Tautomeric Equilibria in Relation to Pi-Electron Delocalization

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Contents

1. Introduction

Tautomerism, a particular case of isomerism, plays an important role in modern organic chemistry, biochemistry, medicinal chemistry, pharmacology, molecular biology, and life itself. Understanding the mechanisms of the many organic reactions[1] and biochemical processes, including those involving specific interactions with proteins, enzymes, and receptors,[2] in which a substrate or an active intermediate tautomerizes requires an understanding of tautomerization.[1] Tautomerism partially explains the structure of nucleic acids and their mutations.[2a] It can also be applied in computer-aided drug design.[3] Although tautomerism is exceptionally difficult to study because tautomeric interconversions are usually very fast processes, the variety and importance of applications continuously encourage researchers to undertake investigations on tautomerism. This is evident from a comparison of the frequency of the use of selected terms in the last eight years (ISI 1996−2003). The term "tautomerism" was used 1612 times in titles, abstracts, and whole texts. Thus, each year tautomerism was discussed in about 200 papers. A similar frequency (1799 times) was found for the term "isomerism", but other more general terms such as "mechanism", "enzyme", "receptor", "DNA", "mutation", "disease", and "drug" were used 50 to 100 times more frequently than "tautomerism" (140 151, 115 514, 138 887, 114 119, 91 761, 160 100, and 111 507 times, respectively).

The term "tautomerism" (Gr., *tauto* − same, and *meros* − part) refers to a compound existing in an equilibrium between two or more labile isomeric forms called the tautomers.[4] Tautomers are interconverted in this reversible process, and the molecular rearrangement is intra-, or more frequently, intermolecular. Tautomeric interconversion consists in a heterolytic splitting of the molecule followed by recombination of the fragments formed. Such isomerism can be accompanied by migration of one or more double bonds and atoms or groups in so-called prototropic, cationotropic, or anionotropic tautomerism[5] or by the opening of a ring in one direction of isomerization and cyclization in the opposite direction in the so-called ring-chain tautomerism.[6] Another type of isomerism, called valence tautomerism, proceeds without migration of atoms or groups but involves only the formation and breaking of bonds, either single or double.[7] Interconversion between thermodynamically stable tautomers is possible in the gas phase for an isolated molecule or under the

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Wanda Kosińska was born in 1951. She studied chemistry at the Warsaw Technical University and obtained her Ph.D. degree in chemistry in 1979. She worked in the Institute of Physics at the Warsaw Technical University till 1988. Since 1988, she has been teaching chemistry at the Warsaw Agricultural University. Her main scientific interests are hydrogen bonding and spectroscopy. She is married and has two children. She loves art, theater, and literature.

action of various influences such as light, temperature, acid, base, solvent, electron solvation, or ionization).[5−8]

Electron delocalization is a concept originally introduced to explain the exceptional stability of benzene.[4,9] According to the Ingold theory of mesomerism, in which electron delocalization was even initially called "intra-annular tautomerism", benzene was represented by a few dynamically interchanging Lewis electronic structures.[10] With the development

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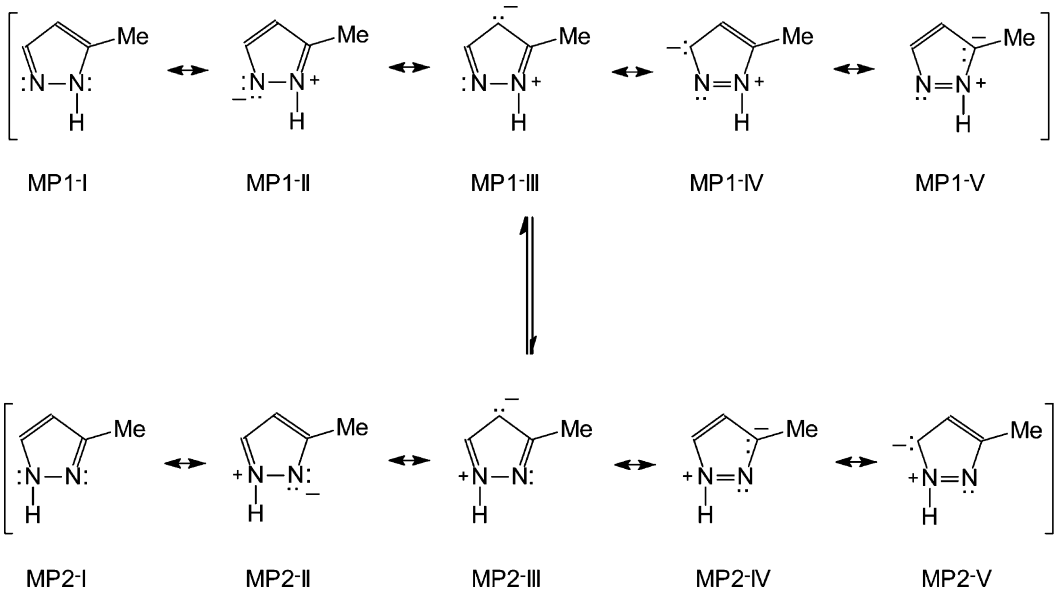
of quantum theory, the term "resonance hybrid", corresponding to a complete electron delocalization, was introduced,[11] and a distinction was made between tautomerism and electron delocalization, also called "resonance". The relation between the phenomena of tautomerism and that of resonance was also formulated.[12]

Pauling, in his famous book *The Nature of the Chemical Bond* (p 566), wrote:[12a] "when the magnitudes of the electronic resonance integral (or integrals) and of the other factors determining the electronic energy function of a molecule are such that there are two or more well-defined stable nuclear equilibrium configurations, we refer to the molecule

Scheme 1. Relation between Tautomerism and π Electron Delocalization in 3(5)-Methylpyrazole



as capable of existing in tautomeric forms; when there is only one well-defined stable nuclear equilibrium configuration, and the electronic state is not satisfactorily represented by a single valence-bond structure, we refer to the molecule as a resonating molecule". In other words, tautomerism implies an equilibrium between two or more isomers (tautomers) existing independently, which differ by their constitution, that is, by differing positions of bonds, atoms, or groups, whereas electron delocalization involves a single arrangement of atoms and is characterized by two or more resonance structures, which differ only by the π or n$-\pi$-electron and charge arrangements. To distinguish these two phenomena, different arrows were proposed: "$\rightleftharpoons$" for tautomeric equilibrium between independent tautomers and "$\leftrightarrow$" for electron delocalization expressed between canonical structures.

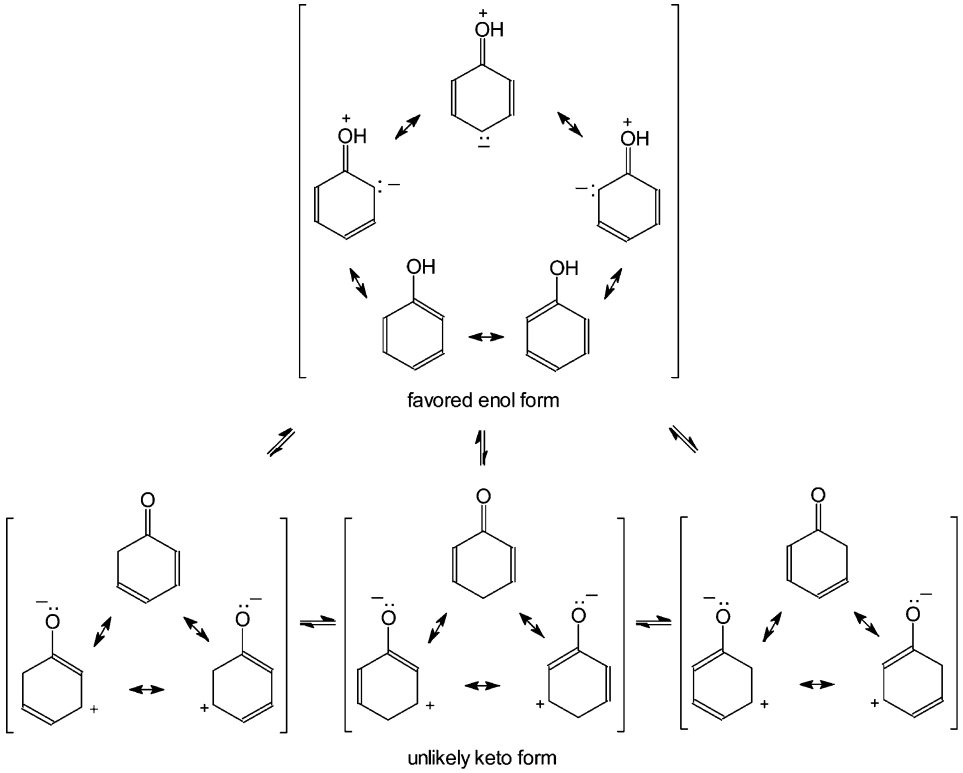
This distinction does not mean that tautomerism and electron delocalization are mutually exclusive, though, because a particular relation does exist between them. A tautomeric substance can exist in two or more tautomeric forms, and each of these forms can be represented, not by one Lewis electronic structure, but by a hybrid of various resonance structures. To illustrate the distinction and the relation between the two phenomena, Pauling chose tautomeric 3(5)-methylpyrazole (MP), which exists as a mixture of two potential tautomers (MP1 and MP2 in Scheme 1). Many researchers considered the interconversion in MP as a 1,2 proton shift (MP1-I $\rightleftharpoons$ MP2-II in Scheme 1). This interpretation, however, is not correct, because the proton transfer in MP (MP1 $\rightleftharpoons$ MP2) also includes the migration of the π-electrons. This means that it should be classified as a 1,5 proton shift in a cyclic conjugated system similar to the shift in the acyclic system $-$N=CH$-$CH=CH$-$NH$-$ $\rightleftharpoons$ $-$HN$-$CH=CH$-$CH=N$-$, in which three carbon atoms are also engaged in the interconversion.[13] Pauling proposed three resonance structures (I$-$III) for each tautomeric form, MP1 and MP2. However, two additional resonance structures (IV and V) may also participate in the resonance hybrid, because MP is classified as an aromatic heterocycle with almost complete π-electron delocalization.[14,15] Probably, however, these last two resonance forms with a cyclic azo structure contribute less to the resonance hybrid.

π-Electron delocalization in tautomeric systems often explains particular tautomeric preferences. In several cases, it helps explain why a particular aromatic compound prefers a different tautomeric form than the corresponding aliphatic compound. For instance, phenol favors its enol form because of a complete electron delocalization (aromaticity) in the ring (Scheme 2), whereas cyclohexanone preferentially takes the keto form (Scheme 3). Electron delocalization in cyclohexanone is possible only in the tautomeric moiety. The transferred proton prefers the carbon atom in the keto form rather than the oxygen atom possessing a positive charge in the resonance structures of the enol forms.

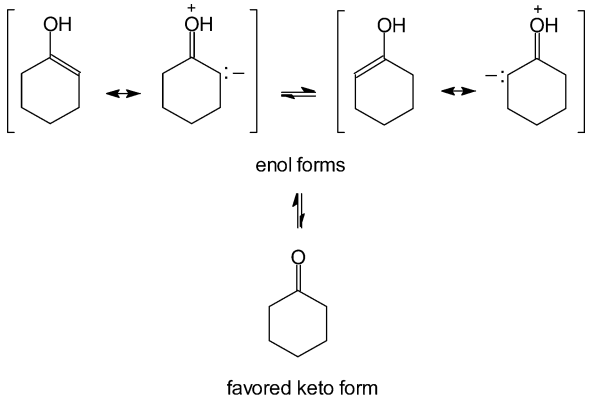
To describe quantitatively the π-electron delocalization in various mono- and polynuclear aromatic compounds and to define their aromatic nature, numerous theories were formulated in the 20th century, for example, Hückel rules,[14] Bird's index I,[16] Krygowski's HOMA,[15d,17] Schleyer's NICS indices,[18] DE, RE, DRE, and REPE ideas,[12a,14,19$-$21] Krygowski HOSE model,[15d,22] and Katritzky PC treatment.[15e,23] Recently, some of these have also been applied to describe the structure and to explain the reactivity of other conjugated systems such as (i) symmetrical, unsymmetrical, neutral, or ionic acyclic conjugated systems and (ii) conjugated radicals in which a double bond is conjugated with a vacant p-orbital, an unpaired electron, or a lone pair of electrons. However, such applications are not as numerous as in the case of homo- and heteroaromatic systems. It is worth noting that the terms "delocalization", "aromatic", and "resonance" were used 3746, 49 646, and 116 280 times, respectively, in titles, abstracts, and whole texts in the last eight years (ISI 1996$-$2003).

Although both ideas, that is, tautomerism and electron delocalization, are more than 100 years old, their relation was first treated quantitatively just 70

Scheme 2. Tautomeric Equilibria and Resonance Structures in Phenol



Scheme 3. Tautomeric Equilibria and Resonance Structures in Cyclohexanone



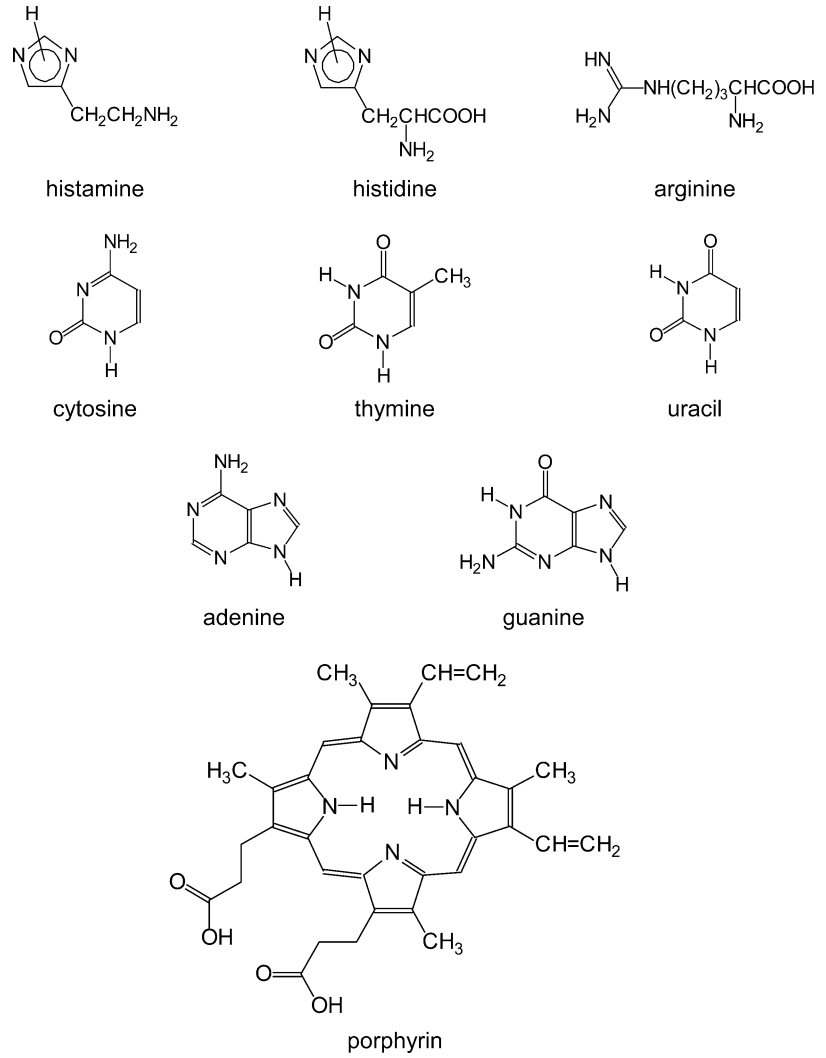
years ago for cyclic (mainly heteroaromatic) and acyclic systems (e.g., guanidines) after the formulation of the Pauling definitions and of the quantitative measures of aromaticity. Aromaticity and tautomerism have been studied and reviewed for heterocyclic systems by Katritzky, Elguero, and their co-workers during the last 40 years.[15e,k,24] Literature data for tautomeric equilibria in acyclic systems are almost as numerous as those for heterocycles.[25] Thousands of tautomeric systems, both cyclic and acyclic, were studied, and various methods, both experimental and computational, were applied. Most of these studies were focused on a variety of tautomeric systems, estimation of tautomeric preferences, investigation of substituent and solvent effects, analysis of intra- and intermolecular stabilities, explanation of reactivities, application to organic syntheses, etc.

Researchers investigating tautomeric systems have often noted the close association between tautomeric interconversions and changes in the electronic structure, electron density distribution, and acid−base properties, all of which can, in turn, be correlated with changes in π-electron delocalization. These changes can be characterized by (i) increased stability compared with an analogous but purely olefinic reference system, (ii) modified bond lengths intermediate between those typical for single and double bonds, and (iii) specific magnetic properties. These enumerated criteria are associated with numerical descriptors of aromaticity classified as energetic, geometric, and magnetic indices, respectively. Analysis of the relations between these characteristics of π-electron delocalization and tautomeric equilibria in selected systems will be the main subject of this review. Since aromatic systems have already been systematically reviewed elsewhere,[15e,k,24] we will pay greater attention to acyclic than to cyclic tautomeric compounds. Some simple natural products will also be discussed.

2. Importance of Tautomeric Equilibria in Natural Science and Life

Tautomerism, in fact, mainly prototropy, occurs frequently in natural products (Scheme 4). Some examples are bioamines such as histamine,[26] amino acids such as histidine and arginine,[27,28] pyrimidine bases (cytosine, thymine, and uracil), purine bases (adenine and guanine),[2a,e,5d,29] and porphyrins.[30] For this reason, explanations of the chemical reactivity of natural products, their biological activity, and structural assignments for them under physiological conditions have often been very difficult for organic chemists and biochemists.[2,26−30] It is not always clear which tautomeric form is responsible for biological activity when the choice is between the thermodynamically most stable tautomer and a less stable

Scheme 4. Examples of Natural Compounds Displaying Prototropic Tautomerism



tautomer with particular acid−base, electrophilic−nucleophilic, redox, or even just geometric properties. Investigations of many important biological transformations show that the energetically less stable tautomer is often an active intermediate and dictates the mechanism and the product formed.[1,2,31,32]

Intramolecular transfer of a proton in tautomeric systems, as well as intermolecular transfer of a proton between neutral or ionic species, or both, is the basic step in numerous biologically important processes.[33] Proton transfer is also responsible for the interactions of active molecules with proteins, enzymes, or specific receptors. Depending on the acid−base properties of the binding center, a molecule may gain or lose a proton and thus attain the form and conformation specifically required by the active pocket.[2c,d] Therefore, it is not always evident that the tautomeric and conformational preferences of a compound are the same in the nanoscopic environment shaped by an active pocket as they are in a homogeneous aqueous environment.[26,34] In many biological processes, proton transfer is the rate-determining step,[35] and in particular, there is evidence that quantum effects such as tunneling[36] play a crucial role in enzyme dynamics and catalytic activity[37] for proton-transfer processes with low and intermediate intramolecular proton-transfer barriers.[38] A proton tunneling model in DNA base pairs was also proposed for spontaneous point mutations in DNA.[39]

DNA mutations are among the most exciting subjects by which many chemists, biochemists, and biologists, including experts in theory and in experiment, have been attracted during the last 50 years. Various hypotheses and models were proposed in the literature, and numerous experimental and theoretical investigations were carried out to explain physicochemical changes in DNA. Any changes in the DNA sequence, the key to all genetic information, can generate mutations during the replication or repair processes. Thus, understanding of DNA mutations is crucial not only to explain but also to predict and consequently to eliminate various diseases affecting human beings. However, the nature and the mechanism of DNA mutations are not quite clear yet.[40]

The complementary pairs of nucleic acids in DNA are stabilized both by stacking and by multiple H-bonding, effects that sometimes compete with one another. It has been found that the H-bonded pairs stabilized by electrostatic interactions are more stable than the stacked structures, which are stabilized by dispersion interactions.[41] The unique and particularly strong H-bonding that is possible between the complementary purine and pyrimidine bases is crucial to life. H-bonding is also a funda-

mental force in the molecular recognition of biological macromolecules. Thus, H-bonded complexes become relevant starting points in modern organic synthesis. Such a noncovalent H-bonding interaction is responsible for the stability of some conglomerates, which include selected tautomers. Dimers, which provide the simplest model used to study transmission of genetic information, can be formed from a pair of identical tautomers of the same compound (homodimers)[42] or from a pair of distinct tautomers of the same compound (heterodimers).[43] Formation of conglomerates that consist of a few selected tautomers can be applied to build matrixes that enable the synthesis of complex derivatives such as enzymes and proteins that have exceptionally interesting properties.[44]

Proton-transfer processes are also relevant to such phenomena as dye phototautomerism at cryogenic temperatures,[45] phase transitions in ferroelectrics,[46] the mechanism of vision,[47] pumping protons across biomembranes,[48] and a great variety of chemical and biochemical catalytic systems.[49] Over the last 2 decades, interest has grown in proton exchange processes in crystalline organic materials as studied by high-resolution solid-state NMR spectroscopy.[50] NMR methods offer the advantage of probing dynamic as well as structural details and are thus complementary to the traditional approach to proton motion in solid samples, which involves X-ray or neutron diffraction techniques.

3. Generalities

3.1. Historical Background and Types and Definitions of Tautomerism

Tautomerism as a phenomenon was already recognized in the 19th century. According to Lippmann,[51] Gerhardt discussed this phenomenon in 1854 in his book on organic chemistry. In 1884, Zincke[52] discovered that the reactions of 1,4-naphthoquinone with phenylhydrazine and of 1-naphthol with benzenediazonium salts gave the same product. The interconversion of phenylhydrazone and the hydroxyazo compound was called "ortsisomerie" by Zincke. The name "tautomerism" was introduced 1 year later by Laar,[53] to describe the properties of organic compounds that can react as if they have two or more structures.

A real expansion of investigations of keto−enol tautomeric systems took place at the end of the 19th century. For instance, as early as 1863 Geuther proposed the enol structure for acetoacetate ester,[54] but a few years later Frankland[55] and then Wislicenus[56] assigned the keto structure. These facts indicated that acetoacetate ester can exist in two forms having different physicochemical properties. The existence of both the keto and enol forms for 1,3-dicarbonyl compounds was proved simultaneously in 1896 by Claisen for acetyldibenzoylmethane and tribenzoylmethane, by Wislicenus for methyl and ethyl formylphenylacetate, and by Knorr for ethyl dibenzoylsuccinate and ethyl diacetylsuccinate.[57] Claisen also found that the ratio of the keto/enol tautomers depends on various factors such as temperature, nature of substituents, and solvent.[57a]

Other types of tautomeric equilibria were independently reported in the literature. For instance, in 1877 Gabriel observed the conversion of a chain form tautomer, carboxylcinnamic acid, to a ring form tautomer, 3-phthalidylacetic acid.[58] In 1895, Pechmann[59] obtained the same tautomeric mixture of *N*-phenyl-*N*′-*p*-tolylbenzamidine by the action of benzoyl-*p*-toluidide iminochloride on aniline as by the action of benzanilide iminochloride on *p*-toluidine. In 1896, nitro−*iso*-nitro tautomerism was observed for phenylnitromethane by Hantzsch and Schultze.[60] The use of the prefix "*aci*" instead of "*iso*" before the name of the nitro compound was introduced later by Hantzsch in 1905,[61] and the nitrolic acid nomenclature is even more recent.[25e] At the end of the 19th century, another type of intramolecular proton transfer called the Behrend rearrangement[25f] was discovered in nitrones.[62]

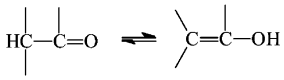
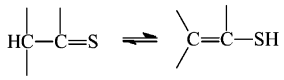
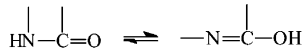
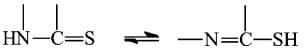
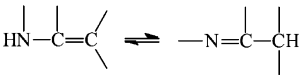
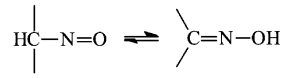
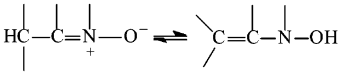
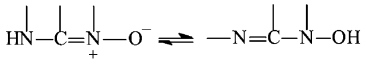
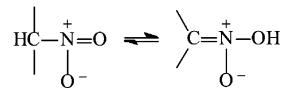
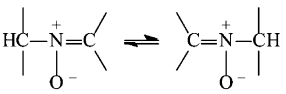
After the beginning of the 20th century, examples of different types of tautomerism appearing in the literature were so numerous that the term "tautomerism" was extended to the ring-chain, valence, prototropic, cationotropic, and anionotropic interconversions.[5a,63] It was generally used to denote reversible isomeric changes, such changes being brought about in solution or in the liquid state, with or without the aid of catalysts, to form equilibrium mixtures of the individual tautomeric forms. Of course, the meanings of the Laar term and of the later one introduced at the beginning of the 20th century were different from that proposed by the IUPAC Commission,[4] because the concept of tautomerism continued to evolve together with the development of the theory of valence, the definitions of chemical bonds, and the theory of resonance.[9−12,14,15] The historical background for this evolution was described by Ingold.[64] The term "annular tautomerism" was frequently used for tautomeric heteroaromatic systems.[5d] The particular term "*trans*-annular tautomerism" was suggested for cases such as anthranol ⇌ anthrone, and the amino ⇌ imino form of 9-aminoantracene, in which the proton migrates across the ring.[65] The term "mesohydric (Gr., *meso* − between) tautomerism", introduced by Hunter,[66] was applied to tautomeric systems such as 1,3-diketone ⇌ enolone, *ortho* isomers of 4-hydroxyazobenzene ⇌ quinonehydrazone, and nitrosophenol ⇌ quinone monooxime, in which the proton responsible for the tautomeric interconversion becomes attached to distant atoms.

According to the *Glossary of Terms Used in Physical Organic Chemistry* (IUPAC recommendations 1994),[4b] tautomerism in bifunctional compounds is defined by general equilibrium (eq 1). In this equi-

$$\underset{T_1}{GX-Z=Y} \rightleftharpoons \underset{T_2}{X=Z-YG} \qquad (1)$$

librium, G, which may be an atom or group, is an electrofuge or nucleofuge and is transferred during rearrangement from X to Y, which serve as a donor and an acceptor of G, respectively. Simultaneously with this transfer of G, π-electrons migrate from the right to the left side of Z. In many heterocyclic aromatic systems (e.g., 4-hydroxypyridine ⇌ 4-pyri-

Table 1. Examples of Prototropic Tautomeric Equilibria

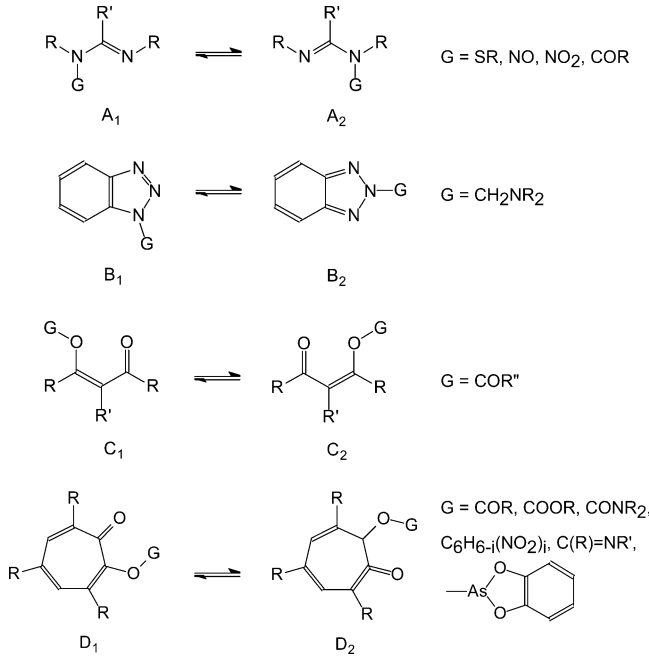
Name of prototropy	X	Z	Y	Equilibrium
keto-enol	C	C	O	
thione-enethiol	C	C	S	
thiol-thione	S	C	O	
amide-iminol	N	C	O	
thioamide-thioiminol	N	C	S	
enamine-imine	N	C	C	
amine-imine (amidine group)	N	C	N	
nitroso-oxime	C	N	O	
nitrone-*N*-hydroxyenamine	C	C	NO	
aminonitrone-*N*-hydroxyimine	N	C	NO	
nitro-*aci*-nitro (nitro-nitrolic acid)	C	NO	O	
Behrend rearrangement	C	NO	C	

done), as well as in acyclic conjugated systems (e.g., acyclic enaminone ⇌ enolimine), π-electron delocalization assists the G transfer between X and Y even over a considerable distance. Each of the atoms X, Y, and Z in eq 1 can be any of C, N, O, or S, and G can be H, Me, CH_2R, Br, NO, SR, or COR. Atoms X and Y can also be separated by a conjugated spacer (e.g., Z might be CH=CH—CH).

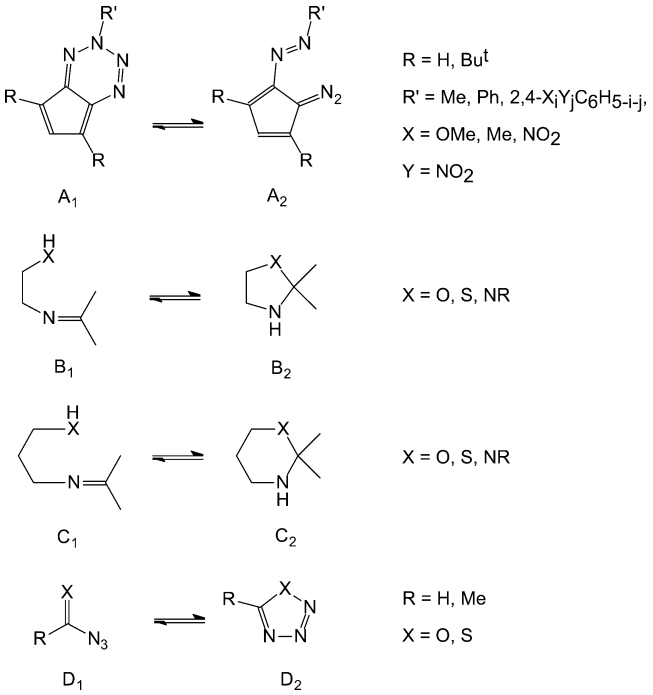
When the transferred group G is a proton, the isomerization is called a "prototropic tautomerism", or simply "prototropy". When G is a cation or an anion, the isomerization is called a "cationotropic" or an "anionotropic tautomerism", or simply "cationotropy" or "anionotropy", respectively.[5] Irrespective of the type of rearrangement, tautomers T_1 and T_2 differ by the location of atoms and by distribution of π-electrons. Table 1 lists names of selected prototropic equilibria and combinations of X, Y, and Z. Scheme 5 gives some cationotropy and anionotropy examples that have been studied by either theory or experiment, or both.[5,67]

Keto−enol tautomerism is one of the most commonly studied forms of prototropy.[1,25a,b,68] This interconversion occurs in different tautomeric systems containing one or more carbonyl groups linked to sp^3-carbons bearing one or more hydrogen atoms. There are also polyfunctional tautomeric derivatives in which the carbonyl groups are separated by a conjugated system. The keto tautomer is generally a more stable form than the enol tautomer for neutral systems, although the availability of additional in-

Scheme 5. Examples of Cationotropic and Anionotropic Interconversions



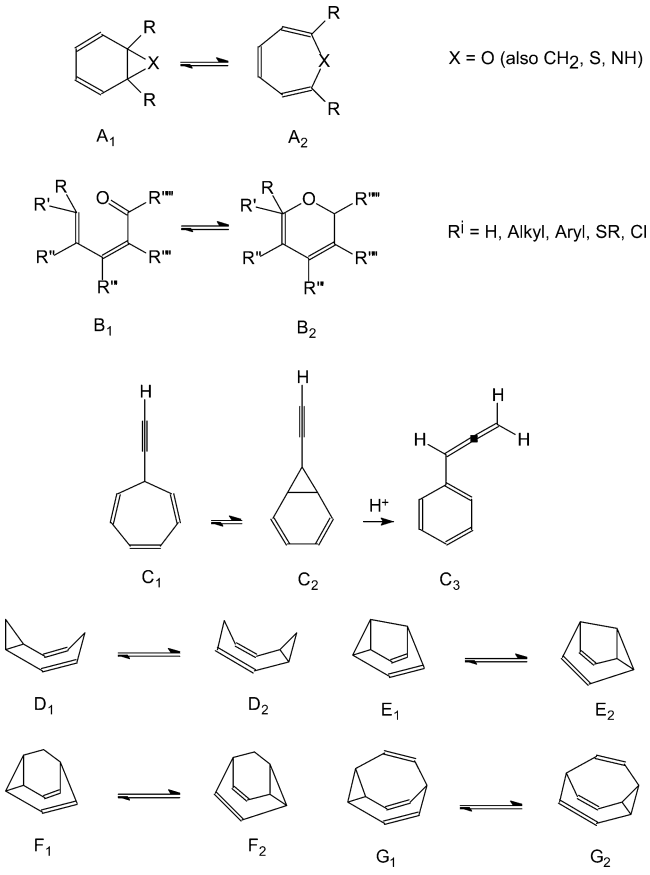
Scheme 6. Examples of Ring-Chain Tautomerism



tramolecular stabilization through, for example, hydrogen bonding (e.g., in acetylacetone or malondialdehyde) or a complete electron delocalization (e.g., in phenol), may cause the enol tautomer to be favored. Other types of tautomerism such as amide−iminol, imine−enamine, nitroso−oxime, nitro−*aci*-nitro, thione−thiol, and thioamide−thioiminol, are also extensively studied and reported.[25c−k] In simple bifunctional molecules (triad systems) that are more or less conjugated, the heteroatom prefers the π-electrons instead of the proton, thus forming a double bond with the neighboring atom and taking the form corresponding to the keto tautomer. This heteroatom plays the role of the basic site in the tautomeric moiety. The other site prefers the proton and is the acidic site. The only exceptions are observed for nitroso−oxime systems, in which the heteroatom O prefers the proton instead of the π-electrons and the oxime form, which corresponds to the enol tautomer, is favored. The less basic tautomer generally predominates in the tautomeric mixture, though in polyfunctional tautomeric systems additional intramolecular interactions may change this behavior.

When the double bond between Y and Z in eq 1 is replaced by a ring, the reversible isomerization is called "ring-chain tautomerism".[4,6] The cyclization and ring opening of aldoses, for example, glucose during mutarotation, may be classified as this kind of isomerism. Scheme 6 shows examples of ring-chain tautomerism in tetrazines, 1,3-*X*,*N*-heterocycles, and acyl azides. 2-Aryl-2-*H*-cyclopenta[*e*]-1,2,3,4-tetrazines (A_1) exist in equilibrium with (arylazo)diazocyclo-pentadienes (A_2). Both tautomers are stable enough to be identified spectroscopically.[69] Their ratio depends strongly on the electronic effects of the substituent R′, but it is independent of the substituent R. The ring-chain tautomerism of 1,3-*X*,*N*-heterocycles ($B_1 \rightleftharpoons B_2$, and $C_1 \rightleftharpoons C_2$) was reviewed recently.[70] This type of isomerism has found wide

Scheme 7. Examples of Valence Tautomerism



application in different areas of organic chemistry and also in physical, medicinal, and peptide chemistry. The ring closure is disfavored for five-membered rings (*5-endo-trig*, $B_1 \rightleftharpoons B_2$), but favored for six-membered heterocycles (*6-endo-trig*, $C_1 \rightleftharpoons C_2$). Acyl azide−oxatriazole interconversions ($D_1 \rightleftharpoons D_2$) were studied only theoretically.[71] It has been shown that acyl azides (D_1) are more stable than the corresponding oxatriazoles (D_2), whereas for the thio derivatives the situation is reversed with D_2 being more stable than D_1.

Another type of tautomerism called "valence tautomerism", which occurs at high temperature in some unsaturated hydrocarbons, is a reversible and generally rapid isomerization involving only the formation and breaking of σ and π bonds.[4,7] It proceeds intramolecularly without the transfer of atoms or groups (Scheme 7). Benzeneoxide−oxepin and its analogous interconversions ($A_1 \rightleftharpoons A_2$) are classical examples of valence isomerizations.[72] Other examples of such phenomena are tautomeric equilibria in pentadienone and pyran derivatives ($B_1 \rightleftharpoons B_2$),[73] where the formation and breaking of σ and π bonds lead to ring opening and cyclization of the systems. Similar isomerizations take place in photochromic and thermochromic spiroheterocyclic compounds (e.g., spiropyrans) as reviewed recently by Minkin.[8a] The acetylene−allene rearrangement ($C_1 \rightleftharpoons C_2 \rightarrow C_3$) is also interesting since it provides a rare application of tautomerism in synthesis of allenes.[74] The $C_1 \rightleftharpoons C_2$ equilibrium refers to valence isomerization of acetylene in the cycloheptatriene moiety. Next, the C_2 tautomer transforms slowly upon protonation to

allene C_3. A peculiar example of valence isomerization is the intramolecular interconversion of 3,4-homotropylidene, which is an identity reaction, that is, one in which the substrate reproduces itself during the process, and is classified as a Cope rearrangement.[75] Low-temperature NMR studies showed that the equilibrium $D_1 \rightleftharpoons D_2$ actually does occur.[76] Semibullvalene ($E_1 \rightleftharpoons E_2$), barbaralane ($F_1 \rightleftharpoons F_2$), and bullvalene ($G_1 \rightleftharpoons G_2$) display similar rearrangements for which low barriers of 4.8, 8.6, and 12.8 kcal mol^{-1}, respectively, were found.[77]

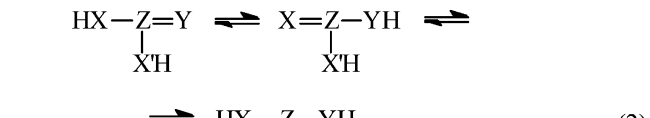
It is interesting in this context that although tautomerism is well-known, it has always presented organic chemists with difficulty in assigning the proper structure. For instance, it was reported that a DMSO solution of 1-(*p*-methylphenacyl)isoquinoline contains 10% of (*Z*)-1-(2-hydroxy-2-phenylvinyl)isoquinoline, the enolimine tautomer, but actually the minor component is (*Z*)-1,2-dihydro-1-benzoylmethyleneisoquinoline, the enaminone tautomer.[78]

3.2. Variety of Prototropic Frameworks

Among different types of tautomerism (see the previous section), prototropy is the most frequently studied interconversion. In prototropic tautomeric systems, the proton is usually provided by OH, SH, NH, or CH groups of more or less acidic character, and it is transferred to O, S, N, or C atoms possessing more or less basic properties. The proton transfer may take place between atoms of the same (e.g., carboxylic acids, imidazoles, pyrazoles) or different elements (e.g., aldehydes, ketones, hydroxytriazenes, hydroxypyridines) and in either acyclic or cyclic conjugated systems. Tautomeric interconversions may be of different types. The most common kind is 1,3-type interconversion for the so-called triad systems, for example, 1,3 proton shifts in acetaldehyde, cyclohexanone, formamide, 2-hydroxypyridine, *N*-methylformamidine, and 4(5)-methylimidazole. Among conjugated systems, that is, the so-called tetrad, pentad, and polyad systems, there are also 1,4-type, 1,5-type, and 1,*n*-type interconversions. These are exemplified by 1,4 proton shifts in hydroxytriazenes, hydroxenamines, and hydroxamic acids for the 1,4-type, by 1,5 proton shifts in 3(5)-methylpyrazole and 4-hydroxypyridine for the 1,5-type, and finally by 1,3, 1,5, and 1,7 proton shifts in purine for the 1,*n*-type.

Prototropic tautomeric equilibria in polyfunctional bioactive molecules are often more complex than those in simple organic ones, because most of the biomolecules possess several conjugated acidic and basic centers and their tautomeric mixture may contain more than two tautomers. Several protons may be transferred between several atoms (X^i and Y^i), and prototropy may be a combination of the same types (e.g., amide−iminol tautomerism in uracil and amine−imine tautomerism in guanidine, purine, and adenine) or different types of rearrangements listed in Table 1 (e.g., amide−iminol and amine−imine interconversions, both of which are possible in cytosine and guanine).

If a tautomeric substance has only two conjugated functional groups, one acidic and the other basic, then just the two tautomeric forms arising from the tautomeric equilibrium (eq 1) are possible in its tautomeric mixture. However, if a tautomeric substance has more than two conjugated acidic and basic functional groups, then the tautomeric mixture contains more than two tautomers and its tautomeric equilibria are more complex. For instance, in trifunctional compounds (e.g., guanidines, 1,3-dicarbonyl compounds, 2-hydroxypyrimidines), tautomeric equilibria may be described by rearrangements 2, 3, or 4 and in tetrafunctional compounds (e.g., biamidines, cytosine, uracil, thymine) by rearrangements 5 or 6.



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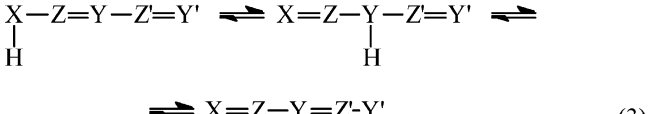

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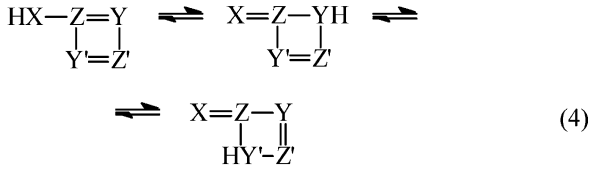
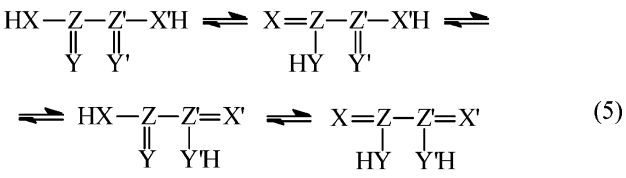
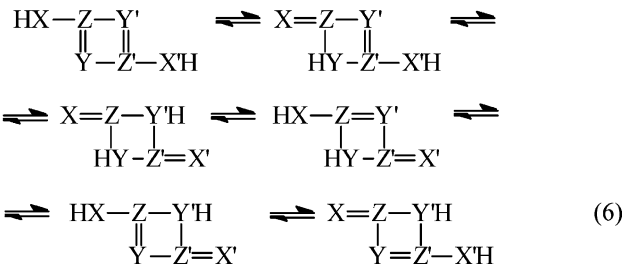


(4)



(5)

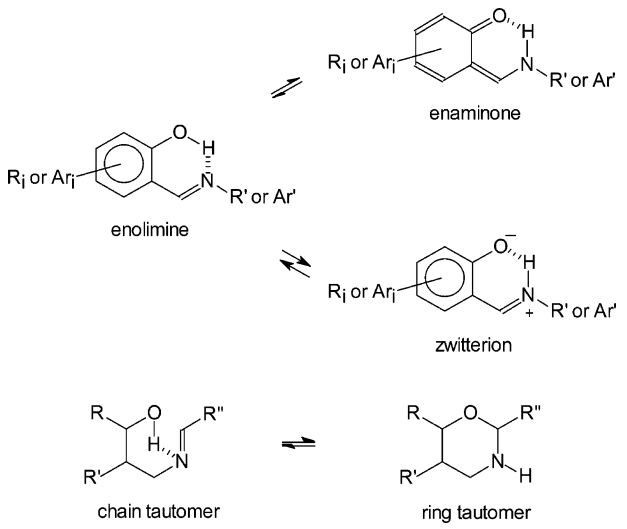


(6)

In equilibria 3 and 4, one proton may be transferred from X to Y or Y′, and in equilibria 5 and 6, two protons may be transferred from X or X′ to Y or Y′, while in equilibrium 2 either of two protons may be transferred from X or X′ to Y.

It is important to mention here that in the literature, the intra- or intermolecular proton transfer from one to another functional group in diamine monocations, amino acids, and dicarboxy monoanions (HX−Z−Y ⇄ X−Z−YH, charge not included) or in other polybases, polyamphoters, and polyacids, is frequently called tautomerism. However, this proton transfer is not accompanied by changes in π-electron distribution, and according to the IUPAC definition of tautomerism and the general tautomeric equilibria

Scheme 8. Tautomers and Zwitterions in Schiff Bases



1−6, it cannot be classified as a prototropy. It is a simple proton transfer similar to the protonation/deprotonation reaction, for which the arrows are the same as for other equilibria (⇆). Different arrows (⇌) are reserved solely to tautomerism. Only in some cases, for example, hydroxy-substituted Schiff bases, where proton transfer is accompanied by migration of π-electrons or by ring-chain rearrangement, may such interconversions be considered as a prototropic tautomerism (Scheme 8).[79]

3.3. Mechanisms of Prototropic Interconversions

The prototropic interconversions discussed above were observed for tautomeric substances in various states, vapor, pure liquid, and solid states, as well as in solution.[5,24,25] The conformational changes required for the tautomerization are not restricted to gaseous or fluid media. Although mobility of the molecular skeleton in the solid state is strictly limited, hydrogen bonds and other inter- and intramolecular interactions allow tautomerism in the solid state.[80] Different tautomers may be present at the same time in a crystal if there are specific interactions between them. For instance, two different tautomeric molecules can form dimers stabilized by intramolecular hydrogen bonds.

The presence of an acid or a base is not necessary to initiate the isomerization since each tautomeric substance possesses amphiprotic properties. During tautomerization, an acidic center may lose a proton and a basic center of the same or another tautomeric molecule may gain it. It is also possible that a basic center of one molecule may attract a proton from an acidic center of the same or another molecule. Only in some cases (for example, for keto−enol tautomerism), where the acidic or basic center or both in the tautomeric substance is too weak, must tautomerization be catalyzed by an acid or a base.[25]

The transfer of the proton may be intramolecular or intermolecular. The intramolecular proton transfer may occur for isolated molecules in the vapor phase at a very low pressure or for molecules at high dilutions in aprotic solvents.[81] An intermolecular proton transfer may take place for dimeric, trimeric, or polymeric aggregates in argon matrixes, in concentrated aprotic solution, or in a crystal lattice.[82] Such aggregates may be formed from identical tautomeric molecules or from different tautomeric molecules if stabilization of their structures is possible by intermolecular H-bonds.

Polar protic solvents (e.g., H_2O or ROH) may participate in the proton transfer by forming a cyclic or a linear complex with the tautomers.[83] Whether the complex formed is cyclic or linear depends on the conformation and configuration of the tautomers. In a strongly polar aprotic solvent and in the presence of an acid or a base, the tautomeric molecule may lose or gain a proton and form the corresponding mesomeric anion or cation, which, in turn, may gain or lose a proton, respectively, and yield a new tautomeric form.[84] Scheme 9 summarizes various types of mechanisms proposed for prototropic interconversions of isolated or associated bifunctional tautomeric substances dissolved in an aprotic or a protic solvent and in the presence of an acid or a base. In each case, the conjugation in the tautomeric moiety assists the proton transfer.

3.4. Physicochemical Measures of Tautomeric Preferences

Irrespective of the type of tautomeric system, a prototropic interconversion between two tautomeric forms is quantitatively described by a tautomeric equilibrium constant, K_T, which is frequently also used in the form $pK_T = -\log K_T$.[5d] For interconversion 1 or any other equilibrium in rearrangements 2−6, the constant K_T is defined as the concentration ratio or, equivalently, the percentage content ratio of the two tautomers, T_i and T_j, that are in tautomeric equilibrium. In eq 7, $[T_i]$ and $[T_j]$ denote the concen-

$$K_T = [T_i]/[T_j] = x/(100 - x) \quad (7)$$

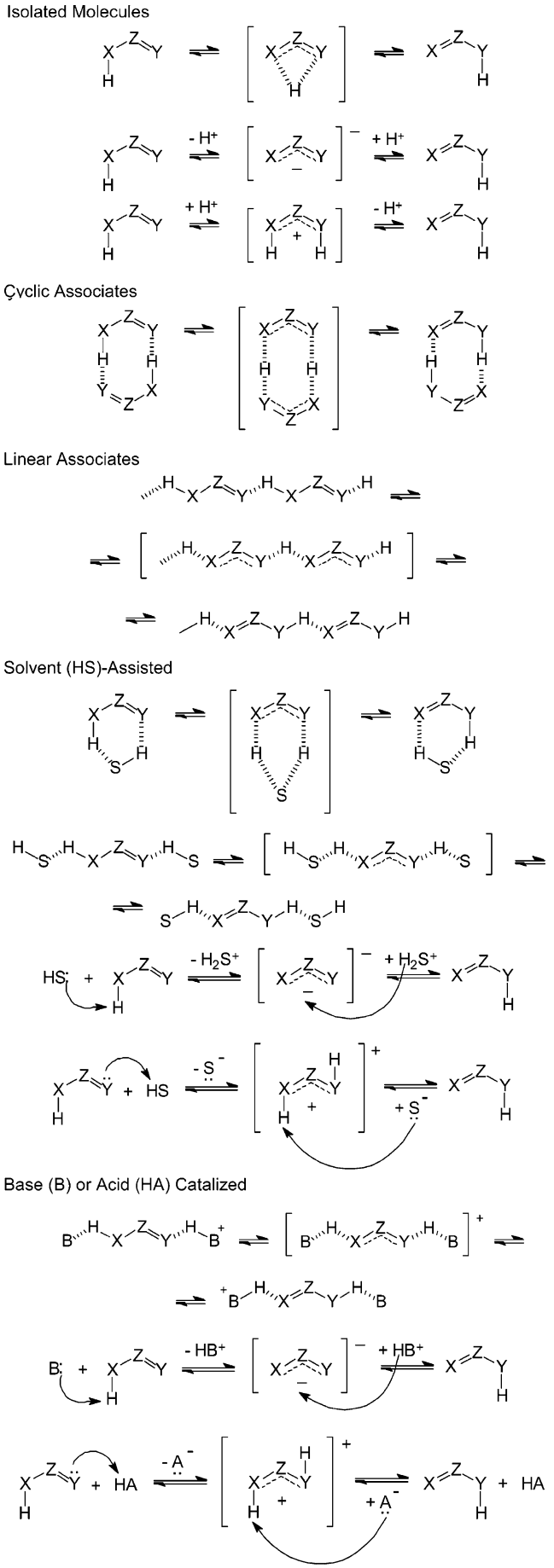
trations of T_i and T_j, and x is the percentage content of T_i. According to the Brönsted and Lowry theory of acids and bases,[85] the pK_T value depends on the acidity (or basicity) of the individual tautomers, which can be described by the acid dissociation constant, K_a (frequently used in the form $pK_a = -\log K_a$), in solution or, in the gas phase, by gas-phase basicity, GB, defined by GB = ΔG, the Gibbs free energy change for the deprotonation reaction of the neutral or ionic tautomer. The relationships between the pK_T, pK_a, and GB values are expressed in eqs 8 and 9. If the differences between the acidities or

$$pK_T = pK_a(T_i) - pK_a(T_j) \quad (8)$$

$$pK_T = [GB(T_i) - GB(T_j)]/(2.303RT) \quad (9)$$

basicities of individual tautomers are extremely large, the "tautomeric" mixture contains exclusively one form. This means that tautomerism in a strict sense does not take place in such cases. Tautomeric equilibria are possible only if the proton transfer is reversible so that two or more tautomers may exist independently.

Scheme 9. Various Types of Mechanisms of Prototropic Interconversions



Tautomeric interconversion can also be described by other thermodynamic parameters, such as the relative energies (ΔE_T), the relative enthalpies (ΔH_T), and the relative Gibbs free energies (ΔG_T) of individual tautomers. The relations between these and pK_T are given in eqs 10−12, where ΔpV is the work

$$\Delta H_T = \Delta E_T + \Delta pV \quad (10)$$

$$\Delta G_T = \Delta H_T - T\Delta S_T \quad (11)$$

$$\Delta G_T = -RT \ln K_T \quad (12)$$

term, and $T\Delta S_T$ is the entropy term. In many cases of prototropic interconversions, which often occur without particular internal or external interactions in individual tautomers, the pV and TS terms are identical for both forms. Thus their relative ΔpV and $T\Delta S_T$ values are near zero, and $\Delta E_T \cong \Delta H_T \cong \Delta G_T$.[86] In cases where those values are not near zero, the entropy term can be determined from the temperature dependence of the pK_T.

The tautomeric preferences and the pK_T, ΔE_T, ΔH_T, or ΔG_T values depend strongly on various internal and external effects that influence electron delocalization in individual tautomers, that is, electronic structure, electron density, acid−base properties, etc. Variation of any internal contributions such as type and position of proton donor and acceptor groups, neighboring and binding groups, size of chain or cycle, substituent effects, intramolecular H-bonds, or repulsion of lone electron pairs, can not only increase or decrease the value of pK_T, ΔE_T, ΔH_T, or ΔG_T but also even change the sign, which means that they can change the tautomeric preference from one (T_i) to the other (T_j) tautomer. The same situation holds for external influences, among which temperature, pressure, phase, light, solvent, acid, base, radical or metal cation, hydroxyl or carboxylate anion, protein or receptor pocket, and even an excess electron are the most important ones.[8,24,25,87] A small variation of environment may cause dramatic changes in tautomeric preferences and consequently in the physiological and biological properties of a tautomeric system. The DNA mutations cited above are such an example. Very many cases of internal and external effects have been extensively studied for different tautomeric systems, and some general relations have been formulated.[88] This subject, however, is very broad, and it is discussed in this review only for selected tautomeric systems.

3.5. Methods of ΔE_T, ΔH_T, ΔG_T, or pK_T Estimations

Most tautomeric systems contain at least one electronegative atom and often two, X and Y (e.g., oxygen and nitrogen), and the proton transfer is such a fast process that separation of the individual tautomers is very difficult and often even impossible. In such cases, tautomeric preferences, described by ΔE_T, ΔH_T, ΔG_T, or pK_T values, can sometimes be obtained directly from spectroscopic measurements (e.g., UV, IR, Raman, NMR, MW, MS, and coupled techniques).[5,24,25,88] This is possible for tautomeric

mixtures containing both tautomers in sufficient quantities that they can be spectroscopically detected. The pK_T, and consequently using eq 12, the ΔG_T can be obtained from the ratio of signal intensities in those cases in which the tautomers give separate nonoverlapping spectroscopic signals proportional to the quantity of tautomer present.

All experimental methods utilized in studies of tautomeric equilibria should be used carefully to avoid misinterpretation of the results obtained. For example, in using NMR analysis one should bear in mind that only one statistically determined signal for each nucleus appears in the NMR spectrum of a tautomeric mixture when the proton exchange between the individual forms is fast on the NMR time scale.[90] On the other hand, strong electron-donating substituents may slow the exchange enough to cause several tautomeric forms to coexist.[90b] Two fast proton exchanges are responsible for the identity reaction in the quinoline-2-yl diacetyl derivative,[91] but this effect is not observed in the dipyridine-2-yl derivative.[92] Single signals are also observed when the system consists practically of only one tautomer. At intermediate rates of proton exchange, broad signals can be seen in the NMR spectrum.[93] Moreover, the electric quadrupole moment of the nitrogen-14 nucleus can also broaden the signal of the N-bound proton even at low exchange rates.[93] Thus there are no simple relations between the number of signals in the spectrum, their line shapes, and the type of tautomeric process.

Alkyl derivatives of individual tautomers were found to be very helpful in studies of proton-transfer processes.[5d,24,90,94] Configurational and conformational similarities of such compounds to the respective tautomers are a precondition for using them as models.[90] Without these similarities, comparison of the spectral data for the tautomeric mixture with the data for the fixed (e.g., methylated) tautomers may lead to the wrong conclusions.[95]

Particular attention should also be paid to the solvent used to dissolve a tautomeric compound and to any substance added to obtain the required pH. In many cases, compounds displaying tautomerism possess very strong basic or acidic centers or both, and their tautomers can react or specifically interact with molecules of the solvent or with an additive containing, for example, a metal cation, a hydroxyl anion, or a carboxyl anion. Such reactions or intramolecular interactions can dramatically change the tautomeric process.[2c] This may be one reason for discrepancies in results obtained for tautomeric substances by different laboratories.[26]

Tautomeric preferences in the gas phase often differ from preferences observed in aqueous solution or in the solid state.[5d,24−26] This great variability of tautomeric preferences is usually due to very complex internal and external effects that influence the tautomerization process. Although these effects cannot be separated and individually studied, quantum-chemical calculations together with spectroscopic and other physicochemical experiments are powerful tools in understanding which effects strengthen T_i preference and which effects strengthen T_j preference.

Both semiempirical and ab initio methods can be used for estimation of ΔE_T, ΔH_T, ΔG_T, or pK_T, as well as for interpretation of the UV, IR, Raman, NMR, and MW spectra.[96] It has been shown that semiempirical PM3 and AM1 results are of comparable quality for intramolecular proton transfers, whereas the PM3 method has been recommended for intermolecular interactions, in particular when water molecules are involved.[97] DFT results have been found to be reliable for geometry optimization and interpretation of spectroscopic signals.[98] HF results for intramolecular proton transfer between atoms of the same element are comparable to those obtained both by DFT and MP2 methods.[26b,99] For proton transfer between different atoms, G2(MP2) results usually reproduce experimental results better than HF, MP2, or DFT.[100] The PCM (or SCI−PCM), SCRF, and Monte Carlo methods are often applied to solvated tautomeric systems.[101] However, the results of these methods should be interpreted carefully, particularly for the PCM and SCRF models, because they only partially take the specific solute−solvent interactions into account.

The basicity method[102] was widely used by Katritzky, Elguero, and their co-workers[5d] for estimation of the pK_T values of tautomeric heterocyclic compounds. It has also been tested for acyclic compounds containing the amidine moiety.[88e,89e,103] In this method, it was assumed that the methylation process does not change the relative basicities of individual tautomers and that the pK_T of the tautomeric compound can be obtained in the gas phase from the GB of the methylated derivatives, $Me-T_i$ and $Me-T_j$, or in solution from their pK_a. The use of other than alkylated derivatives may lead to incorrect conclusions and erroneous pK_T values.

In some cases, tautomeric preferences were estimated from the product ratios between different reactions done on the same tautomeric systems. However, the exceptional rapidity of tautomeric interconversions, particularly for the proton transfer between oxygen and nitrogen atoms, sometimes causes different conclusions to result from kinetic and thermodynamic experiments. Reactivities of individual tautomers often differ significantly, and thus, the ratio of the products obtained from the respective forms is usually not the same as the initial ratio of the tautomers.[5b]

Correlation analysis methods give broad possibilities for the pK_T predictions for series of both aromatic and aliphatic tautomeric systems.[88] Application of the Hammett[104] or Taft and Topsom equations[105] for series containing one variable substituent and two functional groups leads to eqs 13 and 14, respectively.[5d,88a−e,103] The Hammett equation can be used only

$$pK_T = pK_T^\circ - (\rho_1 - \rho_2)\sigma = pK_T^\circ - \rho_T\sigma \quad (13)$$

$$pK_T = pK_T^\circ - \rho_\alpha\sigma_\alpha - \rho_F\sigma_F - \rho_R\sigma_R \quad (14)$$

for aromatic compounds, whereas the Taft and Topsom equation can be applied to both aromatic and aliphatic derivatives. The reaction constants ρ_1 and ρ_2 in eq 13 denote the sensitivity of the functional groups to substitution. Their difference, ρ_T, corre-

sponds to the sensitivity of the tautomeric moiety to substitution. Usually, the ρ_1 and ρ_2 values found for the corresponding model series of nontautomeric derivatives were used in eq 13. In eq 14, the difference in the transmission of partial substituent effects to the functional groups in individual tautomers is determined by ρ_α for polarizability effects, ρ_F for field/inductive effects, and ρ_R for resonance effects. For series containing two variable substituents, eqs 15 and 16 can be applied. Some deviations from these

$$pK_T = pK_T^\circ - (\rho_1 - \rho_2)(\sigma_1 - \sigma_2) = pK_T^\circ - \rho_T\Delta\sigma \quad (15)$$

$$pK_T = pK_T^\circ - \rho_\alpha\Delta\sigma_\alpha - \rho_F\Delta\sigma_F - \rho_R\Delta\sigma_R \quad (16)$$

relations were observed for derivatives in which the substituent interacts intramolecularly with the functional groups. Intramolecular H-bonding (often called "internal solvation") influences the pK_T value and thus may change completely the composition of the tautomeric mixture.[88f,106]

3.6. Quantitative Measures of Electron Delocalization

The phenomenon of π-electron delocalization is frequently used in chemistry to explain the particular stability of chemical compounds as well as their physicochemical and biological properties.[1,2,9,11b] Classical examples are carboxylic acids, for which various controversial explanations (including those based on resonance stabilization of the carboxylate anions) were proposed to explain why they are stronger acids than alcohols.[107] Additional typical examples are stilbene-like species, *meta*- and *para*-substituted aromatic compounds, and other differently substituted conjugated systems, for all of which various methods of separating the π and σ systems and of separating the polarizability, field/inductive, and resonance effects were introduced and applied to understanding the nature of π-electron delocalization.[104,105,108,109] A very interesting case is the azine bridge, which was recently found to be a conjugation stopper.[110]

π-Electron delocalization also participates in many chemical and physicochemical processes.[1] A few of them are worth mentioning: charge-transfer complexes and, associated with them, UV−vis spectra;[111] intramolecular charge-transfer associated with electron excitation as observed in UV−vis spectra;[112] intramolecular charge-transfer associated with resonance substituent effects.[113] The most typical of these is the concept of π-electron delocalization associated with the notion of aromaticity, which was reviewed recently.[15] The present review takes this aspect of π-electron delocalization into account particularly in the intramolecular chemical processes generally called tautomeric interconversions. To treat this more quantitatively and to make this review more comprehensive, some numerical measures of π-electron delocalization are briefly recalled here. In general, they may be classified as local and global measures of π-electron delocalization and are often also called indices of aromaticity. On the other hand, particular experimental approaches to the problem of aromaticity and measurements of various geometric, magnetic, and energetic properties led to the formulation of quantitative measures of aromaticity based separately on geometric, magnetic, and energetic factors.[15d,e,h−k,16−22]

The geometric measures of aromaticity take the planarity of the conjugated system, the equalization of bond lengths and angles, and the molecular symmetry into account.[15d,16,17] The magnetic measures of aromatictity are based on the idea of a ring current and particular magnetic properties.[18] The energetic measures of aromaticity were derived from measurements of heats of combustion and hydrogenation or dehydrogenation, from measurements of proton-transfer equilibria, and from theoretical approximation of the energetic stability of aromatic systems.[12a,14,15e,k,19−21] In acyclic systems, restricted rotation around single and double bonds and the energy barrier for that rotation are also rough measures of electron delocalization. All of these measures, though derived on the basis of experimental observations, can be theoretically estimated with the help of quantum-chemical methods. Although some common relationships were found between various measures of aromaticity, the question of whether aromaticity can be described with a single parameter or whether it has a multidimensional character is still being discussed.[15d,e,i,k,114] It has been concluded from a statistical analysis of the different measures that two or three orthogonal, that is, unrelated, factors are necessary to describe all aspects of aromaticity.[15d,e,23,115]

Among the various measures of aromaticity, the most extensively used are, because of their efficiency as an accurate description of stabilization energies by π-electron delocalization, the geometric indices of Bird, named simply "I",[16] and Krygowski, called HOMA for "harmonic oscillator model of aromaticity",[17] and the magnetic index of Schleyer, called NICS for "nuclear-independent chemical shift".[18] The Bird index was based on an idea of Julg and François,[116] in which the variation of bond lengths was replaced by the variation of Gordy bond orders.[117] The index I can be calculated from eq 17, in which V

$$I = 100(1 - V/V_k) \quad (17)$$

$$V = 100/N_m\sqrt{[\sum(N_i - N_m)^2/n]}, \quad N_i = a/(R^2 - b)$$

is the coefficient of variation for the bond orders of the heterocycle of interest, N_i are the individual bond orders, and N_m is the arithmetic mean bond order. R is the observed bond length, and n is the number of bonds. The values of the constants a and b depend on the kinds of atoms that form the bond considered. The normalizing constant V_k is 33.3 for a six-membered heterocycle and 35 for a five-membered heterocycle. For a heterocycle with complete electron delocalization, this will give $V = 0$. For a nondelocalized conjugated structure such as a Kelulé form, the value of V will depend on the type of ring system.

The HOMA index, which was initially named HOMAS for "harmonic oscillator model of aromatic

stability",[17a,118] was based on the concept of optimal bond length.[17] It was defined by eq 18, where R_i and

$$\mathrm{HOMA} = 1 - (\alpha/n)\sum(R_{\mathrm{opt}} - R_i)^2 \qquad (18)$$

R_{opt} are the individual and optimal bond lengths, n is the number of bonds in the sum, and α is an empirical normalization constant. For a system with all bonds equal to R_{opt}, that is, with full delocalization of the π-electrons, HOMA = 1. For nonaromatic systems, originally taken as the Kekulé structure of benzene for carbocyclic systems and similarly for hetero π-electron systems, α is adjusted to give HOMA = 0.

The NICS(d) index was defined as the negative value of the absolute magnetic shielding computed at a distance d (in Å) above the center of the ring. Negative NICS values correspond to aromatic systems and positive NICS values to antiaromatic systems.[18] Recently, it has been shown that the NICS(1) index calculated 1 Å above the ring center describes the π-electron delocalization better than the NICS(0) calculated at the center of the ring.[18c]

Definitions of energetic indices depend on theoretical concepts of aromaticity.[15,119] For instance, the delocalization energy (DE) in molecular orbital theory was defined on the basis of Hückel rules,[14] and the resonance energy (RE) was defined in valence bond theory.[12a] Neither DE nor RE differentiate aromatic from nonaromatic systems, nor do they differentiate between benzene and larger benzenoid hydrocarbons. The distinction between aromatic, nonaromatic, and antiaromatic systems was taken into account in a new definition of the Dewar resonance energy (DRE), which was included in molecular orbital theory.[20] The distinction between the RE of benzene and the RE of large benzenoid hydrocarbons was considered by Hess and Schaad,[21] who proposed the term REPE for "resonance energy per electron", defined by REPE = RE/n, where n is the number of electrons. The concept of isodesmic[120] and homodesmic reactions[121] led to various definitions of stabilization energies (SE), including those of aromatic systems, called the aromatic stabilization energy (ASE).[15a,114c,118]

The model called HOSE for "harmonic oscillator stabilization energy" is less popular, though it has the advantages that it can be applied to cyclic systems, to acyclic systems, to entire π-electron molecules, or to their conjugated fragments and it also permits estimation of resonance structure weights.[22] This model was defined as the negative of the energy necessary to deform the geometry of the real molecule with delocalized π-electrons into the geometry of the Lewis structures with localized single and double bonds. The energy of deformation was based on a simple harmonic oscillator potential.

The experimentally or computationally estimated ΔE_{T}, ΔH_{T}, ΔG_{T}, and $\mathrm{p}K_{\mathrm{T}}$ for tautomeric systems are related to energy-based parameters. They give information not only about tautomeric preferences in the tautomeric mixture but also about the differences in the stabilities of individual tautomers. They are thus related to differences in electron delocalization in tautomeric forms and are similar to differences of the aromaticity indices (ΔI, ΔHOMA, ΔNICS, ΔDE, ΔRE, ΔDRE, etc.) between the tautomeric forms in equilibrium.

4. Open Chain Molecules

Prototropic tautomeric equilibria in simple open chain conjugated systems such as formamide, formamidine, formic acid, or guanidine are frequently used as model reactions to understand intramolecular proton transfer processes occurring in tautomeric biomolecules. It is obvious that such an approximation only partially explains various factors that affect intramolecular interactions. These interactions are usually more complex in polyfunctional biomolecules than in simple model derivatives. However, knowledge of simple relations in simple compounds enables us to formulate more complex relations and to solve more complex structural problems in large biomolecules. This is why we begin our discussion of tautomeric equilibria in relation to π-electron delocalization with the simplest open chain tautomeric systems.

4.1. Simple Triad Systems

Simple triad tautomeric systems of general formula HX—Z=Y ⇌ X=Z—YH contain two conjugated sites, X and Y, between which one proton is transferred by a 1,3 proton shift along with a simultaneous migration of π-electrons. Generally, the acid−base properties of X and Y, that is, their relative ability to lose or gain a proton, are the main factors that dictate tautomeric preferences. To explain which of the two tautomers HX—Z=Y and X=Z—YH is favored in the tautomeric mixture, one can consider the anionic structure of the triad system described by $^{-}$X—Z=Y ↔ X=Z—Y^{-}, which is stabilized by resonance, and compare the basicities of the X^{-} and Y^{-} sites. The more basic site takes the proton and the corresponding form predominates in the tautomeric mixture. Certainly, the basicity of the sites depends on the electronegativities of X^{-} and Y^{-}, but other factors such as electron delocalization (e.g., hyperconjugation or n−π conjugation), electronic effects of the groups linked to the X, Y, or Z atom (e.g., polarizability, field/inductive or resonance effects) and environment (e.g., the nature of the solvent and the presence of ions, electrons, or other molecules) may also influence the basicity difference between the X^{-} and Y^{-} sites. Only for isolated molecules in the gas phase are the effects of environment negligible, leaving "pure" intramolecular interactions to play the principal role. This is the main reason why electron delocalization and substituent effects in tautomeric equilibria were so extensively studied by quantum chemical methods in simple molecules during the past decade. Looking over the results for the simplest open chain tautomeric systems, one can obtain a general picture of the actual knowledge about the relation of tautomeric equilibria to π-electron delocalization. Also, calculations are easier than experiments.

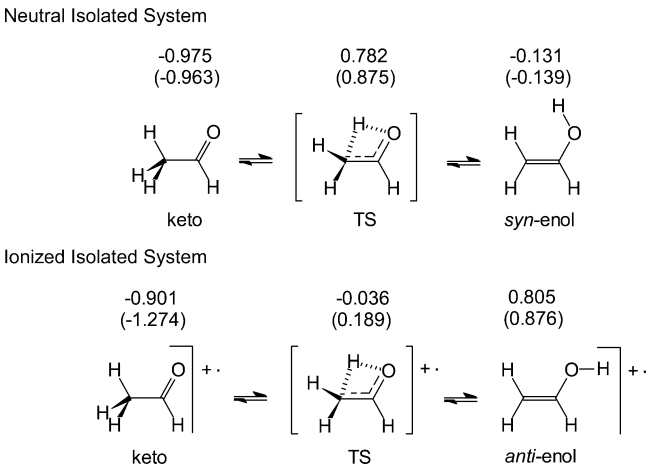
Acetaldehyde is the simplest triad carbonyl compound that displays keto−enol tautomerism (H_3C—

CH=O ⇌ H_2C=CH−OH).[1,25a,b,122−124] Its enol tautomer (vinyl alcohol) is a transient intermediate in various organic reactions. It is formed during the very-low-pressure pyrolysis of cyclobutanol and has a half-life of 30 min before tautomerizing to its isomer, acetaldehyde.[125] The keto → enol isomerization in the gas phase is endothermic by about 10 kcal mol^{-1} for the isolated neutral system, whereas the same process for the ionized system is exothermic by 15−20 kcal mol^{-1}.[124] This reverse energetic situation indicates that the tautomeric preferences are not the same and that they change during ionization from the neutral keto form (acetaldehyde) to the enol (vinyl alcohol) radical cation. That a large energy barrier for the keto → enol isomerization is observed in both cases (68 and 40 kcal mol^{-1}, respectively)[124] also explains why the keto−enol tautomeric interconversion is so slow that other reactions, for example, dissociation, can be observed for the acetaldehyde radical cation instead of its isomerization to the thermodynamically more stable enol radical cation.[123] Only the assistance of protic solvent molecules such as water or alcohol or of an appropriate base can drastically decrease, even by more than 20 kcal mol^{-1}, the energy barrier and thereby facilitate isomerization.[122,124] However, interactions with water molecules have a small effect on relative stabilities. The tautomeric equilibrium constant in aqueous solution is equal to 6.23.[68] This gives 8.5 kcal mol^{-1} for the energy of isomerization. For the methanol-solvated system, the transition state of the tautomerization process lies below even the $MeCHO^{+\bullet}$ + MeOH ground-state asymptote,[123] which is why enolization of the ionized acetaldehyde has been observed during ion cyclotron resonance (ICR) experiments.[126] Similar results were reported for acetone radical cation although different mechanisms of proton transfer were indicated.[127]

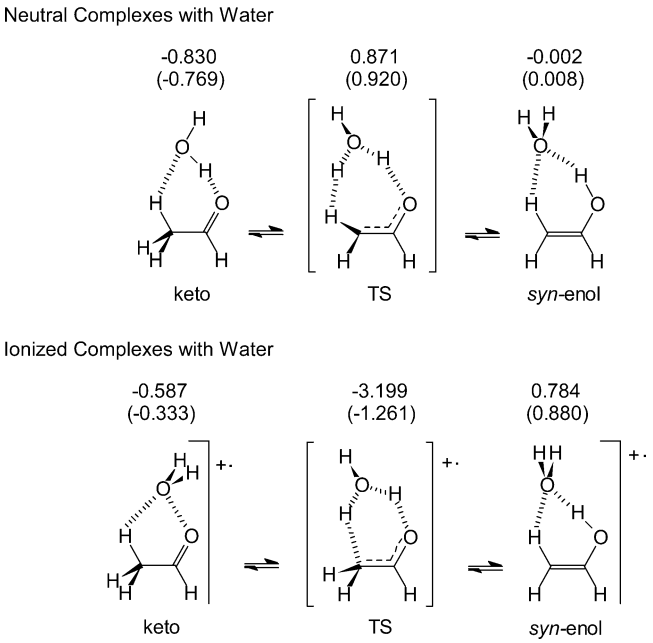
Interesting studies were recently reported by Schleyer and co-workers[128] for formaldehyde and its analogues (R_2XO, X = C, Si, Ge, Sn, Pb) indicating that their stabilities depend strongly on the X atom. The H_2X=O form is preferred only for X = C (formaldehyde). Silicon and all the metals favor the divalent form HX^{-}=$O^{+}H$, which has cis and trans isomers of nearly equal energy. Among the analogues of acetone, dimethylstananone (X = Sn) and dimethylplumbanone (X = Pb) are not likely to exist. Two analogue series of acetaldehyde and acetone {H_3CC(=X)R, R = H or Me and X = O, S, Se, or Te} were studied by Sklenák, Apeloig, and Rappoport.[129] They showed that the relative energies decrease in the order O > S > Se > Te. Exceptionally, the telluroenol form seems to be more stable by a few kilocalories per mole than the tellurocarbonyl form. This trend is parallel to that observed for the calculated C=X π-bond energies, which also decrease on going down the Periodic Table.

For the gaseous neutral acetaldehyde/vinyl alcohol system, the most stable enol isomer possesses a syn conformation of the OH group with respect to the C=C group. This was confirmed experimentally by IR spectra in low-temperature matrixes[130] and by ab initio calculations.[122c,131,132] The same conformation

Scheme 10. HOMA Indices {MP2/cc-aug-pVDZ and DFT(B3LYP)/cc-aug-pVDZ in Parentheses} for Isolated Neutral and Ionized Tautomers of Acetaldehyde and Its Transition State[133]



Scheme 11. HOMA Indices {MP2/cc-aug-pVDZ and DFT(B3LYP)/cc-aug-pVDZ in Parentheses} for Neutral and Ionized Complexes of Acetaldehyde Tautomers with One Water Molecule and Its Transition State[133]



was found by calculations on the most stable enol isomer associated with one water molecule for both neutral and ionized systems.[131] Only the radical cation of vinyl alcohol prefers the anti conformation.[131] An analysis of geometric parameters such as experimental and computed bond lengths[122c,131] indicated that n−π-electron distribution varies when proceeding not only from the keto to the enol tautomer but also from the neutral to the ionized and from the isolated to the solvated system. These variations are well described by the HOMA indices estimated for the geometries optimized at the MP2/cc-aug-pVDZ and DFT(B3LYP)/cc-aug-pVDZ levels (Schemes 10 and 11).[131,133] The negative values of HOMA result most often from the fact that in such cases double bonds are substantially shorter and single bonds are substantially longer than those that

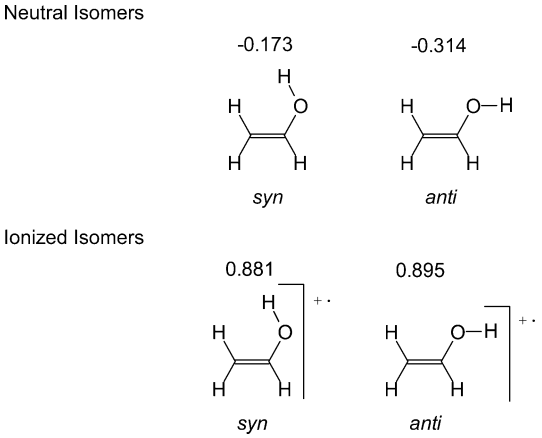
were used for the reference bonds in the procedure for R_{opt} estimation.[17]

Comparison of the HOMA indices for the neutral individual tautomers calculated using MP2 and DFT with those estimated on the basis of the experimental CC and CO bond lengths[122c] in acetaldehyde (−0.834) and vinyl alcohol (−0.213) makes it clear that the n- and π-electrons are strongly localized in individual forms, giving negative HOMA values. This suggests that other factors may determine the stability of both tautomers. Only the cyclic transition state displays any particular electron delocalization with a HOMA of 0.8−0.9, which confirms that there is some kind of relation between tautomeric equilibria and electron delocalization in open chain tautomeric systems. One water molecule slightly decreases the negative values of HOMA for individual tautomers and slightly increases the electron delocalization in the transition state, giving a HOMA close to 0.9.

For the ionized gaseous acetaldehyde/vinyl alcohol system, the relationship is reversed. This phenomenon was called a "stability inversion" by Haselbach and co-workers.[134] Bertran and co-workers[131] noted that removing an electron from the n orbital of the carbonyl oxygen in the keto tautomer has no important influence on the localization of the π-electrons, whereas removing an electron from the π orbital of the enol tautomer causes strong electron delocalization. This behavior is well described by the HOMA index estimated for the MP2 and DFT geometries optimized using the cc-aug-pVDZ basis set.[131] The HOMA index is negative for the less stable acetaldehyde radical cation and is highly positive (0.8−0.9) for the more stable vinyl alcohol radical cation.[133] The positive HOMA value for the enol form may partially explain why it is favored by an ionized system. On the other hand, the negative HOMA index for the ionized transition state indicates that delocalization of the n- and π-electrons, which is possible in the neutral transition state, does not take place in the ionized transition state. Quite a different situation was observed by Sklenák, Apeloig, and Rappoport for thiocarbonyl/thioenol systems.[129] For the radical cations, the thiocarbonyl forms are more stable than the thioenol forms, just as for the neutral system.

The rotation of the OH group from the syn to the anti conformation with respect to the C=C group in vinyl alcohol and its methyl derivatives, studied theoretically by Tureček and Cramer[132] (Scheme 12), has no important effect on the HOMA indices estimated for the MP2(full)6-31+G** optimized geometries.[132] The HOMA indices increase slightly in negative values for the neutral forms when going from the syn to the anti conformation by 0.1−0.2 units.[133] It is interesting to mention that the same trends were also observed for other tautomers such as the iminol form of formamide and formaldehyde oxime.[133] For the radical cations of vinyl alcohol, variations in the positive values of HOMA are considerably lower and do not exceed 0.05 units. The electron-donating effect of the methyl group slightly decreases the HOMA indices.[133] This effect is stronger for the C-carbonyl than for the $^{\alpha}$C-substituted derivatives. For instance, the HOMA index of *syn*-CH_2=C(Me)−$OH^{+\bullet}$ decreases by about 0.1 units whereas that of *syn*-*E*-MeCH=CH−$OH^{+\bullet}$ decreases only by about 0.01 units in comparison when compared to that of vinyl alcohol, indicating a stronger cross than push−pull hyperconjugation effect of the methyl group on electron delocalization in vinyl alcohol derivatives. (The symbol *E* in the $^{\alpha}$C-substituted derivative denotes the trans configuration of the methyl group with respect to the OH group).

Scheme 12. HOMA Indices {MP2(full)/6-31+G} for Syn and Anti Conformations of Neutral and Ionized Vinyl Alcohol[133]**



Longer series of substituted acetaldehyde/vinyl alcohol systems were investigated by Bouma and Radom,[135] Lien,[136] Rappoport,[137] Khalil, and their coworkers.[138] The replacement in acetaldehyde of a hydrogen atom by an electron-donating substituent (e.g., NH_2, OH, F, Cl, or Me) or an electron-accepting substituent (e.g., CN, NC, NO, or BH_2) at the C-carbonyl to give a series H_3C−C(R)=O ⇌ H_2C=C(R)−OH or the $^{\alpha}$C atom to give a series RH_2C−CH=O ⇌ RHC=CH−OH leads to interesting studies of partial substituent effects, particularly as regards the resonance effect that influences n−π-electron distribution in the tautomeric system. In the C-carbonyl substituted derivatives, R is directly bonded to the central atom of the tautomeric moiety, and thus an electron-donating substituent can directly interact with the strong electron-accepting C=O group in the keto tautomer via the resonance R−$C(CH_3)$=O ↔ $^{+}$R=$C(CH_3)$−O^{-} as well as with the less electron-accepting ene group in the enol tautomer via the resonance R−C(OH)=CH_2 ↔ $^{+}$R=C(OH)−CH_2^{-}. In the $^{\alpha}$C-substituted derivatives, R cannot directly interact through resonance with the C=O group in the keto form due to its separation by the CH_2 group. The so-called push−pull resonance interaction is only possible in the enol form for an electron-accepting substituent R as in, for example, the resonance R−CH=CH−OH ↔ $^{-}$R=CH−CH=OH^{+}. Similar substituent effects take place in $^{\alpha}$C-substituted ketene−ynol tautomeric systems (RHC=C=O ⇌ RC≡CH−OH)[139] and in imine−enamine tautomeric systems (RH_2C−CH=NH ⇌ RHC=CH−NH_2).[140]

The differences in resonance effects in both series of substituted acetaldehyde/vinyl alcohol systems were verified quantitatively by application of the Taft and Topsom equation[105] to the HOMA indices[133] as well as to the total energy change for the keto → enol

Table 2. Rho Constants (ρ_α, ρ_F, and ρ_R), Intercept, Correlation Coefficients (r) and Standard Deviations (s) of Correlations between Geometry-Based (HOMA) and Energy-Based Parameters (ΔE_T and $\Delta E^\ddagger$) and Substituent Constants for the Acetaldehyde/Vinyl Alcohol Series (R = NH_2, OH, F, Me, H, and CN)[133]

property	ρ_α	ρ_F	ρ_R	intercept	r	s
		$H_3C-C(R)=O \rightleftharpoons H_2C=C(R)-OH$				
HOMA(keto)	0.44 ± 0.23	0.53 ± 0.20	0.52 ± 0.24	−0.856 ± 0.091	0.929	0.11
HOMA(enol)	0.49 ± 0.19	0.48 ± 0.16	0.68 ± 0.19	−0.109 ± 0.075	0.958	0.09
HOMA(TS)	0.28 ± 0.08	0.17 ± 0.71	0.39 ± 0.04	0.918 ± 0.033	0.966	0.04
ΔE_T	16.0 ± 7.2	8.8 ± 6.2	−31.2 ± 7.5	19.2 ± 2.9	0.972	3.35
$\Delta E^\ddagger$	17.0 ± 7.0	12.2 ± 6.0	2.2 ± 7.3	75.0 ± 2.8	0.906	3.26
		$RH_2C-CH=O \rightleftharpoons RHC=CH-OH$				
HOMA(keto)	0.63 ± 0.32	−1.00 ± 0.21	0.45 ± 0.40	−0.754 ± 0.101	0.970	0.11
HOMA(enol)	−0.34 ± 0.31	0.34 ± 0.21	0.28 ± 0.39	−0.235 ± 0.098	0.905	0.11
HOMA(TS)	0.06 ± 0.03	−0.10 ± 0.02	0.07 ± 0.03	0.899 ± 0.008	0.978	0.01
ΔE_T	10.4 ± 1.9	−5.3 ± 1.3	0.4 ± 2.4	17.6 ± 0.6	0.989	0.67
$\Delta E^\ddagger$	12.8 ± 5.1	−6.0 ± 3.4	3.1 ± 6.4	73.9 ± 1.6	0.938	1.82

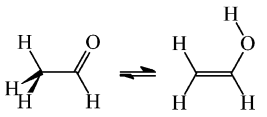
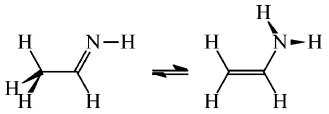
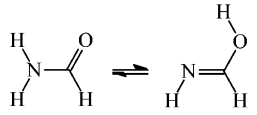
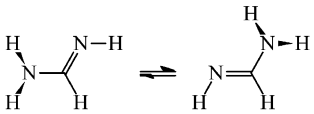
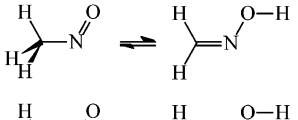
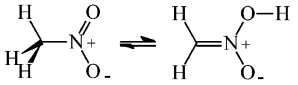
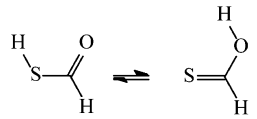
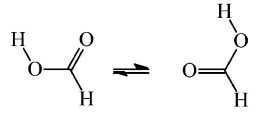
interconversion (ΔE_T) and to the height of the keto → TS barrier ($\Delta E^\ddagger$),[136] all estimated at the MP2(full)/6-31G* level. Indeed, the geometric and the energetic parameters correlate quite well with the polarizability, field/inductive, and resonance substituent constants[141] (Table 2). Although in a few cases errors in the ρ estimation are greater than the estimated ρ values, some general conclusions can be drawn. For the HOMA indices, the resonance effect seems to be more important in the C-carbonyl ($\rho_R/\rho_F \geq 1$) than in the $^\alpha$C-series ($\rho_R/\rho_F < 0.8$).[133] The difference in the contribution of partial substituent effects on the HOMA indices in the transition states is also interesting. In the C-carbonyl series, these differences are larger than in the $^\alpha$C-series by about 5 times for the polarizability effects, 2 times for the field/inductive effects, and 6 times for the resonance effects, indicating the importance of the polarizability and resonance effects in the former series and of the field/inductive effect in the latter one. A similar general behavior is found for ΔE_T. The resonance effect is very important in the former series ($\rho_R/\rho_F = 3.5$), whereas in the latter one it can be neglected ($\rho_R/\rho_F = 0.1$). A different situation exists for $\Delta E^\ddagger$, which mainly depends on the polarizability and field/inductive effects ($\rho_R/\rho_F < 0.5$).

The substituent effects that influence the geometric and the energetic parameters in the $^\alpha$C-substituted keto−enol tautomeric series ($RH_2C-CH=O \rightleftharpoons RHC=CH-OH$) are almost collinear with those observed for the imine−enamine tautomeric series ($RH_2C-CH=NH \rightleftharpoons RHC=CH-NH_2$).[133] However, in the latter series, the tautomeric preferences as given by ΔE_T depend strongly on substitution.[140] The imine form seems to be favored in the tautomeric mixture for derivatives containing an electron-donating substituent, while the enamine form seems to be favored for derivatives with an electron-accepting substituent. The lack of experimental data and the strong dependence of calculated results on the level of theory used for the imine−enamine interconversion as well as for the $E-Z$ isomerization around the C=N double bond of the imine tautomer do not allow more general conclusions to be drawn for the imine−enamine tautomeric series.

Toro-Labbé and Pérez[142] recently analyzed two series, $H_3C-CR=O \rightleftharpoons H_2C=CR-OH$ and $H_3C-CR=NH \rightleftharpoons H_2C=CR-NH_2$, of the keto−enol and imine−enamine tautomeric systems substituted at the $^\alpha$C atom in terms of global descriptors of reactivity such as the electronic chemical potential and the chemical hardness and softness. Chemical hardness and chemical softness, which are related to the molecular polarizability, were used to study the relative stabilities in the context of the hard and soft acids and bases (HSAB) principles, that is, of the maximum hardness principle (MHP) and of the minimum polarizability principle (MPP), respectively. From this analysis, it was concluded that the transferred proton, a hard species, interacts favorably with the hard $^\alpha$C atom to give the most stable tautomer corresponding to the keto form. The hardness profiles show a minimum value close to the position of the transition state, where the energy exhibits a maximum. The energy and hardness profiles are opposite to each other, as is consistent with the MHP and the MPP. Accurate activation energy barriers for the intramolecular proton transfer were discussed in terms of the Marcus equation.

For the simplest imine−enamine system, namely acetaldimine interconverting with vinylamine by a 1,3 proton shift according to $H_3C-CH=NH \rightleftharpoons H_2C=CH-NH_2$, in which both forms having been detected in interstellar clouds and in circumstellar shells,[143] the calculated relative energy between the two tautomeric forms was estimated to be about 0 ± 10 kcal mol^{-1}.[25j,144,145] Only recent studies by Lammertsma and Prasad[146] have clarified all discrepancies in the theoretical results and showed that to obtain reliable theoretical results, electron correlation must be included for geometry optimization, and large basis sets as well as extensive correlation must be used for energy estimation. In this way, the *E*-isomer of acetaldimine was found to be energetically more stable in the gas phase than the *Z*-isomer with an energy difference of 0.9 kcal mol^{-1} calculated at the MP4/6-311++G**//MP2/6-31G* (+ ZPVE) level. This value is in good agreement with microwave and infrared experiments.[147] The SCRF solvent effect for acetonitrile decreases this energy difference only slightly to 0.5 kcal mol^{-1} but does not change the conformational preferences. The *E*-isomer of acetaldimine was also found to be more stable than vinylamine with energy differences of 3.9 and 3.8 kcal mol^{-1} at the G2 and G1 levels, respectively. This energy difference increases only slightly to 4.3 kcal mol^{-1} in the acetonitrile solution as estimated by the SCRF method, and the increase causes no change in

Table 3. Comparison of HOMA Indices and Relative Total Energies {$\Delta E_T = E$(X=Z−YH) − E(HX−Z=Y) in kcal mol^{-1}} for Triad Systems HX−Z=Y ⇌ X=Z−YH[133]

Tautomeric system	HOMA HX−Z=Y	HOMA X=Z−YH	ΔE_T
	-0.791	-0.167	10.8
	-0.569	0.499	3.9
	0.834	0.255	11.5
	0.793	0.793	0.0
	0.012	0.123	-12.0
	-0.068	0.083	14.1
	0.355	0.328	4.8
	0.178	0.178	0.0

the tautomeric preference of the acetaldimine/vinylamine system when going from the gas phase to solution. In the absence of experimental data for tautomeric interconversion, the G2 estimates can be accepted.

The smaller energy of tautomerization for acetaldimine (4 kcal mol^{-1}) than for acetaldehyde (11 kcal mol^{-1} at the same level of theory) also indicates greater stability for vinylamine than for vinyl alcohol. Indeed, the stronger resonance electron-donating effect of the NH_2 group compared to the OH group gives a stronger resonance interaction, that is, n−π heteroallylic conjugation, in vinylamine between the NH_2 and CH=CH_2 groups than the resonance interaction in vinyl alcohol between the OH and CH=CH_2 groups, which leads to increased electron delocalization and a positive HOMA value (0.499) for vinylamine[133] as estimated for geometries optimized at the MP2/6-31G* level[146] (Table 3). In turn, for the anionic form,[146] the n- and π-electrons are completely delocalized with a HOMA of 0.998 at the same level of theory. It is interesting to mention that the energy barrier for the acetaldimine → vinylamine rearrangement in the gas phase is almost as high as that for the acetaldehyde → vinyl alcohol process (i.e., about 71 kcal mol^{-1} at the MP2/6-31G** level),[136,140] indicating that both interconversions need the assistance of a catalyst.

The relationships in neutral and ionized gaseous acetaldimine/vinylamine systems resemble those in acetaldehyde/vinyl alcohol pairs. Neutral imine is more stable than enamine, whereas the relationship is reversed for the radical cations.[148] The only difference is in the relative energies. For example, at the G2(MP2) level, neutral imine is only marginally, 4 kcal mol^{-1}, more stable than enamine, while the enamine radical cation is considerably, 29 kcal mol^{-1}, more stable than the imine radical cation. The HOMA index, which measures electron delocalization, is more positive (0.898) for ionized than for neutral enamine (0.499) and more negative for ionized (−0.756) than for neutral imine (−0.569). This relationship in electron delocalization may partially explain the difference in the relative energies of the neutral and ionized systems. All values of HOMA mentioned in this paragraph were estimated for geometries optimized at the MP2/6-31G* level.[148]

A particularly strong electron delocalization occurs in the amide−iminol tautomeric system such as formamide/formamidic acid mixture H_2N−CH=O ⇌ HN=CH−OH.[25d,149] This system is often used as a model for understanding the properties of materials containing peptide bonds, such as proton transfer in proteins and hydrolysis of the peptide bond in biological systems, as well as for understanding proton transfer in the nucleic base pairs.[150] Although formamide can exist in the amide and iminol forms, experimental results indicated that irrespective of the environment the amide tautomer is thermodynamically more stable.[151,152] The amide form is also more stable than the iminol form for the thio and seleno analogues of formamide.[153] For formamidic acid, the iminol form of formamide, the syn conformation of the OH group with respect to the C=N group is more stable than the anti conformation. Various types of associated structures such as chain, cyclic dimers, and mixed ring and chain structures, were proposed in the literature.[152]

The HOMA indices estimated for the two tautomeric forms of formamide from geometries optimized at the MP2/6-31G** level[154] are exceptionally positive at 0.834 and 0.255 (Table 3).[133] For the amide form, the HOMA index is even not very different from unity. This may partially explain the high resonance stability of H_2N−CH=O and its predominance in the tautomeric mixture. The HOMA indices for individual forms associated with one water molecule are also highly positive, being 0.894 and 0.561 at the same level of theory. Cyclic dimerization, which helps the tautomeric interconversion, also increases the HOMA indices of formamide and its iminol form to 0.939 and 0.795, respectively. Although the positive values of the HOMA index are exceptionally large, the energy of tautomerization is close to that found for the acetaldehyde/vinyl alcohol system. When a water molecule mediates the proton transfer, only the barrier for isomerization is greatly reduced (by more than 20 kcal mol^{-1}).[153d,154,155] A single water molecule assists the tautomerization of formamide directly by

acting as a bridge for proton transfer from the donor (−NH) to the acceptor site (=O). The energy barrier is also greatly reduced for self-assisted processes, such as in cyclic dimers, and for acid−base-assisted processes involving, for example, HF, NH_3, and proton exchanging zeolites.[156] The role of the catalyst in the tautomeric interconversion formamide → formamidic acid depends on the relative acid−base properties of the neutral catalyst and formamide. It was suggested[156b] that for H_2O the acidic catalysis is slightly more favorable, whereas for NH_3 and HF the preferred mode of catalysis is basic and acidic, respectively. These interactions with H_2O, NH_3, or HF molecules have, however, a small effect on the energy of tautomerization. Similar behaviors were observed for thio and seleno analogues of formamide.[153d] Detailed analyses of the solvent effects in the formamide/formamidic acid system on solvation free energies, solvation structures, and solute electronic structures from a microscopic point of view revealed that the ability of the solvent to form hydrogen bonds is very important, and that the amide form is more strongly stabilized than the iminol form.[157]

The 1,3 proton shift in acyclic amidines (RHN−CR′=NR″ ⇌ RN=CR′−NHR″) is another exceptional case of prototropic tautomerism and n−π-electron delocalization in triad systems. The proton is transferred between atoms of the same element, from the amino to the imino nitrogen atom, and the migration of π-electrons does not change the character of the n−π conjugation. Only changes in substitution of the amidine moiety can influence electron delocalization, basicity of nitrogen atoms, and consequently the tautomeric equilibrium constant (K_T). Extensive studies have been carried out during the last 50 years on a large number of series of differently substituted amidines, and they were recently reviewed.[25i,88c,e,158] Generally, for derivatives containing at least one aryl group at the nitrogen atom, the tautomer containing this group at the imino nitrogen atom predominates in the tautomeric mixture, and the pK_T values can be predicted from the Hammett equation. The same situation holds for derivatives containing at least one group with heteroatoms, for example, OR, COR, SO_2R, CN, NO, or NO_2. The tautomer containing this group at the imino nitrogen atom is favored.

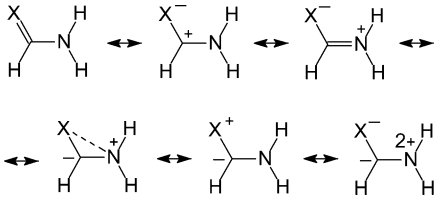
For the parent formamidine, called methanimidamide (H_2N−CH=NH ⇌ HN=CH−NH_2), the two tautomeric forms are identical and thus the tautomeric equilibrium constant is equal to unity and the energy of tautomerization is equal to zero, which is also the case for all amidine derivatives symmetrically substituted at the nitrogen atoms.[88e,158] Unfortunately, formamidine is not stable. Hence, it has not yet been isolated and investigated experimentally as a free base. Only theoretical data on its structure are available.[159] However, they depend strongly on the level of calculations because the structural changes do not require much energy. The two isomers (*E* and *Z* with respect to the C=N double bond) differ only by 1−2 kcal mol^{-1}. Recent studies by Prasad et al.[160] performed at the HF/6-31G* and MP2/6-31G* levels for all possible isomers of formamidine showed that the *E* isomer (i.e., that with the H and NH_2 in the trans configuration on the C=N double bond) with the pyramidal NH_2 group and a smaller dipole moment (2.89 D) is more stable (by 1.5 and 1.6 kcal mol^{-1}, respectively) than the *Z* isomer with a larger dipole moment (3.67 D). Tartajada et al.[159c] predicted a similar energy difference (1.8 kcal mol^{-1}) for both isomers at both the G2(MP2) and the G2 level of theory. However, the *E*/*Z* isomerization barrier was found to be exceptionally large at about 25 kcal mol^{-1}). Although isomers *E* and *Z* were predicted to have nearly planar structures at the MP2/6-31G* level, the transition state for *E*/*Z* isomerization has the imino hydrogen out of the molecular plane, showing that the isomerization of formamidine is not an "in-plane" process. Analogues of formamidine containing phosphorus and arsenic atoms instead of imino nitrogen, H_2N−CH=PH and H_2N−CH=AsH, exhibit reverse stability, and the more polar *Z* isomer seems to be more stable.[160]

The HOMA index for *E*-formamidine with the pyramidal NH_2 group estimated from geometry optimized at the HF/6-31G* level[160] is equal to 0.784, indicating important electron delocalization in the amidine moiety.[133] In the planar *E* isomer, which is less stable by 0.9 kcal mol^{-1}, the n−π resonance conjugation is stronger, and it is obvious that the geometric parameter describing electron delocalization is also larger, HOMA being equal to 0.852. Changing the configuration from *E* to *Z* in formamidine does not dramatically affect the n−π-electron distribution in the amidine moiety. The HOMA indices are only slightly reduced, being 0.747 and 0.817 for the NH_2 pyramidal and planar structure, respectively. Protonation or deprotonation of the amidine group leads to equalization of the CN bonds and to an increase of n−π-electron delocalization due to the symmetry of the system.[161] The HOMA indices at the MP2/6-31G* level for the most stable *E* and *Z* isomers and the protonated form are 0.793, 0.752, and 0.963, respectively, which are not very different from those estimated at the HF/6-31G* level, thus indicating that there is only a small effect of electron correlation on the geometric parameter.

Formamidine is frequently used as a model compound for understanding proton transfers in enzymes and DNA base pairs. For instance, double proton transfer and solvent effects were studied for formamidine homodimer, formamidine−formic acid complexes, and formamidine−formamide complexes.[150d,162] A smaller barrier of about 4 kcal mol^{-1} was found for formamidine−formic acid than the barrier of about 10−15 kcal mol^{-1} found for other associates, indicating the dependence of the barrier height on differences in acid−base properties of substrates forming associated complexes. In such complexes, the electron delocalization in the amidine moiety is slightly smaller than that in the protonated form (e.g., a HOMA of 0.910, estimated for the geometry of formamidine dimer optimized at the B3LYP/6-31G** level[162a]).

The phenomenon of strong electron delocalization in the system of general formula X=CH−NH_2 ⇌ HX−CH=NH, where X = CH_2, NH, O, SiH_2, PH, S,

Scheme 13. Resonance Structures for Vinylamine and Its Analogues, X=CH−NH$_2$ (X = CH$_2$, NH, PH, AsH, O, S, or Se)[164]



AsH, or Se, is still in debate.[160,163,164] Conclusions consistent as well as inconsistent with the resonance model[11] have been derived during the last 2 decades. Generally, the resonance model predicts that the electron delocalization in such systems (Scheme 13) is directly linked with the electronegativity of the atom doubly bonded with the CH group: the more electronegative the atom, the greater the delocalization. However, population analyses, geometric changes, charge variations, orbital interactions, and changes of the NH$_2$ group rotational barrier as studied by quantum-chemical methods suggested that the electron delocalization does not increase with the electronegativity of the doubly bonded atom. The CN partial double bond character, supported by the C−N bond rotational barriers, increases in formamide and its S and Se analogues in the order O < S < Se. A similar order, CH < NH < PH < AsH, is found for vinylamine and its N, P, and As analogues. Only recently Mó et al.,[164] using a block localized wave function method, decomposed the rotational barriers into various energy components, including resonance conjugation energy, σ-framework steric effects, hyperconjugation energy, and pyramidization energy, and showed thereby that both ground-state π resonance and σ steric effects are crucial in determining the rotational barrier. On the basis of this analysis, they suggested that the rotational barrier is not a good measure of the "pure" n−π conjugation.

For the neutral parent nitroso−oxime (H$_3$C−N=O ⇌ H$_2$C=N−OH)[165] and the nitro−*aci*-nitro {H$_3$C−N$^+$(O$^-$)=O ⇌ H$_2$C=N$^+$(O$^-$)−OH}[166] systems, the general behavior of the n−π-electron distribution is similar to that observed for the neutral keto−enol interconversion of acetaldehyde (Table 3).[133] The HOMA indices based on geometries optimized at the MP2/6-31G* level for individual tautomers are close to zero and the absolute energies of tautomerization are close to that for acetaldehyde. The only difference is the change of tautomeric preferences in the nitroso−oxime system in which the formaldehyde oxime (corresponding to the enol form), instead of nitrosomethane (corresponding to the keto form), is the favored tautomer. It should be mentioned that a 1,2 proton shift is also possible in the less stable nitrosomethane. This proton transfer leads to the nitrone H$_2$C=NH$^+$−O$^-$, which is almost isoenergetic with nitrosomethane. Since migration of π-electrons does not take place here, this 1,2 proton shift cannot be classified as a tautomeric interconversion.

Lammertsma and co-workers[165b] showed in addition that aqueous bulk solvation as treated by SCI−PCM stabilizes formaldehyde oxime by an additional 1−2 kcal mol^{-1} in comparison to nitrosomethane. This stabilization, however, could not be explained by dipole moment variations because, surprisingly, nitrosomethane has a larger dipole moment (2.81 D) than *anti*-formaldehyde oxime (0.71 D). Only the *syn*-formaldehyde oxime, which is less stable by a few kilocalories per mole, has a larger dipole moment (3.54 D) than nitrosomethane. Complexes with two water molecules, such as those considered for modeling specific interactions such as H-bonding, which play a significant role in aqueous solvation, stabilize the oxime relative to the nitroso form by an additional 4 kcal mol^{-1}, confirming that stronger H-bonds are formed for the oxime, which can act both as a donor and as an acceptor, than for the nitroso form, which can react only as an acceptor. Finally, combination of the SCI−PCM method, which includes mainly nonspecific solvation effects, with the specific solvation effects in bis-water complexes led to a nearly zero change in the energy difference between the two tautomers.

In the case of thiol−thione tautomerism in the thioformic acid (O=CH−SH ⇌ HO−CH=S), which favors the thiol form,[167] the general behavior of the n−π-electron distribution is also similar to that observed for the neutral keto−enol interconversion in acetaldehyde (Table 3).[133] The HOMA indices (0.355 and 0.328) estimated from geometries optimized at the MP2/6-311++G** level[167] for the individual tautomers are not very different from zero. Only the cyclic transition state displays a complete electron delocalization with a HOMA close to unity (0.993). An association with one molecule of dimethyl ether increases the HOMA indices for individual tautomers by 0.1 to 0.2 units and decreases the HOMA index for the transition state only by 0.01 units. Cyclic homodimerization of two O=CH−SH or two of its tautomer S=CH−OH also augments the HOMA indices by 0.2−0.3 units. The HOMA index for the cyclic heterodimer is between those for cyclic homodimers. All these observations indicate that in both tautomers association increases electron delocalization and favors tautomeric interconversion.

Surprisingly, the polarity of the solvent strongly influences tautomeric preferences in mono- and dichalcogenide analogues of thioformic acid (X=CR−YH ⇌ HX−CR=Y, where R = H, alkyl, or aryl and X, Y = O, S, Se, or Te).[167−169] Kato and co-workers[168] found on the basis of their experiments for monochalcogeno carboxylic acids (Y = O) that the thione acid (S=CR−OH) exists predominantly in polar solvents at very low temperatures, while the thiol acid (HS−CR=O) is favored in nonpolar solvents. These various experimental solvent effects indicate how important specific solute−solvent interactions are in this case. However, these kinds of interactions are exceptionally difficult to confirm by theoretical models such as PCM or SCI−PCM, which take mainly nonspecific solute−solvent interactions into account.[167,169]

Formic acid (HO−CH=O ⇌ O=CH−OH)[169] is a particular case of triad compounds displaying 1,3 proton shift. The two tautomeric forms are identical, just as in the isoelectronic formamidine. Hence, the tautomeric equilibrium constant is equal to unity, and the energy of tautomerization is equal to zero

(Table 3). Although the cyclic transition state displays a complete electron delocalization (HOMA = 0.999), the π-electrons in formic acid are strongly localized. The HOMA index, both from MP2/6-311G(2d) and experiment,[169] is close to zero (0.178 and 0.231, respectively).[133] The energy barrier for isomerization ($\Delta E^{\ddagger}$) is lower than that for acetaldehyde and is equal to 33 kcal mol^{-1} by both MP2/6-311G(2d) and B3LYP/6-311G(2d).[169] The influence of solvation on the $\Delta E^{\ddagger}$ was studied using two theoretical models, SCRF and SCI−PCM, and neither showed any substantial solvent effects.

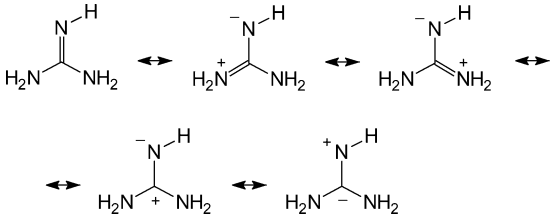
Other tautomeric equilibria possible in simple open chain bifunctional (triad) compounds such as nitramide {$H_2N-N^+(O^-)=O \rightleftharpoons HN=N^+(O^-)-OH$}, cyanamide ($H_2N-C\equiv N \rightleftharpoons HN=C=NH \rightleftharpoons N\equiv C-NH_2$), diazohydroxide (HO−N=NR ⇌ O=N−NHR), and triazenes (RHN−N=NR′ ⇌ RN=N−NHR′) have been mentioned in the literature. For instance, nitramide {$H_2N-N^+(O^-)=O$} was found to be more stable than its *aci*-nitramide {$HN=N^+(O^-)-OH$} by 8.8 kcal mol^{-1} at the G2 level of calculations.[165b] Carbodiimide (HN=C=NH) was identified by matrix IR spectroscopy as one of the products of photochemical fragmentation of unsubstituted triazoles and tetrazole, as well as by matrix photolysis of cyanamide itself.[170] Diazohydroxide (HO−N=NR, R = CH_2CH_2Cl) was proposed in mechanisms for the breakdown of fotemustine and identified by electrospray ionization mass spectrometry (ESI-MS).[171] The mechanism of intramolecular proton transfer in triazenes was studied by dynamic NMR.[81a] A better known system exibiting isomerization is the pair hydrogen cyanide and hydrogen isocyanide (HCN ⇌ HNC).[172] HNC was observed for the first time as a photoisomerization product of HCN in low-temperature rare gas matrixes[173] and later in the gas phase.[174] It was also detected in interstellar space in clouds and in comets, including the Hale−Bopp comet.[175,176]

Perusal of the total energies of tautomerization (e.g., the ΔE_T given in Table 3) computed at the G2 or the MP2/6-311++G** level[165,167] for tautomeric interconversion in simple open chain systems of the general formula HX−Z=Y ⇌ X=Z−YH provide some general information on tautomeric preferences in the gas phase. In all cases, except nitroso−oxime and symmetrically substituted systems (formamidine and formic acid), the positive values of ΔE_T indicate that the form corresponding to the keto tautomer is favored in the tautomeric mixture. This could suggest that this preference is caused by particular stability resulting from electron delocalization. However, the comparison of the ΔE_T with differences between the HOMA indices estimated for individual tautomers (ΔHOMA) does not reveal a linear relationship between the energetic parameters for tautomeric equilibria and the geometric indices for n−π-electron distribution.

4.2. Y-Conjugated Compounds

Y-Conjugated compounds belong to tetrad tautomeric systems. Usually they contain two protons that may occupy two of three sites, and prototropy is a combination of three identical or different types of

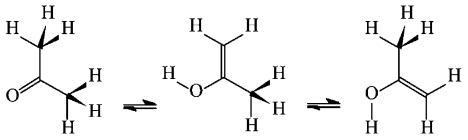
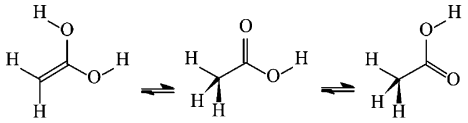
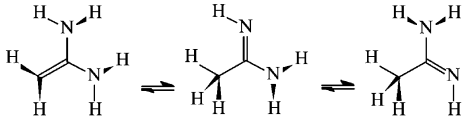
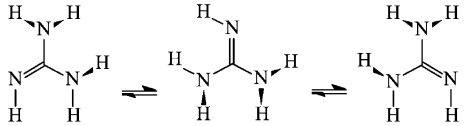
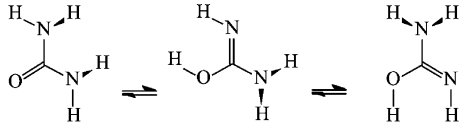
Scheme 14. Resonance Structures for Guanidine



the rearrangements given in Table 1. Each 1,3 proton shift is accompanied by migration of π-electrons. In Y-conjugated systems of general formula HX−Z(=Y)−X′H ⇌ X=Z(YH)−X′H ⇌ HX−Z(YH)=X′, tautomeric equilibria depend on the acid−base properties of the X, X′, and Y atoms. The two more basic sites take the protons, and the corresponding tautomer predominates in the tautomeric mixture. For the most symmetrical systems (X = X′ = Y), prototropy is a combination of three identical rearrangements between three tautomers having identical structure, for example, keto-hydroxy in carbonic acid (X, X′, Y = O, Z = C), and amine−imine in guanidine (X, X′, Y = NH, Z = C). The tautomeric equilibrium constant for each proton transfer is equal to unity, and the energy of tautomerization is equal to zero. Exceptional resonance stability, comparable to aromatic benzene, was observed for the carbonate dianion and the guanidinium cation.[177]

The biological activity of guanidine {$H_2N-C(=NH)-NH_2 \rightleftharpoons HN=C(NH_2)-NH_2 \rightleftharpoons H_2N-C(NH_2)=NH$}, its electronic structure, resonance stability, and the exceptionally large difference between its gas and solution phase basicity were the subject of numerous discussions in the literature[178] and were recently reviewed.[179] As shown by high-level ab initio calculations, the guanidine CN_3 moiety is planar and the NH_2 groups are pyramidal. Since the amino groups are not strictly equivalent, the barrier to rotation of the NH_2 pyramid about the C−NH_2 bond axis is different for each amino, but only by 0.5 kcal mol^{-1}. For the *cis*-NH_2, this barrier is higher than that for the *trans*-NH_2 (5.2 kcal mol^{-1} at the G2 level) with respect to the imino hydrogen.[178c] The C=N double bond is slightly shorter than the C−N single bonds, indicating particular delocalization of π-electrons (Scheme 14). The HOMA index estimated for the MP2/6-31G* geometries[178c] is equal to 0.666 (Table 4). No experimentally determined geometry for guanidine itself is available. Only guanidines substituted at the nitrogen atoms, in which various intra- and intermolecular interactions such as substituent effects and hydrogen bonds in the crystal lattice, were reported.[180] That HOMA indices are larger for crystalline guanidine derivatives (e.g., 0.83−0.91 for *N*-phenylguanidine)[179] than for isolated unsubstituted guanidine indicate that the guanidine moiety is very sensitive to structural effects, which in consequence lead to equalization of the CN bonds. Fascinated by the remarkable stability of the guanidinium cation, Gund proposed a new type of aromaticity, the so-called "Y-aromaticity".[181] Indeed, Krygowski et al.[177c] found HOMA = 1.011 for guanidinium salts retrieved from the Cambridge Structural Database (CSD).[182] Bharatam et al.[183] confirmed excep-

Table 4. Comparison of HOMA Indices and Relative Total Energies {ΔE_T = E[HX−Z(=Y)−XH] − E[X=Z(YH)−XH] in kcal mol^{-1}} for Y-Conjugated Tetrad Systems HX−Z(=Y)−XH ⇌ X=Z(YH)−XH ⇌ HX−Z(YH)=X[184]

Tautomeric system	HOMA HX−Z(=Y)−XH	HOMA X=Z(YH)−XH	ΔE_T
	-1.717	-0.788	18.6
	-0.225	-0.682	-35.3
	0.516	-0.442	-10.0
	0.666	0.666	0.0
	0.727		

tionally high electron delocalization by calculating the HOMA (0.999) and NICS indices (−44.1 ppm) for the guanidinium ion at the MP2(full)/6-31G* level. However, opponents of the Y-aromaticity concept in guanidinium ion indicated many other reasons such as charge distribution, a rotational barrier of 10−20 kcal mol^{-1} around one single bond, and a strong solution phase basicity versus a moderate gas-phase basicity to explain the exceptional stability of guanidine and its cation.[178a,b] Actually, there is no theory that would be generally accepted by chemists and that could explain the high stability of the guanidinium cation.

In other Y-conjugated systems, when only X and X′ are the same, but different from Y, prototropy is a combination of three equilibria, two of which are identical and one different (Table 4), for example, one so-called three carbons equilibrium and two keto−enol equilibria in acetone (X, X′ = CH_2, Y = O, Z = C), one keto-hydroxy equilibrium and two keto−enol equilibria in acetic acid (X, X′ = O, Y = CH_2, Z=C), one amine−imine equilibrium and two imine−enamine equilibria in acetamidine (X, X′ = NH, Y = CH_2, Z = C), and, finally, one amine−imine equilibrium and two amide−iminol equilibria in urea (X, X′ = NH, Y = O, Z = C). In such cases, only one tautomer {HX−Z(=Y)−XH} has a different structure than the other two identical ones {X=Z(YH)−XH, and HX−Z(YH)=X}.

Acetone {H_3C−C(=O)−CH_3 ⇌ H_2C=C(OH)−CH_3 ⇌ H_3C−C(OH)=CH_2} prefers the keto form just as does triad acetaldehyde. Its energy of tautomerization is slightly higher, and its energy barrier to enolization is slightly lower than those for acetaldehyde, by 2 and 1 kcal mol^{-1}, respectively, at the MP2/6-31G* level.[136a] The π-electrons are also localized in each tautomeric form giving a negative HOMA, and it seems that they have no effect on the tautomeric preference. Only the cyclic transition state for keto−enol isomerization displays any particular electron delocalization, as evidenced by a HOMA of 0.817 at the same level of theory.[184]

Lack of π-electron delocalization, that is, a negative HOMA, also occurs in tautomers of acetic acid {H_3C−C(=O)−OH ⇌ H_2C=C(OH)−OH ⇌ H_3C−C(OH)=O}. Acetic acid does not favor the enol form. The enol tautomer was identified and characterized only in some cases of carboxylic acids, for example, in cyclopentadiene derivatives.[68a] The energy of tautomerization and the energy barrier for enolization are greater than those of acetone by 16 and 8 kcal mol^{-1}, respectively, at the MP2/6-31G* level,[136a] and electron delocalization is possible only in the four-membered cyclic transition state of acetic acid, which has a HOMA of 0.841, estimated at same level of theory.[184] That, however, is due to the cyclic transition state rather than to the Y-character of the system.

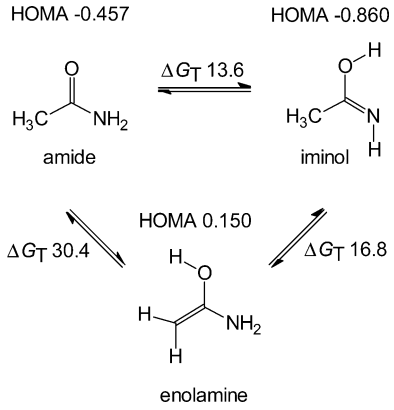
An interesting behavior was observed for acetamidine {H_3C−C(=NH)−NH_2 ⇌ H_2C=C(NH_2)−NH_2 ⇌ H_3C−C(NH_2)=NH}.[185] Although electron delocalization in the imine−enamine tautomer {H_2C=C(NH_2)−NH_2, i.e., 1,1-diaminoethylene} seems to be exceptionally strong (HOMA estimated for MP2/6-31G* geometries[185] 0.516) in comparison to the enol form of acetic acid {H_2C=C(OH)−OH, i.e., 1,1-dihydroxyethylene with HOMA(MP2/6-31G*) −0.225},[184] 1,1-

diaminoethylene is disfavored in the tautomeric mixture by 10 kcal mol^{-1} at the G2 level. The tautomerization barrier for the acetamidine → 1,1-diaminoethylene process is almost as high as in keto−enol tautomeric systems (62 kcal mol^{-1}). Acetamidine tautomers {$H_3C-C(=NH)-NH_2 \rightleftharpoons H_3C-C(NH_2)=NH$} prefer the *E* configuration around the C=N double bond, that is, the structure with the pyramidal NH_2 group in the trans position with respect to the imino hydrogen. The *E* isomers have lower energy by 1 kcal mol^{-1} than the *Z* isomer, which has the NH_2 group in the cis position with respect to the imino hydrogen. The energy barrier of *E*−*Z* isomerization was found to be 26 kcal mol^{-1}, and the energy barrier for the NH_2 rotation was 9 kcal mol^{-1}. Protonation of acetamidine increases the energy barrier for the NH_2 rotation to 21 kcal mol^{-1}. However, electron delocalization in the monocation considered as a Y-conjugated tetrad system is very small {HOMA(MP2/6-31G*) 0.011}. The π-electrons are only delocalized in the protonated triad amidine moiety {HOMA(MP2/6-31G*) 0.984} and in the cyclic transition state for enamine−amidine izomerization {HOMA(MP2/6-31G*) 0.715}.

Unfortunately, prototropy in the next interesting Y-conjugated system, urea {$H_2N-C(=O)-NH_2 \rightleftharpoons HN=C(OH)-NH_2 \rightleftharpoons H_2N-C(OH)=NH$}, has not been studied by modern spectroscopic techniques. Only recently, the UV induced proton-transfer process in monomeric thiourea, a thione−thiol interconversion with an MP2 energy of tautomerization of 13 kcal mol^{-1}, was reported for the isolated system in an argon matrix by Nowak and co-workers.[186] The electronic structure of urea itself and its analogues {$H_2N-C(=X)-NH_2$, X = C, S, or Se} has attracted the interest of researchers in the past decade more than has its tautomerism.[178b,187] It was found that the amino groups in urea are less pyramidal in the gas phase than the amino groups in guanidine. The energy barrier for rotation of each NH_2 group in urea is slightly higher, about 1 kcal mol^{-1}, than that in guanidine as predicted at the same level of theory.[178b] Interestingly, the HOMA index at the MP2/6-31G* level is larger for urea (0.727) than for guanidine (0.666) and acetamidine (0.516). This HOMA order follows the order of electronegativity (O > N > C), which is consistent with the resonance model.[11] On the other hand, Prasad et al.[163g] investigating the series urea, thiourea, and selenourea showed that the rotational barriers for the NH_2 at the G2 level, which were 7.5, 8.8, and 9.4 kcal mol^{-1}, increase in the order O < S < Se just as in the case of formamide and its S and Se analogues. This conclusion was considered as contrary to the resonance model, because the order of rotational barriers does not follow the increasing electronegativity order. As mentioned above, some explanation for this discrepancy was given by Mó et al.[164]

When all three sites X, X′, and Y are different in a Y-conjugated system, the tautomeric process is a combination of three different equilibria, for example, keto−enol, amide−iminol, and enamine−imine in acetamide (X = CH_2, X′ = NH, Y = O, Z = C). In such cases, the three possible tautomers are different.

Scheme 15. Gibbs Free Energies of Tautomerization (ΔG_T in kcal mol^{-1})[137d] and HOMA Indices {MP2(full)/6-31G} for Acetamide and Its Tautomers[184]**

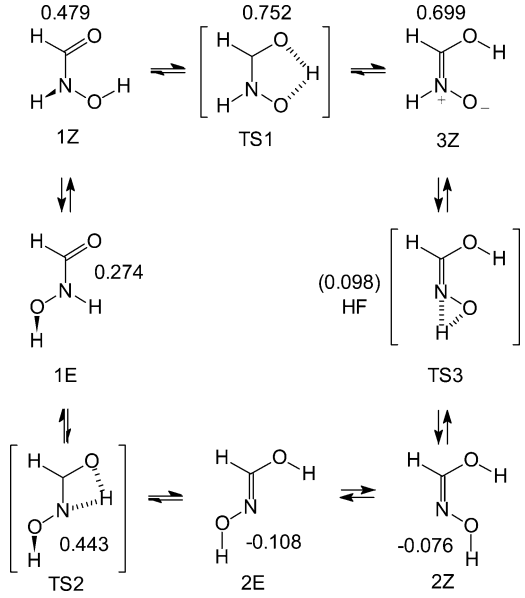


Sklenák, Apeloig, and Rappoport,[137d] applying various theoretical methods such as B3LYP, MP2(full), and CCSD(T) to the tautomeric equilibria in acetamide {$H_3C-C(=O)-NH_2 \rightleftharpoons H_2C=C(OH)-NH_2 \rightleftharpoons H_3C-C(OH)=NH$}, confirmed that the amide tautomer is the most stable form. The energy of the iminol form is higher by 12−14 kcal mol^{-1} than that of the amide form but is lower by 15−17 kcal mol^{-1} than that of the hydroxyenamine tautomer. Scheme 15 summarizes the relative Gibbs free energies and the HOMA indices estimated for the MP2(full)/6-31G** geometries.[137d] Their direct comparison, however, does not explain why the amide with a HOMA of −0.457 is the most stable form and the hydroxyenamine with a HOMA of 0.150 is the least stable form. Experimentally, the iminol form of acetamide was found only in a few cases, mainly in complexes with metal cations.[188] It is also favored for the ionized system.[189] The energy of the iminol radical cation is lower than that of the acetamide radical cation by 18.9 kcal mol^{-1}, and the energy barrier for tautomerization is about 30 kcal mol^{-1} at the G2(MP2) level.[190] Stable enol forms of other amides were identified for derivatives containing strong electron-accepting groups (e.g., aryl, CN, NO_2, COR).[191] For thioacetamide, the iminol form was recently UV induced and observed in the IR spectrum of thioacetamide isolated in an argon matrix.[192]

4.3. Linear Tetrad Nitrones

Tautomeric interconversion by 1,3 and 1,4 proton shifts frequently occurs in linear nitrones of the general formula $HX-C(R)=NH^+(O^-) \rightleftharpoons X=C(R)-NH(OH) \rightleftharpoons HX-C(R)=N(OH)$, where X = CH_2, NH, or O in the simplest derivatives. Like Y-conjugated compounds, nitrones are classified as tetrad tautomeric systems. Three tautomers are possible, but only two tautomeric equilibria, 1,3 and 1,4 proton transfer, occur. The intramolecular 1,2 proton shift between the nitrogen and oxygen atom in the nitrone group is not accompanied by a migration of π-electrons and thus cannot be classified as a tautomeric process. Numerous tautomeric nitrones, mainly cyclic derivatives, were studied and reported.[25h,193] For linear nitrones, investigations were more difficult due to the structural complexity of the system. Hydrox-

Scheme 16. HOMA Indices (MP2/6-31+G) for Tautomers−Rotamers and Transition States of Formohydroxamic Acid[184]**



amic acids {HO−C(R)=NH$^+$(O$^-$) ⇌ O=C(R)−NH-(OH) ⇌ HO−C(R)=N(OH)} are such examples because three types of isomerism (tautomeric, geometric, and rotational) may take place.[194] Three tautomers (N-oxide of imidic acid, hydroxyamide, and iminediol) corresponding to different proton transfers are possible, among which the energy barrier for the 1,4 proton shift seems to be the lowest one.[195]

Stinchcomb and Pranata[196] recently attempted a complete analysis of all possible isomers of formohydroxamic acid (R = H), and found 12 tautomers−rotamers: three rotamers for the hydroxyamide form, O=CH−NH(OH), with different conformations around the C−N and N−O single bonds, five isomers for the iminol form, HO−CH=N(OH), and four isomers for the N-oxide of imidic acid, HO−C(R)=NH$^+$(O$^-$), with different configurations (*E* or *Z*) around the C=N double bond and with different conformations around the C−O or N−O single bonds. Using various levels of theory, they showed that larger basis sets and inclusion of electron correlation are necessary to estimate the relative energies between these different tautomers. In this way, four tautomers−rotamers among 12 (all three isomers of hydroxyamide and one *Z* isomer of the iminol form) were found at the MP2/6-311G** level to have very close energies (ΔE < 1.5 kcal mol^{-1}). The energy of one additional *E* isomer of the iminol form was not greater than 5 kcal mol^{-1} above those of the four isomers, and that *E* isomer was also considered in the tautomeric mixture. The energies of other tautomers−rotamers were greater by 9−32 kcal mol^{-1}, and their percentage contents in the mixture were relatively very low.

Wu and Ho[195] chose five isomeric tautomers of formohydroxamic acid (Scheme 16): two hydroxyamide forms (1*E* and 1*Z*), two iminol forms (2*E* and 2*Z*), and one N-oxide of imidic acid with separated charges (3*Z*), and they analyzed tautomeric interconversions via intramolecular proton transfer for these five isomers including transition states using the MP2 and G2 methods. The transition state TS1 between the 1*Z* and 3*Z* forms corresponds to the 1,4 proton shift, the transition state TS2 between the 1*E* and 2*E* forms to the 1,3 proton shift, and the transition state TS3 between the 3*Z* and 2*Z* forms to the 1,2 proton shift. The most probable proton transfer is the 1,4 proton shift with an energy barrier for the 1*Z* → TS1 process of 13 kcal mol^{-1} at the G2 level. The other proton transfers need more than 40 kcal mol^{-1}. Among the five tautomeric forms, the 1*Z* tautomer was found to be the most stable form and the 3*Z* tautomer the least stable. Their order of decreasing stabilities is 1*Z* > 2*Z* > 1*E* > 2*E* > 3*Z* with relative energies equal to 0.0, 0.1, 1.9, 5.1, and 13.1 kcal mol^{-1}. The 1*Z* form is also favored in the solid state and in solution as shown using X-ray[197] and ^{17}O NMR.[198]

The HOMA indices estimated for the MP2/6-31+G** geometries[195] of the five isomers of formohydroxamic acid (Scheme 16) do not follow the order of energetic stabilities, confirming the lack of linear relationship between the geometric and the energetic parameters observed for other simple open chain molecules.[184] The values of HOMA are negative only for the iminol forms 2*Z* and 2*E* indicating strong localization of the C=N double bond. In these isomers, the resonance electron-donating effects of the OH groups linked to the C and N atoms seem to cancel. There is apparently some electron delocalization in the most stable hydroxyamide isomer 1*Z* (HOMA 0.479) and in a second hydroxyamide isomer 1*E* (HOMA 0.274). An exceptionally high HOMA value of 0.699 is observed for the less stable 3*Z* form, probably due to the separation of the charge. As would be expected, electron delocalization increases in the cyclic transition states TS1 and TS2, and thus the HOMA indices also increase to 0.752 and 0.443, respectively, but to a greater extent for the TS1, a five-membered cycle including the proton, than for TS2, a four-membered cycle. Electron delocalization does not occur (HOMA 0.098) in the less stable TS3, a three-membered cycle.

The important question of whether formohydroxamic acid is an O-acid or an N-acid, which has been discussed for a long time in the literature,[194−196] has not yet been answered definitively. It has only been suggested that the disagreement between experimental conclusions may be due to different solvents being used in measurements, because it has been proved that solvent effects may change the acidity of the OH and NH groups. Only recent high-level ab initio calculations indicated that the N-anion is more stable than the O-anion and hence that hydroxamic acids may be classified as N-acids in the gas phase.[194h] A similar conclusion has been derived from the transition barrier for intramolecular proton transfer.[195]

5. Resonance-Assisted Hydrogen Bonding Effect in Compounds Displaying Prototropic Tautomerism

Hydrogen bonding is one of the most important factors governing tautomeric equilibria. Energies of

typical H-bond interactions are usually between 2 and 15 kcal mol^{-1}, and in the case of very strong interactions, they may be even greater than 20 kcal mol^{-1}.[199] These values partially explain why H-bond formation between the tautomeric XH and Y groups very often changes tautomeric preferences in systems where absolute tautomerization energies are between 0 and 20 kcal mol^{-1}. Such situations occur even in simple linear pentad systems (e.g., 1,3-dicarbonyl compounds, β-thioketones, β-ketoimines, β-diimines) and also in the more complex Schiff bases, where the XH and Y groups are separated by the planar π-electron conjugated spacer built of three heavy atoms (e.g., —CH=CH—CH=). This separation makes the system very flexible and sensitive to internal and external effects. The linear pentad can easily change its conformation. It can adopt either a cyclic structure in which an intramolecular X—H···Y bridge can be formed or an open chain conformation where only intermolecular H-bonds are possible. Depending on the environment, there may be competition between the intra- or intermolecular H-bonds. The strength of these interactions is determined by the nature of the X and Y atoms (e.g., by their electronegativity, net atomic charges, and conjugation) and also by the nature of the active sites of the environment. In most cases of tautomeric pentad systems, the H-bonds between the XH and Y groups are very strong. To explain the reason for the formation of such strong X—H···Y hydrogen bonds, a model called RAHB (resonance-assisted hydrogen bonding) was proposed by Gilli and co-workers,[200] and successfully employed for tautomeric systems.[200,201] This model shows that the H-bond is strengthened by the interplay with the heteroconjugated π bond system. A simple arithmetic treatment based on this model allows the estimation of H-bond energies. Their magnitude is 10—20 kcal mol^{-1} or even more. Unfortunately, the energy associated with the H-bonding is not physically observable and cannot be measured. Alkorta et al.[202] showed by a detailed analysis of the NMR properties of oxygen-containing systems that neither the coupling constants nor the chemical shifts provide any evidence for the existence of the RAHB effect.

Chemists have also focused much attention on the shape of the potential energy function for the proton migration in the X—H···Y bridge.[203] It has been suggested that in those cases where the X···Y distances are very small (e.g., less than 250, 265, and 263 pm for O···O, O···N, and N···N distances, respectively), the proton is confined to a single minimum potential well with no barrier or to a double potential well with a very low barrier to proton transfer between the donor and acceptor groups. In these cases, the H-bonds are very strong. The observation of negative isotope effects (^{2}H and ^{3}H) was attributed to a single potential well and that of positive isotope effects to a double potential well.[204] For neutral tautomeric systems bearing a 1,3-diketo fragment in its enol form and a strong intramolecular H-bond between tautomeric functions, experimental results were interpreted on the basis of both single (O···H···O) and double proton sites (O—H···O $\rightleftharpoons$ O···H—O).[200a,205]

5.1. Conjugated Pentad Systems

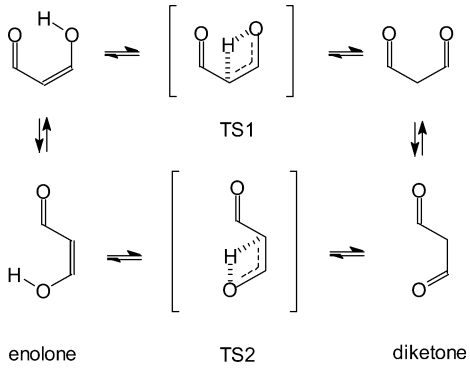
For conjugated pentad tautomeric systems of the general formula X=Z—YH—Z′=Y′ $\rightleftharpoons$ HX—Z=Y—Z′=Y′ $\rightleftharpoons$ X=Z—Y=Z′—Y′H, three tautomers are possible, between which three types of tautomeric interconversions take place: two 1,3 (from YH to X or Y′ and from XH or Y′H to Y) and one 1,5 proton shift (from XH to Y′ or from Y′H to X). The latter two tautomers have the advantage that intramolecular H-bonding between the XH and Y′ as well as between the X and Y′H groups is possible within the molecule. This additional interaction, which is often of RAHB nature,[200] stabilizes the cyclic chelated structure and favors the proton transfer.

Malondialdehyde (O=CH—CH_2—CH=O $\rightleftharpoons$ HO—CH=CH—CH=O $\rightleftharpoons$ O=CH—CH=CH—OH), which contains two carbonyl functions separated by the methylene group, is the simplest pentad compound in which three proton transfers occur. Among those transfers, two 1,3 proton shifts corresponding to keto—enol interconversion are identical to one another but different from the 1,5 proton shift corresponding to keto—hydroxy interconversion. Therefore, among the three tautomers (one diketone and two enolones), the two enolone forms are identical, and the 1,5 proton shift, which is possible, for example, in the intramolecular O—H···O bridge, is symmetrical.

In aqueous solution, malondialdehyde is completely enolized and is as acidic as carboxylic acids.[206] This is in striking contrast to the aliphatic β-diketones, which are only 10—20% enolized in water and are as weakly acidic as phenols. NMR investigations revealed that the enolone form of malondialdehyde and its alkyl derivatives has the cyclic H-bonded (called cis) and open chain linear (called trans) conformation in nonaqueous and aqueous solvents, respectively.[207] This conclusion was supported by an analysis of the IR spectra.[208] No diketo form of malondialdehyde was detected in chloroform solution nor was its hydrated *gem*-diol form, O=CH—CH_2—$CH(OH)_2$, detected in water solution.[207] (The absence of a diketo form is consistent with very rapid proton exchange between terminal oxygen atoms rather than between oxygen and carbon atoms). More detailed analyses of the ^{1}H NMR spectra of malondialdehyde recorded a few years later in different solvents at variable temperatures confirmed earlier NMR observations and gave more information on solvent effects.[209] For instance, it was found that in very weak hydrogen bonding solvents such as methylene chloride, the bridged *cis*-enolone form is present, whereas in diethyl ether, its interaction with the enolone OH group (OH···OEt_2), stabilizes the *trans*-enolone form. Moreover, the *cis*-enolone form may also change into the trans form in the presence of a typical base. All of these results were confirmed by UV spectra.[209]

Microwave studies showed that in the vapor phase malondialdehyde exists in the planar intramolecularly H-bonded *cis*-enolone form with two equivalent tautomeric equilibrium configurations.[210] IR spectra of the vapor phase and matrix isolated molecules supported this structure determined by microwave.[211] These results were also consistent with the high-

Scheme 17. Two Types of 1,3-Proton Transfer from the Enolone to Diketone Form in Malondialdehyde[216]



resolution far-IR studies.[212] X-ray photoelectron spectroscopy proved that the intramolecularly H-bonded *cis*-enolone form of malondialdehyde has C_s symmetry in the gas phase.[205a,b] Molecular dynamics simulations with the projector augmented wave method, which combines classical dynamics with ab initio quantum mechanical forces, showed in addition that the proton transfer between two identical *cis*-enolone forms of malondialdehyde occurs via the tunneling effect.[213] The quantum mechanical tunneling between the C_s structures apparently occurs even at room temperature and thus through a relatively low potential energy barrier.[214] In fact, this barrier was found to be equal to 6−7 kcal mol^{-1}.

Various semiempirical and ab initio quantum-chemical calculations performed on the diketo and enolone forms of malondialdehyde and its derivatives confirmed that the *cis*-enolone tautomer, which is stabilized by the intramolecular H-bond, is the most stable form, and the 1,5 proton transfer in this form is favored.[215] Recently, Delchev and Nikolov[216] treated different types of through-space 1,3 proton transfers (Scheme 17) by HF/6-311G** calculations and found that the energy barrier of 77 kcal mol^{-1} for the enolone → TS1 → diketone conversion in the so-called "ω-shaped" form without rotation around the C−C single bond is lower than the barrier of 130 kcal mol^{-1} for the enolone → TS2 → diketone conversion in the so-called "sickle-shaped" form. This observation indicated that the through-space proton transfer in the ω-shaped enolone to yield the diketone form is much more favorable than the proton transfer in the sickle-shaped form. However, it is energetically less probable than the 1,5 proton shift in the chelated *cis*-enolone form.

The intramolecular H-bonding in the *cis*-enolone form of malondialdehyde so strongly increases π-electron delocalization that the HOMA index for geometries optimized at the HF/6-311G** level[216] increases from a negative value of −1.669 for the open chain diketone to a positive value of 0.323 for the cyclic enolone form. This electron delocalization in the enolone form is better described by high-level MP2 and DFT(B3LYP) calculations with the 6-311++G-(2df,2p) basis set, both of which calculations lead to a larger HOMA value (0.668 and 0.675, respectively),[217] close to those observed for aromatic compounds containing the oxygen atom.[15d] Hence, the bridged *cis*-enolone form of malondialdehyde may be classified as a strongly electron delocalized quasi-heteroaromatic compound.

Table 5. HOMA Indices and Energies of Tautomerization (ΔE_T + ZPVE in kcal mol^{-1}) for Nitrogen Derivatives of Malondialdehyde Estimated at the DFT(B3LYP)/6-311+G(2df,2p) Level[217]

a **b**

A	B	C	HOMA(**a**)	HOMA(**b**)	ΔHOMA[a]	ΔE_T[a]
CH	CH	CH	0.675	0.675	0	0
CH	N	CH	0.779	0.779	0	0
N	CH	N	0.769	0.769	0	0
N	N	N	−0.586	−0.586	0	0
N	CH	CH	0.448	0.937	0.489	7.9
N	N	CH	0.512	0.778	0.266	4.6

[a] Differences between parameters for tautomer **b** and **a**.

The replacement of the CH groups in malondialdehyde by the N atoms strongly influences electron delocalization of the enolone-like form (Table 5).[217] Generally, the HOMA{DFT(B3LYP)/6-311+G(2df,2p)} values increase for derivatives with nitrogens except when all of the CH groups are replaced by N atoms (HO−N=N−N=O ⇌ O=N−N=N−OH), in which case electron delocalization is completely destroyed and the HOMA drops to a negative value. Only in compounds with sufficient symmetry that the two *cis*-enolone forms are the same are differences in the HOMA indices and also differences in the energies of both tautomers equal to zero. For unsymmetrical compounds, these geometric and energetic parameters are different from zero, and it seems that energetic tautomeric preferences do not follow the HOMA index order. The energetically favored tautomer (**a** with the AO−H···OC bridge) has a lower value of the HOMA index than the other one (**b** with the AO···H−OC bridge). This suggests that the RAHB effect and electron delocalization are not the main factors that determine tautomeric preferences in chelated systems. They may only explain the higher stability of cyclic than of open chain tautomers. Other factors such as differences between functional group stabilities, for example, between the oxime and nitroso groups, seem to play a more important role.

Among the nitrogen derivatives of malondialdehyde (Table 5) only nitrosoacetaldehyde (O=N−CH_2−CH=O), which interconverts by 1,3 and 1,5 proton transfers to nitrosovinyl alcohol (O=N−CH=CH−OH) and glyoxal monooxime (HO−N=CH−CH=O), was investigated by Bouma and Radom.[218] Their ab initio calculations indicated that the glyoxal monooxime chelated structure is energetically favored over the nitrosovinyl alcohol chelated structure. The open chain nitrosoacetaldehyde (not shown in Table 5) has the highest energy. This is in agreement with experiment, which also showed that nitroso compounds generally exist as their monooxime tautomers in cis or trans conformation in gas, solution, and solid state.[219]

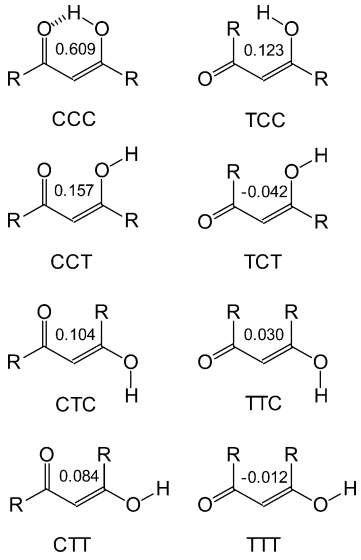
Krygowski et al.,[220] investigating substituent effects on electron delocalization in malondialdehyde derivatives, recently analyzed electron delocalization in terms of HOMA and NICS descriptors for fluoro and chloro derivatives of the *cis*-enolone form of malondialdehyde monosubstituted at the C-carbonyl or $^{\alpha}$C atom and found that the quasi-aromaticity of the system depends strongly on the substituent and its position. Interestingly, the HOMA values correlate well with the energy of intramolecular H-bonding but only in the case where electron correlation was included (MP2/6-311++G**). For the NICS(0) and NICS(1) values, no such correlation was found. The NICS(0) and NICS(1) indices are close to zero due to lack of the ring current typical for aromatic systems. As was expected, the replacement of hydrogen by lithium in the bridged *cis*-enolone forms led to a large increase in π-electron delocalization, and the HOMA values for all lithium derivatives are exceptionally large (>0.93).

Derivatives of malondialdehyde with the so-called "inorganic" substituents at the carbonyl carbons are particular cases. Substituents such as fluoro and chloro at the C-carbonyl in malonyl difluoride {O=C(F)−CH_2−C(F)=O} and dichloride {O=C(Cl)−CH_2−C(Cl)=O} increase the preference for the open chain diketo forms.[221] Malonyl choride alkyl esters {O=C(Cl)−CH_2−C(OR)=O} have exclusively the diketo forms.[222] In malondiamide, the enolone form as well as the additional possible ketoiminol form {HO−C(=NH)−CH_2−C(NH_2)=O} also have higher energies than the diketo form, and no enol form was observed for this molecule in its IR, Raman, and NMR spectra recorded in the solid state or in organic solvents.[223] Only the enol form was reported for malondiamide in aqueous solution.[224]

For "organic" substituents such as methyl, trifluoromethyl, phenyl, methoxyl, or ethoxyl groups linked to the C-carbonyl in acetylaldehyde {O=C(CH_3)−CH_2−CH=O},[207,209] acetylacetone {O=C(CH_3)−CH_2−C(CH_3)=O},[225] trifluoroacetylacetone {O=C(CF_3)−CH_2−C(CH_3)=O},[226] hexafluoroacetylacetone {O=C(CF_3)−CH_2−C(CF_3)=O},[227] benzoylacetone {O=C(Ph)−CH_2−C(CH_3)=O},[228] dibenzoylmethane {O=C(Ph)−CH_2−C(Ph)=O},[229] or acetoacetate {O=C(CH_3)−CH_2−C(OR)=O},[230] a high percentage of the cyclic enol form with an asymmetric hydrogen bridge was observed. In general, the population of this form decreases with increasing dielectric constant of the solvent.[88f] The energy barrier between the cyclic enol forms was found to be very small, only a few kilocalories per mole, and thus all these derivatives show rapid keto−enol tautomerization with the exception of 2-acetylcyclohexanone, for which the keto−enol interconversion seems to be a slow reaction.[231]

The influence of various internal and external factors on the fast enolone−enolone tautomeric equilibria in 1,3-dicarbonyl compounds unsymmetrically substituted at the C-carbonyl and $^{\alpha}$C atoms by "organic" substituents, a situation in which the diketo form is usually not present, was investigated by Koltsov and co-workers.[232] They found that the 1,5-proton transfer in cyclic short-lived enolone forms seems to be independent of solvent polarity. However, the population of the two tautomers is very sensitive to the electronic properties of the substituents in the conjugated systems. 1,3-Ketoaldehydes enolize mainly via the formyl group, whereas for benzoylacetones enolization of the benzoyl group is more probable. Enolization of the benzoyl group in benzoylacetones was found to be increased by electron-withdrawing substituents. The Hammett equation was applied to describe the relation between the relative energies and substituent constants. The importance of steric substituent effects on tautomeric equilibria was described by Jios and Duddeck.[233]

Scheme 18. Eight Possible Enol Isomers of 1,3-Diketones and HOMA Indices {DFT(B3LYP)/6-31G*} Estimated for Acetylacetone (R = Me)[184]



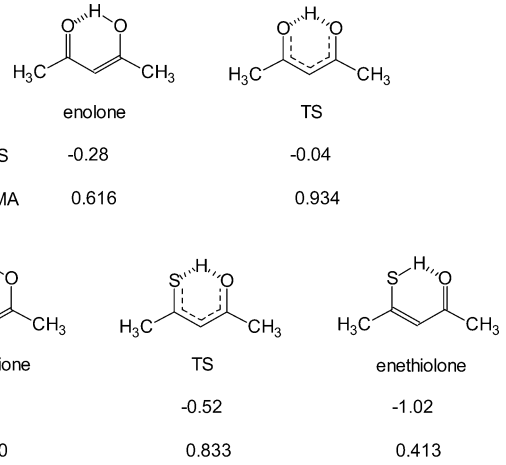
A recent conformational analysis of the enolone forms of malondialdehyde, acetylacetone, and hexafluoroacetylacetone yielded more information on dicarbonyl derivatives. Describing the conformation of the three quartets of atoms in the enolone atom chain by C for cis and T for trans, this detailed analysis led to eight enolone isomers: one chelated cyclic (CCC) enolone isomer and seven nonchelated open chain (CCT, CTC, CTT, TCC, TCT, TTC, and TTT) enolone isomers (Scheme 18).[211a,227b,234] Perusal of their geometric parameters confirmed the greater electron delocalization in the chelated CCC form than in the open chain structures. The CCC form was found to be favored in the gas phase. Its energy is lower by a few kilocalories per mole than that of the keto form. Other nonchelated enol forms have higher energies than that of the keto form, and they were not observed in low-temperature argon matrix by IR spectra. As was shown by Nakata and co-workers,[227b,234c] identification of some less stable enol isomers by the same method was only possible upon UV irradiation of the most stable chelated CCC form, which isomerizes under such conditions to the CTC, TCT, and TTC isomers for acetylacetone and to the CCT isomer for hexafluoroacetylacetone.

Interesting tautomeric equilibria were observed for asymmetric pentad systems. β-Thioxoketones isomerize to more stable enethiolone and enolthione forms {S=C(R)−CH(R′)−C(R″)=O ⇌ HS−C(R)=C(R′)−

C(R″)=O ⇌ S=C(R)−C(R′)=C(R″)−OH} by two 1,3 and one 1,5 proton shifts corresponding to the thione−enethiol, keto−enol, and enethiol−enol interconversions. In general, the chelated *cis*-enolthione tautomer {S=C(R)−C(R′)=C(R″)−OH}, which is similar in conformation to the CCC form in Scheme 18, seems to be a thermodynamically more stable form at room temperature as shown by X-ray and neutron diffraction, UV, IR, and NMR spectroscopy and various quantum-chemical calculations.[235] However, on the basis of the NMR experiments in solution, Hansen and co-workers[236] proposed an equilibrium between chelated *cis*-enolthione and *cis*-enethiolone forms {HS−C(R)=C(R′)−C(R″)=O ⇌ S=C(R)−C(R′)=C(R″)−OH} with a very low interconversion barrier. Measurements performed in parallel at low temperature indicated the presence of three tautomers: two intramolecularly H-bonded enolthione and enethiolone forms chelated like CCC and one open chain nonchelated enethiolone CCT form with the mercapto group rotated 180° relative to the chelated one. Photoreactivity of β-thioketones at low temperatures is still under debate. Recent structure assignment by low-temperature matrix isolation IR for the product of photoinduced transformation of the chelated *cis*-enolthione form corresponds to the nonchelated SH *exo*-rotameric *cis*-enethiolone like CCT in Scheme 18.[237]

Mó and co-workers,[238] in a theoretical investigation of malondialdehyde, thiomalonaldehyde, and their asymmetric Se and Te derivatives, considered not only eight isomers for both enolthione and enethiolone tautomers (as in Scheme 18) but also four isomers for the β-thioxoketone form. At the G2(MP2) level, the chelated enolthione and enethiolone isomers were found to be the most stable ones for thiomalonaldehyde. The energy difference is only 0.2 kcal mol^{-1} in favor of the chelated enethiolone form. It was shown that the specific solute−solvent H-bonding interactions cannot be neglected. When the hydrogen atom involved in the intramolecular H-bond is replaced by deuterium, the stability order is reversed, and the chelated enolthione is more stable than the chelated enethiolone form by 0.5 kcal mol^{-1} at the same level of theory. The H-bond in the enolthione seems to be more stable than that in the enethiolone form. These intramolecular H-bonds stabilize the chelated structures and increase electron delocalization. The HOMA indices estimated for geometries found at the MP2/6-31+G(d,p) level for the chelated enethiolone, enolthione, and transition state are 0.585, 0.715, and 0.957, respectively, indicating almost complete electron delocalization in the transition state and higher electron delocalization in the enolthione than enethiolone form. Importantly, two nonchelated isomers corresponding to the TTC and TTT structures (Scheme 18) have energy close to the most stable chelated enethiolone with ΔE + ZPVE being less than 0.5 kcal mol^{-1} at the same level of theory. The energy barrier for the 1,5 proton shift in the enethiolone−enolthione system is quite small in comparison to those for the 1,3 proton shifts in the thioxoketone−enethiolone and thioxoketone−enolthione systems.[239]

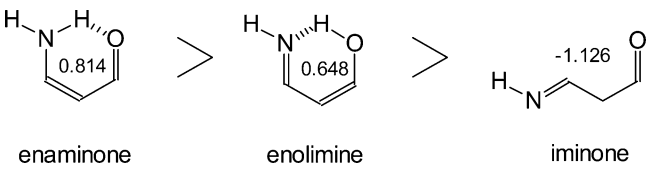
Scheme 19. Comparison of NICS[241] and HOMA Indices (B3LYP/6-311++G)[184] Estimated for Enol Tautomers and Transition States (TS) for Acetylacetone and Thioacetylacetone**



In selenium- and tellurium-containing analogues of malondialdehyde and thiomalonaldehyde, the keto forms were also found to be less stable than the enol forms.[238c,d] Selenovinylaldehyde (with a O−H···Se bridge) and selenothiovinylaldehyde (with a S−H···Se bridge), both having the CCC structure, are slightly favored over the other chelated structures. The second local minimum of the potential energy surface corresponds to the CCT structure stabilized by O···Se and S···Se interactions observed earlier by Minyaev and Minkin.[240] Due to the decrease of the relative strengths of H-bonding in Se and Te analogues, the most stable isomers are the CCT forms stabilized by X···Te interactions. The chelated structures have slightly lower energies.

Mó and co-workers[238b] showed in addition that substituents at the carbon atoms, particularly at the carbons linked with heteroatoms, have an important influence on the intramolecular H-bond and on electron delocalization and thus on tautomeric preferences in unsymmetrical systems. Independently, Fischer and Fabian[241] derived the same conclusion while investigating acetylacetone and its thio analogue at the same level of theory. The chelated *cis*-enolothione form has lower Gibbs free energy than the chelated *cis*-enethiolone form by 0.3 kcal mol^{-1} {G2(MP2)}, and the O−H···S hydrogen bond seems to be stronger than the S−H···O one. An analysis of the NICS indices calculated for the chelated enol isomers (Scheme 19) at the GIAO−RHF/6-31+G*//RB3LYP/6-311++G** level led the above authors to a conclusion contrary to the classical resonance and RAHB models,[11,200] that is, that there is no indication of electron delocalization in the chelated enol structures. The NICS values, which are around zero even for the transition state, are outside the range of typical aromatic structures (less than −3 ppm). According to the definition of NICS both derivatives are nonaromatic. However, quite a different conclusion can be derived on the basis of the HOMA indices estimated for the RB3LYP geometries, which are close to experimental ones.[241] All HOMA indices are positive and very different from zero, thus confirming electron delocalization in the cyclic structures. This

Scheme 20. Order of Energetic Stabilities[246] and HOMA Indices (B3LYP/6-31G)[184] for Three Stable Tautomers of β-Aminoacrolein**



suggests that the geometric HOMA index describes electron delocalization in RAHB tautomeric systems better than the magnetic NICS index because of the lack of any ring current in such systems.

β-Carbonylenamines are another class of unsymmetrical pentad tautomeric systems {O=C(R)−CH(R′)−C(R″)=N(R‴) ⇌ HO−C(R)=C(R′)−C(R″)=N(R‴) ⇌ O=C(R)−C(R′)=C(R″)−NH(R‴)}, in which three proton transfers, two 1,3 proton shifts (keto−enol and imine−enamine) and one 1,5 proton shift (enolimine−enaminone) occur. Various experimental results indicated that the enaminone form is favored in unsubstituted β-aminoacrolein (R, R′, R″, R‴ = H) as well as in most of its derivatives.[242] Crystalline β-aminoacrolein has a nonchelated open chain structure. This structure is also favored in polar solvents. In nonpolar solvents, the enaminone form chelated by the intramolecular H-bond is in equilibrium with the nonchelated open chain isomer with the chelated enaminone form being preferred. The chelated enaminone form is also dominant in the gas phase. Only for some α,β-diphenyl derivatives was the chelated structure of the enaminone form found to be favored in both the solid state and in solution.[243] In the case of 2-benzoylacetamidate and 2-benzoylacetamidine in ethanolic solution, the chelated enolimine forms, HO−C(Ph)=CH−C(OEt)=NH and HO−C(Ph)=CH−C(NH_2)=NH, respectively, are preferred instead.[244]

Semiempirical and ab initio studies,[245] enriched recently by the detailed theoretical conformational analysis of Buemi et al.,[246] showed that the chelated enaminone tautomer is the most stable form for unsubstituted β-aminoacrolein although the O−H···N bridge (RAHB) in the other chelated enolimine tautomer, which is less stable by about 7 kcal mol^{-1} at the B3LYP/6-31G** level, seems to be the strongest bridge. The strength of the O−H···N bridge is slightly greater than that of the O−H···O bridge in malondialdehyde. The open chain keto-imine form may be absent in the tautomeric mixture with ΔE_T about 15 kcal mol^{-1} at the same level of theory. Interestingly, the order of stabilities of the three tautomers follows that of the HOMA indices estimated for the B3LYP geometries (Scheme 20).

Dervatives of keto-hydrazone {O=C(R)−CH(R′)−N=NR″ ⇌ HO−C(R)=C(R′)−N=NR″ ⇌ O=C(R)−C(R′)=N−NR″H} can also form N−H···O or O−H···N bridges (RAHB) in the most stable chelated keto-hydrazo or azo-enol forms, respectively, as was shown by Gilli and co-workers[247] on the basis of compounds retrieved from the CSD.[182] A similar type of intramolecular H-bonding (N−H···O or O−H···N) was also found for nitrosoimines, which interconvert with more stable iminooximes or nitrosovinylamines {O=N−CH(R)−C(R′)=NR″ ⇌ HO−N=C(R)−C(R′)=NR″ ⇌ O=N−C(R)=C(R′)−NR″H}.[248] Depending on solvent polarity and temperature, a fast equilibrium between the chelated or open chain iminooxime and nitrosovinylamine structures was observed. Even in the solid state, there are examples of the chelated nitrosovinylamines with exceptionally strong intramolecular H-bonds with O···N distances of about 258 pm.[248c]

For 2-nitroethenol {O=CH−CH_2−$N^+(O^-)$=O ⇌ HO−CH=CH−$N^+(O^-)$=O ⇌ O=CH−CH=$N^+(O^-)$−OH} and 2-nitrovinylamine {HN=CH−CH_2−$N^+(O^-)$=O ⇌ H_2N−CH=CH−$N^+(O^-)$=O ⇌ HN=CH−CH=$N^+(O^-)$−OH}, Lammertsma and Bharatam[249] recently found that the ab initio {G2(MP2)} barriers calculated for the 1,5 proton transfer in the chelated structures are equal to 5 and 13.2 kcal mol^{-1}, respectively, and together with the short O···O and N···O distances, these indicate strong H-bonds in these molecules. The rotation barrier method (RBM) proposed by Buemi and Zuccarello[250] provided more information on the stabilities of various intramolecular H-bridges.

The symmetric N−H···N bridge in formazan (HN=N−CH_2−N=NH ⇌ H_2N−N=CH−N=NH ⇌ HN=N−CH=N−NH) studied by Buemi et al.[251] is weaker than the symmetric O−H···O bridge in malondialdehyde. The chelated and nonchelated structures of formazan were identified for its phenyl derivatives in various solvents.[252] It was shown that the intramolecular H-bond in the chelated structure of formazan is responsible for the hypsochromic effect of the UV absorption band. Chelated formazans are red and open chain formazans are yellow in solution. In the crystalline state, 1,5-diphenylformazan (PhHN−N=CH−N=NPh) has an open chain structure.[253] For unsymmetric 1,5-diphenyl-1,2,5-triazapentadiene (PhHN−N=CH−CH=NPh) in $CHCl_3$, an aprotic weakly polar solvent, the chelated form was found to be in equilibrium with the open chain structure, whereas in DMSO, a more polar aprotic solvent, only one open chain structure was present.[254]

DFT(B3LYP) studies using the 6-311++G(2df,2p) basis set performed for chelated pentad tautomeric systems containing the O−H···N (or N−H···O) and N−H···N bridges and the CH groups replaced by N atoms confirmed that the intramolecular H-bonding increases electron delocalization in the chelated pentad systems.[217] In all cases, the HOMA indices for tautomers with 1,5 proton transfer are positive and in the range 0.45−0.96. However, there is no direct linear relation between the geometric and energetic parameters as was observed for simple open chain malondialdehyde derivatives. Preferences in electron delocalization measured by the geometric parameter seem not to be parallel to tautomeric preferences measured by the energy of tautomerization (Tables 6 and 7).

5.2. Schiff Bases

The Schiff bases derived from substituted *ortho*-hydroxy aromatic aldehydes are a particular case of unsymmetric pentad systems (Scheme 8) in which the spacer between the tautomeric functions is a part of an aromatic ring. They have attracted considerable

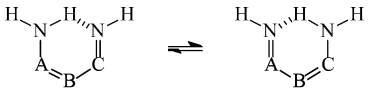
Table 6. HOMA Indices and Energies of Tautomerization (ΔE_T + ZPVE in kcal mol^{-1}) for Nitrogen Derivatives with the O−H···N Bridge Estimated at the DFT(B3LYP)/6-311+G(2df,2p) Level[217]

a b

A	B	C	HOMA(**a**)	HOMA(**b**)	ΔHOMA[a]	ΔE_T[a]
CH	CH	CH	0.638	0.800	0.162	−8.1
N	CH	CH	0.480	0.964	0.484	1.7
CH	N	CH	0.778	0.885	0.107	−8.7
CH	CH	N	0.756	0.709	−0.047	−10.3
N	N	CH	0.562	0.854	0.292	−3.8
N	CH	N	0.633	0.906	0.273	−0.3
CH	N	N	0.641	0.817	0.176	−6.8

[a] Differences between parameters for tautomer **b** and **a**.

Table 7. HOMA Indices and Energies of Tautomerization (ΔE_T + ZPVE in kcal mol^{-1}) for Nitrogen Derivatives with the N−H···N Bridge Estimated at the DFT(B3LYP)/6-311+G(2df,2p) Level[217]



a b

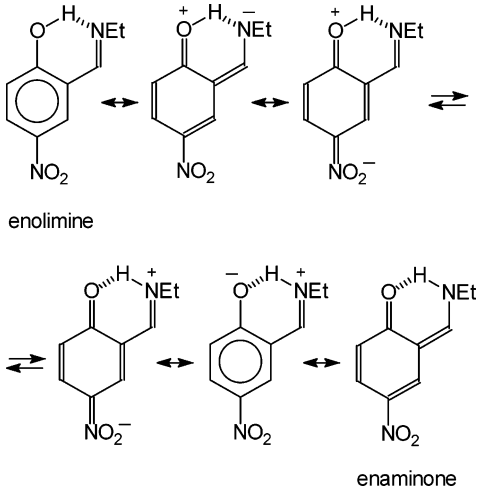
A	B	C	HOMA(**a**)	HOMA(**b**)	ΔHOMA[a]	ΔE_T[a]
CH	CH	CH	0.780	0.780	0	0
CH	N	CH	0.891	0.891	0	0
N	CH	N	0.857	0.857	0	0
N	N	N	0.569	0.569	0	0
N	CH	CH	0.720	0.891	0.171	−3.1
N	N	CH	0.837	0.757	−0.080	−1.5

[a] Differences between parameters for tautomer **b** and **a**.

attention from reaserchers because of their interesting photochromic, thermochromic, and solvatochromic properties, which may find diverse potential applications in the development of optical recording technology, molecular electronics, photonics, and computing.[8,203,255] Among the various proton transfers possible in the above Schiff bases, prototropy induced by intramolecular proton transfer from the hydroxyl oxygen to the imine nitrogen through the O−H···N hydrogen bond accompanying a π-electron configuration change was the most extensively studied.[79,203,256] These studies revealed that the photochromic, thermochromic, and solvatochromic properties of the Schiff bases originate mainly from the prototropic tautomerism between the enolimine (OH) and enaminone (NH) forms through the intramolecular O−H···N and O···H−N hydrogen bridges.[203,257] When the O···N distances in the Schiff bases are very small, the proton transfer is governed by the tunneling effect.[258]

Tautomeric equilibria in these Schiff bases depend strongly on various internal factors such as structure, substituents, and intramolecular H-bonding, as well as external factors such as temperature, light, solvent, and the presence of ions. For aromatic derivatives, the enolimine tautomer is usually more stable than the corresponding enaminone form, and the

Scheme 21. RAHB and Proton Transfer in 5-Nitro-*N*-salicylideneethylamine[262]



enaminone tautomer is favored for alkyl derivatives.[259] Substituents at the aryl rings seem to have insignificant effect on tautomeric equilibria. However, there are examples of some compounds that take only one form, either OH or NH, in the solid state and also of other compounds that exist as a mixture of both tautomers in nearly equal populations in crystals.[260] A similar situation was observed in solution. Some derivatives prefer only one tautomeric form, but others are an equilibrium mixture of both tautomers.[79,257,259,261] Tautomeric equilibria often depend on solvent polarity. Nonpolar and nonprotonating solvents shift the equilibrium toward the enolimine form, whereas the enaminone form is favored in polar solvents.

It was suggested by Gilli and co-workers,[200] that these Schiff bases are a case of synergism between the strength of H-bonding and the degree of π-electron delocalization. In some cases, resonance and inductive effects of electron-accepting substituents in the aryl groups increase the strength of the intramolecular H-bond. Krygowski and co-workers showed[262] that in the case of 5-nitro-*N*-salicylideneethylamine (Scheme 21), the nitro group is responsible for the spontaneous proton transfer in the molecule and also for the formation of a very strong intramolecular H-bond in the solid state, which probably has fully ionic character ($O^-\cdots H-N^+$). A consequence of this interaction is a remarkable deformation of the ring geometry, which leads to a considerable decrease in aromatic character of the ring measured by the HOMA index (0.732) as compared to *p*-nitrophenol (0.996) and salicylaldoxime (0.960). On the basis of the solid-state NMR results and the electron density maps, it has been suggested that the proton can probably occupy either of two positions within the $O^-\cdots H-N^+$ bridge.

When the strength of the H-bond in the above Schiff bases was analyzed in relation to π-electron delocalization, Krygowski and co-workers[263] selected the spacer built of five heavy atoms (O, C, C, C, N) and consisting of four bonds (two CC, one CO and one CN) between the H-bond donating and the H-bond accepting group. For this analysis, almost 50 molecular geometries retrieved from the CSD[182] were

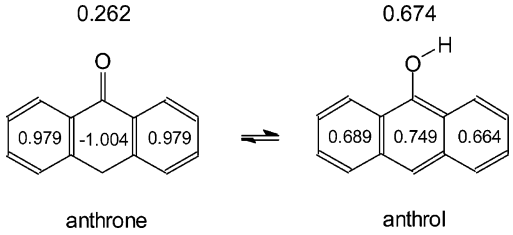
used, and the HOMA index was calculated. The large variation (0.05−0.65) found for the HOMA values indicates a significant and widely varying degree of π-electron delocalization in the spacer. However, comparison of the interatomic O···N distances, which depend on the H-bond strength, with the estimated HOMA indices, which measure π-electron delocalization, showed no dependence in a scatter plot of the delocalization of π-electrons and the H-bond strength. The most important factor that affects the π-electron delocalization in the spacer seems to be the substituent effect of the groups attached to the ring the bond of which is a part of the spacer. The largest HOMA values ($\geq$0.5) were observed for derivatives with substituents interacting strongly with the OH and C=N groups of the spacer.

A similar lack of dependence between the π-electron delocalization and the H-bond strength was observed by Krygowski and co-workers[264] for N-oxides of the Schiff bases. The variation of the HOMA as applied to the spacer built of six heavy atoms (O, C, C, C, N, O) by 0.2−0.6 units indicated significant changes in the π-electron delocalization. These variations, however, were not collinear with the variations of the H-bond energies. On this basis, it was suggested that the H-bond interactions did not affect the π-electron delocalization in the spacer. In turn, the positive NICS values calculated for model systems indicated the lack of aromaticity, that is, the absence of ring current, in these systems. Only replacement of the proton in the H-bond by a lithium cation in a model system increases significantly the HOMA value to 0.945 and decreases the NICS index to a negative value of −1.7, showing that the system so modified is slightly aromatic.

6. Tautomeric Moiety as Part of an Aromatic System

Aromaticity is an important structural factor, which, together to some extent with others such as functional group stability, intramolecular H-bonding, and various substituent effects, plays a principal role in tautomeric systems. Generally, the energies describing aromatic stability (e.g., RE) are considerably larger than typical absolute tautomerization energies. For simple aromatic hydrocarbons and heterocycles (e.g., benzene, pyridine, pyrimidine, imidazole, pyrrole), the RE values estimated on the basis of various experiments are between 30 and 50 kcal mol^{-1}.[11b,15d,e,k,121] Similar energies for stabilization of simple aromatics were recently predicted by Schleyer and Pühlhofer on the basis of the isomerization method.[265] Such large RE values in aromatic systems explain why in some cases, when a part of the tautomeric moiety (one function) is not included in the ring (according to the *exo*-mode), tautomeric preferences are not the same as in aliphatic derivatives.[5d,15e,k,266] In other cases, when the whole tautomeric moiety is included in the aromatic ring (according to the *endo*-mode), aromaticity plays a secondary role, and tautomeric equilibria depend on other internal or external factors. This kind of situation exists in azoles.[5d,106,158,267] To show a general picture of tautomeric equilibria in aromatic systems, we have chosen a few typical examples that are often used as model compounds to understand more complex proton transfer processes in biomolecules, particularly in the nucleic acids.

Scheme 22. HOMA Indices {B3LYP/6-311++G(2df,2p)} for Individual Rings and Whole Molecules of the Anthrone/Anthrol System[270]



6.1. Homo- and Heteroaromatics with an *exo* XH Group

A classical example of a homoaromatic system with an *exo* XH group is phenol, which displays keto−enol tautomerism.[15e,k] Although in most of the typical aliphatic open chain and cyclic keto−enol systems the keto form is favored, phenol prefers its enol form because the proton transfer from the hydroxy group to the aromatic carbon atom destroys the aromaticity of the ring and strongly destabilizes the keto form in comparison to the enol one. On the other hand, heteroaromatic compounds such as pyridines retain their aromatic character upon protonation, and thus amide−iminol tautomeric equilibria in hydroxypyridines are not so drastically shifted to the iminol form in comparison to aliphatic open chain and cyclic amide−iminol systems. Tautomerization energies in hydroxypyridines are not as high as in the case of phenol, and other energetically less important factors such as substituent effects and intra- and intermolecular H-bonding may determine tautomeric preferences.[5d,268]

For the unsubstituted phenol, intramolecular proton transfers corresponding to three prototropic rearrangements, that is, two 1,3 proton shifts and one 1,5 proton shift, are possible (Scheme 2). They lead to two identical 2,4-cyclohexadienones and one 2,5-cyclohexadienone, respectively. As early as 1972, Katritzky and co-workers[266a] estimated the aromatic resonance energy difference between tautomeric forms of phenol by considering only 2,4-cyclohexadienone for the keto form and using the tautomeric equilibrium constants for the enolization process in 2,4-cyclohexadienone and cyclohexanone (Scheme 3) in aqueous solution ($pK_T = -9.5 \pm 2.5$ and 5.4 ± 0.4, respectively). The value obtained (25 ± 5 kcal mol^{-1}) was close to that estimated for simple aromatic hydrocarbons. In this way, they confirmed quantitatively the higher stability of phenol attributed to its aromaticity than of the keto tautomer. In contrast to this result, for the anthrone ⇌ 9-anthrol system (Scheme 22), Kresge and separately More O'Ferrall and co-workers[269] confirmed earlier observations that anthrone, the keto form, is more stable than 9-anthrol, the enol form. Resonance stabilization of the keto form in this case comes from the central ring and the aromaticity of the two marginal rings. The

HOMA index of the central ring estimated for the B3LYP/6-311+G(2df,2p) geometries with six carbons and one oxygen taken into account decreases from a positive value of 0.749 in anthrol to a negative value of −1.004 in anthrone.[270] On the other hand, the HOMA indices of the marginal rings increase from 0.689 and 0.664 in anthrol to 0.979 in anthrone. However, the HOMA index estimated for the whole molecule of anthrone is 0.262, which is significantly lower than that of anthrol (0.674) indicating that in this case the aromaticity of individual rings may determine the tautomeric preference. The tautomeric equilibrium constant measured for the keto−enol interconversion ($pK_T = 2.10$ in aqueous solution)[269b] is not large, indicating that both forms can be observed experimentally.[271] The stable keto forms for hydroxynaphthalenes and hydroxylated naphthazarins were independently identified using various spectroscopic techniques such as IR and NMR.[272]

The three keto forms of phenol, although energetically unfavorable, are often an important intermediate in various organic reactions, for example, the oxidative metabolism of aromatic compounds, the electrophilic substitution of phenol, the Kolbe−Schmitt (*ortho* vs *para* carboxylation) and Reimer−Tiemann reactions.[273] Some interesting experiments were reported by Capponi and Gut,[274] who generated 2,4-cyclohexadienone by flash photolysis. Investigating the kinetics of 2,4-cyclohexadienone → phenol enolization in acidic and neutral aqueous solutions, they estimated the equilibrium constant ($pK_T = -13 \pm 1$) as being only slightly greater than that derived by Katritzky and co-workers from the RE estimation.[266a] Parallel experiments of Shiner et al.,[275] based on measurements of the gas-phase acidities and the heats of formation of both keto forms, suggested that the linearly conjugated dienone (2,4-cyclohexadienone) is more stable than the cross-conjugated one (2,5-cyclohexadienone) by a few kilocalories per mole. However, high-level ab initio calculations including HF, MP2, and B3LYP indicated a slightly higher stability for 2,5-cyclohexadienone than for 2,4-cyclohexadienone.[276] The two keto forms have higher energies than phenol by 16−19 kcal mol^{-1}, and the tautomeric equilibrium constant estimated for 2,4-cyclohexadienone → phenol enolization in the gas phase ($pK_T = -13 \pm 1$) is almost the same as that found in aqueous solution. This may suggest that solvation effects have no important influence on the keto−enol tautomerism in phenol.

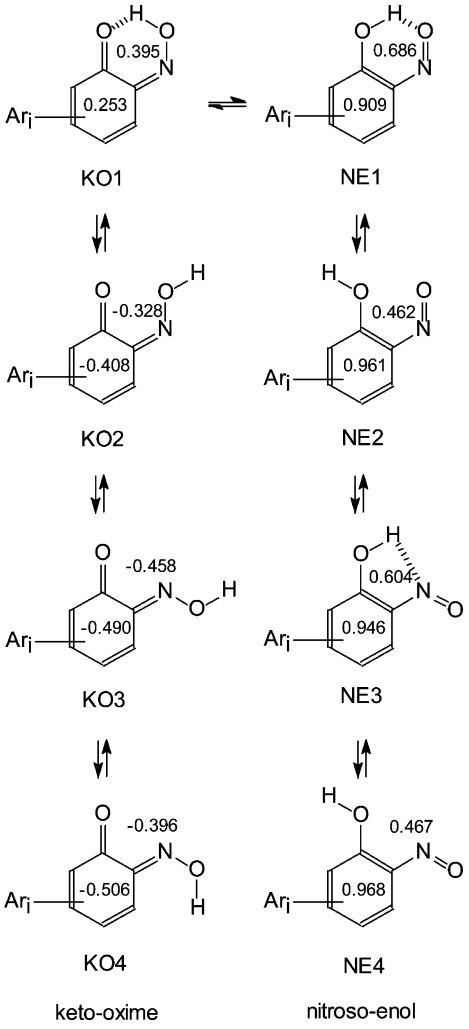
Considerably larger values of the relative energies were recently reported by Le et al.[277] for singly ionized phenol and its ionized keto tautomers. At the B3LYP/6-311++G** level, the energies of 2,4- and 2,5-cyclohexadienone radical cations were higher than that of ionized phenol by 35 and 32 kcal mol^{-1}, respectively. These values show that the ionized system evidently prefers the enol form, that is, phenol$^{+\bullet}$, just as the neutral system prefers phenol. This behavior is completely different from that observed for the acetaldehyde/vinyl alcohol pair: due to higher stability of functionality, acetaldehyde, the keto form, predominates for the neutral system. However, the large ionization energy difference favoring the enol form over the keto form changes the stability of both tautomers so that the enol radical cation is preferred for the ionized system. In the case of phenol, the difference in the ionization energies adds to the relative energy of the neutral forms in favor of the phenol form, which explains the increase of the relative stabilities of the ionized (radical-cationic) tautomers in comparison to the neutral ones.

Analyzing the geometric parameters for the neutral and ionized phenolic forms,[277] one finds no particular change in the HOMA indices estimated at the B3LYP level for the whole tautomeric conjugated system, the scaffold of which is built of seven non-hydrogen atoms, six carbons and one oxygen. The HOMA indices are negative for both the neutral and ionized keto forms showing strong localization of π-electrons, whereas they are highly positive for the aromatic neutral and ionized phenol isomers with values of 0.742 and 0.703, respectively. This observation indicates the great importance of aromaticity in the system in that even ionization does not significantly change electron delocalization.

The *ortho*-nitrosophenols (Scheme 23) are also interesting cases, which combine two systems, nitroso−oxime tautomerism and keto−enol tautomerism by a 1,5 proton shift. Formation of the intramolecular H-bond, similar to that in the pentad systems and Schiff bases discussed above, seems to facilitate tautomeric interconversion. However, there is some debate between the Kržan and Enchev groups on the tautomeric and conformational preferences for *ortho*-nitrosophenols in solution and in gas phase.[278] The discrepancies between the results obtained by these different laboratories may be a consequence of low energies of tautomerization and of isomerization and also of low energy barriers for proton transfer in the O−H···O bridge as well as for rotation around the single bonds. Only X-ray data in the solid state showed beyond doubt that *ortho*-nitrosophenols and 1-nitroso-2-naphthol exist as nonchelated (i.e., syn) oxime tautomers.[279]

For isolated structures of unsubstituted *ortho*-nitrosophenol ($Ar_i = H$), DFT(B3LYP)/6-311+G(2df,-2p) calculations indicated that only one among the keto-oxime isomers, the chelated structure (KO1), displays some electron delocalization, giving positive HOMA values for both cycles.[280] This structure, however, has a higher Gibbs free energy than the most stable chelated nitroso-enol form (NE1) by 3.2 kcal mol^{-1}. For the other nonchelated keto-oxime structures (KO2−KO4), the π-electrons are strongly localized. The HOMA values are negative for the O=CH−CH=N−OH moiety and also for the ring (Scheme 23). The Gibbs free energy values of the isomers KO2−KO4 are greater than that of the chelated nitroso-enol form (NE1) by more than 10 kcal mol^{-1}. On the other hand, in all of the nitroso-enol structures (NE1−NE4), the phenyl ring has strong aromatic character (HOMA ≥ 0.91). π-Electrons in the HO−CH=CH−N=O moiety are also delocalized (HOMA ≥ 0.46), even for the nonchelated structures (NE2−NE4). In the most stable NE1

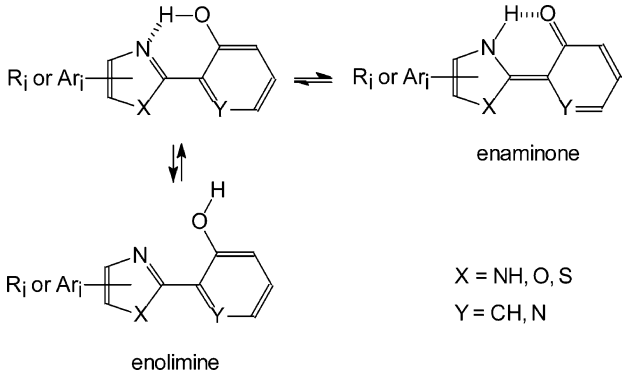
Scheme 23. Rotational Isomerism, Tautomeric Equilibria, and H−Bonding for *ortho*-Nitrosophenols and HOMA Indices {DFT(B3LYP)/6-311+G(2df,2p)} for the Parent Derivative (Ar_i = H)[280]



structure, resonance stabilization of the *exo*-cycle (HOMA 0.686) seems to come partially from the benzene ring (HOMA = 0.909). Exceptionally high stabilization is also exhibited by the HO−CH=CH−N=O moiety in the nonchelated NE3 structure (HOMA = 0.604), which has a Gibbs free energy only 2.6. kcal mol^{-1} higher than that of the NE1 structure. The other nitroso-enol structures (NE2 and NE4) have higher Gibbs free energies than that of the NE1 structure by 8.5 and 10.0 kcal mol^{-1}, respectively. The HOMA indices estimated for the quasi-ring in the KO1 and NE1 structures (0.395 and 0.686 in Scheme 23) can be compared with those for simple chelated pentad tautomers: glyoxal monooxime and nitrosovinyl alcohol, O=CH−CH=N−OH and HO−CH=CH−N=O (0.480 and 0.964 given in Table 6). This comparison indicates that generally, the phenyl rings in *ortho*-nitrosophenol tautomers decrease the RAHB effects in the quasi-rings. As was expected, the calculated magnetic NICS(*d*) indices confirm aromatic character only for the phenyl rings in the NE1−NE4 structures.

Enchev and co-workers, investigating other aromatic systems with N=O and OH groups, found that

Scheme 24. Rotational Isomerism, Tautomeric Equilibria, and H−Bonding in 2-(2-Hydroxyaryl)-azoles

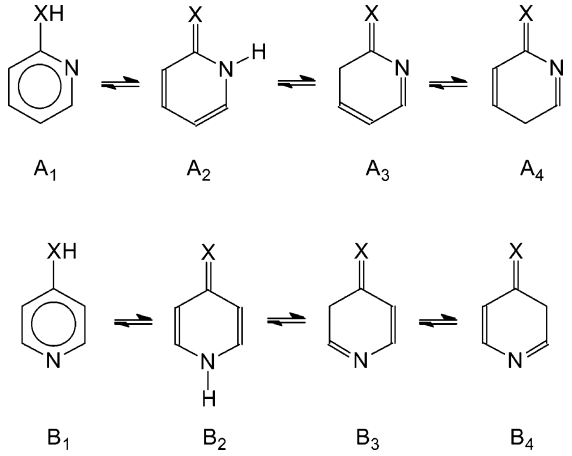


the symmetric monooxime of 1,2,3-phenalenetrione and of 1,2,3-indantrione exist exclusively as the oxime tautomer.[281] In the gas phase and in nonpolar solvents, they prefer the closed chelated structure of monooxime stabilized by intramolecular H-bonding, while in polar solvents and in the solid state, the open nonchelated rotamer stabilized by intermolecular H-bonding is favored. Similar behavior was found for the monooxime of acenaphthenequinone.[282]

2-(2-Hydroxyaryl)azoles are examples of substituted phenols (Scheme 24) in which keto−enol tautomerism in the hydroxyaryl group is combined with imine−amine tautomerism of the substituted azole. These derivatives may be classified as pentad tautomeric systems conjugated with aryl rings similar to the Schiff bases discussed above. Their tautomeric and conformational preferences are a consequence of aromaticity, intramolecular H-bonding, and solute−solvent interactions. Generally, in the gas phase and in neutral solutions, the closed chelated enolimine form with an intramolecular H-bond is the most stable, followed by the open nonchelated enolimine form, and finally by the closed chelated enaminone form with the intramolecular H-bond.[283] The aromatic character of the phenyl ring explains the higher stability of the enolimine than the enaminone form, which shows a higher degree of π-electron localization. In a polar solvent, the stability of tautomers depends on the ability of the solvent to form intermolecular H-bonds. For instance, the enaminone tautomer of 4,5-dimethyl-2-(2-hydroxyphenyl)imidazole was not detected in ethanol, whereas it is exclusively favored in neutral water.[283a]

Hydroxypyridines (X = O, Scheme 25) are the simplest hydroxyazines that exhibit more complex proton transfers than unsubstituted phenol. Three types of tautomerism, amide−iminol, enamine−imine, and keto−enol, are possible by 1,3 and 1,5 proton shifts. Hence, four tautomers can be distinguished for 2-hydroxypyridine (A_1−A_4) and for 4-hydroxypyridine (B_1−B_4). The interconversions $A_1 \rightleftharpoons A_2$ and $B_1 \rightleftharpoons B_2$ correspond to amide−iminol tautomerism, while $A_2 \rightleftharpoons A_3$, $A_2 \rightleftharpoons A_4$, $B_2 \rightleftharpoons B_3$, and $B_2 \rightleftharpoons B_4$ correspond to enamine−imine tautomerism, and $A_1 \rightleftharpoons A_3$, $A_1 \rightleftharpoons A_4$, $B_1 \rightleftharpoons B_3$, and $B_1 \rightleftharpoons B_4$ correspond to keto−enol tautomerism. Analogous tautomeric equilibria are possible for thiol (X = S) and amino (X = NH) derivatives. In the interconversions correspond-

Scheme 25. Tautomeric Equilibria in Hydroxypyridines (X = O), Thiolpyridines (X = S), and Aminopyridines (X = NH)[15k]



ing to keto−enol tautomerism, A_3 and A_4 are less stable than A_1, and B_3 and B_4 are less stable than B_1 due to great loss of aromaticity, just as in the case of the keto forms of phenol. In the interconversions corresponding to enamine−imine tautomerism, A_3 and A_4 are also less stable than A_2, and B_3 and B_4 are also less stable than B_2. These relative stabilities are independent of environment, and thus A_3, A_4, B_3, and B_4 very often are omitted in the tautomeric mixtures.

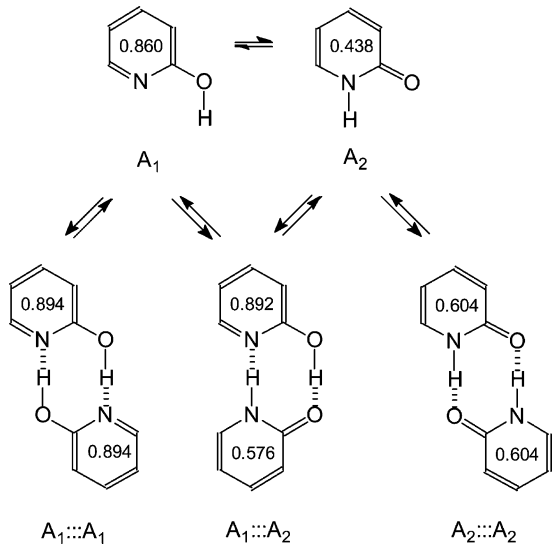
Searching for an explanation for tautomeric preferences in hydroxypyridines and their thiol and amino analogues, Katritzky and co-workers[266b−d] applied the same method for the RE estimation as mentioned above for phenol. They used tautomeric equilibium constants in aqueous solution for XH−pyridines and for the corresponding nonaromatic analogues and found that 2- and 4-pyridones (A_2 and B_2) are about 6−7 kcal mol^{-1} less aromatic than pyridine, the parent of both A_1 and B_1, and that their aromatic resonance energies are about 25 kcal mol^{-1}. A similar behavior was observed for thiol and amino derivatives, with a slightly greater energy difference between the 2- and 4-aminopyridines. Bird,[284] using the geometric I index of aromaticity, derived differences between the aromatic resonance energies for hydroxypyridine/pyridone systems as equal to 7.1 and 7.5 kcal mol^{-1} for 2- and 4-substituted derivatives, respectively, and to 5.9 kcal mol^{-1} for the 2-thiol/2-thione derivative. These values are in good agreement with experimental estimations made by Katritzky and co-workers for aqueous solutions.[266b−d] However, Schleyer and co-workers,[285] calculating the magnetic NICS(1) index for the 2-thiol derivative, found only a slightly negative value (−3.5 ppm) for the thione in comparison to the thiol form (−8.8 ppm) and pyridine (−10.1 ppm). On this basis, they inferred a lack of electron delocalization at the ring center of the thione form. This is in contrast with estimations by Katritzky and Bird who obtained 6 kcal mol^{-1} for the difference in the resonance energies of the 2-thiol and 2-thione forms and suggested that the thione form retains most of the aromaticity of pyridine. In turn, the HOMA indices estimated for tautomers of hydroxypyridines confirmed both some aromatic character for pyridones A_2 and B_2 with positive HOMA values >0.4 and also the lack of electron delocalization in the less stable keto forms A_3, A_4, B_3, and B_4, all with negative HOMA values. 4-Pyridone seems to be less delocalized than 2-pyridone, the difference in the HOMA favoring 2-pyridone by about 0.1 as described by Katritzky[266b−d] and Bird.[284] On the basis of acidity measurements in DMSO, Bordwell et al.[286] found a difference of 3 kcal mol^{-1} between 4- and 2-pyridone, which they attributed to differences in electron delocalization.

The position of the tautomeric equilibrium between the hydroxy and the oxo forms in hydroxypyridines depends strongly on the medium and on pyridyl ring substituents.[5d,15e,k,88f,268,287] The hydroxy form is preferred in the gas phase for both derivatives. For 2-hydroxypyridine, two conformations are possible for the OH group, but the only conformer detected was the syn conformer, in which the hydrogen atom of the OH group can interact intramolecularly with the heteroatom. For both derivatives, the oxo form is favored in both apolar solvents (e.g., CCl_4 and cyclohexane) and polar solvents (e.g., chloroform, acetonitrile, ethanol, and water). The contribution of the oxo form increases with increasing solvent polarity. In the solid state, both hydroxypyridines exist exclusively in the oxo form and dimerize.[288] For ionized hydroxypyridine/pyridone systems, the question of whether 2-hydroxypyridine exists as the "pure" hydroxy radical cation or, alternatively, as a mixture of both the hydroxy and the oxo radical cations is not yet resolved.[289]

The results of quantum-chemical calculations used for estimations of the relative energies in hydroxypyridines depend strongly on the level of calculations, including such factors as, for example, the basis set, zero-point vibrational energy, and electron correlation. Some calculations show the oxo instead of the hydroxy form as the favored tautomer in the gas phase. Those that indicate the hydroxy form usually overestimate its stability. The "best" theoretical relative energies, that is, those close to the values obtained from experiment, have, surprisingly, been found at the semiempirical AM1 level as well as at the ab initio HF/6-31G**//HF-3-21G and QCISD/6-31+G**//HF/6-31G** levels.[267,290] Similar discrepancies in theoretical results were also observed for the 2-thiol derivative and were summarized recently.[285,291] Energy differences between tautomers of the amino derivatives are considerably larger in favor of the amino form in the gas phase. Therefore, the computed tautomeric preferences depend less on the level of calculations.[292] Only for a strong electron-withdrawing substituent at the *exo* nitrogen is the imino form favored.[158,292,293]

Due to the importance of tautomerization and H-bonding for specific nucleic bases in the DNA mutation process, chemists have investigated in some detail the question of self-association in cyclic dimers and the interactions of hydroxypyridines and their thiol and amino derivatives with other molecules.[291,292,294] These interactions increase electron delocalization in the associated molecules. For instance, the HOMA index (Scheme 26) estimated for

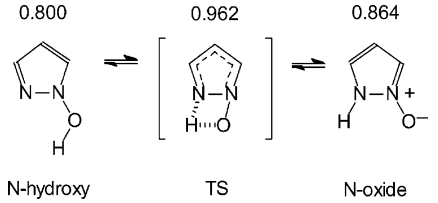
Scheme 26. Variations of HOMA Indices (HF/6-31G) When Going from Monomers of 2-Hydroxypyridine/2-Pyridone System to Their Dimers**



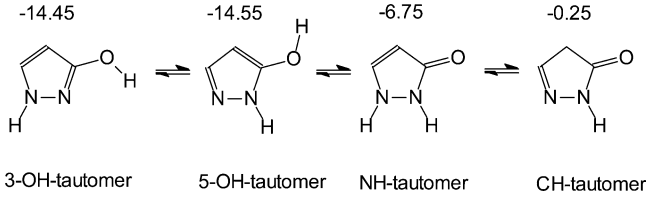
the HF/6-31G** geometries[279a] and including all seven conjugated non-hydrogen atoms is 0.438 for 2-pyridone, the iminol form A_2, and is significantly greater for the homodimer (A_2:::A_2, 0.604). The 2-pyridone HOMA index also increases, though by a smaller amount, in going to the heterodimer with 2-hydroxypyridine (A_1:::A_2, 0.576). The increase of electron delocalization upon dimerization for the more aromatic 2-hydroxypyridine, the amide form A_1, is less remarkable, being from 0.860 for the monomer A_1 to 0.894 and 0.892 for the dimers A_1:::A_1 and A_1:::A_2, respectively. The change in electron delocalization upon excitation is also interesting. For instance, the HOMA index estimated for the geometry of 2-aminopyridine homodimer optimized at the MP2/6-31G** level[294b] increases only slightly when going from the ground state (0.926) to the lowest $\pi\pi^*$ singlet excited state (0.929). On the other hand, the imino tautomer of 2-aminopyridine, i.e., 1,2-dihydro-2-iminopyridine, forms a homodimer related to that of 2-aminopyridine by a double proton transfer, but the change in the HOMA index estimated in the same way as above for going from the ground state to the lowest $\pi\pi^*$ singlet excited state of the imino tautomer homodimer is exceptionally large, going from 0.777 for the ground state to 0.944 for the excited state. Comparison of the results obtained for the excited state of the homodimers show that electron delocalization seems to be greater for the imino than for the amino homodimer. This observation may help in better understanding the DNA mutation process, which may take place in the excited state.

Chemists have also concentrated particularly on the hydroxyl derivatives of azoles. In such derivatives, the proton may be shifted from the *exo*-OH group to the ring atom. Depending on the position of the OH group, proton transfers to either the carbon or the nitrogen atoms may be possible, just as in phenols and hydroxypyridines. In the case of 1-hydroxypyrazole (Scheme 27), the proton may be transferred from the OH group to the nitrogen atom by a

Scheme 27. HOMA Indices (MP2/6-31G) for 1-Hydroxypyrazole Tautomers and Its Transition State**



Scheme 28. NICS Indices (HF/6-31+G*//MP2/6-31G) for 3(5)-Hydroxypyrazole Tautomers[298]**



1,6 proton shift to form pyrazole *N*-oxide. All computational and experimental data are consistent with the predominance of 1-hydroxypyrazole.[5d,295] The hydroxy form has lower energy than the N-oxide by 16 kcal mol^{-1} at the MP2/6-31G** level, and the energy barrier separating 1-hydroxypyrazole and the transition state is of approximately the same height (55 kcal mol^{-1}) as those for open chain triad systems.[295] This tautomeric preference does not correspond to electron delocalization. Proton transfer from the OH group to the ring nitrogen does not reduce the aromaticity of pyrazole *N*-oxide as it does in pyridones. The HOMA index estimated for the geometry optimized at the MP2/6-31G** level and considering all six non-hydrogen atoms is actually slightly greater for the less stable N-oxide (0.864) than for the favored 1-hydroxypyrazole (0.800). Both values of HOMA are typical for substituted pyrazoles.[15d] For the transition state, there is a complete electron delocalization (HOMA 0.962) just as for simple triad systems. The difference found between the tautomeric preference (1-hydroxypyrazole) and the preference in electron delocalization (pyrazole *N*-oxide) suggests that the stability of functionalities in 1-hydroxypyrazole may play a more important role than electron delocalization in pyrazole *N*-oxide.

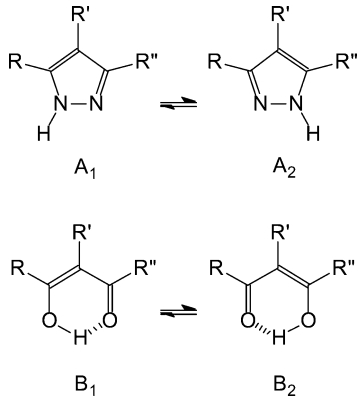
Tautomeric equilibria in 3(5)-hydroxypyrazole are more complex than in 1-hydroxypyrazole because there are two mobile protons and three atoms (oxygen, nitrogen, and carbon) on which the protons may reside. Various 1,3 and 1,5 proton shifts are thus possible, producing amine−imine interconversions as in pyrazole, keto−enol interconversions as in phenol, and amide−iminol interconversions as in hydroxypyridine. At least four tautomers, two OH (3- and 5-hydroxypyrazole) forms, one NH (4-pyrazolin-3-one) form, and one CH (2-pyrazolin-5-one) form can be distinguished for 3(5)-hydroxypyrazole (Scheme 28). This compound seems to be the simplest of all hydroxypyrazoles but is one of the most difficult to synthesize and to investigate experimentally. Therefore, only ab initio calculations were available. Since the differences in the energies of these tautomers are not very large, ab initio results depend strongly on

the level of calculations, and it is not surprising that inconsistent conclusions were reported at first.[296] Comparing various results, Luque et al.[297] found that the computed difference in stabilities between the hydroxy and keto forms is particularly sensitive to electron correlation effects. Taking this fact into account, Yranzo et al.[298] recently used the MP2 method to study the tautomeric equilibria in the 3(5)-hydroxypyrazole system as well as the aromatic character of the four tautomers. Using the 6-31G** basis set, they showed that the 3-OH-tautomer of 3-hydroxypyrazole with the hydrogen of the OH group pointing to the nitrogen is the most stable tautomer in the gas phase at 298.15 K. 2-Pyrazolin-5-one, the CH-tautomer, has a higher Gibbs free energy by only 0.7 kcal mol^{-1}. The Gibbs free energies of the next less stable tautomers, 5-hydroxypyrazole, the 5-OH-tautomer, and 4-pyrazolin-3-one, the NH-tautomer, differ from the most stable tautomer by 3.2 and 10.5 kcal mol^{-1}, respectively. This order of stabilities was compared with the order of aromaticity. The HF/6-31+G* calculations of the NICS indices for geometries optimized at the MP2/6-31G** level revealed that the thermodynamic stability order (3-OH > CH > 5-OH ≫ NH) is not the same as the NICS index order (5-OH ≈ 3-OH > NH > CH). The most stable 3-hydroxypyrazole (NICS = −14.45) is slightly less aromatic than 5-hydroxypyrazole (NICS = −14.55) showing a higher Gibbs free energy. Both OH forms are less aromatic than the unsubstituted pyrazole (NICS = −14.95). Just as was found for pyridines, 2-pyrazolin-5-one, which has a comparable Gibbs free energy to the 3-OH form, is not aromatic according to the NICS definition (NICS = −0.25). This simple comparison of the thermodynamic and magnetic parameters indicates that there is no linear relation between them.

6.2. Heteroaromatics with an *endo* —HN—(CH)$_n$=N— Moiety

Many heteroaromatics such as simple azoles (e.g., pyrazoles, imidazoles, triazoles, tetrazoles) and condensed systems (e.g., purines) contain the tautomeric moiety —HN—(CH)$_n$=N— (n = 0, 1, 2, etc.) completely included in the ring according to the *endo* mode. Therefore, the proton transfer from the amino to the imino nitrogen atom, similar to that in acyclic amidines, is always accompanied by migration of the ring π-electrons (see Scheme 1). The other proton transfer to the carbon atom usually leads to highly unstable structures that in general are not considered in the tautomeric mixture.[5d] The exceptionally high aromaticity of unsubstituted azoles in comparison to other five-membered heterocycles containing oxygen or sulfur was well described by various aromaticity parameters.[15,299] Krygowski and co-workers[300] showed that only particular *exo*-substituents may drastically decrease the aromaticity descriptors of azoles, even giving negative HOMA values. Substituents at the carbon atoms also influence amine−imine tautomeric equilibria. In most cases, the equilibria were investigated experimentally because the energies of tautomerization are not very high.[5d,24b,d] A large collection of ^{15}N NMR parameters for 420 azoles was published by Claramunt, Elguero, and their co-workers.[301] GIAO calculations of absolute shieldings and their relationship with experimental chemical shifts were reviewed by Alkorta and Elguero.[302]

Scheme 29. Comparison of Annular Tautomerism in *N-H*-Pyrazoles and Chain Tautomerism (with RAHB) in the Enolone Form of β-Dicarbonyl Compounds[304]

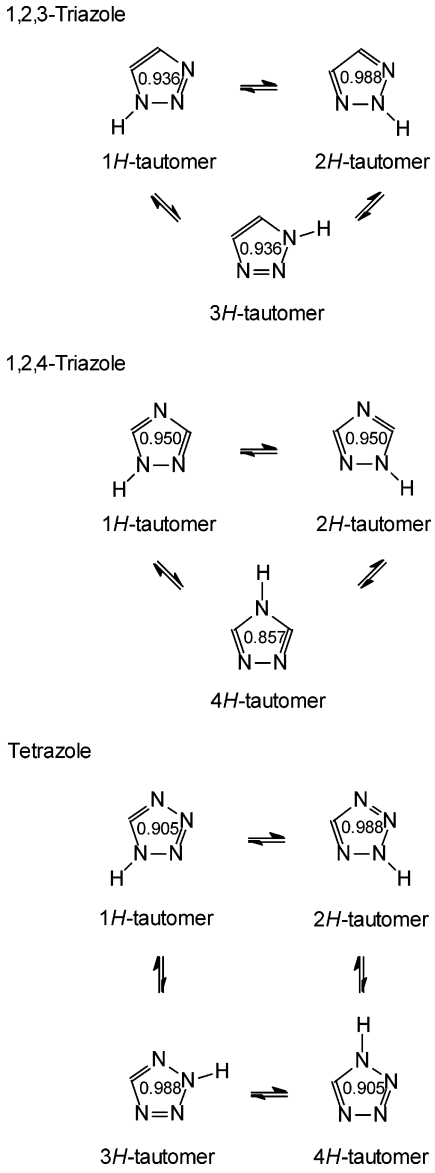


Due to the symmetry of the system, the two tautomers of the unsubstituted *N-H*-pyrazole are identical and the energy of tautomerization is equal to zero. This behavior may be easily destroyed by substitution at the carbon atoms.[5d,303] An interesting relationship for substituent effects was found by Elguero and co-workers.[304] Comparing annular tautomerism in *N-H*-pyrazoles with tautomerism in the enolone form of β-dicarbonyl compounds (Scheme 29), they proved that when substituents R, R′, and R″ favor one of the two tautomers in pyrazoles (e.g., A_1), the same type of tautomer (B_1) is favored in the enolone forms. A good linear relationship was proposed between the energies of tautomerization calculated at the AM1 level for these two systems. This relationship confirms (i) similarities in the transmission of the substituent effects, (ii) similarities in the proton transfer, that is, both are by a 1,5 proton shift, and (iii) similarities in π-electron conjugation. It also explains some differences in the transmission of substituent effects in azines (six-membered rings) and in azoles (five-membered rings).[5d]

Depending on the environment, proton transfers in pyrazoles may be of differing natures. In the solid state, trimers with strong H-bonds were observed, for which a triple proton transfer with tunneling effects was proposed.[305] The intramolecular proton transfer between two nitrogen atoms, even though theoretically possible in gaseous *N-H*-pyrazole, is probably forbidden since it must overcome a high energy barrier (47 kcal mol^{-1} by B3LYP/6-31G*).[13] The mechanism of tautomerization is probably intermolecular and the proton transfer occurs in dimers, trimers, or tetramers. Molecules of a solvent, an acid, or a base may reduce the barrier to as low as just a few kilocalories per mole by participating in the proton transfer.[306]

The unsubstituted imidazole also contains two nitrogen atoms like pyrazole, but they are separated by a CH group.[5d] This structural difference has no important effect on the aromaticity of the ring and on the energy of tautomerization. The HOMA index

Scheme 30. HOMA Indices (B3P86/6-311G) for Triazole and Tetrazole Tautomers**



of imidazole (0.918) is almost the same as that of pyrazole (0.922).[299b] The two tautomers of imidazole are identical, and the energy of tautomerization is equal to zero. The only difference is in proton transfer, which in imidazole occurs by a 1,3 proton shift as in acyclic amidines. Depending on their electronic properties and on interactions with the atoms of the —NH—CH=N— moiety, substituents can shift tautomeric equilibria and change the tautomeric preference from one to the other tautomer.[5d,267b,c,307] Among substituted imidazoles, 4(5)-methylimidazole was the most frequently studied as a model compound for understanding tautomeric equilibria in histamine and histidine.[297,308] The proton transfer reactions in 4(5)-methylimidazole in comparison to histamine were recently reviewed.[26b]

The compounds shown in Scheme 30, that is, 1,2,3- and 1,2,4-triazoles, which possess three nitrogens in the ring and one acidic proton, which may be transferred from one nitrogen to the other by a 1,3 or 1,5 proton shift similar to that in imidazole and pyrazole, respectively, are interesting cases.[5d,24b,d] At least three tautomers are possible, among which two forms (1*H*- and 3*H*-tautomers for 1,2,3-triazole, and 1*H*- and 2*H*-tautomers for 1,2,4-triazole) are identical. All of them are aromatic since the HOMA indices estimated for the geometries of all tautomers optimized at the DFT(B3P86)/6-311G** level[309] are highly positive (>0.85). The same holds for tetrazole. However, 2*H*-1,2,3-triazole (HOMA = 0.988) exhibits a slightly greater electron delocalization than 1*H*-1,2,3-triazole (HOMA = 0.936). The difference between electron delocalization of 1,2,4-triazole tautomers is a little larger (HOMAs of 0.950 and 0.857 for the 1*H*- and 4*H*-tautomer, respectively). These values for electron delocalization seem to be parallel to energetic stabilities in the gas phase. In solution and in the solid state, additional intermolecular interactions change this energetic behavior.

The 2*H*-tautomer is the most stable form in the gas phase for 1,2,3-triazole, whereas in solution the more polar 1*H*-tautomer becomes the most stable species, and in the solid state 1,2,3-triazole exists as a 1:1 mixture of the 1*H*- (+ 3*H*-) and 2*H*-tautomers.[310] Rauhut[311] recently performed calculations treating double proton transfer in homo- and heterodimers of 1,2,3-triazole and found very low energy barriers. 1,2,4-Triazole exists only as the 1*H*-tautomer; however, Elguero and co-workers found examples of 3(5)-substituted 1,2,4-triazoles, to wit, the halogeno derivatives, which prefer the 4*H*-tautomer.[312] In other cases of C-substituted triazoles, tautomeric equilibria are also very complex.[5d,313] Benzotriazole, for example, exists in the gas phase at 0 K as the 2*H*-tautomer, but with increasing temperature its population decreases in favor of the 1*H*-tautomer, which is the form exclusively observed in the solid state and in solution.[24d,314]

Tetrazole contains four nitrogens and one acidic proton, which may be transferred from one nitrogen to the other by a 1,3 or 1,5 proton shift just as in triazoles (Scheme 30).[5d] Four tautomers are possible, among which the pairs 1*H*-, 4*H*- and 2*H*-, 3*H*- are identical, and thus only two tetrazole forms, the 1*H*- and 2*H*-tautomers, are usually considered in the literature. Their population depends strongly on the medium. In the solid state, tetrazole exists exclusively as the 1*H*-tautomer.[315] Two forms, the 1*H*- and 2*H*-tautomers, coexist in solution.[316] The population of the more polar 1*H*-tautomer increases with an increase of solvent polarity. In nonpolar solvents (ϵ < 7) and in the gas phase, the 2*H*-tautomer seems to be favored,[317] although microwave experiments in the gas phase indicated the 1*H*-tautomer as the most stable.[318] The seemingly strong temperature dependence of the population ratio of the two tautomers in the gas phase[319] may provide a partial explanation for these facts.

A complete analysis of electron delocalization and of aromaticity in unsubstituted and C-substituted tetrazoles was recently performed by Sadlej-Sosnowska,[320] who calculated the geometric (I_5, and HOMA), the energetic (ASE for a homodesmic reaction), and the magnetic (NICS) parameters estimated at the B3LYP/6-311++G** level. For most derivatives studied, the descriptors of aromaticity are larger

Table 8. Energy of Tautomerization (ΔE_T in kcal mol^{-1})[a] and Differences between Aromaticity Descriptors (ΔI_5, ΔHOMA, ΔASE in kcal mol^{-1}, ΔNICS in ppm)[a] Estimated (B3LYP/6-311++G) for C-Substituted Tetrazoles[b]**

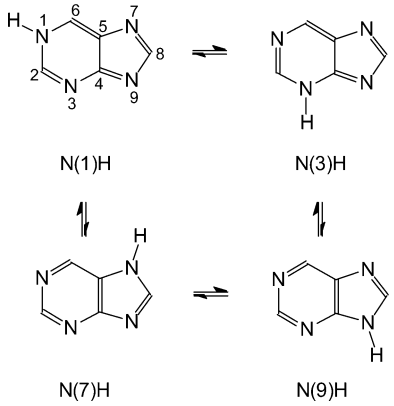
group	ΔE_T	ΔI_5	ΔHOMA	ΔASE	ΔNICS
NH_2	−3.62	15.77	0.171	13.58	−0.73
OMe	−0.94	18.55	0.158	15.14	−1.83
Me	−2.65	12.88	0.126	8.52	−0.63
H	−2.91	14.75	0.135	8.58	−0.13
F	−5.24	20.50	0.189	21.78	−2.06
Cl	−3.56	15.80	0.142	21.28	−1.25
Br	−3.02	15.15	0.137	20.74	−1.14
CN	−3.89	6.65	0.074	10.68	−0.22
NO_2	−3.00	10.74	0.087	18.17	−1.74
BH_2	−1.23	−7.69	−0.021	6.87	−0.39

[a] Differences between parameters estimated for 2*H*- and 1*H*-tautomer. [b] According to the literature data.[320]

for the 2*H*-tautomer than for the 1*H*-tautomer (Table 8), indicating higher aromaticity of the former tautomer. One exception was observed for the BH_2 group, for which only the energetic (ASE) and the magnetic (NICS) parameters are larger for the 2*H*-tautomer. This general order of aromaticity follows the energetic stabilization. For all derivatives, the 2*H*-tautomer is more stable than the 1*H*-tautomer. However, substituent effects on the respective aromaticity descriptors are not parallel. The order of the thermodynamic ΔE_T values (F, CN, NH_2, Cl, Br, NO_2, H, Me, BH_2, OMe) is completely different from that of the energetic ΔASE values (F, Cl, Br, NO_2, OMe, NH_2, CN, H, Me, BH_2). The orders of the geometric ΔI_5 (F, OMe, Cl, NH_2, Br, H, Me, NO_2, CN, BH_2) and ΔHOMA values (F, NH_2, OMe, Cl, Br, H, Me, NO_2, CN, BH_2) are almost the same, but completely different from that of the magnetic ΔNICS values (F, OMe, NO_2, Cl, Br, NH_2, Me, BH_2, CN, H) and from that of the energetic ΔASE values. Interestingly, only fluoro, the smallest substituent, takes the first place in each order indicating the greater variations of all parameters when going from the 1*H*- to the 2*H*-tautomer. The BH_2 group often takes the last place. Other substituents change their position in the ordering. On the basis of these observations, it was concluded that no one-dimensional ordering for tautomeric preferences and electron delocalization is possible in C-substituted tetrazoles.

The molecule of purine (consisting of fused pyrimidine and imidazole rings) contains one acidic hydrogen and four nitrogens. Therefore, at least four tautomers are possible, where the proton may be transferred by 1,3, 1,5, and 1,7 proton shifts (Scheme 31). Two of them, the N(1)H and N(3)H tautomers, are highly disfavored, and they are usually absent in the tautomeric mixture.[5d] Two others, the N(7)H and N(9)H tautomers, possess comparable stabilities, and the tautomeric preference depends strongly on the medium. The N(7)H tautomer is favored in the solid state.[321] In aqueous solution, purine seems to exist as a mixture of the N(7)H and N(9)H forms with a slight predominance of the N(7)H tautomer.[5d,322] The N(9)H tautomer is preferred in solvents of medium polarity such as DMSO.[323] In the gas phase and in nonpolar solvents, the N(9)H form is dominant.[324] The relative energy estimated at the MP2/6-31G* level is 3.9 kcal mol^{-1}.[325] In the pyrimidine, imidazole, and the whole condensed purine system, electron delocalization measured by the HOMA index estimated for the MP2/6-31G* geometries[325] is also slightly higher in the N(9)H (0.963, 0.857, and 0.906, respectively) than in the N(7)H tautomer (0.951, 0.843, and 0.892, respectively). Tautomeric and electron delocalization preferences are parallel. Association of the N(7)H form, which is favored in the solid state,[321] and formation of H-bonds increase electron delocalization, the HOMAs rising to 0.986, 0.919, and 0.952, respectively. Substitution of purine at the carbon atoms, particularly by groups that can participate in tautomeric interconversion, leads to more complex tautomeric equilibria and to other tautomeric preferences than those found in unsubstituted purine.[326]

Scheme 31. Tautomeric Equilibria in Purine[5d]



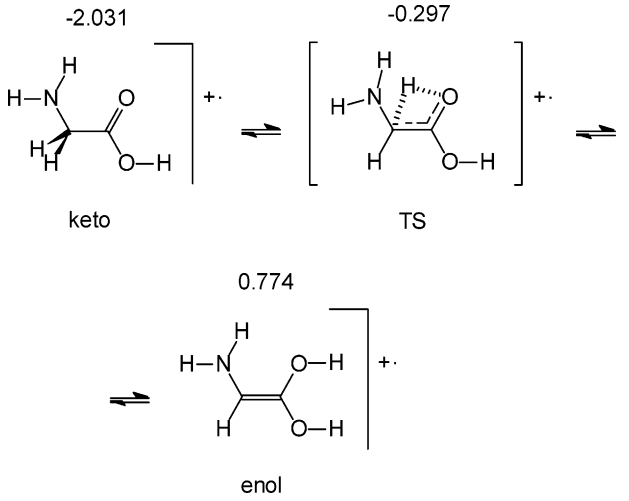
7. Tautomeric Equilibria in Simple Natural Products

The same types of prototropic tautomerism that take place in simple organic compounds and the same internal and external effects that affect tautomeric equilibria also occur in natural products. However, proton-transfer reactions are often more complex, because even such simple biomolecules as amino acids, α-keto acids, bioamines, pyrimidine bases, and purine bases contain more than two functionalities. These functionalities may participate directly in the tautomeric interconversion or may interact as substituents with the tautomeric moiety. The interactions depend strongly on the structure. In simple flexible open chain structures, stabilities of functionalities, intramolecular H-bonds, or both often determine tautomeric preferences. In rigid cyclic structures, aromaticity and *exo*-substituents seem to play the principal role.

7.1. Acyclic Conjugated Systems

The most commonly studied keto−enol tautomerism occurs even in the simplest amino acid, glycine, $H_2NCH_2COOH \rightleftharpoons H_2NCH{=}C(OH)_2$, just as in carboxylic acids $RCH_2COOH \rightleftharpoons RCH{=}C(OH)_2$. Although formation of the zwitterionic form ($^+H_3N{-}CH_2{-}COO^-$) is the most important proton transfer process in glycine in aqueous solution, glycine in the gas phase exists solely in the neutral form ($H_2N{-}CH_2{-}COOH$)

Scheme 32. HOMA Indices (B3LYP/6-31++G) Estimated for Ionized Tautomers of Glycine and Its Transition State**

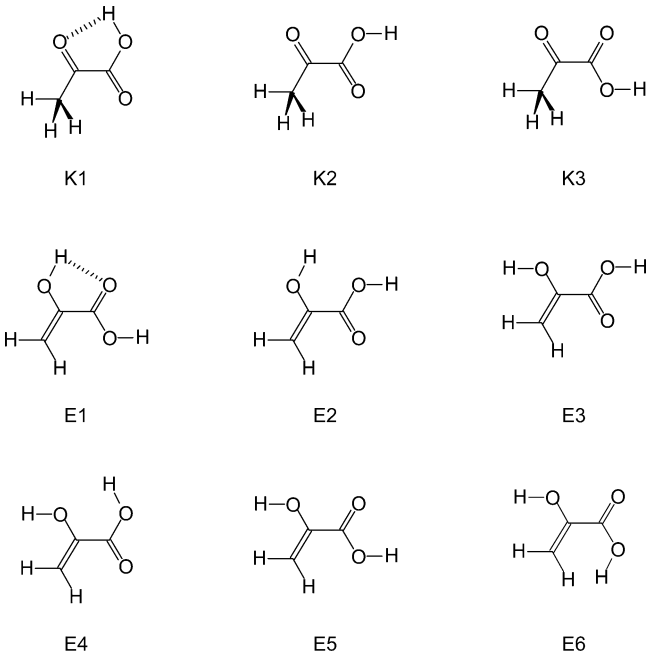


and the formation of the zwitterionic form is not possible.[327] The main reason for this behavior is a substantial difference in the acidity−basicity scales in water and in the gas phase.[328] The zwitterionic form can be formed in the gas phase only in the presence of a stabilizing agent, such as another amino acid molecule, water molecules, an alkali cation, a proton, or an excess electron.[329]

The enol form of glycine {$H_2N-CH=C(OH)_2$} can be generated in the gas phase by neutralization of the corresponding radical cation formed by dissociative electron ionization of isoleucine or phenylalanine.[330] Bertran and co-workers[331] showed by B3LYP/6-31++G** calculations performed for radical cations that the enol form of glycine has lower Gibbs free energy than its keto form by 24 kcal mol^{-1}. The large energy barrier for keto → enol interconversion (39 kcal mol^{-1})[331] also explains why the keto glycine radical cation does not isomerize to the more stable enol radical cation. In turn, the enol radical cation does not isomerize to the keto radical cation but instead primarily loses H_2O.[330] This energy behavior is similar to that found for the acetaldehyde/vinyl alcohol system.[131] A similar situation also occurs for electron delocalization as measured by the HOMA index (Scheme 32). The values of HOMA (B3LYP/6-31++G**) estimated for the CCO fragment are negative for the ionized keto glycine (−2.031) and for the transition state (−0.297). The HOMA value is positive only for the most stable glycine enol radical cation (0.774), which displays an exceptionally strong electron delocalization just as does the vinyl alcohol radical cation.

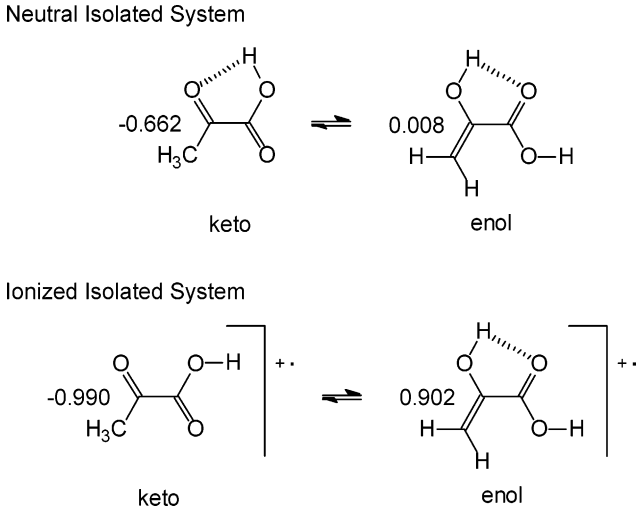
Keto−enol tautomerism is also possible in α-keto acids.[332] For instance, although enolpyruvate {$CH_2=C(OH)COO^-$} has higher energy than its tautomeric ketopyruvate (CH_3COCOO^-) form, it is the substrate for reactions catalyzed by pyruvate kinase, pyruvate carboxylase, and transcarboxylase.[31a−c] Enolpyruvate was also found to be the reactive component in the first step of the Shikimic acid pathway through which bacteria, plants, and fungi synthesize aromatic compounds.[32] Recently recorded FT-IR spectra for α-keto pyruvic acid and quantum-chemical calculations

Scheme 33. Thermodynamically Stable Keto and Enol Structures of Pyruvic Acid[333]



performed in parallel using the HF, MP2, and DFT-(B3LYP) methods with various basis sets revealed that among three stable keto and six stable enol structures at least four isomers, three keto (K1, K2, and K3) and one enol (E1), are present in solution (Scheme 33).[333] The population of the intramolecularly H-bonded enol form (E1) in the mixture varies when proceeding from CCl_4 to other nonpolar solvents. It increases in CH_2Cl_2, a weak H-bond donor solvent, and decreases in benzene, a weak H-bond acceptor solvent. Regardless of solvent properties, in each case the intramolecularly H-bonded keto structure (K1) is favored. For neutral isolated molecules in the gas phase, the intramolecularly H-bonded enol form (E1) has a higher energy than the most stable keto form (K1) by 7 kcal mol^{-1}. The stability order for the stable keto and enol structures is K1 > K2 > K3 > E1 > E2 > E3, E4, E5 > E6. Although the difference between the energies of K1 and E1 seems to be exceptionally high in the gas phase, it was well documented for arylpyruvic acids that some solvents (e.g., DMSO) strongly influence keto−enol tautomeric equilibria in favor of the enol form.[334] The enol form of pyruvic acid was also identified in an IR spectrum of the pure liquid phase of the α-keto acid.[335] In the gas phase, the enol form can be neglected in the tautomeric mixture, and only three keto rotamers (K1, K2, and K3) need to be considered.[336] For the ionized pyruvic acid system, the situation is similar to that for the acetaldehyde/vinyl alcohol pair. The enol E1 radical cation is the most stable structure among all keto (K1−K3) and enol isomers (E1−E6) considered.[337] The energy difference between the most stable keto K2 and the most stable enol E1 isomers is equal to about 7 kcal mol^{-1} at the B3LYP/6-31++G** level. The HOMA indices estimated at the B3LYP/6-31++G** level for the CCO fragment are negative for the neutral keto and enol forms and also for the ionized keto form (Scheme 34). The

Scheme 34. HOMA Indices (B3LYP/6-31++G) for Neutral and Ionized Keto and Enol Forms of Pyruvic Acid[337]**



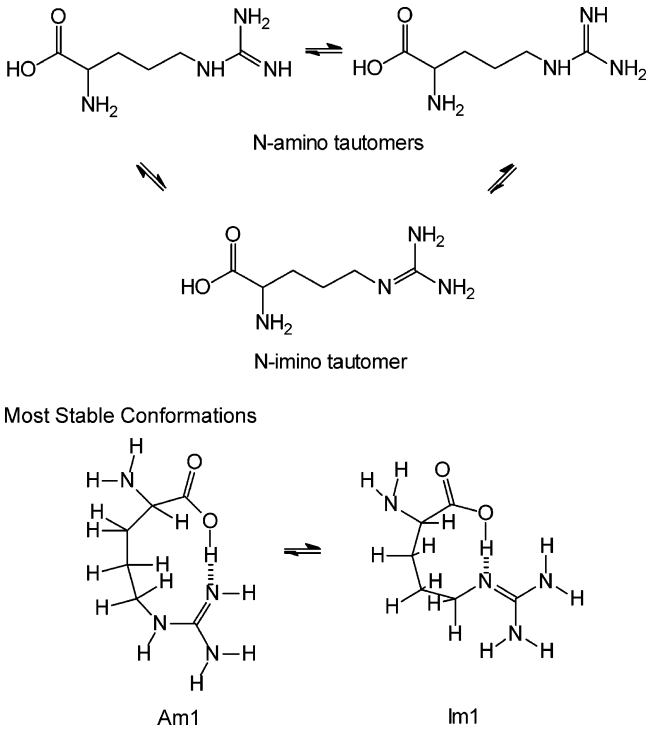
HOMA value is positive only for the enol E1 radical cation, for which it has the value 0.902.

An interesting case of enamine−imine tautomerism was observed in α,β-unsaturated-α-amino acids {RR′C=C(COOH)−NH_2 ⇌ RR′CH−C(COOH)=NH}.[338] The tautomeric equilibrium depends strongly on the nature of the R and R′ substituents and on the pH of the medium. For open chain dehydrovaline (R, R′ = Me) and dehydrophenylalanine (R = Ph, R′ = H), protonation in the form of the hydrochloride salts and deprotonation in the form of the sodium salts stabilize the enamine tautomer. For the cyclic aliphatic dehydropipecolinic acid {R, R′ = $(CH_2)_3$}, the sodium salt and ester favor the enamine form, while the hydrochloride salt exists as the imine form.

Amine−imine tautomeric equilibria in the guanidine moiety of arginine (Scheme 35) are similar to those in N-substituted guanidines with the difference that the other functions (NH_2 and COOH or NH_3^+ and COO^-) present in the arginine molecule may interact with the tautomeric guanidine group.[28] In water solution, the guanidine, being more basic than the amino group, takes the proton from the COOH group and arginine exists exclusively in the zwitterionic form {$^+NH_2$=C(NH_2)NH(CH_2)$_3$C(NH_2)COO^-}, where the amine−imine tautomerism is absent. In the gas phase, formation of the zwitterionic form for isolated neutral arginine is not possible.[327,328] This behavior may be changed only by the presence of other molecules of amino acid or of water, an excess electron, a proton, or an alkali cation.[339]

Gutowski and co-workers,[28] investigating neutral arginine in the gas phase by high-level ab initio calculations, found only one conformation for the *N*-imino-substituted tautomer (Im1) and four conformations for the *N*-amino-substituted tautomer, among which Am1 is the most stable. The two tautomers Am1 and Im1 are stabilized by intramolecular H-bonds between the carboxyl OH group and the guanidine imino nitrogen (OH···N=C). The electronic energies of the Am1 and Im1 forms calculated using the B3LYP, MP2, and CCSD methods with the 6-31++G** basis set are almost the same, and the relative energy is close to zero. Electron delocalization in the guanidine moiety, which is engaged in the intramolecular H-bond with the carboxyl OH group, is also similar in both forms.

Scheme 35. Tautomeric Equilibria and Most Stable Conformations of *N*-Amino (Am1) and *N*-Imino (Im1) Tautomers for Arginine[28]

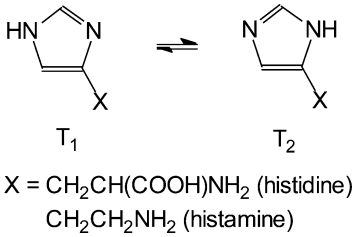


7.2. Aromatic Systems

Although the amino acid histidine and its biogenic amine histamine possess the rigid imidazole ring (Scheme 4), they belong to the class of nitrogen ligands with a flexible conformation. They contain three functions with nitrogens: the amino and imino groups in the imidazole ring and the amino group in the side chain. Histidine contains in addition the carboxyl group in the side chain. Therefore, these two biomolecules display complicated systems of different protonated, tautomeric, and conformational states that depend strongly on environment (phase, solvent, pH, metal cation, and hydroxyl or carboxylate anion).[26,27] Various types of intra- and intermolecular interactions appearing in the solid, aqueous, or gas phases complicate even more the structure of both compounds so that it is difficult to define general correlations between the structure and the medium. It is well-known that only in aqueous solution the chain amino group is the first to be protonated,[340] whereas in the gas phase the ring imino nitrogen is more basic and is preferentially protonated.[341]

Due to polyfunctionality, different proton transfers are possible within the histidine and histamine molecules. Typical intramolecular proton transfers from one to another functional group similar to transfers in bifunctional derivatives without concomitant migration of π-electrons, such as transfers from the carboxyl group to the chain amino nitrogen in histidine with the formation of the zwitterionic

Scheme 36. Tautomeric Equilibria in Histidine and Histamine



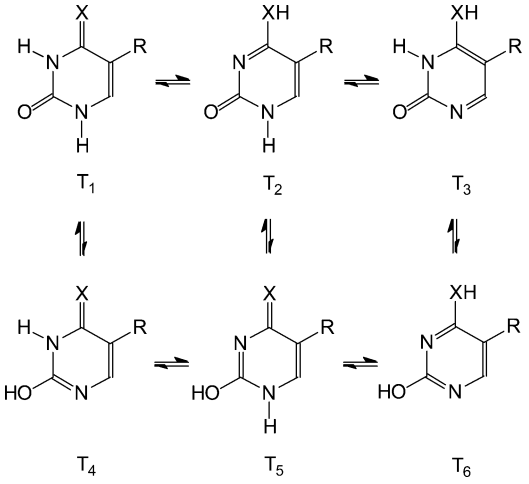
form or from the ring imino nitrogen to the chain amino nitrogen in protonated histamine when going from the gas phase to aqueous solution, cannot be classified as tautomeric interconversions. Only the intramolecular proton transfer in the imidazole ring from the amino to the imino nitrogen, which takes place in the neutral molecules and in the chain amino protonated molecules, can be considered as an amine−imine prototropy (Scheme 36).

Since the tautomeric moiety (−NH−CH=N−) is completely included in the aromatic ring, transfer of the proton from one to the other nitrogen atom has no important influence on π-electron delocalization in the imidazole ring.[34b] The HOMA indices estimated for the HF/6-31G* geometries of the imidazole ring in the neutral histamine tautomers and in their chain *N*-amino protonated forms are almost the same (0.82−0.86). Similarly, the NICS(1) index calculated by the GIAO/HF/6-31+G*//HF/6-31G* method varies only from −10.3 to −10.5. Intramolecular H-bonds possible in the gauche conformations and protonation of the chain amino group have no effect on the high aromaticity of the imidazole ring. Quite a different situation was observed for relative energies. In the gas phase, protonation of the chain amino group in histamine changes tautomeric preference from the 5-substituted tautomer (T_2) for the neutral gauche molecule ($\Delta E_T \leq 3$ kcal mol^{-1}) to the 4-substituted tautomer (T_1) for the gauche N-amino protonated form ($\Delta E_T \leq -20$ kcal mol^{-1}).[34b] Similar tautomeric preferences were found in the solid state, with the difference that the trans conformations are favored for the neutral species and the chain N-amino protonated species.[342] The presence of other molecules or ions may change this behavior in the solid state.[26]

Weinstein et al.[2c] showed by calculations that the relative stability of the chain N-amino protonated tautomers depends on some kind of interaction of the histamine monocation with a negatively charged group (e.g., OH^- or COO^-) that may be present in an active site of the histamine-specific receptors. Neutralization of the positively charged aminoalkyl side chain by an anion leads to a change of its electronic properties and in consequence to a change of the tautomeric preference. In such a case, the 5-substituted N-amino protonated form (T_2) associated with an anion is favored, just as it is for the neutral histamine.

Pyrimidine (cytosine, uracil, and thymine) and purine (adenine and guanine) bases (Scheme 4) are more rigid than histidine and histamine because they possess small *exo*-groups drawn from the set CH_3, O/OH, and NH/NH_2. However, their tautomeric

Scheme 37. Tautomeric Equilibria in Pyrimidine Bases, Uracil (R = H, X = O), Thymine (R = CH_3, X = O), and Cytosine (R = H, X = NH)

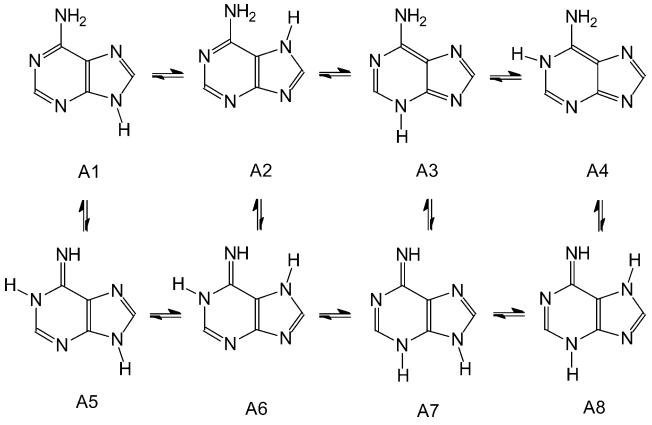


preferences seem to be particularly sensitive to various internal and external effects. Pyrimidine bases contain four functions (two ring nitrogens and two *exo*-groups with heteroatoms) and two protons that may be transferred from the *exo*- to the *endo*-heteroatom. The combination of two types of tautomerism, amide−iminol and amine−imine, leads to six possible tautomeric forms (Scheme 37). Taking into account rotations of the *exo*-groups, 13 structures can be considered for uracil and thymine. Among them, the 2,4-dioxo tautomer (T_1) is the most stable in the gas phase, in solutions, and in solids as was supported by various spectroscopic (X-ray, UV, IR, NMR, MW) and computational (HF, MP2, DFT) studies.[5d,182,343] The diketo tautomer (T_1) of uracil and thymine was found to be more stable than the lowest energy monohydroxy and dihydroxy tautomers by greater than 10 kcal mol^{-1}. In the case of cytosine, 14 tautomers−rotamers are possible. Among them, the 2-oxo-4-amino tautomer (T_2) is found in DNA and in aqueous solution.[2a,e,5d] In the gas phase, the situation remains somewhat unclear because several tautomers (T_1, T_2, T_6) were calculated to be close in energy, and the relative ordering of their stabilities was found to be method-dependent.[344] Comparison of computational with experimental (IR, MW) data is difficult, and there is as yet no conclusive evidence on tautomeric preference.[344,345]

In the case of purine bases, the situation is more clear for adenine, which contains only nitrogens as heteroatoms, than for guanine, which also has an oxygen in the *exo*-group. Amine−imine tautomerism in adenine leads to eight tautomers (Scheme 38), among which tautomers A5−A8 also display geometric isomerism of the =NH group so that two diastereoisomeric structures are possible for each of these four tautomers. In turn, combination of the amide−iminol and amine−imine tautomerism in guanine leads to 14 tautomers (Scheme 39). When rotational isomerism of the OH group, and geometric isomerism of the =NH group is considered, there are 32 possible tautomers−rotamers for guanine.

Experimental and computational studies of adenine[346] suggest that only one of eight tautomers (i.e.,

Scheme 38. Tautomeric Equilibria in Adenine

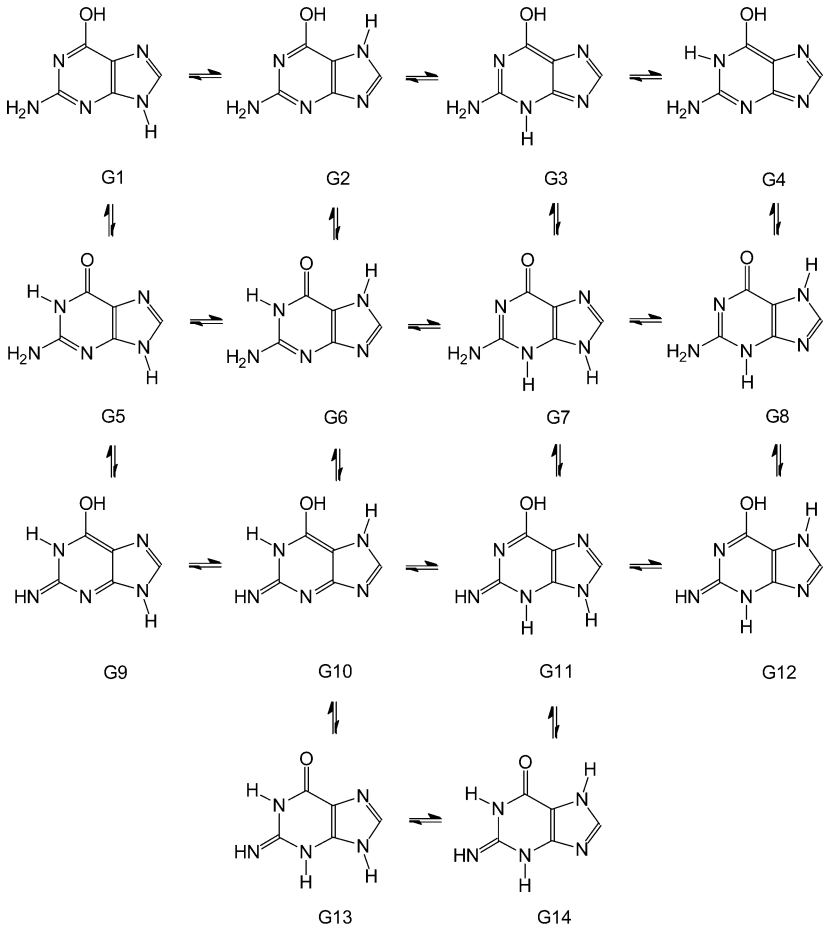


A1, which has the lowest energy) is present in the gas phase, whereas two tautomers (A1 and A2) coexist in polar solvents. Water molecules significantly stabilize the more polar A2 tautomer, but A1 remains the lowest energy tautomer. Crystalline guanine takes the G5 form.[347] This tautomer seems to be favored also in a polar environment.[348] In the gas phase, quantum-chemical calculations (i.e., HF, MP2, and DFT) indicated several tautomers close in energy, the relative stabilities of which were very sensitive to the level of theory.[349] Only recent IR and UV studies of Mons et al.[350] provided evidence for the simultaneous existence of four tautomers in the gas phase, two being the hydroxyl forms G1 and G2 and two being the oxo forms G5 and G6.

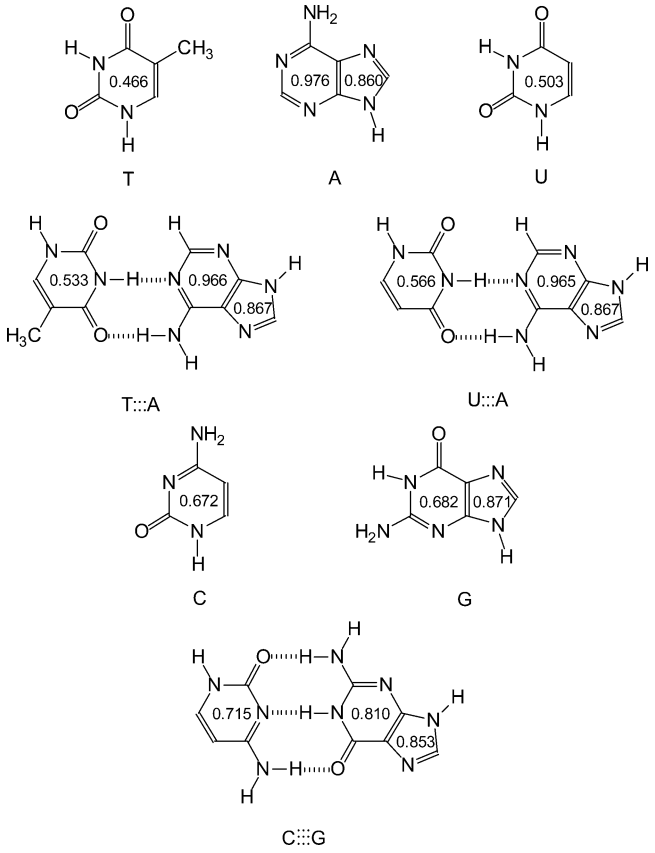
The similar energies of tautomers of pyrimidine and purine bases, the order of stabilities of which may be easily changed by external effects (e.g., UV irradiation), seem to be one of the main reasons for DNA mutations.[40,351] A double proton transfer by prototropic tautomerism, in which both bases are simultaneously converted into another pair of tautomers, was also proposed as another cause of DNA mutations.[352] Although this proposal is sound, there is no experimental information on how environment (e.g., water molecules, other bases in nucleic acids, proteins, or UV) may influence the interconversion and the stability of both tautomers.

The electron delocalization in the nucleobases constituting DNA and RNA was recently investigated by Krygowski and co-workers.[353] They applied the HOMA, NICS(0), and NICS(1) aromaticity indices to adenine, guanine, cytosine, thymine, and uracil tautomers present in the nucleic acids and also to other selected tautomers. The HOMA indices estimated for nucleotautomers (whole systems) based on the MP2/6-311+G** and B3LYP/6-311+G** optimized geometries are close to those based on experimental structures retrieved from the CSD.[182] The agreement is better for the MP2 than for the B3LYP geometries. Larger differences were found for the less strongly aromatic thymine and uracil. These differences, however, may result from substituents present in crystal structures, which may affect aromaticity. Generally, the aromaticity of nucleotautomers decreases with the increase of the number of C=X (X

Scheme 39. Tautomeric Equilibria in Guanine



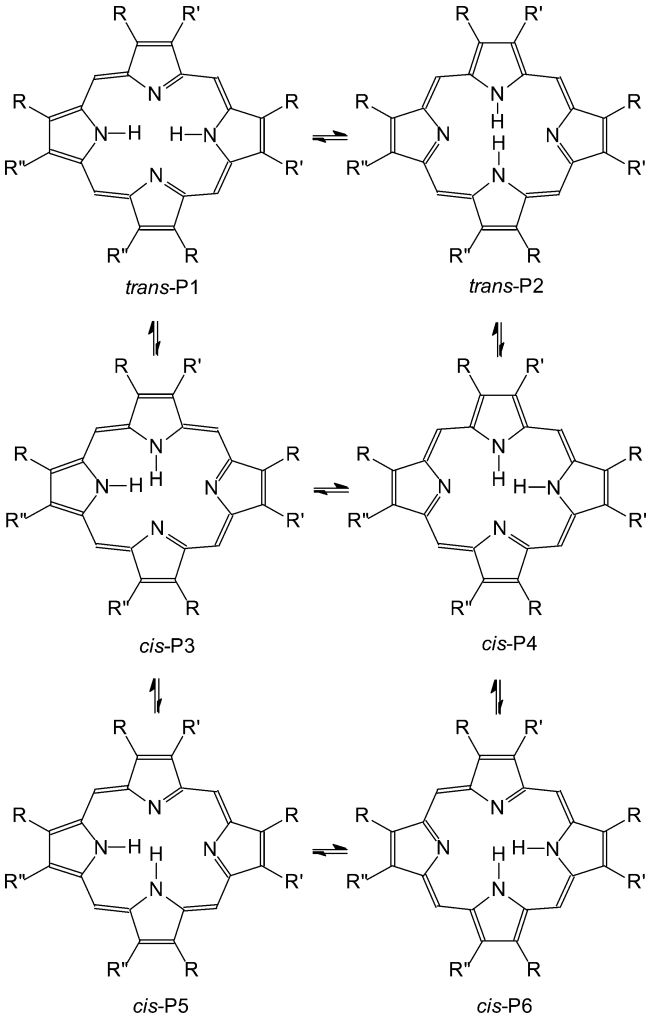
Scheme 40. HOMA Indices (B3LYP/6-311+G) for Heterocycles in Nucleobases and Watson−Crick Pairs[353]**



= O or NH) groups in the ring, that is, in the order adenine > guanine > cytosine > uracil > thymine. The HOMA values decrease from 0.926 to 0.495 and from 0.917 to 0.466 at the MP2/6-311+G** and B3LYP/6-311+G** levels, respectively. The same order was found for nucleobases in Watson−Crick pairs. As expected, H-bonding increases electron delocalization in less aromatic rings (Scheme 40). According to the NICS indices, high aromaticity is displayed only by the imidazole ring in adenine and guanine bases and by the pyrimidine ring in adenine. In other rings, aromaticity is reduced by C=X groups. As was also observed for simple linear tautomeric systems, the relative energies calculated between the nucleotautomers and other rare tautomeric forms of adenine, guanine, cytosine, thymine, and uracil do not correlate with the relative descriptors of aromaticity.

Porphyrins are an interesting class of molecules from the biological, physical, and chemical viewpoints.[30] Exchange of two protons between the four nitrogens, which leads to six tautomeric forms (Scheme 41) is the most important chemical process occurring in the free base. The double proton-transfer reaction may proceed in the ground state and also after absorption of a photon, both in the solid state and in solution.[5d,30,354] Since porphyrins possess extended π-electron systems, they exhibit high stability. However, the partially double CC bond character of the bridges between the pyrrole rings causes a substantial decrease of their aromatic character in comparison to pyrrole derivatives. In 456 porphyrin

Scheme 41. Tautomeric Equilibria in Porphyrin



derivatives including only trans systems retrieved from CSD,[182] the HOMA values estimated for pyrrole rings range from 0.45 (for deprotonated rings) to 0.66 (for protonated rings).[355] For the less perturbed pyrrole derivatives containing single-bonded substituents at the 2 or 5 positions or both, the HOMA values vary from 0.907 to 0.932. The lesser aromatic character of the deprotonated than of the protonated pyrrole rings was also evidenced by the calculated NICS values of −4.5 and −15.2 ppm, respectively. The NICS value for rings with the NH group (−15.2 ppm) is practically identical to that for pyrrole (−15.1).[18b] There are two kinds of pyrrole rings in porphyrins: those with pyramidal nitrogen and those with planar nitrogen. Interestingly, the HOMA indices for the free base and metal complex of a porphyrin do not differ significantly either when calculated for the whole system, giving 0.652 for the free base and 0.656 for the complex, or when calculated for the selected internal cross, giving 0.880 for the free base versus 0.872 for the complex. However, coordination of metal with four nitrogens leads to almost equal aromaticity of both types of pyrrole rings (0.566 and 0.524). The same behavior is found for the NICS values (−10.0 ppm for both types of rings in metal complexes).[355,356] Tautomerization in the free base has no particular effect on the NICS values {−15.1 and −14.9 ppm calculated for the

B3LYP/6-31G** geometries of the trans and cis tautomers, respectively, for porphin (R, R′, R″ = H)}.[357] The similarity in aromatic character of porphyrin tautomers does not explain why the energy of tautomerization is different from zero. For porphin, it was found to be equal to 8 kcal mol^{-1} at the B3LYP/6-31G** level. This fact again indicates that the indices of aromaticity seem not to be correlated with the thermodynamic stabilities of tautomeric systems.

8. Conclusions

Tautomeric equilibria are very important intramolecular proton-transfer reactions, which by definition are associated with changes in π-electron distribution. In general, π-electron delocalization plays a principal role in tautomeric systems and affects tautomeric preferences. However, other internal effects (such as stability of functionalities, n−π or Y-conjugation, push−pull effect, aromaticity, substituent effects, or intramolecular H-bonding) and external influences (light, temperature, acid, base, solvent, ion, electron solvation, or ionization) may change this general behavior.

Many numerical measures of π-electron delocalization, often also called indices of aromaticity, are proposed in the literature. Among them, the geometric index (HOMA) describes the electron delocalization in both acyclic and cyclic compounds very well. The magnetic parameter (NICS) can only be applied to aromatic compounds. In RAHB as well as in acyclic tautomeric systems, the NICS index seems not to distinguish electron delocalization. The relative electronic energies used to characterize the changes in π-electron delocalization in various tautomers are not necessairily always in line with changes in other delocalization parameters. This is in good agreement with earlier conclusions derived on the basis of detailed analyses of aromaticity in heterocyclic π-electron systems.[114,115] It seems that each parameter describing tautomeric preferences and electron delocalization should be analyzed taking various partial factors into account so that those of the greatest importance and strongest influence can be selected. Such an analysis could explain why a one-dimensional ordering for tautomeric preferences and electron delocalization seems to be impossible.

Finally, it is obvious that the topic of this review could not be fully covered here. There are thousands of tautomeric systems reported in the literature, and it was not possible to analyze them all in one review. The material was selected to assess major problems in the relation between tautomeric equilibria and π-electron delocalization. We have chosen simple tautomeric cyclic and acyclic systems and mainly those often used as models for biological molecules.

9. Glossary of Abbreviations

AM1	Austin model 1
ASE	aromatic stabilization energy
B3LYP	Becke three-parameter hybrid method, which includes a mixture of HF and DFT exchange terms with nonlocal correlation provided by the Lee, Yang, and Parr (LYP) expression
CCSD	coupled-cluster level of theory with single and double excitations
CSD	Cambridge Structural Database
DE	delocalization energy
DFT	density functional theory
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acids
DRE	Dewar resonance energy
ESI-MS	electrospray ionization mass spectrometry
G1	Gaussian-1 theory
G2	Gaussian-2 theory
G2(MP2)	MP2 variant of Gaussian-2 theory
GB	gas basicity
GIAO	gauge-independent atomic orbital
HF	Hartree−Fock level of theory
HOMA	harmonic oscillator model of aromaticity index
HOSE	harmonic oscillator stabilization energy
HSAB	hard and soft acids and bases
ICR	ion cyclotron resonance
IR	infrared
ISI	Institute for Scientific Information, Philadelphia
MHP	maximum hardness principle
MO	molecular orbital
MP2	second-order Möller−Plesset perturbation theory
MPP	minimum polarizability principle
MS	mass spectrometry
MW	microwave
NBO	natural bond orbital analysis
NCBI	National Center for Biotechnology Information
NICS	nuclear-independent chemical shift
NMR	nuclear magnetic resonance
PA	proton affinity
PC	principal component
PCM	polarized continuum model
PM3	parametric method 3
RAHB	resonance-assisted hydrogen bonding
RBM	rotation barrier method
RE	resonance energy
REPE	resonance energy per electron
SCI−PCM	self-consistent isodensity polarized continuum model
SCRF	self-consistent reaction field
SE	stabilization energy
UV	ultraviolet
UV−vis	ultraviolet−visible
ZPVE	zero-point vibrational energy

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