The Life and Achievements of Robert Burns Woodward

Long Literature Seminar
July 13, 2009
Erika A. Crane
"The structure known, but not yet accessible by synthesis, is to the chemist what the unclimbed mountain, the uncharted sea, the untilled field, the unreached planet, are to other men. The achievement of the objective in itself cannot but thrill all chemists, who even before they know the details of the journey can apprehend from their own experience the joys and elations, the disappointments and false hopes, the obstacles overcome, the frustrations subdued, which they experienced who traversed a road to the goal. The unique challenge which chemical synthesis provides for the creative imagination and the skilled hand ensures that it will endure as long as men write books, paint pictures, and fashion things which are beautiful, or practical, or both."

Robert Burns Woodward

- Graduated from MIT with his Ph.D. in chemistry at the age of 20
- A tenured professor at Harvard by the age of 29
- Published 196 papers before his death at age 62
- Received 24 honorary degrees
- Received 26 medals & awards including the National Medal of Science in 1964, the Nobel Prize in 1965, and he was one of the first recipients of the Arthur C. Cope Award in 1973

Woodward taught by example and captivated the young... “Woodward largely taught principles and values. He showed us by example and precept that if anything is worth doing, it should be done intelligently, intensely and passionately.”

-Daniel Kemp
Robert Burns Woodward was born to Arthur and Margaret Woodward in Boston, Massachusetts on April 10, 1917.

In 1918, Robert’s father, Arthur, died in the great influenza pandemic.

Robert’s mother, Margaret, remarried but was soon abandoned to raise Robert on her own.
RBW: The Early Years

- Robert grew up and was educated in Quincy, Massachusetts
- When Robert was 8 years old in 1925, he received his first chemistry set
- By the age of 12 in 1929, Robert had completed all of the experiments in Ludwig Gattermann’s *Practical Methods of Organic Chemistry* (1894)

“I fell in love with the field [of organic synthesis] when I was a small boy and the affair is still going on.”

-RBW

Bridging into Academia: RBW at MIT

- Woodward enrolled at MIT in 1933, at the age of 16
- After his freshman year, he was given his own laboratory
- At the end of the first semester of his sophomore year, Robert was advised to withdrawal from college due to his neglect of his classes

Courtesy of MIT Museum
Bridging into Academia: RBW at MIT

- Robert spent a semester as an employee of the MIT biology department

- He was permitted to re-enroll in school through the good offices of James F. Norris

- RBW earned a B.S. and a PhD from MIT in only four years, graduating in 1937 at the age of 20

James F. Norris, professor of organic chemistry at MIT and president of the American Chemical Society (1925-1926)
"We saw we had a person who possessed a very unusual mind in our midst. We wanted to let it function at its best. If red tape which was necessary for other less brilliant students had to go, we cut it. We did for Woodward what we have done for no other student in the department. And we think he will make a name for himself in the scientific world."

-James F. Norris

From the interview of James F. Norris at RBW's graduation by the Boston Globe
8 June 1937

James F. Norris, professor of organic chemistry at MIT and president of the American Chemical Society (1925-1926)
Love & Marriage

- In 1937, Robert married a high school classmate, Irja Pullman

- They had two children in their 10 years together: Siiri Anne and Jean Kirsten

Courtesy of Harvard University Archives
RBW spent the summer of 1937 teaching at the University of Illinois.

He “managed through his intelligence and impatience to alienate several of the leading figures of organic chemistry in the United States”.

Frank Westheimer, a colleague and friend, said he believed “that Bob failed to conceal adequately that he was much brighter than the Illinois professors.”

**A Summer at the University of Illinois**

Professor Roger Adams, Chemistry Department Chair, University of Illinois (1926-1957)

Professor Carl “Speed” Marvel
University of Illinois (1915-1961)

Courtesy of C&EN News

Courtesy of the University of Illinois
Moving to Harvard

- In fall of 1937 through 1938, Robert worked as an Research Assistant to Elmer P. Kohler
- In 1938, RBW was appointed as a Junior Fellow in the Society of Fellows until 1940
- In 1941, Robert was made an official instructor of chemistry

“That marvelous institution was founded, at Harvard, by A. Lawrence Lowell, whose conviction it was that scholars should be gentleman, entirely free to follow their intellectual interests...One could read, learn, cogitate—even work, if one felt the urge—and plan the future, however unconsciously.”

-RBW

Address on receiving the American Chemical Society’s Arthur C. Cope Award in Organic Chemistry, 28 August 1973.
Woodward’s Inspiration

“From the first awakening of my interest in chemistry, I have found its history absorbing, and have been particularly entranced by the concept of bonding in the most general sense.”

-RBW

Address on receiving the American Chemical Society’s Arthur C. Cope Award in Organic Chemistry, 28 August 1973.

• Woodward was particularly drawn to the work of Friedrich August Kekule and Archibald Scott Cooper
Woodward’s Inspiration

Friedrich August Kekule

Kekule structures
Woodward’s Inspiration

tartaric acid

Archibald Scott Cooper
In 1927, at the age of 10, RBW proposed his own structure of benzene.

He later realized that this was simply a 2D representation of the prism structure proposed by Albert Ladenburg 50 years prior.

However, it was Kekule’s structures that inspired Woodward to propose that benzene could be made by adding an olefin to a diene.

In the Nr. 1 issue of Liebig’s Annalen for 1928 was “Synthesen in der hydroaromatischen Reine” by Otto Diels and Kurt Alder.
The Woodward Rules (1941-1942)

- The Woodward Rules (also known as the Woodward-Fieser rules) were proposed in 4 papers in 1941-1942.
- In his first paper, he founds that generalizations could be made between spectra if the absorption effects of different solvents was accounted for.
- He also found that the extent of substitution at the α and β positions of a α,β-unsaturated ketone could be determined from the UV spectra.

The Woodward Rules (1941-1942)

- The first article was based solely on the experimental work of others, citing more than forty papers.
- In particular, the work by Heinz Dannenburg was pertinent to Woodward’s evaluation.
- His rules concentrated on numerical analysis and built support for these rules with many examples.

The Woodward Rules (1941-1942)

- The last three papers adapted the rules to α,β-unsaturated ketones and conjugated dienes within and external to ring structures


The Woodward Rules (1941-1942)

- Woodward provided evidence against the then-accepted structure of 3-acetoxo-6-keto-7-hydroxy-$\Delta^4$-cholestene.
- The compound had a $\lambda_{\text{max}}$ of 230 m\(\mu\) when it should be at 239 $\pm$ 5 m\(\mu\) with a small intensity band at 300 m\(\mu\) too.
- Proposed the structure of 3-acetoxo-$\Delta^5$-(6)-norcholestene-7-carboxylic instead.

The Woodward Rules (1941-1942)

- In 1949, the rules were extended by Louis and Mary Fieser
- UV spectroscopy was later superseded by newer structure determination techniques such as nuclear magnetic resonance spectroscopy, mass spectroscopy and X-ray crystallography
- The use of physicochemical measurements in structural organic chemistry was a major landmark

The elucidation of these rules demonstrated RBW’s remarkable power of analysis and his passion for scientific order
Synthesis of Quinine 1943-1944

- Quinine was discovered by the Quechua Indians of Peru in the 17th century in the bark of cinchona trees
- Jesuits recognized it's ability to treat malaria and sent it back to Europe
- The cinchona bark was ground up in put in sweetened water to offset the bitter taste—known as tonic water today
Synthesis of Quinine 1943-1944

- Natural sources were being exhausted by the nineteenth century
- In William Henry Perkin’s attempts to synthesize it in 1856, he made the first synthetic dye, mauveine
- Quinine became the “Holy Grail” of organic chemistry

William Henry Perkin
Synthesis of Quinine 1943-1944

- During World War II in March of 1942, the Japanese invaded Java and cut off the major supply of quinine, the most effective antimalarial agent at the time.

- Edwin Land of the Polaroid Corporation hired Woodward to find a light polarizer replacement for quinine.

- Land agreed to finance Woodward and a new Harvard Ph.D., William Doering, in the synthesis of quinine.
Woodward’s genius lied in his ability to see what others had not seen already in the known.


**Synthesis of Quinine 1943-1944**
Synthesis of Quinine 1943-1944


These conditions are essential in order to obtain desired selectivity without loss of hydroxy group.

Work by Fritsch

Initial attempts to induce reductive cleavage of the piperidino group failed.

Mixture of cis and trans isomers

Adam’s catalyst

95% yield over 2 steps
Synthesis of Quinine 1943-1944


* cis configuration essential for the desired cis-3,4-disubstitution of the piperdine ring

* mixture of isomers

* Hoffmann elimination

* 60% K/NaOH, NEt₃, 140 °C

* 70% yield

* H₂CrO₄, AcOH

* 68% yield

* EtONO₂, NaOEt, EtOH

* 42% yield over 5 steps

* KCN, H₂O

* homomeroquinone

**Synthesis of Quinine 1943-1944**

1. 0.1 N aq. HCl, Δ
2. Ag₂O then H₂S

**resolved as dibenzoyl-d-tartrate**

1. HCl, EtOH
2. benzoyl chloride, K₂CO₃
96% yield over 4 steps

N-benzoylhomomeroquinene ethyl ester

6 N HCl
50% yield over 2 steps

**Claisen condensation**

**quinotoxine**

**Rabe and Kindler 1918**

**quinine**

**dry NaOEt Δ**

ethyl quininate
Synthesis of Quinine 1943-1944

Woodward worked with William von E. Doering for fourteen months on the molecule and isolated 30 mg of d-quinotoxine.

However, they were not able to successfully convert quinotoxine to quinine leading to the Stork/Woodward controversy.

Doering and Woodward in 1944, shortly after the quinotoxine synthesis

Courtesy of Harvard University Archives
This synthesis was hailed by the New York Times and featured in Life Magazine.

In this cartoon from the Oregon Journal, synthetic chemistry is displayed as America’s hero in the loss of supplies of oil, rubber and quinine.

However, this route was not commercially viable.

$3,000 per pound as opposed to $16 per pound for natural quinine.
Moving Up

- RBW was promoted to Assistant Professor at Harvard in 1944, at the age of 27.
- In 1945, Woodward received the John Scott Medal of the Franklin Institute along with Doering for the total synthesis of quinine.
- In 1946, Robert was promoted again to Associate Professor at Harvard.

The John Scott Medal

• In 1946, RBW divorced Irja Pullman and married Eudoxia Muller, an artist and technician whom he met at the Polaroid Corporation

• They had two children together: Crystal Elizabeth and Eric Richard Arthur

(1948) Eudoxia with Crystal and the children from RBW’s first marriage, Jean and Siiri

Courtesy of Eudoxia Woodward
Structure elucidation (1945-1956)

- Starting in 1945, Woodward focused a lot on structure elucidation
- He proposed structures for penicillin, patulin, strychnine, oxytetracycline (terramycin), carbomycin (magnamycin), santonic acid, calycanthine, and aureomycin.
Steroid Synthesis (1951)

- The chemistry of steroids become a “hot” area in organic chemistry in the 1940s and early 1950s because of their potential therapeutic value
- Cholesterol was first isolated in 1769 by French physicist/chemist François Poulletier de la Salle from gallstones
- Cortisone was isolated in 1930's by a group of scientists lead by Tadeua Reichstein (Zurich), Edward, C. Kendall (Mayo Clinic, MN), and Oskar Wintersteiner (Columbia University) from the adrenal glands of cattle
Woodward’s interest in steroids stemmed from his desire to construct them utilizing a Diels-Alder reaction.

He was unsuccessful in his attempts to make estrone using a Diels-Alder reaction in his PhD research in 1947.

**Steroid Synthesis (1951)**

- Woodward chose a "relay" approach to the synthesis of the steroids by first making the etiocholatrienate intermediate, which contained the core structure and could be further functionalized.

```
chlesterol

polres
terone

testosterone
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Steroid Synthesis (1951)

The B ring was added by a Robinson annulation.

The A ring was appended on by a Michael addition of acrylonitrile.

Rings C and D were assembled by a Diels-Alder reaction.

Methyl dl-3-keto-Δ4,9(11),16-ethiolatrienate
Steroid Synthesis (1951)


Prepared previously by Orchin and Butz in 1943.

**Diels-Alder**

\[
\text{MeO} \quad \text{Me} \\
\text{O} \quad \text{Me} \\
\text{MeO} \quad \text{Me}
\]

\[\overset{\text{benzene}}{\text{C}}\]

\[
\text{NaH then } H^+ \\
\text{40% yield over 2 steps}
\]

\[
\text{LiAlH}_4
\]

**Michael addition**

\[
\overset{\text{Ac}_2\text{O}, \text{Zn}}{\text{Me}} \\
\text{O} \quad \text{Me} \\
\text{Me}
\]

\[45\% \text{ yield over 3 steps}\]

**The more thermodynamically stable product**

\[
\overset{\text{cat. } t\text{BuOK, BuOH}}{\text{B}} \\
\]

\[\text{KOH, dioxane, 50% yield over 3 steps}\]

**Cyclization & deformylation**
Steroid Synthesis (1951)

Need to protect olefin for formation of A ring

Intramolecular aldol reaction

Mixture of isomers

Methyl dl-3-keto-Δ4,9(11),16-etochochatrienate

Stable isomer carried on

Cyanoethylation

Protect the most base-sensitive center

Dieckmann-like condensation

Steroid Synthesis (1951)

methyl dl-3-keto-$\Delta^{4,9(11),16}$-etiocholatrienate

to effect dehydration at C20 and acetylate at C3

1. $\text{H}_2$, reduced Pt
2. $\text{H}_2\text{CrO}_4$, AcOH

1. NaBH$_4$
2. hydrolysis
3. Ac$_2$O, pyr

routes from cholestanol, to cholesterol already described
Steroid Synthesis (1951)

**alpha isomer**

1. NaOMe, NaOH
2. Na₂Cr₂O₇
3. CrO₃ − H₂O

**Heymann & Feiser**

1. NaBH₄, EtOH
2. Ac₂O, pyr

**installing the α-hydroxy ketone at C19**

1. KOH
2. SOCl₂
3. CH₂N₂
4. KOH
5. Ac₂O
6. CrO₃

**Lardon & Reichstein**

1. Nal, acetone
2. KOAc, Δ

**Sarett**

1. KCN, AcOH
2. OsO₄, pyr then Na₂SO₃

**oxidize the cyanohydrin intermediate**

1. Br₂
2. pyridine
3. hydrolysis

**cortisone**

Moving Up

• RBW was promoted to Full Professor at Harvard in 1951, at the age of 34

(1951) Woodward and Sir Robert Robinson of MIT; two chemists who were often in competition

Courtesy of John D. Roberts
Peter Pauson and his student, Tom Kealy, of Duquesne University in Pittsburgh were trying to make fulvalene by adding ferric chloride to cyclopentadienyl magnesium bromide.

On August 7, 1951, they reported the new organometallic compound in Nature.

On January 30, 1952 both Geoffrey Wilkinson and Robert Woodward read the Nature article and determined that the proposed structure was incorrect.

Woodward and Wilkinson agreed to work together on the project.
They argued that the proposed structure was likely incorrect because its isolation stood “in striking contrast to the failure of previous investigators”.

Obtained UV spectra and proved the compounds dimagnetism and lack of a dipole moment.

Determined later that summer by Fischer that the structure was antiprismatic.

The discovery of ferrocene initiated a revolution in organotransition metal chemistry.
RBW was promoted to Morris Loeb Professor at Harvard in 1953, at the age of 36

That year he was also elected into the National Academy of Science
Synthesis of Strychnine (1954)

- Strychnine was first isolated in 1818 by Pierre-Joseph Pelletier and Joseph Bienaimé Caventou.
- In 1838, Victor Regnaut determined its molecular formula of $\text{C}_{21}\text{H}_{22}\text{N}_2\text{O}_2$.
- 1898: Julius Tafel proposed the left-hand side of the molecule as an aromatic ring attached to a N.
- 1910-1932: William H. Perkin and Robert Robinson published a series of papers about the south face of the molecule, including correctly identifying it as an indole derivative.
- 1932: Robinson and a competitor, Hermann Leuchs, mapped out the structure of the lower two rings.
- The structure of ring V remained in debate however.
- 1945: Vladimir Prelog proved that ring VI was a 6-membered ring.

50 mg is lethal for an adult human!

Seeds of the Strychnoe nux vomica tree
Synthesis of Strychnine (1954)

- 1948: Using Prelog’s conclusion, Woodward proved that ring V was a five-membered ring, contrary to what Robinson thought
- Made biogenetic arguments and based rationale on his own experiments
- J. B. Hendrickson once called Strychnine the “Mount Everest of structural organic chemistry”
- In 1952, Robert Robinson claimed, “For its molecular size it is the most complex substance known”

Seeds of the Strychnoe nux vomica tree


**Synthesis of Strychnine (1954)**

- Strychnine: 24 atoms, 7 rings, 6 contiguous chiral centers
- 2-veratrylindole: open ring with $O_3$ to form ring III
- Blocking the α position for form ring V

**Synthesis of Strychnine (1954)**

The two other aromatic rings should be electron deficient enough to inert to oxidation.

Stereochemistry unknown at formed center.

Only one isomer obtained.

5-membered lactam will not form due to E geometry of enoate.

Isomerization from α,β-unstaturated ester to a β,γ-unstaturated ester already established.

*N*-phenylpyridone confirmed by UV and IR.

**Synthesis of Strychnine (1954)**

- **Dakin & West 1928**
  1. aq. HCl, AcOH
  2. SeO₂, EtOH

- **Dieckmann condensation**
  1. NaOMe, MeOH
  2. Ac₂O, pyr
  3. NaOMe, MeOH, Δ

- **confirmed enol structure by UV**
  1. TsCl, pyr
  2. NaSCH₂C₆H₇

- **addition-elimination**

- **multiple acidic sites present could pose a problem in enol form, but were able to utilize it in the synthesis**

- **cis ester obtained as major product but easily converted into the more stable trans ester**

- **V**

- **VI**
  goes through a glyoxal intermediate
**Synthesis of Strychnine (1954)**

**strychnine**

1. NaC≡CH, THF
2. Lindlar’s, H₂

**isostrychnine**

1. HBr, AcOH
2. aq. H₂SO₄,

**Prelog 1948**

KOH, EtOH

**VII**

| need to reduce the pyridone ring on the concave side without touching the carbonyl |
| the hydride is delivered intramolecularly |

**obtained 8 mg!**
"The beauty of the strychnine synthesis resides principally in the flexible strength of its master plan, and especially in the seemingly effortless disposal of one stereochemical problem after another."

- John Cornforth
Synthesis of Reserpine (1956)

- Extract from Indian snake root, or *Rauwolfia serpentina*, had been used by traditional doctors to treat insect or reptile bites.
- 1930s: Scientists discovered it could be used to treat hypertension, nervous disorders or even schizophrenia.
- 1952: Emil Schlittler isolated reserpine at CIBA in Basel and coined the name.
- By 1955 the structure was fully elucidated.

*A Rauwolfia serpentina plant*

**Synthesis of Reserpine (1956)**

Aimed to get the most chiral centers into the molecule as early as possible

Diels-Alder

6-methoxytryptamine
Synthesis of Reserpine (1956)

Synthesis of Reserpine (1956)


1. CH₂N₂, pyr
   2. Ac₂O, pyr
   3. OsO₄, then NaClO₃

lose formaldehyde!
1. aq. HIO₄
2. CH₂N₂, CH₂Cl₂

prepared in 1930 by Akabori and Saito

reductive amination
1. benzene
2. NaBH₄, MeOH

NaBH₄, MeOH

need to invert newly formed stereocenter!
Synthesis of Reserpine (1956)

most stable conformation–can’t isomerize center with acid

very strained intermediate

isomerization driven by strain relief

1. KOH, MeOH
2. DCC, pyr

1. methanolysis
2. pyr, OMe

Synthesis of Reserpine (1956)

- This synthesis was Woodward’s favorite and is arguably one of the best of Woodward’s array of landmark syntheses.
- 1958: the French company, Roussel-Uclaf took Woodward’s synthetic route to industrial scale.

*It was the first time stereoselectivity was maintained throughout a long synthetic sequence in such a particularly elegant manner.*
**Synthesis of Chlorophyll (1960)**

“Man cannot give a true reason for the grass under his feet, why it should be green rather than red or any other color.”

-Sir Walter Raleigh

- Chlorophyll was first isolated in 1818 by Pierre-Joseph Pelletier and Joseph Bienaimé Caventou

- 1905-1914: Richard Willstätter demonstrated that magnesium was contained in chlorophyll, he purified chlorophyll’s $a$ and $b$, and isolated the phytol alcohol side chain
  - He won the Nobel Prize in 1915 for this work

- 1930s: Hans Fischer performed chemical studies and later proposed a structure in 1936
  - He won the Nobel Prize in 1930 for synthesizing heme

- 1950s: R. P. Linstead also performed chemical studies and proposed the structure that later RBW was skeptical of but accepted and turned out to be correct
Synthesis of Chlorophyll (1960)

Chlorophyll contained an extra ring fused to ring III

It also possessed two “extra” hydrogen in ring IV
Synthesis of Chlorophyll (1960)


work by Triebs, Schmidt & Zinsmeister in 1957

aldehyde masking group!

the other α position is too electron deficient to react

the thioaldehyde was a new concept!


**Synthesis of Chlorophyll (1960)**

The synthesis of chlorophyll involved several key steps:

1. **Schiff base formation**: The reaction of a phlorin salt with acetaldehyde to form a Schiff base.

2. **Oxidation**: The oxidation of the Schiff base with iodine to form an intermediate product.

3. **Further oxidation**: Further oxidation with acetic anhydride in pyridine to yield a porphyrin, with a 50% yield over 5 steps.

The use of the thioaldehyde doubled the yield of this process!

It was known that phlorin salts can be readily oxidized by air, and no other contaminant!

A porphyrin was obtained as the final product.
This remarkable reaction represents the first instance ever observed of reversible interconversion of a porphyrin and a chlorin.”

- RBW

**Synthesis of Chlorophyll (1960)**

**elimination of trimethylammonium species**

1. 1 N HCl, MeOH
2. Me$_2$SO$_4$
3. NaOH, MeOH

**Hofmann Elimination**

**keto-aldehyde formation most likely strain driven**

**Dieckmann condensation**

**chlorin e$_6$ trimethyl ester**

**chlorophyll-a**

**unexpected methoxy-lactone formation**
Synthesis of Chlorophyll (1960)

The synthesis took 4 years and 17 post docs in groups of 3 to 6 at a time to complete.

elimination of trimethyl-ammonium species

Hofmann Elimination

keto-aldehyde formation most likely strain driven

Dieckmann condensation

chlorin e₆ trimethyl ester

Willstätter & Fischer

chlorophyll-a
The practical execution of the synthesis “might as well have been impossible without his resource, his awareness, his sensitivity to the slightest clues and his insistence on obtaining the maximum information.”

- John Cornforth
RBW was promoted to a Donner Professor of Science in 1960, at the age of 43.
In 1895, Aimé August Cotton observed that the optical rotation changed dramatically when measured around the wavelength absorbed by the chiral molecule.

If the partial rotation curve became strongly positive and then sharply negative, it was a positive Cotton effect.

A negative Cotton effect is observed when the curve becomes negative and then positive.

The Octant Rule (1961)

- From 1952-1957 Carl Djerassi at Wayne State University in Detroit applied optical rotatory dispersion to organic molecules.

- In 1957 William Klyne showed that introduction of a halogen α to a ketone in the equatorial position of a steroid caused a small change in the Cotton effect compared to the parent compound.

- However, introduction of a halogen in the axial position caused a large change in the Cotton effect.
In 1958, Djerassi gave a seminar at Harvard and met Woodward, Moffitt and Moscowitz who were working on a theory of optical activity.

**The Octant Rule (1961)**

- **positive Cotton effect**
  - chrysanthene in isooctane
  - Me Me
  - O

- **negative Cotton effect**
  - Me OH O Me
  - O OH O
  - OH

- **MeOH in water**

The Octant Rule (1961)

“The connection was clear because every prediction by Moffitt and Moscowitz was immediately supported by my production some experimental verification. The octant rule explained virtually all of our published and unpublished results.”

-Carl Djerassi
“Steroids Made It Possible”
The Octant Rule (1961)

Absolute configurations can be assigned using this method!

The space around a carbonyl of an asymmetric ketone can be divided into octants.

The octants are assigned signs based on empirical evidence of the contribution of each atom in a given octant toward the Cotton effect.

A substituent not in the Z plane of the carbonyl group will contribute to the chiral ketone’s asymmetry.

<table>
<thead>
<tr>
<th>Octant</th>
<th>Contribution</th>
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<tbody>
<tr>
<td>+x+y+z</td>
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<tr>
<td>+x-y-z</td>
<td>+</td>
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<tr>
<td>-x+y+z</td>
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<td>-x-y+z</td>
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Djerassi & Klyne
The Octant Rule (1961)

The Octant Rule (1961)

- Even though this rule was established in 1958, the results weren’t published until 1961
- Unfortunately Moffitt passed away unexpectedly in December 1958
- Moffitt introduced Woodward to molecular orbital theory and if he had remained alive the Woodward-Hoffmann Rules may have been the Woodward-Moffitt Rules

(1958) Woodward and William Moffitt reenacting the afternoon when the octant rule was discovered

Courtesy of Carl Djerassi
The Woodward Research Institute (1963)

- In 1963, the Woodward Research Institute was established by CIBA limited in Basel, Switzerland.
- RBW was allowed to carry out his research of choice “in the field of chemical compounds or processes associated in some way with living organisms.”
- CIBA had hoped that the advances Woodward made at this institute would benefit the company.

The door to the Woodward Research Institute at CIBA-Geigy in Basel, Switzerland

Courtesy of Harvard University Archives
The National Medal of Science (1964)

RBW received the National Medal of Science Award in the physical sciences in 1964 for

“an imaginative new approach to the synthesis of complex organic molecules and, especially, for [his] brilliant syntheses of strychnine, reserpine, lysergic acid and chlorophyll.”

(1965) Woodward accepting the National Medal of Science from President Lyndon Johnson

Courtesy of Harvard University Archives
There was much debate during the 1930s over whether the mechanism of the Diels-Alder reaction was concerted or stepwise.

In 1942, Woodward had proposed an ionic mechanism involving electron transfer and an ion pair.

Woodward felt as though he fully understood and could predict the outcome of the Diels-Alder reaction until his endeavors in the vitamin B$_{12}$ synthesis.

Working with his post doc, Subramania Ranganathan, RBW discovered that he did not in fact make the expected product when trying the following Diels-Alder reaction.
The Woodward-Hoffmann Rules (1964-69)

Subramania Ranganathan described that when RBW “had discovered that his predictions relating to stereochemistry had gone awry...his enormous and rightful self-confidence would not accept the outcome meekly, and the result was, of course, the Woodward-Hoffmann rules.”
The Woodward-Hoffmann Rules (1964-69)

- It was already accepted that electrons possessed both particle-like and wave-like properties and that these wave-like properties can change with energy level.
- It was also accepted that these electrons occupy orbitals which can be calculated by quantum (wave) mechanics.
- Bonding was visualized by orbitals overlapping, enabling the electron density to spread over two or more atoms.

The significant detail that Woodward and Hoffmann established was that the orbitals must be in the same phase in order to bond.
The Woodward-Hoffmann Rules (1964-69)

- In the first paper, Woodward and Hoffmann found that under thermal conditions cyclobutenes underwent a conrotatory ring closure, while hexatrienes underwent a disrotatory ring closure.

“...the steric course of the electrocyclic transformation is determined by the symmetry of the highest occupied molecular orbital of the open-chain partner.”
The Woodward-Hoffmann Rules (1964-69)

In a $4n \pi$-electron system, the symmetry of the HOMO must allow for a bonding interaction between “orbital envelopes on opposite faces of the system”, or via a conrotatory closure

In a $4n+2 \pi$-electron system, the symmetry of the HOMO must allow for a bonding interaction between “orbital envelopes on the same face of the system”, or via a disrotatory closure

Under photochemical conditions, the $4n \pi$-electron system will undergo a disrotatory closure and the $4n+2 \pi$-electron system will undergo a conrotatory closure
The Woodward-Hoffmann Rules (1964-69)

- In the second paper, Woodward and Hoffmann introduce orbital correlation diagrams and explain how they can be used to predict whether a given electrocyclic reaction will undergo a conrotatory or a disrotatory closure under thermal or photochemical conditions.

Classify whether the orbitals in the starting materials and product are symmetric or antisymmetric with respect to the selected symmetry element.

Correlate the orbitals with the same symmetry.

If the energy of the correlation between the HOMOs of the starting material and the product decreases in energy, then the process is favorable.

photochemically allowed!
The Woodward-Hoffmann Rules (1964-69)

- In the second paper, Woodward and Hoffmann introduce orbital correlation diagrams and explain how they can be used to predict whether a given electrocyclic reaction will undergo a conrotatory or a disrotatory closure under thermal or photochemical conditions.
The Woodward-Hoffmann Rules (1964-69)

- In the third paper, Woodward and Hoffmann introduce the selection rules for sigmatropic [1,3], [1,5] and [1,7] shifts

1,3 sigmatropic shifts:

<table>
<thead>
<tr>
<th>[1,3]</th>
<th>Thermal</th>
<th>Excited state</th>
</tr>
</thead>
<tbody>
<tr>
<td>[1,3]</td>
<td>Antarafacial ($C_2$)</td>
<td>Suprafacial ($\pi$)</td>
</tr>
<tr>
<td>[1,5]</td>
<td>Suprafacial ($\sigma$)</td>
<td>Antarafacial ($C_2$)</td>
</tr>
<tr>
<td>[1,7]</td>
<td>Antarafacial ($C_2$)</td>
<td>Suprafacial ($\sigma$)</td>
</tr>
</tbody>
</table>
The Woodward-Hoffmann Rules (1964-69)

the controversy...

Elias J. Corey

Roald Hoffmann

- In his 2004 Priestly Medal address, E. J. Corey claimed that he has provided RBW with the idea of the conservation of orbital symmetry

- That same year, Hoffmann published a tell-all account of what he knew and what he didn't know about Corey's contribution to the Woodward-Hoffmann rules

R. B. Woodward
The Woodward-Hoffmann Rules (1964-69)

the controversy...

“I believe that E. J. Corey’s perception of the consequences of what he told R. B. Woodward is just that—what he, Corey, believes.”

-Roald Hoffmann

“In 1963-64, E. J. Corey and A. G. Hortmann accomplished the total synthesis of dihydrocostunolide. A crucial step involved a stereospecific electrocyclic reaction. The two papers on the work do not have any reference to an electronic factor in the stereoselectivity.”

R. B. Woodward

“Woodward had a habit of posing to people problems of great interest. And also of posing such problems as puzzles, even if he had the solution...I think that May 4 conversation [between RBW and EJC] perhaps might have prompted Woodward to push on, and to ask for my assistance with calculations supporting the frontier orbital approach.”
The Woodward-Hoffmann Rules (1964-69)

The controversy...

“I believe that E. J. Corey’s perception of the consequences of what he told R. B. Woodward is just that—what he, Corey, believes.”

-Roald Hoffmann

“I asked him directly if Corey had a role in this work. He said “no”—this was our (R.B.W. and R.H.) work.”

-Roald Hoffmann

“In 1963-64, E. J. Corey and A. G. Hortmann accomplished the total synthesis of dihydrocostunolide. A crucial step involved a stereospecific electrocyclic reaction. The two papers on the work do not have any reference to an electronic factor in the stereoselectivity.”

-R. B. Woodward
Synthesis of Cephalosporin C (1965)

Cephalosporin C Lecture
The Nobel Prize (1965)

“It is sometimes said that organic synthesis is at the same time an exact science and a fine art. Here Nature is the uncontested master, but I dare say the prize-winner of this year, Professor Woodward, is a good second.”

-Arne Fredga

Les Prix Nobel en 1965 (Stockholm: Almquist & Wiksell, 1966)

Woodward reading the telegram announcing that he had won the Nobel Prize with his loyal secretary, Dolores “Dodie” Dyer looking on

From Aldrichimica Acta 10:1 (1977)
The Nobel Prize (1965)

The Nobel Prize winners in Stockholm for the ceremony in 1965: Robert B. Woodward (chemistry); Julian Schwinger and Richard P. Feynman (physics); François Jacob, André Lwoff, and Jacques Monod (physiology or medicine); and Mikhail Sholokhov (literature)

for his “meritorious contributions to the art of organic synthesis”
Love & Marriage

- Robert and his second wife, Eudoxia Miller, were divorced in 1972
The Arthur C. Cope Award (1973)

“[I]n chemistry, one’s ideas, however beautiful, logical, elegant, imaginative they may be in their own right, are simply without value unless they are actually applicable to the one physical environment we have—in short, they are only good if they work! I personally very much enjoy the challenge which this physical restraint on fantasy presents.”

From RBW’s address upon receiving the American Chemical Society’s Arthur C. Cope Award in Organic Chemistry, 28 August 1973.

Hoffmann, Herman Bloch (chairman of the board of the ACS), Harriet Cope and Woodward after Woodward and Hoffmann had received the first Arthur C. Cope Award for outstanding achievement in organic chemistry

Courtesy of Harvard University Archives
Vitamin B$_{12}$ Synthesis (1960-76)

- In 1926, George Minot (a Harvard professor of medicine) successfully used liver to treat pernicious anemia
- In 1928, Eli Lilly & Co. introduced liver extract to the market
- Ed Rickus of Merck was finally able to isolate the red crystals of vitamin B$_{12}$
Vitamin $B_{12}$ Synthesis (1960-76)

- In 1956, Dorothy Hodgkin was able to obtain and solve the X-ray crystal structure of vitamin $B_{12}$
- Wilhelm Friedrich and Konrad Bernhauer from Stuttgart successfully converted cobryic acid to vitamin $B_{12}$

Dorothy Hodgkin

Won the Nobel Prize in 1964 for her advancement of X-ray crystallographic techniques in the structural determination of biological molecules
Vitamin $B_{12}$ Synthesis (1960-76)

- In 1959, Albert Eschenmoser began working on the synthesis of the corrin system of vitamin $B_{12}$
- During 1960-61, Woodward began working on rings A and D, or the western portion of the molecule
- Also in 1960, Eschenmoser began working on the eastern portion of the molecule, rings B and C
- By 1964, Eschenmoser had finished the corrin system
- Eschenmoser and Woodward finally agreed to collaborate and finish the molecule together in 1965

The corrin system is the porphyrin ring system of the molecule without the cobalt.
Vitamin B\textsubscript{12} Synthesis (1960-76)

This type of corrin system had never been made before—needed to pioneer a route.

The direct link between the A and D rings with no intervening carbon was going to be a challenge.

In this synthesis they needed to master the stereochemical complexity as well as master the complexity inherent in large, macrocyclic, highly unsaturated, nitrogen-containing chromophore structures.

The molecule contains 9 stereocenters, which means it has 512 possible stereoisomers.
Vitamin B<sub>12</sub> Synthesis (1960-76)

the transition state with the methyl groups
syn to one another is lower in energy

resolved by urea formation with (+)-α-
phenylethyl isocyanate

took 16 steps total

Woodward, R. B.; Recent advances in the chemistry of natural products. Pure Appl. Chem. 1968, 17, 519-547.
**Vitamin B$_{12}$ Synthesis (1960-76)**


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![Chemical structure diagram for Vitamin B$_{12}$ synthesis](image)
**Vitamin B\textsubscript{12} Synthesis (1960-76)**


Birch reduction need to protect both carbonyls cyclohexene and cyclopentene ring are opened!

got oximation of both ketones but can remove unfavored oximino group

cyclohexene and cyclopentene ring are opened!

**Vitamin B<sub>12</sub> Synthesis (1960-76)**

Specific conditions necessary to get desired cyclization of the diketones confirmed by X-ray crystallography!

Hesperimine

- HCl, MeOH

Beta-corrnorsterone

- 1. strong base, Δ
- 2. CH<sub>2</sub>N<sub>2</sub>

Alpha-corrnorsterone

- 1. NaBH<sub>4</sub>, MeOH
- 2. MsCl, pyr
- 3. LiBr, DMF

D ring formed through a intramolecular Michael addition

Western fragment complete
Vitamin $B_{12}$ Synthesis (1960-76)

The original route to eastern fragment developed by Eschenmoser but several routes were developed by both Zurich and Cambridge for this fragment.

Ring B is formed through a Diels-Alder cyclization and a Arndt-Eistert homologation.

Ring C is derived from (+)-camphor.

Sulfur-extrusion coupling method developed by Zurich in 1965.

Mechanism unknown of sulfur-extrusion but suspect that an episulphide involved.

Mechanism involves oxidation to the disulphide and then attack by the eneamide.

Vitamin $B_{12}$ Synthesis (1960-76)

- **Diastereomers separated by HPLC**

- **Western fragment**

- **Eastern fragment**

- **Block the C10 position by formation of the lactone from undesired methylation**

- **Separated diastereomers by HPLC**

- **Cobryic acid**

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Eschenmoser was able to successfully link together the A and D rings through a photochemical sigmatropic [1,16] H-shift on the basis of the Woodward-Hoffmann rules.
Vitamin $B_{12}$ Synthesis (1960-76)

Woodward and Mark Wuonola on March 17, 1976, the day that the total synthesis of vitamin $B_{12}$ was completed

- The synthesis of this molecule began in 1960 and involved over 100 chemists from 20 different nations

This synthesis serves as an example of the role of natural product synthesis in generating fundamental knowledge in organic chemistry
Vitamin $B_{12}$ Synthesis (1960-76)

Woodward and Eschenmoser admiring the “marvelous $B_{12}$ machine” at the Zurich symposium

“What really grew out of the decision to join forces in the $B_{12}$ venture was the fine and delicate art of ‘collaborative competition’...In practice this partnership entailed a continuous and rigorously open discussion of the project’s present and future, an immediate exchange of information about anything that happened to succeed or fail in either of the two laboratories...On a more personal level it meant rejoicing wholeheartedly in the partner’s success. Perhaps above all it meant basic harmony between our attitudes toward our science...”

-Albert Eschenmoser

Courtesy of Dorothy Felix
The “Woodward Lectures”

- In later years, Woodward ran a notorious research seminar on Thursday nights for faculty, postdoctoral students and other students.
- He would start by lining up his cigarettes and colored chalk on 2 white handkerchiefs and he would write on the board from memory starting at the upper left-hand corner of the board and ending in the lower right-hand corner.
- RBW would often drink an entire pitcher of daiquiris while he lectured without noticeable affect and would smoke all of his cigarettes using the old one to light the next one.
- The lectures would last three hours or more and would often run past 1:00 am.
- Roald Hoffmann used to joke that he measured lecture time in “milliwoodwards.”

“I teach all the time so that I don’t have to teach formal courses.”

-RBW
Death

- Woodward passed away on July 9, 1979 in his sleep from a heart attack

“All in all Bob was bigger than life. His chemistry and the great impact that he had on other people’s chemistry survive him and stand as a monument to his achievements. His friends are the poorer now that he is no longer needling us, while the entire field of organic chemistry will benefit forever because he converted synthesis into a much more highly rational procedure.”

-Frank Westheimer
“Woodward in his role as a pioneer of modern natural-product synthesis did not exert his influence on synthetic chemistry through any explicit proposition of principles and rules that could be used as recipes for designing a synthetic plan. He reached his contemporaries through teaching by example. It was not his way to routinize and ‘technify’ his art of synthetic design by giving such recipes; what he did was to put up one masterpiece after the other, masterpieces that were universally recognized as such by his fellow chemists, achievements that not only were chemically inspiring but also captivated the young.”

-Albert Eschenmoser
Resources


- And all of the references included herein