The Chemistry of Color

How and why we see color:

- **Transmission**: liquids/transparent materials vs opaque solids
- **Reflection**: interesting facts:
  - 8% of males and 0.5% of females have abnormal color vision (Color vision comes from X chromosome)

What can happen when light strikes an object?
1. All wavelengths reflected: object appears white
2. All wavelengths absorbed: object appears black
3. All wavelengths transmitted: object appears colorless
4. Some wavelengths reflected, others absorbed: object appears as a certain color

Interesting fact:
- 8% of males and 0.5% of females have abnormal color vision (Color vision comes from X chromosome)

Why are certain molecules colored?
- Portion of light absorbed is determined by the structure of the compound
- Most simple organic compounds do not absorb visible light; they appear white or colorless
- Complex molecules with conjugated \(\pi\) systems appear colored
- Absorption of light pushes electrons to higher energy states (ground state to excited state)
- For conjugated systems, ground and excited states are closer (smaller HOMO-LUMO gap), lower energy of light required for excitation (able to be absorbed)
- Conjugated systems absorb low energy light and reflect what is not absorbed, this reflected portion is perceived as color
  - **Color reflected is complementary to color absorbed**

Covered in this GM:
- Chemistry of color from an organic perspective
- A synthesis-focused examination of colorful molecules
- Classes of pigments/dyes:
  1. Flavonoids
  2. Carotenoids
  3. Aza-annulenes
  4. Pteridines
  5. Triarylmethines
  6. Carboxyls
- Color in Total Synthesis
- Color in Pharma
- Colorimetry/Diagnostics

Not covered in this meeting:
- Fluorescent compounds
- Inorganic pigments

Other Baran GMs on this topic:
- Food Chemistry, Peters 2019
- Chemistry of Cultural Heritage, Palkowitz 2021

‘Particle in a Box’ Theory of Color:
- Smaller “confined space” for electron: larger energy level spacing
- ‘Box’ the size of a covalent bond: absorb UV, appear colorless
- ‘Box’ between 0.6–0.8 nm: absorb visible light

Conjugated systems absorb low energy light and reflect what is not absorbed, this reflected portion is perceived as color

**The Color Wheel** (Newton’s Disc)

Not covered in this meeting:
- Fluorescent compounds
- Inorganic pigments

Other Baran GMs on this topic:
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‘Particle in a Box’ Theory of Color:
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Color reflected is complementary to color absorbed

**The Electromagnetic Spectrum**

Conceptualized by Sir Isaac Newton and first reported in 1671, based on experiments refracting visible light through glass prisms

**The Electromagnetic Spectrum**

- High energy
- Low energy

Conjugated systems absorb low energy light and reflect what is not absorbed, this reflected portion is perceived as color

Color reflected is complementary to color absorbed

\[\text{Me} \quad \text{Me} \quad \text{Me} \quad \beta\text{-carotene (absorbs blue)} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{OH} \]

\[\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{retinol (absorbs violet)} \]

\[\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{Me} \quad \text{l-ycopene (absorbs green)} \]

Link: [Visible Light Spectrum](https://www.once.lighting/visible-light-spectrum/)

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*A Brief Discussion on Color*
UMass Chem Department
Hach DOC 042.52.00019, 2016

Resonance 2001, Mar, 66–75
Introduction to Natural Dyes and Pigments

Case Study: Why leaves change color in autumn:
- Cold weather destroys chlorophyll, pigment responsible for green color in leaves
- Carotene, also present in leaves, is much more stable at low temperature
- As chlorophyll degrades, leaves change from green to yellow
- Sugar stored in leaves can react to form flavonoid pigments (bright red colors)

Class 1: Flavonoids

Cyanidins
- All fruits or flowers appearing bright red, blue, or purple contain cyanidin-based compounds
- Discovered by R M Willstätter, who won a Nobel prize in 1915 for his work on plant pigments
- Color is dependent upon pH of cell sap in which cyanidin pigments are dissolved

Anthocyanins
- Largest class of water-soluble dyes in the plant kingdom
- First isolated in 1913 from *Centaurea cyanus* (cornflower)
- Over 700 related structures identified in nature
- Play an important role in plant reproduction:
  - attracting pollinators and seed dispersers with bright colors
  - Protect plants from stresses (possess antioxidant activity)
- Attractive to scientific community due to chromatic and physiochemical properties

Anthocyanins: cyanidins with attached sugar at R3

General Structure & Nomenclature

Dye vs. Pigment

Dye: soluble, appear transparent
Pigment: insoluble (suspended in media), opaque

 Classes:
- anthocyanins: R^3=OGly, R^4=OH or OGly
- 3-deoxyanthocyanins: R^3=H, R^4=OH
  (Gly=glycoside)
The Chemistry of Color

**Anthocyanin Biosynthesis:**
**General Flavonoid Pathway**

![Chemical reaction diagram]

**Flavylum Synthetic Strategies**

- **C-ring syntheses**
  - resorcinol or phloroglucinol
  - aroylketones
  - cinnamic aldehydes

- **Aldol Strategies**
  - acetophenones
  - 2-hydroxychalcones

**Chem. Rev. 2022, 122, 1416–1481**

**Strategies via chalcones**
**Anthocyanin Reactivity:**
*Chem. Rev. 2022, 122, 1416–1481*

pyrananthocyanins

<table>
<thead>
<tr>
<th>R1</th>
<th>R2</th>
<th>R3</th>
</tr>
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<tbody>
<tr>
<td>CHO</td>
<td>Glc</td>
<td>R1</td>
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<td>Me</td>
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<td>R1</td>
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<td>Me</td>
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</tbody>
</table>

General Synthetic Strategies

FG = CHO, CH₂PR₃X, etc.

<table>
<thead>
<tr>
<th>FG</th>
<th>FG'</th>
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<tbody>
<tr>
<td>C₁₀ unit</td>
<td>C₁₂ unit</td>
</tr>
</tbody>
</table>

Class 2: Carotenoids/Polynes

**C₁₀ Carotenoids**
(reds, yellows, oranges)

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>Z</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>Me</td>
<td>Me</td>
</tr>
</tbody>
</table>

J. Nat. Prod. 2013, 76, 783–793
Chem. Rev. 2014, 114, 1–125
Plants 2020, 9, 1039

**cantaxanthin** (X, Y = H; Z = (O))
*Plants 2020, 9, 1039*

Traditional synthesis of cyclohexene piece (1982)

<table>
<thead>
<tr>
<th>Me</th>
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<tbody>
<tr>
<td>CHO</td>
<td>Glc</td>
<td>R1</td>
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<td>Me</td>
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1. H₂O₂, NaOH
2. Zn/MeOH
3. iBuOH 91%

**isophorone**

<table>
<thead>
<tr>
<th>Me</th>
<th>Me</th>
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<tbody>
<tr>
<td>CHO</td>
<td>Glc</td>
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</tbody>
</table>

1. Me |
| Me |
| CHO |

**Modern synthesis of cantaxanthin** (2020)

<table>
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<tr>
<th>Me</th>
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<tbody>
<tr>
<td>CHO</td>
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</table>

1. mCPBA
2. NaOMe 83%
3. Oppenhauer 56%, 3 steps

Further converted to Wittig salt or sulfone

<table>
<thead>
<tr>
<th>β,β-carotene (X, Y, Z = H)</th>
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<tbody>
<tr>
<td>Me</td>
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<tr>
<td>Me</td>
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<tr>
<td>Me</td>
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</table>

1. CH₂(PO(OEt)₂)₂
2. Me |
| Me |
3. Oppenhauer 493–497

BASF original commercial process (1950)

<table>
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<th>Me</th>
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**Plants** 2020, 9, 1039
**The Chemistry of Color**

**Class 3: Aza-annulenes**

*Porphyrrins:*
- From the Greek porphyra, meaning purple
- Known as Nature's workhorse macrocycle, coordination environment can be tuned by varying substitution and axial ligands
- Form complexes with both metals and some non-metals
- Notable porphyrrins: heme, chlorins, cytochromes
- Hans Fischer won 1930 Nobel Prize for Explorations of Hemin and Chlorophyll

Chlorophyll synthesis by R. B. Woodward

"the most conspicuous natural product"

**Colors in the Body**

*Heme degradation pathway*

Fun fact: hemoglobin analog in horseshoe crab (hemocyanin) binds Cu rather than Fe, leading to blue blood

**Melanin**
- Five basic types
- Responsible for skin, hair, and eye color
- Present in cephalopod ink and bird feathers

**Baran Group Meeting**

03/19/22
**The Chemistry of Color**

**Class 4: Naturally Occuring Pteridines: Flavins and Pterins**

- **Pteridines**
  - From Greek pteron, meaning wing
  - First discovered in the pigments of butterfly wings
  - Can suffer from regioselectivity issues but can control with reagent choice

- **Sepiapterin**
  - Yellow pigments found in *Drosophila* fruit fly (above)

**Flavin**
- From Latin *flavus*, meaning “yellow”
- Tricyclic isoaalloxazine core
- Properties differentiated based on R group

- Natural source of flavin: Riboflavin (vitamin B2)
- Used as a yellow/orange food coloring
- Produced biosynthetically in bacteria/fungi/plants
- Manufacturing scale production uses fermentation rather than chemical synthesis

**Pterins - Synthetic Strategies:**
- Gabriel-Isay condensation
- Timmis reaction (regioselective)
- Polonovski-Boon reaction (dihydropterins)

**For more on food additives, see Baran GM on Food Chemistry (Peters 2019)**

**Natural Product Communications 2014, 9, 37–38**

**A Brief Tangent... Bioluminescence**

Luciferase substrate syntheses

- Inexpensive reagents
- Faster processing (one pot)
- Gram scalable

**Compounds responsible for the yellow-green light from fireflies**
### The Chemistry of Color

#### pH Indicators
- Same principle as in cyanidins, protonation state affects color in solution

**Phenolphthalein**
- In acidic solution (colorless)
- In basic solution (pink)
- Color change ~pH 8.2

#### Ninhydrin Test
- Used to identify presence of amines/amino acid
- Employed in fingerprinting
- Reaction of ninhydrin with amine leads to formation of dark purple dimer (Ruhemann’s purple)

#### Methyl violet and Fuchsin
- Triarylmethine Dyes
- Methyl violet: R = Me, R’ = H or Me
- Fuchsin: R = R’ = H, substituents on rings

#### Malachite Green and Victoria Blues
- Triarylmethine Dyes
- Malachite Green: R = Me, R’ = H or Me
- Victoria Blues: R = R’ = H, substituents on rings

#### Phenols
- Phenolphthalein in acidic solution (colorless)
- Phenolphthalein in basic solution (pink)
- Color change ~pH 8.2
- Same principle as in cyanidins, protonation state affects color in solution

#### Synthetic approaches:
- Commonly derived from Michler’s ketone derivatives
- Phenolic derivatives prepared via Friedel Crafts with phthalic anhydride

#### Class 6: Carbonyl Dyes
- Baeyer Drewson indigo synthesis, lab scale (1882)
- First commercial route, Heumann (1897)
- Second commercial route, Pfiger (1901)

#### Indigo

#### Synthetic approaches:
- Commonly derived from Michler’s ketone derivatives
- Phenolic derivatives prepared via Friedel Crafts with phthalic anhydride

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For more on azo dyes and pigments: 
Baran GM on [Chemistry of Cultural Heritage](Palkowitz 2021)
The Chemistry of Color

Total synthesis of azepinobisindole iheyamine A

\[
\begin{align*}
\text{MeO} & \quad \text{OAc} & \quad \text{F}_3\text{C} & \quad \text{NH} \\
\text{N} & \quad \text{H} & \quad \text{MeO} & \quad \text{OAc} & \quad \text{N} & \quad \text{Me} & \quad \text{O} & \quad \text{N} \quad \text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{MeO} \\
\text{MeO} & \quad \text{OAc} & \quad \text{F}_3\text{C} & \quad \text{NH} & \quad \text{MeO} & \quad \text{OAc} & \quad \text{N} & \quad \text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{Me} & \quad \text{O} & \quad \text{N} & \quad \text{MeO} \\
\end{align*}
\]

\text{cross-Mannich}

\[\text{[:1,2-shift]}\] \[\text{-AcOH} 93\%\]

\[\text{I}_2 \text{KOH}\]

\[\text{MeO} \quad \text{OAc} \quad \text{F}_3\text{C} \quad \text{NH} \quad \text{MeO} \quad \text{OAc} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{MeO} \]

\[\text{K}_2\text{CO}_3 \Delta, \text{air}\]

\[\text{69\%}\]

\[\text{SiO}_2 \text{air}\]

\[\text{87\%}\]

\[\text{MeO} \quad \text{OAc} \quad \text{F}_3\text{C} \quad \text{NH} \quad \text{MeO} \quad \text{OAc} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{MeO} \]


Total synthesis and structural revision of pseudocerosine

\[\text{MeO} \quad \text{OAc} \quad \text{F}_3\text{C} \quad \text{NH} \quad \text{MeO} \quad \text{OAc} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{MeO} \]

\[\text{NBS; NaSMe} \quad \text{Na}_2\text{S}_2\text{O}_4 \quad \text{TMSCHN}_2\]

\[\text{HCl} \quad \text{biomimetic cyclization}\]

\[\text{MTO}\]

\[\text{MeO} \quad \text{OAc} \quad \text{F}_3\text{C} \quad \text{NH} \quad \text{MeO} \quad \text{OAc} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{MeO} \]

\[\text{MeO} \quad \text{OAc} \quad \text{F}_3\text{C} \quad \text{NH} \quad \text{MeO} \quad \text{OAc} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{Me} \quad \text{O} \quad \text{N} \quad \text{MeO} \]

\[\text{Org. Lett. 2020, 22, 3495–3498}\]

Pyridoacridine Natural Products
- Isolated from mollusks, tunicates and marine sponges
- Two basic pyridine-like nitrogen atoms in these alkaloids create \(e^-\) cloud, extended conjugation, charge transfer spectra
- Leads to unique coloration

\[\text{Org. Lett. 2020, 22, 3495–3498}\]
The Chemistry of Color

Color in Pharma: Usually a Bad Thing...

Colored impurity in rofecoxib prodrug

- 1.5% in 2, which can oxidize in presence of base (ring-open species)
- Highly conjugated system leading to strong absorption at long wavelength, bright yellow color
  
  <0.01% by LC but product failed color spec

Tenofovir (PMPA) Alternate Route Development

- Nucleotide analogue reverse transcriptase inhibitor (NRTI)
- TAF/TDF intermediate (frontline treatment for HIV)

Initial route:

Polymerization a common issue in this chemistry...

- Use of barium hydroxide over NaOH prevented formation of red polycyanide polymers (clogged filters, contaminated product)
- HCN polymers important in prebiotic chemistry, thought to be responsible for orange/red coloration of Jupiter and Saturn

A colored impurity in a hyperpigmentation drug

…and a novel Ti coupling

Discovery Route:

Multiple PG swaps

5 steps 24% yield

Process Route:

2 steps 42% yield

New Route:

- Operationally simple
- 99.2% purity product
- Bulky Ti ligands suppress bis addition (< 3% in crude product)

Impurity formation: Air oxidation of product, accelerated by base
Solution: buffer crystallization with AcOH

Color as a Diagnostic Tool

Color Change: Crystal Habit

- Solid-solid phase transformation


Image of XRPD solid phase analysis

Ru nEtOH Ru 3H₂O

2Theta in °


Planet, Space Sci. 1996, 44, 1365–1370
The Chemistry of Color

Quantifying Color

- Color assessment focuses on the optical characteristics of the material, i.e., its ability to modify incident light waves.
- A mathematically defined color space was created by the International Commission on Illumination (CIE) in 1931.
- US Pharmacopeia now uses 20 reference solutions based on this system to define coloring of APIs.

Colorimetric Testing - Lateral Flow and ELISA

Pregnancy Tests

Pantone employee Lawrence Herbert devised the first standardized color matching system (PMS) in 1963.

Ehrlich's Reagent

- Binds to C2 position of two indole moieties to form resonance-stabilized carbenium ion complex (pink/purple color).
- Also used to detect presence of high levels of urobilinogen in urine (indicative of liver issues).
- Dr. Paul Ehrlich received the Nobel prize in medicine in 1908 for use of this reagent in typhoid diagnostics.

COVID Tests

ELISA: Enzyme-linked Immunoabsorbent Assay

- Measures presence of human chorionic gonatropin (HCG), secreted soon after implantation of egg into uterine wall.
- Color comes from a dye (rhodamines, porphyrins, etc.) adhered to a polystyrene microsphere.
- More modern tests use aggregation of gold/silver nanoparticles as colorimetric indicator.

https://www.pantone.com/about-pantone

Hach DOC042.52.00019, 2016: Objective color assessment and quality control in the chemical, pharmaceutical and cosmetic industries.

ACS Cent. Sci. 2020, 6, 591–605

https://www.once.lighting/visible-light-spectrum/
The Chemistry of Color

The Color of Mind Control?!
The Curious Case Study of Baker-Miller Pink

A study conducted by Alexander Schauss in the 1970s at the American Institute for Biosocial Research on the calming effects of a certain shade of pink. The color was named for the commander (Baker) and warden (Miller) of the Washington State Department of Corrections who agreed to paint cells this color and observe the behavior of inmates. Exposure to the color for 15 minutes was reported to cause a short-term decrease in aggression.

Results of the study were later called into question due to irreproducible results. However, several prisons still use the color in the holding cells...

HEX #FF91AF Baker-Miller Pink (Schauss Pink)
RGB(255, 145, 175)

Schauss' work was inspired by that of Swiss psychiatrist Max Lüscher, who noticed a correlation between color preference and psychological state.

Baker-Miller Pink is also commonly referred to as Drunk-Tank Pink. In 2013, a book entitled ‘Drunk Tank Pink: And Other Unexpected Forces That Shape How We Think, Feel, and Behave’ was written by Adam Alter. It is a NYT Bestseller

In the 1980s, the Colorado State football team painted their away team locker rooms pink to “relax” the other team. The impact was apparently so detrimental that the Western Athletic Conference governing body introduced regulation requiring both home and away locker rooms to be painted the exact same color.

Researchers at John Hopkins Health, Weight, and Stress Clininc reported the color to have an appetite suppression effect. In 2017, Kendall Jenner reportedly painted a wall in her home this color for this reason...

Int. J. Biosocial Research 1985, 7, 55-64.
https://www.colormatters.com/color-and-the-body/drunk-tank-pink