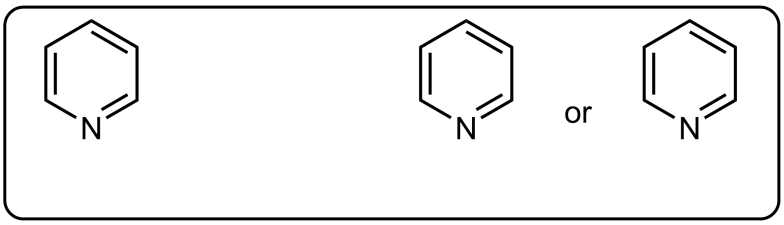
CONCEPT: EAS REACTIONS OF PYRIDINE

- Unlike the 5-membered aromatic heterocycles, pyridine is significantly _____ reactive than benzene.
  - □ Pyridine ring is electron _____.
  - □ N gets a __ charge under EAS conditions.



- _____ groups can help pyridine undergo EAS reactions more effectively.

EXAMPLE: Unlike pyrrole, pyridine undergoes nitration under extreme conditions. Why?

a) Pyridine tends to form radicals under acidic conditions, making nitration reaction difficult.

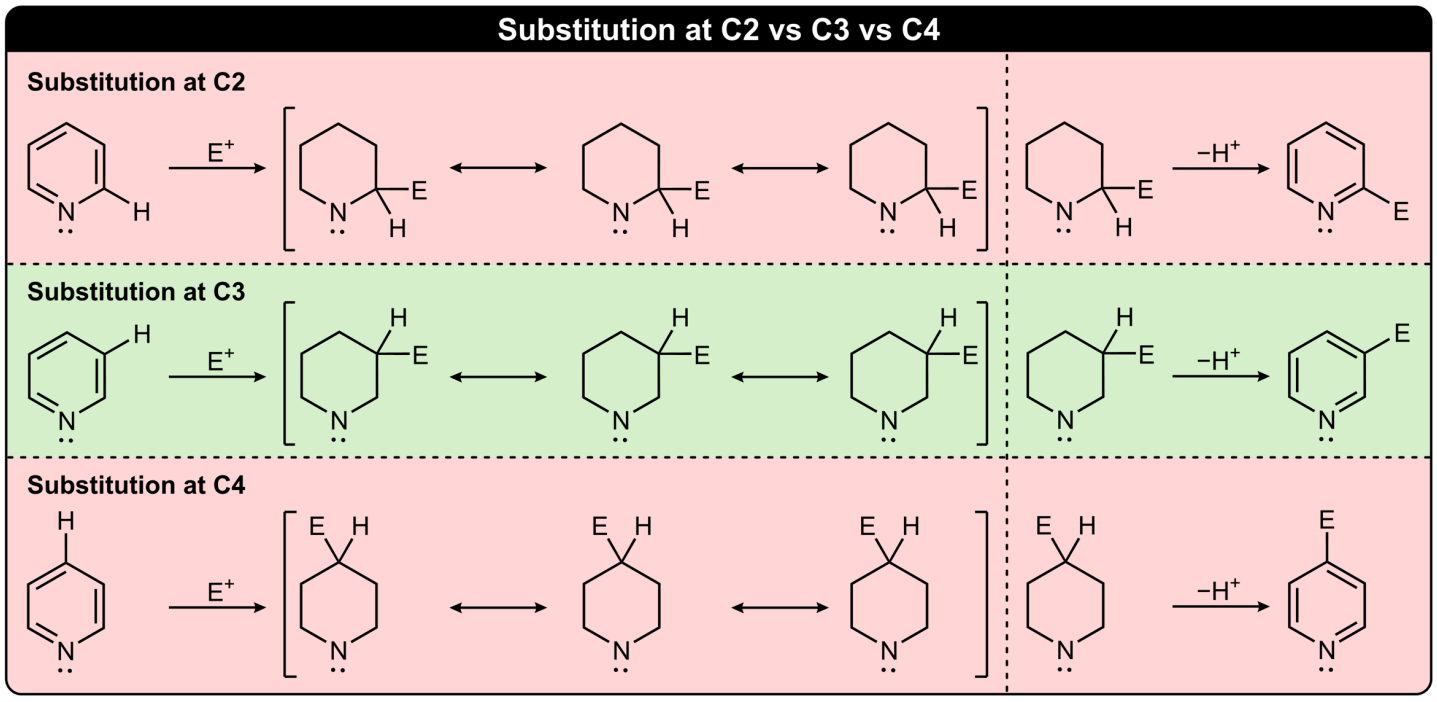
b) Pyridine ring (through C3) attacks the protons instead of the nitronium ion.

c) Under nitration conditions, the N atom in the pyridine ring is protonated, which makes carbocation formation difficult.

d) Pyridine undergoes nitration in multiple steps, requiring a lot of energy.

Substitution at C2 vs C3 vs C4

- EAS reactions of pyridine yield products by substitution at ____.
  - □ Substitution at C__ and C__ usually _____ _____ take place.



CONCEPT: EAS REACTIONS OF PYRIDINE

EXAMPLE: Why does the pyridine ring not undergo nitration at C4?

a) Being the farthest from the nitrogen, the C4 position is the least activated.

b) The reaction intermediate has an electron-deficient nitrogen atom with a + charge.

c) The pyridine ring is more easily nitrated at the nitrogen atom instead of C4.

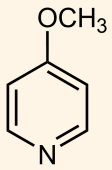
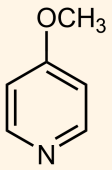
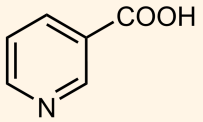
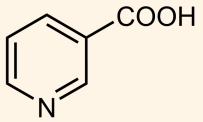
d) The C4 position gets protonated under the acidic conditions of nitration.

Directing Effects in Substituted Pyridines

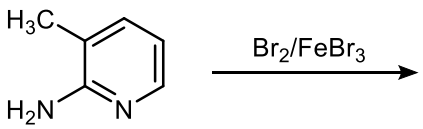
- Similar to 5-membered heterocycles, *o*, *m*, and *p* positions are assigned through the C framework.
- **RULE 1:** Directing effects are the _____ as EAS on benzene rings.
  - □ For polysubstituted rings, the most _____ group takes precedence.
- **RULE 2:** C__ substitution is always preferred.

Directing Groups	
ortho/para	*meta*
—N:	—NO_2
—O:	—NR_3^+
—N(:)—C=O	—SO_3H
—R	—CN
—X	—C=O

EAS Directing Effects

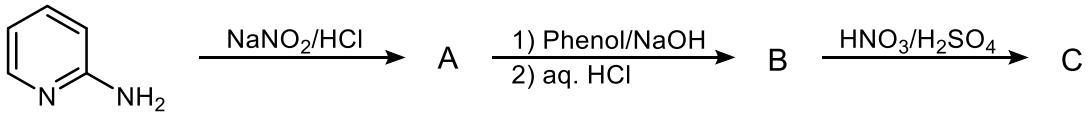
Reactant	Reagents	Directing Effect	Product
	$Br_2/FeBr_3$, 100 °C	OCH_3 → ___ N → ___	
	HNO_3/H_2SO_4, 300 °C	COOH → ___ N → ___	

EXAMPLE: Predict the product of the following reaction.



CONCEPT: EAS REACTIONS OF PYRIDINE

PRACTICE: Draw the structures of products A, B, and C in the following reaction sequence.



PRACTICE: Pyrrolopyridines are a group of fused heterocycles where a pyrrole ring is fused with a pyridine ring. Nitration of the following pyrrolopyridine produces the 7-nitro product while the 5-nitro product is not seen. Draw resonance structures to show why the 5-nitro product is not formed. (Hint: Draw 5 resonance structures).