

THE USE OF DEUTERIUM OXIDE TO STABILIZE PHARMACEUTICALS AGAINST CHEMICAL DEGRADATION

KHO KIAT NEE

What is deuterium oxide?

- DEUTERIUM
 - ^2H , D
 - rare, stable, non-radioactive, natural heavy isotope of hydrogen, ^1H
 - one proton + one neutron in nucleus
 - twice the mass of hydrogen
 - same electronic configuration
 - isotopes:
 - similar chemical properties
 - same chemical reaction but different rates
 - » ISOTOPIC EFFECT

- ISOTOPIC EFFECT

- a difference in rate due to a difference in the isotope present in the reaction system
- important in deuterium/hydrogen reactions

- DEUTERIUM OXIDE (D₂O)

- differs from ordinary water (H₂O) in many of its physical properties
- different ionic equilibrium
 - ionic constant of D₂O = 10^{-15}
 - ionic constant of H₂O = 10^{-14}
 - » pH differs from pD
 - » chemical activity of D⁺, H⁺ are different
 - » pK_a values of weak acids and bases in deuterium oxide are different from those in water

Table 1: Some physical properties of water and deuterium oxide

PROPERTY	WATER (H₂O)	DEUTERIUM OXIDE (D₂O)
Melting point, °C	0.00	3.81
Boiling point, °C	100.00	101.42
Density, g/cc	0.9982	1.1056
Temp. of max density, °C	3.98	11.23
Viscosity, centipoise, 20°C	1.005	1.25
Surface tension, dynes-cm, 25°C	71.97	71.93
Dielectric constant, 25°C	78.54	78.93
Heat of formation, cal/mole, liq.	-68,320	-70,410
Free energy of formation, cal/mole, liq	-56,690	-58,200
Entropy, e.u./mole, liq.	16.75	18.19
Heat of fusion, cal/mole	1,436	1,515
Heat of vaporization, cal/mole, 25°C	10,515	10,846
Zero point energy, cal/mole	13,219	9,664

What make deuterium oxide useful in stabilize pharmaceuticals against chemical degradation?

- Deuterium has double the mass of hydrogen
 - large influence of isotopic effect in reactions involving deuterium
 - slower chemical reactions with deuterium
- Deuterium oxide ionize to a lesser extent than water
 - important in reactions dependent on H^+ ion, eg. protonation and deprotonation
 - slower the rate of these reactions in deuterium oxide
- Deuterium bonds are stronger than hydrogen bonds
 - provide stronger hydrophobic interactions
 - more energy required to break the deuterium bonds than hydrogen bonds

Use of deuterium oxide in stabilizing compounds

- Trivalent Oral Poliovaccine
 - suspended in 87-90% deuterium oxide
 - 45°C, 1000-fold increase in stability
 - 42°C, 100-fold increase in stability
 - 37°C, 3-10-fold increase in stability
- Indocyanine green
 - diagnostic dye
 - undergoes rapid hydrolysis in aqueous solution
 - 1.5 fold reduction of hydrolysis rate in deuterium oxide

- Tauromustine
 - taurine-based nitrosourea
 - alkylating antineoplastic agent
 - unstable in aqueous solution
 - ionization of N-3 proton of nitrosourea moiety
 - 1.2 fold reduction of degradation rate in deuterium oxide
 - deuterium exchange with hydrogen at N-3 position
 - slower rate of protonation reaction



- Benactyzine
 - combination with atropine and oxime to use as an antidotal treatment for poisoning of organophosphorous agents and pesticides
 - undergoes rapid hydrolysis of ester group in aqueous solution
 - hydrolysis: pre-equilibrium protonation --> nucleophilic addition of water molecule
 - water is a stronger nucleophile than deuterium oxide
 - nucleophilic addition is faster in water --> increase hydrolysis rate

How safe deuterium oxide is?

- natural isotopic abundance of deuterium = 0.0156% (1-6400)
 - human body normally contains 75mg of deuterium per kg of body weight
 - i.e. 225mg in 3kg newborn, 5g in 70kg adult
- Used extensively as tracer for biomedical experimentation and diagnoses
- safety at low concentrations has been investigated and proved
- toxic threshold = above 20% of total body fluid
 - 1,785 times greater than that normally present in nature

- if a 1 ml IV dose of deuterium oxide is given to a 70kg adult, deuterium would constitute 2.2% of total body water hydrogen, this is far below the toxic threshold of deuterium oxide
- extra burden of deuterium oxide in small volume parenterals should be harmless to human
 - transitory enrichment of body water with deuterium oxide would not exceed the toxic threshold
 - deuterium would be cleared rapidly from the body with water turnover rate
- further investigations and clinical trials are necessary

Availability of deuterium oxide

- Readily available with various isotopic purities
- current price (1999) for pure deuterium oxide (100% D, with 99.996% isotopic purity) is ~A\$114 per 10g
- the price is considerably lower for isotopic purities below 99%

OBJECTIVE

- To investigate the effect of deuterium oxide on the degradation rate of a chemical compound formulated in deuterium oxide
 - Deuterium oxide would only be useful for compounds that are
 - expensive
 - unstable
 - small volume parenteral
 - given intravenously or followed admixture with small volume parenteral
 - Proposed chemical compounds
 - Prostaglandin E
 - Polynucleotides

Prostaglandin E

- highly unstable, difficult to formulated and handle
- readily undergoes dehydration in acidic and basic aqueous solution to prostaglandin A, then isomerised to prostaglandin B

Prostaglandin E

- PGE₁
 - expensive
(1mg~A\$110)
 - formulated in 4% alcohol, 0.9% saline
 - 4°C t₉₀ = 106.5 days
 - 4°C t₉₅ = 51.8 days
 - 25°C t₉₀ = 9.8 days
 - 25°C t₉₅ = 4.8 days
 - marketed products
 - Prostin VR
 - stored at 2-8°C
 - Caverject
 - stored at -5°C
- PGE₂
 - expensive
(1mg ~A\$100)
 - formulated in concentrated alcoholic solution
 - stored at -20°C
 - pH 3.5, 25°C
 - half-life = 40 days
 - shelf-life = 133 hours
 - pH10, 25 °C
 - shelf-life = 0.45 hours
 - diluted with saline
 - used within 24 hours

Polynucleotides

- New, prospective compounds, used for the treatment of life threatening diseases
 - eg. viral infections, cancer, vascular disease
- Very unstable
- Expensive
- Stability depends upon intermolecular hydrogen bonds
- Potential use of deuterium oxide to stabilise the structure

METHODOLOGY

- Prostaglandin E
 - experiment will be conducted with reference to British Pharmacopoeia 1999 under Assay of Prostaglandin E and the related impurities
 - prostaglandin will be formulated in small volume of deuterium oxide (deuterated ethanolic solution may be used as prostaglandin is very insoluble in water)
 - prostaglandin in non-deuterated ethanol will be used as the control solutions
 - Analytical method: High Performance Liquid Chromatography (HPLC)

METHODOLOGY

- Polynucleotides
 - similar to those of prostaglandin
 - Analytical method: Capillary Zone Electrophoresis (CZE)
- validation of the tests would be necessary
- high cost compounds - representative small scale stability studies

Potential problems arising from formulation of drug compounds in deuterium oxide

- pD is different from pH
 - adjustment of pD using pD correction factor
 - $pD = pH \text{ (pH meter reading)} + 0.4$
 - deuterated buffer will be made by carrying out isotopic exchange of aqueous solution with deuterium oxide
- deuteration of other ingredients in the formulation
 - compounds would be deuterated at different rate
 - carboxylic acids, alcohols, amino compounds: instantaneously deuterated
 - hydrogen α -carbonyl group: exchange slowly with deuterium
 - proteins, polynucleotides : deuterated much slower
 - deuterated position will exchange back with hydrogen at the same relative rate following dilution and administration into body

- Deuterium undergoes exchange reaction in the body
 - deuterium would deuterate organic molecules in the body
 - eg. glucose, amino acids
 - would not be a problem, our body already contains small amount of deuterium oxide due to natural isotopic abundance
 - deuterium oxide administered would be distributed and excreted rapid with water turnover rate
- Safety
 - extra burden of deuterium oxide in small volume parenterals should be harmless to human
 - transitory enrichment of body water with deuterium oxide would not exceed the toxic threshold
 - deuterium would be cleared rapidly from the body with water turnover rate
 - further investigations and clinical trials are necessary

EXPECTED OUTCOMES

- Deuterium oxide improve stability of unstable drugs
 - improve stability of prostaglandin preparation as deuterium substitute with hydrogen atoms thus reducing the degradation rate
 - increase stability of polynucleotide preparation as deuterium oxide strengthen the hydrogen bonding within molecules thus stabilize polynucleotide structure



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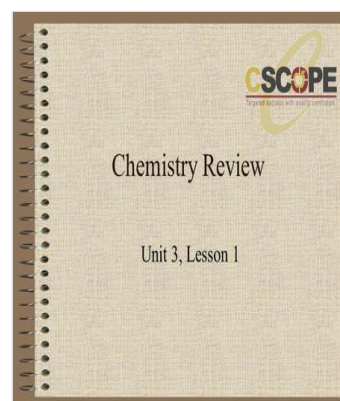
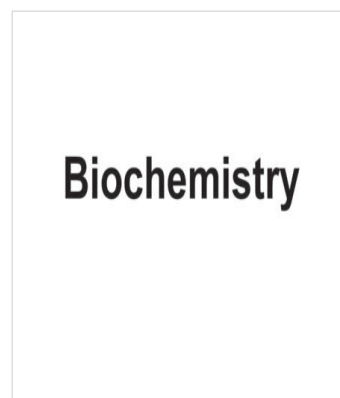
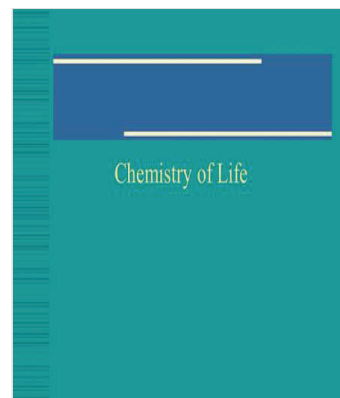
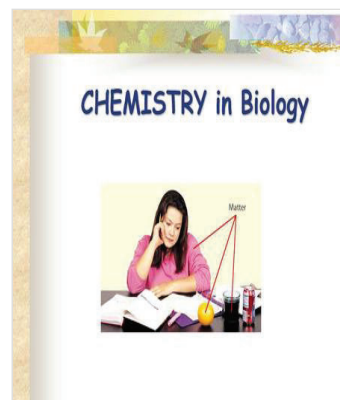
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deuterium oxide

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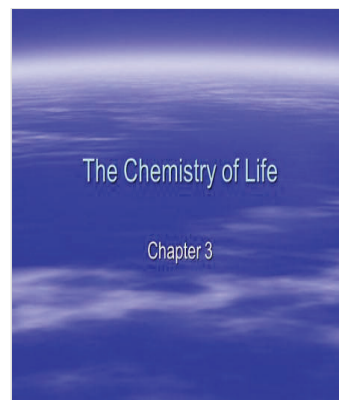
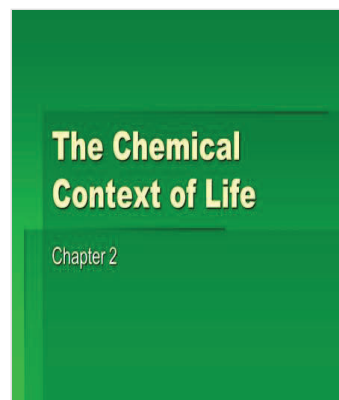
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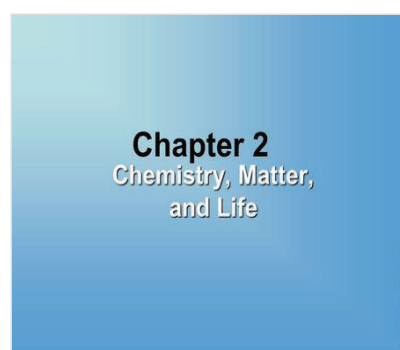
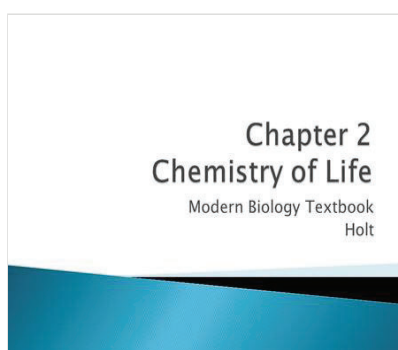
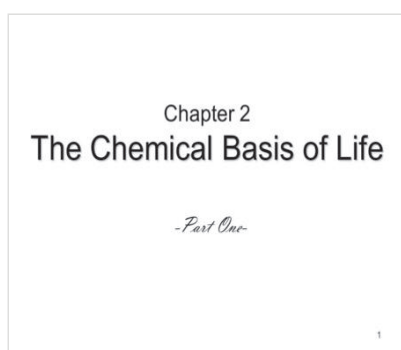
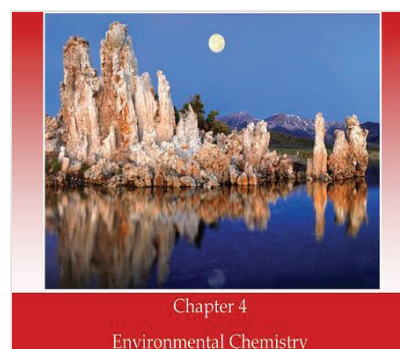
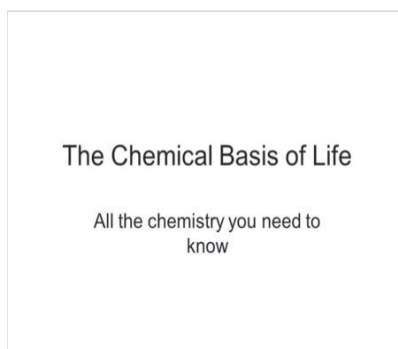
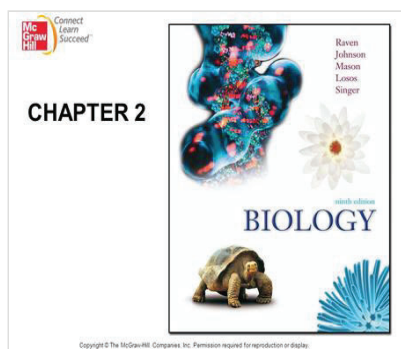
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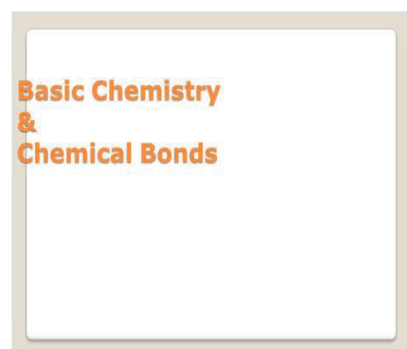
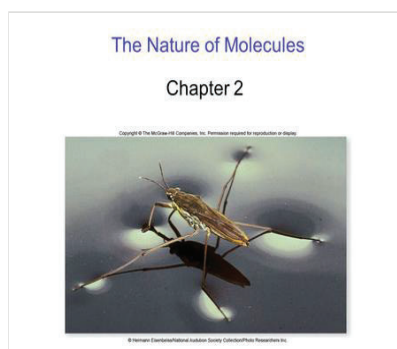
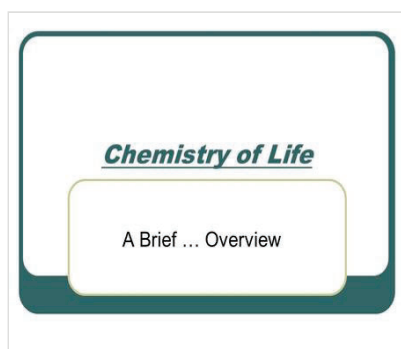
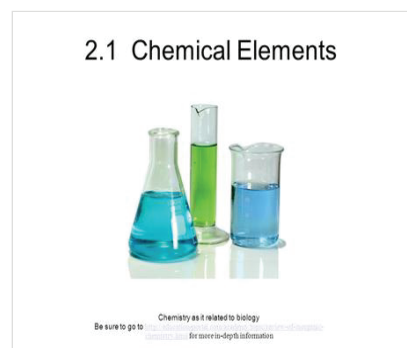
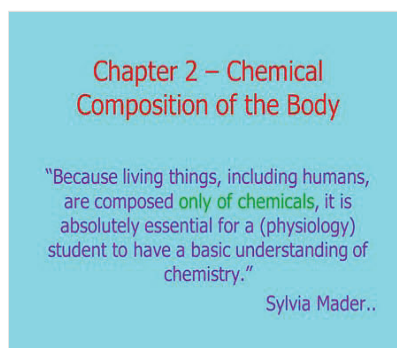
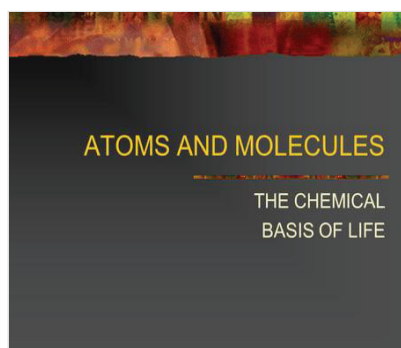
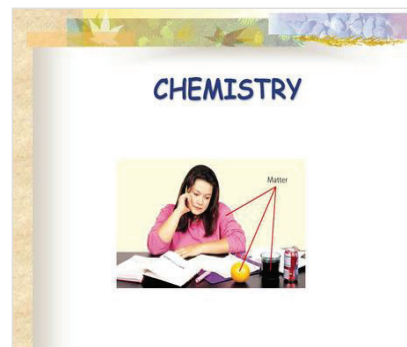
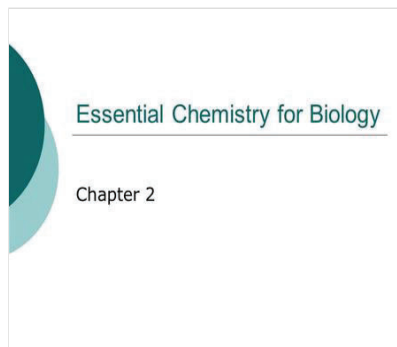
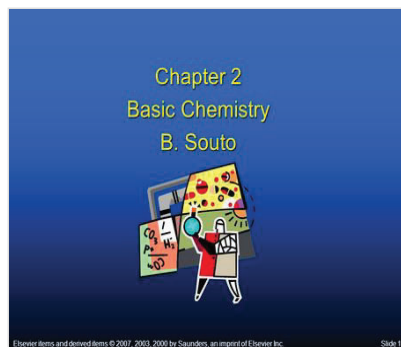
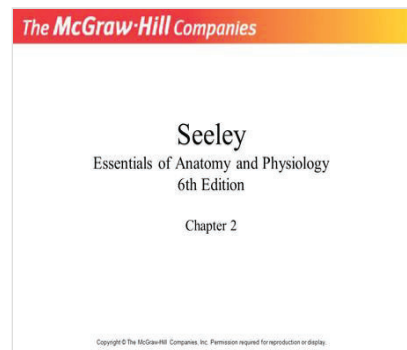
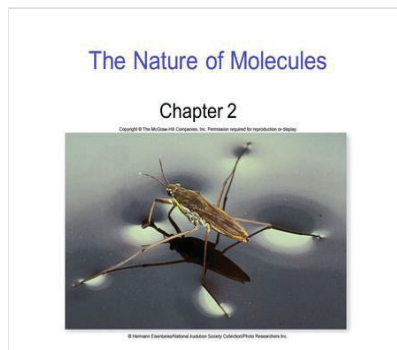
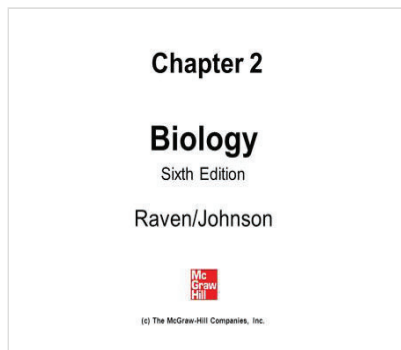
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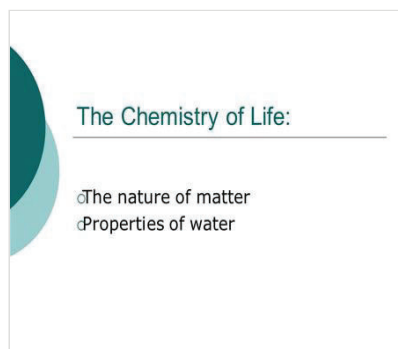
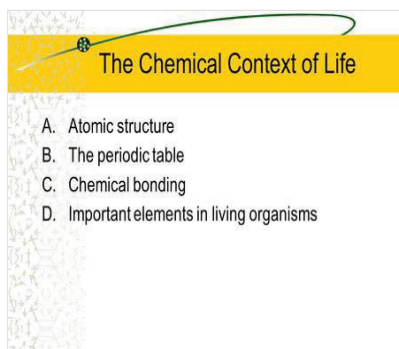
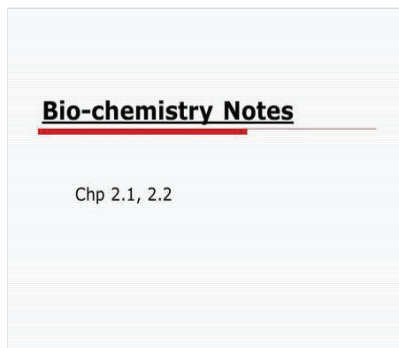
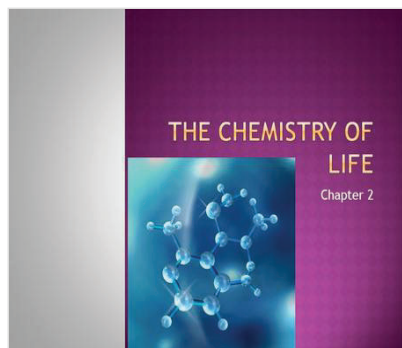
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