Handout IRTG-4, May 27 2009

- Jan Reedijk.
  Leiden Institute of Chemistry
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From Structural Biomimetics to Functional Catalysts

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Bifunctionality in ligands and coordination compounds: application in design of new materials, catalysts and drugs.

IRTG: Spring 2009, Münster

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Lectures overview

- 1a. Introduction Ligands (general)
- 1b. Introduction Bifunctionality
- 2. Introduction Metal-DNA binding and anticancer drugs, followed by: Bifunctionality in M-DNA binding
- **3.** Bifunctionality in Molecular Materials
- **4. Bifunctionality Homogeneous Catalysis**
- **Conclusions and Outlook**

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Lecture Content

- Introduction group and biomimetics
- Introduction Cu proteins
- Biomimetic Oxidations with Cu compounds
- Other metals and other oxidations: Paint Drying alternatives
- Concluding remarks

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Why interest in Biomimetics?

1. Better Understanding
a) speculative (protein structure unknown)
b) corroborative (when structures are available for proteins)

2. Application in mind
a) Metal transport (in vivo; waste water)
b) Metal catalysis

Approach:
1. Design and synthesis
2. Structure and characterisation
3. Tests in applications (functionality)

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Molecular roles of metal ions in living systems

Also often called
"biocoordination chemistry"

1. Understanding the role of metal ions in living systems (toxic and beneficial).
2. Application of knowledge of effects of metal ions (and compounds) in living systems.

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Definition Bioinorganic Chemistry:

- A branch of science dealing with the study of the role and effect of metal ions and metal compounds in "living" systems.

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Characteristics

- **Proteins: Many contain metals or need metals**
- **Enzymes: Over 40% has a metal at the active site; at least another 25% require a metal ion for activation and operation**

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Definitions and descriptions:

- **Catalysis:**

  The process in which a specific reaction occurs for a certain (selectively chosen) (group of) compound(s), according to a mechanism in which a unique site is involved. This site can be used repetitively.

- **(bio-)Catalyst: A compound (a system) that allows a certain specific reaction to take place repetitively, selectively, and efficiently.**

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Role of metal (ion) in catalysis

a) as a Lewis acid (acceptor)
b) as a Π base (donor)
c) as a redox source

- **ACTIONS OF METAL ARE EITHER:**
- Stabilisation of a reactive intermediate
- Activation of an inert substrate
- As a ***template*** for bringing together reactants in the optimal geometry

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Important reactions in biology with small molecules

1. Photosynthesis H_2O ---> O_2
2. Cytochrome oxidase O_2 ----> H_2O
3. Nitrogenase N_2 ----> 2 NH_3
4. Superoxide dismutase 2 $O_2^{\bullet -}$ ----> H_2O_2 + O_2
5. Catalase 2 H_2O_2 ----> 2 H_2O + O_2
6. Methane monooxygenase CH_4 ----> CH_3OH

All these enzymes use metal-ions; often more than one metal ion!

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Fast and specific biocatalytic reactions

- Catalase *(Fe containing heme)*

$H_2O_2 \longrightarrow O_2 + H_2O$ [2x10^6/sec]

- Superoxide Dismutase *(Cu containing)*

$O_2^- \longrightarrow H_2O_2 + O_2$ [2x10^9/sec]

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For a difficult Job Nature uses Metal Ions!!

For a VERY difficult Job, Nature uses CLUSTERS of metal Ions!

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Metalloproteins, enzymes, mimics

- Selection of short examples: Zn, Fe,Mn
- Major example: Copper proteins
- Transport: electron and dioxygen
- Catalysis with Cu and Mn biomimetics

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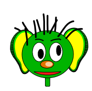
The Biroinorganic Chemistry of Alcohol

- Intake of EtOH: "Happy"
  Zn in Alcohol dehydrogenase

- Formation of Acetaldehyde: "Hangover"

  Mo in Aldehyde Oxidase



- Formation of Acetic Acid:
  The Recovery Stage

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Functions of Metals in Biology

- Transport functions:
  electrons, dioxygen, metals
- Chaperones and DNA binders, such as Zinc fingers (structure organisers)
- Charge compensation for anions
- Catalysis (6 enzyme classes)

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Metals & applications in Biology

- Structure organiser (Ca; Zn; Zn finger)
- Catalyst (Mn, Co, Fe, Zn, Cu, Mo, V)
- Drug (Au, Pt, Bi, Li, Ag)
- Diagnostic (signal from metal: Tc, Gd)
- Analytical reagent (probe; Os, Pt)
- Transporter of electrons (Cu, Fe)
- Transporter of ligands, like dioxygen

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What is special in Metals?

1. Geometry preferences
   (Oxidation-state dependent; size dependent)
2. Binding strengths (weak, strong)
3. Binding kinetics (fast, slow)
4. Binding preferences for ligands (HSAB)
5. Reactivity patterns
   a) Redox properties
   b) Photoreactivity and charge transfer
   c) Coordination changes (catalysis)
   d) Powerful template possibilities
6. Cluster formation possibilities

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Reactivity and ligand exchange reactions

Kinetics versus Thermodynamics

Kinetics and Thermodynamics are influenced by:

a) metal ion (intrinsic property)
b) ligand (strength, covalency, steric bulk)
c) (macro-)chelate effect
d) solvent assistance

Mechanistic discriminations (associative, dissociative, intermediate mechanisms).

Metalloproteins and metalloenzymes

- Proteins: Transport, storage (metals, electrons) myoglobin, azurin, cytochromes, ferritin
- Enzymes: Catalytic reactions P-450, ascorbate oxidase, catalase
  - Co-enzyme: Agent that actives an enzyme
  - Apo-enzyme: Enzyme without a metal (usually inactive)
  - Pro-enzym: Inactive enzyme, lacking the activator
  - Synzyme: Biomimetic product micking the enzyme (structure, activity)

Biomimetic Copper Chemistry

- Copper proteins (introduction)
- Why biomimetics studied?
- Reactions with dioxygen species
- Example of stable dioxygen adducts with dinuclear Cu sites and catalytic oxidation reactions
- Applications in Oxidations

Copper Protein Examples

- *Spectroscopic Classification*
- Type 1: Blue; unusual EPR
- Type 2: Normal spectroscopy
- Type 3: Dinuclear; EPR silent

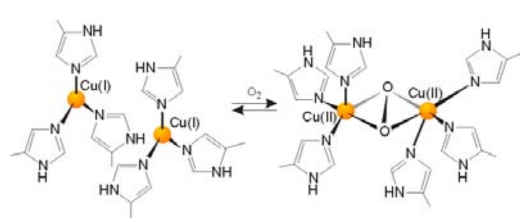
Type A: Dinuclear Blue (purple)
Type B: Mixed Fe-Cu
Type Z: Tetranuclear
Type 4: Mixtures of types 1,2,3,A

Common features in Cu redox proteins

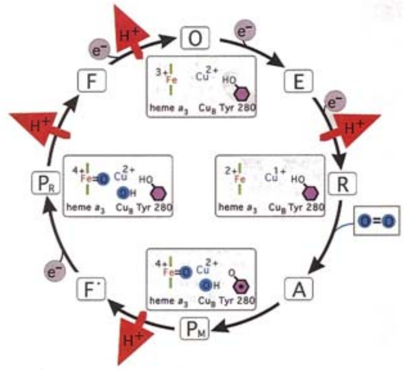
- All Cu ions have at least an imidazole ligand (from Histidine).
- Many have 2 or 3 imidazole ligands
- In SOD Cu has 4 imidazole ligands

- Note: Non-redox Cu proteins have NO imidazole ligands (Thioneines)

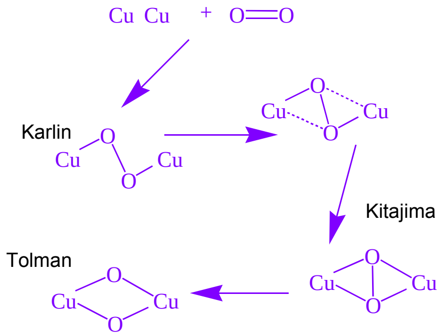
Hemocyanin Active site: type 3



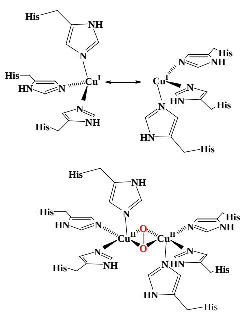
Cytochrome oxidase



Process of dioxygen binding

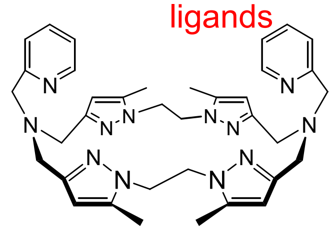


Dinuclear copper protein containing the type-3 site: hemocyanin



- Cu-Cu distance: ~ 3.6 Å in oxy-hemocyanin
- O_2 coordination mode: side-on μ-η^2:η^2
- EPR silent
- UV/Vis: 345 nm (ε=20000)
  570 nm (ε=1000)
- Raman: ν(O-O) = 750 cm^{-1}

Synthetic peroxido dicopper(II) complexes using macrocyclic ligands



+ 2 eq Cu(I) + O_2

MePy22Pz

Johan Bol, PhD Thesis

Synthesis of the peroxido complex

1/ Under argon, at RT, in CH_2Cl_2:

$[Cu^I_2(MePy22Pz)]^{2+} + O_2 \longrightarrow [Cu^{II}_2(MePy22Pz)O_2]^{2+}$

purple solution

↓ **15 min**

green solution

Synthesis of the peroxido complex

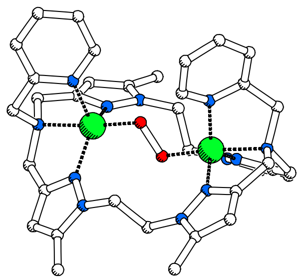
2/ At -30 °C, and after evaporation of the solvent:

$[Cu^I_2(MePy22Pz)]^{2+} + O_2 \longrightarrow [Cu^{II}_2(MePy22Pz)O_2]^{2+}$

purple powder

stable at room temperature

Dinuclear structure for a dicopper peroxide-bridged system



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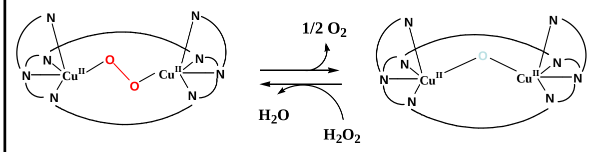
Decomposition of the purple peroxido complex



μ-peroxido μ-oxido

Applicable in catalysis???

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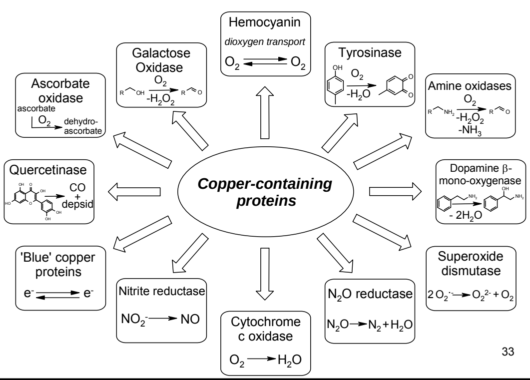
Overall scheme Cu oxidations



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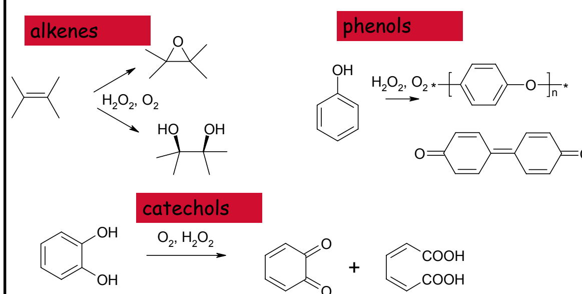
Most important oxidation reactions studied (Leiden):



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Oxidation reactions

1. Oxidative phenol coupling (dehydrogenation)
   * polymerisation (desired)
   * dimerisation (not desired)
2. Epoxidations (with Mn)
3. Paint drying (oxidations)

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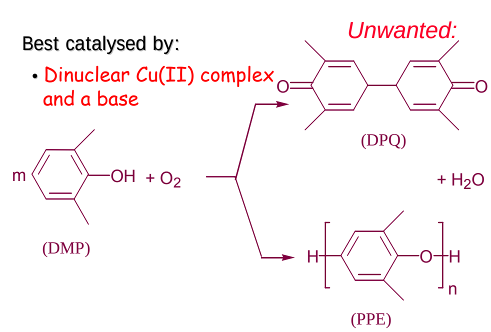
Reaction Process

Best catalysed by:

- Dinuclear Cu(II) complex and a base



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Why research on the oxidative coupling of DMP?

- Oxidative coupling of DMP (2,6-dimethylphenol) produces a high-performance thermoplast.
- It can provide a better understanding in type III copper proteins used in dioxygen metabolism.

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Findings in Oxidative Coupling

- Cu(II) complexes of ligands with N-donor atoms are best catalysts.
- Basicity of the ligand increases activity .
- Bulkiness of the ligand increases activity.
- Dualistic character of water: some needed; too much water poisons the catalyst.
- Standard ligand N-methylimidazole (Nmiz).
- Preferred solvent: acetonitrile.

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Major recent mechanistic findings (Aubel, Boldron, Gamez)

1. Dinuclear catalytic species most likely: second order kinetics in Cu; first order in Cu for preformed dinuclear species
2. Two-electron transfer reactions and phenoxonium species most likely.
3. Reoxidation with dioxygen is rate limiting

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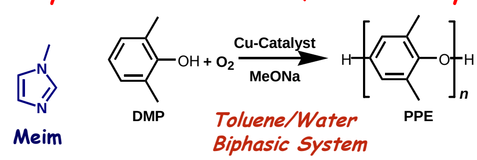
Polymerization of 2,6-dimethylphenol



Ligand	Base	°C	Atm.	% H_2O	Conv.	Min.	TON	R_0	M_w
30 Meim	1.5	25	O_2	33.3	100	33	60	13	21,900
30 Meim	2	25	O_2	33.3	100	32	60	15	78,000
30 Meim	2.5	25	O_2	33.3	100	26	60	15	44,500
30 Meim	3	25	O_2	33.3	100	23	60	17	50,100
30 Meim	2	25	Air	33.3	100	47	60	11	61,400
4 Meim	2	25	Air	33.3	71	270	43	0.5	2,800
4 Meim	2	25	O_2	33.3	85	270	51	0.7	4,000

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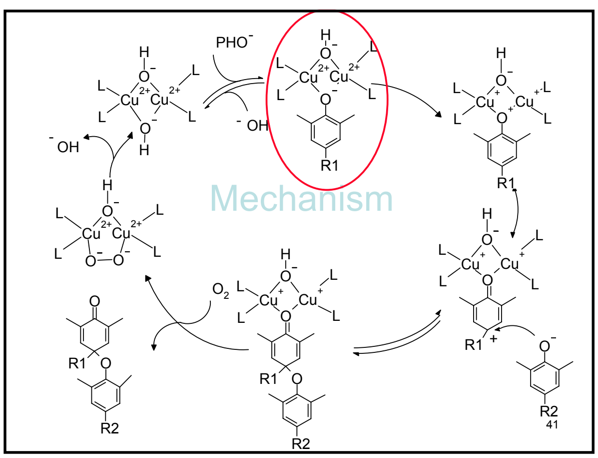

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Outlook Phenol Coupling

- Ligands: More dinucleating ligands
- Solvents: Mixtures; biphasic; water role
- Reoxidation mechanism from Cu(I)
- Chain growth and rearrangements
- Other metal ions: Fe, Mn
- Other alcoholic substrates

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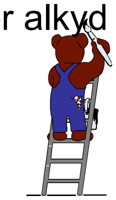
The transition-metal chemistry of alkyd paints.

Watching paint dry

Substitutes for cobalt complexes in driers for alkyd paints



1. Mechanistic studies, with commercial (Nuodex) and synthetic systems
2. Search for other metals and reagents

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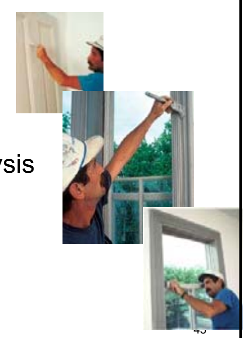
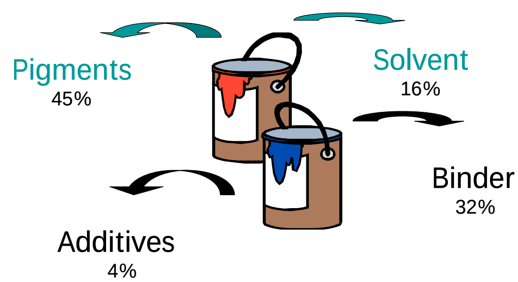
Outline

- What is alkyd paint
- The problem
- Model system and analysis
- A possible solution



What is in a can of paint?



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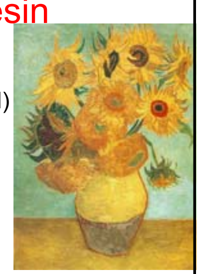
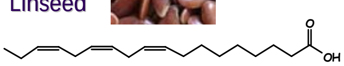
Binder: alkyd resin

Polyester of:
- Polyol (glycerol)
- Phthalic acid
- Fatty acid

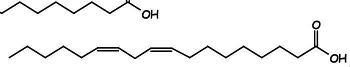
Linseed



Sunflower



Linolenic acid



Linoleic acid

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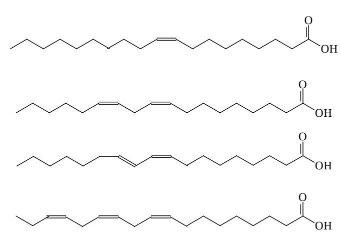
Fatty acids



Oleic acid

Linoleic acid

Ricinoleic acid

Linolenic acid

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Initiation: Radical Generation

Via oxygen activation:

$Co^{3+} + O_2 \rightarrow CoOO^{3+}$

$CoOO^{3+} + RH \rightarrow CoOOH^{3+} + R\cdot$

Via direct hydrogen abstraction

$Co^{3+} + RH \rightarrow Co^{2+} + H^{+} + R\cdot$

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Free radical chain autoxidation

Initiation

$RH \rightarrow R\cdot + H\cdot$

Propagation

$R\cdot + O_2 \rightarrow ROO\cdot$

$ROO\cdot + RH \rightarrow ROOH + R\cdot$

$ROOH + M^{n+1} \rightarrow ROO\cdot + M^{n+} + H^{+}$

$ROOH + M^{n+} \rightarrow RO\cdot + M^{n+1} + OH^{-}$

Termination

$2\ ROO\cdot \rightarrow ROOR + {}^{1}O_2$

$2\ ROO\cdot \rightarrow ROH + R{=}O + {}^{1}O_2$

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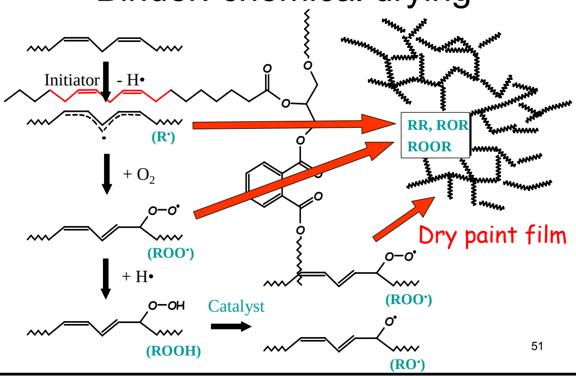
Binder: chemical drying



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Additives

- Drying catalyst
  - Cobalt octoate (primary drier)
  - Ca, Zr, Sr (secondary driers)
- Anti-skinning agent
  - Methyl ethyl ketoxime (MEKO)
- Anti-foaming agents
- Emulsifying agents

Suspected carcinogenic

The problem!

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Coatings Project

- Understand role of methyl ethyl ketonoxim (Meko) as antiskin agent
- Find suitable model paint system
- Measure initiation (FTIR)
- Measure propagation (Size exclusion chromatography, SEC)

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Aim

Replacement of Co as active drying species by environmentally more acceptable Mn complexes

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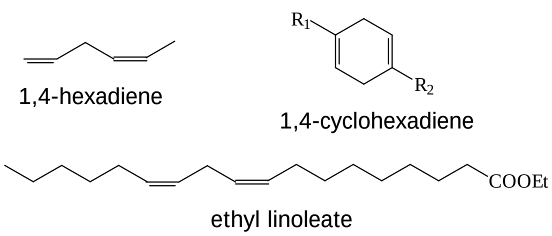
Used model compounds for the alkyd resin



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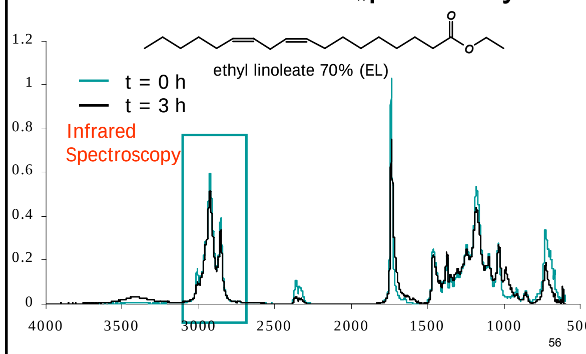
How do we watch „paint“ dry?



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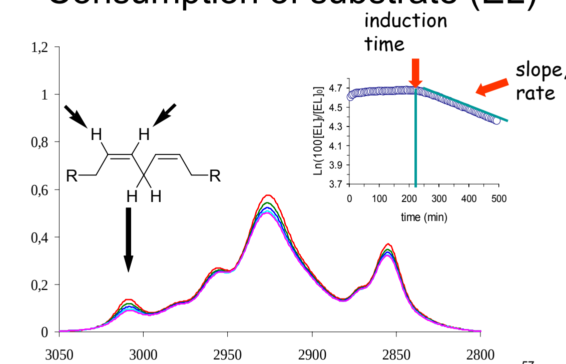
Consumption of substrate (EL)



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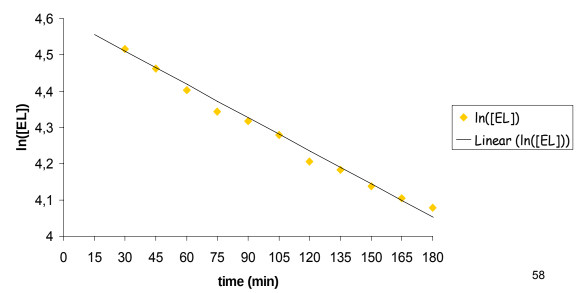
S. Warzeska *et al.*, *Prog.Org.Coat.* **2002**, *44*, 243

Proces shows First order kinetics



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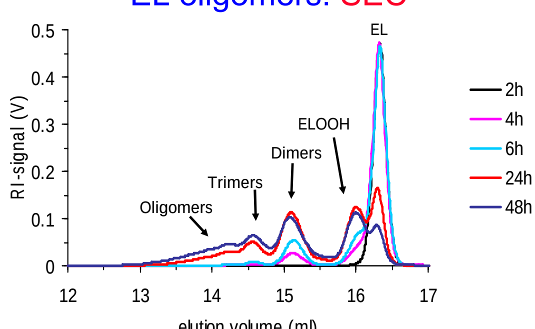
Second TOOL: Formation of the EL oligomers: SEC



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Tests in alkyd paints

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Example Uralac AD 152 WS-40 from DSM

	drying by hand on glass 60 µm		drying time Braive recorder, 76 µm at 23 °C and 50% relative humidity		
drier	s.d	t.d	stage a	stage b	stage c
Co-Ca-Sr	1.45	2.15	1.15	2.15	6.45
Mn-Ca-Zr	> 6.00	-	1.30	12.30	16.00
Mn-bipy	3.00	> 6.00	1.30	6.30	10.00
$Mn(acac)_3$	2.00	2.30	1.15	2.15	4.00

R. van Gorkum *et al.* EP1382648 A1, 2004

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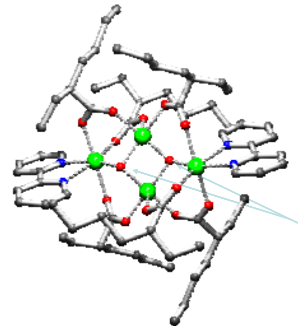
Isolated from catalyst: Structure of $Mn_4O_2(bpy)_2(2\text{-ethylhexanoate})_6$



Mixed valence!

2 Mn^{2+}
2 Mn^{3+}
6 2-ethylhexanoate
2 bipyridine
2 O^{2-}

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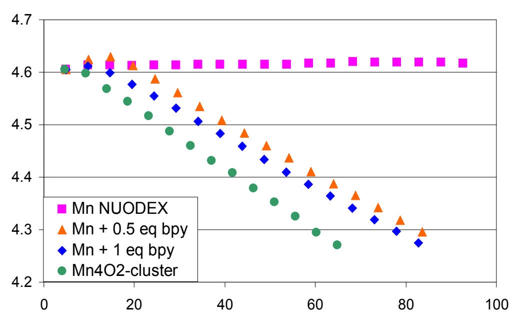
Activity of the Mn cluster in $Mn_4O_2(bpy)_2(2\text{-ethylhexanoate})_6$



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Most active systems

- $Mn(acac)_3$ as such: good results
- BUT: even better when bpy is added to the solution of $Mn(acac)_3$
- Substituted acac ligands and co-ligands (chelating N donor ligands): further improvements

R. van Gorkum, E. Bouwman and J. Reedijk. (2004). Drier for alkyd based coating; Pat. Appl. 02077904.7 EP 1 682 648 A1 (The Netherlands)

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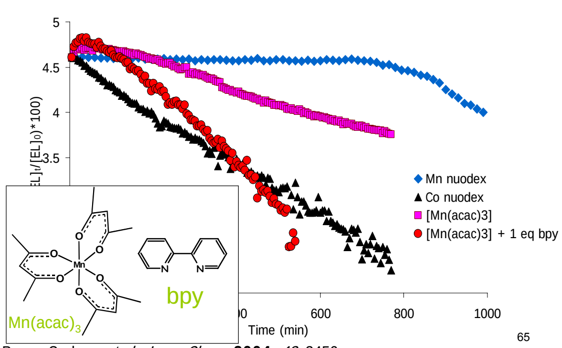
Results: FT-IR plots of (new) driers



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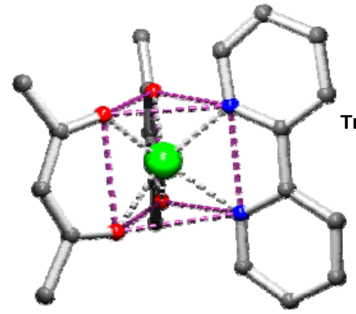
R. van Gorkum *et al.*, *Inorg.Chem.* **2004**, *43*, 2456

$[Mn^{II}(acac)_2(bpy)]$ structure



Trigonal prismatic coordination geometry

R. van Gorkum *et al.*, submitted for publication

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The magic of bipyridine:

Bipyridine facilitates the reduction of Mn(III) to Mn(II)

This enhances the initiation...

$[Mn^{III}(acac)_3]$ + EL-H $\xrightarrow{+\ bpy}$ $[Mn^{II}(acac)_2(bpy)]$ + EL$^{\bullet}$ + Hacac

...and also the peroxide decomposition

$[Mn^{III}(acac)_3]$ + ROOH $\xrightarrow{+\ bpy}$ $[Mn^{II}(acac)_2(bpy)]$ + ROO$^{\bullet}$ + Hacac

$[Mn^{II}(acac)_2(bpy)]$ + ROOH $\xrightarrow{+\ Hacac}$ $[Mn^{III}(acac)_3]$ + RO$^{\bullet}$ + H_2O + bpy

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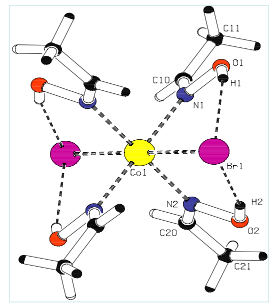
X-ray structure of $[Co(acetaldoxime)_4Br_2]$



Co-Br = 2.65 Å
Co-N = 2.15 Å
O---Br = 3.1 Å

- Intramolecular hydrogen bonding

Several related complexes made with other oximes

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Conclusions Mn catalysts

- Mn compounds offer a good alternative to Cobalt drying catalysts; good prototype: $[Mn(acac)_3]$
- Tripodal, tetradentate ligands have been used successfully in Mn paint-drying catalysts
- With these ligands Mn is much more active than Fe and even better than the best so far: $[Mn(acac)_3]$
- A rate difference is observed when peroxides are present initially compared to clean model systems
- The rate is influenced by the pK_a of the ligands
- The differences in induction time cannot be fully understood at the moment

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Conclusions Co replacers

- Mn-Nuodex + bipyridine
  - 2 equivalents bpy bound to Mn-Nuodex in situ
  - best activity (FTIR): Mn-Nuodex + 2 equiv. bipy
  - active species?: $Mn_4O_2(bpy)_2$(2-ethylhexanoate)$_6$
- Co-Nuodex + bipyridine
  - 1 equivalent bipy is bound to Co-Nuodex in situ
  - adding bpy has a negative influence on the performance of Co-Nuodex (FTIR)

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Fundamental Chemist: It is a pity that this reaction does not run; fortunately, I do know why!

Applied Chemist: It is a pity that we do not know why this catalyst works; however, it runs with a good yield.

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Concluding Remarks and Outlook

- Ligands are THE tool for all coordination chemist whether making materials or catalysts or drugs.
- Fine tuning applications of coordination compounds, requires always also DESIGN & FINETUNING of the ligands

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