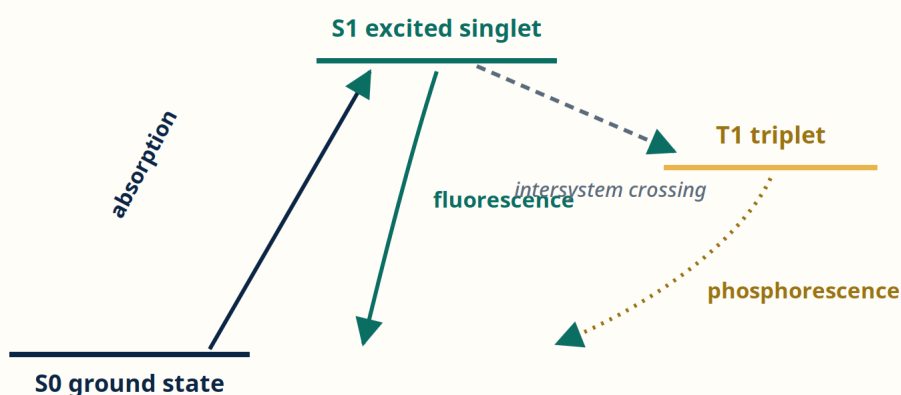


3.1 Basic principles of photochemical reactions

Where the photon energy goes: the Jablonski diagram



Chemistry happens mainly from S1 and the long lived T1.

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Figure: The Jablonski diagram: absorption reaches S1; fluorescence returns directly, while intersystem crossing reaches the long lived triplet T1, home of much photochemistry.

A photochemical reaction is driven by the energy of an absorbed photon rather than by heat. Two classical laws frame the subject. The **Grotthuss-Draper law** states that only light actually absorbed by a molecule can cause it to react; transmitted or scattered light does nothing. The **Stark-Einstein law** states that each absorbed photon activates one molecule in the primary step. The energy carried by one mole of photons is large by chemical standards: at 300 nm it is about 400 kJ per mole, comparable to the strength of the bonds being broken, which is why photochemistry reaches reactive states (excited singlets and triplets, radicals, carbenes) that thermal chemistry cannot. The efficiency of the overall change is the **quantum yield**, molecules reacted per photon absorbed; it can be far below one (most excitation is wasted as heat or light) or far above one (a radical chain reaction, where one photon starts a chain that consumes many molecules).

What happens after absorption is mapped on a **Jablonski diagram**. A molecule in its ground singlet state (S0) absorbs a photon and reaches an excited singlet (S1, S2), with the spin of the promoted electron unchanged. It can fall back by emitting fluorescence, lose energy internally as heat (internal conversion), or undergo **intersystem crossing** to the triplet state (T1), in which the promoted electron's spin has flipped. The triplet lives much longer (it returns to S0 only slowly, sometimes emitting phosphorescence), so most bimolecular photochemistry, and nearly all synthetic photochemistry, happens from triplets, often reached indirectly by **sensitisation**: a sensitizer such as benzophenone absorbs the light and transfers its triplet

energy to the substrate. The practical consequence is that light gives the chemist a reagent of precise energy, switched on and off instantly, leaving no residue, which is why photochemical steps have become attractive in green process chemistry and in flow reactors, where thin channels let light penetrate the whole reaction volume.

3.2 Photo-oxidation

Photo-oxidation chemistry is dominated by **singlet oxygen**, an excited state of oxygen (written $^1O_2$) generated when a triplet sensitizer (rose bengal, methylene blue, tetraphenylporphyrin) transfers its energy to ordinary ground state triplet oxygen. Singlet oxygen is a selective, electrophilic oxidant with three characteristic reactions:

- **The ene reaction:** an alkene with an allylic hydrogen gives an allylic hydroperoxide with the double bond shifted. The industrial oxidation of citronellol to a hydroperoxide on the way to rose oxide, and the key step of the artemisinin semi-synthesis (the ene reaction of dihydroartemisinic acid with singlet oxygen, followed by acid-catalysed Hock cleavage and cyclisation) are the textbook examples.
- **[2+2] cycloaddition:** electron-rich alkenes such as enol ethers give 1,2-dioxetanes, unstable four-membered peroxides that cleave to two carbonyl fragments, sometimes with emission of light (chemiluminescence).
- **[4+2] cycloaddition:** conjugated dienes give endoperoxides; the classic case is alpha-terpinene to ascaridole, one of the oldest known photochemical syntheses.

Photo-oxidation by electron transfer rather than by singlet oxygen also exists, particularly with strongly oxidising excited photocatalysts, and aerobic photoredox oxidation has become a modern extension of the same idea.

3.3 Photo-addition

In photo-addition, an excited molecule adds across a pi system in a way that the ground state forbids. The flagship reaction is the **[2+2] photocycloaddition** of two alkenes to a cyclobutane: thermally forbidden (section 3.6), photochemically routine. Enones are the most used partners, adding to alkenes through their triplet state; run intramolecularly, the reaction builds strained polycyclic skeletons rapidly, a strategy used in classic syntheses of cage and cyclobutane-containing natural products. The **Paterno-Buchi reaction** is the carbonyl analogue: an excited aldehyde or ketone adds to an alkene to give an oxetane, a four-membered oxygen ring that is itself a valuable intermediate and a motif in medicinal chemistry. Alkenes also add to excited benzene rings (the meta photocycloaddition), a reaction Wender used to build the tricyclic core of the sesquiterpene alpha-cuparenone in a single step. Photo-addition illustrates the general principle of this unit: photochemistry does not merely accelerate thermal reactions, it runs reactions whose orbital symmetry makes them impossible in the ground state.

3.4 Photo-fragmentation

Excited carbonyl compounds also break apart, in two patterns named for Ronald Norrish:

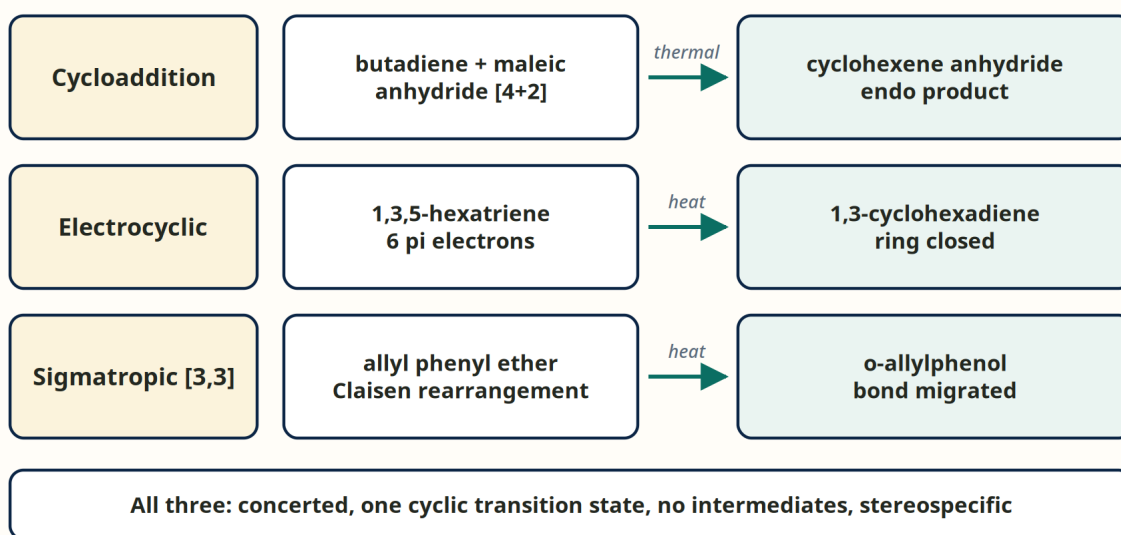
- **Norrish Type I reaction:** the bond between the carbonyl carbon and an alpha carbon cleaves (alpha cleavage) to give an acyl radical and an alkyl radical. The radicals can recombine, lose carbon monoxide (decarbonylation), or abstract hydrogen; in cyclic ketones the cleavage opens the ring to a biradical that closes to an aldehyde or ketene product.
- **Norrish Type II reaction:** the excited carbonyl oxygen abstracts a hydrogen from the gamma carbon through a six-membered transition state (possible because the excited oxygen behaves like an alkoxy radical), giving a 1,4-biradical. The biradical either cleaves between the alpha and beta carbons,

producing an alkene and an enol that tautomerises to a ketone, or cyclises to a cyclobutanol (the Yang cyclisation).

The **Barton reaction** is a designed fragmentation of the same family: photolysis of a nitrite ester breaks the weak O-N bond to an alkoxy radical, which performs a precise 1,5-hydrogen abstraction from a delta carbon; capture of the resulting carbon radical by nitric oxide and hydrolysis installs a hydroxyl-derived oxime at an otherwise unreachable, unactivated position. Barton used it to functionalise the angular methyl group in the synthesis of aldosterone, a demonstration that photochemistry could do surgery on a steroid skeleton where no conventional reagent could reach. Photolysis more generally is the standard route to carbenes and nitrenes from diazo compounds and azides (compare MPC102T, Unit 1) and to radicals from peroxides and halogen compounds.

3.5 Pericyclic reactions: the family and its rules

The three pericyclic families



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Figure: Cycloaddition, electrocyclic and sigmatropic reactions: three families, one shared pericyclic mechanism through a cyclic transition state.

A **pericyclic reaction** is a concerted reaction in which the bonds break and form simultaneously through a single cyclic transition state, the electrons moving in a closed loop. There are no intermediates, ionic or radical, and the reactions are characteristically **stereospecific**: the stereochemistry of the reactants maps predictably onto the products. Whether a pericyclic reaction can proceed thermally is decided by orbital symmetry, summarised in the **Woodward-Hoffmann rules**: a thermal pericyclic reaction is allowed when the number of suprafacial ($4q + 2$) electron components and antarafacial ($4r$) electron components in the transition state totals an odd number. In practice the student applies three memorised selection rules, one per family, set out in the sections below and the closing table. The three syllabus families are cycloadditions, electrocyclic reactions and sigmatropic rearrangements; two relatives, the ene reaction and cheletropic reactions (such as the extrusion of sulfur dioxide from a sulfone), complete the family picture.

3.6 Cycloaddition reactions

In a **cycloaddition**, two (or more) pi systems combine to form a ring, two new sigma bonds appearing at the expense of two pi bonds. The notation counts the pi electrons of each partner: the Diels-Alder reaction is a [4+2] cycloaddition. The **Diels-Alder reaction** between a conjugated diene and a dienophile (an

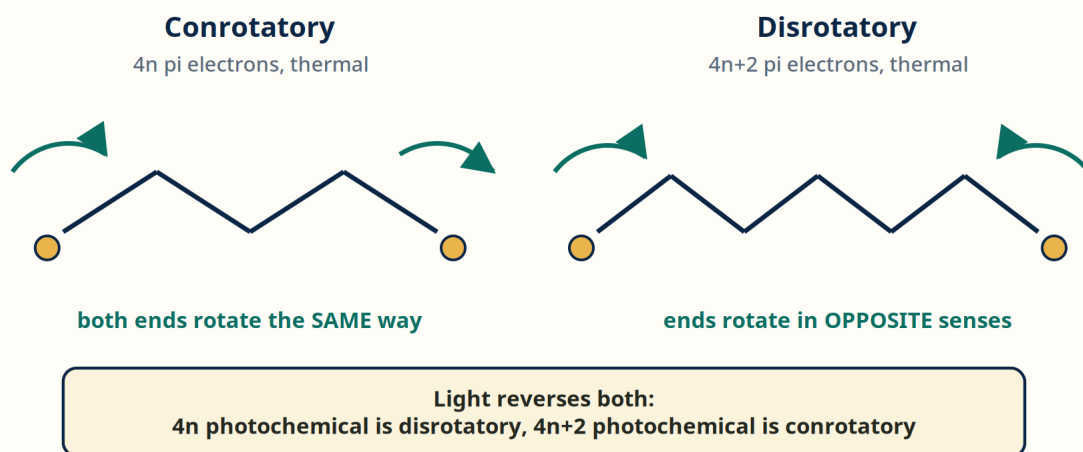
alkene, made more reactive by electron withdrawing groups in the normal electron demand version) is governed by rules a drug chemist uses constantly:

- The diene must adopt the s-cis conformation; locked s-cis dienes such as cyclopentadiene are exceptionally reactive.
- The reaction is stereospecific: substituents cis on the dienophile stay cis in the product (the cis principle), and the diene geometry is likewise preserved.
- The **endo rule**: the preferred transition state places the dienophile's substituents under the diene's pi system, giving the endo product, although the exo product is usually more stable; the preference is attributed to secondary orbital interactions and disappears when the reaction is run long enough to become reversible.
- Regiochemistry follows matching of the largest frontier orbital coefficients: electron donating groups on the diene and electron withdrawing groups on the dienophile reinforce so that the substituents emerge ortho or para to each other.
- The retro-Diels-Alder reaction, run on heating, unmask dienes (cyclopentadiene is cracked from its dimer before use) and serves as a thermal protecting strategy for double bonds.

1,3-Dipolar cycloadditions are the other great family: a 1,3-dipole (azide, nitrile oxide, diazo compound, ozone) adds across a multiple bond to give a five-membered ring. The azide-alkyne cycloaddition to a triazole, made perfectly regioselective by copper catalysis (click chemistry), is now a standard bond construction in drug discovery; the first step of ozonolysis (MPC102T) is a 1,3-dipolar cycloaddition of ozone to an alkene.

3.7 Electrocyclic reactions

Conrotatory and disrotatory: how the ends rotate



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Figure: In conrotatory closure both termini rotate the same way; in disrotatory closure they rotate in opposite senses. The Woodward-Hoffmann rules choose between them.

An **electrocyclic reaction** interconverts a conjugated polyene and a cyclic isomer with one fewer double bond: one pi bond is traded for a sigma bond and a ring (opening runs the same road backwards). The stereochemical signature is the way the terminal carbons rotate as the sigma bond forms: **conrotatory** (both termini rotate in the same sense) or **disrotatory** (opposite senses). The selection rule turns on the number of pi electrons:

- Systems with $4n$ pi electrons (butadiene, 4): thermal reactions are conrotatory, photochemical reactions disrotatory.
- Systems with $4n + 2$ pi electrons (hexatriene, 6): thermal reactions are disrotatory, photochemical reactions conrotatory.

The consequences are exact: thermal conrotatory closure of (2E,4Z)-hexa-2,4-diene gives cis-3,4-dimethylcyclobutene, while the (2E,4E) isomer gives the trans cyclobutene, and no change of conditions can swap these outcomes, because the forbidden mode would require the molecule to break the orbital symmetry rule. Nature and medicine use the 6 pi version: the photochemical disrotatory ring opening of 7-dehydrocholesterol in skin gives previtamin D, the first step of vitamin D synthesis, a pericyclic reaction every student has personally performed.

3.8 Sigmatropic rearrangements

A **sigmatropic rearrangement** migrates a sigma bond across a pi framework: the bond breaks at one position and forms at another, with the pi bonds reorganising around it, all in one concerted step. Reactions are labelled $[i,j]$ by counting the atoms on each side of the migrating bond. The rules of allowedness mirror the electrocyclic ones; thermally, $[1,5]$ hydrogen shifts are allowed suprafacially and are fast and common (cyclopentadiene scrambles its hydrogen this way, which is why all its ring positions become equivalent), while $[1,3]$ hydrogen shifts are effectively forbidden because the required geometry cannot be reached.

The workhorse examples are the **$[3,3]$ rearrangements**:

- **Cope rearrangement**: a 1,5-diene rearranges to its isomeric 1,5-diene through a chair-like transition state; substituent effects and ring strain can drive it completely to one side. The **oxy-Cope** variant (a hydroxyl group at the 3 position) is faster, and its anionic version, with the alkoxide formed by strong base, is faster by many orders of magnitude and ends in an enolate that is protonated to a carbonyl compound.
- **Claisen rearrangement**: an allyl vinyl ether, or in its aromatic form an allyl phenyl ether, rearranges to a gamma,delta-unsaturated carbonyl compound or an ortho-allyl phenol respectively; the aromatic Claisen (Claisen, 1912) is the standard way to install an ortho allyl group on a phenol, and further cyclisation of the product builds the benzopyran ring systems of many natural products. The Ireland-Claisen variant rearranges silyl ketene acetals of allyl esters and sets two stereocentres predictably through its chair transition state.
- **$[2,3]$ -Wittig rearrangement**: an allylic ether deprotonated beside oxygen migrates so that the bond from oxygen shifts from the 1 to the 3 position of the allyl system, giving a homoallylic alcohol with useful stereocontrol.

Biochemistry runs the same reactions: the conversion of chorismate to prephenate on the shikimate pathway (used by bacteria and plants to make aromatic amino acids, and absent in humans, which is why the pathway is an antimicrobial target) is an enzymatic Claisen rearrangement.

Pericyclic family	What changes	Thermal rule	Photochemical rule	Classic example
Cycloaddition [4+2]	Two pi systems form a ring	Allowed suprafacial-suprafacial ($4n$ plus 2 total pi electrons)	Generally requires one component excited; [2+2] becomes allowed	Diels-Alder; [2+2] photoaddition
Electrocyclic, $4n$ pi electrons	Polyene to ring	Conrotatory	Disrotatory	Butadiene to cyclobutene

Pericyclic family	What changes	Thermal rule	Photochemical rule	Classic example
Electrocyclic, $4n$ plus 2 pi electrons	Polyene to ring	Disrotatory	Conrotatory	Hexatriene to cyclohexadiene; vitamin D ring opening
Sigmatropic [1,5]-H	Sigma bond migrates	Allowed suprafacial	Not normally used	Cyclopentadiene hydrogen scrambling
Sigmatropic [3,3]	Sigma bond migrates across two allyl units	Allowed, chair-like transition state	Not normally used	Cope and Claisen rearrangements

Identifying a pericyclic reaction and predicting its mode

Does a sigma bond migrate across a pi system with no ring size change?

-> sigmatropic: count the atoms each side for the [i,j] label

Do two pi components join into a ring (or a ring break into two)?

-> cycloaddition: add the pi electrons; 6 electron [4+2] is thermal, 4 electron [2+2] needs light

Does one chain cyclise (or a ring open) with one pi bond traded for sigma?

-> electrocyclic: count pi electrons; $4n$ thermal conrotatory, $4n$ plus 2 thermal disrotatory, and light reverses both

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