

University of Canterbury

End of Year Examinations 2007

Prescription Number(s):	CHEM 465 BCHM 402
Paper Title:	Biological Chemistry

Time Allowed: **THREE HOURS**

Number of pages: **EIGHT**

Answer **FOUR** questions, including at least **ONE** question from each section (A and B and C).

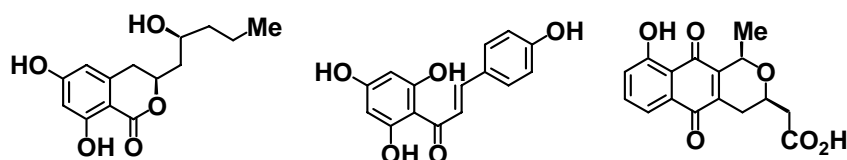
All questions are of equal value.

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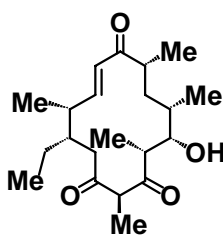
SECTION A

(Answer **AT LEAST ONE** question from this section)

1. (a) Discuss the major features of the three main types of *iterative* polyketide synthase (PKS). Your answer should include the type of organism in which they are found, a summary of the organisation at the protein and genetic levels and a summary of any key features of the chemistry that they control. Each of the following molecules is produced by one of the three types and you should include a brief discussion of how they are formed in your answer.



- (b) The polyketide precursor to the antibiotic pikromycin is shown below. Assuming that it is produced by a modular PKS in which each protein catalyses two condensation cycles, draw out the predicted domain structure that would account for the overall structure of the molecule. Indicate whether each acyl transferase domain is specific for propionate (AT_P), malonate (AT_M) or methyl malonate (AT_{Me}).

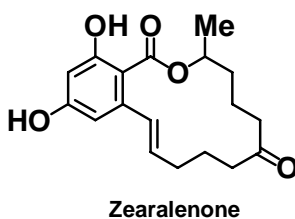


TURN OVER

2. (a) Describe the different NMR methods for the direct and indirect detection of biosynthetic incorporation of deuterium. What are the advantages and disadvantages of the different methods?

The structure of the fungal polyketide metabolite zearalenone is shown below.

- (b) Deduce the structure of the 'reduced' polyketide (nonaketide) intermediate assembled by the zearalenone polyketide synthase, PKS, and show how it would be converted to the final metabolite.
- (c) Redraw the molecule and indicate on it the numbers of acetate-derived hydrogen atoms which will be retained at each carbon atom that is derived from the methyl carbon of acetate



SECTION B

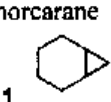
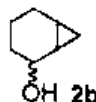
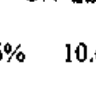
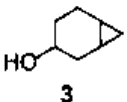
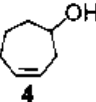
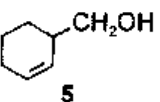

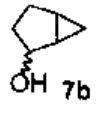
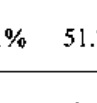
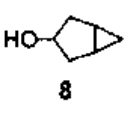
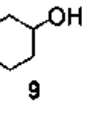
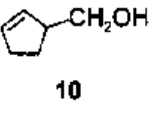
(Answer **AT LEAST ONE** question from this section)

3. (a) Compare and contrast the inner-sphere and outer-sphere mechanisms for electron transfer reactions. Include examples of situations where an electron transfer reaction can be identified with some certainty as proceeding by each of these mechanisms.
- (b) Discuss the reasons that may lie behind the widespread occurrence of outer-sphere (as opposed to inner-sphere) electron transfer reactions in biological systems.
- (c) Outline the means by which the rates and potentials of electron transfer reactions can be tuned in electron transfer proteins. Use your knowledge of how this is achieved in cytochromes as a basis on which to predict how such tuning might be done in blue-copper proteins similar to plastocyanin. Discuss experiments that you could use to test your predictions.

TURN OVER

4. (a) Discuss the means by which information can be gathered about the mechanistic cycle of oxygenase enzymes.
- (b) The following table has been taken from a recent paper (*J. Am. Chem. Soc.*, 2007, **129**, 3514-3515) that describes mechanistic studies on an enzyme system, naphthalene 1,2-dioxygenase (NDOS), that can also achieve monooxygenase reactions on a wide range of substrates.

Table 1. Product Distribution from Probe Oxidation by NDOS

probe conditions	2-endo product	2-exo product	3-ol product	cation product	radical product	radical lifetime
norcaradiene  1	 2a	 2b	 3	 4	 5	
multiple turnover	19.6%	10.6%	7.9%	0%	61.8%	10.6 ±1.6 ns
single turnover	16.3%	7.3%	7.1%	0%	69.2%	14.6 ns
bicyclohexene  6	 7a	 7b	 8	 9	 10	
multiple turnover	10.1%	51.7%	~2% ^a	3.9%	32.3%	18.0 ± 3.0 ns

^a This product elutes in a position that is not fully resolved from that of the 2-*endo* product, so a small amount may be produced.

- What is the key difference between a dioxygenase enzyme and a monooxygenase enzyme?
- Explain how products 2a, 2b, and 5 might arise from oxidation of norcaradiene.
- How are the lifetimes in the last column of the table determined?
- What do the presence and relative amounts of products 2a, 2b, 7a, and 7b tell you about the enzyme?
- Products 4 and 9 are known to result from rearrangements of cationic species derived from the substrates. Show how this may occur and then examine whether they could also result from radical rearrangements.
- Explain the significance of the detection of product 9 in the context of your answer to part (v), and then discuss what further experiments might be required to clarify the situation.

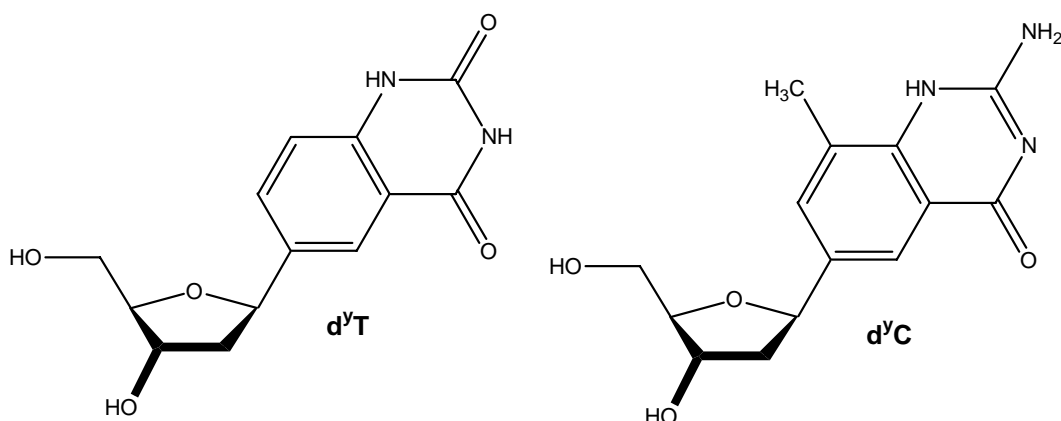
SECTION C

(Answer **AT LEAST ONE** question from this section)

5. Give a critical account of the interactions between bases in duplex nucleic acid structures and the factors that affect these interactions. Incorporate a range of specific examples in your account, including a discussion of synthetic nucleic acids incorporating analogues of the normal bases. You may choose to discuss some possible technological applications of nucleic acids containing base analogues.

In your account, you should also include a discussion of the following information.

The base analogues, d^yT and d^yC, have been incorporated into synthetic oligodeoxyribonucleotides (*J. Am. Chem. Soc.*, 2005, **127**, 3332 -3338). The melting temperatures of some duplexes formed from these oligonucleotides, together with a related unmodified DNA duplex, are given in the **Table**.

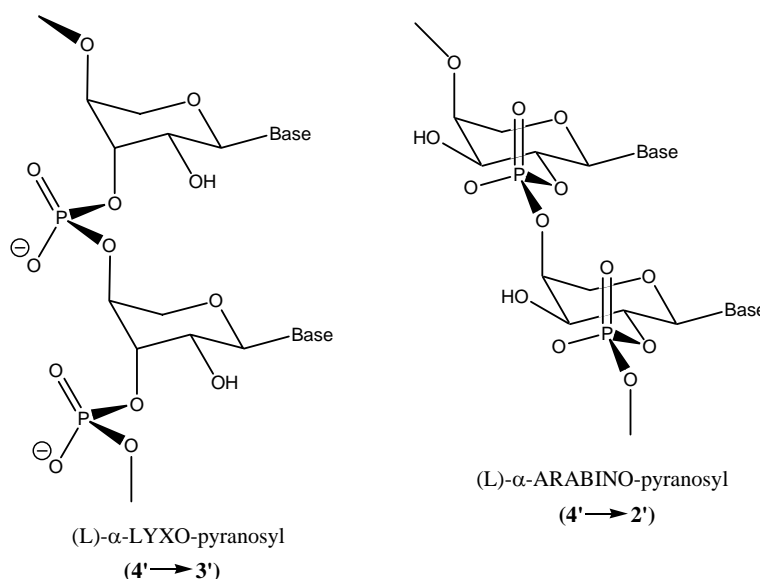
**Table**

Oligonucleotide duplex	Melting temperature, T_m (°C)
5' C C C G C G G G 3' 3' G G G C G C C C 5'	53.4 ± 0.5
5' ^y C ^y C ^y C G ^y C G G G 3' 3' G G G ^y C G ^y C ^y C ^y C 5'	71.1 ± 0.5
5' ^y C ^y C ^y T ^y T ^y C ^y T ^y C ^y C 3' 3' G G A A G A G G 5'	52.3 ± 0.5
5' ^y C ^y C ^y T ^y T ^y C ^y T ^y C ^y C 3' 3' G G A G G A G G 5'	38.3 ± 0.5
5' ^y C ^y C ^y T ^y T ^y C ^y T ^y C ^y C 3' 3' G G A T G A G G 5'	25.6 ± 0.5

TURN OVER

6. Give a critical account of the way in which synthetic chemistry has been used to elucidate the role of sugar residues in the structure and properties of nucleic acids. You should include a discussion of nucleic acids derived from ribose, 2'-deoxyribose, and from synthetic analogues. Illustrate your answer with a wide range of specific examples. You should include a discussion of the following information.

A range of pentopyranosyl units, including (L)- α -ARABINO-pyranosyl and (L)- α -LYXO-pyranosyl, have been incorporated into oligonucleotides via (4' \rightarrow 2') and (4' \rightarrow 3') links. Melting temperatures for homo- and heteroduplex formation have been measured and compared with those for RNA duplex stability. Some representative structures and data for homo-duplex stability are given below. (L)- α -LYXO-pyranosyl (4' \rightarrow 3') oligonucleotides were also found to form stable duplexes with RNA. Under these conditions no stable homo- or hetero-duplex formation is found for the equivalent (L)- α -ARABINO-pyranosyl (4' \rightarrow 3') oligonucleotides.



Table

Pentose	Oligonucleotide duplex								Melting temperature, T_m ($^{\circ}$ C)		
pLYXO	4'	T	T	T	T	A	A	A	A	2'	46.9
pLYXO	2'	A	A	A	A	T	T	T	T	4'	
pARABINO	4'	T	T	T	T	A	A	A	A	2'	69.8
pARABINO	2'	A	A	A	A	T	T	T	T	4'	
pLYXO	4'	T	T	T	T	T	T	T	T	3'	41.2
pLYXO	3'	A	A	A	A	A	A	A	A	4'	
RNA	5'	T	T	T	T	T	T	T	T	3'	ca. 20
RNA	3'	A	A	A	A	A	A	A	A	5'	

END OF PAPER