PROTOTROPIC TAUTOMERISM OF HETEROAROMATIC COMPOUNDS

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Abstract- This review deals mainly with the prototropic side chain tautomerism of heteroaromatic compounds. Particular reference is made to molecular orbital calculations of equilibrium constants.

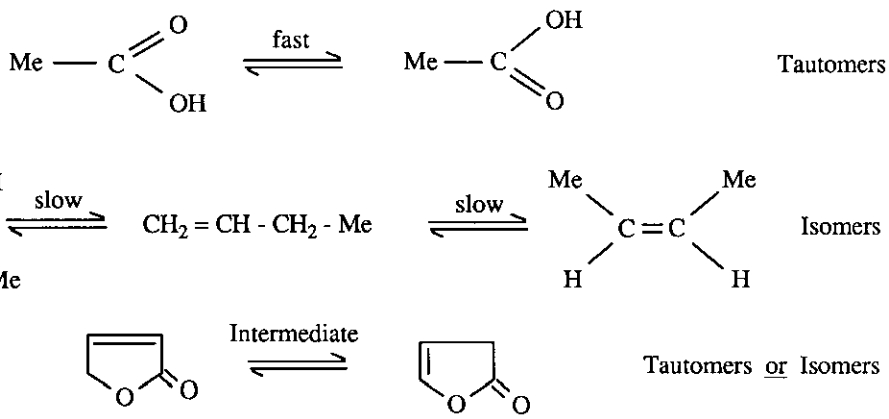
CONTENTS

1. Classification and Importance

1.1 Definitions

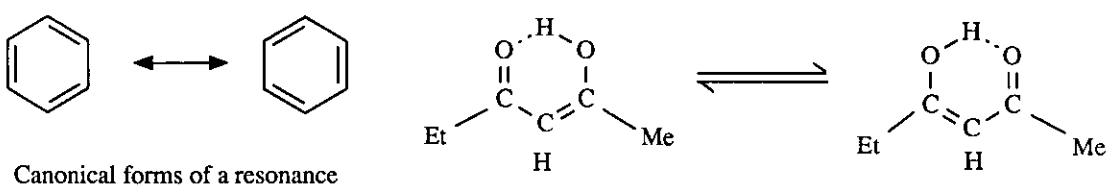
Tautomerism is defined as a phenomenon in which two or more molecular structures exist in dynamic equilibrium with each other, i.e. the energy barrier between them is small. There is no hard and fast dividing line between tautomerism and isomerism, but in general, tautomers readily interconvert whereas isomers interconvert much less easily. For example, the two forms of a carboxylic acid are definitely in tautomeric equilibrium, whereas 1-butene and the 2-butenes are considered as isomers since they are easily separable - see Scheme 1. However, there are some borderline cases. For example, because the two butyrolactones can be isolated but are readily convertible, they can be considered both as tautomers and as isomers.

Scheme 1. Tautomerism and Isomerism



On the other hand, the distinction between tautomerism and mesomerism is usually much better defined. Two tautomers are individual compounds separated by an energy barrier. By contrast, a single compound exhibiting mesomerism exists at an energy minimum between two or more canonical forms which contribute to the actual structure. However, even here some cases near the dividing line do exist. For example, the enol of propionylacetone is hydrogen-bonded and there is only a small energy gap between it and the other hydrogen-bonded tautomer (see Scheme 2). Cases are known of symmetrical hydrogen bonds and therefore the concept of tautomerism and mesomerism can also be considered to merge in rare cases.

Scheme 2. Tautomerism and Mesomerism



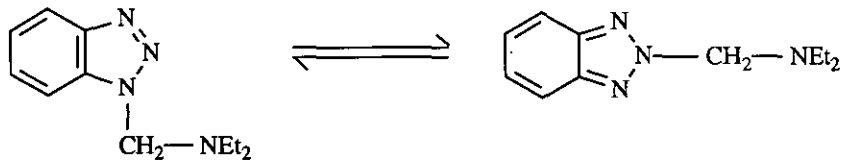
Canonical forms of a resonance hybrid: Mesomerism

tautomers separated by a very low energy barrier

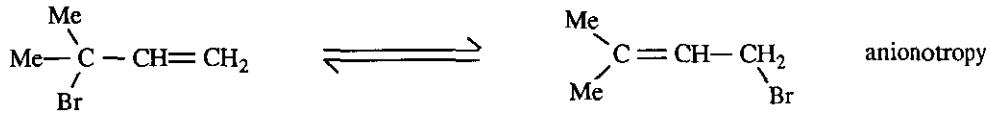
1.2 Types of Tautomerism

We will be considering in this account mainly prototropic tautomerism where a proton moves from one position in a molecule to another. However, several other types of tautomerism do exist: for example, certain substituted benzotriazoles are tautomeric between the *1-substituted and the 2-substituted benzotriazole forms*,[1] anionotropy involving the allyl cation is well known,[2] and ring-chain tautomerism is well established[3] (see Scheme 3).

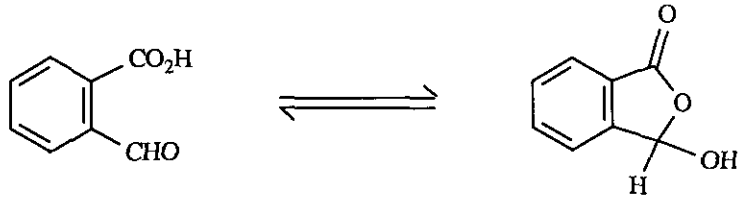
Scheme 3. Tautomerism Other than Prototropic Tautomerism



N-(α-aminoalkyl)benzotriazoles



anionotropy



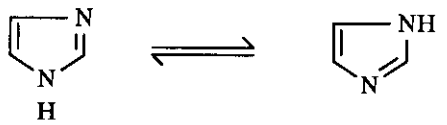
ring-chain tautomerism

1.3 Prototropic Tautomerism in Heterocyclic Chemistry

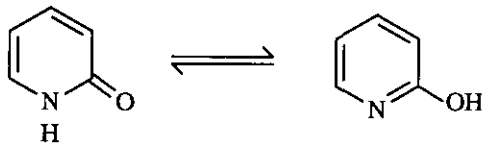
The first systematic reviews of this subject were published in 1963,[4-7] and in 1976 one of the present authors, with others, presented a monograph[8] which remains the definitive work on the subject. The purpose of the present overview is to place some of the recent advances, particularly the application of theoretical methods, into the context of the subject as a whole.

In heterocyclic chemistry, we distinguish between annular and side chain tautomerism. In the former, the atom or atomic group is exchanged between the ring carbon- or heteroatoms, whereas in the latter, the exchange takes place between a ring and a side-chain atom. Examples of both are shown in Scheme 4.

Scheme 4. Annular and Side-Chain Prototropic Tautomerism of Heteroaromatic Compounds



Imidazole: annular tautomerism



2-Pyridone/2-Hydroxypyridine: side chain tautomerism

In this overview we shall concentrate on side-chain tautomerism. The important potentially tautomeric substituents which we will deal with are listed in Scheme 5

Scheme 5. Tautomeric Substituents

-OH, hydroxy	⇌	:O, oxo		-CH_3, methyl	⇌	:CH_2, methylene
-SH, thiol	⇌	:S, thione		.NHX	⇌	:NX
-NH_2, amino	⇌	:NH, imino		.CHXY	⇌	:CXY

1.4 The Importance of Tautomeric Equilibria in Chemistry

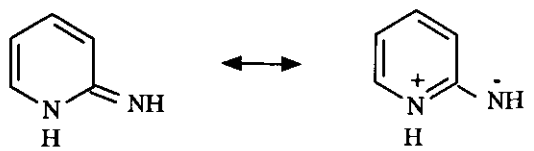
Reactivity and reactive mechanisms in heterocyclic chemistry can only be properly rationalized if the tautomeric structures of the compounds are known[4] (Scheme 6) and there is some appreciation of the energy differences between the alternative tautomers.

Scheme 6. Importance of Tautomeric Equilibria

Amino Form of 2-Aminopyridine

Electrophiles should attack ring nitrogen

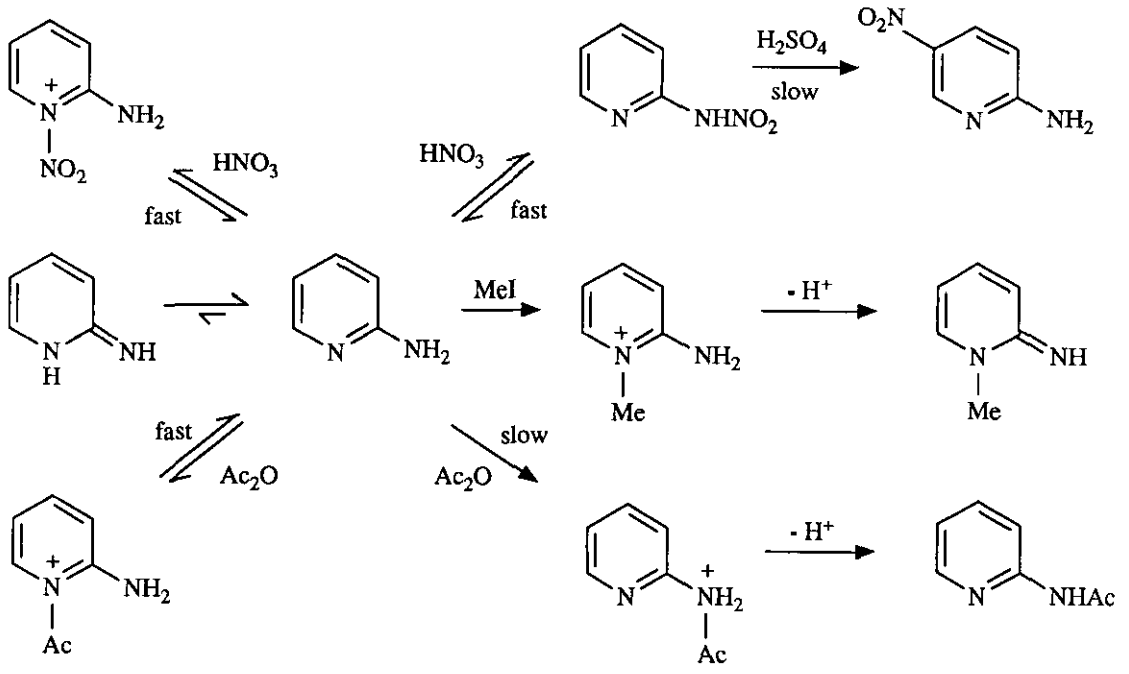
Tautomeric Imino Form



Electrophiles should attack exocyclic nitrogen

An example of the importance of this is shown in Scheme 7 where the reactions of 2-aminopyridine are considered.[8] 2-Aminopyridine exists very predominantly in the amino-form shown, yet on reactions with electrophiles it can yield products of reaction either at the cyclic nitrogen, the acyclic nitrogen, or a ring carbon atom. Thus, methyl iodide gives the product of the reaction of the cyclic nitrogen, whereas acetic anhydride yields the product of reaction at the exocyclic nitrogen, and yet again nitric acid mixed with sulfuric acid yields the 5-nitro compound. However, all these reagents first react at the cyclic nitrogen as would be expected from the mesomeric contribution of the zwitterionic structure to the 2-amino form (see Scheme 6). In the case of methyl iodide, the reaction is irreversible and this determines the product. With acetic anhydride, the reaction is fast at the cyclic nitrogen but reversible, and a slower irreversible reaction takes place at the acyclic nitrogen. In the case of nitric acid (nitronium cation), reaction at both nitrogens is reversible, and in time, the kinetically third preferred, but thermodynamically most stable 2-amino-5-nitropyridine is formed via a rearrangement of the 2-nitroaminopyridine.

Scheme 7. Reactions of 2-Aminopyridine

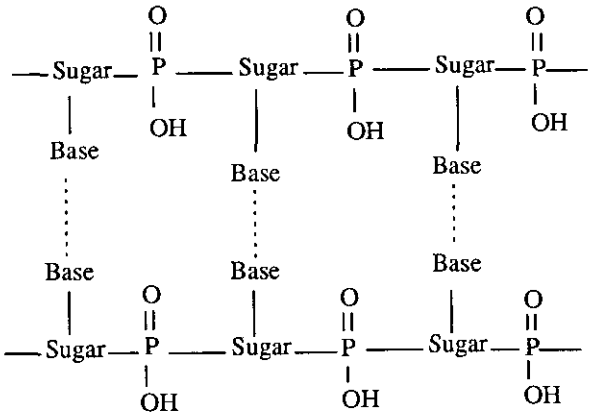


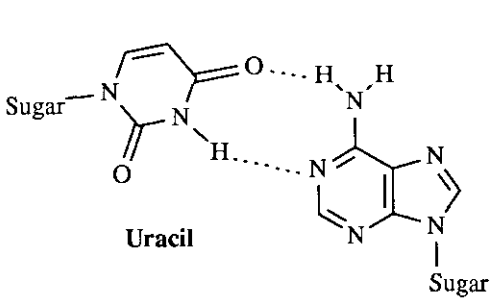
Clearly, any attempted rationalization of the reactivity of 2-aminopyridine in terms of the imino form would be most misleading. An early example of the consequences of neglecting tautomerism was the confusion between pyridinethiols and pyridinethiones. These were referred to as pyridinethiols "to follow Chemical Abtracts" and the acidity, alkylation and mechanism of oxidation of non existent thiol groups were described.[9]

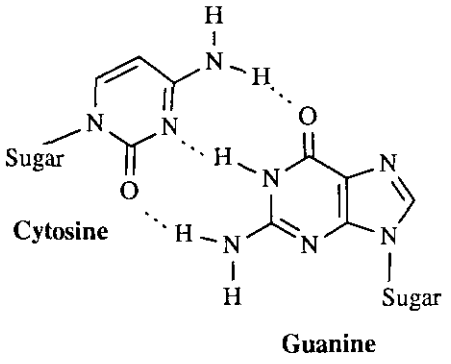
1.5 Biological Importance of Heteroaromatic Tautomerism

It is well known that nucleic acid bases exist as double helixes in which the two strands are held together by the so-called base pairing. The tautomeric form of the nucleic acid bases is crucial to this base pairing as shown in Scheme 8.[6,10-13]

Scheme 8. Tautomerism in the Nucleic Acids



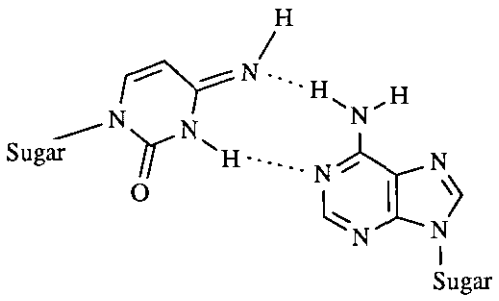




Moreover, tautomerism is of the highest biological importance because it usually determines the frequency of mutations.[14-16] In its minor tautomeric form, uracil can act as a mimic of cytosine in the base pairing, and conversely, cytosine can act as a mimic of uracil as shown in Scheme 9.

Scheme 9. Mispairing of Nucleic Acid Bases

Cytosine in imino-form acting as mimic of uracil pairs with adenine, leads to a mutation

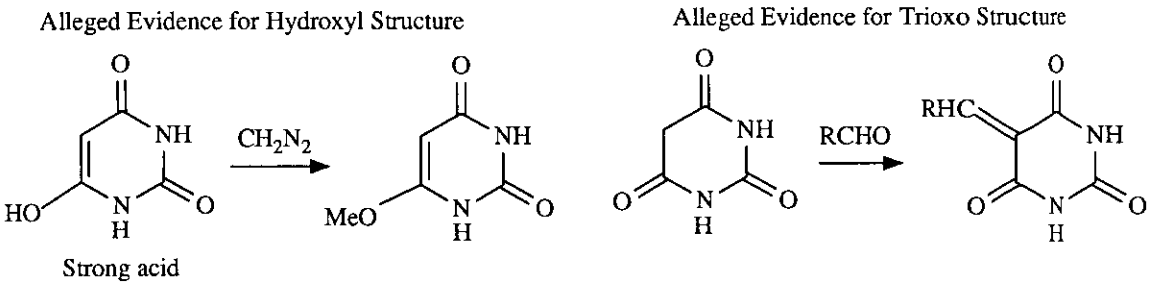


2. Methods for the Study of Aromatic Tautomerism

2.1 Chemical Methods

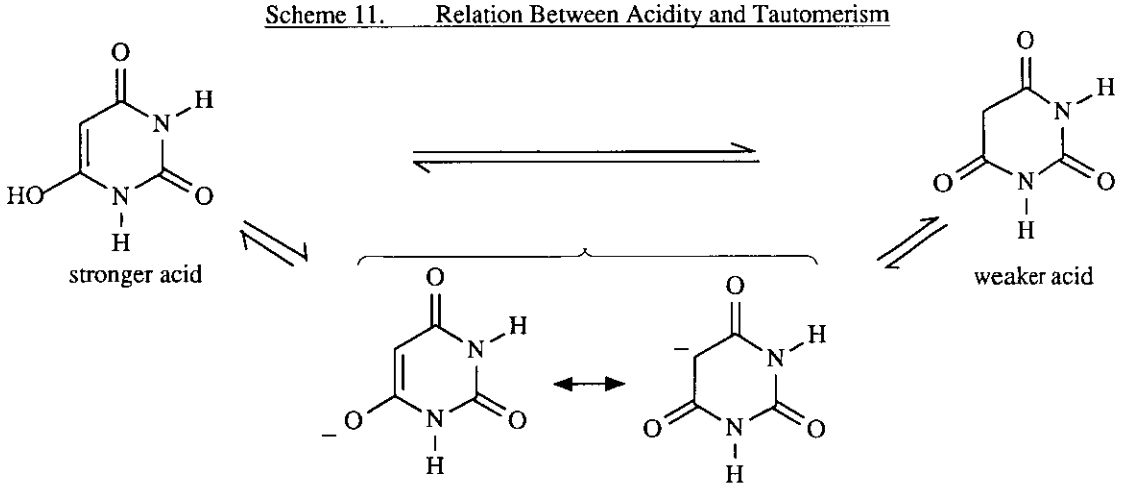
Chemical arguments have often been used, although in many cases quite incorrectly. An early example of this applies to barbituric acid, as is shown in Scheme 10.

Scheme 10. Chemical Methods for the Investigation of Tautomerism



One set of authors[17-19] argued for the hydroxyl structure for barbituric acid on the basis that it was a strong acid and it gave the methoxy derivative with diazomethane. Another set of authors[20] argued that the trioxo form was correct because of the condensation reaction of barbituric acid with aldehydes. All of this reasoning is completely incorrect. The correct relationship between acidity and tautomerism is shown in Scheme 11.[8] If a pair of tautomers is in equilibrium with the same mesomeric anion, then the weaker acid of the two tautomers will always predominate, and indeed the tautomeric equilibrium constant will be equal to the quotient of the two dissociation constants. It is well known that diazomethane reacts with active hydrogen compounds by proton abstraction to give the methyldiazonium cation which then reacts with the anion. Similarly, the reaction with aldehydes is an aldol condensation which also goes through the anion. In each case, the anion is a mesomeric anion derived from both the OH and the CH forms, and the explanation for its reactivity with the methyldiazonium cation and in the aldol reaction can be rationalized by the "soft-hard" reagent rule.

Scheme 11. Relation Between Acidity and Tautomerism

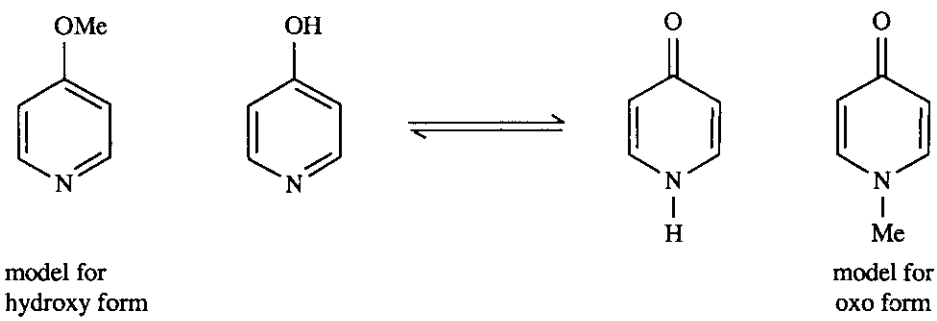


2.2 Physical Methods for the Determination of Tautomeric Equilibrium

Many physical methods can be used to determine tautomeric equilibria. Spectroscopic methods include nmr for structural determination, dynamic nmr for equilibria involving C-H bond cleavage, infrared and Raman spectroscopy, ultraviolet/visible spectroscopy, ultraviolet photoelectron spectroscopy (PES), X-ray photoelectron spectroscopy (ESCA), mass spectroscopy and ion cyclotron resonance spectrosopy.[8] Non-spectroscopic methods include the determination of basicity (solution) or proton affinity (gas phase), dipole moment measurements in either gas phase or solution and X-ray, electron and neutron diffraction methods.

The application of physical methods to tautomeric equilibria can be divided into two main types: those that utilize "fixed derivatives" and those that do not. The concept of "fixed derivatives" is shown in Scheme 12.[8] The methyl or other alkyl derivatives are non-tautomeric compounds of fixed structure and they act as models for the individual tautomers. When using fixed derivatives, the properties of the tautomeric compound are compared with the properties of the two models (or more, if necessary).

Scheme 12. Concept of "Fixed" Derivatives

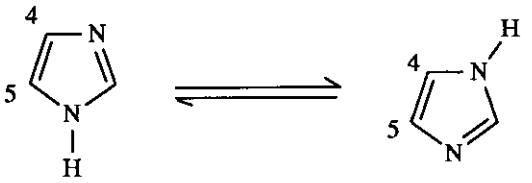


2.3 Investigation of Tautomeric Equilibrium in Solution

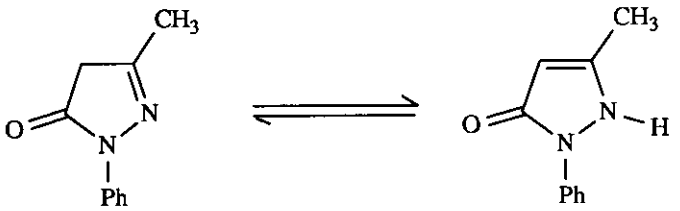
The use of nmr spectroscopy is of particular importance but can also be misleading if incautiously used. Individual tautomers can only be observed by nmr spectroscopy when the rate of interconversion is slow on the nmr time scale. As an approximate generalization, it can be stated that in solution, equilibria not involving CH bond cleavage (i.e. where the proton moves between oxygen, nitrogen or sulfur atoms) are fast on the nmr time scale at room temperature, whereas those equilibria which involve a proton moving to or from a carbon atom are normally slow (Scheme 13).

Most of the nmr investigations on tautomeric equilibria have been carried out on proton and carbon-13 spectra.[21-26] However, due to instrumental advances in recent years, nitrogen-15 nmr spectroscopy[27-30] is now widely used for the study of heterocyclic tautomerism, along with nmr techniques using other magnetically active nuclei (^{17}O, ^{14}N etc.).

Scheme 13. Nmr Investigation of Tautomerism



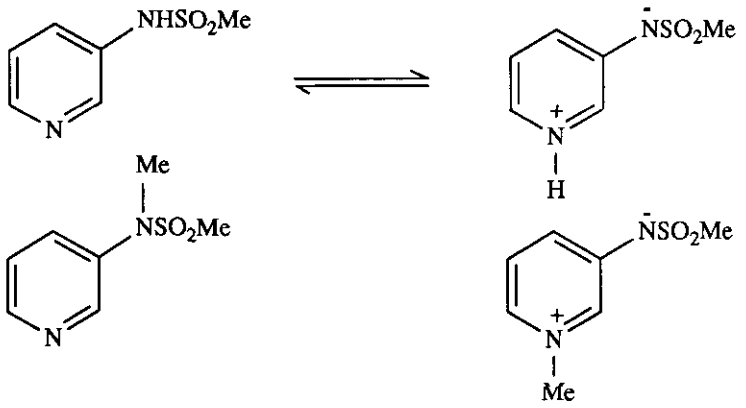
Tautomerism rapid: 4- and 5-positions show singlet signals in ^{1}H- (2H) and ^{13}C-nmr in solution, even at low temperatures.



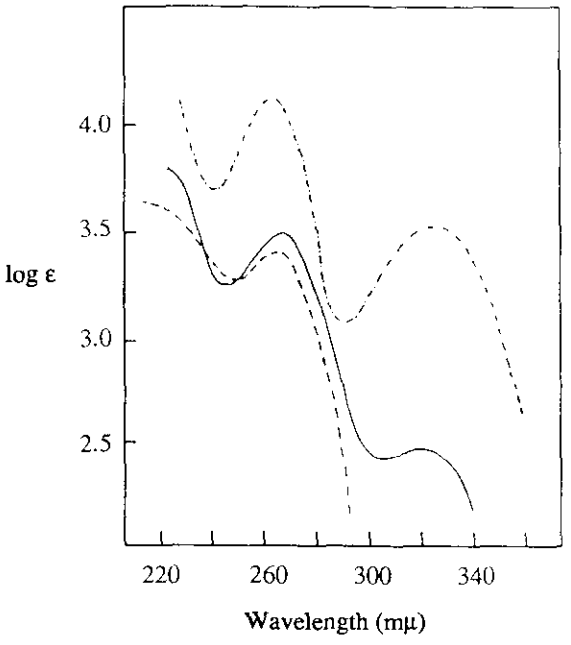
Tautomerism slower: distinct peaks shown for 4-position CH_2 and 4-position CH in the two isomers in both ^{1}H and ^{13}C nmr.

As an example of the determination of a tautomeric equilibrium constant using ultraviolet spectroscopy, we take 3-methanesulfonamidopyridine.[31] The structures are shown in Scheme 14 and the ultraviolet spectrum of the tautomeric compound and its two models are shown in Scheme 15. The spectrum of 3-methanesulfonamidopyridine resembles that of the exocyclic N-methyl derivative, but absorption does occur in the 325 nm region, and calculation indicates that 10% exists in the zwitterionic form in aqueous solution.

Scheme 14. Models for Ultraviolet Study of Tautomerism



Scheme 15. Uv Spectrum of 3-Methanesulfonamidopyridine and Derivatives



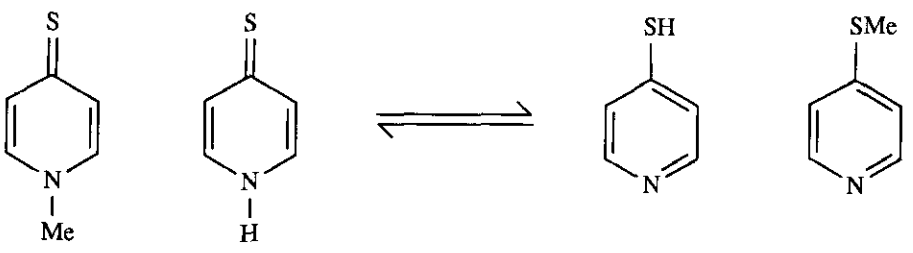
——— *3-Methanesulphonamidopyridine at pH 5.15*

····· *3-N-Methylmethanesulphonamidopyridine at pH 10*

– · – · – *Anhydro-3-methanesulphonamido-1-methylpyridinium hydroxide in N-NaOH*

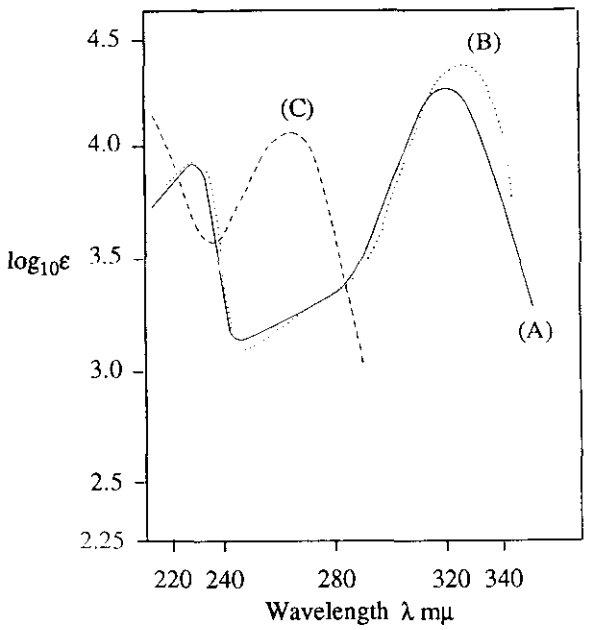
The same technique can be applied to the case of 4-pyridinethione.[32] The structures are shown in Scheme 16 and the ultraviolet spectrum in Scheme 17. It is clear that 4-pyridinethione exists mainly in the thione form. However, in this case it is not possible to come to any quantitative estimate of the tautomerism constant because the observed differences between the 4-thione and 1-methyl-4-thione ultraviolet spectra could easily be accounted for by the replacement of a hydrogen atom with a methyl group.

Scheme 16. Tautomerism of 4-Pyridinethione



model model

Scheme 17. Ultraviolet Spectrum of (A) 4-Pyridinethione, (B) 1-Methyl-4-pyridinethione, and (C) 4-Methylthiopyridine

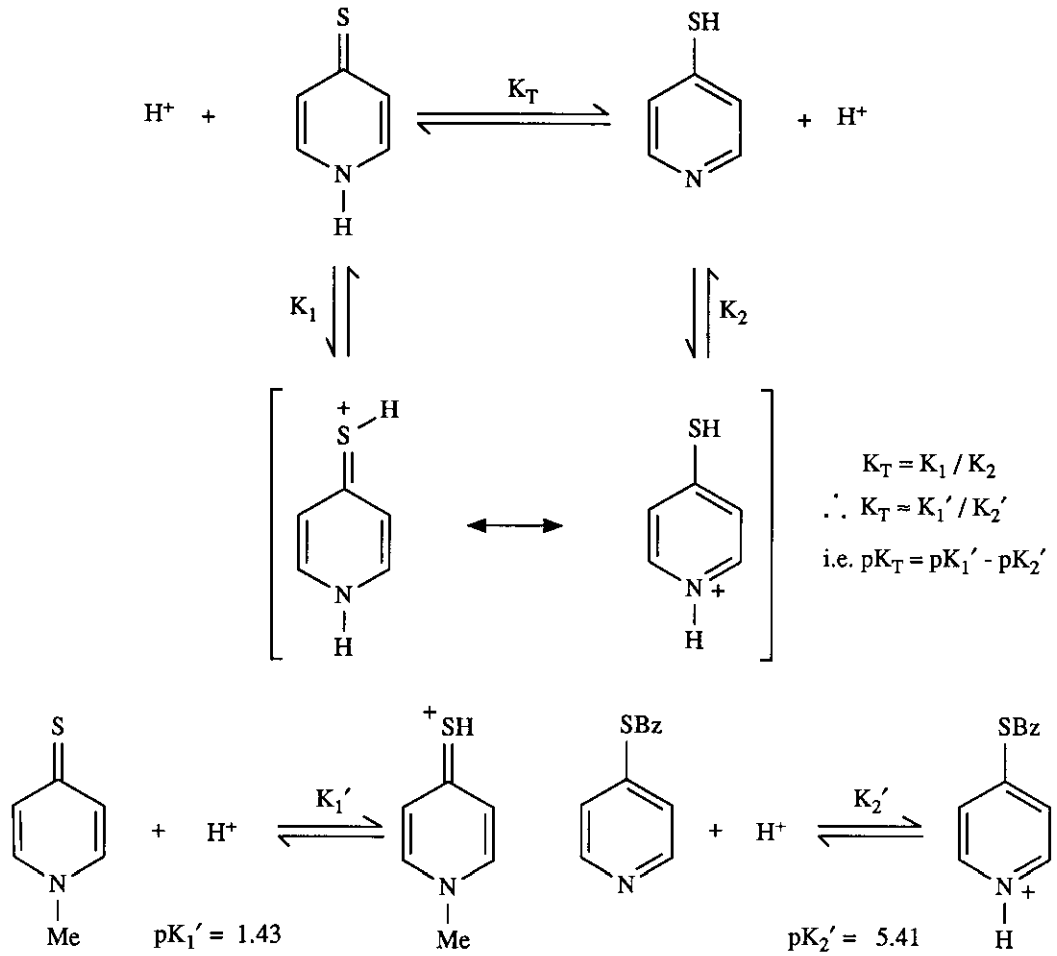


This lack of quantitative information on tautomeric equilibria which are heavily biased towards one tautomer (by a ratio of greater than 10:1) is a serious limitation, and it applies to almost all the physical methods. The main way to overcome this experimentally is by use of the so-called basicity method[8] which is illustrated for 4-pyridinethione in Scheme 18.[33] This method can be applied when compounds are available which form cations of similar structure to each other and to the common cation formed from the tautomers under consideration. In such a case, K_1' and K_2' are approximations to K_1 and K_2, and because $K_T = K_1/K_2$, we can evaluate it as approximately equal to K_1'/K_2'. In the example under discussion, we conclude that K_T for 4-pyridinethione in aqueous solution is ca. 10^4.

2.4 Investigation of Tautomeric Equilibria in Gas Phase and in Inert Gas Matrices

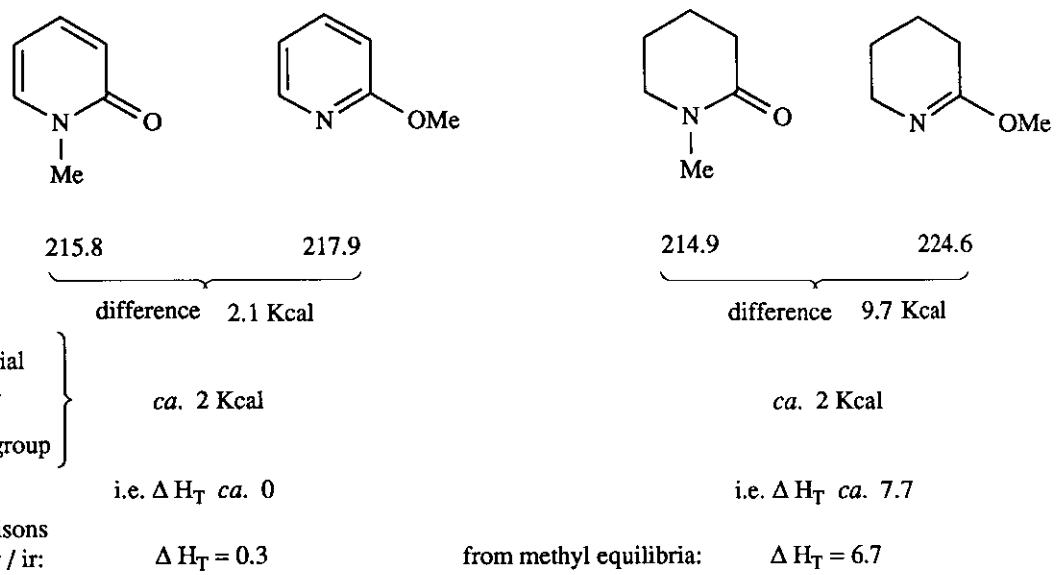
Many physical methods can be applied in the gas phase; examples are the use of ir,[34,35] uv,[35] and PE[36] spectroscopy, ionization potentials,[37] mass spectroscopy/isotope effects[38,39] and proton affinities[40] for the case of pyridones and pyridinethiones.

Scheme 18. Basicity Method Applied to 4-Pyridinethione



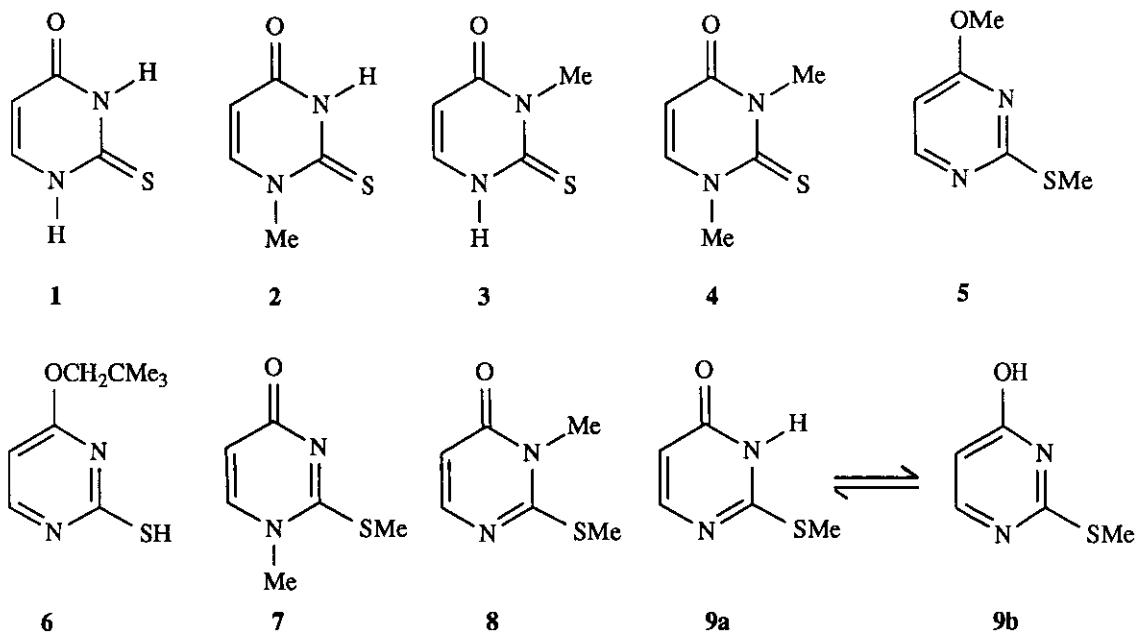
An extension of the basicity method to the gas phase is possible by using proton affinities as illustrated in Scheme 19.[40] The tautomeric equilibria can be determined by the difference in proton affinities of the methyl derivatives after taking into account the effect of O-methylation on the basicity.

Scheme 19. Gas Phase Basicity Applied to Tautomeric Equilibria



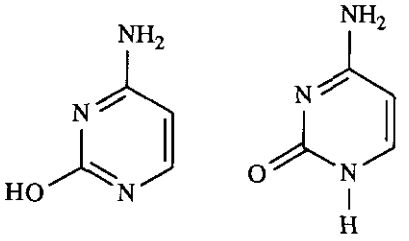
Unfortunately, not enough is yet known about the differential effects of OMe, NMe, and SMe groups as compared to the non-methylated derivatives on gas phase proton affinities, which limits the accuracy of the method. A more recent application[41] to some thio analogues of the nucleic acid base uracil is shown in Scheme 20, which displays the predominant gas phase tautomers for monothiouracil and its methyl derivatives.

Scheme 20. Predominant Gas Phase Tautomers for Monothiouracils



The infrared spectroscopy of tautomeric heterocyclic compounds in inert gas (Ar or N_2) matrices has been widely applied for the qualitative and quantitative investigation of the prototropic equilibria of isolated molecules, particularly for the nucleic acid bases and their analogues.[42-46] For example, cytosine is found as a 2 : 1 mixture of hydroxyamino- and oxoamino-forms in matrices, whereas in the solution or crystalline form, the latter tautomer strongly dominates.

Scheme 21. Relative Abundance of Cytosine Tautomers in Different Media



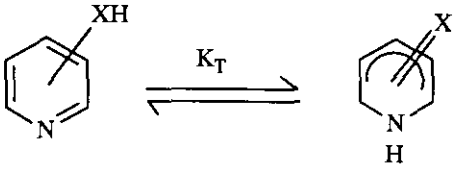
hydroxyamino		oxoamino	
2	:	1	(Ar matrix 15° K) [49]
1	:	10^6	(solution) [13]

2.5 Molecular Orbital Calculations of Tautomeric Equilibria

Many theoretical calculations on the prototropic equilibria of tautomeric heterocycles using quantum-chemical methods at both semi- and non-empirical levels have been published, and as time has progressed increasing accuracy has been attained. The earlier calculations gave results which are not comparable quantitatively to the answers derived from experimental data, and for these, we refer to the reviews.[11,12,15]

Some of the most important work has been accomplished in the last decade.[47-63] An extended basis set and account for electronic correlation energy is necessary for good results in ab initio calculations.[62] However, AM1 and PM3 semiempirical parametrizations by Dewar[64] and Stewart,[65] respectively, seem to be satisfactory for the description of the tautomeric equilibria of isolated molecules.[66] It is of the greatest importance to account for the solvent effects in theoretical calculations of tautomeric equilibria.[67-77] Frequently, there is little difference in the specific solvation (i.e. hydrogen bonding) energies of different tautomeric forms. However, the electronic distribution in the ring may be changed significantly from one tautomer to another, leading to large differences in non-specific polar solvation terms. Recently,[76] it was shown that a self-consistent reaction field molecular orbital (SCRF MO) theory[78,79] in combination with Dewar's AM1 parametrization[64] gives a quantitative prediction of the tautomeric equilibrium constants in aqueous solution.

Scheme 22. Tautomeric Equilibria in Substituted Pyridines



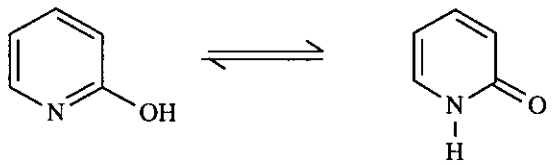
X = O, S, NH or CH_2

$\log K_T = \log A + \Delta H / RT$

$\log K_{T(calc)} = \delta \Delta H / RT$

As an example, the equilibrium between 2-hydroxypyridine and 2-pyridone is illustrative, showing the quality of different quantum-chemical methods for the tautomeric equilibrium calculations.

Scheme 23. Tautomerism of 2-Hydroxypyridine vs. 2-Pyridone



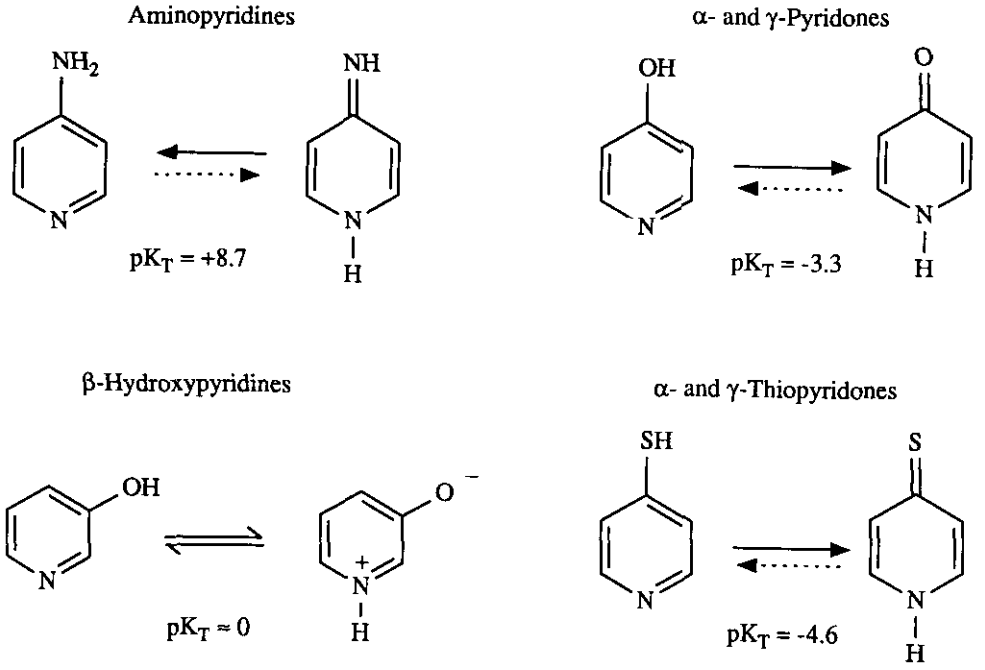
2-Hydroxypyridine favored by Kcal mol^{-1}	2-Pyridone favored by Kcal mol^{-1}	Method
.....	15.4	STO-3G [80]
.....	14.2	MINDO/2 [81]
.....	3.7	MINDO/3 [80]
1.7	.....	3 - 21G [80]
11.3	.....	CNDO/2 [82]
1.2	.....	MP2/6 - 31G* [80]
0.4	.....	AM1 [83]
0.3 ± 2.5	.....	exp. (gas phase) [35]
.....	3.8	AM1 (solution) [76]
.....	4.2	exp. (solution) [76]

3. Tautomeric Equilibria of Pyridines

3.1 Structural and Environmental Effects

The experimental method discussed above has shown that in aqueous solution aminopyridines exist largely as such, but the 2- and 4-pyridones, and 2- and 4-thiopyridones exist, largely in the oxo or thiooxo forms,[8] as shown in Scheme 24. 3-Hydroxypyridine is in equilibrium with an approximately equal amount of the zwitterion.

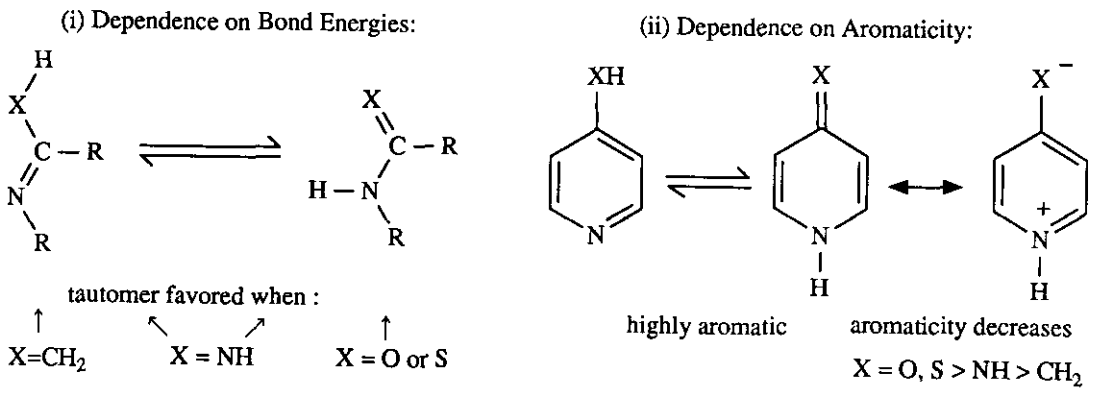
Scheme 24. Tautomerism of Pyridines



(All pK_T values refer to aqueous solutions)

The tautomeric equilibria of substituted pyridines in aqueous solution as shown in Scheme 24 is determined by the interplay of bond energies and the aromaticities of the molecules.

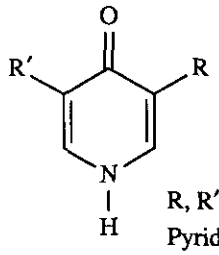
Scheme 25. Rationalization of Tautomerism of Pyridines



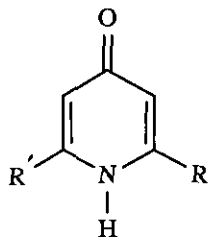
3.2 Effect of Substituents on the Tautomeric Equilibrium in Pyridines

The introduction of substituents, depending on both their nature and position, can either drastically affect the position of tautomeric equilibria, or have little influence. Thus, the effect of chlorine substitution on the tautomerism of 4-hydroxypyridine to 4-pyridone is shown in Scheme 26.[8] Clearly, substitution of chlorines in the 3 or in both the 3 and 5 positions have little effect, but for substitution at the 2 and 6 positions, one chlorine makes the two forms almost of equal energy whereas double substitution causes the hydroxypyridine form to be strongly favoured.

Scheme 26. Pyridone Tautomerism: Effect of Chlorine Substitution



R, R′ = H or Cl : Pyridone form always favored by a factor of *ca.* 10^3



R, R′ = H : Pyridone form favored by a factor of *ca.* 10^8

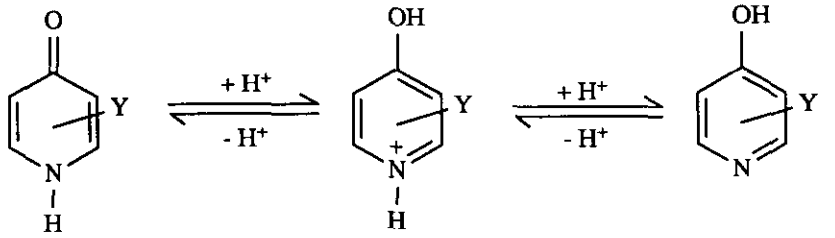
R = Cl, R′ = H : Pyridone:hydroxypyridine *ca.* 1:1

R, R′ = Cl : Hydroxypyridine favored by a factor of *ca.* 10^8

(all K_T values refer to aqueous solution)

The quite different effects of the chlorine atom at the 2- and 3-positions can be easily understood by considering the common cation formed by both tautomers, and the effect of substituents on the relative acidity of the two protons. As shown in Scheme 27, whereas a substituent at either the 3 or 5 position is at a distance of three bonds from the NH and OH protons, substituents in the 2 and 6 positions are much closer to the NH than to the OH.[8] This argument can be made quantitative, and indeed it is possible to derive an equation for the dependence of K_T on substitution. The relevant equations are given below.[84]

Scheme 27. Effect of Additional C-Substituents on Tautomeric Pyridines



Common Cation

Loss of H from N: pK (substituted pyridine) = 5.25 - 5.90 σ_s

Loss of H from O: pK (substituted pyridone) = 10.00 - 2.11 σ_s - 2.11 σ_z

(Where σ_s refers to a substituent constant and σ_z to a heterogroup constant)

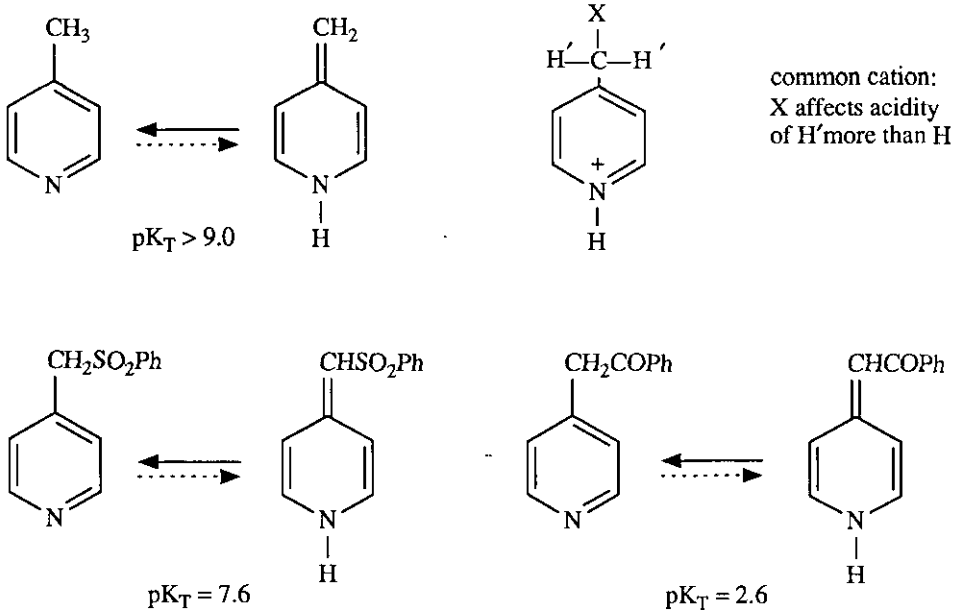
The application of this equation to common substituents is shown in Scheme 28,[84] where the $\log K_T$ values are predicted to fair precision.

Scheme 28. Effect of C-Substituents on Tautomerism of 4-Pyridone

Substituents	$\log_{10}K_T$	
	calc	obs
3-NH_2	5.0	3.6
3,5-Cl_2	2.2	2.4
2-Cl	-0.1	-0.3
2,6-Me_2	2.1	3.7
2,6-$(CO_2Me)_2$	-1.4	-1.1
3-NO_2	1.8	3.4
2,3,5-Cl_3	-1.7	0.0

Similarly, substituents in the methyl group of 4-methylpyridine can considerably influence the tautomeric equilibrium as illustrated in Scheme 29.[85,86] Again, the rationalization follows from the relative effects of the substituent on the two alternative protons that can be lost from the common cation.

Scheme 29. Tautomerism of Picoline Derivatives

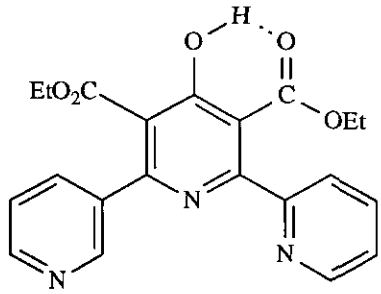


A different type of substituent influence is observed when intramolecular hydrogen bonding can stabilize one of the tautomers. Examples are shown in Scheme 30.[87,88]

Scheme 30. Intramolecular Hydrogen-Bonding in Tautomeric Pyridines

partly OH (in H_2O solution) completely OH

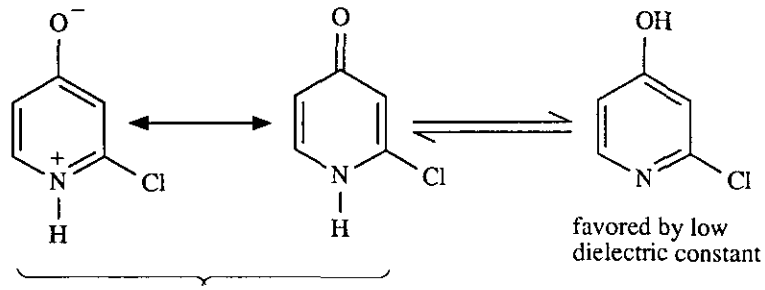
H-bonding to an exocyclic oxygen is generally less effective but it can occur:



3.3 Effect of Environment

Moving away from water through non-polar solvents to the gas phase changes the tautomerism of pyridines significantly. This is because the importance and contribution of charged separated canonical forms to the stability of the molecule decreases as the dielectric constant of the medium decreases.[8]

Scheme 31. Tautomeric Pyridines: Change of State



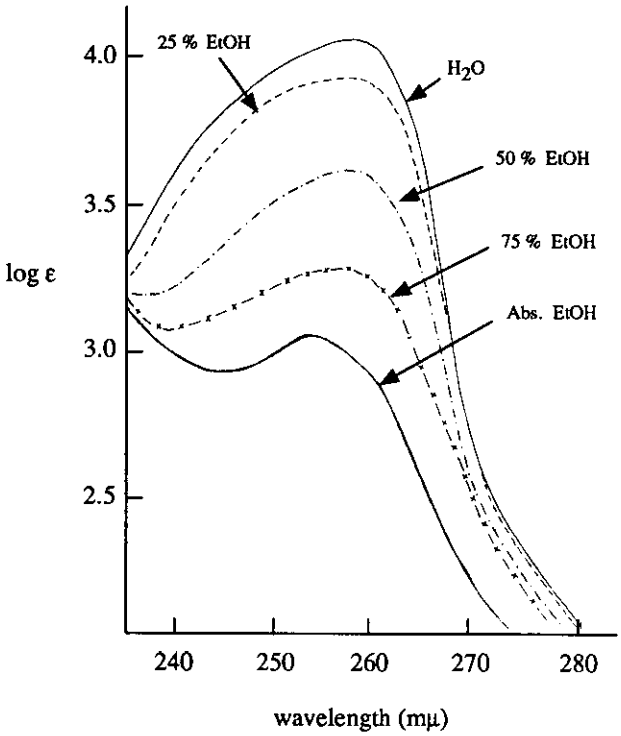
Favored by high dielectric constant

favored by low dielectric constant

(Solid state normally same tautomeric form as aqueous solution.)

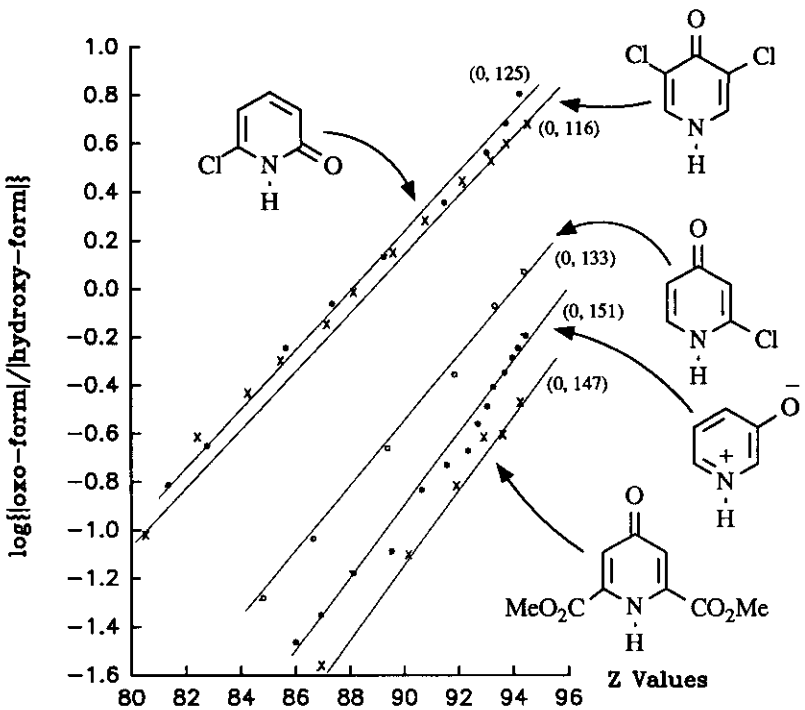
2-Chloro-4-pyridone exists in aqueous solution to the extent of 55% in the carbonyl form and 45% in the hydroxy form.[89] The effect of changing the solvent on its overall ultraviolet spectrum is shown in Scheme 32, clearly indicating a swing towards the hydroxy form as the dielectric constant decreases.

Scheme 32. Effect of Solvents on the UV Spectrum of 2-Chloro-4-pyridone



Quantitative correlations exist. Thus, in Scheme 33, log K_T is plotted against Z values of solvent polarity for a number of pyridones[90] to give straight lines. Using this method, extrapolation of such lines leads to predictions that, for example, 4-pyridone, in non-polar cyclohexane, will exist predominantly in the 4-hydroxypyridine form (see Scheme 34).[91]

Scheme 33. Plot of $\log K_T$ Against Z-Values of Solvent Polarity



Scheme 34. Pyridones in Non-Polar Solvents

Predicted /Calculated pK_T Values in Cyclohexane

pK_T 4-pyridone	-1.3	pK_T 4-quinolone	0.4
pK_T 2-pyridone	0.2	pK_T 2,6-di-*t*-butyl-4-pyridone	- 0.9

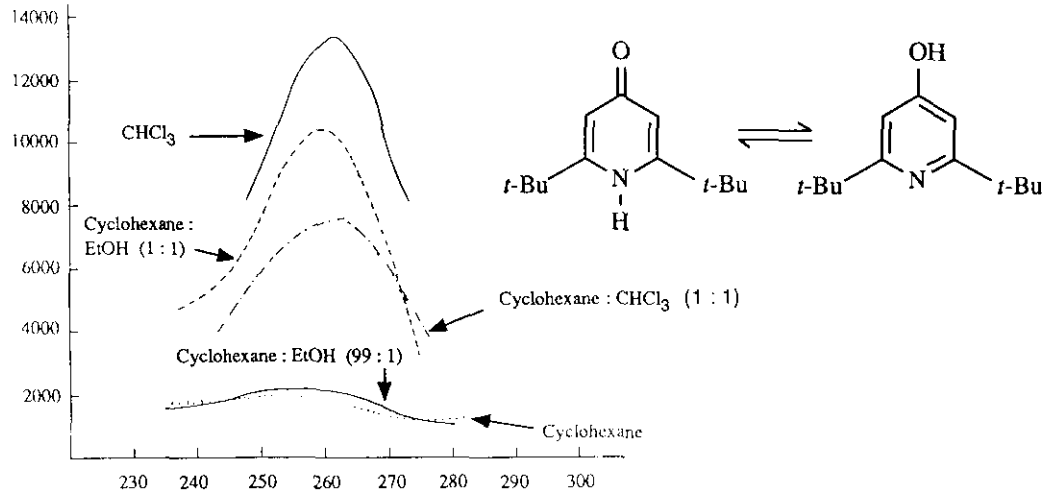
Uv Absorption Maxima and Intensities in Various Solvents

	m μ	log ε
2-Pyridone (EtOH)	299	3.87
2-Pyridone (C_6H_{12})	295	3.68
4-Pyridone (MeOH)	256	4.15
2,6-di-*t*-butyl-4-pyridone (MeOH)	258	4.17
2,6-di-*t*-butyl-4-pyridone (C_6H_{12})	255	3.35

This is supported by results on 2,6-di-*t*-butyl-4-pyridone which has the needed solubility in cyclohexane.

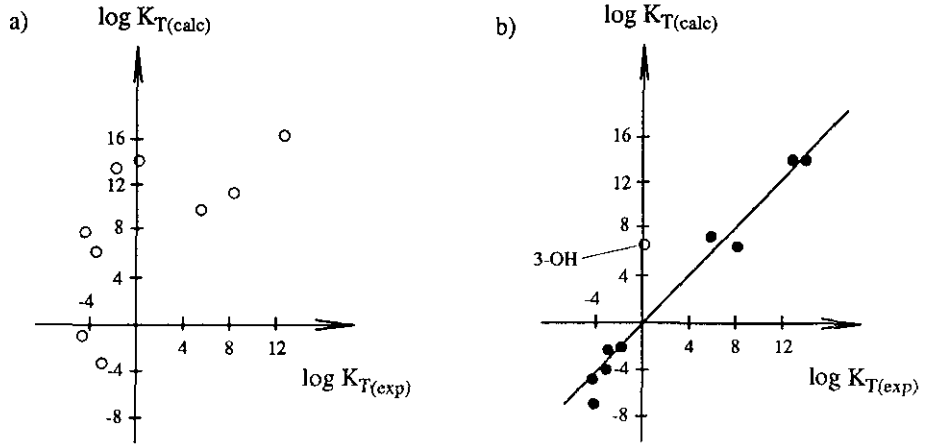
This is supported by results on 2,6-di-*t*-butyl-4-pyridone which has the needed solubility in cyclohexane.

Scheme 35. Dependence of Tautomeric Structure on Solvent (di-*t*-Butyl-4-Pyridone)



Recently, a significant breakthrough has been made in the application of MO calculations to the tautomerism of pyridines. The AM1 calculated K_T values are in good agreement with the (limited) data for the K_T of pyridines in the vapor phase (Scheme 36). More significantly, excellent agreement is found between the aqueous solution experimental K_T values and those calculated by AM1 with a reaction field corrected for the medium dielectric constant.

Scheme 36. The Relationship between AM1 SCRF Calculated logK_T Values for 2-, 3-, and 4-substituted Pyridines in Their Isolated Form (a), and in Dielectric Medium of Relative Permittivity $\epsilon = 80$ (b) and Experimental log K_T Values in Aqueous Solution

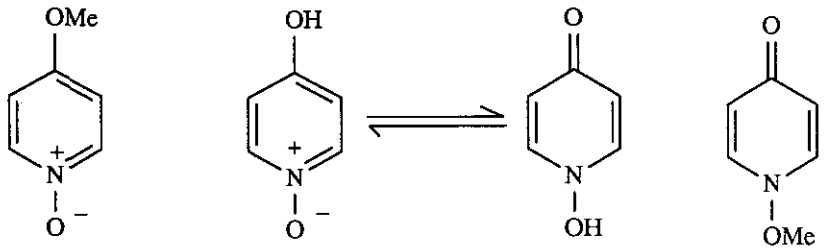


4. Other Six-Membered Rings

4.1 Pyridine N- Oxides

The tautomeric equilibria of 4-hydroxypyridine N-oxide is illustrated in Scheme 37.[92] The pKa value of the tautomeric compound in this case lies in between those of the two fixed derivatives, showing only that the tautomers are probably of almost equal energy. Uv-spectroscopic determination of the relative amounts fails as there is insufficient differentiation of the spectral maxima.

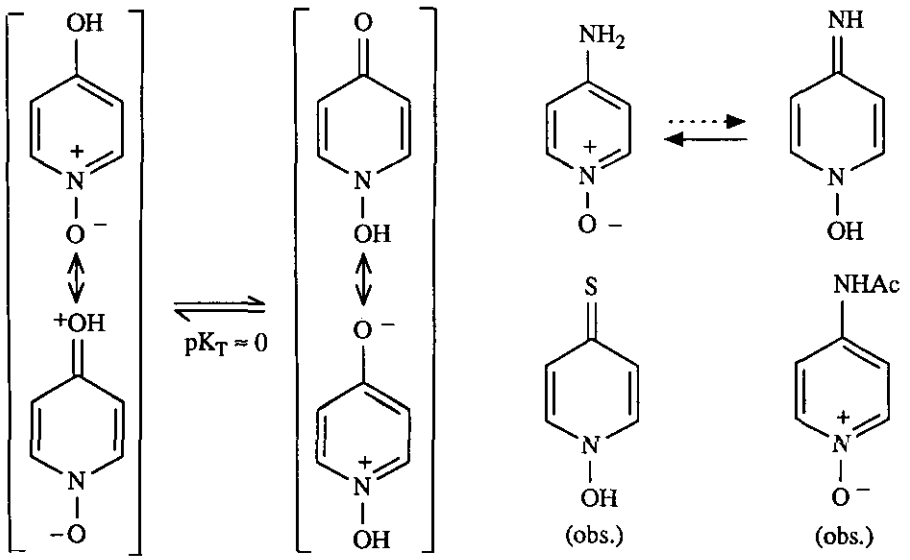
Scheme 37. Tautomerism of 4-Hydroxypyridine N-Oxide



pKa		2.05	2.45	2.57
		Nmr Chemical Shifts (τ $SiMe_4$ external)		
Water	α - H	1.47	1.51	1.52
	β - H	2.45	2.70	3.10
20 N H_2SO_4	β - H	2.12	2.13	2.10

In the crystalline state, an almost symmetrical hydrogen bond exists, thus reducing the distinction between the two tautomers. The position for other N-oxides is summarized in Scheme 38.[93]

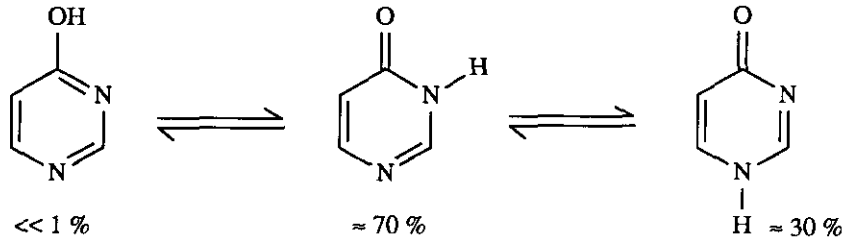
Scheme 38. Tautomerism of Pyridine N-Oxides



4.2 Tautomeric Diazines

In the case of a diazinone, there are at least two alternative NH forms. This is illustrated in Scheme 39 for pyrimidin -4-one which exists in aqueous solution to the extent of approximately 70% in the "amide form" and approximately 30% in the "vinylogous amide form", with only very little present in the hydroxy form. It is quite generally found that "amide forms" are usually more stable than "vinylogous amide forms", but the stability difference is not very large.[8]

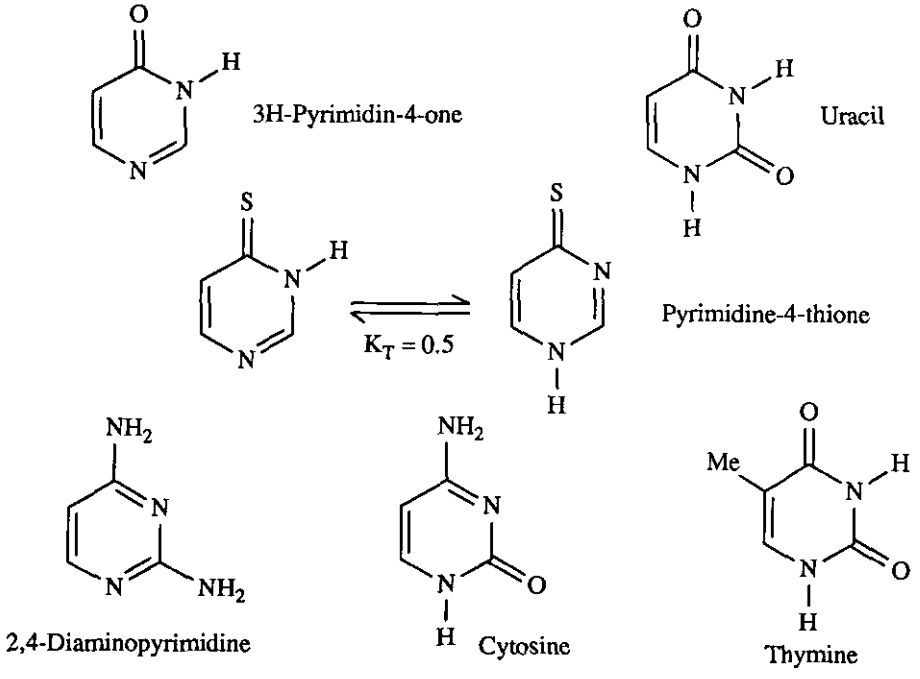
Scheme 39. Tautomeric Azines in Aqueous Solution



"Amide" forms usually more stable than "vinylogous amide" forms.

The general pattern for tautomerism among diazines follows quite closely to that for pyridines. Thus, in aqueous solution, the potential hydroxy and mercapto compounds exist predominantly as diazinones and diazinethiones, whereas methyl- and amino-azines exist predominantly as such. Scheme 40 shows the predominant tautomer for each of a variety of common compounds.[8]

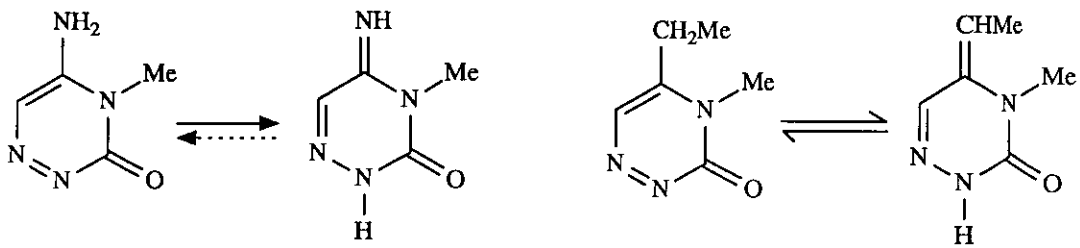
Scheme 40. Predominant Tautomeric Forms in Aqueous Solutions of Various Azines



There are certain rare cases where this pattern is not followed. One of the causes of this is an aversion to dominant canonical forms containing NN double bonds. Thus, the aminotriazinone shown in Scheme 41 exists to a significant extent in the imino form.[94] Even more surprisingly, the ethyl derivative exists to quite some extent in the ethylidine form.[95] However, these are rare exceptions to the above generalizations.

Scheme 41. Tautomeric Triazinones in Solution

Effect of N=N-bonded forms:



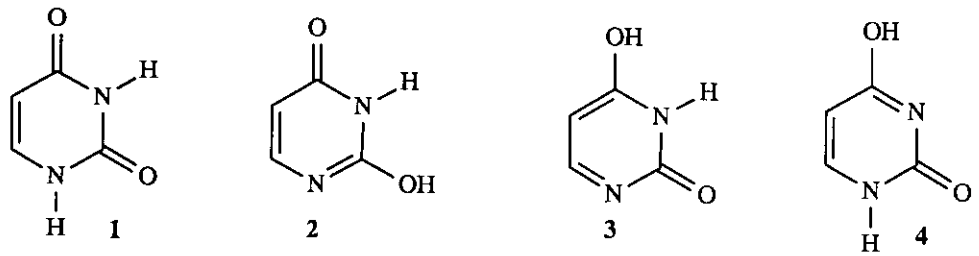
4.3 Tautomerism of the Nucleic Acid Bases

As mentioned earlier in this review, the tautomerism of nucleic acid bases is of special importance, both because it determines the double helix structure of DNA, and because it is important for the so-called spontaneous mutations which are important in genetics and natural selection.

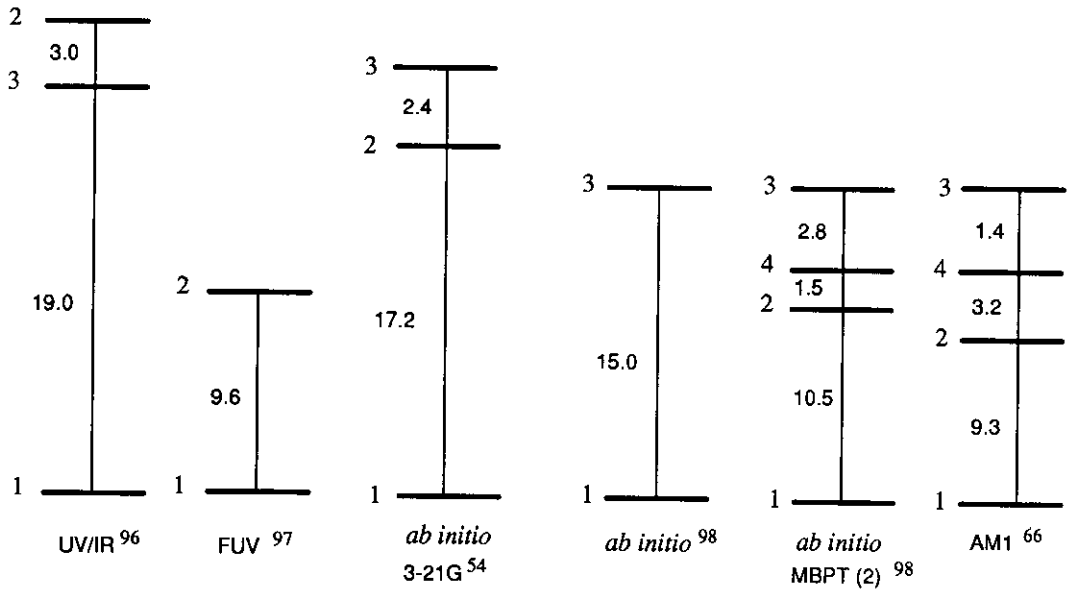
The dominant structure of the nucleic acid bases (i.e. oxo and amino forms exist) is not in dispute, and numerous physical methods are in agreement with this point (so-called exceptions have always been later disproved!). However, it is clearly of major importance to know quantitatively the extent to which minor tautomers can exist because of their importance in mutations. Clarification of this point has been very difficult and controversial. For example, for uracil it has long been clear that the dicarbonyl form is certainly the most stable, but the degree of its stability over the other structures has been much less well understood.

Recently, we have applied molecular orbital calculations using the AM1 method with a correction for the dielectric constant to clarify the tautomerism of uracil and cytosine. The results are shown for uracil in Scheme 42,[66] in which the calculated values are compared with the available experimental results. The simple-to-apply AM1 method clearly gives results for the isolated molecules in excellent agreement with our available data. This encourages confidence also in the aqueous solution values.

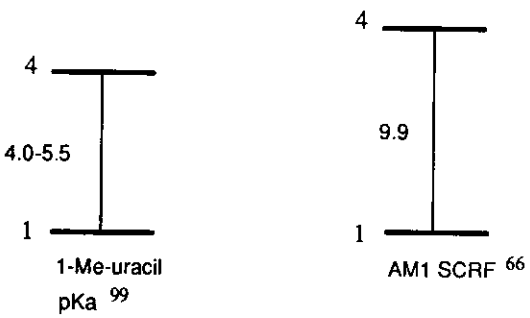
Scheme 42. Experimental and Theoretical Estimations of the Relative Uracil Tautomer Energies (Kcal mol^{-1})



(a) Isolated Molecules (gas phase)

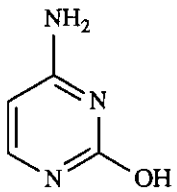


(b) Aqueous solution

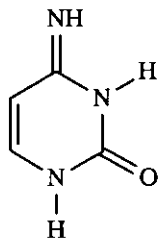


Similar data has been obtained for cytosine. Cytosine has a large number of possible tautomers: those which preserve the cyclic conjugation are shown in Scheme 43. It has been quite clear for a long time that the 1H-2-oxo-4-amino form (**3**) greatly predominates, and although various claims have been made to the contrary, they have all proved to be incorrect. For example, one of them based on nmr line-broadening, which purported to show that ΔH was only 1.1 calories, was really caused by paramagnetic ions.[100,101]

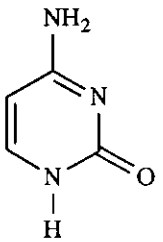
Scheme 43. Tautomeric Forms of Cytosine



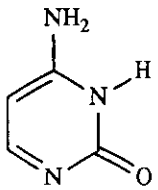
1



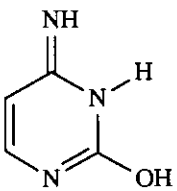
2



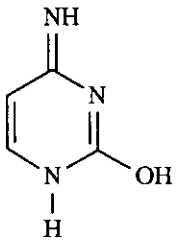
3



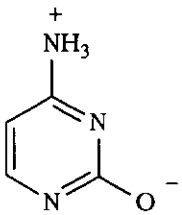
4



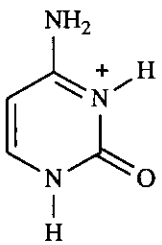
5



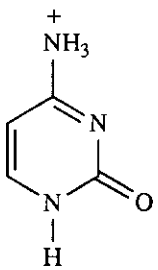
6



7

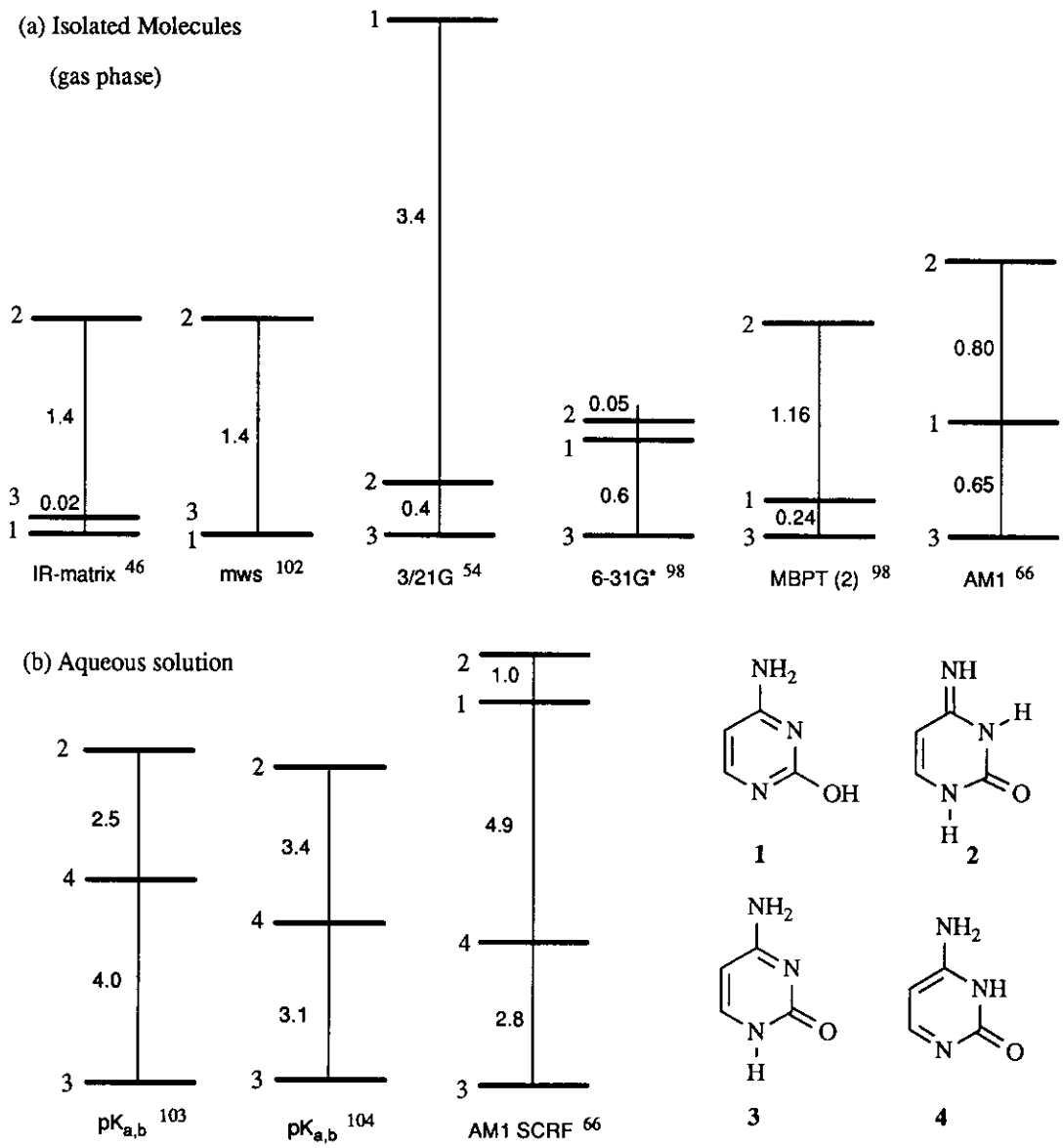


(cytosine cation)



Our calculated results for these equilibria are shown in Scheme 44. Once again, these results are overall in very good agreement with the best availble *ab initio* methods in the vapor phase and with the experimental data for the solution phase.

Scheme 44. Experimental and Theoretical Estimations of the Relative Cytosine Tautomer Energies (Kcal mol^{-1})

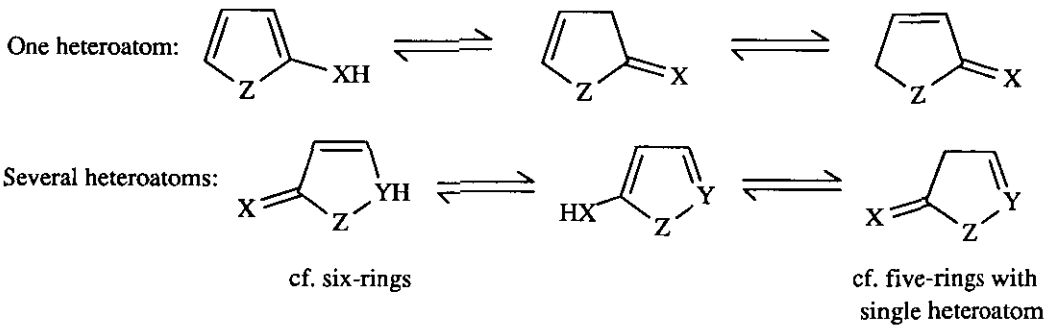


5. Five-Membered Rings

5.1 Five Membered Rings with one Heteroatom

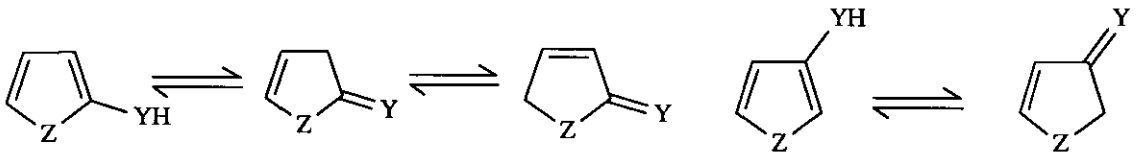
The tautomeric possibilities of five-membered rings with one heteroatom (as shown in Scheme 45) are different from those found in the pyridines and azines insofar as only one of the tautomers is aromatic.

Scheme 45. Tautomeric Possibilities in Five-Ring Heterocycles

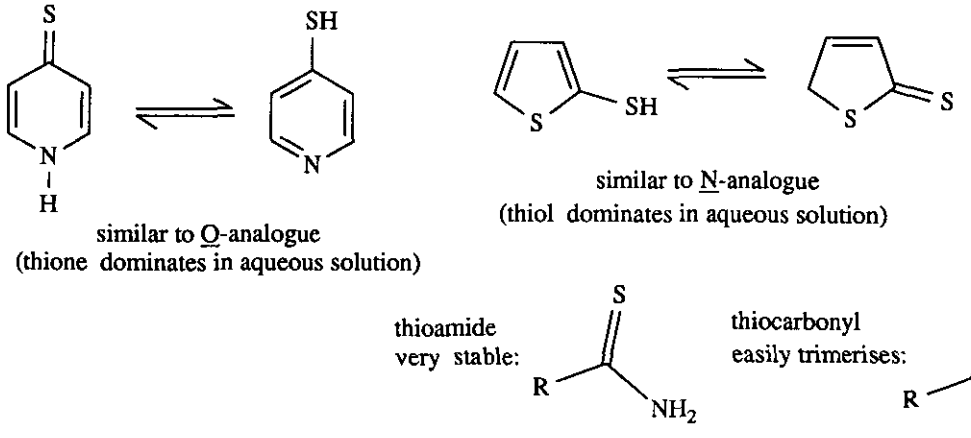


Scheme 46 summarizes the position for tautomeric furans, thiophenes, and pyrroles with hydroxyl, mercapto or amino groups. In these compounds, for Y=O, non-aromatic forms are usually preferred. For Y=S, or NH, the aromatic form is favored but usually only very slightly. Also, tautomerism between two non-aromatic forms is always slow and individual tautomers can be isolated. It is of interest that mercapto compounds in these five-membered rings resemble the N-analogs, rather than the O-analogs as is found with the six-membered ring compounds. The reason for this can be understood by reference to Scheme 47.

Scheme 46. Tautomeric Furans, Thiophenes, Pyrroles



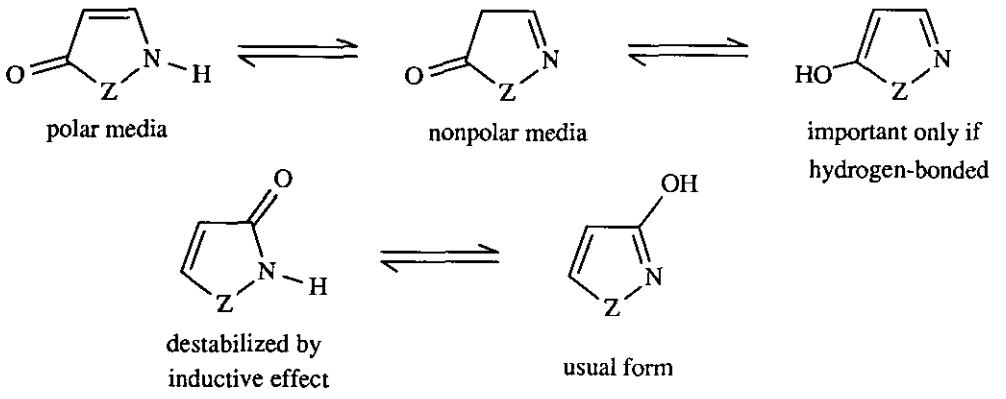
Scheme 47. Comparison of SH with OH and NH_2 Substituents



5.2 Tautomerism in the Azoles

In the azoles, we also find that mercapto and amino derivatives usually exist as such. However, the pattern for the hydroxy compounds is more complex (Scheme 48). In the first place, both hydroxy and carbonyl tautomers can exist, and secondly, two alternative carbonyl tautomeric forms are frequently possible.

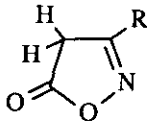
Scheme 48. Tautomerism of Hydroxyazoles Versus Azolinones with Adjacent Heteroatoms



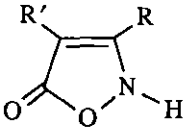
These apply to Z = O, S, NR and also for thiadiazole, oxadiazoles and triazoles.

The situation for isoxazolin-5-one is summarized in Scheme 49.[8] The 4H-oxo tautomer exists for the 4-unsubstituted derivatives in non-polar solvents and the solid state, and as the dominant tautomer in water. A substituent in the 4-position tips the equilibrium towards the 2H-4-oxo tautomer which now dominates in aqueous solution and the solid state, whereas in non-polar solvents, it is mainly in the 4H-form. Finally, a substituent in the 4-position which can hydrogen-bond with a 5-hydroxyl group can stabilize that tautomer.

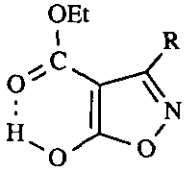
Scheme 49. Tautomerism of Isoxazolin-5-ones: Summary of Predominant Forms



R = Me, *t*-Bu, Ph, *p*-NO_2Ph, *p*-MeOPh
CH in cyclohexane, CCl_4, $CHCl_3$ and solid state
ca. 3:1 CH:NH in H_2O



R′= Me, Br, Br, Br, Br
R = Ph, *t*-Bu, Ph, *p*-MeOPh, *p*-NO_2Ph
CH in cyclohexane, mostly CH in $CHCl_3$.
NH in H_2O, solid state



R = Me, Ph
OH in cyclohexane
OH + NH in $CHCl_3$
NH in H_2O and solid state

Much further work has been carried out, usually on a qualitative basis by spectroscopic comparisons with fixed derivatives, to elucidate the predominant tautomer present. We have recently carried out calculations[77] and compared the results with the experimental data. As is shown in Schemes 50-52, in all cases, the predominant form in aqueous solutions is predicted correctly. In the cases of 5-hydroxyoxazole and 5-hydroxyisoxazole, the oxo-form is predominant in chloroform; the dielectric constant of chloroform is much closer to that of a vacuum than to that of water.

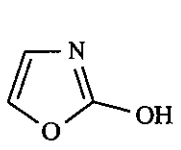
Scheme 50. Tautomerism of Five-Membered Heterocycles

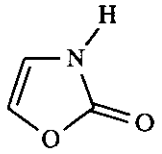
AM1 SCRF calculated relative energies of tautomers in Kcal mol^{-1}.

Experimentally observed are denoted by (+).

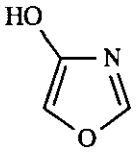
Solution refers to the highly polar medium of the dielectric constant of water (ϵ=80).

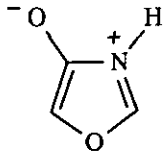
(a) Hydroxyoxazoles:

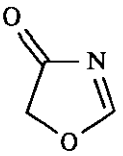




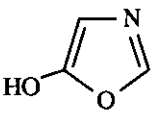
AM1 (gas)	13	0
AM1 (solution)	23	0
Experimental (solution)	-	(+)

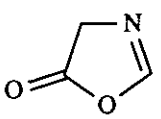


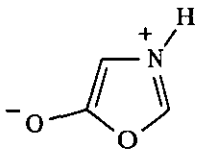




AM1 (gas)	14	23	0
AM1 (solution)	18	8	0
Experimental (solution)	-	-	(+)





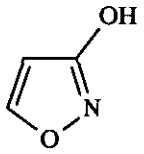
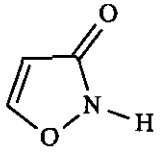


AM1 (gas)	13	0	19
AM1 (solution)	28	17	0
Experimental ($CHCl_3$)	-	(+)	-

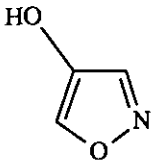
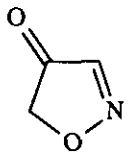
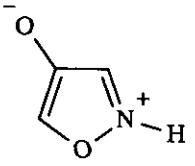
Scheme 51. Tautomerism of Five-Membered Heterocycles

AM1 SCRF calculated relative energies of tautomers in Kcal mol^{-1}.
Experimentally observed are denoted by (+).
Solution refers to the highly polar medium of the dielectric constant of water (ϵ=80).

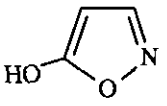
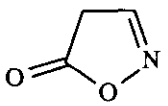
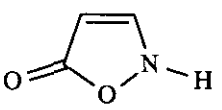
(b) Hydroxyisoxazoles:

AM1 (gas)	0	0.1
AM1 (solution)	0	2.6
Experimental (solution)	(+)	--

AM1 (gas)	10.4	0	46
AM1 (solution)	0	0.3	21
Experimental (solution)	(+)	--	--

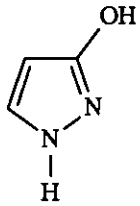
AM1 (gas)	14.8	0	15.4
AM1 (solution)	17.4	1.1	0
Experimental ($CHCl_3$)	--	(+)	--
Experimental (solution)	--	--	(+)

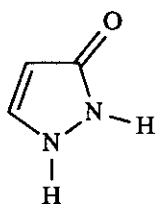
In summary this theoretical approach always predicts the correct tautomer in aqueous solution for hydroxy-(oxy-) substituted five-membered heterocycles with two ring heteroatoms.[77]

Scheme 52. Tautomerism of Five-Membered Heterocycles

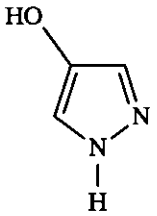
AM1 SCRF calculated relative energies of tautomers in Kcal mol^{-1}.
Experimentally observed are denoted by (+).
Solution refers to the highly polar medium of the dielectric constant of water (ϵ=80).

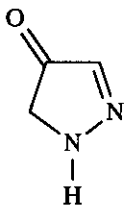
(c) Hydroxypyrazoles:

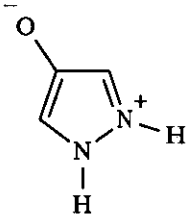




AM1 (gas)	0	6.6
AM1 (solution)	11.8	0
Experimental (solution)		(+)



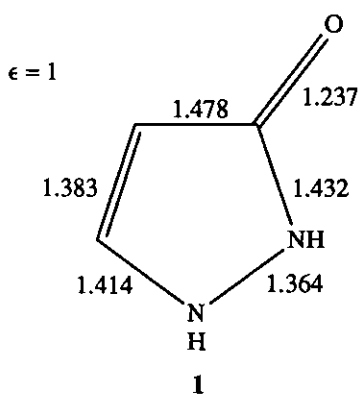




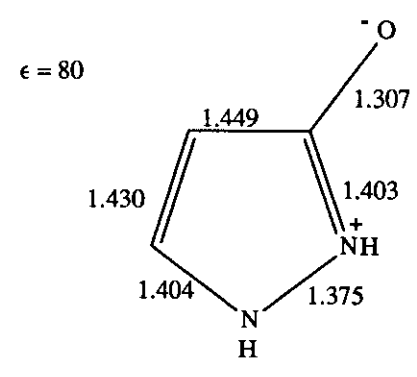
AM1 (gas)	1.6	0	41.3
AM1 (solution)	13.2	9.0	0
Experimental (solution)			(+)

There is also a substantial solvent-assisted increase in the dipole moments of the more polar tautomeric forms with zwitterionic resonance structures. This is reflected in significant changes in the geometry of those tautomers. As demonstrated in Scheme 53, the 2H-oxo form of 3-hydroxypyrazole has a C-O AM1 calculated bond length of = 1.237 Å, which is close to the standard value of a C=O double bond length (corresponding to the non-zwitterionic resonance form **1**). However, the AM1 SCRF calculated C-O bond length in a medium with the relative permittivity of water (ϵ = 80) is 1.307 which is now closer to the standard value for a C-O single bond. Thus, this bond length is more closely related to the zwitterionic resonance form **2**.

Scheme 53. Geometry of 2H-Oxo Form of 3-Hydroxypyrazole



1

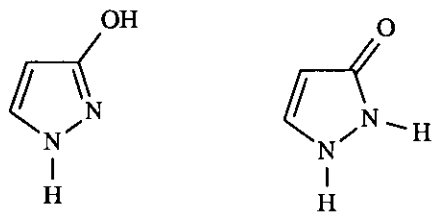


2

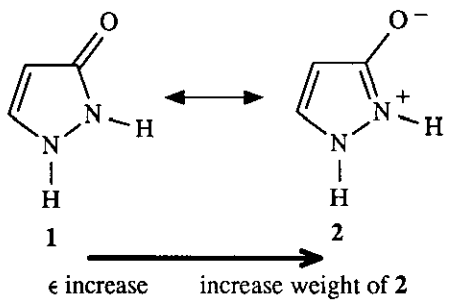
5.3 Rationalization of Azole Tautomerism

The reasons for the different tautomeric patterns for the different azoles, and for the variation with environment, arise from the relative basicity of the nitrogen atom and also from the fact that the oxo derivatives with the carbonyl group conjugated with the nitrogen have large dipole moments and are more stable in polar media (cf. Scheme 54).[77]

Scheme 54. Solvent Influence on the Dipole Moment of Tautomers of 3-Hydroxypyrazole (Hydroxy- vs. Oxo-form), Calculated by the AM1 SCRF Method



Dielectric constant of solvent	μ(D)	μ(D)
$\epsilon = 1$	3.457	5.577
$\epsilon = 80$	4.559	10.363
$\Delta\mu$	31.9 %	85.8 %



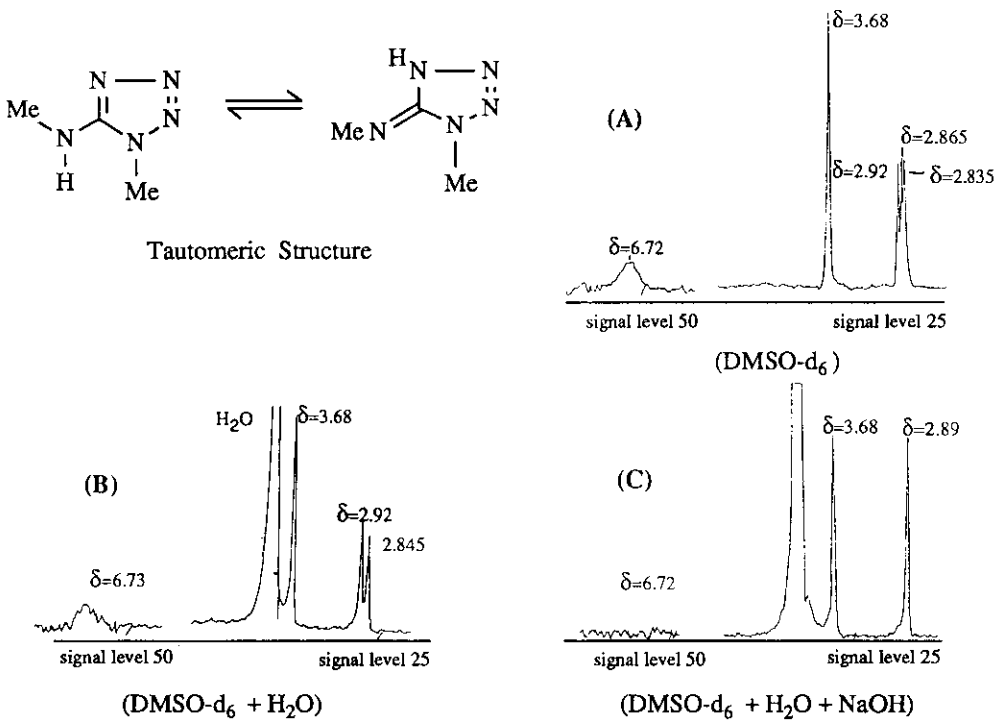
1 **2**

ϵ increase increase weight of **2**

5.4 Tautomerism of Azoles - Apparent Exceptions to above Rules

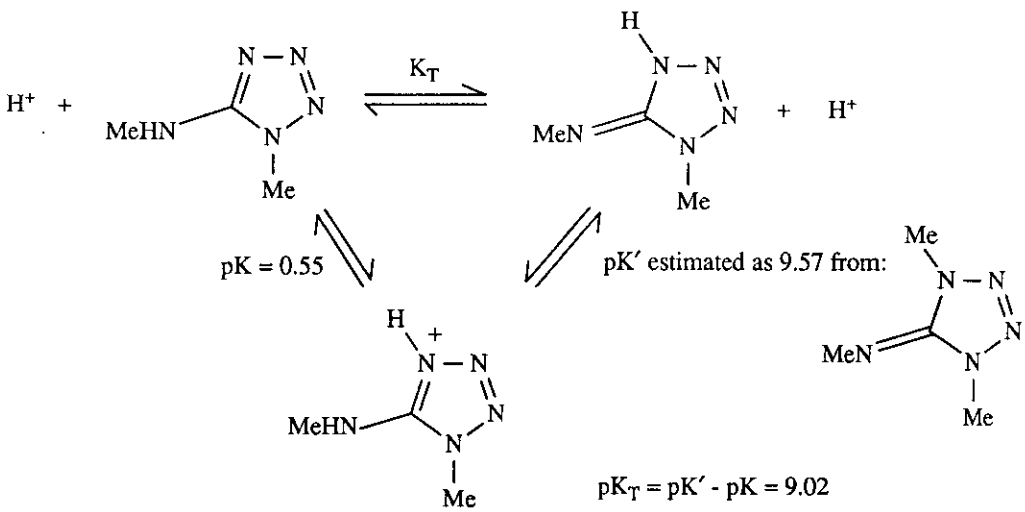
An apparent exception to the rule that aminoazoles exist as such was claimed for 1-methyl-5-methylaminotetrazole which was stated to exist to the extent of approximately 1/3 in the imino form in aqueous solution.[105] The ^{1}H nmr spectrum of the compound is shown in Scheme 55.

Scheme 55. ^{1}H Nmr Spectra of 1-Methyl-5-methylaminotetrazole



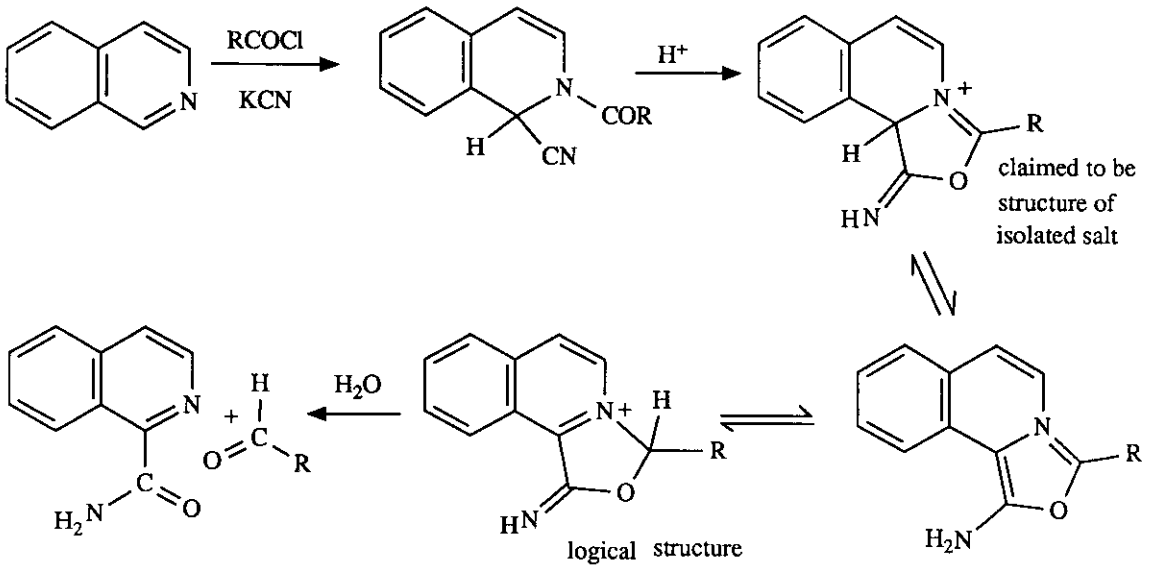
However, it turned out that the equilibrium constant is probably 10^9 in favour of the amino form[106] - Scheme 56, and the incorrect conclusion was due to the appearance of a third band in the nmr spectrum caused by H/D exchange taking place in the D_2O contaminated DMSO-d_6 solvent.

Scheme 56. Quantitative Assessment of Equilibrium Constant



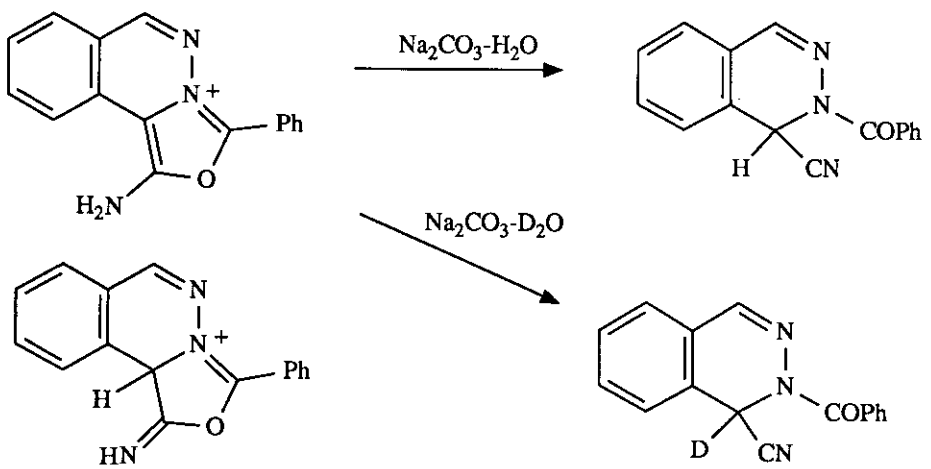
Another example arises in the Reissert salt intermediates formed in the synthesis of aldehydes. These were claimed to exist in the imino form which is highly unlikely, the amino form being expected.[107]

Scheme 57. Reissert Synthesis of Aldehydes



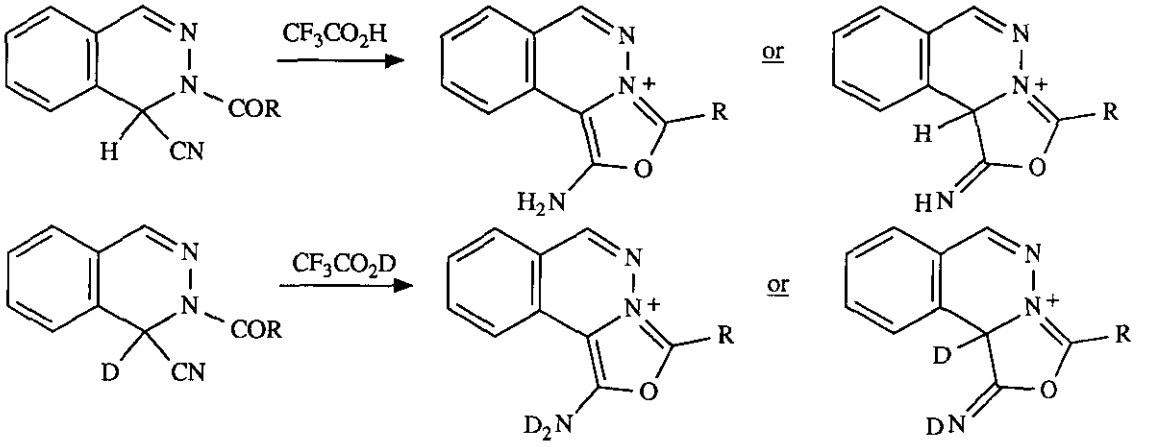
Once again, it could be proved conclusively[108] that the amino form was correct because of reconversion in water and in D_2O to the non-deuterated and deuterated cyano compound, respectively - Scheme 58.

Scheme 58. Reconversion of Reissert Salts to Reissert Compound



Furthermore, comparison of the nmr spectra of the products of the reaction with both deuterated and non-deuterated trifluoroacetic acid showed no difference as would be expected from the amino form (see Scheme 59).

Scheme 59. Reissert Salts: Nmr Evidence of Structure



structures should show **same** nmr structures should show **different** nmr

6. Summary and Conclusions

Some generalizations that can be made regarding the tautomeric structure of substitiuted heterocycles are that NH_2 and CH_3 compounds exist as such with very few exceptions. Hydroxy/oxo compounds with the potential OH group α or γ to a cyclic nitrogen usually exist in the oxo form unless electron withdrawing substituents near the nitrogen, or nonpolar solvents, or substituents that can hydrogen bond with the OH group help stabilize the OH form. Thiol/thione compounds resemble OH derivatives in six membered rings and in azoles, but resemble NH_2 compounds in five membered rings with one heteroatom.

For molecular orbital calculations of tautomeric equilibrium constants, AM1 calculations give reliable results for isolated molecules in media of a low dielectic constant, whereas AM1 calculations with reaction field constants give good results for K_T in media of a high dielectric constant. Finally, for complex equilibria between many tautomers, and for strongly biased equilibria, these MO calculations often offer the only practical approach to a quantitative picture.

7. References

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