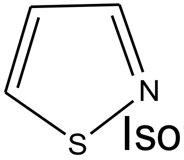
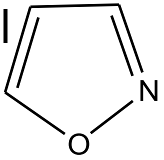
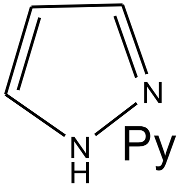
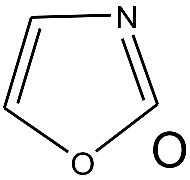
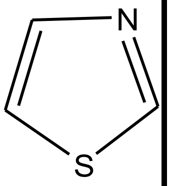
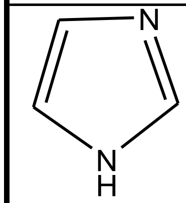
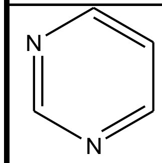
Tautomerism in Alkyl and -OH Derivatives of Heterocycles containing Two Heteroatoms

Colette Jermann
Master in chemistry - Year 4

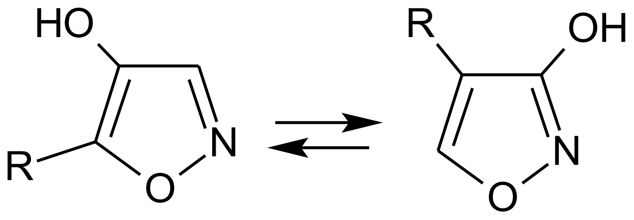
Summary

	Type of tautomerism
 Isothiazole  Isoxazol	-Keto-enol -Substituent
 Pyrazole	-Substituent -Annular
 Oxazole  Thiazole	-Substituent -Ring-chain -No annular tautomerism
 Imidazole	-Annular -Ring-substituent
 Pyrimidine	-keto-enol

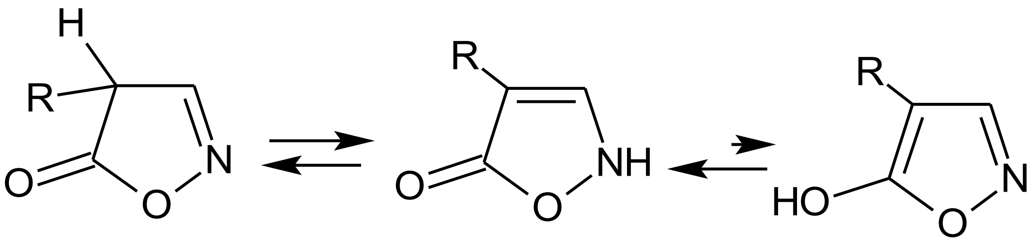
Keto-enol tautomerism

- Isoxazole:

3- and 4-substituted isoxasole



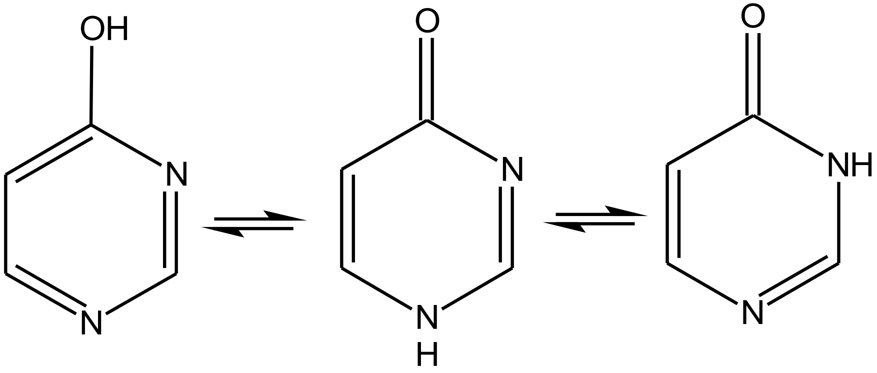
5-substituted isoxasole



⇨ Enol form favoured

⇨ Keto form favoured

- Pyrimidine:

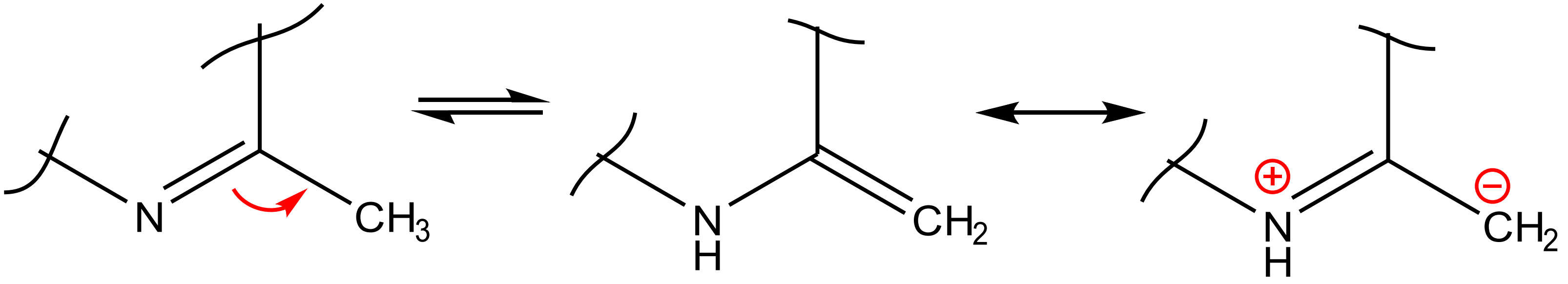


4-hydroxypyrimidine

1H and 3H pyrimidone form

Alkyl substituent in pyrimidine

Methylene tautomer:



Reduced aromaticity

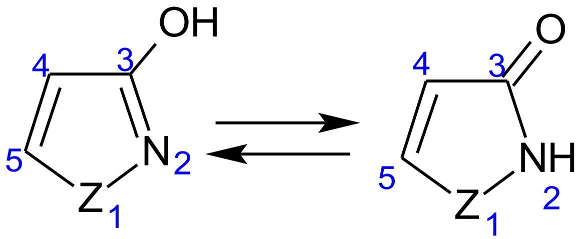
Resonnance form

⇨ Substituent α and γ to N not favourable

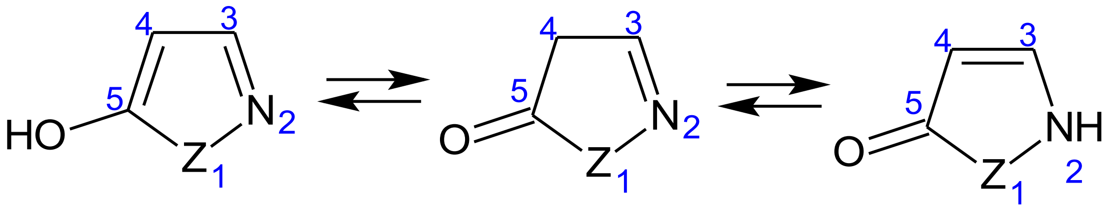
Substituent tautomerism

- Isoxasoles, pyrasoles and isothiasoles:

3-substituted



5-substituted



⇨Enol form favoured

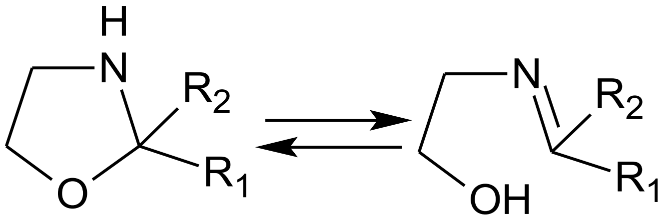
⇨Keto form favoured

- 2-substituted 2,3-azoles:

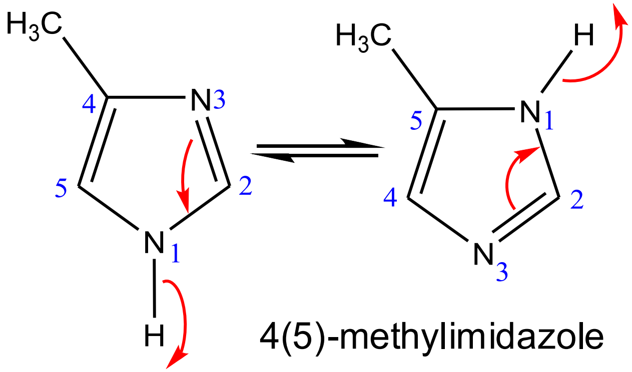
⇨ Keto form favoured

Ring-chain

- Oxazoles:



Annular tautomerism

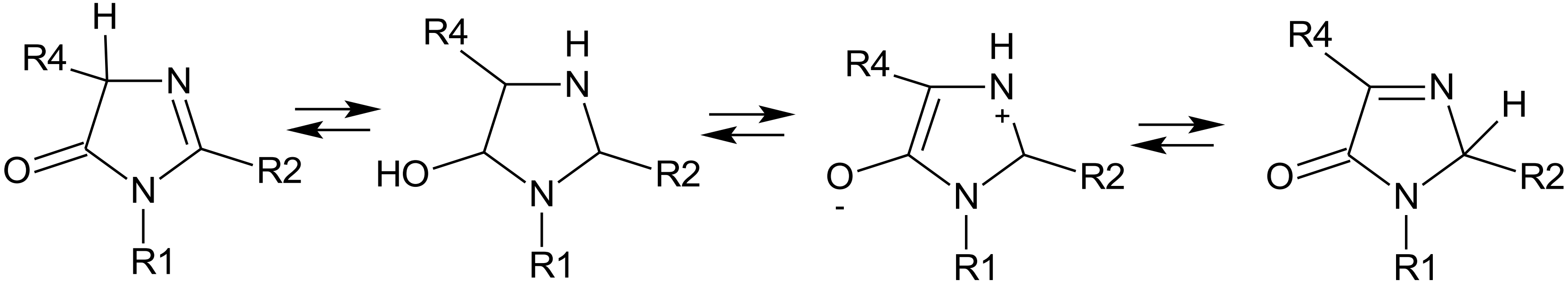


4(5)-methylimidazole

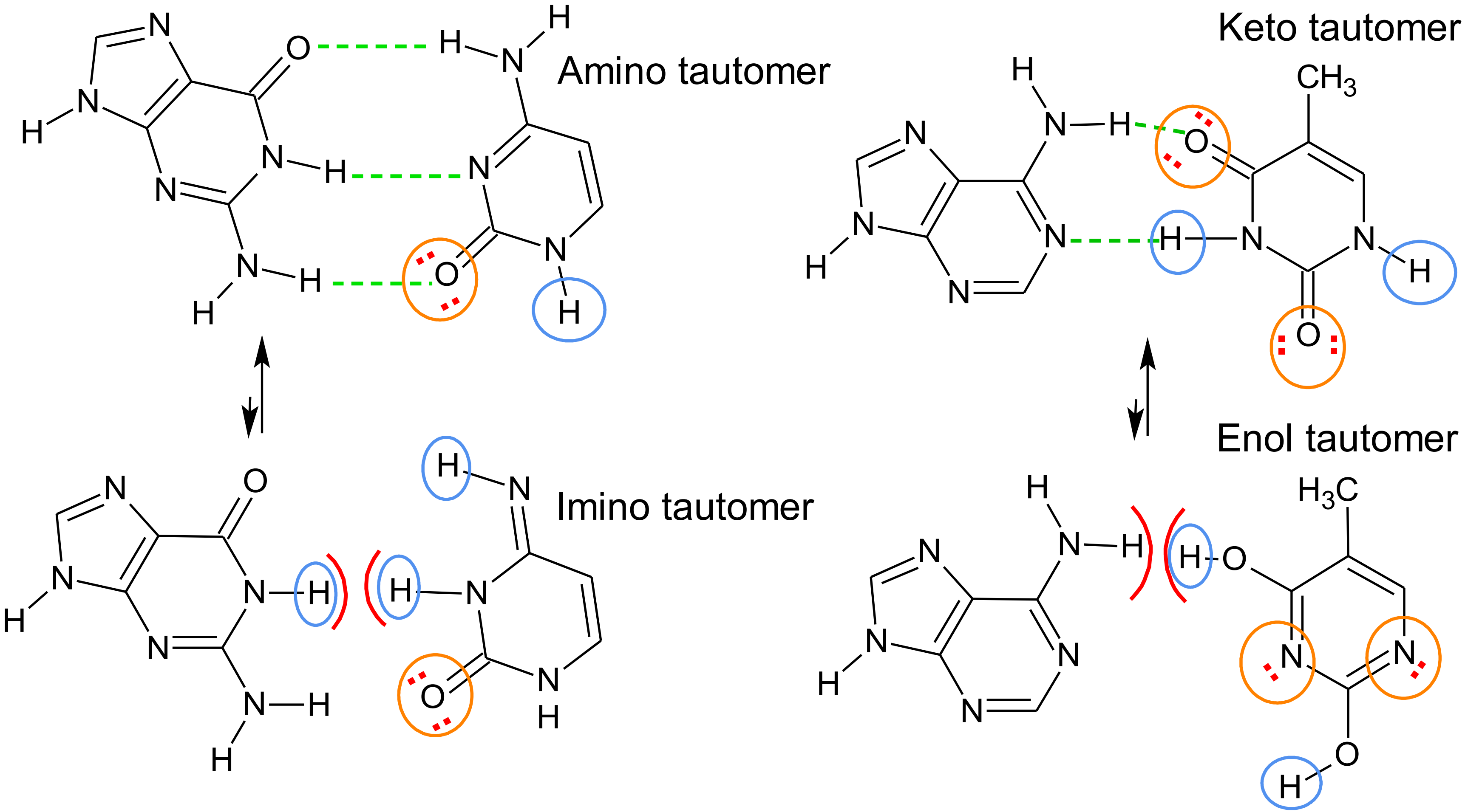
⇒ Rapidly equilibrating mixture

Ring-substituent tautomerism

- 1-substituted imidazole:



DNA and tautomerism



Guanine

Cytosine

Adenine

Thymine

References

- Adrien Albert, Heterocyclic chemistry : an introduction, 2nd ed., Athlone P, 1968 547p.

- Alan R. Katritzky, Comprehensive heterocyclic chemistry : the structure, reactions, synthesis and uses of heterocyclic compounds, Vol.3, 5 and 6, Oxford : Pergamon, 1984, 1111p.

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- Christopher K. Mathews, Biochemistry, Menlo Park, Calif: Benjamin/Cummings Pub. Co., 1990, ISBN 0805350152

- M. B. Smith, Advanced Organic Chemistry, 5th ed., Wiley Interscience, New York, 2001; p 1218-1223. ISBN 0471585890

- Katarzyna Zientara, DFT Studies of Amide-Iminol and Amine-Imine Tautomerism for Cytosine, 2006, 18th Conference on Physical Organic Chemistry (available on http://www.science24.com/paper/8325)

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Heterocyclic Chemistry Coursework

Summary

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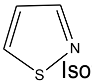
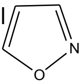
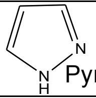
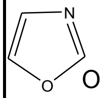
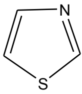
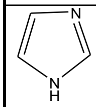
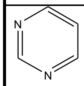
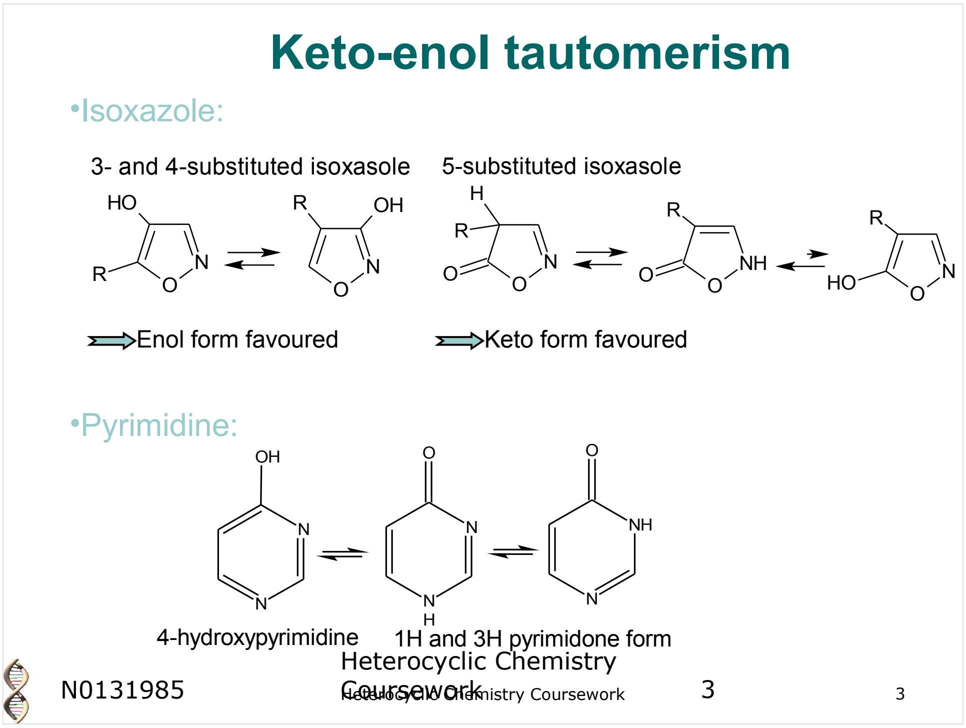
 Isoxazol  Isothiazole	-Keto-enol -Substituent
 Pyrazole	-Substituent -Annular
 Thiazole  Oxazole	-Substituent -Ring-chain -No annular tautomerism
 Imidazole	-Annular -Ring-substituent
 Pyrimidine	-keto-enol

Heterocyclic Chemistry Coursework



Keto-enol tautomerism

- Isoxazole:

3- and 4-substituted isoxasole

5-substituted isoxasole

Enol form favoured

Keto form favoured

- Pyrimidine:

4-hydroxypyrimidine

1H and 3H pyrimidone form

Heterocyclic Chemistry Coursework 3

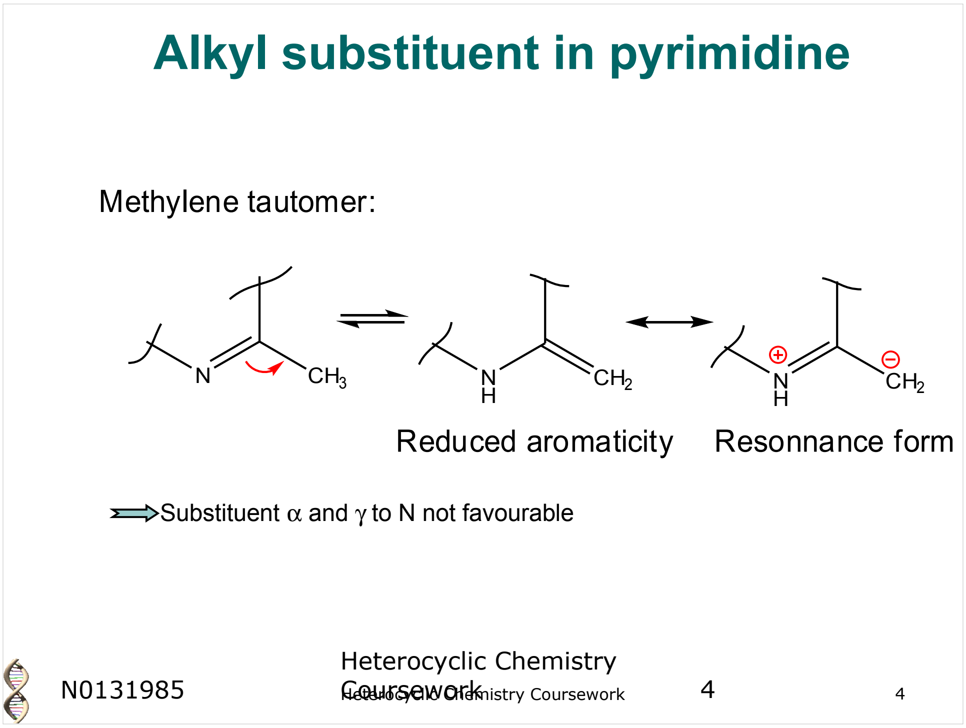
Prototropic tautomerism involving a carbon atom is characterised by the apparent movement of a double bond in a ring. The red arrows show the movement of the double bond. Keto-enol tautomerism is a form of prototropic tautomerism between a carbon and an oxygen atom. A keto structure occurs when the hydrogen atom bonds to a nitrogen atom within the ring. An enol structure occurs when the hydrogen atom bonds to an nearby oxygen atom that sticks out from the ring.

Three tautomeric forms are possible for 5-substituted isoxasol-5-ones. The OH form does not contribute to the equilibrium mixture unless some stabilising influence is present. For example, a 4-carbonyl substituent would stabilise this form by H-bonding. Medium and substituent effects influence the proportion of the CH form (on the left) and the NH form in the middle.

With 3- and 4-substituteed isoxasoles, the tautomeric form nomally present is the OH form.

3-Hydroxyisothiazole exists in the hydroxy from in non polar solvents (cyclohexane, ether). The Keto form in majoritarly present in aqueous solution (polar solvent).

However it is the contrary in the case of thiazoles.



Alkyl substituent in pyrimidine

Methylene tautomer:

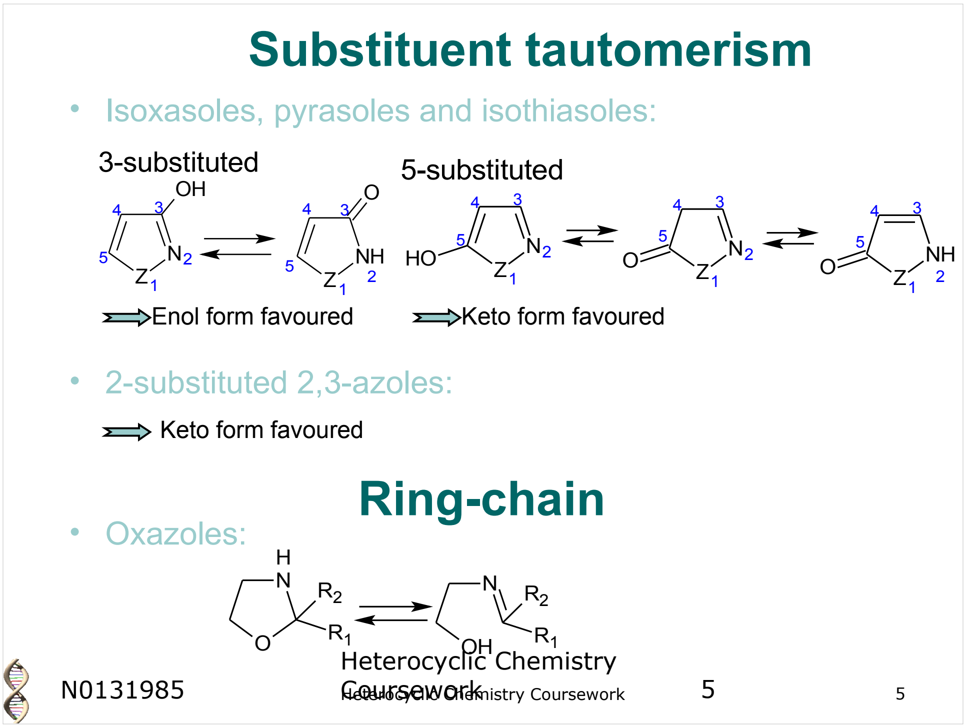
Reduced aromaticity

Resonnance form

⇨Substituent α and γ to N not favourable

Heterocyclic Chemistry Coursework 4

The effect of substituent on a group involved in tautomers can be very important. Tautomerism in a methyl group alpha or gamma to a ring nitrogen is not favourable. This is the reason why there is a carbanion-stabilising group on the methyl group equilibrium.



Substituent tautomerism

- Isoxasoles, pyrasoles and isothiasoles:

3-substituted

5-substituted

Enol form favoured

Keto form favoured

- 2-substituted 2,3-azoles:

Keto form favoured

Ring-chain

- Oxazoles:

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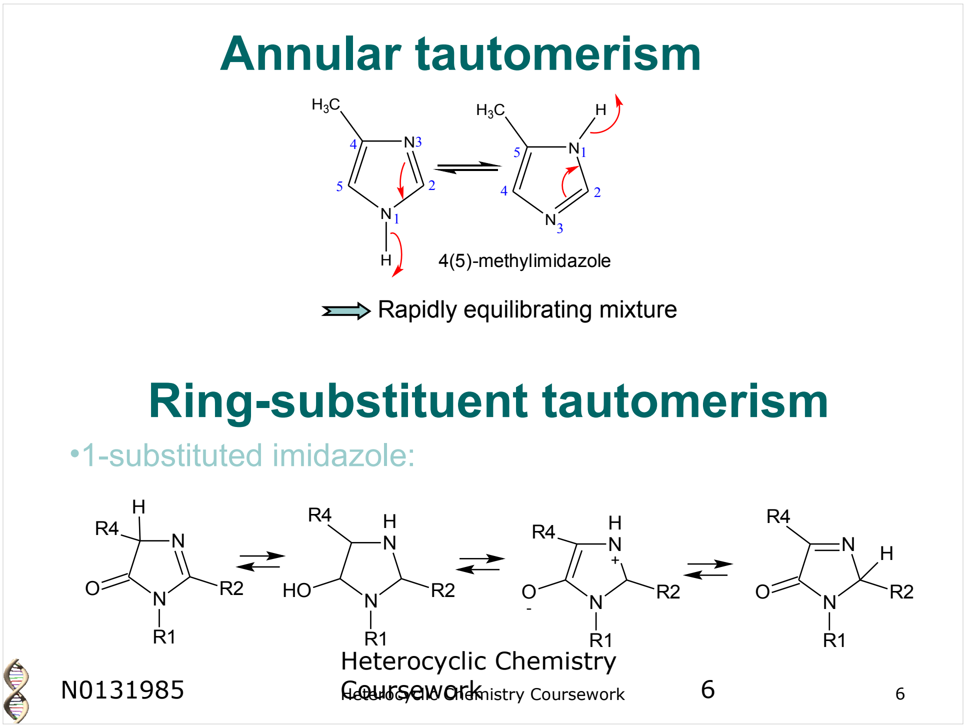
Heterocyclic Chemistry Coursework 5

The oxazolone from is favoured compared to the hydroxyoxazole from in substituent tautomerism.

3- (and 4-) substituted isoxasoles, pyrasoles and isothiasoles can exist in two tautomeric forms. On the slide Z is either O, S, or N atom. The hydroxy form is present under most conditions for 3- (and 4-) substituted analogs. Its stability is explained by the weakened acidity of the ring nitrogen atom (at the 2 position) due to the adjacent heteroatom (at the 1 position) and the O substituent (at the 3 position). This concentration of eletron withdrawing groups near the basic nitrogen atom causes theses compounds to exist mainly in the OH form.

For 5-substituted isoxasoles, pyrasoles and isothiasoles, three uncharged tautomeric forms are possible. Contrary to 3- and 4-substituted analogs, the OH form is of little importance except when a suitable substituent in the 4 position can form a H bond with the 5 hydroxy group. The occurrence of the two keto form depend on the substitution pattern and on the solvent. RHS tautomer is more polar than the middle one. It is hence favoured by polar media. A substituent at the 4 position favours RHS tautomer because of conjugation or hyperconjugation of the 4-substitution with the 3,4-double bond.

Substituted oxazolidines: Ring-chain tautomerism occurs when the movement of the proton is accompanied by a change from an open structure to a ring, The proportion of open form is higher if R1=R2=methyl than for R1=methyl and R2=ter-butyl. In solution, the equilibrium shifts in favour of the open isomers in solvents that can form Hydrogen bonds.



Annular tautomerism

4(5)-methylimidazole

Rapidly equilibrating mixture

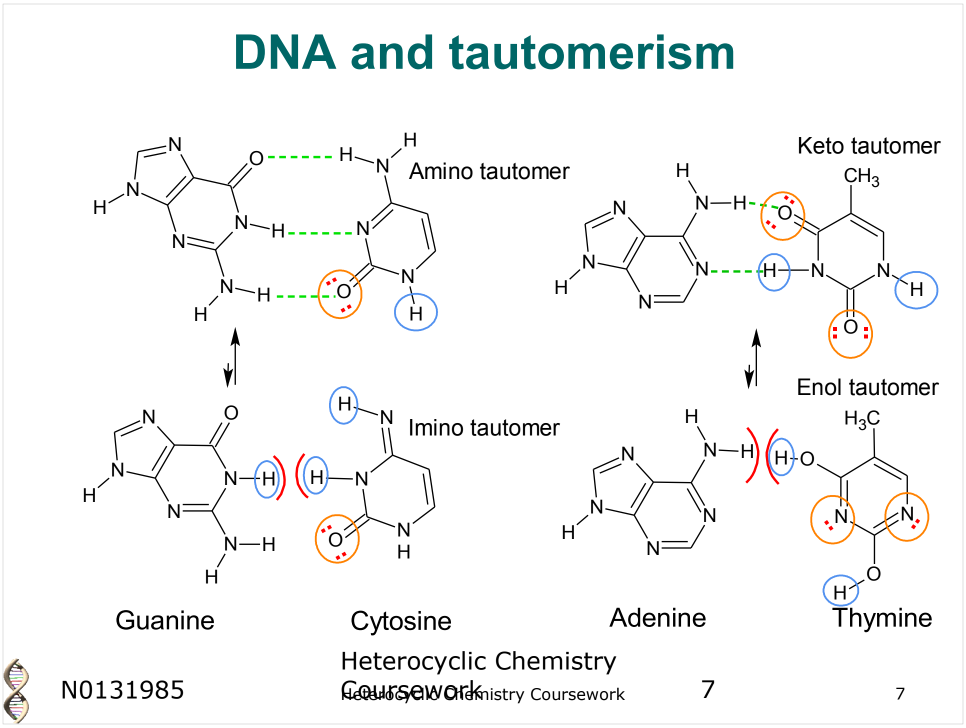
Ring-substituent tautomerism

- 1-substituted imidazole:

Heterocyclic Chemistry Coursework 6

Annular taumerism involves the movement of a proton between two annular nitrogen atoms. In other word, it is prototropic tautomerism between nitrogen atoms. There is a rapid proton transfer from position 1 and 3. Methylimidazole exists as a rapidly equilibrating mixture of 4-methyl (on the left) and 5-methyl (on the right) tautomers which cannot be separated. It is referred to as 4(5)-methylimidazole. Pyrazole has the same behaviour.

Ring substituent. 4 possible tautomeric forms in imidazol-5-one. Substituents have a marked effect on defining the preferred form.



DNA and tautomerism

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Heterocyclic Chemistry Coursework 7

The DNA bases Cytosine (C) and Thymine (T) are pyrimidines. Despite the added stabilisation of an aromatic ring, C and T prefer to adopt amide-like structures. The hydrogen bond acceptor are circled orange and the donor in blue. The more stable tautomer are drawn on the top. Tautomerism reverses the hydrogen bonding behaviour of the nitrogen and oxygen functions (the N-H group of the pyridone becomes a hydrogen bond donor and the carbonyl oxygen an acceptor). It is only when C is in the amino form and T in the keto form that it is possible to bond guanine (G) with cytosine (C) and adenine (A) with thymine (T) via hydrogen bonding (top line). This pairing led to suggest a double helix structure for DNA

The enol form is not favoured because the hydrogen of the enol is repealing the one of the amine. The force binding the two molecules is lower and hence the DNA needs
the amino form of C and keto form of T to adopt the double helix structure.

References

- Adrien Albert, Heterocyclic chemistry : an introduction, 2nd ed., Athlone P, 1968 547p.

- Alan R. Katritzky, Comprehensive heterocyclic chemistry : the structure, reactions, synthesis and uses of heterocyclic compounds, Vol.3, 5 and 6, Oxford : Pergamon, 1984, 1111p.

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