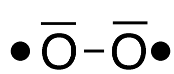
Photo-Dynamic Therapy: PDT



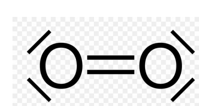
triplet states can have “bi-radical character”



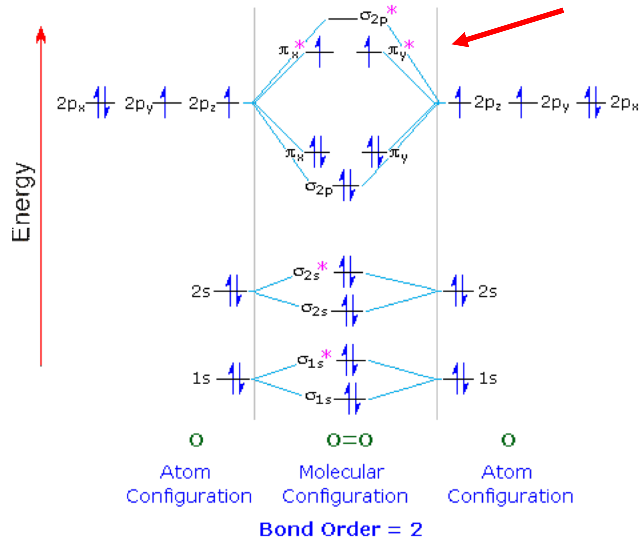
Triplet Ground state



oxygen gas

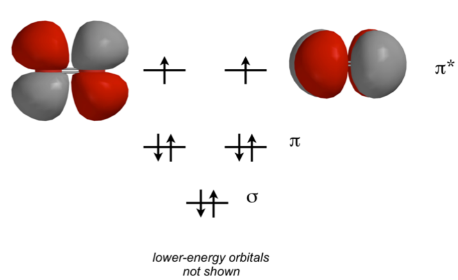


“conventional” Lewis structure



"cross-over" from N_2 to O_2

oxygen: a triplet ground state



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oxygen quenching

- a special case of energy transfer
- works especially for triplet states
- *controlled by diffusion* ***and spin statistics***

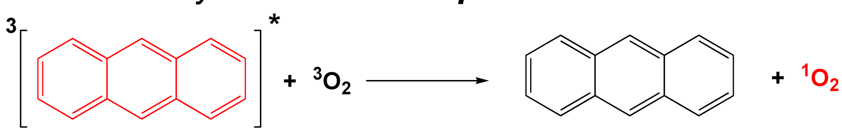

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Table 6a Diffusion-Controlled Rate Constants

No.	Solvent	η (20°C) (10^{-3} Pa s)	k_{diff} (20°C) (L mol^{-1} s^{-1})	η (25°C) (10^{-3} Pa s)	k_{diff} (25°C) (L mol^{-1} s^{-1})
1	Isopentane	0.225	2.9×10^{10}	0.215	3.1×10^{10}
2	Diethyl ether	0.242	2.7×10^{10}	0.224	3.0×10^{10}
3	Pentane	0.235	2.8×10^{10}	0.225	2.9×10^{10}
4	Hexane	0.3126	2.1×10^{10}	0.2942	2.2×10^{10}
5	Acetone	0.322	2.0×10^{10}	0.307	2.1×10^{10}
6	Acetonitrile			0.341	1.9×10^{10}
7	Heptane	0.4181	1.6×10^{10}	0.3967	1.7×10^{10}
8	Dichloromethane	0.434	1.5×10^{10}	0.414	1.6×10^{10}
9	Tetrahydrofuran	0.575	1.3×10^{10}	0.460	1.4×10^{10}
10	Isooctane	0.504	1.3×10^{10}		
11	Octane	0.5466	1.2×10^{10}	0.5151	1.3×10^{10}
12	Chloroform	0.564	1.2×10^{10}	0.5357	1.2×10^{10}
13	Methanol	0.5929	1.1×10^{10}	0.5513	1.2×10^{10}
14	Toluene	0.5859	1.1×10^{10}	0.5525	1.2×10^{10}
15	Benzene	0.6487	1.0×10^{10}	0.6028	1.1×10^{10}

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466 *Handbook of Photochemistry*

Table 6c Triplet-State Quenching of Organic Molecules

No.	Quencher	Mecha-nism	Solvent	K_q (L mol^{-1} s^{-1})	Ref.
218	**Porphyrin, tetraphenyl-**				
	O_2		Cyclohexane	2.1×10^9	[0301]
219	**Porphyrin-2,18-dipropanoic acid, 7,12-diethenyl-3,8,13,17-tetramethyl-, dimethyl ester**				
	O_2		Benzene	2.7×10^9	[7706]
220	**Porphyrin-2,18-dipropanoic acid, 3,7,12,17-tetramethyl-, dimethyl ester**				
	O_2		Benzene	2.3×10^9	[8015]

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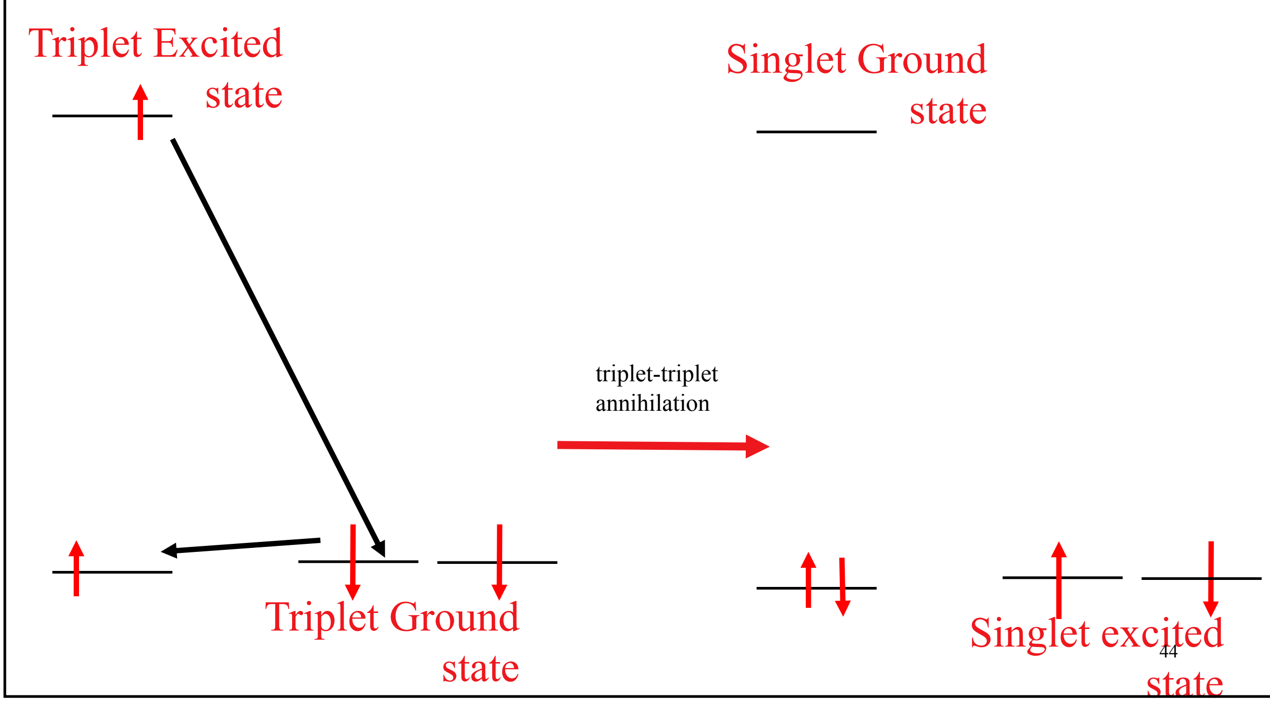

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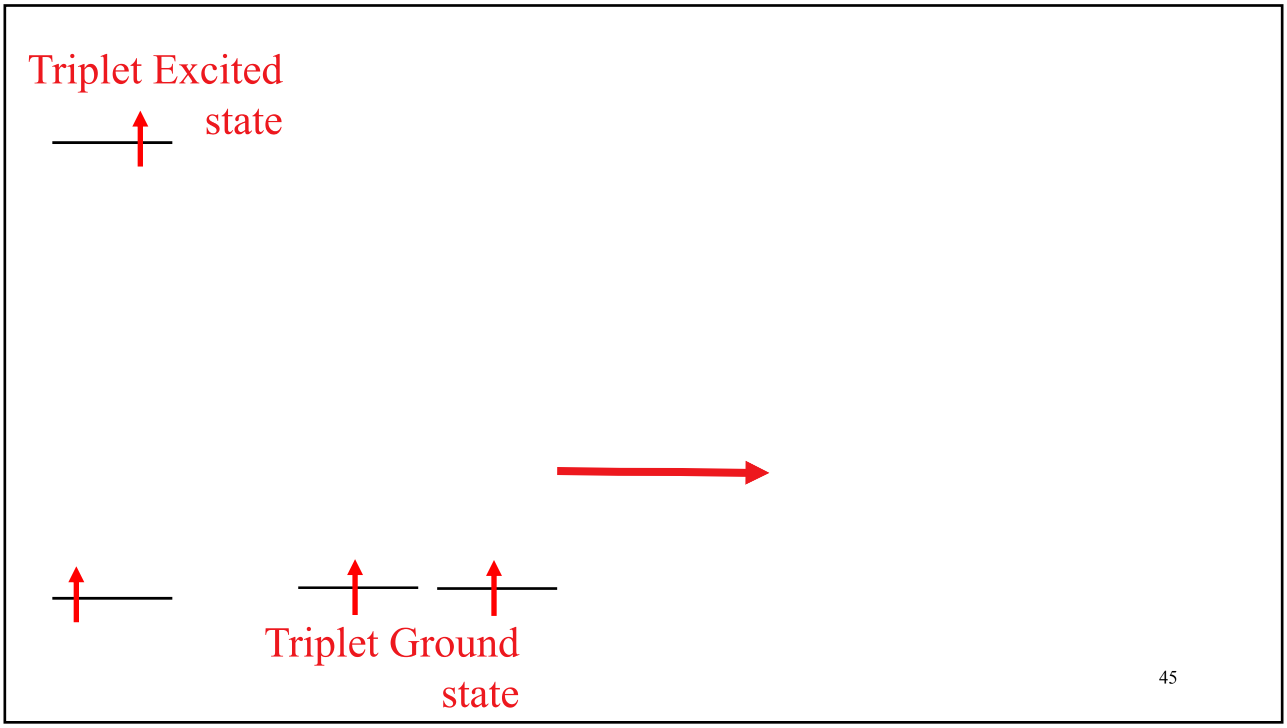
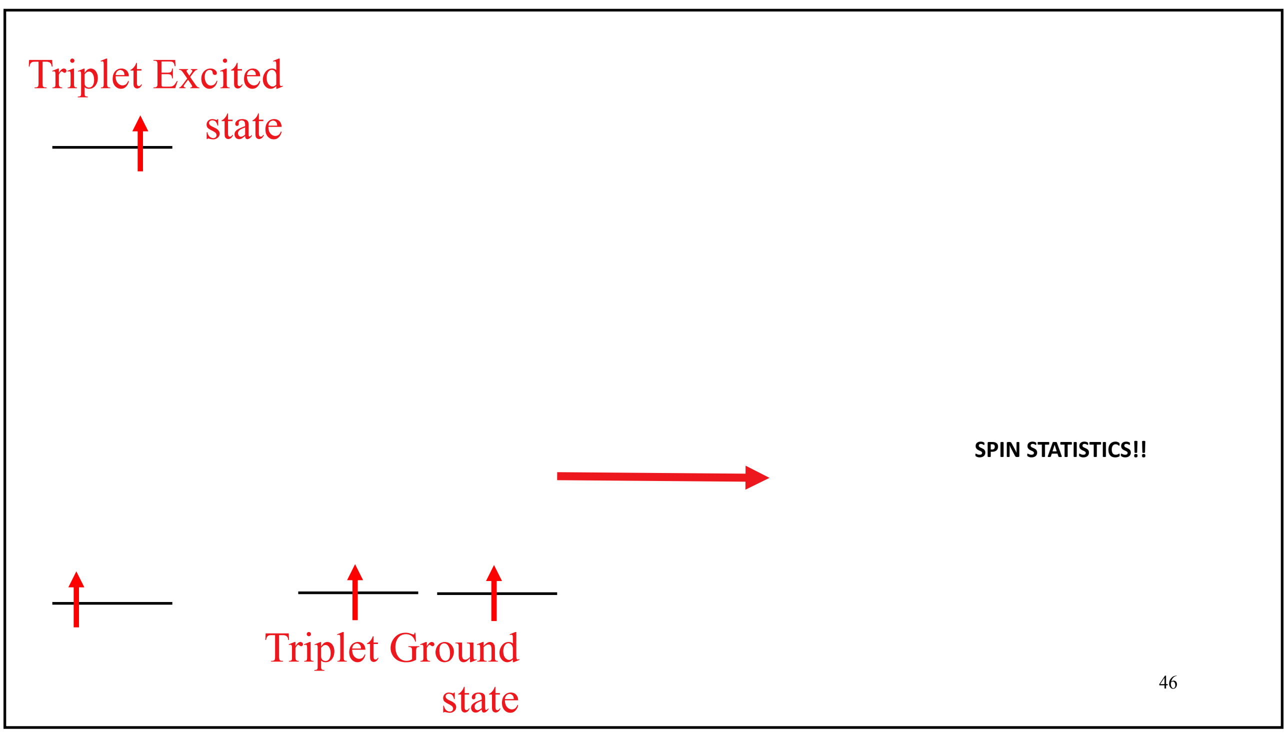

Triplet Excited
state
Triplet Ground
state
45


Triplet Excited
state
SPIN STATISTICS!!
Triplet Ground
state
46

$$^3M^* + O_2(^3\Sigma_g^-) \underset{k_{-d}}{\overset{1/9\,k_d}{\rightleftharpoons}} {}^1(^3M^*..O_2, {}^3\Sigma_g^-)^* \xrightarrow{k_{et}^{1\Sigma}} M + O_2^*(^1\Sigma_g^+) \quad \text{(1a)}$$

$$^1(^3M^*..O_2, {}^3\Sigma_g^-)^* \xrightarrow{k_{et}^{1\Delta}} M + O_2^*(^1\Delta_g) \quad \text{(1b)}$$

$$^3M^* + O_2(^3\Sigma_g^-) \underset{k_{-d}}{\overset{3/9\,k_d}{\rightleftharpoons}} {}^3(^3M^*..O_2, {}^3\Sigma_g^-)^* \xrightarrow{k_{cisc}^{3\Sigma}} M + O_2(^3\Sigma_g^-) \quad \text{(2)}$$

$$^3M^* + O_2(^3\Sigma_g^-) \underset{k_{-d}}{\overset{5/9\,k_d}{\rightleftharpoons}} {}^5(^3M^*..O_2, {}^3\Sigma_g^-)^* \quad \text{(3)}$$

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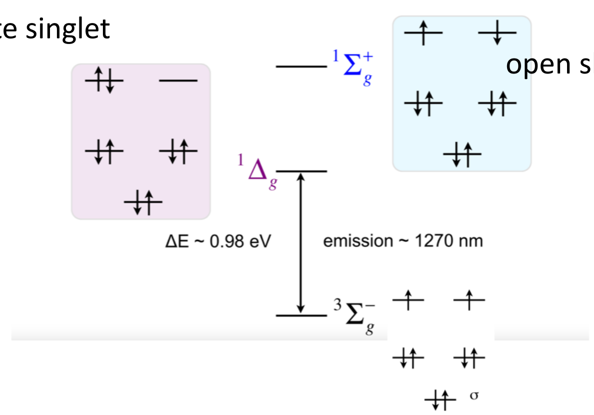
singlet oxygen is highly reactive in several ways
It is used in photodynamic therapy

closed shell excited state singlet

open shell excited state singlet



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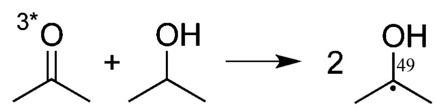
Singlet oxygen: *impressions*

- Rubrene in toluene: total discoloration under indoor conditions in 1 hour!!
- C_{60}-PDI in toluene: no signal!! (only in benzonitrile!)
- Singlet oxygen emission does not go down if bubbling sample with Argon for 30 minutes!!
- UNINANOCUPS: anthracene guests in cyclodextrins hosts: PROBLEMS
- *singlet oxygen can give hydrogen atom abstraction!!?? (ene reaction)*
- *It can react a bit like ozone ([2+2] and [4+2] cycloadditions).*

(NY-’99: acetone-isopropanol with 308 nm excitation:
ketyl radicals)



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singlet oxygen

Peter Ogilby

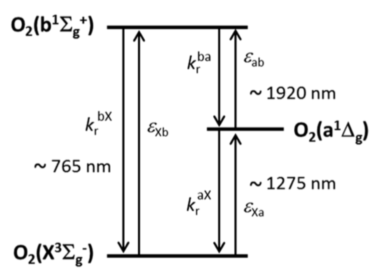
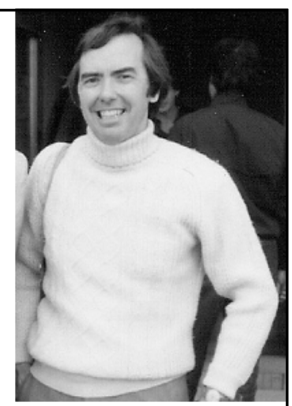


Figure 1. Diagram illustrating absorptive and emissive transitions between the three lowest-lying electronic states of molecular oxygen. The radiative rate constants for emission, k_r, the molar absorption coefficients, ε, and the approximate spectral position, given in nanometers, of the transitions are also shown.



Frank Wilkinson

(18) Bregnhøj, M.; Krægpøth, M. V.; Sørensen, R. J.; Westberg, M.; Ogilby, P. R. Solvent and Heavy-Atom Effects on the $O_2(X^3\Sigma_g^-) \rightarrow O_2(b^1\Sigma_g^+)$ Absorption Transition. *J. Phys. Chem. A* **2016**, *120*, 8285–8296.

DOI: 10.1021/acs.accounts.7b00169
Acc. Chem. Res. 2017, 50, 1920–1927

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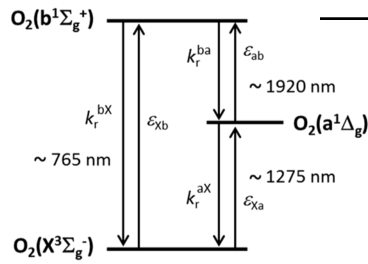
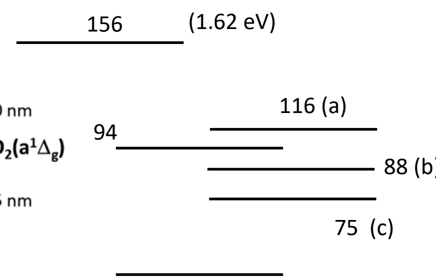
singlet oxygen

energies in kJ/mol





direct optical transitions are very weak!!

Figure 1. Diagram illustrating absorptive and emissive transitions between the three lowest-lying electronic states of molecular oxygen. The radiative rate constants for emission, k_r, the molar absorption coefficients, ε, and the approximate spectral position, given in nanometers, of the transitions are also shown.

triplet state energies of
(a) perylene bisimide
(b) beta-carotene
(c) pentacene

beta-carotene and pentacene can not generate singlet oxygen, but they can quench singlet oxygen (forming their triplets)

Montalti et al. Handbook of photochemistry, 2006 51

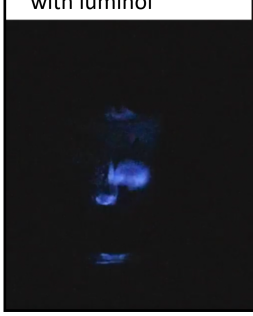
singlet oxygen

emission absorption NIR emission

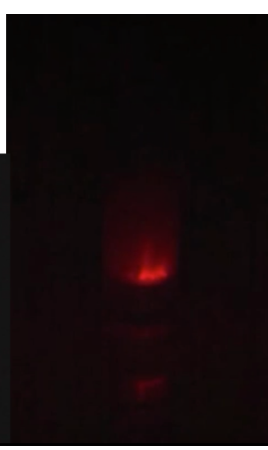
chlorine gas and hydrogen peroxide

chemiluminescence

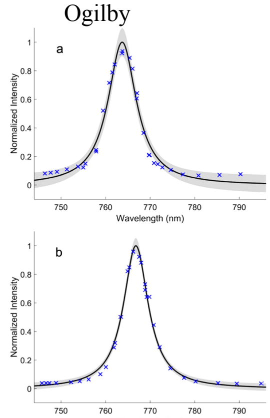
with luminol



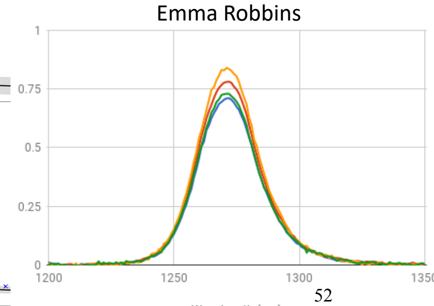
bimolecular at 634 nm



at ~765 nm
Ogilby



at ~1275 nm
in CS_2
C60-PDI
Emma Robbins



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Singlet oxygen emission lifetime and oxygen concentrations in various solvents

Solvent	tau (µs)	$[O_2]$ ambient	$[O_2]$, under O_2	REF
C_6F_6	3600			7
CS_2	1500			3
CCl_4	900			3
$CHCl_3$	244			3
CH_3CN	61			3
$(CH_3)_2(CO)$	45			3
benzene	31			3
Toluene	25			3
THF	23			Wilkinson
2-propanol	22.1			3
Cyclohexane	20			3
ethanol	16			Wilkinson
Methanol	9			4
H_2O	4			4
D_2O	61			Wilkinson

Some representative singlet oxygen decay rates, together with oxygen concentrations from various sources.[7],[8]

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Singlet oxygen

- The first detection of $O_2(^1\Delta_g)$ singlet oxygen emission in solution was achieved by Krasnovsky in **1976**.
- It can diffuse over distances of **20 nm** (cells) to 1 µm (solvents)
- emission lifetime of 4 µs in water, **0.04 µs** in cells

(Chem. Rev., 2003, Vol. 103, No. 5 Schweitzer, Schmidt)

- reaction with sodium **azide** in water according to the Stern-Volmer equation with the quenching rate constant

$(4\pm0.6)\cdot10^8\ M^{-1}s^{-1}$. A.A. Krasnovsky

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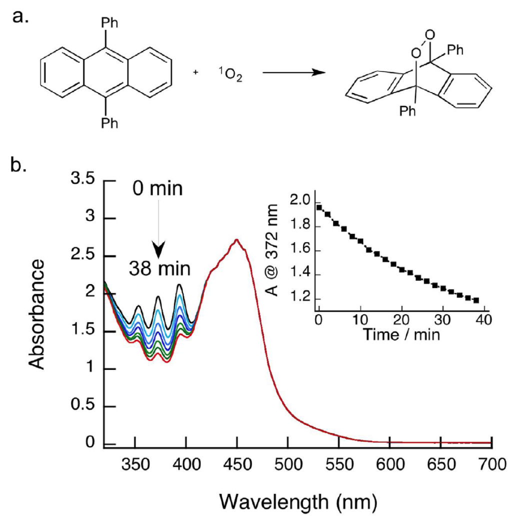
DPA as $^1O_2$ sensor



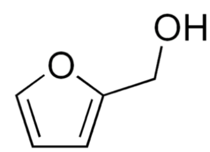
SCIENTIFIC REPORTS

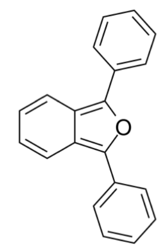
OPEN

Visible-Light Actinometry and Intermittent Illumination as Convenient Tools to Study $Ru(bpy)_3Cl_2$ Mediated Photoredox Transformations

Received: 13 July 2015
Accepted: 07 October 2015
Published: 18 November 2015

Spencer P. Pitre*, Christopher D. McTiernan*, Wyatt Vine, Rebecca DiPucchio, Michel Grenier & Juan C. Scaiano





furfuryl alcohol in water

DPBF organics

nature COMMUNICATIONS

ARTICLE

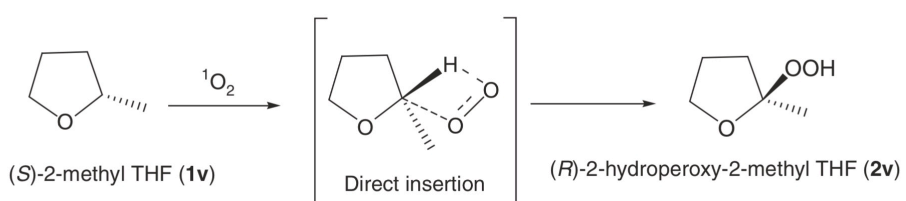
DOI: 10.1038/s41467-017-01906-5 OPEN

Singlet oxygen-mediated selective C–H bond hydroperoxidation of ethereal hydrocarbons

Arunachalam Sagadevan[1], Kuo Chu Hwang[1] & Ming-Der Su[2,3]

2017
also with THF

NATURE COMMUNICATIONS | DOI: 10.1038/s41467-017-01906-5



$[\alpha]_D$ + 19.40° in $CHCl_3$ (observed)
(C: 10 mg per mL), 98% ee

$[\alpha]_D$ - 12.626° in $CHCl_3$
(C: 10 mg per mL), 96.4% ee

Wilkinson

QUANTUM YIELDS FOR FORMATION

Quantum Yields for the Photosensitized Formation of the Lowest Electronically Excited Singlet State of Molecular Oxygen in Solution

Francis Wilkinson
Department of Chemistry, University of Technology, Loughborough, Leicestershire, LE11 3TU, UK
and
W. Phillip Helman and Alberta B. Ross
Radiation Chemistry Data Center, Radiation Laboratory, University of Notre Dame, Notre Dame, IN 46556

Received June 5, 1992; revised manuscript received September 15, 1992

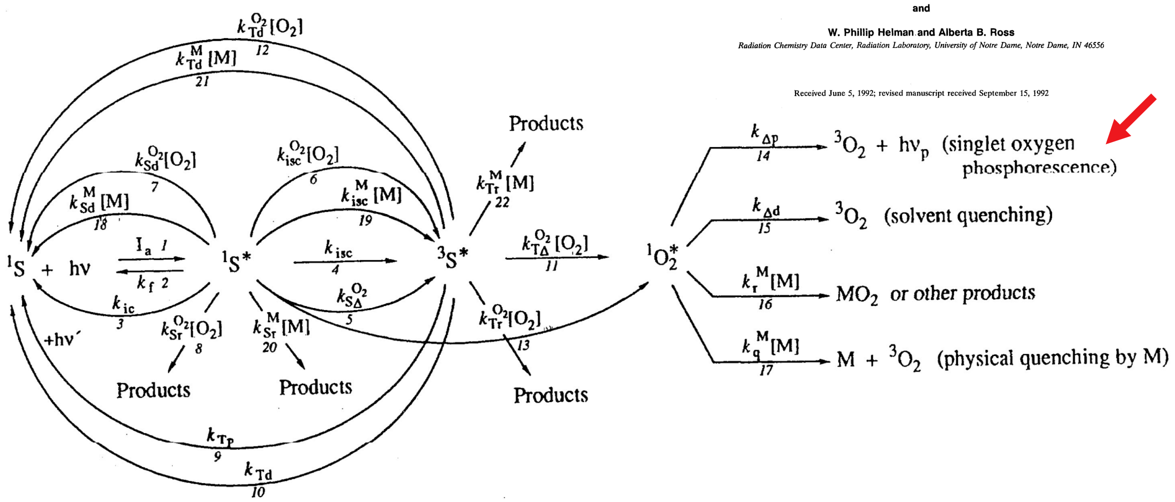


FIG. 3. Pictorial representation of full kinetic scheme [steps *1* to *22*, see text] for photosensitized oxidation involving singlet oxygen. S = Sensitizer, M = Substrate.

M′ can be solvent

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Singlet oxygen

- The phosphorescence quantum yield of $O_2(^1\Delta_g)$ singlet oxygen in water $\mathbf{\Phi}_{phos}$ $(O_2(^1\Delta_g)) = 10^{-6}$
- Recent revival of organic photocatalysis using singlet oxygen

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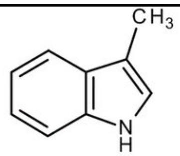

Quim. Nova, Vol. 31, No. 6, 1392-1399, 2008

Artigo

SINGLET OXYGEN REACTIVITY IN WATER-RICH SOLVENT MIXTURES

Cristina Sousa
Departamento de Química, Universidade de Évora, Largo dos Colegiais 2, 7000 Évora, Portugal
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Recebido em 18/7/07; aceito em 17/12/07; publicado na web em 31/7/08

The 3-methylindole (3MI) oxygenation sensitized by psoralen (PSO) has been investigated in 100%, 20% and 5% O_2-saturated water/dioxane (H_2O/Dx) mixtures. The lowering of the $^1O_2^*$ chemical rate when water ($k_{chem\Delta}^{3MI} = 1.4 \times 109\ M^{-1}\ s^{-1}$) is replaced by deuterated water ($k_{chem\Delta}^{3MI} = 1.9 \times 108\ M^{-1}\ s^{-1}$) suggests that hydrogen abstraction is involved in the rate determining step. A high dependence of the chemical rate constant on water concentration in H_2O/Dx mixtures was found showing that water molecules are absolutely essential for the success of the 3MI substrate oxidation by $^1O_2^*$ in water-rich solvent mixtures.

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Antibody Catalysis of the Oxidation of Water

Paul Wentworth Jr.,[1] Lyn H. Jones,[1] Anita D. Wentworth,[1] Xueyong Zhu,[1] Nicholas A. Larsen,[1] Ian A. Wilson,[1] Xin Xu,[2] William A. Goddard III,[2] Kim D. Janda,[1] Albert Eschenmoser,[1,3] Richard A. Lerner[1]

Recently we reported that antibodies can generate hydrogen peroxide (H_2O_2) from singlet molecular oxygen ($^1O_2^*$). We now show that this process is catalytic, and we identify the electron source for a quasi-unlimited generation of H_2O_2. Antibodies produce up to 500 mole equivalents of H_2O_2 from $^1O_2^*$, without a reduction in rate, and we have excluded metals or Cl^- as the electron source. On the basis of isotope incorporation experiments and kinetic data, we propose that antibodies use H_2O as an electron source, facilitating its addition to $^1O_2^*$ to form H_2O_3 as the first intermediate in a reaction cascade that eventually leads to H_2O_2. X-ray crystallographic studies with xenon point to putative conserved oxygen binding sites within the antibody fold where this chemistry could be initiated. Our findings suggest a protective function of immunoglobulins against $^1O_2^*$ and raise the question of whether the need to detoxify $^1O_2^*$ has played a decisive role in the evolution of the immunoglobulin fold.

???

Science, 2001

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What could the next generation PDT agent look like…

- very strong light absorption at 808 nm
- high triplet yield and singlet oxygen production
- a bit of fluorescence for image guided surgery
- targeting by folic acid groups/antibodies/???
- water solubility for very fast uptake and fast excretion
- take advantage of pH difference around the cancer cell
- …aPDT: antimicrobial, anti-viral, anti-biotics

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FINAL REMARKS

- Controlling the levels of **reactive oxygen species** and **reactive nitrogen species** and their location in the human body can lead to control over cancer.
- The formation of **triplet excited states** with light can give a handle to do that.
- **Targeting** strategies are essential for new PDT drugs.
- Porhyrins, chlorins, bacteriochlorins and phthalocyanines can be **bio-compatible** medications.
- **singlet oxygen** reactivity in **aqueous** environment still poses questions.

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Singlet oxygen

- reaction with water with the quenching rate constant

$k_q = 1 \times 10^6$ $M^{-1}s^{-1}$ (Turro MMP page 593)
- 55.5 M pure liquid water -> $k_{qr} = 5.55 \times 10^7$ s^{-1}
- competitive with emission decay of 4 μs!!

- **But reference is not on reactions!! But on e-v interactions**

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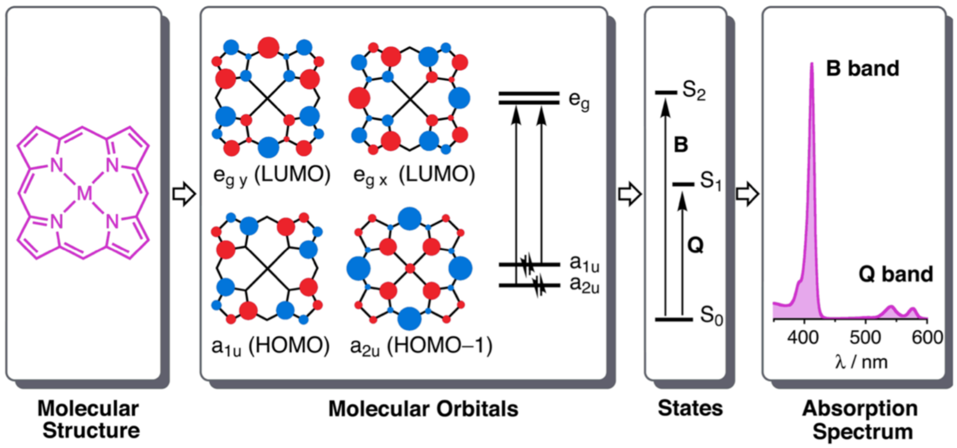
Porphyrin electronic structure



Harry L. Anderson
Oxford, UK