I. Basic Principles

ID. Oxidation Reactions - Continued

Boger Notes: p. 41 - 94 (Chapters IV & V)
Carey/Sundberg: p. 757-820 (Chapter B 12.2 - 12.7)

Phenol Oxidation [Phl(OAc)$_2$]


**Conversion of Phenols to para-Quinone Monoacetals**

* Metal salts (Cu(I), Mn(II), Ag(I), Ce(III), Fe(III))
* Electrochemical oxidations
* DDQ (Büchi, G.; Chu, P.-S.; Hoppmann, A.; Mak, C-P.; Pearce, A. J. Org. Chem. 1976, 43, 3983)
**A Highly Selective Diastereotopic End Group Differentiation**


**Moriarty's Oxidative Cleavage of Tyrosyl Peptides**

- Moriarty, R. M.; Prakash, O.; *Acc. Chem. Res* 1986, 19, 244.
Phenol Oxidation [PhI(OAc)$_2$]


Enzymatic Oxidoreductions


Nicotinamide adenine dinucleotide (NAD) and the analogous 2'-phosphate (NADP) are involved in many 2-electron oxidations catalyzed by dehydrogenases. The reversible hydride transfer from a reduced substrate to NAD(P), and that from NAD(P)H to an oxidized substrate, is stereoselective and characteristic of individual enzymes. Due to the high cost of NAD and NADPH, recycling and solvent stability are crucial issues in using nicotinamide cofactors.
Enzymatic Oxidoreductions

Horse liver alcohol dehydrogenase (HLADH) has received more attention than any other alcohol dehydrogenase. There are a number of models that allow the prediction whether a particular compound will be a substrate for the enzyme.

Industrial vitamin C synthesis:

D-glucose $\xrightarrow{\text{Acetobacter suboxydans}}$ L-idonic acid

1. MeOH, $H^+$
2. NaOMe
3. $H^+$
Enzymatic Oxidoreductions

The enzymatic Baeyer-Villiger reaction (Branchaud, B. P.; Walsh, C. T. J. Am. Chem. Soc. 1985, 107, 2153) requires flavoenzyme in the presence of NAD(P)H. The enzymatic reaction proceeds with similar stereochemistry to that of the chemical reaction and catalyze enantioselective transformations. Cyclohexanone monoxygenase accepts a broad range of ketones.

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Enzymatic Oxidoreductions

Mechanism of action of cytochrome P₄₅₀ oxidation:


- **Structural & electronic aspects of Complex chemistry**
- **The bioinorganic chemistry of Cobalt**
Fatty acid metabolism

- The oxidation of fatty acids proceeds in three stages

Propionyl Co-A enters the citric acid cycle using three steps; methyl-malonyl-CoA isomerizes in two isomerization steps to succinyl-CoA

- Propionyl Co-A is carboxylated to form methyl-malonyl CoA (catalyzed by the biotin containing propionyl-CoA carboxylase)
- Methyl-malonyl CoA is also an intermediate in the catabolism of methionine, isoleucine, threonine and valine to succinyl-CoA
- Methyl-malonyl epimerase catalyzes L-D conversion
- Methyl-malonyl-CoA mutase (a vitamin B<sub>12</sub> dependent enzyme) catalyzes the second to form succinyl-CoA
Vitamin $\text{B}_{12}$ catalyzes intramolecular proton shift

$\text{H} - \text{C} - \text{H} - \text{C} - \text{CO}^-$

\[ \text{L-Methylmalonyl-CoA} \xrightarrow{\text{coenzyme } \text{B}_{12}} \text{H} - \text{C} - \text{C} - \text{C} - \text{CO}^-$

\[ \text{methylmalonyl-CoA mutase} \]

\[ \text{H} - \text{C} - \text{H} - \text{C} - \text{CO}^- \]

\[ \text{S-CoA} \]

\[ \text{H} - \text{C} - \text{H} - \text{C} - \text{CO}^-$

\[ \text{S-CoA} \]

\[ \text{H} - \text{C} - \text{C} - \text{C} - \text{X} \]

\[ \text{H} - \text{C} - \text{C} - \text{X} \]

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\[ \text{H} - \text{C} - \text{C} - \text{X} \]
Attachment of upper ligand of Coenzyme B₁₂ is an example of triphosphate displacement from ATP

- Cobalamin → Coenzyme B₁₂

The other such reaction where this is observed is formation of adenosyl-methionine (vide infra)

Proposed mechanism for methyl-malonyl CoA mutase
Cobalamine-dependent methyltransferases

• In addition to the formation of adenosylcobalamine, cobolamine plays a major role in methyl transfer reactions. The best studied reaction is that catalyzed by cobolamine-dependent methionine synthase.

Structure of methylcobalamin

Mechanism of cobalamin-dependent methionine synthase

This enzyme catalyzes the transfer of a methyl group from CH₃⁺ H₄folate to homocysteine. Ultimately, this generates SAM, an ubiquitous biological methyl group transfer agent.
Mechanism of cobalamin-dependent methionine synthase

**Oxidative addition mechanisms:** (A) for methyl transfer to cobalamine from CH$_3$-H$_4$folate and (B) for the reaction of homocysteine with methylcobalamine

$$\begin{align*}
\text{(A)} & : \quad \text{R} + \text{CH}_3\text{B} \rightarrow \text{R} + \text{CH}_3\text{B} + \text{H}^+ \\
\text{(B)} & : \quad \text{H}_2\text{C}=\text{S} + \text{CH}_3\text{B} \rightarrow \text{S} + \text{CH}_3\text{B} + \text{H}^+
\end{align*}$$

Single electron transfer mechanisms: (A) for methyl transfer to cobalamine from CH$_3$-H$_4$folate and (B) for the reaction of homocysteine with methylcobalamine

$$\begin{align*}
\text{(A)} & : \quad \text{H}_2\text{N} + \text{Me} + \text{CH}_3\text{B} \rightarrow \text{H}_2\text{N} + \text{Me} \text{MeB} + \text{H}^+ \\
\text{(B)} & : \quad \text{B} + \text{H}_2\text{C} = \text{S} + \text{Me} \text{MeB} \rightarrow \text{B} + \text{H}_2\text{C} = \text{S} + \text{Me} \text{MeB} + \text{H}^+
\end{align*}$$

Both mechanisms have their strengths and weaknesses, and 50 years after elucidation of the structure of cobalamin and 40 years after the methyl transfer functions of methylcobalamin, the actual process is still unknown. Matthews, R. G. "Cobalamin-dependent methyltransferases." Acc. Chem. Res. 2001, 34, 681-689. Could a stereochemical analysis solve this problem?
Mechanism of cobalamin-dependent methionine synthase


Mechanism of cobalamin-dependent methionine synthase

2nd Preparation of enantiomerically enriched substrate and enzyme conversion
Mechanism of cobalamin-dependent methionine synthase

Chirality analyses

![Chemical reactions diagram]

KCN HMPA

Mechanism of cobalamin-dependent methionine synthase

Chirality analyses

![Chemical reactions diagram]
Methyl groups originating from SAM:

Dimerization of palmitic acid to diabolic acid is closely related to these methylation processes; both reacting carbon centers show inversion of configuration:

Arigoni’s mechanism for formation of diabolic acid
Model reaction in support of Arigoni’s mechanism

\[ \text{Co}^{(III)} \xrightarrow{\Delta \text{ or } h\nu} \text{Co}^{(II)} + 2 \]