Corrin Chemistry: from B₁₂ to the Origin of Life

Corrin:

Name "corrin" proposed by those who established its structure because it is the core of the vitamin B₁₂ molecules.

The most ancient of the uroporphinoids: the primitive anaerobes which make B₁₂ can be dated back 3.79 x 10⁹ years.

Some Uroporphinoids:

corrole

tetrahydrocorphin: coenzyme F₄₃₀

chlorin: chlorophyll

porphyrin: heme

Vitamin B₁₂ x-ray structure:

Structure: Crowfoot-Hodgkin 1955
(1964 Chemistry Nobel Prize)

One of the "finest contributions of British science to the chemistry of low-molecular-weight natural products"
-A. Eschenmoser

"Of all that architecture and organic synthesis have in common, one thing is this: for the works of both, explicit goals are usually set, but after the works are done, their raison d'être often lies within themselves."

– A. Eschenmoser, Robert Robinson Lecture 1976

2 Science, 1977, 196, 1410; Classics in Total Synthesis
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Corrin Chemistry

\[ \text{Product} \rightarrow \text{Reaction Conditions} \]

1. MeO\(_2\)C-\(\text{H} \rightarrow \text{D} \)
   - P\(_2\)S\(_5\), 4-methylpyridine,
   - xylene, 130 °C (84%)

2. 1. t-BuOK, t-BuOH,
    - THF, 25 °C; D
   2. (NC(CH\(_2\))\(_2\))\(_3\)P,
      - TFA, sulfolane,
      - 60 °C
      - (64% overall)
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**Corrin Chemistry**

1. A, NaHMDS, PhH, 25 °C
2. Cd(ClO₄)₂, MeOH, 25 °C

![Chemical Structures]

1. Ph₃P, TFA, PhH, 80 °C
2. Cd(ClO₄)₂, tPr₂NET, PhH, MeOH, 25 °C then NaCl workup (46% overall)
3. DBU, sulfolane, 60 °C

1. hν (visible), 60 °C
2. CoCl₂, 58 °C
3. KNC, air, H₂O, CH₂Cl₂, 0 °C (46% overall)
A solution to *meso* methyl introduction:
Jacobi, *JOC*, 1999, 64, 1778

For a particularly elegant approach to Vitamin B₁₂ by R. V. Stevens see "Isoxazoles and Isothiazoles in Synthesis" (Mitsos, 2004)
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Corrin Chemistry

Synthetic Analysis of Specific Structural Elements of Vitamin B_{12}:

Towards a Chemical Rationalization of Structure

"Can work done on the chemical synthesis of vitamin B_{12} be extended to make a contribution to the problem of vitamin B_{12} biosynthesis? This question began to motivate and direct our activity in the field of corrin chemistry soon after the smoke on the battlefield of total synthesis had disappeared."

"[An] objective that can and should be studied with the tools of natural product synthesis [is a] systematic delimitation of the boundary separating the reactivity of biomolecules from structural changes."

"Can experiments aimed at a deeper understanding of the molecular structure of cofactors tell us something about that early phase of biological evolution?"

Darwinian paradigm of molecular evolution: structure a result of selection

structural preformation \rightarrow selection \rightarrow emergence of biosynthetic pathway

biotic prebiotic

mutations reproduction feedback

- specific arrangement of double bonds in corrin chromophore
- contracted dimension compared with corphin ring
- specific attachment of nucleotide ligand to ring D
- arrangement of substituents on the ligand periphery

"Chemists engaged in natural product synthesis are probably in the best position to grasp the vast number as well as the nature of lucky prerequisites that must be fulfilled for a multistep biosynthesis of a complex natural product to emerge."

Eschenmoser, ACIEE, 1988, 27, 5.
Specific arrangement of double bonds in corrin chromophore

What is the position of the tautomeric equilibrium between the tetrapyrrolic arrangement of double bonds in a porphyrinogen and the arrangement in its corphinoid counterpart?

- In complexed form, thermodynamic equilibrium of tautomers favors the corrinoid system
- Analogous reactivity seen with Zn(II) and Ni(II) complexes

*ACIEE, 1983, 22, 630 & 632*
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Corrin Chemistry

Contracted dimension of the corrin ring

Unfavorable "ligand ruffling" observed in hydroporphinoid metal complexes that is not seen in the corresponding corrinoids:

Since the coordination hole of corrinoid ligands is better suited to the spatial demands of the metal(II) ion a corphinoid to corrinoid rearrangement should be possible:


Specific attachment of nucleoside ligand to ring D

Is the f-ester inherently more reactive?

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![Corrin Chemistry Diagram]

\[
R, R' = \text{CN, OAc (mix)}
\]

1. 2,4-pentanediol/THF
20 °C, 185 h
2. NH\(_2\)/NH\(_4\)Cl, 20 °C, 20 h
(50 % conv)

**vitamin B\(_{12}\) + cobyramide (\sim 1:1)**

- The nucleotide loop to the propionic acid side chain of ring D represents, of all possible regioisomers, the thermodynamically most stable
- The present day biosynthesis makes no use of this

**Arrangement of substituents on the ligand periphery**

- The kinetic product is a type I uro'gen, but under thermodynamic conditions the type III predominates
- The enzymatic biosynthesis of uro'gen III is "chemomimetic," i.e. a non-enzymatic synthesis takes place with great ease
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Corrin Chemistry

The distribution is the same even at concentrations as low as 1 mg per 5 L!

The arrangement of side chains around B₁₂ corresponds to the thermodynamically favored arrangement

Some glimpses of B₁₂ biosynthesis:
