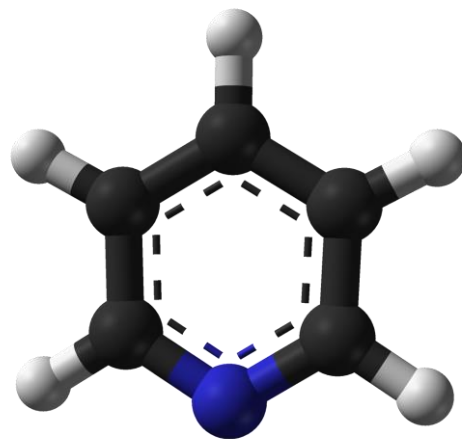


Lecture 3-1

Reactivities of Heteroaromatic – Reaction at Nitrogen



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Recommended Textbook:

Heterocyclic Chemistry, 5th Edition, J. A. Joule, K. Mills, **2010**, Wiley

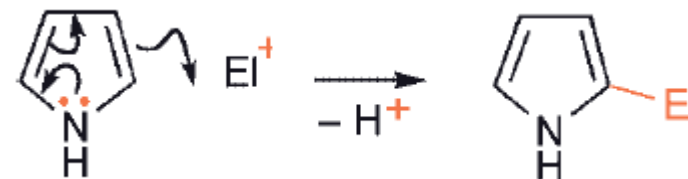
Typical Reactions of Aromatic Heterocycles

- **Reaction at Nitrogen**



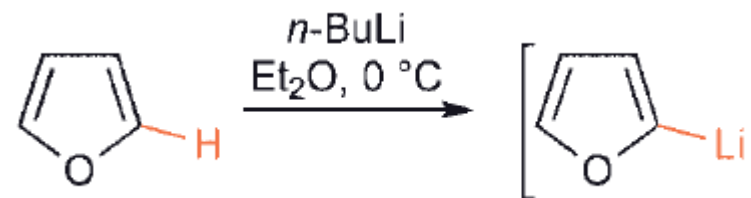
- **Substitution Reactions**

- **Electrophilic Substitution at Carbon**
- **Nucleophilic Substitution at Carbon**
- **Radical Substitution at Carbon**



- *Oxidation and Reduction of Heterocyclic Ring*

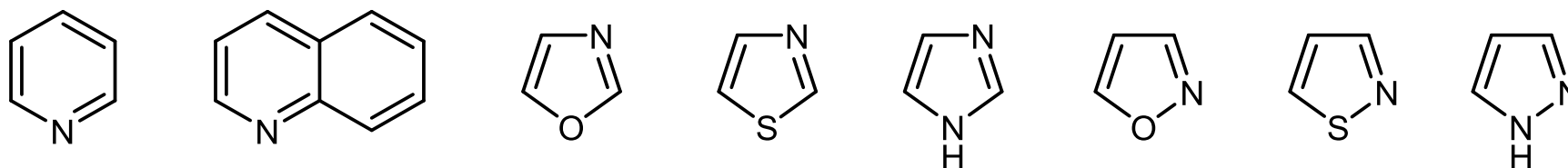
- **Formation and Reactions of Organometallic Compounds**



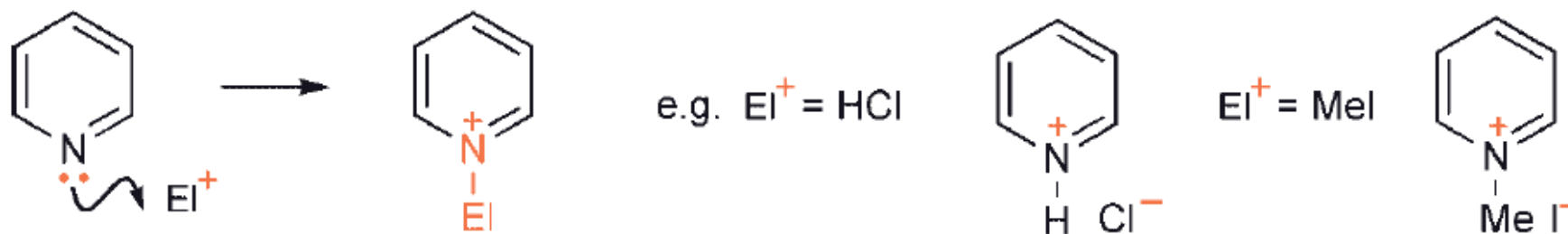
- *Transition Metal-Catalysed Reaction*

1) Reaction at Nitrogen

- Heterocycles which contain an **imine unit (C=N)** as part of their ring structure do not utilise the nitrogen lone pair in their aromatic π -system and therefore it is available for donation to electrophiles



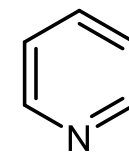
- Such heterocycles are **basic** and will react with **protons**, or other **electrophilic species**, by addition at nitrogen



- In many instances the products from such additions – **salts** – are isolable

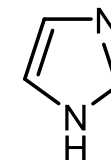
1) Reaction at Nitrogen

- Basicity** : For the reversible addition of a **proton**, the position of equilibrium depends on the pK_{aH} of the heterocycle, and this in turn is influenced by the **substituents present on the ring**



pyridine

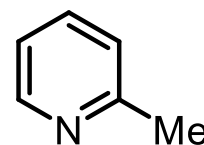
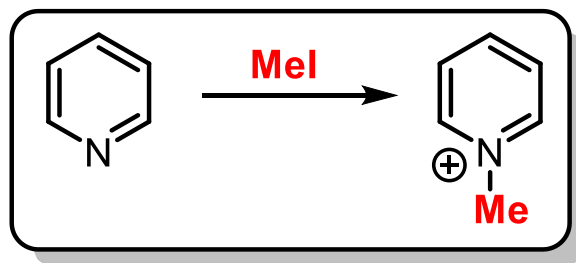
$pK_{aH} = 5.0$



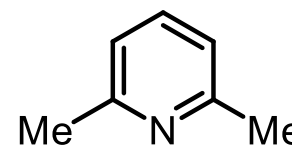
imidazole

$pK_{aH} = 7.1$

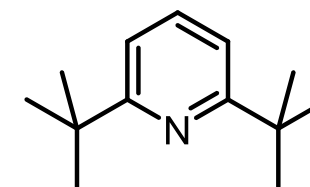
- Nucleophilicity** : Related to basicity, but certainly not always mirroring it. The presence of **substituents adjacent to the nitrogen** can have a considerable effect on how easily reaction with electrophile takes place



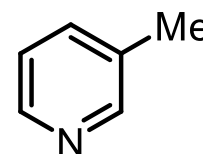
3 times slower



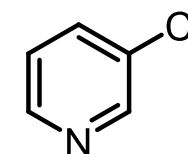
12 times slower



no reaction



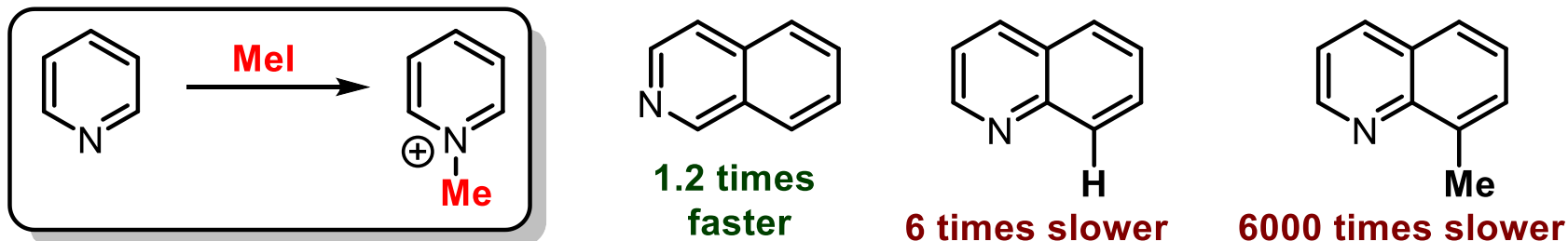
1.6 times faster



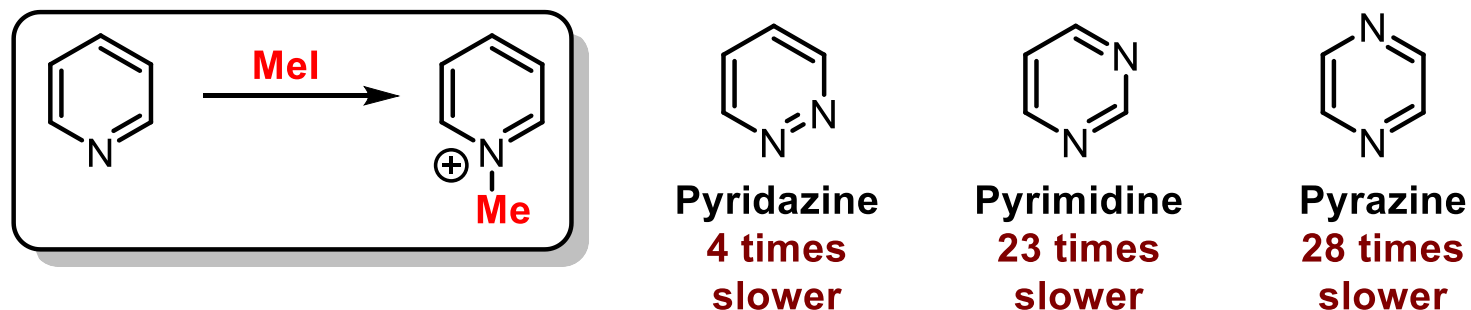
7 times slower

1) Reaction at Nitrogen

- In **bicyclic** molecules, *peri* substituents have a significant effect on the relative rates of reaction with electrophiles

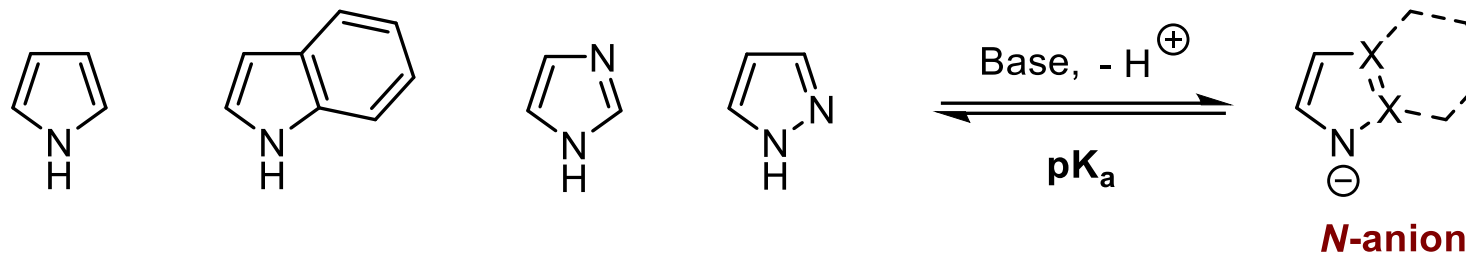


- All the **diazines** react with iodomethane more slowly than does pyridine. Pyridazine reacts with electrophiles faster than the other diazines, due to the ' **α effect**' (the increased nucleophilicity is deemed to be due to **electron repulsion between the two adjacent nitrogen** lone pairs)



1) Reaction at Nitrogen – Deprotonation

- Pyrroles, imidazoles, pyrazoles and benzo-fused derivatives that have a free **N-hydrogen** have pK_a values for the loss of the *N*-hydrogen



- They can be completely converted into *N*-anions by reaction with **strong bases** like sodium hydride or *n*-butyllithium

1) Reaction at Nitrogen – Deprotonation

- These **N-anions** are **nucleophilic at the nitrogen**, in direct contrast to the neutral heterocycle, and thus provide the means by which the nitrogen of azoles can be substituted

