Chapter 14
Sunscreen Photostability

Craig A. Bonda and Dennis Lott

Key Points

- Sunscreens are photochemical systems, and their behavior is best understood through the science of photochemistry.
- Deeper understanding of the complex photochemistry of avobenzone has led to better formulating methods and improved sunscreen performance.
- The photostability of sunscreen products is a function of the photostabilities of the individual UV filters and the photochemical and photophysical interactions between them.
- Photostability will retain a leading role in sunscreen product design as costs and regulatory issues continue to drive sunscreen formulating worldwide.
- Though significant challenges remain, the availability of photostabilizers and, in many areas, new UV filters has allowed the sunscreen industry to make great strides in improving photoprotection.

14.1 A Brief History

Photostability became a genuine concern to the sunscreen industry with the introduction in Europe of avobenzone (butyl methoxydibenzoylmethane or BMDM) in the 1980s and in the USA in the early 1990s. This photolabile

---

C.A. Bonda (✉)
Inception Partners, LLC, 0s630 Madison Street, Winfield, IL 60190, USA
e-mail: craigbonda@gmail.com

D. Lott
Florida Suncare Testing, Inc, 101 N. Bay Street, PO Box 758, Bunnell, FL, USA
e-mail: lott@live.com

S.Q. Wang, H.W. Lim (eds.), *Principles and Practice of Photoprotection*,
DOI 10.1007/978-3-319-29382-0_14

compound was the first and for years remained the only UV filter to be effective at protecting skin from longer wavelength UVA radiation (320–400 nm), widely believed to be a primary cause of early skin aging and certain skin cancers [1]. Avobenzone degrades rapidly in sunlight [2] and may react chemically with other organic compounds [3]. This spawned an "arms race" among both UV filter suppliers and sunscreen manufacturers to discover ways to photostabilize or replace avobenzone. Scientists in Europe focused on developing photostable UV filters to compete with avobenzone, while other scientists in the USA and Europe focused on discovering new photostabilizers. Both groups were successful: the resulting new UVA filters and photostabilizers are now in widespread use throughout the world.

Several photostable European UVA filters have been submitted for approval to the US Food and Drug Administration for inclusion in the monograph for OTC sunscreen drug products. In 2014, all were deemed by the FDA to have insufficient data on which to base the requisite "generally regarded as safe and effective" (GRASE) determination and were returned to their sponsors for additional information [4]. This signals a continuing role for photostabilizers in sunscreens, especially those to be marketed in the USA but also in other parts of the world where global acceptability is desired and where cost considerations favor the continued use of inexpensive avobenzone as the primary UVA filter.

14.2 Photochemistry of Photostability

The definitive source for general knowledge of organic photochemistry is *Modern Molecular Photochemistry of Organic Molecules* by N.J. Turro, V. Ramamurthy, and J.C. Scaiano (2010, University science Books, Sausolito, CA) [5]. Following is a very brief summary of some of the key aspects as they relate to the subject at hand, sunscreen photostability.

Organic chromophores convert the energy in a quantum of light – a photon – into electronic excitation energy (Turro et al. 2010, p. 27). One photon excites one molecule, and, with rare and obscure exceptions, one and only one of a molecule's electrons is excited to a higher energy state at any one time.

Once excited, a chromophore has several photophysical pathways available to dissipate its excited state energy. These pathways may be "radiative" or "non-radiative." By radiative is meant that the excited chromophore sheds some or all of its energy by emitting a photon; non-radiative pathways expend energy kinetically or vibrationally as heat, or by transferring energy to another molecule (Turro et al. 2010, p. 18–19).

The photostable situation may be represented as follows:

$$R + h\nu \rightarrow {}^{*}R \rightarrow_{\mathrm{pp}} R$$

where R is a chromophore in its ground state, $*R$ is a chromophore in its excited state, $h\nu$ is the energy in a photon, and $\rightarrow_{\text{pp}}$ is energy dissipation purely by photophysical (radiative and non-radiative) processes, thus returning the excited chromophore to the ground state with no changes in its structure or geometry (Turro et al. 2010, p. 40).

Photostable chromophores undergo billions of such cycles – photon absorption, excitation, energy dissipation, and relaxation to the ground state – with a low (not zero!) probability that there will be a net chemical change. In contrast, photolabile chromophores have a relatively high probability that excitation will lead to a net chemical change. The consequence of photolability is photodegradation or photodecomposition, characterized by a loss of absorbance and the appearance of new chemical entities. In sunscreens, photodegradation results in less protection for the skin than would otherwise be expected and exposure of the skin to unwanted photoproducts.

The photolabile situation may be represented as follows:

$$R + h\nu \rightarrow *R \rightarrow_{\text{pc}} I \rightarrow_{\text{T}} P$$

where $\rightarrow_{\text{pc}}$ is a photochemical process, I is a reactive intermediate, $\rightarrow_{\text{T}}$ is a thermal chemical process, and P is a chemical product (Turro et al. 2010, p. 10).

For absorption of a photon and excitation to occur, the energy gap between the electron's ground state orbital, known as the highest occupied molecular orbital or HO, and its initial excited state orbital, known as the lowest unoccupied molecular orbital or LU, must match exactly the energy of the photon. This energy matching requirement is known as the "resonance condition" (Turro et al. 2010, p. 27).

For the UV filters used in sunscreens, the resonance condition requires encounter wavelengths and energies that correspond to the UV portion of the solar spectrum.

The HO of an organic chromophore in the ground state contains a pair of electrons. The electron pairs most commonly involved in excitation of an organic chromophore are those in bonding or π orbitals (e.g., $c=\text{c}$) and nonbonding or n orbitals such as those found associated with oxygen in carbonyls ($c=\text{o}$). The transition to the LU by the excited electron is to an anti-bonding orbital, π^*. Thus, the two most common transitions are represented by $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$ (Turro et al. 2010, p. 52–55).

In the ground state, the two electrons in the HO are in the singlet state (Fig. 14.1) in which the electrons are "spin-paired," meaning they are spinning about opposite vectors – "up" and "down" – and, in a magnetic field, are precessing 180° out of phase. The ground state is conveniently represented by S_0 and symbolized by $\underline{\uparrow\downarrow}$. This spin-paired configuration is what allows two negatively charged electrons to overcome their repulsion and occupy the same orbital. The spin-paired configuration is maintained in the initial transition from ground (S_0) to excited state even as the two electrons become orbitally unpaired. Thus, the initial transition after photon absorption is known as the "singlet excited state" which may have more than one energy level and is represented by $S_{1,}$ $S_2 \ldots S_n$ and symbolized by $\begin{smallmatrix}\underline{\;\;\downarrow}\\ \underline{\uparrow\;\;}\end{smallmatrix}$.

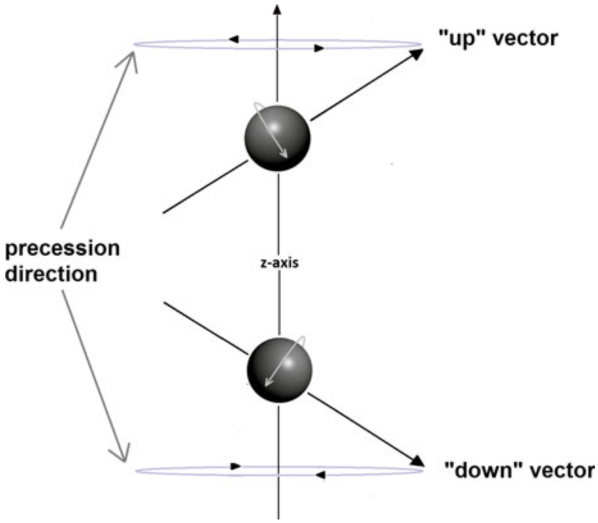
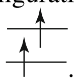


Fig. 14.1 In the singlet state, two paired electrons spin about opposite vectors ("*up*" and "*down*") and, in a magnetic field, precess 180° out of phase. The *z*-axis is either aligned or opposed to the direction of the magnetic field

Transitions are favored between states that "look like" each other in the sense that their electronic, vibrational, and spin configurations are similar (Turro et al. 2010, p. 45–47, 117). Upon photon absorption, an electron in the singlet ground state naturally transitions to a singlet excited state and almost never to a triplet excited state. For many chromophores, the reverse is also true: an electron in the singlet excited state will tend to relax to the singlet ground state either by dissipating its excess energy as heat (internal conversion) or by emitting a photon (fluorescence).

The return to the ground state from the singlet excited state tends to happen quickly; nanosecond time scales are common. Such a rapid return to the ground state favors photostability since there is little time for chemical processes to compete.

Figure 14.2 depicts the electron configurations of the triplet excited state which is represented by T_1 and symbolized by . An excited electron reaches a triplet excited state by undergoing a spin flip and phase change usually as the result of a magnetic interaction between the electron's spin and another electron's orbital motion (Turro et al. 2010, p. 144). The transition from the singlet excited state to a triple excited state is called "intersystem crossing." The triplet excited state is metastable; that is, the two electrons are unable to re-pair in their HO unless and until the excited electron undergoes another spin flip and phase change. A chromophore in the triplet excited state behaves as a diradical (i.e., having two unpaired electrons) (Turro et al. 2010, p. 718). This fact coupled with its typically longer lifetime makes the triplet excited state highly reactive and the starting point for most photochemical reactions (Turro et al. 2010, p. 521).

Photochemists use experimental methods to determine the processes a particular chromophore will take in a given set of conditions and record their findings on state

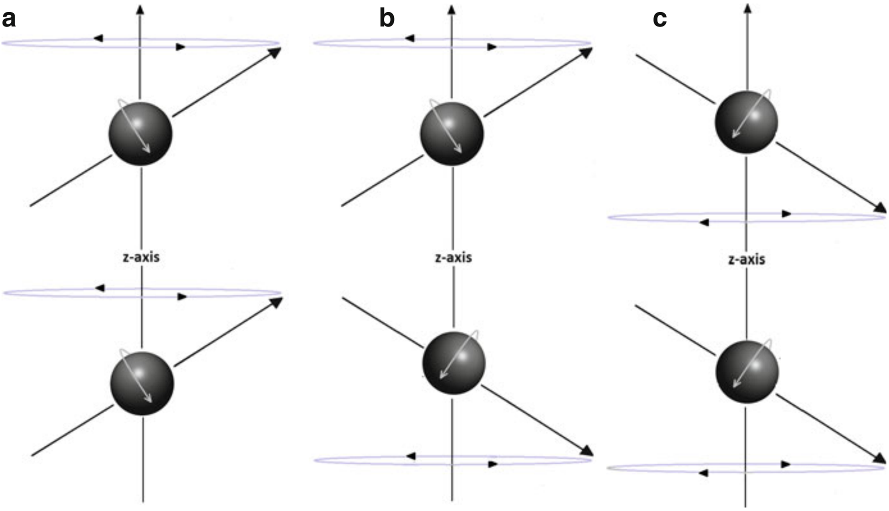


Fig. 14.2 In the triplet state, there are three possible orientations for the electron pair: (**a**) both electron spin about "up" vectors; (**b**) the electrons spin about opposite vectors while precessing in phase; (**c**) both electrons spin about "down" vectors

energy diagrams, also known as Jablonski diagrams, like the one in Fig. 14.3. Key parameters for any photophysical process are its energy (E), its quantum yield (∅), its rate constant (k), and its lifetime (τ). (Since $1/k = \tau$, it is only necessary to measure one: either rate constant or lifetime.) Quantum yield is a measure of the efficiency of a process and is calculated either as the fraction of absorbed photons that produce a specific sequence or by comparing the rate of a specific pathway to the sum of the rates of all competing pathways. For example, if 10 out of 100 excited molecules fluoresce, then the quantum yield of fluorescence is 0.10 (10 %).

Another way for an excited chromophore to return to the ground state is by transferring its energy to another molecule, known as the quencher, Q. Energy transfer can be represented schematically by

$$*R + Q \rightarrow_{\mathrm{ET}} R + *Q$$

where $\rightarrow_{\mathrm{ET}}$ is energy transfer (Turro et al. 2010, p. 390). Thus, the excited chromophore transfers its excited state energy to the ground state quencher which deactivates the chromophore to the ground state and raises the quencher to the excited state. The relative efficiency of a quencher to quench the excited state of a chromophore is characterized by a quenching rate constant, k_{ET}, where ET stands for energy transfer. The actual rate this happens in a solution (or, presumably, in a sunscreen) is the product of the quenching rate constant and the concentration of the quencher, $[Q]$, plus the sum of all other deactivation pathways, k_{D}.

$$k_{\mathrm{q\,obs}} = k_{\mathrm{D}} + k_{\mathrm{ET}} \times [Q]$$

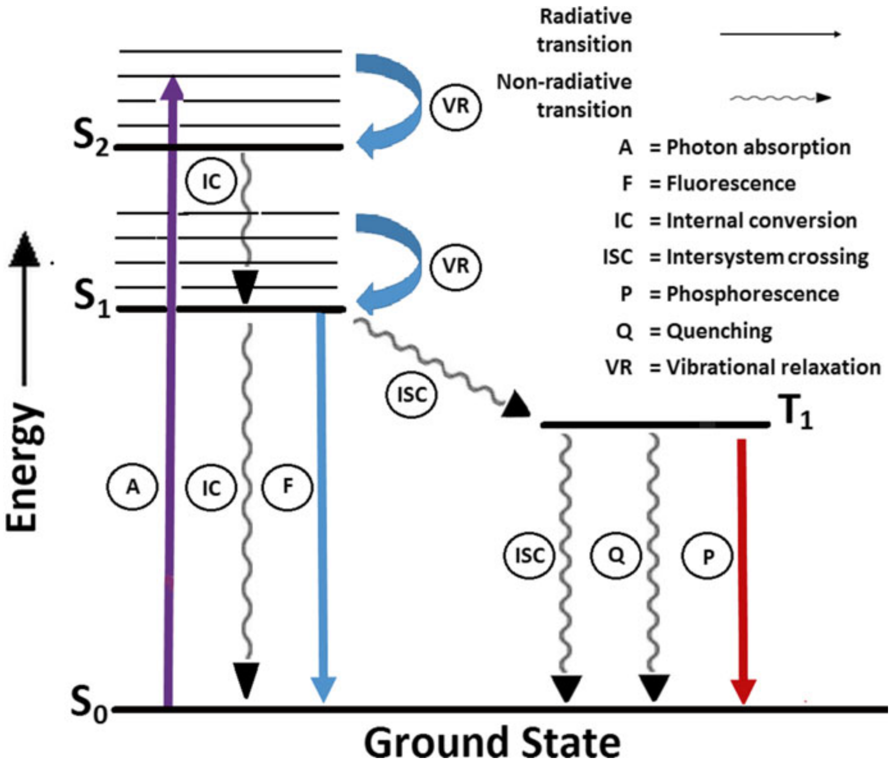


Fig. 14.3 A state energy or “Jablonski” diagram like this is used by photochemists to keep track of an organic chromophore’s three most important states: the ground state, S_0; the lowest energy singlet excited state, S_1; and the lowest energy triplet state, T_1. The upward arrow on the left represents photon absorption and excitation. The downward and diagonally pointing arrows represent photophysical processes that drain the chromophore’s excited state energy. Key parameters are the energies, quantum yields, and lifetimes of each state and the rates of interstate transitions

where $k_{q\ obs}$ is the quenching rate observed experimentally (Turro et al. 2010, p. 390–391).

This is the basic mechanistic scheme for most of the photostabilizers to be discussed later in this chapter. First, we turn to avobenzone as the exemplar of a photolabile UV filter to find out why photostabilizers are needed in the first place.

14.3 Photochemistry of Avobenzone

Seminal studies published in 1995 by Schwack and Rudolph and in 1997 by Andrae et al. contributed greatly to the early understanding of this important sunscreen ingredient.

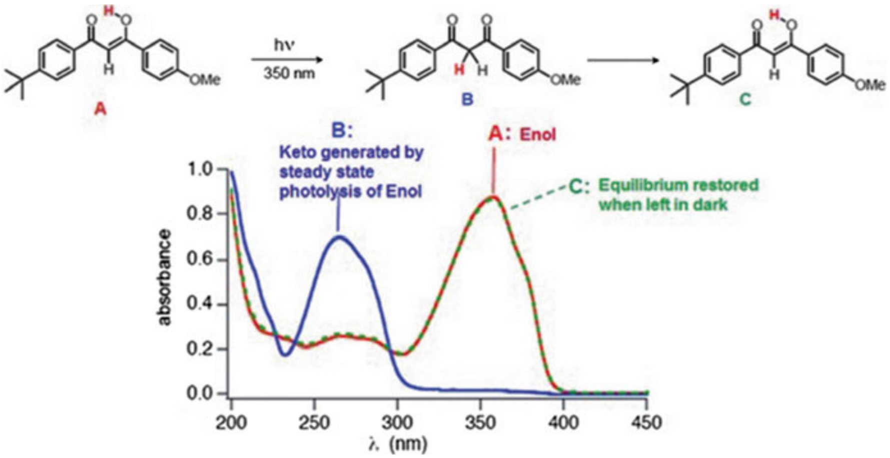


Fig. 14.4 Graph shows that steady-state irradiation of the enol tautomer (*A*) generates the keto tautomer (*B*) which, when left in the dark, spontaneously converts back to the enol form (*C*). (Bonda et al. [2], reprinted with permission)

To investigate the photodegradation of avobenzone, Schwack and Rudolph irradiated 3.5 mmol solutions of avobenzone in non-deaerated cyclohexane, isooctane, isopropanol, and methanol for up to 8 h using a solar simulator filtered to deliver radiation either above 260 nm or 320 nm. Photodegradation progress was monitored by HPLC, and the photoproducts were identified by GC-MS. About 12 photoproducts were identified, all of which originated from one of two radical precursors: a benzoyl radical or a phenacyl radical. Photodegradation proceeded in the nonpolar solvents cyclohexane and isooctane, but not in the polar, protic solvents isopropanol and methanol. In the nonpolar solvents, photodegradation was almost twice as rapid under shorter wave irradiation (>260) than under longer wave irradiation (>320). To find out why avobenzone is photolabile in cyclohexane and isooctane and photostable in isopropanol and methanol, Schwack and Rudolph carried out ^{1}H NMR measurements of avobenzone solutions dissolved in cyclohexane-d_{12} and isopropanol-d_8 (.03 mol). In cyclohexane-d_{12}, avobenzone exhibited 3.5 % keto form, but in isopropanol-d_8, no keto form was detected. Based on these findings, Schwack and Rudolph concluded that avobenzone photodegradation “depends strongly on the presence of the 1,3-keto form” [6]. Therefore, discovering the origins of the keto form and its subsequent behavior under irradiation became of primary interest to researchers.

Andrae et al. showed that photolysis with UV radiation drives the conversion of the enol tautomer to the keto form (Fig. 14.4) [7]. They applied steady-state irradiation to avobenzone in acetonitrile (10^{-5}–10^{-10} M) using both a high-pressure mercury lamp and a xenon light source, observing a decline in peak absorbance at 355 nm and a corresponding increase in peak absorbance at 265 nm. Based on NMR, IR, and HPLC studies, they attributed the spectral change to the light-induced conversion of the enol tautomer to the keto tautomer. Andrae et al. also applied a

14 ns laser pulse of 355 nm to dilute solutions of avobenzone in acetonitrile, observing a transient species with peak absorption at 300 nm. The group attributed the transient absorbance either to an excited *E*-isomer of the enol or to an enol rotamer which were assumed to be intermediates in the conversion to the keto form (see Cantrell and McGarvey and Yamaji and Kida below).

A number of more recent studies published in the literature provide additional guidance to avobenzone's photoinduced behavior under various conditions. Many of the gaps in avobenzone's state energy diagram have now been filled in, providing much needed clarity to its complex photophysics and photochemistry. Following is a sample of the many studies published in the literature.

Cantrell and McGarvey employed nanosecond laser flash photolysis at 355 nm and 266 nm on dilute (10^{-5} M) solutions of avobenzone in acetonitrile [8]. Photolysis at 355 nm produced transient absorbance changes with a new peak at 300 nm and bleaching (loss of absorbance) at 360 nm. No peak at 260 nm was observed, leading to the comment that formation of the keto form must have a low quantum yield (see Yamaji and Kida below). They attributed the transient peak at 300 nm to a non-chelated enol rotamer (NCE), which is a *Z*-isomer. Hill had earlier determined the quantum yield of formation of the 300 nm-absorbing species to be ≈ 0.25 [9]. The lifetime of the NCE rotamer is solvent dependent and ranges from 159 ms in acetonitrile to 0.7 ms in butanol. Upon photolysis at 266 nm, Cantrell and McGarvey observed a permanent loss of absorbance at 360 nm and no increase of absorbance at 260 nm, suggesting that excitation of the keto form leads directly to avobenzone decomposition. Nanosecond excitation at 266 nm of a pre-irradiated solution in deoxygenated acetonitrile generated a transient absorbance spectrum from 300 to 500 nm which was attributed to the triplet state of the keto form. A further experiment found the keto triplet to be quenched by molecular oxygen with a rate constant of 5×10^9 mol^{-1} s^{-1} and a quantum yield of singlet oxygen formation of 0.18.

Huong et al. studied avobenzone photostability in three environments: diluted solutions in laboratory solvents of varying polarity, concentrated solutions in non-volatile solvents, and in commercially available sunscreen products [10]. In dilute solutions irradiated in a xenon test chamber, the study found avobenzone to be photostable or nearly so in dioxane, acetonitrile, ethyl acetate, tetrahydrofuran, ethanol, and isopropanol and photolabile in hexane, heptane, and cyclohexane. The photolability manifested as a rapid decline of absorbance at 350–360 nm and a corresponding increase in absorbance at 260–270 nm. However, in confirmation of work previously reported by Bonda et al. [11], Huong et al. also found that the photodegraded solutions, when left in the dark and monitored for UV absorbance at timed intervals, slowly recovered their initial absorption at 350–360 nm, while their absorption at 260–270 also declined to pre-irradiation levels (Fig. 14.4). They also confirmed another of the findings of Bonda et al. (1997): that as little as 1 % isopropanol in the hexane solution completely inhibited avobenzone's loss of absorption at 350–360 nm upon irradiation. In concentrated solutions of 2 and 4 % (w/w) in various cosmetic oils (mineral oil, isostearyl isostearate, alkyl tartrate, alkyl lactate), photodegradation of avobenzone appeared to be relatively independent of the solvent with as much as 80 % of the avobenzone converted to photoproducts. A total of

11 commercially available European sunscreen products were tested by applying each in a measured amount to a polymethyl methacrylate (PMMA) plate and irradiating it in a xenon test chamber. After irradiation, the sunscreen was extracted with solvent and the resulting solutions analyzed by HPLC. The study found the behavior of avobenzone in these sunscreens to be highly variable, with the loss of compound ranging from 3 % to over 90 %. Loss of SPF ranged from 0 to 50 %.

Mturi and Martincigh employed UV spectroscopy, HPLC, GC-MS, and NMR to investigate avobenzone's photostability in solvents of differing polarity and proticity [12]. As others had, they found avobenzone to be photostable in the polar, protic solvent methanol. In polar, aprotic DMSO, loss of absorbance was attributed to photoisomerization from the enol form to the keto form. However, in nonpolar, aprotic cyclohexane, loss of absorbance was due primarily to photodegradation. In moderately polar, aprotic ethyl acetate, both photoisomerization and photodegradation occurred. However, photoisomerization only occurred in the presence of oxygen, while photodegradation occurred irrespective of oxygen.

In their 2013 paper, Yamaji and Kida reported on their photochemical and kinetic studies of the enol-keto and keto-enol tautomerization processes [13]. Steady-state photolysis of avobenzone in acetonitrile (~10^{-5} mol) produced the characteristic decline in absorbance of the enol form at 356 nm and a corresponding increase in absorbance of the keto form at 265 nm. This happened both in the presence and absence of oxygen. They did not observe generation of the keto form during photolysis of avobenzone in cyclohexane, though production of photodegradation products was observed. Using laser flash photolysis on avobenzone in acetonitrile, Yamaji and Kida were able to determine the quantum yield (Φ_k) of keto tautomer formation to be 0.014 with the value being independent of dissolved oxygen. Laser flash photolysis at 266 nm performed on the keto form produced a new absorption band with a 390 nm peak and a broad band from 450 to 600 nm which was attributed to absorbance of the triplet keto form. The 390 nm signal subsequently decayed at the rate (k) of $1.6 \times 10^6\ \mathrm{s}^{-1}$ in the absence of oxygen (lifetime: $\tau_{KT} = 6.25 \times 10^{-7}$ s)[1] and $7.6 \times 10^6\ \mathrm{s}^{-1}$ (lifetime: $\tau_{KT} = 1.32 \times 10^{-7}$ s) in aerated acetonitrile solutions. After formation by photolysis of the enol form, the lifetime (τ_K) of the keto form in the dark was determined to be 5.1 h.

Kikuchi, Oguchi, and Yagi studied the excited states of avobenzone and a specially synthesized model of avobenzone's keto form, observing the UV absorption, fluorescence, phosphorescence, and electron paramagnetic resonance spectra (EPR) of both compounds in ethanol at 77° K [14]. From the intersection of the UV absorption and fluorescence spectra, they were able to determine the singlet excited state energy (E_{S1}) of the enol form to be 25,600 cm^{-1} (73.19 kcal mol^{-1}). By similar means, they determined the singlet excited state energy of the keto form analog to be 27,000 cm^{-1} (77.20 kcal mol^{-1}). From the first peak of phosphorescence, they determined the triplet excited state energy (E_{T1}) of the enol form to be 20,400 cm^{-1} (58.33 kcal mol^{-1}) and the triplet excited state energy of the keto form to be 24,400 cm^{-1} (69.76 kcal mol^{-1}). From the decay of the first peak of phosphorescence,

---

[1] τ_{KT} represents the lifetime of the keto triplet.

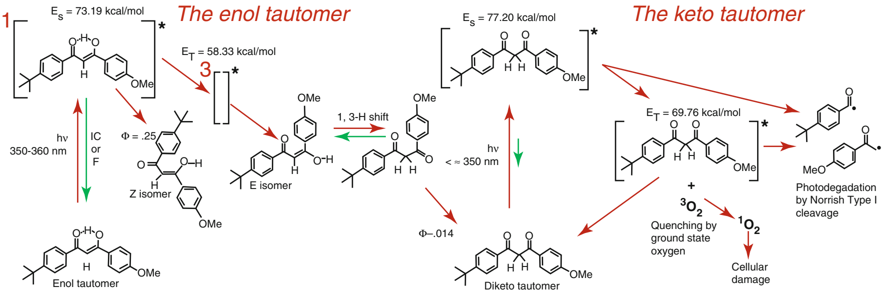


Fig. 14.5 A state energy diagram for avobenzone, compiled primarily from studies conducted at low concentrations in acetonitrile solutions. Photolysis of the enol tautomer drives an increase in the concentration of the keto tautomer, which, when excited by UVR, undergoes a Norrish type I cleavage to produce benzoyl and phenacyl radicals. The *asterisks* signify that the molecule within the brackets is in an excited state (Bonda et al. [2], reprinted with permission)

Kikuchi et al. determined the triplet excited state lifetime (τ_{phos}) of the enol form to be 30 ms and the triplet excited state lifetime of the keto form to be 190 ms.

A compound's fluorescence lifetime puts an upper limit on the lifetime of the singlet excited state. As reported by Bonda et al. (2009), measurements conducted at the University of California-Riverside determined the fluorescence lifetime of the enol form to be 13 ps [15].

From these and other studies, a picture of avobenzone's photophysics and photochemistry has emerged, which is depicted graphically in Fig. 14.5.

14.4 Photostabilities of Other UV Filters

Avobenzone is not the only photolabile UV filter used in sunscreens. In fact, there are no perfectly photostable UV filter, though some are nearly so.

Tarras-Wahlberg et al. irradiated OMC mixed with petrolatum first with 20 MED of UVB radiation and then with 100 J/cm^2 of UVA radiation. They observed slight loss of peak absorption after the UVB dose and a much larger loss of peak absorption after the UVA dose. HPLC analysis of the sample following irradiation revealed formation of a new peak which the researchers attributed to OMC's *cis* isomer, indicating that irradiation drove conversion of the normally dominant *trans* isomer to its *cis* counterpart, which absorbs UV with a similar peak but at a significantly lower molar extinction coefficient [16]. Others have found that when present in high concentrations, OMC can react with itself as two molecules undergo a [2+2] cycloaddition reaction [17].

The photostabilities of 18 UVB filters approved for the use in sunscreens in the EU were studied in vitro by Couteau et al. [18]. Each UV filter was incorporated into its own standardized oil-in-water emulsion. The researchers applied 30 mg of each formulation to roughened PMMA plates. The plates were irradiated in a xenon test

Table 14.1 Photostabilities of UVB Filters [18]

UVB filters (from most to least photostable)	Rate constant of photodecay (k min^{-1})
Iscotriazine (DBT)	.00008
PABA	.0001
Bisoctrizole (MBBT)	.0004
Oxybenzone (OXY)	.0005
Ensulizole (PBSA)	.0005
Benzophenone-5	.0006
Octocrylene (OC)	.0014
Enzacamene (4-MBC)	.0021
Octyl triazine (EHT)	.0022
Homosalate	.0023
3-Benzylidene camphor	.0031
Octinoxate (OMC)	.0031
Polysilicone-15	.0038
Anisotriazine	.0044
Amiloxate	.0059
PEG-25 PABA	.0061
Padimate O	.0062
Octisalate	.0075

Each of the 18 UV filters, listed above from most to least photostable, was incorporated into its own standardized oil-in-water emulsion, which was applied to a substrate and irradiated in a xenon test chamber. Measurements were taken at timed intervals and the rate constant of photodecay (k) calculated by the equation $SPF/SPF_0 = e^{-kt}$

chamber filtered to block radiation <290 nm. The SPF was measured at timed intervals with a UV transmittance analyzer. Photodegradation of each formulation was expressed in three ways: as the number of minutes of irradiation required to cause the coated plate to lose 50 % of its SPF ($t_{50\%}$); as the number of minutes of irradiation required to cause the coated plate to lose 10 % of its SPF ($t_{90\%}$); and as the rate constant of photodecay (k) according to the equation $SPF/SPF_0 = e^{-kt}$. Table 14.1 presents the results of the study in rank order from most to least photostable.

Herzog et al. studied the photostabilities of ethylhexyl methoxycinnamate (OMC), ethylhexyl triazine (EHT), avobenzone, BEMT, and OC [19]. They incorporated each UV filter into its own oil-in-water emulsion which they applied to a quartz plate and irradiated in a xenon test chamber. At timed intervals, they used solvent to extract the residual emulsion containing the UV filter from the quartz plate and then analyzed the solution by HPLC. After 50 MED, OC and BEMT were found to be photostable. OMC and avobenzone were strongly degraded (<20 % and <1 % were recovered, respectively), and EHT was less degraded (approximately 50 % was recovered). The researchers noted degradation of OMC is not observed in ethanol solutions at low concentrations. A rapid initial loss of absorption is attributed to a change in the equilibrium between the *trans* and cis isomers (toward the *cis*) which quickly stabilizes and after which no further drop occurs.

14.5 Sunscreen Products and UV Filter Combinations

UV filters are almost never used alone in sunscreen products, which may contain up to six UV filters. Bimolecular interactions between UV filters of the same or different species, or between the UV filters and inactive ingredients with which they are paired, can have a positive, negative, or no effect on the sunscreen's photostability, as illustrated in the studies referenced below.

A major sunscreen manufacturer and marketer in the USA reported studies of the photostabilities of numerous sunscreen products in their comments to the FDA in 2007 [20] and their follow-up supplement in 2008 [21]. In one study, commercially available sunscreen products were applied in measured amounts to microscope slides and exposed to natural sunlight until 7.5 MED was reached as measured by a radiometer. The UV filters were then assayed by HPLC. Independent labs in Sydney, Australia, Winston-Salem, North Carolina, and Ormond Beach, Florida, took part. Some of the products were tested by all three labs, others were tested by two. The 14 products ranged from SPF 30 to SPF 80 and comprised 10 lotions, one lotion spray, two continuous sprays, and one stick product. Four of the products contained OMC in combination with avobenzone, and nine combined OC with avobenzone, two of which also contained OMC. Three contained avobenzone without either OC or OMC. The results may be found in Table 14.2, which groups the products tested by the presence or absence of the three UV filters. Clearly, of the products tested, the most photostable are those that contain OC and avobenzone and no OMC, or do not contain avobenzone at all. In all 12 of the products containing them, the two salicylates, octyl salicylate and homosalate, showed significant photolability, declining on average by about 24 % and 15 %, respectively.

Beasely and Meyer determined the impact of avobenzone photolability on SPF and UVA-PF [22]. They started with a model SPF 50 sunscreen product which contained 3 % avobenzone photostabilized with 7 % OC. They then prepared a

Table 14.2 % UV filters remaining after 7.5 MED of natural sunlight by HPLC

UV Filters	OC + Avo, no OMC (*N*=9)	OC + Avo + OMC (*N*=2)	Avo + OMC, no OC (*N*=2)	OMC, no Avo (*N*=1)
Octocrylene (OC)	100 %	100 %		100 %
Oxybenzone	96.8 %	94.9 %	100 %	97.0 %
Avobenzone (Avo)	91.0 %	59.6 %	25.0 %	
OMC		49.4 %	41.0 %	65.1 %
Octyl salicylate	77.8 %	75.8 %	76.3 %	75.1 %
Homosalate	86.4 %	81.4 %	86.8 %	84.2 %

14 commercially available sunscreen products were applied to microscope slides and exposed to natural 7.5 MED of natural sunlight. The studies were duplicated or triplicated by labs in Australia, North Carolina, and Florida. After exposure, each sunscreen was extracted from the slide by solvent and analyzed by HPLC to determine the amount of each UV filter remaining. The two salicylates showed significant loss in all products. Avobenzone was most photostable when combined with octocrylene (OC) without OMC

series of four new photostable formulations identical in every way to the original except that the avobenzone concentration was reduced by 20 %, 33 %, 67 %, and 100 % (no avobenzone), respectively, in order to simulate corresponding degrees of avobenzone loss due to photodegradation. These products were then tested on human volunteers and the SPF and UVA-PF determined for each and compared to the original. As expected, the researchers found that reducing the avobenzone concentration had the greatest effect on UVA-PF, though SPF suffered significant losses as well. Small losses of avobenzone ($\leq$20 %) had little effect on either SPF or UVA-PF. However, reductions of avobenzone concentrations of 33 % and 67 % resulted in the SPF declining from 51 to about 48 and 45, respectively, and the UVA-PF from about 18 to about 14 and 12, respectively. The formulation containing no avobenzone, which simulated a complete loss of the UVA filter due to photodegradation, achieved SPF 40 and UVA-PF 8.

To approximate the environment in human skin below the surface, Damiani and co-workers prepared liposomes containing pairs of UV filters and suspended them in saline. The suspensions were placed in the wells of cell culture plates and irradiated with UVA delivered by a commercial sun lamp. The total dose was calculated as equivalent to about 90 min of exposure on the French Riviera on a sunny summer day. The irradiated samples were collected, diluted with ethyl acetate, and centrifuged to recover the UV filters, after which UV absorption measurements were made and compared to non-irradiated controls. The photostable combinations paired avobenzone with bis-ethylhexyloxyphenol methoxyphenyl triazine (BEMT), methylene bis-benzotriazolyl tetramethylbutylphenol (MBBT), and diethylamino hydroxybenzoyl hexyl benzoate (DHHB). The combination with OC improved avobenzone's UVA absorption by 35 %, while the combinations with OMC and EHT showed the least photostability, losing most of their absorption throughout the entire UVA range. Combinations of OMC with BEMT, MBBT, DHHB, and EHT were photostable [23].

The oft-used combination of avobenzone and OMC was studied by Herzog and co-workers (2009). They prepared a sunscreen emulsion containing 3.4 % OMC and 2.4 % avobenzone and compared the amount of OMC recovered after irradiation with the amount recovered from the emulsion containing OMC alone. They noted a significant acceleration of OMC photodegradation when avobenzone was added and attributed the increase to the availability of a second pathway to a [2+2] cycloaddition (the first being the reaction of OMC with itself) stemming from the reaction of the enol form of avobenzone with OMC. On the other hand, adding OMC to avobenzone did not affect the amount of avobenzone recovered, indicating that the OMC-avobenzone reaction competed successfully with formation of avobenzone's keto form to reduce the pathway to the Norrish type I cleavage.

As of this writing, the FDA does not permit avobenzone to be combined with either TiO_2 or ZnO in sunscreens marketed in the USA [24]. Both combinations are permitted in many other venues throughout the world however. TiO_2 in particular is widely used in combination with organic UV filters.

Titanium dioxide exists naturally in three crystalline forms: rutile, anatase, and brookite. The TiO_2 grades used in sunscreens are made from rutile or anatase. Both forms are available in a range of particle sizes, from nano to micron. In general, the larger the particle size, the more whitening is the effect on the skin. Both TiO2 and ZnO are semiconductors with band gaps in the solar UV range. Absorption of a photon with energy equal to or greater than the band gap promotes an electron from the valance band to the conduction band, which creates an electron (−)/hole (+) pair. When this happens, molecules close to or adsorbed to the particle surface can interact with these charge carriers to become reduced (gain an electron) or oxidized (lose an electron). Because of this, these metal oxides have photocatalytic properties and can behave as either oxidant or reductant to generate reactive oxygen species (ROS) such as hydroxyl radicals (OH) and superoxide anion (O_2−). These ROS in turn can react with the organic components in sunscreens including UV filters, contributing to their degradation [25]. Of the TiO_2 crystalline forms, anatase is regarded as the more photocatalytically active [26]. For that reason, there have been recent calls to limit the TiO_2 in sunscreens to grades derived from rutile [27]. Commonly, though not always, the TiO_2 and ZnO grades used in sunscreens are passivated (rendered less reactive) by treating the surfaces of the particles with chemically inert substances such as silica, dimethicone, or aluminum hydroxide. Other surface treatments are used to improve the particles' oil or water dispersibility [28].

Kockler et al. studied the influence of TiO_2 particles size on the photostabilities of avobenzone and OC by preparing oil-in-water emulsions in which the avobenzone and OC were dissolved in the oil phase, and various grades of TiO_2 were dispersed in the water phase [29]. TiO_2 grades tested included a silica-coated rutile TiO_2 with a mean particle size of 119 nm, an uncoated anatase nano TiO_2 with mean particle size of 25 nm and an uncoated anatase micro TiO_2 with a mean particle size of 0.6 μm. Measured amounts of the emulsions were applied to glass plates and irradiated for 14.6 h at 400 W/m^2 in a xenon test chamber. After irradiation, solvent was used to extract residual emulsion from the plates, and the solutions were analyzed by HPLC. From the emulsions containing avobenzone alone or combined with coated, micro, and nano TiO2, recovery of avobenzone after irradiation ranged from 0 to 3.81 %. From the emulsion containing OC alone, or combined with coated, micro, and nano TiO2, recovery of OC ranged from 88.33 to 99.98 %. From the emulsions containing avobenzone and OC plus coated, micro, and nano TiO2, recovery of avobenzone was 16.0 %, 12.6 %, and 0.6 %, respectively, and recovery of OC was 98.2 %, 95 %, and 92.5 %, respectively. A separate experiment determined that neither avobenzone nor OC adsorb onto any of the TiO_2 particles' surfaces. The authors concluded that uncoated nano-TiO_2 is more deleterious to both avobenzone and OC than either micro or coated TiO_2.

Nguyen and Schlossman studied avobenzone photostability in dilute solutions in ethanol in the presence of various grades of TiO_2, coated and uncoated, and one untreated and four treated ZnO grades [30]. The ethanol solutions contained 0.04 % avobenzone and 4 % of metal oxide. Each sample was irradiated using a UV lamp for 1 week. Afterwards, each sample was centrifuged to remove the metal oxide from the solution, and the solution's UV absorption and transmittance were measured with a UV/Vis spectrophotometer. Both anatase and rutile forms of TiO_2 were tested. Primary particle sizes ranged from 15 nm to 300 nm. Surface treatments included octyltriethoxysilane, methicone, dimethicone, silica, aluminum stearate, and C9-15 fluoroalcohol phosphate. Among the anatase samples, the one treated with octyltriethoxysilane show the least negative effect, with 19 % of avobenzone's absorbance remaining after irradiation compared to <1 % for the other treatments. Among the first group of rutile samples, the one treated with methicone produced the best result with 38 % of avobenzone's absorbance remaining after irradiation compared to <1 % for the others. Among the second group of rutile samples, the one treated with silica (primary particle size 90 nm) was the best with 76 % of avobenzone's UV absorbance remaining after irradiation compared to 28 % and 3 % for the C9-15 fluoroalcohol phosphate and aluminum stearate treated samples, respectively. Among the ZnO samples tested, the two treated with silica fared the best, with avobenzone retaining 49 % and 18 % of its UV absorbance compared to <1 % and 3 % for the methicone- and silane-treated samples, respectively. The authors concluded that when combining avobenzone with TiO_2, rutile is superior to anatase. Also, surface-treated TiO2 and ZnO are better than uncoated TiO_2 and ZnO for limiting loss of avobenzone's absorbance following irradiation. They also noted that in this study, silica-treated TiO_2 proved to be superior to all other treated metal oxides tested for limiting loss of avobenzone's absorbance following irradiation.

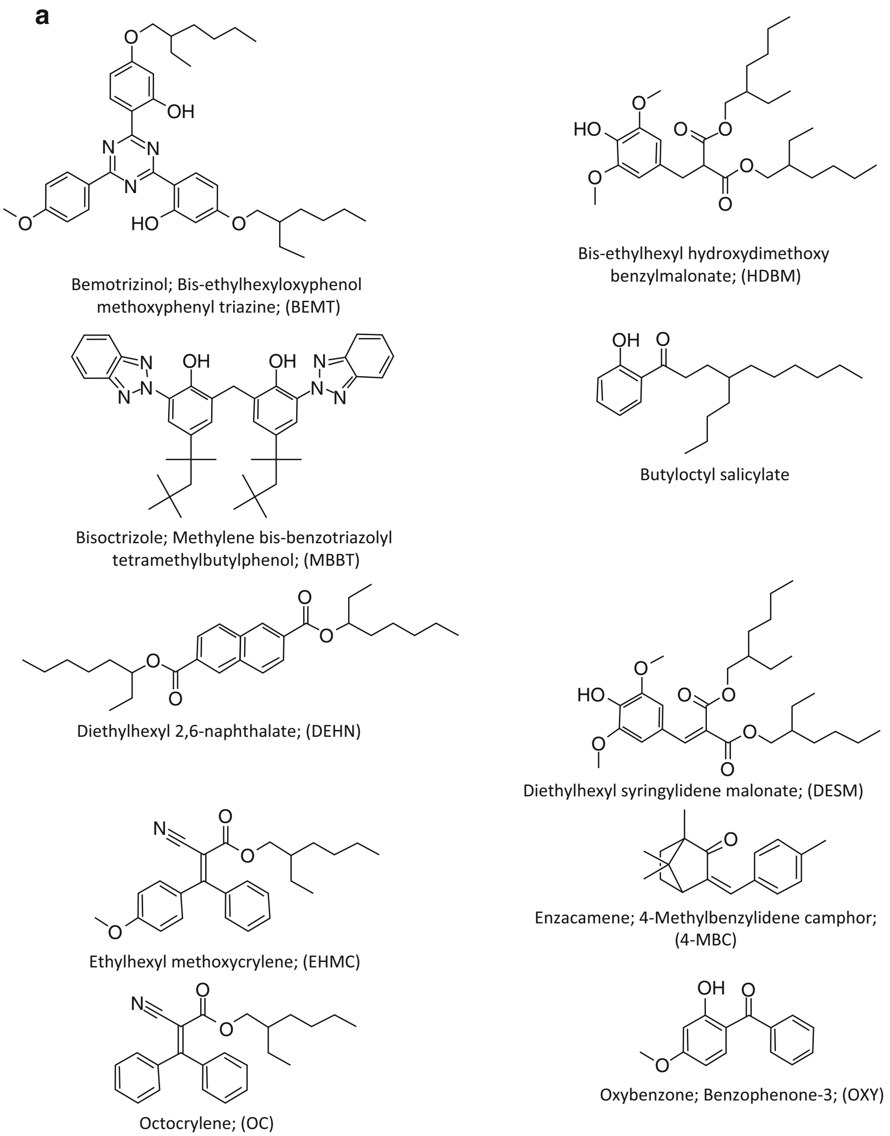
14.6 Photostabilizing Sunscreens

According to an Internet search conducted in November 2014, there are 12 photostabilizers in use in sunscreens somewhere in the world including three UV filters – BEMT, 4-MBC, and OC – that are known to have photostabilizing properties [31]. Of these, only OC is globally approved; the other two are not permitted for use in sunscreens in the United States. The molecular structures of the photostabilizers and other compounds discussed in this chapter may be found in Fig. 14.6.

Herzog et al. showed that one way to increase the photostability of a photolabile UV filter like avobenzone is to increase the optical density of the system, effectively increasing the competition for the same photons. The idea is that the fewer photons absorbed by the photolabile UV filter, the lower will be its photodegradation. They illustrated this by comparing ethanolic solutions of EHT of low and high optical density. After exposure to the same amount of radiation, the solution of lower density displayed a half-life of 61 min compared to 210 min for the solution of higher density. The authors note that this strategy is effective only in cases where increasing the optical density does not also increase the rate of bimolecular chemical reactions, as it does when OMC is added to avobenzone [19].

Herzog et al. also compared and contrasted OC, a photostable UVB filter that is known to quench avobenzone's triplet excited state [32], with BEMT, a broadband (UVA and UVB) UV filter [33]. They determined the quenching rate constants of OC and BEMT for avobenzone, finding that OC is about 2.5 times more efficient than BEMT in stabilizing avobenzone. The authors also concluded that BEMT's stabilizing effect may in part be due to competition with avobenzone for photons.

Another UV filter that has considerable overlap with avobenzone's absorption spectrum is oxybenzone (benzophenone-3). Mendrok-Edinger et al. reported that adding 2 % oxybenzone to 4 % avobenzone increases photostability to 80 % compared to 23 % without [34]. Since it is energetically unlikely that Oxybenzone quenches



Bemotrizinol; Bis-ethylhexyloxyphenol methoxyphenyl triazine; (BEMT)

Bis-ethylhexyl hydroxydimethoxy benzylmalonate; (HDBM)

Bisoctrizole; Methylene bis-benzotriazolyl tetramethylbutylphenol; (MBBT)

Butyloctyl salicylate

Diethylhexyl 2,6-naphthalate; (DEHN)

Diethylhexyl syringylidene malonate; (DESM)

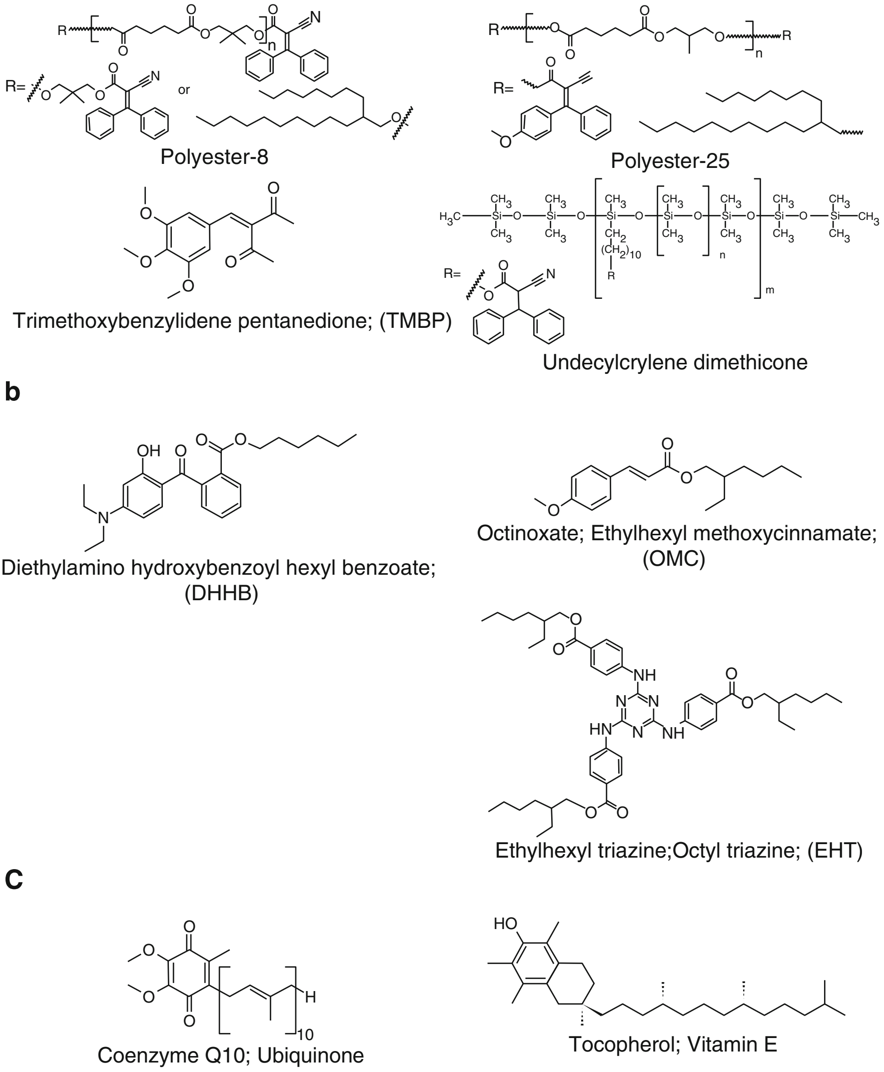
Ethylhexyl methoxycrylene; (EHMC)

Enzacamene; 4-Methylbenzylidene camphor; (4-MBC)

Octocrylene; (OC)

Oxybenzone; Benzophenone-3; (OXY)

Fig. 14.6 Key chemical compounds discussed in this chapter, identified by their USAN (when relevant), INCI name, and (abbreviation) as used in this chapter. (**a**) Photostabilizers including photostabilizing UV filters, (**b**) Other UV Filters, (**c**) Antioxidants



Polyester-8

Polyester-25

Trimethoxybenzylidene pentanedione; (TMBP)

Undecylcrylene dimethicone

Diethylamino hydroxybenzoyl hexyl benzoate; (DHHB)

Octinoxate; Ethylhexyl methoxycinnamate; (OMC)

Ethylhexyl triazine;Octyl triazine; (EHT)

Coenzyme Q10; Ubiquinone

Tocopherol; Vitamin E

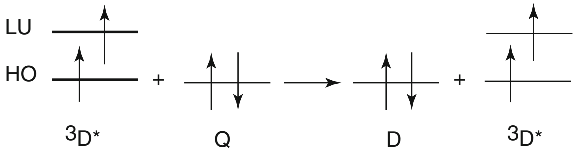
Fig. 14.6 (continued)

avobenzone triplets (using the measured triplet energy of 4-methoxybenzophenone as a proxy) [35], its competition for photons may explain the photostabilizing effect.

For excited state quenching to occur, the transfer of energy from excited UV filter to quencher must be energetically downhill (Turro et al., 2010, p. 385). That is, the excited state energy of the quencher must be lower than the excited state energy of the UV filter *for the same multiplicity* (singlet to singlet, triplet to triplet).

There are two common mechanisms by which an excited state donor (D) transfers energy to a ground state quencher (*Q*). The first is a dipole-dipole interaction (also known as “Coulombic” or “Förster” energy transfer) in which the electric field generated by the excited electron of the donor resonates with an electron of the quencher, essentially transferring the donor’s energy *through space* to the quencher (Turro et al., 2010, p. 399). Thus, the donor returns to the ground state, and the quencher is raised to the excited state. This mechanism diminishes with the inverse sixth power of the distance between donor and acceptor (Turro et al., 2010, p. 402). Energy transfer by the dipole-dipole mechanism is the mechanism most often responsible for singlet-singlet quenching.

The second mechanism is known as the electron exchange mechanism (also known as “Dexter” exchange). In this mechanism, the excited donor (^{3}D*) and quencher (*Q*) collide such that the donor exchanges its excited state electron for one of the quencher’s ground state electrons, returning the donor (D) to the ground state and elevating the quencher ($^3Q^*$) to the excited state. Energy transfer by the Dexter exchange mechanism is easily visualized as follows:



The Dexter exchange mechanism is the most common one for triplet-triplet quenching. The majority of photostabilizers on the market today (2014) function as quenchers of avobenzone’s triplet excited state.

OC has long been recognized as a triplet quencher for avobenzone. Mendrok-Edinger et al. (2009) reported that 3.6 % OC added to 4 % avobenzone in a sunscreen emulsion conferred 90 % photostability. Lhiaubet-Vallet et al. tested avobenzone alone and in combination with six other UV filters, measuring by HPLC the amount of avobenzone and UV filter recovered after irradiation for four hours (!) with a solar simulator. The UV filters tested were OMC, OC, BEMT, diethylamino hydroxybenzoyl hexyl benzoate (DHHB), EHT, and dioctyl butamido triazone (DBT). The combination of OC and avobenzone was the clear winner with 84 % of the avobenzone and 100 % of the OC recovered. Next was BEMT and avobenzone, with 72 % of the avobenzone and 96 % of the BEMT recovered. With no photostabilizer, only 41 % of the avobenzone was recovered [36].

Polyester-8 is a low molecular weight (ca. 1900 daltons) organic polymer that is terminated with cyanodiphenyl propenoic acid, the same chromophore as OC. According to its manufacturer, it retains OC’s ability to photostabilize avobenzone by a triplet quenching mechanism though with lower efficiency [37]. Undecylcrylene dimethicone (UCD) is a silicone polymer that also incorporates the OC chromophore. The manufacturer’s literature states that it “enhances the photostability of the UVA filter avobenzone by quenching its triplet excited state” [38].

Ethylhexyl methoxycrylene (EHMC) is a commercially available cosmetic ingredient that is marketed as a photostabilizer for avobenzone and other photolabile compounds [39]. Kikuchi and co-workers determined EHMC’s excited singlet and triplet state energies to be 72.3 kcal mol^{-1} and 55.5 kcal mol^{-1}, respectively [40]. These excited state energies are below those measured by Kikuchi et al. (2009 and 2010) for avobenzone (73.2 kcal mol^{-1} and 58.3 kcal mol^{-1}, respectively) and for OMC (85.49 kcal mol^{-1} and 55.75 kcal mol^{-1}, respectively), making the quenching of the singlet and triplet excited states of both compounds by EHMC energetically feasible. Researchers at the University of California-Riverside confirmed the ability of EHMC to quench avobenzone's singlet excited state. The researchers employed a streak scope (also known as a streak camera) to measure avobenzone's fluorescence lifetime in the absence and presence of varying concentrations of EHMC. At 10 mmol concentration of EHMC, the singlet excited state lifetime of avobenzone was reduced from 1.3×10^{-11} s to 1.86×10^{-12} s, shorter by about an order of magnitude [41].

Bonda et al. (2010) compared EHMC and OC to photostabilize the combination of avobenzone and OMC. The researchers prepared three solutions of 3 % avobenzone and 7.5 % OMC in ethyl acetate. One solution contained 3 % EHMC, one contained 3 % OC, and a third control solution contained no photostabilizer. The solutions were applied to PMMA plates and allowed to dry before they were irradiated with a solar simulator. After 25 MED, the control with no photostabilizer retained 44.5 % of its UVA absorbance compared to 53.9 % with 3 % OC and 83.7 % with 3 % EHMC.

4-Methylbenzylidene camphor (4-MBC; USAN Enzacamene) is a UV filter that functions as an avobenzone photostabilizer, almost certainly by a triplet quenching mechanism. Though not permitted in the USA, it has been used in Europe for decades at concentrations up to 4 %. Mendrok-Edinger et al. (2009) prepared a solution of 4 % 4-MBC and 4 % avobenzone which they applied to a roughened glass plate and then irradiated with 25 MED. Afterward, the plate was washed with solvent, and the resulting solution was analyzed by HPLC. Subsequently, 88 % of the avobenzone was recovered compared to 23 % from the solution containing no photostabilizer.

Another triplet quencher for avobenzone is diethylhexyl 2,6-naphthalate (DEHN) [42]. Mendrok-Edinger et al. (2009) found DEHN to be mildly effective. In their experiment, less than 50 % of avobenzone was recovered after 25 MED. Bonda and Steinberg reported that matched sunscreens containing 3 % avobenzone and either 0 % or 4 % DEHN were exposed to 10 MED of solar-simulated radiation and then analyzed on a UV transmittance analyzer. In the sunscreen without DEHN, UVB and UVA attenuation declined to 77 % and 64 %, respectively, while in the sunscreen with 4 % DEHN, UVB and UVA attenuation remained at 92 % and 91 %, respectively [43].

Polyester-25 is a low molecular weight polymer that is marketed as a photostabilizer for avobenzone [44]. Based on examination of its structural components, it would be expected to function mechanistically in a manner similar to EHMC.

A recent entry to the photostabilizer category is trimethoxybenzylidene pentanedione (TMBP) [45]. The manufacturer tested ethanol solutions containing 3 % avobenzone, 5 % octisalate, and 15 % homosalate to which was added either 4 % OC, 2 % DESM, or 2 % TMBP, measuring UVA absorption before and after irradiation. After 100 J/cm^2, the solution containing TMBP retained about 70 % of its UVA absorption compared to 60 % for OC and about 30 % for DESM.

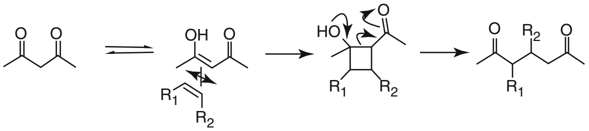
Another concept is to use antioxidants to photostabilize avobenzone. Afonso et al. investigated this strategy by combining ubiquinone (coenzyme Q-10) and tocopherol (vitamin E) at various ratios with avobenzone in model sunscreen emulsions [46]. They reported a 62.2 % increase in avobenzone photostability when avobenzone was combined with ubiquinone at a 2:1 ratio and a 15.3 % improvement when avobenzone was combined with tocopherol at a 1:2 ratio.

Bis-ethylhexyl hydroxydimethoxy malonate (HDBM) is marketed as an antioxidant that improves avobenzone photostability. According the manufacturer, HDBM's triplet energy is too high to quench avobenzone's triplet excited state. Rudolph et al. tested a solution of 2 % HDBM and 2 % avobenzone in isopropyl myristate which they spread on PMMA plate. The plate was irradiated in a xenon test chamber with the equivalent of 5 MED, after which the sample was extracted with solvent and the absorption of the solution measured. At 355 nm, the avobenzone peak, the sample lost 41 % of its absorbance compared to the control with 2 % avobenzone alone which lost 58 %. A structurally similar compound, DESM, was also tested. DESM is marketed by its manufacturer as both an antioxidant and a triplet quencher for avobenzone. After irradiation, the solution of 2 % DESM and 2 % avobenzone lost 29 % of its absorbance at 355 nm [47].

Butyloctyl salicylate was found by Mendrok-Edinger et al. (2001) to be moderately effective in photostabilizing avobenzone. When butyloctyl salicylate was added at 5 % to a 4 % avobenzone solution then irradiated with 25 MED, 50 % of the avobenzone was recovered compared to 23 % without butyloctyl salicylate. Excited state quenching by butyloctyl salicylate of avobenzone is energetically unfavorable and is therefore ruled out [48]. As a liquid phenol, butyloctyl salicylate, like other salicylate esters, is a protic solvent. Recalling that avobenzone is essentially photostable in protic solvents such as isopropanol, it is likely that the stabilizing effect on avobenzone is due to butyloctyl salicylate's proticity. This effect was previously reported by Bonda et al. (1997).

Sunscreens that combine avobenzone and OMC present a special challenge for photostabilization. Under exposure to UVR, avobenzone and OMC engage in a reaction known as the De Mayo reaction. The De Mayo reaction describes the reaction of an enol with an alkene to produce a [2+2] cycloaddition followed by a retro aldol cleavage [49]. The reaction usually proceeds through the excited enol. However, in the case of avobenzone and OMC, the reaction probably proceeds through the excited alkene, OMC. This view is supported by Kikuchi and Yagi who observed the intermolecular triplet-triplet energy transfer from avobenzone to OMC through measurements of EPR and time-resolved phosphorescence spectra [50]. First they noted that triplet-triplet energy transfer from avobenzone to OMC is energetically favorable because avobenzone's triplet energy ($E_{T1\ enol} = 58.3$ kcal mol^{-1}; $E_{T1\ keto} = 69.8$ kcal mol^{-1}) lies above that of OMC ($E_{T1} = 55.75$ kcal mol^{-1}), while avobenzone's singlet excited state ($E_{S1\ enol} = 73.2$ kcal mol^{-1}) lies below that of OMC ($E_{S1} = 85.5$ kcal mol^{-1}), thus ruling out singlet-singlet energy transfer.

Lhiaubet-Vallet et al. determined the bimolecular quenching rate constant of the methylated avobenzone analog, BM-DBM-Me by OMC to be 7.3×10^9 M^{-1} s^{-1}. For reference, the researchers also measured the bimolecular quenching rate constant by OC to be 3.8×10^9 M^{-1} s^{-1}. By inference from these findings, avobenzone efficiently transfers its triplet energy to OMC which elevates ground state OMC to its triplet excited state. OMC triplets then become the aggressive species in the previously described De Mayo reaction to photodegrade both compounds and produce photoproducts. OC's quenching rate constant, at only about half of OMC's, is not competitive.



The De Mayo reaction

Chatelain and Gabard (2001) studied the ability of BEMT to photostabilize the OMC-avobenzone combination, finding that BEMT exerted a protective effect on both UV filters. In sunscreens containing 5 % each of avobenzone and OMC, adding 5 % BEMT decreased photodegradation of OMC from about 65 % to about 48 % and photodegradation of avobenzone from 45 % to about 35 %. Photostabilizing the combination of OMC and avobenzone remains one of the great challenges in sunscreen formulating.

14.7 Testing Sunscreen Photostability

There are many ways to measure photostability. In this section we are concerned only with methods that measure the photostability of fully formulated sunscreen products as opposed to solvent systems that contain one or two UV filters.

One of the easiest methods to test sunscreen photostability is to monitor the change in transmission of an otherwise transparent plate (e.g., quartz or PMMA) that has been coated with the sunscreen being tested while it is being irradiated by UVR. In this method, the coated plate and suitable controls are placed in the path of the UV beam. Transmission is monitored by a detector in line with the beam but placed on the other side of the plate. The change in UV transmission seen by the detector may be quite rapid for a photolabile product. For example, if the output of the solar simulator is 150 MED/hour, the solar simulator is emitting approximately 0.042 MED per second or about 1 MED every 24 s. Theoretically, the initial output through the product covered plate would be 5 MED/hour for an SPF 30 sunscreen. The MED/hour would rapidly climb for a photolabile product as the sunscreen's ability to absorb UV rapidly declines. The advantage of this method is it is simple and fast. A second advantage is that it somewhat mimics the SPF test. The sunscreen product sees the same spectra in the photostability test as it does in the actual SPF test. If a product is seen to deteriorate rapidly in the photostability test, then essentially the product must be formulated with a heavier load of sunscreen actives than a photostable product would need to obtain the same SPF. The disadvantages of the test are that (1) the photostability of the product may be worse in sunlight than under the solar simulator; and (2) the test does not identify which ingredient or ingredients may be degrading.

A second method involves scanning a spot on a UV-transparent plate such as PMMA or quartz to which a sunscreen has been applied, then irradiating the plate and rescanning in the exact same spot. The scan should be made with a spectrophotometer designed for this application. Most companies in the industry use an instrument called a UV transmittance analyzer for this purpose. It is recommended that several scans in different locations on the plate be made. The irradiation source can be any device that emits UV energy. If a solar simulator is utilized, it is recommended that it has a beam sufficient to cover the entire plate. Of course, natural sunlight can be used as the UV source. In either case a radiometer or spectroradiometer is used to measure the amount of radiation employed. This method also has an advantage in that it is relatively simple. Another advantage is that a variety of irradiation sources can be utilized. Another advantage is that many of the spectrophotometers that are routinely used to test samples like this have software that will automatically calculate such things as SPF, critical wavelength, UVA-PF, etc. Yet another advantage is that the change in absorption at different wavelengths can be seen. This provides some guidance as to which UV filters might be degrading. For example avobenzone is the only UV filter approved in the USA with a maximum absorbance at around 360 nm. If a loss of absorption is greater around this wavelength, then it is reasonable to assume that the avobenzone is degrading. A major disadvantage of this method is, again, it only shows where loss of absorption occurs and does not identify each individual sunscreen.

In the next method, the sunscreen coating the plate is extracted with solvent after exposure to UVR and analyzed by HPLC in order to measure quantitatively the amount off each UV filter that remains. This method is much more precise than the previous two. It also has the advantage that both broad-spectrum UVR sources and natural sunlight can be used for irradiation.

Though this method supplies some of the best information concerning photostability, it does have one distinct disadvantage in that it requires development of a validated analytical method for each different UV filter combination that might be encountered. The difficulty here is that in HPLC the peaks for different compounds often overlap or obscure each other completely, making quantification impossible. To be meaningful, the peaks must be separated, which is a time and resource consuming process.

The fourth method is an in vivo one. As such it is perhaps the most revealing but also the most difficult to perform. It is similar to the previous (HPLC) method in that it involves assaying product to see which individual sunscreens degrade. A measured amount of a sunscreen product is applied to a human volunteer. After irradiation, the application site is washed with a suitable solvent (e.g., ethanol or isopropanol), and the resulting solution is analyzed by HPLC.

The result is a real-world evaluation of how a sunscreen product performs on the skin after UV exposure. A broad-spectrum UV source can be used for irradiation, but even better, natural sunlight can be used.

There are disadvantages. This method is difficult and requires the most skill of several disciplines to accomplish. The analytical method must be validated. The ability to swab most if not all of the available sunscreen from the skin must be validated. The ability to extract the sunscreen from the swab material must be validated. It requires trained clinical personnel to apply the product and monitor the subjects during all phases of the test. Institutional Review Board approval may be required before starting the test.

For additional detail and approaches to measuring sunscreen photostability, the reader is referred to Sayre et al. (2009) [51], Moyal et al. (2002) [52], and Ou-yang et al. (2010) [53].

Before concluding, we offer a few words about light (radiation) sources:

A number of published studies have found that, both theoretically and experimentally, solar simulators differ from each other in the SPF they provide and that even solar simulators that comply with regulatory standards may not provide the same SPF as natural sunlight [54–58]. Whether or not this is due to differences in photostability in natural sunlight compared to artificial sunlight is an open question. Gonzalez et al. (2007) report a case in which photostability of a sunscreen was greater in natural sunlight than in artificial sunlight. On the other hand, Lott contends in his patent titled "Natural Sunlight Photostable Composition" (US 7,309,481) that "…wavelengths present in natural sunlight that are missing in the artificial spectra, or are present in much less relative amounts than in natural sunlight, are responsible (at least in part) for degradation reactions in many sunscreens."

14.8 Summary and Conclusion

The organic UV filters in sunscreens are photochemicals that absorb the energy in ultraviolet radiation (UVR) by converting it to electronic excitation energy. At a molecular level, this is understood as the promotion of a single electron in an outer or valence orbital from its lowest energy state to a previously unoccupied orbital of higher energy, referred to as the excited state. Subsequently if physical processes drain the excess energy so that all of the molecules of the compound return unchanged to the ground state, then the compound is photostable. If, however, the excess energy fuels chemical processes that change some or all of the molecules, the compound is photolabile. Photolabile compounds lose effectiveness as UV absorbers as they are exposed to UVR. So it is with some of the organic chromophores contained in sunscreens and, therefore, with sunscreens themselves.

As recognition of the skin-damaging effects of UVA radiation has grown, sunscreen scientists and photochemists have increasingly turned their attention to understanding avobenzone, still the only effective organic UVA protectant approved worldwide. Today, after 20 years of study, a comprehensive (though still incomplete) picture of avobenzone's complex photochemistry has emerged. In a nutshell, UVR exposure induces fragmentation and radical formation in a dose-related manner. Exactly how this happens is not yet fully understood. What is known is that avobenzone photodegradation is mitigated or curtailed by combining it with compounds that quench its excited states. When combining avobenzone with TiO_2 or ZnO, coated is better than uncoated, and rutile is better than anatase.

All UV filters have been shown to be photolabile to some degree, though under conditions of actual use, many can be considered to be photostable. In contrast, the most widely use UVB filter in the world, OMC, is relatively photostable when tested at low concentration in ethanol, but quite photolabile when tested at realistic concentrations and in formulated products. When OMC and avobenzone are combined, UVR catalyzes a photochemical reaction that degrades both compounds, a result that continues to vex sunscreen formulators and for which no complete "cure" has yet been found though both BEMT and EHMC have been reported to help.

A number of photostabilizers have been developed that are more or less effective at preserving avobenzone from photodegradation. Protic solvents help, as does increasing optical density. The best photostabilizers quench avobenzone's excited states. Most of these are triplet quenchers; one has been shown to quench avobenzone's singlet excited state.

Testing sunscreen photostability is straightforward: a measured amount of product is placed on a substrate and analyzed before and after exposure to UVR and the results compared. Ideally, the sun would serve as the radiation source. As a practical matter, solar simulators must suffice for the foreseeable future.

The saga of sunscreen photostability has already produced a lasting dual legacy: for consumers, the widespread availability in much of the world of photostable sunscreens, and among sunscreen scientists, a new and deeper understanding of sunscreen photochemistry. Just as the former promises better health for millions, the latter portends a future of continual improvement in skin photoprotection.

References

1. Polefka TG, Meyer TA, Agin PP, Bianchini RJ (2012) Effects of solar radiation on the skin. J Cosmetic Dermatol 11:134–143
2. Bonda C, Hu R, Jockusch S (2014) Avobenzone photochemistry: improving photoprotection by stabilizing avobenzone with ethylhexyl methoxycrylene. HPC Today 9:6–10
3. Dondi D, Albini A, Serpone N (2006) Interactions between different solar UVB/UVA filters contained in commercial suncreams and consequent loss of UV protection. Photochem Photobiol Sci 5:835–843
4. http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/over-the-counterotcdrugs/statusofotcrulemakings/ucm072134.htm
5. Turro NJ, Ramamurthy V, Scaiano JC (2009) Principles of molecular photochemistry: an introduction. University Science Books, Sausalito

6. Schwack W, Rudolph TJ (1995) Photochemistry of dibenzoy methane UVA filters – part 1. Photochem Photobiol B Biol 28:229–234
7. Andrae I, Bringhen A, Bohm F, Gonzenbach H, Hill T, Mulroy L, Truscott TG (1997) A UVA filter (4-*tert*-butyl-4'-methoxydibenzoylmethane): photoprotection reflects photophysical properties. J Photochem Photobiol B Biol 37:147–150
8. Cantrell A, McGarvey DJ (2001) Photochemical studies of 4-*tert*-butyl-4' methoxydibenzoylmethane (BM-DBM). J Photochem Photobiol B Biol 64:117–122
9. Hill TJ (1994) Molecular mechanisms of photoprotection. PhD thesis, Keele University
10. Huong SP, Rocher E, Fourneron J-D, Charles L, Monnier V, Bun H, Andrieu V (2008) Photoreactivity of the sunscreen butylmethoxydibenzoylmethane (DBM) under various experimental conditions. J Photochem Photobiol A Chem 196:106–112
11. Bonda CA, Marinelli PM, Trivedi J, Hopper S, Wentworth G (1997) Avobenzone Photostability in Simple Polar and Non-Polar Solvent Systems. Presentation made to the Society of Cosmetic Chemists Annual Scientific Seminar, Seattle
12. Mturi GJ, Martincigh BS (2008) Photostability of the sunscreening agent 4-*tert*-butyl-4'-methoxydibenzoylmethane (Avobenzone) in solvents of different polarity and proticity. J Photochem Photobiol A Chem 200:410–420
13. Yamaji M, Kida M (2013) Photothermal tautamerization of a UV sunscreen (4-tert-butyl-4'-methoxydibenzoylmethane) in acetonitrile studied by steady-state and laser flash photolysis. J Phys Chem A 117:1946–1951
14. Kikuchi A, Oguchi N, Yagi M (2009) Optical and electron paramagnetic resonance studies of the excited states of 4-tert-butyl-4'-methoxydibanzoylmethane and 4-tert-butyl-4'-methoxydibenzoylpropane. J Phys Chem A 113:13492–13497
15. Bonda C, Pavlovic A, Hansen K, Bardeen C (2009) Singlet quenching proves faster is better for photostability. Cosm Toil 125:40–48
16. Tarras-Wahlberg N, Stenhagen G, Larko O, Rosen A, Wennberg A-M, Wennerstrom O (1999) Changes in ultraviolet absorption of sunscreens after ultraviolet irradiation. J Invest Dermatol 113:547–553
17. Schrader A, Jakupovic J, Baltes W (1994) Photochemical studies on trans-3-methylbutyl 4-methoxycinnamate. J Soc Cosm Chem 45:43–52
18. Couteau C, Faure A, Fortin J, Paparis E, Coiffard LJM (2007) Study of the photostability of 18 sunscreens in creams by measuring the SPF in vitro. J Pharm Biomed Anals 44:270–273
19. Herzog B, Wehrle M, Quass K (2009) Photostability of UV absorber systems in sunscreens. Photochem Photobiol 85:869–878
20. SaNogueira J, Lott DL (2007) Letter to FDA with comments to proposed sunscreen monograph. http://www.regulations.gov/#!documentDetail;D=FDA-1978-N-0018-0652
21. SaNogueira J, Lott DL (2008) Letter to FDA with supplement to comments to proposed sunscreen monograph. http://www.regulations.gov/#!documentDetail;D=FDA-1978-N-0018-0653
22. Beasely DG, Meyer TA (2010) Characterization of the UVA protection provided by avobenzone zinc oxide, and titanium dioxide in broad-spectrum sunscreen products. Am J Clin Dermatol 11(6):413–421
23. Damiani D, Baschong W, Greci L (2007) UV-filter combinations under UV-a exposure: concomitant quantification of over-all spectral stability and molecular integrity. J Photochem Photobiol B Biol 87:95–104
24. Federal Register/Vol. 64, No. 98/Friday, May 21, 1999/Rules and Regulations/Part 352-Sunscreen drug products for over-the-counter human use/subpart B-active ingredients/§352.20 permitted combinations of active ingredients
25. Lewicka ZA (2009) The characteristics of nanoscale sunscreen particles. Thesis submitted for Master of Science degree, Rice University
26. Luttrell T, Halpegamage S, Tao J, Kramer A, Sutter E, Batzill M (2014) Why is anatase a better photocatalyst than rutile? – Model studies on epitaxial TiO2 films. Sci Rep 4:4043
27. Turci F, Peira E, Corazzari I, Fenoglio I, Trotta M, Fubini B (2013) Crystalline phase modulates the potency of nanometric TiO2 to adhere to and perturb the stratum corneum of porcine skin under indoor light. Chem Res Toxicol 26:1579–1590

28. Carlotti ME, Ugazio E, Sapino S, Fenoglio I, Greco G, Fubini B (2009) Role of particle coating in controlling skin damage photoinduced by titania nanoparticles. Free Radic Res 43:312–322
29. Kockler J, Oelgemoller M, Robertson S, Glass BD (2014) Influence of titanium dioxide particle size on the photostability of the chemical UV-filters butyl methoxy dibenzoylmethane and octocrylene in a microemulsion. Cosm 1:128–139
30. Nguyen U, Schlossman D (2001) Stability study of Avobenzone with inorganic sunscreens. Poster Presentation at the Annual Scientific Meeting of the Society of Cosmetic Chemists, New York
31. http://www.justaboutskin.com/sun-protection-guide/how-to-evaluate-uva-protection/sunscreen-active-ingredients/sunscreen-photostabilizers/www.merck-performance-materials.com; www.sytheonltd.com; www.personal-care.basf.com
32. Gonzenbach H, Hill TJ, Truscott TG (1992) The triplet energy levels of UVA- and UVB-sunscreens. J Photochem Photobiol B Biol 16:377–379
33. Chatelain EB, Gabard B (2001) Photostabilization of butyl methoxydibenzoylmethane (avobenzone) and ethylhexyl methoxycinnamate by bis-ethylhexyloxyphenol methoxyphenyl triazine (tinosorb S), a new broadband filter. Photochem Photobiol 74:401–406
34. Mendrok-Edinger C, Smith K, Janssen A, Vollhardt J (2009) The quest for stabilizers and sunscreen photostability. Cosm Toil 124(2):47–54
35. Lin Z-P, Aue WA (1999) Triplet-state energies and substituent effects of excited aroyl compounds in the gas phase. Spectrochimica Acta Part A 56:111–117
36. Lhiaubet-Vallet V, Marin M, Jimenez O, Gorchs O, Trullas C, Miranda MA (2010) Filter-filter interactions. Photostabilization, triplet quenching and reactivity with singlet oxygen. Photochem Photobiol Sci 9(4):552–558
37. HallStar Product Information Sheet PC11030 (2011) http://www.in-cosmeticsasia.com/__novadocuments/15139?v=634826419407530000
38. HallStar Product Information Sheet PC1A054 (2011) http://www.in-cosmeticsasia.com/__novadocuments/15140?v=634826420506970000
39. HallStar Product Information Sheet PC1H044 http://www.hallstar.com/pis.php?product=1h044
40. Kikuchi A, Hata Y, Kumasaka R, Yagi M (2013) Photoexcited singlet and triplet states of a UV absorber ethylhexyl methoxycrylene. Photochem Photobiol 89:523–528
41. Bonda C, Pavlovic A, Hansen K, Bardeen C (2010) Singlet quenching proves faster is better for photostability. Cosme Toil 125:40–48
42. Bonda CA, Marinelli PJ, Hessefort YZ, Trivedi J, Wentworth G (1999) U.S. Patent No 5,993,789
43. Bonda C, Steinberg D (2000) A new photostabilizer for full spectrum sunscreens. Cosm Toil 115:37–45
44. HallStar Product Information Sheet PC11031 (2013) http://www.hallstar.com/pis.php?product=11031
45. Sytheon brochure for Synoxyl HSS. Available online at http://www.in-cosmetics.com/__novadocuments/46438?v=635285132501130000
46. Afonso S, Horita K, Silva e Sousa JP, Almeida IF, Lobao PA, Costa PC, Miranda MS, da Esteves Silva JCG, Sousa Lobo JM (2014) Photodegradation of avobenzone: stabilization effect of antioxidants. J Photochem Photobiol B Biol 140:36–40
47. Rudolph T, Pan J, Scheurich R, Pfluecker F, Graf R, Epstein H (2009) Superior two step approach to completely photoprotect Avobenzone with a designed organic redox pair. SOFW J 135(9):14–19
48. Massaro RD, Blaisten-Barojas E (2011) Theoretical investigation of the photophysics of methyl salicylate isomers. J Chem Phys 135:164306
49. http://www.rocheresearchgroup.com/wp-content/uploads/2011/06/DeMayo_ReactionSR.pdf
50. Kikuchi AM, Yagi M (2011) Direct observation of the intermolecular triplet-triplet energy transfer from UV-a absorber 4-tert-butyl-4’-methoxydibanzoylmethane to UV-B absorber octyl methoxycinnamate. Chem Phys Let 513:63–66

51. Sayre RM, Dowdy JC, Stanfield JW (2009) In vitro sunscreen transmittance measurement with concomitant evaluation of photostability: evolution of a method. Photochem Photobiol 85(4):1038–1040
52. Moyal D, Refregier JL, Chardon A (2002) In vivo measurement of the photostability of sunscreen products using diffuse reflectance spectroscopy. Photodermatol Photoimmunol Photomed 18:14–22
53. Ou-yang HJ, Stanfield JC, Cole CY, Appa Y (2010) An evaluation of ultraviolet a protection and photostability of sunscreens marketed in Australia and New Zealand. Photodermatol Photoimmunol Photomed 26:336–337
54. Sayre RM, Dowdy JC (2010) The FDA proposed solar simulator versus sunlight. Photochem Photobiol Sci 9:535–539
55. Sayre RM, Stanfield JW, Bush A, Lott D (2001) Sunscreen standards tested with differently filtered solar simulators. Photoderm Photoimmunol Photomed 17:278–283
56. Uhlmann B, Mann T, Gers-Berlag H, Sauermann A (1996) Consequences for sun protection factors when solar simulator spectra deviate from the spectrum of the sun. Inter J Cosm Sci 18:13–24
57. Young A, Boles J, Herzog B, Osterwalder U, Baschong W (2010) A sunscreen's labeled sun protection factor may overestimate protection at temperate latitudes: a human in vivo study. J Invest Dermatol 130:2457–2462
58. Lott D (2013) Testing SPF15-100, indoor vs outdoor. Cosm Toil 9:638–647