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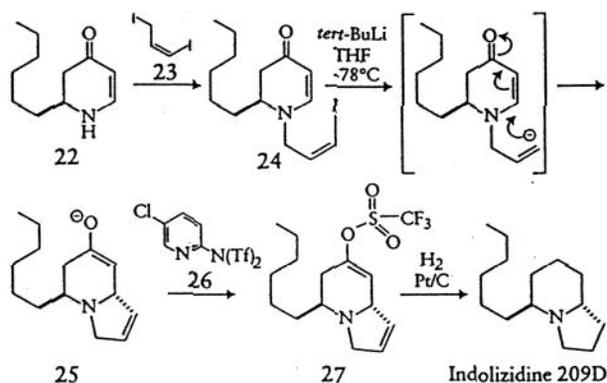


Fig. 9. Reactive path from vinylogous amide to vinyl triflate.

Cope pericyclic reaction to give the alkenylcycloheptadiene 18. In Figure 8 the vinyl bromide 19 is metalated (converted by an organolithium to a vinyl anion). The vinyl anion reacts immediately by intramolecular addition to the ketone to give a product (21) related to the highly fragrant patchouli alcohols. In Figure 9 the vinylogous amide 22 undergoes *N*-alkylation by the diiodoalkene 23. This diiodoalkene has both vinyl iodide and allyl iodide functional groups: the vinyl iodide is completely unreactive to nucleophiles, while the allyl iodide is highly reactive, reacting at the nitrogen to give 24. The very poor reactivity of vinyl halides toward nucleophiles is a consequence of the greater electronegativity of the  $sp^2$  hybridization, which destabilizes the accumulation of negative charge on the halide that must occur in the transition state for nucleophilic displacement. Following metalation, vinyl iodide 23 undergoes intramolecular conjugate addition to give enolate 25, which is trapped by the triflate donor 26 to give the vinyl triflate 27. Catalytic hydrogenation reduces the alkene and vinyl triflate functional groups to complete a synthesis of the indolizidine 209D, one of several structurally related neurotoxins secreted by the neotropical poison dart frogs. In Figure 10, the enolate of the methoxy enone 28 is trapped by trimethylsilylchloride to give the diene

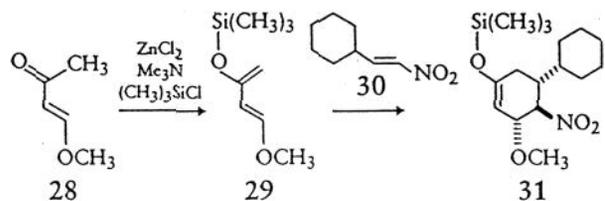


Fig. 10. Reactive path from the enolate of the methoxy enone to vinyl silyl ether.

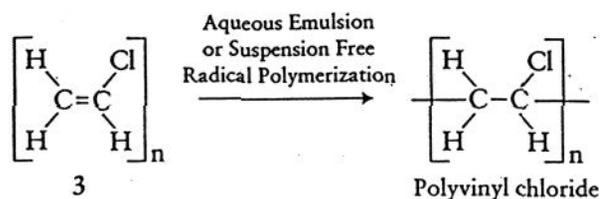


Fig. 11. Polymerization of vinyl chloride.

29. This diene undergoes DIELS-ALDER cycloaddition with the nitroalkene 30 to provide the vinyl silyl ether 31.

The important vinyl polymers include polyvinyl acetate, polyvinyl alcohol, polyvinyl ether, polyvinylidene chloride, and the polyvinyl halides. The best known vinyl polymer is polyvinyl chloride (PVC), a thermoplastic polymer. Vinyl chloride is polymerized (Figure 11), typically with a radical initiator, to provide a powder that upon heating in a mold fuses (cross-links) to a tough, durable plastic. The addition of plasticizers, or copolymerization with (for example) vinyl acetate or acrylonitrile, gives equally durable but malleable PVC polymers. Polyvinyl acetate is used as a binder for paints and as adhesives; polyvinyl alcohol is also an important component of adhesives and, as it has properties similar to starch, is used as an emulsifier and thickener.

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JED F. FISHER

## Vision, Chemistry of

Vision is a specialized form of light detection. The eye is the organ of vision. It consists of optical elements, such as the lens, and a network of sensory cells and neurons known as the retina. There are two types of photoreceptor cells in the retina: rods and cones, named because of their characteristic shapes. Rod cells are responsible for dim-light black-and-white vision, and cone cells are responsible for bright-light color vision. Light striking a photoreceptor cell is converted into an electrical signal by a photochemical reaction. The signal is processed by other cells in the retina and sent to the brain. Key elements of vision in humans include high acuity, color sensitivity, and the capability for a large dynamic range of signal intensity.

## Photoreceptor Molecule

### VITAMIN A AND RHODOPSIN

A *chromophore* is a chemical group that produces color by absorbing light. The chromophore in nearly all vertebrate visual pigments is derived from vitamin A<sub>1</sub>, a fat-soluble terpene alcohol of the formula C<sub>20</sub>H<sub>30</sub>O. Vitamin A<sub>1</sub> is an example of a compound with a highly conjugated system of alternating single and double bonds, a polyene. It has five carbon-carbon double bonds. The overlapping *p*-orbitals of adjacent carbon atoms form a  $\pi$ -bond. Each double bond between adjacent carbon atoms consists of one  $\sigma$ - and one  $\pi$ -bond.

Vitamin A<sub>1</sub> is enzymatically oxidized in the retina to an aldehyde, retinal. Retinal is covalently attached to a specific lysine residue in the AMINO ACID sequence of the opsin protein to form the visual pigment rhodopsin. Rhodopsin is the photoreceptor molecule of the rod cell. It consists of a protein (opsin) embedded into the specialized disk membrane of the rod cell and a chromophore (retinal). The protein-chromophore linkage in rhodopsin is an unusually stable protonated Schiff base bond.

The bonding of the retinal chromophore polyene cannot be adequately described by a single electron structure. Therefore, the bonding is delocalized and displays resonance, a weighted average of canonical structural forms.

The retinal in the inactive, or dark-adapted, state of rhodopsin is a specific geometric isomer, 11-*cis*-retinal. Geometric isomers are possible because there is hindered rotation about carbon-carbon double bonds. The 11-*cis* notation refers to the fact that the carbon atom chains attached to carbon atoms 11 and 12 lie on the same side of the C<sub>11</sub>-C<sub>12</sub> double bond. This results in a bend in the carbon backbone in addition to a slight twist because of steric effects of

the methyl group on carbon 13. The single carbon-carbon double bond in the ionone ring of retinal (C<sub>5</sub>-C<sub>6</sub>) is also in the *cis* orientation in rhodopsin. The three other carbon-carbon double bonds in the retinal polyene chain are in the *trans* orientation.

### RHODOPSIN PHOTOACTIVATION

Visual excitation is triggered by photoisomerization of 11-*cis*-retinal to the 11-*trans* isomer within the retinal binding pocket of rhodopsin. The absorption of a photon, a quantum of energy, by rhodopsin causes the photoisomerization. Although rhodopsin can absorb a fairly wide range of light energies, green light is most effective in activating rhodopsin. The wavelength of light that is maximally absorbed ( $\lambda_{\max}$  value) is 500 nm.

Rhodopsin has an unusually high quantum yield for a biological system. The quantum yield is defined as the fraction of absorbed light that results in a particular outcome. The primary quantum yield of rhodopsin is about 0.67, meaning that about two of three rhodopsin molecules that absorb a photon undergo retinal photoisomerization.

The retinal photoisomerization is the only light-dependent event in vision. Retinal isomerization very rapidly converts light energy into molecular motion, or thermal energy. The newly formed 11-*trans*-retinal isomer can then interact with specific amino acids of rhodopsin to cause a change in receptor conformation. The active receptor conformation binds to a specific signal-transducing protein in the cytoplasm of the rod cell called transducin. In this way, a photon of a specific wavelength is absorbed by rhodopsin and converted into a biochemical signal.

## Biochemistry of Vision

### G PROTEIN CASCADE

The rod cell protein transducin transmits a biochemical signal from rhodopsin to a cellular effector molecule. Transducin is a guanine nucleotide-binding regulatory protein, or G protein. Photoactivated rhodopsin catalyzes the exchange of guanosine 5'-diphosphate (GDP) for guanosine 5'-triphosphate (GTP) by multiple transducin molecules. The activated transducin, with GTP in its nucleotide-binding pocket, then transmits a chemical signal to the effector molecule in the signaling cascade. The effector molecule in the vertebrate visual system is the enzyme guanosine 3' : 5'-cyclic monophosphate (cyclic GMP) phosphodiesterase. A single transducin molecule activates a single phosphodiesterase molecule.

Phosphodiesterase catalyzes the hydrolysis of cyclic GMP to guanosine 5'-monophosphate (GMP)

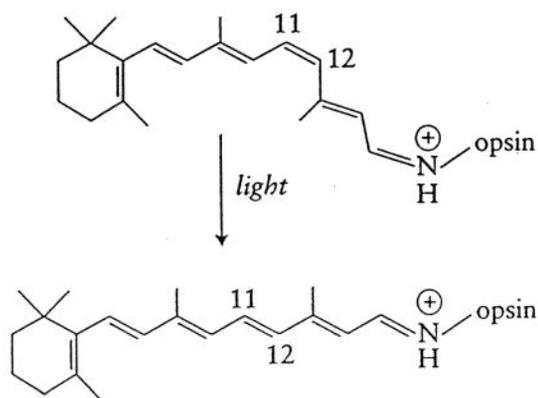


Fig. 1. The chemical process of vision.

and intracellular levels of cyclic GMP drop. The lower levels of cyclic GMP cause a rod cell plasma membrane cation channel to close. Since the plasma membrane is selectively permeable to ions, which are electrically charged, an electrical potential difference exists between the inside and the outside of the rod cell. The potential increases as cation channels are closed and the influx of sodium and calcium ions, which carry positive charge, is slowed. The result is that the rod cell becomes hyperpolarized in response to light. The increase in potential varies proportionally with the strength of the light signal. The change in membrane potential is sent as an electrical signal from the plasma membrane to the synaptic terminal of the rod cell, where it is transmitted to other specialized cells of the retina.

#### SIGNAL AMPLIFICATION

A properly dark-adapted rod cell can detect a single photon. This extreme sensitivity is possible in part because of two important features of the visual system: (1) the stability of rhodopsin in darkness to thermal activation and (2) the high degree of signal amplification by the biochemical cascade of vision. It has been estimated that the spontaneous thermal isomerization of 11-*cis*-retinal in rhodopsin in darkness takes place roughly once in 300–1,000 years. In contrast, a single photon can theoretically cause as many as 1,000 cation channels in a rod cell membrane to close.

The light signal is turned off by a number of biochemical mechanisms. Light-activated rhodopsin becomes phosphorylated by a specific rhodopsin kinase enzyme. The phosphorylated form of rhodopsin can no longer interact with transducin. The active GTP-bound form of transducin has an intrinsic enzymatic GTP hydrolysis activity. Over time, the bound GTP is converted to GDP, and transducin returns to its inactive state. In addition, intracellular calcium levels drop after the cation channel of the rod cell closes. A fall in intracellular calcium concentration mediates photoreceptor cell recovery and adaptation.

The process of adaptation allows the sensitivity of the retina to adjust based on the level of light in a visual scene. Adaptation is extremely important for a useful visual system since the magnitude of light varies widely in the environment. For example, bright sunlight and dim starlight differ in luminance by at least several orders of magnitude.

#### Color Vision

Humans possess trichromatic color vision, or trichromacy. Most people can match any given reference

color by combining the three primary colors. The three primary colors for additive color mixtures are red, green, and blue. In 1802, Thomas Young hypothesized that trichromacy resulted from humans having three separate color-sensing mechanisms. It is now known that the retina contains three classes of cone photoreceptor cells. Each class of cone cell is sensitive to a specific wavelength of light.

At the molecular level, human trichromatic color vision requires the presence of three cone pigments with broad overlapping spectral absorption. Each specific cone class contains only one type of photoreceptor molecule. The three types of cone photoreceptor molecules (red, green, and blue) are homologues of rhodopsin. The amino acid sequences of these opsins are about 40 percent identical to that of human rhodopsin. The green and red opsins are about 96 percent identical to each other and about 43 percent identical to the blue opsin.

The spectral properties of human cone pigments have been studied by a variety of techniques ranging from psychophysical color matching to microspectrophotometry. Using techniques of molecular biology, the human cone pigment genes were expressed in tissue culture cells, reconstituted with 11-*cis*-retinal chromophore, and studied by ultraviolet-visible absorption spectroscopy. The  $\lambda_{\max}$  values of the pigments were estimated to be 425 nm (blue cone), 530 nm (green cone), and 560 nm (red cone). These studies confirmed the previous assignments of the cloned pigment genes, which were based on a genetic analysis.

Rhodopsin and the three cone pigments all use the same chromophore, 11-*cis*-retinal. This single chromophore allows all visible wavelengths of light, which range from about 400 nm (violet) to 600 nm (deep red), to be detected. A spectral tuning mechanism exists so that a particular opsin protein can modulate the absorption spectrum of its retinylidene chromophore. Spectral tuning is possible because specific amino acid side chains of each opsin can interact with the chromophore and shift its  $\lambda_{\max}$  value.

Among the fifteen differences between the 364 amino acid human green and red pigments, seven amino acid changes are responsible for the observed 30-nm spectral shift in going from the green to the red pigment. Most of this shift is caused by amino acid side chains that contain a hydroxyl group: tyrosine, serine, and threonine.

Genetic variations in color vision may result from a mutation in one of the genes encoding a cone opsin. If the amino acid change affects spectral tuning in one of the cone pigments, then one of the cone types will contain a pigment with an anomalous absorption

spectrum. Individuals with this genetic variation are called anomalous trichromats. The most common type of anomalous trichromacy is called red-green color blindness. Red-green color vision variations affect males predominantly since the genes for the red and green opsin genes are found only on the X-chromosome.

Severe color vision defects may result from complete deficiencies of one or more of the three cone opsin genes. Individuals who lack a functional red or green photoreceptor are called dichromats.

### Related Signaling Systems

Rhodopsin is a member of a family of related seven-helical membrane receptor proteins. Other notable members of this family include receptors for the hormones adrenaline and glucagon. Transducin is also a member of a family of related signal-transducing G proteins. The same general system of related membrane receptors and G proteins is used by all eukaryotic organisms—from humans to yeast.

Membrane receptor molecules undergo a conformational change in response to the specific binding of a hormone ligand in the case of hormone receptors, or the absorption of light in the case of rhodopsin. This conformational change allows the portion of the receptor on the cytoplasmic surface of the plasma membrane to interact with specific proteins in the cytoplasm of the cell.

G proteins are one class of cytoplasmic proteins that interact with the activated membrane receptor. The active receptor catalyzes the exchange of GDP for GTP by multiple G protein molecules. The activated G protein then transmits a chemical signal to a cellular effector molecule.

Effector molecules may be enzymes or ion channels. An effector enzyme produces a small bioactive compound known as a second messenger molecule. For example, adrenaline is secreted into the bloodstream and binds to the seven-helical adrenergic receptor. The hormone-receptor complex activates a specific G protein, which in turn activates the effector enzyme adenylyl cyclase to produce adenosine 3':5'-cyclic monophosphate (cAMP), which affects cellular physiology. In the visual system, the effector enzyme is cyclic GMP phosphodiesterase, and the second messenger molecule is cyclic GMP.

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### Vitamins

Vitamins are substances that are essential for life in addition to the proteins, minerals, fats, and carbohydrates in foods. To be considered a vitamin, a substance must meet the following criteria:

- It is an organic compound distinct from fats, carbohydrates, and proteins; it must be a natural component of foods, where it is usually present in minute amounts.
- It is essential, also usually in minute amounts, for normal physiological function (i.e., maintenance, growth, development, and/or production).
- Its absence or underutilization must cause a specific deficiency syndrome.
- It is not synthesized by the host in amounts adequate to meet normal physiological needs.

This definition is not perfect in that many species can synthesize at least some of these substances. For example, most species can synthesize ascorbic acid (vitamin C), cholecalciferol (vitamin D), and niacin. Only the few (e.g., guinea pigs, humans) who lack the enzyme L-gulonolactone oxidase require a dietary source of vitamin C, and only individuals not exposed to sunlight cannot perform the photolysis of its precursor metabolite, thus requiring vitamin D in their diets. Only those species (e.g., cats, ducks, and fishes) who are very inefficient in converting the AMINO ACID tryptophan to niacin require the latter as a vitamin. Thus the definition of a vitamin should