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Visions of Dalton

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Abstract: Alkene isomerization is key to the functioning of photoreceptors in the retina of mammals; a lack of specific photoreceptors leads to colour blindness, a condition suffered by John Dalton and investigated by him in the late 1700s.

Keywords: Alkene isomerization · Chemical education · Colour blindness · John Dalton · Rhodopsin

Vitamin A is a mixture of retinol, retinal, retinoic acid and esters, and β-carotene (Fig. 1). The trivial names for retinol and its derivatives arise from 'retina' – the layer of epithelial tissue at the back of the eye that detects light. The names follow from the fact that, among its functions in humans and other mammals, vitamin A is an essential nutrient for normal vision. Vitamin A is stored in the retinal epithelium where retinyl esters undergo enzyme-catalysed hydrolysis to give (2*E*,4*E*,6*E*,8*E*)-retinol[1] followed by isomerization to (2*E*,4*Z*,6*E*,8*E*)-retinol. Oxidation of (2*E*,4*Z*,6*E*,8*E*)-retinol produces (2*E*,4*Z*,6*E*,8*E*)-retinal[1] (Fig. 2).

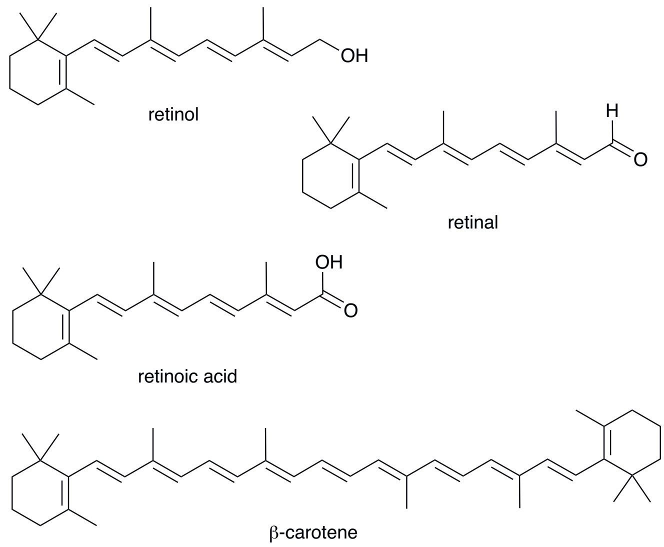
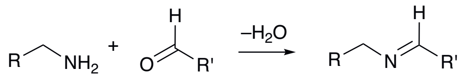


Fig. 1. Vitamin A comprises a mixture of retinol, retinal, retinoic acid and esters and β-carotene. All the alkene functionalities in the long chains are in an (*E*)-configuration.

Photoreceptors in the retina of humans and animals fall into two groups, rods and cones, which facilitate dim- and bright-light vision, respectively. Both rods and cones contain an *opsin* protein and the chromophore (2*E*,4*Z*,6*E*,8*E*)-retinal. Opsins belong to a large family of membrane receptors called G-protein-coupled receptors (GPCRs). Dim-light vision depends upon the photoreceptor *rhodopsin* which is activated by light and is responsible for switching on the signalling pathway that leads to vision. The names *opsin* and *rhodopsin* derive from the Ancient Greek ὄψις (*ópsis*) meaning 'sight' and *rodon* meaning 'rose coloured'.[2] The latter describes 'visual purple'; rhodopsin absorbs light with a wavelength around 500 nm (green light), the complementary colour of which is purple. (2*E*,4*Z*,6*E*,8*E*)-Retinal is bound to the opsin protein through an L-lysine residue (Fig. 2) present in the protein backbone. A Schiff base condensation (Scheme 1) of the primary amine group in the L-lysine residue in opsin with the aldehyde functionality in retinal leads to rhodopsin. This covalent linkage has been confirmed in the single crystal structure of rhodopsin.[3]



Scheme 1. Schiff base condensation of primary amine (in this case in an L-lysine residue in opsin) with an aldehyde (in this case in retinal).

The absorption of light by rhodopsin triggers the isomerization of (2*E*,4*Z*,6*E*,8*E*)-retinal to (2*E*,4*E*,6*E*,8*E*)-retinal as illustrated in Fig. 2. This photo-isomerization occurs in around 200 fs (1 fs = 10^{-15} s) and causes a conformational change in the protein opsin which activates it. Whereas opsin binds (2*E*,4*Z*,6*E*,8*E*)-retinal, it has a low affinity for (2*E*,4*E*,6*E*,8*E*)-ret-

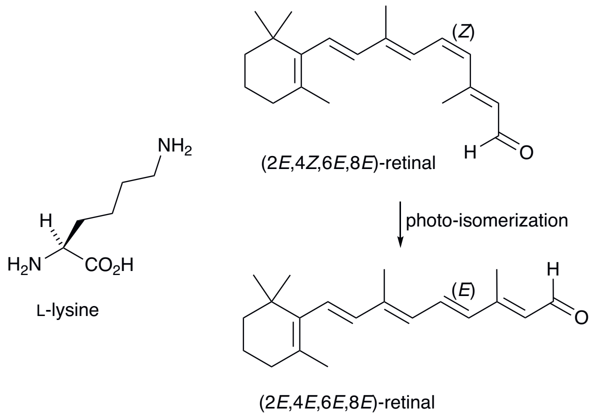


Fig. 2. The structure of the amino acid L-lysine and the photo-isomerization of (2*E*,4*Z*,6*E*,8*E*)- to (2*E*,4*E*,6*E*,8*E*)-retinal; during the isomerization, the alkene is covalently bound to the protein opsin in rhodopsin.

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inal and the latter is released from the protein after hydrolysis of the N=C linkage in rhodopsin. (2*E*,4*E*,6*E*,8*E*)-Retinal that is released is transported to pigment epithelium cells and is converted back to (2*E*,4*Z*,6*E*,8*E*)-retinal in an enzyme-catalysed process. (2*E*,4*Z*,6*E*,8*E*)-Retinal is returned to opsin where it binds again (Scheme 1) and the light-induced cycle is repeated.

Although we focused above on rhodopsin in rods, the chromophore is the same for all visual pigments in mammals. More than a thousand opsin proteins are known, and it is the details of the interaction between the L-lysine residue in a given protein and (2*E*,4*Z*,6*E*,8*E*)-retinal that is responsible for the spectral characteristics of a particular pigment.[4] Trichromatic colour (our ability to see different colours) is controlled by three types of cone photoreceptors with sensitivity to wavelengths *ca*. 560 nm (L, yellow-green), *ca*. 530 nm (M, green) and 430 nm (S, red).[5] A lack of the 530 nm photoreceptors leads to a form of colour blindness called deuteranopia, while protanopia is caused by missing the 560 nm photoreceptors. Both conditions result in a person being unable to differentiate between red and green colours.

Chemists typically associate the name of John Dalton (1766–1844) with atomic theory (Fig. 3a). He is undoubtedly best remembered for developing the modern atomic theory, which was first published in '*A New System of Chemical Philosophy*'[6] and proposed that all elements consisted of indivisible atoms with unique weights. Dalton made significant contributions to the study of gases, formulating his law of partial pressures, which describes how gases in a mixture exert pressure independently. It is usually thought that these studies on gases led to the development of his concept of atomic weight and the atomic theory. Dalton is also credited with being one of the scientists who developed the law of multiple proportions.

Fig. 3. (a) John Dalton [Credit: Henry Roscoe (author), William Henry Worthington (engraver), and Joseph Allen (painter), Public domain, *via* Wikimedia Commons]. (b) *Pelargonium zonale* in the Botancal Gardens in Bern [Credit: Chrisaliv, CC BY 4.0 <https://creativecommons.org/licenses/by/4.0>, via Wikimedia Commons]

Dalton had a broad interest in science and made meticulous meteorological observations throughout his career. Dalton also initiated the first investigations and gave the first descriptions of colour blindness. He observed that his own and his brother's perceptions of colour differed from other people's. Among the anecdotes of his observations was that the pink flowers of the geranium *Pelargonium zonale* (Fig. 3b) appeared to him 'sky-blue by daylight, but very near yellow, but with a ticture of red by candlelight'.[7] In 1798, Dalton published a paper '*Extraordinary facts relating to the vision of colours*' (reprinted in 1831)[8] in which he stated:

"*My observations began with the solar spectrum, or coloured image of the sun, exhibited in a dark room by means of a glass prism. I found that persons in general distinguish six kinds of colour in the solar image; namely red, orange, yellow, green, blue, and purple. Newton, indeed, divides the purple into indigo and violet. To me it is quite otherwise: – I see only two or at most three distinctions. These I should call yellow and blue; or yellow, blue and purple*."

Dalton proposed that his perception of colour was caused by his vitreous humour (the gel-like part of the eye) being coloured blue; as a result, he proposed that his eyes selectively absorbed longer wavelengths of light. Dalton directed that after his death, his eyes should be dissected to confirm (or not) his hypothesis. His wish was carried out in 1844, and it was shown that his vitreous humour was colourless. Fortunately, the remaining eyeball was preserved, and in 1995, DNA analysis[7] revealed that he had deuteranopia caused by a missing gene for the green receptor pigment. Specifically, changes to the OPN1LW or OPN1MW genes, responsible for synthesising the L and M pigments in the cones, result in changes to the spectral sensitivity in affected individuals.

Although the English language forgets Dalton's connection to colour blindness, he is remembered in the French (daltonisme), Italian (Daltonico) and German (Daltonismus) words for the syndrome.

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[1] The IUPAC systematic name for retinal is (2*E*,4*E*,6*E*,8*E*)-3,7-dimethyl-9-(2,6,6-trimethylcyclohex-1-en-l-yl)nona-2,4,6,8-tetraenal. In this article, we refer to the isomers of retinal as (2*E*,4*E*,6*E*,8*E*)- and (2*E*,4*Z*,6*E*,8*E*)-retinal, and similarly for retinol.

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